Cholesterol Example2: Two-Factor Repeated Measures with different Covariance Structures

We extend Cholesterol Example1, this time considering a control group with thirteen subjects was given a placebo and measured over the same six periods. Hence we have a two-factor repeated measures design with treatment as the between-subjects factor and period as the within-subjects factor.

Important Note: Since each subject recieves just one treatment (either placebo or test), subject is nested within trt. However, since we have unique subject IDs, the nesting does not need to be explicity specified in the model.

```
library(ggplot2)
library(nlme)
library(emmeans)
CholData <- read.csv("C:/hess/STAT512/RNotes/Random3/R3_Cholesterol2.csv")
str(CholData)
```

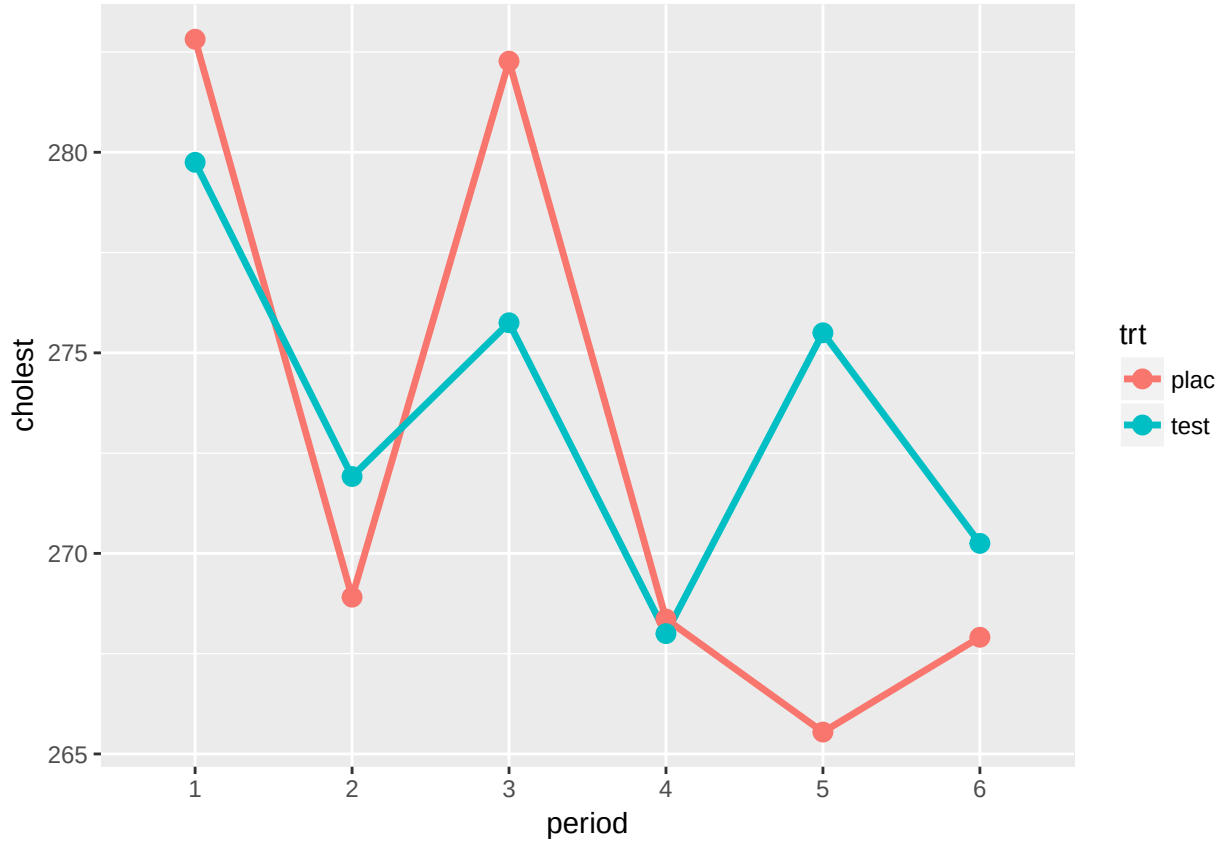
```
## 'data.frame':    138 obs. of  4 variables:
##  $ subject: int  1 1 1 1 1 1 2 2 2 2 ...
##  $ period : int  1 2 3 4 5 6 1 2 3 4 ...
##  $ cholest: int  317 280 275 270 274 266 186 189 190 135 ...
##  $ trt    : Factor w/ 2 levels "plac","test": 2 2 2 2 2 2 2 2 2 2 ...
```

```
#Important: Need to define Subject as.factor!!!
