Cholesterol Example1: One-Factor Repeated Measures with different Covariance Structures

Twelve subjects were given a drug designed to lower serum cholesterol. Their cholesterol was measured at the end of six four-week periods. (Period 1 is baseline, before treatment).

For this example, we start by using the "basic" repeated measures analysis (which assumes compound symmetry), then consider unstructured (corSymm) and AR(1) covariance structures. We compare models using AIC.

```
library(dplyr)
library(nlme)
library(emmeans)
CholData <- read.csv("C:/hess/STAT512/RNotes/Random3/R3_Cholesterol1.csv")
str(CholData)
```

```
## 'data.frame':    72 obs. of  3 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 ...
```

```
#Important: Need to define Subject as.factor!!!
CholData$subject <- as.factor(CholData$subject)
CholData$period <- as.factor(CholData$period)
#Summary Statistics
SumStats <- summarize(group_by(CholData, period),
                  n = n(),
                  mean = mean(cholest),
                  sd = sd(cholest),
                  SE = sd/sqrt(n))
SumStats
```

```
## # A tibble: 6 x 5
##   period     n  mean    sd    SE
##   <fct>  <int> <dbl> <dbl> <dbl>
## 1 1         12  280.  55.6  16.1
## 2 2         12  272.  54.9  15.9
## 3 3         12  276.  47.9  13.8
## 4 4         12  268.  53.3  15.4
## 5 5         12  276.  49.1  14.2
## 6 6         12  270.  42.4  12.2
```

Model1: Basic Model (random subject = compound symmetry)

```
Model1 <- lme(cholest ~ period, random = ~1|subject, data = CholData)
summary(Model1)
```

```
## Linear mixed-effects model fit by REML
##  Data: CholData
##        AIC      BIC    logLik
##   660.0632 677.5805 -322.0316
##
```

```
## Random effects:
##  Formula: ~1 | subject
##         (Intercept) Residual
## StdDev:    45.96642 21.50985
##
## Fixed effects: cholest ~ period
##                 Value Std.Error DF   t-value p-value
## (Intercept) 279.75000  14.65033 55 19.095134  0.0000
## period2      -7.83333   8.78136 55 -0.892041  0.3763
## period3      -4.00000   8.78136 55 -0.455510  0.6505
## period4     -11.75000   8.78136 55 -1.338061  0.1864
## period5      -4.25000   8.78136 55 -0.483980  0.6303
## period6      -9.50000   8.78136 55 -1.081837  0.2840
##  Correlation:
##         (Intr) perid2 perid3 perid4 perid5
## period2 -0.3
## period3 -0.3    0.5
## period4 -0.3    0.5    0.5
## period5 -0.3    0.5    0.5    0.5
## period6 -0.3    0.5    0.5    0.5    0.5
##
## Standardized Within-Group Residuals:
##          Min           Q1          Med           Q3          Max
## -2.152639692 -0.534115213 -0.005275056  0.536387851  2.304971476
##
## Number of Observations: 72
## Number of Groups: 12
```

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

```
##             numDF denDF  F-value p-value
## (Intercept)     1    55 364.6241  <.0001
## period          5    55   0.4743  0.7938
```

```
emmeans(Model1, pairwise ~ period)
```