CholData$subject <- as.factor(CholData$subject)
CholData$period <- as.factor(CholData$period)
#Check for Unique Subject IDs
with(table(subject, trt), data = CholData)
```

```
##        trt
## subject plac test
##      1     0    6
##      2     0    6
##      3     0    6
##      4     0    6
##      5     0    6
##      6     0    6
##      7     0    6
##      8     0    6
##      9     0    6
##      10    0    6
##      11    0    6
##      12    0    6
##      13    6    0
##      14    6    0
##      15    6    0
##      16    6    0
##      17    6    0
##      18    6    0
##      19    6    0
##      20    6    0
##      21    6    0
##      22    6    0
```

```
##      23    6    0
```

```
SumStats <- aggregate(cholest ~ trt + period, FUN = mean, data = CholData)
qplot(x = period, y = cholest, colour = trt, group = trt, data = SumStats) +  geom_line(size=1.2) +
  geom_point(size=3)
```



Model1: Basic Model (equivalent to using corCompSymm)

Note the use of the contrasts option to get meaningful Type3 tests when model includes interaction between factors.

```
options(contrasts=c("contr.sum","contr.poly"))
Model1 <- lme(cholest ~ period*trt, random = ~1|subject, data = CholData)
summary(Model1)
```

```
## Linear mixed-effects model fit by REML
##  Data: CholData
##        AIC      BIC    logLik
##   1259.244 1298.952 -615.6219
##
## Random effects:
##  Formula: ~1 | subject
##         (Intercept) Residual
## StdDev:    48.24366 19.88316
##
## Fixed effects: cholest ~ period * trt
```

```
##                  Value Std.Error  DF   t-value p-value
## (Intercept)  273.08207 10.210551 105 26.745086  0.0000
## period1        8.20202  3.788277 105  2.165106  0.0326
## period2       -2.66919  3.788277 105 -0.704593  0.4826
## period3        5.92929  3.788277 105  1.565169  0.1206
## period4       -4.90025  3.788277 105 -1.293531  0.1987
## period5       -2.55934  3.788277 105 -0.675596  0.5008
## trt1          -0.44571 10.210551  21 -0.043652  0.9656
## period1:trt1   1.97980  3.788277 105  0.522612  0.6023
## period2:trt1  -1.05808  3.788277 105 -0.279304  0.7806
## period3:trt1   3.70707  3.788277 105  0.978564  0.3300
## period4:trt1   0.62753  3.788277 105  0.165649  0.8688
## period5:trt1  -4.53157  3.788277 105 -1.196208  0.2343
##  Correlation:
##              (Intr) perid1 perid2 perid3 perid4 perid5 trt1   prd1:1
## period1       0.000
## period2       0.000 -0.200
## period3       0.000 -0.200 -0.200
## period4       0.000 -0.200 -0.200 -0.200
## period5       0.000 -0.200 -0.200 -0.200 -0.200
## trt1          0.043  0.000  0.000  0.000  0.000  0.000
## period1:trt1  0.000  0.043 -0.009 -0.009 -0.009 -0.009  0.000
## period2:trt1  0.000 -0.009  0.043 -0.009 -0.009 -0.009  0.000 -0.200
## period3:trt1  0.000 -0.009 -0.009  0.043 -0.009 -0.009  0.000 -0.200
## period4:trt1  0.000 -0.009 -0.009 -0.009  0.043 -0.009  0.000 -0.200
## period5:trt1  0.000 -0.009 -0.009 -0.009 -0.009  0.043  0.000 -0.200
##              prd2:1 prd3:1 prd4:1
## period1
## period2
## period3
## period4
## period5
## trt1
## period1:trt1
## period2:trt1
## period3:trt1 -0.200
## period4:trt1 -0.200 -0.200
## period5:trt1 -0.200 -0.200 -0.200
##
## Standardized Within-Group Residuals:
##         Min          Q1         Med          Q3         Max
## -2.29404293 -0.54517358 -0.04163739  0.52221579  2.47926645
##
## Number of Observations: 138
## Number of Groups: 23
```

```
anova.lme(Model1, type = "marginal")
```

```
##             numDF denDF  F-value p-value
## (Intercept)     1   105 715.2996  <.0001
## period          5   105   1.8133  0.1165
## trt             1    21   0.0019  0.9656
## period:trt      5   105   0.4673  0.7998
```

```r
emmeans(Model1, dunnett ~ period|trt)
```

```
## $emmeans
## trt = plac:
##  period   emmean       SE df lower.CL upper.CL
##  1      282.8182 15.73297 21 250.0997 315.5367
##  2      268.9091 15.73297 21 236.1906 301.6276
##  3      282.2727 15.73297 21 249.5542 314.9912
##  4      268.3636 15.73297 21 235.6451 301.0821
##  5      265.5455 15.73297 21 232.8269 298.2640
##  6      267.9091 15.73297 21 235.1906 300.6276
##
## trt = test:
##  period   emmean       SE df lower.CL upper.CL
##  1      279.7500 15.06317 21 248.4244 311.0756
##  2      271.9167 15.06317 21 240.5911 303.2423
##  3      275.7500 15.06317 21 244.4244 307.0756
##  4      268.0000 15.06317 21 236.6744 299.3256
##  5      275.5000 15.06317 21 244.1744 306.8256
##  6      270.2500 15.06317 21 238.9244 301.5756
##
## Confidence level used: 0.95
##
## $contrasts
## trt = plac:
##  contrast    estimate       SE  df t.ratio p.value
##  2 - 1    -13.9090909 8.478207 105  -1.641  0.3433
##  3 - 1     -0.5454545 8.478207 105  -0.064  0.9998
##  4 - 1    -14.4545455 8.478207 105  -1.705  0.3094
##  5 - 1    -17.2727273 8.478207 105  -2.037  0.1675
##  6 - 1    -14.9090909 8.478207 105  -1.759  0.2826
##
## trt = test:
##  contrast    estimate       SE  df t.ratio p.value
##  2 - 1     -7.8333333 8.117265 105  -0.965  0.7564
##  3 - 1     -4.0000000 8.117265 105  -0.493  0.9538
##  4 - 1    -11.7500000 8.117265 105  -1.448  0.4557
##  5 - 1     -4.2500000 8.117265 105  -0.524  0.9459
##  6 - 1     -9.5000000 8.117265 105  -1.170  0.6316
##
## P value adjustment: dunnettx method for 5 tests
```

```r
emmeans(Model1, pairwise ~ trt|period)
```

```
## $emmeans
## period = 1:
##  trt    emmean       SE df lower.CL upper.CL
##  plac 282.8182 15.73297 21 250.0997 315.5367
##  test 279.7500 15.06317 21 248.4244 311.0756
##
## period = 2:
##  trt    emmean       SE df lower.CL upper.CL
##  plac 268.9091 15.73297 21 236.1906 301.6276
##  test 271.9167 15.06317 21 240.5911 303.2423
```

```
##
## period = 3:
##  trt    emmean       SE df lower.CL upper.CL
##  plac 282.2727 15.73297 21 249.5542 314.9912
##  test 275.7500 15.06317 21 244.4244 307.0756
##
## period = 4:
##  trt    emmean       SE df lower.CL upper.CL
##  plac 268.3636 15.73297 21 235.6451 301.0821
##  test 268.0000 15.06317 21 236.6744 299.3256
##
## period = 5:
##  trt    emmean       SE df lower.CL upper.CL
##  plac 265.5455 15.73297 21 232.8269 298.2640
##  test 275.5000 15.06317 21 244.1744 306.8256
##
## period = 6:
##  trt    emmean       SE df lower.CL upper.CL
##  plac 267.9091 15.73297 21 235.1906 300.6276
##  test 270.2500 15.06317 21 238.9244 301.5756
##
## Confidence level used: 0.95
##
## $contrasts
## period = 1:
##  contrast      estimate       SE df t.ratio p.value
##  plac - test  3.0681818 21.78131 21   0.141  0.8893
##
## period = 2:
##  contrast      estimate       SE df t.ratio p.value
##  plac - test -3.0075758 21.78131 21  -0.138  0.8915
##
## period = 3:
##  contrast      estimate       SE df t.ratio p.value
##  plac - test  6.5227273 21.78131 21   0.299  0.7675
##
## period = 4:
##  contrast      estimate       SE df t.ratio p.value
##  plac - test  0.3636364 21.78131 21   0.017  0.9868
##
## period = 5:
##  contrast      estimate       SE df t.ratio p.value
##  plac - test -9.9545455 21.78131 21  -0.457  0.6523
##
## period = 6:
##  contrast      estimate       SE df t.ratio p.value
##  plac - test -2.3409091 21.78131 21  -0.107  0.9154
```