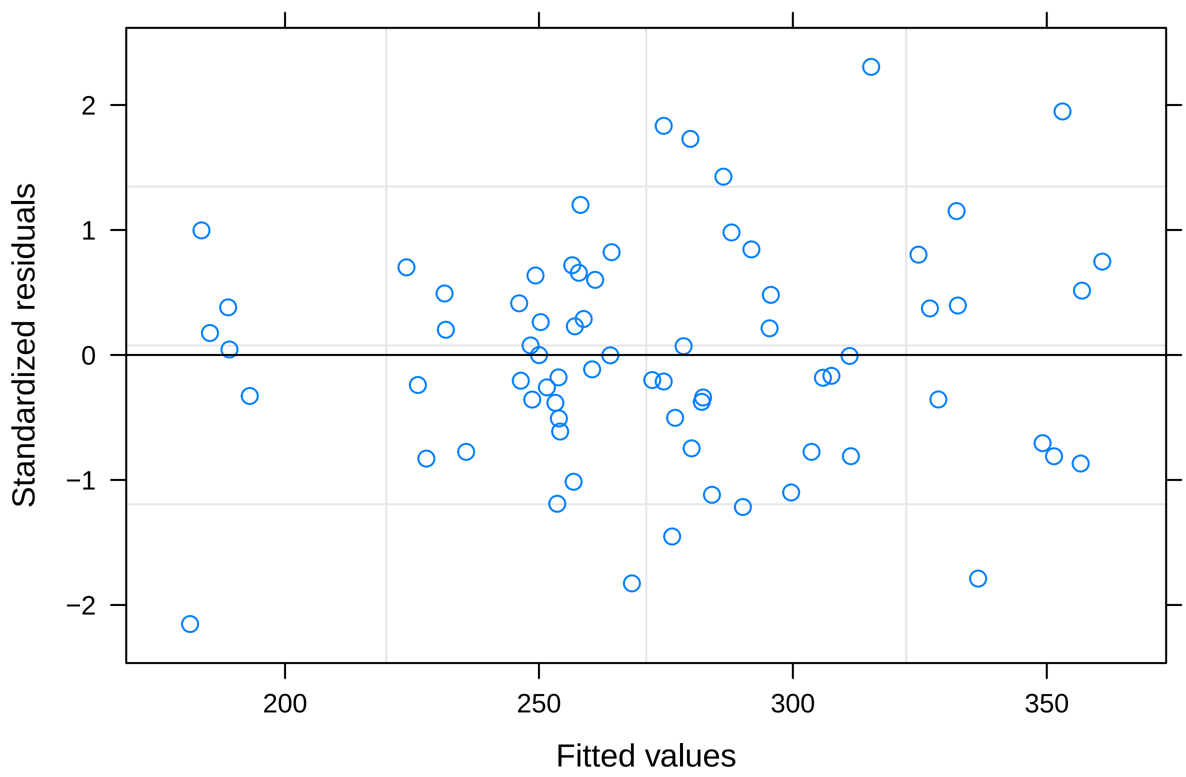
```
## $emmeans
##  period   emmean       SE df lower.CL upper.CL
##  1      279.7500 14.65033 11 247.5048 311.9952
##  2      271.9167 14.65033 11 239.6715 304.1618
##  3      275.7500 14.65033 11 243.5048 307.9952
##  4      268.0000 14.65033 11 235.7548 300.2452
##  5      275.5000 14.65033 11 243.2548 307.7452
##  6      270.2500 14.65033 11 238.0048 302.4952
##
## Confidence level used: 0.95
##
## $contrasts
##  contrast  estimate      SE df t.ratio p.value
##  1 - 2     7.833333 8.78136 55   0.892  0.9468
##  1 - 3     4.000000 8.78136 55   0.456  0.9974
##  1 - 4    11.750000 8.78136 55   1.338  0.7627
##  1 - 5     4.250000 8.78136 55   0.484  0.9965
##  1 - 6     9.500000 8.78136 55   1.082  0.8865
##  2 - 3    -3.833333 8.78136 55  -0.437  0.9979
```

```
##  2 - 4     3.916667 8.78136 55   0.446  0.9977
##  2 - 5    -3.583333 8.78136 55  -0.408  0.9985
##  2 - 6     1.666667 8.78136 55   0.190  1.0000
##  3 - 4     7.750000 8.78136 55   0.883  0.9491
##  3 - 5     0.250000 8.78136 55   0.028  1.0000
##  3 - 6     5.500000 8.78136 55   0.626  0.9886
##  4 - 5    -7.500000 8.78136 55  -0.854  0.9556
##  4 - 6    -2.250000 8.78136 55  -0.256  0.9998
##  5 - 6     5.250000 8.78136 55   0.598  0.9908
##
## P value adjustment: tukey method for comparing a family of 6 estimates
```

```
getVarCov(Model1, individual = 1, type = "marginal")
```

```
## subject 1
## Marginal variance covariance matrix
##        1      2      3      4      5      6
## 1 2575.6 2112.9 2112.9 2112.9 2112.9 2112.9
## 2 2112.9 2575.6 2112.9 2112.9 2112.9 2112.9
## 3 2112.9 2112.9 2575.6 2112.9 2112.9 2112.9
## 4 2112.9 2112.9 2112.9 2575.6 2112.9 2112.9
## 5 2112.9 2112.9 2112.9 2112.9 2575.6 2112.9
## 6 2112.9 2112.9 2112.9 2112.9 2112.9 2575.6
##   Standard Deviations: 50.75 50.75 50.75 50.75 50.75 50.75
```

```
plot(Model1)
```



Model2: corCompSymm (Same as Model1 above!)