Model2: corSymm

```
Model2 <- lme(cholest ~ period*trt, random = ~1|subject,
              correlation = corSymm(form = ~1|subject), data = CholData)
```

```r
summary(Model2)
```

```
## Linear mixed-effects model fit by REML
##  Data: CholData
##        AIC      BIC    logLik
##   1258.037 1340.289 -600.0183
##
## Random effects:
##  Formula: ~1 | subject
##         (Intercept) Residual
## StdDev:    49.75592 20.14795
##
## Correlation Structure: General
##  Formula: ~1 | subject
##  Parameter estimate(s):
##  Correlation:
##   1      2      3      4      5
## 2  0.186
## 3 -0.277  0.478
## 4 -0.443 -0.297  0.143
## 5 -0.484 -0.152  0.510  0.151
## 6 -0.153  0.167  0.431 -0.147  0.569
## Fixed effects: cholest ~ period * trt
##                   Value Std.Error  DF   t-value p-value
## (Intercept)  273.08207 10.557429 105 25.866342  0.0000
## period1        8.20202  4.722589 105  1.736764  0.0854
## period2       -2.66919  3.627205 105 -0.735881  0.4634
## period3        5.92929  2.798345 105  2.118857  0.0365
## period4       -4.90025  4.347237 105 -1.127211  0.2622
## period5       -2.55934  3.450046 105 -0.741829  0.4598
## trt1          -0.44571 10.557429  21 -0.042217  0.9667
## period1:trt1   1.97980  4.722589 105  0.419219  0.6759
## period2:trt1  -1.05808  3.627205 105 -0.291707  0.7711
## period3:trt1   3.70707  2.798345 105  1.324737  0.1881
## period4:trt1   0.62753  4.347237 105  0.144350  0.8855
## period5:trt1  -4.53157  3.450046 105 -1.313480  0.1919
##  Correlation:
##              (Intr) perid1 perid2 perid3 perid4 perid5 trt1   prd1:1
## period1      -0.083
## period2       0.012  0.195
## period3       0.106 -0.568  0.124
## period4      -0.053 -0.239 -0.438 -0.147
## period5       0.030 -0.561 -0.626  0.125  0.026
## trt1          0.043 -0.004  0.001  0.005 -0.002  0.001
## period1:trt1 -0.004  0.043  0.008 -0.025 -0.010 -0.024 -0.083
## period2:trt1  0.001  0.008  0.043  0.005 -0.019 -0.027  0.012  0.195
## period3:trt1  0.005 -0.025  0.005  0.043 -0.006  0.005  0.106 -0.568
## period4:trt1 -0.002 -0.010 -0.019 -0.006  0.043  0.001 -0.053 -0.239
## period5:trt1  0.001 -0.024 -0.027  0.005  0.001  0.043  0.030 -0.561
##              prd2:1 prd3:1 prd4:1
## period1
## period2
## period3
## period4
```

```
## period5
## trt1
## period1:trt1
## period2:trt1
## period3:trt1  0.124
## period4:trt1 -0.438 -0.147
## period5:trt1 -0.626  0.125  0.026
##
## Standardized Within-Group Residuals:
##         Min          Q1         Med          Q3         Max
## -2.20615500 -0.63804366 -0.09002825  0.61036964  2.08857982
##
## Number of Observations: 138
## Number of Groups: 23
```

```
getVarCov(Model2, individual = 1, type = "marginal")
```

```