For Illustration: We now omit the random subject effect (and use the gls() function) and specify correlation = corCompSymm. This gives exactly the same results as Model1 above.

```
Model2 <- gls(cholest ~ period, correlation = corCompSymm(form = ~1|subject), data = CholData)
summary(Model2)
```

```
## Generalized least squares fit by REML
##   Model: cholest ~ period
##   Data: CholData
##        AIC      BIC    logLik
##   660.0632 677.5805 -322.0316
##
## Correlation Structure: Compound symmetry
##  Formula: ~1 | subject
##  Parameter estimate(s):
##       Rho
## 0.8203617
##
## Coefficients:
##                 Value Std.Error   t-value p-value
## (Intercept) 279.75000  14.65033 19.095134  0.0000
## period2      -7.83333   8.78136 -0.892041  0.3756
## period3      -4.00000   8.78136 -0.455510  0.6502
## period4     -11.75000   8.78136 -1.338061  0.1855
## period5      -4.25000   8.78136 -0.483980  0.6300
## period6      -9.50000   8.78136 -1.081837  0.2833
##
##  Correlation:
##         (Intr) perid2 perid3 perid4 perid5
## period2 -0.3
## period3 -0.3    0.5
## period4 -0.3    0.5    0.5
## period5 -0.3    0.5    0.5    0.5
## period6 -0.3    0.5    0.5    0.5    0.5
##
## Standardized residuals:
##        Min         Q1        Med         Q3        Max
## -2.6206779 -0.5406380 -0.1009848  0.6490119  2.4252765
##
## Residual standard error: 50.75023
## Degrees of freedom: 72 total; 66 residual
```

```
anova(Model2)
```

```
## Denom. DF: 66
##             numDF  F-value p-value
## (Intercept)     1 409.9541  <.0001
## period          5   0.4743  0.7941
```

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

```
## Marginal variance covariance matrix
##        [,1]   [,2]   [,3]   [,4]   [,5]   [,6]
## [1,] 2575.6 2112.9 2112.9 2112.9 2112.9 2112.9
```

```
## [2,] 2112.9 2575.6 2112.9 2112.9 2112.9 2112.9
## [3,] 2112.9 2112.9 2575.6 2112.9 2112.9 2112.9
## [4,] 2112.9 2112.9 2112.9 2575.6 2112.9 2112.9
## [5,] 2112.9 2112.9 2112.9 2112.9 2575.6 2112.9
## [6,] 2112.9 2112.9 2112.9 2112.9 2112.9 2575.6
##   Standard Deviations: 50.75 50.75 50.75 50.75 50.75 50.75
```

Model3: corSymm (Unstructured)

Note: Variance is still the same for each period. This can be adjusted, using varIdent (not shown).

```
Model3 <- lme(cholest ~ period, random = ~1|subject, correlation = corSymm(form = ~1|subject), data = Ch
summary(Model3)
```

```
## Linear mixed-effects model fit by REML
##  Data: CholData
##        AIC      BIC    logLik
##   652.5514 702.9134 -303.2757
##
## Random effects:
##  Formula: ~1 | subject
##         (Intercept) Residual
## StdDev:    44.87503 25.20851
##
## Correlation Structure: General
##  Formula: ~1 | subject
##  Parameter estimate(s):
##  Correlation:
##   1      2      3      4      5
## 2  0.111
## 3 -0.504  0.764
## 4 -0.509  0.428  0.743
## 5 -0.689  0.273  0.600  0.460
## 6 -0.540  0.236  0.563  0.305  0.806
## Fixed effects: cholest ~ period
##                 Value Std.Error DF   t-value p-value
## (Intercept) 279.75000 14.858323 55 18.827831  0.0000
## period2      -7.83333  9.701205 55 -0.807460  0.4229
## period3      -4.00000 12.621340 55 -0.316924  0.7525
## period4     -11.75000 12.640315 55 -0.929565  0.3567
## period5      -4.25000 13.376386 55 -0.317724  0.7519
## period6      -9.50000 12.769859 55 -0.743939  0.4601
##  Correlation:
##         (Intr) perid2 perid3 perid4 perid5
## period2 -0.326
## period3 -0.425  0.933
## period4 -0.425  0.788  0.915
## period5 -0.450  0.755  0.876  0.833
## period6 -0.430  0.711  0.857  0.772  0.941
##
## Standardized Within-Group Residuals:
##         Min          Q1         Med          Q3         Max
## -1.67393520 -0.73913364 -0.01433354  0.69363378  2.23690417
```

```
##
## Number of Observations: 72
## Number of Groups: 12
```