## subject 1
## Marginal variance covariance matrix
##        1      2      3      4      5      6
## 1 2881.6 2551.2 2363.3 2296.0 2279.3 2413.6
## 2 2551.2 2881.6 2669.5 2355.1 2414.1 2543.4
## 3 2363.3 2669.5 2881.6 2533.8 2682.7 2650.8
## 4 2296.0 2355.1 2533.8 2881.6 2537.0 2416.0
## 5 2279.3 2414.1 2682.7 2537.0 2881.6 2706.6
## 6 2413.6 2543.4 2650.8 2416.0 2706.6 2881.6
##   Standard Deviations: 53.68 53.68 53.68 53.68 53.68 53.68
```

Model3: corAR1

```
Model3 <- lme(cholest ~ period*trt, random = ~1|subject,
              correlation = corAR1(form = ~1|subject), data = CholData)
summary(Model3)
```

```
## Linear mixed-effects model fit by REML
##  Data: CholData
##       AIC      BIC    logLik
##    1249.1 1291.644 -609.5498
##
## Random effects:
##  Formula: ~1 | subject
##         (Intercept) Residual
## StdDev:     47.0107 22.53079
##
## Correlation Structure: AR(1)
##  Formula: ~1 | subject
##  Parameter estimate(s):
##       Phi
## 0.4451394
## Fixed effects: cholest ~ period * trt
##                   Value Std.Error  DF   t-value p-value
## (Intercept)  273.08207 10.203219 105 26.764305  0.0000
## period1        8.20202  4.094922 105  2.002973  0.0478
```

```
## period2       -2.66919  3.690000 105 -0.723358  0.4711
## period3        5.92929  3.527740 105  1.680762  0.0958
## period4       -4.90025  3.527740 105 -1.389063  0.1678
## period5       -2.55934  3.690000 105 -0.693589  0.4895
## trt1          -0.44571 10.203219  21 -0.043683  0.9656
## period1:trt1   1.97980  4.094922 105  0.483476  0.6298
## period2:trt1  -1.05808  3.690000 105 -0.286743  0.7749
## period3:trt1   3.70707  3.527740 105  1.050834  0.2957
## period4:trt1   0.62753  3.527740 105  0.177883  0.8592
## period5:trt1  -4.53157  3.690000 105 -1.228067  0.2222
##  Correlation:
##               (Intr) perid1 perid2 perid3 perid4 perid5 trt1   prd1:1
## period1       -0.030
## period2        0.009  0.193
## period3        0.025 -0.216  0.058
## period4        0.025 -0.385 -0.361  0.014
## period5        0.009 -0.401 -0.481 -0.361  0.058
## trt1           0.043 -0.001  0.000  0.001  0.001  0.000
## period1:trt1 -0.001  0.043  0.008 -0.009 -0.017 -0.017 -0.030
## period2:trt1  0.000  0.008  0.043  0.003 -0.016 -0.021  0.009  0.193
## period3:trt1  0.001 -0.009  0.003  0.043  0.001 -0.016  0.025 -0.216
## period4:trt1  0.001 -0.017 -0.016  0.001  0.043  0.003  0.025 -0.385
## period5:trt1  0.000 -0.017 -0.021 -0.016  0.003  0.043  0.009 -0.401
##               prd2:1 prd3:1 prd4:1
## period1
## period2
## period3
## period4
## period5
## trt1
## period1:trt1
## period2:trt1
## period3:trt1  0.058
## period4:trt1 -0.361  0.014
## period5:trt1 -0.481 -0.361  0.058
##
## Standardized Within-Group Residuals:
##         Min          Q1         Med          Q3         Max
## -2.29550056 -0.52640976 -0.08454841  0.48900092  2.07552953
##
## Number of Observations: 138
## Number of Groups: 23
```

```
anova.lme(Model3, type = "marginal")
```

```
##             numDF denDF  F-value p-value
## (Intercept)     1   105 716.3280  <.0001
## period          5   105   2.3605  0.0450
## trt             1    21   0.0019  0.9656
## period:trt      5   105   0.5660  0.7258
```

```
emmeans(Model3, dunnett ~ period|trt)
```

```
## $emmeans
## trt = plac:
```

```
##  period   emmean       SE df lower.CL upper.CL
##  1      282.8182 15.71809 21 250.1306 315.5057
##  2      268.9091 15.71809 21 236.2215 301.5967
##  3      282.2727 15.71809 21 249.5852 314.9603
##  4      268.3636 15.71809 21 235.6761 301.0512
##  5      265.5455 15.71809 21 232.8579 298.2330
##  6      267.9091 15.71809 21 235.2215 300.5967
##
## trt = test:
##  period   emmean       SE df lower.CL upper.CL
##  1      279.7500 15.04893 21 248.4540 311.0460
##  2      271.9167 15.04893 21 240.6207 303.2126
##  3      275.7500 15.04893 21 244.4540 307.0460
##  4      268.0000 15.04893 21 236.7040 299.2960
##  5      275.5000 15.04893 21 244.2040 306.7960
##  6      270.2500 15.04893 21 238.9540 301.5460
##
## Confidence level used: 0.95
##
## $contrasts
## trt = plac:
##  contrast    estimate       SE  df t.ratio p.value
##  2 - 1    -13.9090909 7.156275 105  -1.944  0.2016
##  3 - 1     -0.5454545 8.602840 105  -0.063  0.9998
##  4 - 1    -14.4545455 9.173687 105  -1.576  0.3795
##  5 - 1    -17.2727273 9.416669 105  -1.834  0.2473
##  6 - 1    -14.9090909 9.522836 105  -1.566  0.3853
##
## trt = test:
##  contrast    estimate       SE  df t.ratio p.value
##  2 - 1     -7.8333333 6.851611 105  -1.143  0.6487
##  3 - 1     -4.0000000 8.236593 105  -0.486  0.9555
##  4 - 1    -11.7500000 8.783136 105  -1.338  0.5245
##  5 - 1     -4.2500000 9.015774 105  -0.471  0.9588
##  6 - 1     -9.5000000 9.117421 105  -1.042  0.7113
##
## P value adjustment: dunnettx method for 5 tests
```

```
emmeans(Model3, pairwise ~ trt|period)
```

```
## $emmeans
## period = 1:
##  trt    emmean       SE df lower.CL upper.CL
##  plac 282.8182 15.71809 21 250.1306 315.5057
##  test 279.7500 15.04893 21 248.4540 311.0460
##
## period = 2:
##  trt    emmean       SE df lower.CL upper.CL
##  plac 268.9091 15.71809 21 236.2215 301.5967
##  test 271.9167 15.04893 21 240.6207 303.2126
##
## period = 3:
##  trt    emmean       SE df lower.CL upper.CL
##  plac 282.2727 15.71809 21 249.5852 314.9603
##  test 275.7500 15.04893 21 244.4540 307.0460
```

```
##
## period = 4:
##  trt    emmean       SE df lower.CL upper.CL
##  plac 268.3636 15.71809 21 235.6761 301.0512
##  test 268.0000 15.04893 21 236.7040 299.2960
##
## period = 5:
##  trt    emmean       SE df lower.CL upper.CL
##  plac 265.5455 15.71809 21 232.8579 298.2330
##  test 275.5000 15.04893 21 244.2040 306.7960
##
## period = 6:
##  trt    emmean       SE df lower.CL upper.CL
##  plac 267.9091 15.71809 21 235.2215 300.5967
##  test 270.2500 15.04893 21 238.9540 301.5460
##
## Confidence level used: 0.95
##
## $contrasts
## period = 1:
##  contrast      estimate       SE df t.ratio p.value
##  plac - test  3.0681818 21.76071 21   0.141  0.8892
##
## period = 2:
##  contrast      estimate       SE df t.ratio p.value
##  plac - test -3.0075758 21.76071 21  -0.138  0.8914
##
## period = 3:
##  contrast      estimate       SE df t.ratio p.value
##  plac - test  6.5227273 21.76071 21   0.300  0.7673
##
## period = 4:
##  contrast      estimate       SE df t.ratio p.value
##  plac - test  0.3636364 21.76071 21   0.017  0.9868
##
## period = 5:
##  contrast      estimate       SE df t.ratio p.value
##  plac - test -9.9545455 21.76071 21  -0.457  0.6520
##
## period = 6:
##  contrast      estimate       SE df t.ratio p.value
##  plac - test -2.3409091 21.76071 21  -0.108  0.9154
```

Compare Models using AIC

```
AIC(Model1, Model2, Model3)
```

```
##        df      AIC
## Model1 14 1259.244
## Model2 29 1258.037
## Model3 15 1249.100
```