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

```
##             numDF denDF  F-value p-value
## (Intercept)     1    55 354.4872  <.0001
## period          5    55   4.3122  0.0022
```

```r
emmeans(Model3, pairwise ~ period)
```

```
## $emmeans
##  period   emmean       SE df lower.CL upper.CL
##  1      279.7500 14.85832 11 247.0471 312.4529
##  2      271.9167 14.85832 11 239.2137 304.6196
##  3      275.7500 14.85832 11 243.0471 308.4529
##  4      268.0000 14.85832 11 235.2971 300.7029
##  5      275.5000 14.85832 11 242.7971 308.2029
##  6      270.2500 14.85832 11 237.5471 302.9529
##
## Confidence level used: 0.95
##
## $contrasts
##  contrast  estimate        SE df t.ratio p.value
##  1 - 2     7.833333  9.701205 55   0.807  0.9650
##  1 - 3     4.000000 12.621340 55   0.317  0.9995
##  1 - 4    11.750000 12.640315 55   0.930  0.9371
##  1 - 5     4.250000 13.376386 55   0.318  0.9995
##  1 - 6     9.500000 12.769859 55   0.744  0.9754
##  2 - 3    -3.833333  5.000941 55  -0.767  0.9720
##  2 - 4     3.916667  7.782027 55   0.503  0.9958
##  2 - 5    -3.583333  8.776738 55  -0.408  0.9985
##  2 - 6     1.666667  8.995554 55   0.185  1.0000
##  3 - 4     7.750000  5.221487 55   1.484  0.6755
##  3 - 5     0.250000  6.511895 55   0.038  1.0000
##  3 - 6     5.500000  6.801056 55   0.809  0.9647
##  4 - 5    -7.500000  7.560148 55  -0.992  0.9186
##  4 - 6    -2.250000  8.580289 55  -0.262  0.9998
##  5 - 6     5.250000  4.527355 55   1.160  0.8537
##
## P value adjustment: tukey method for comparing a family of 6 estimates
```

```r
getVarCov(Model3, individual = 1, type = "marginal")
```

```
## subject 1
## Marginal variance covariance matrix
##        1      2      3      4      5      6
## 1 2649.2 2084.6 1693.4 1690.6 1575.7 1670.8
## 2 2084.6 2649.2 2499.2 2285.9 2187.1 2163.7
## 3 1693.4 2499.2 2649.2 2485.7 2394.8 2371.7
## 4 1690.6 2285.9 2485.7 2649.2 2306.3 2207.5
## 5 1575.7 2187.1 2394.8 2306.3 2649.2 2526.3
## 6 1670.8 2163.7 2371.7 2207.5 2526.3 2649.2
##   Standard Deviations: 51.471 51.471 51.471 51.471 51.471 51.471
```

Model4: corAR1

```r
Model4 <- lme(cholest ~ period, random = ~1|subject, correlation = corAR1(form = ~1|subject), data = Ch
summary(Model4)
```

```
## Linear mixed-effects model fit by REML
##  Data: CholData
##        AIC      BIC    logLik
##   644.5804 664.2873 -313.2902
##
## Random effects:
##  Formula: ~1 | subject
##         (Intercept) Residual
## StdDev:    35.40944 35.52677
##
## Correlation Structure: AR(1)
##  Formula: ~1 | subject
##  Parameter estimate(s):
##       Phi
## 0.8038124
## Fixed effects: cholest ~ period
##                 Value Std.Error DF   t-value p-value
## (Intercept) 279.75000 14.479814 55 19.320000  0.0000
## period2      -7.83333  6.424153 55 -1.219357  0.2279
## period3      -4.00000  8.628029 55 -0.463605  0.6448
## period4     -11.75000 10.055240 55 -1.168545  0.2476
## period5      -4.25000 11.069846 55 -0.383926  0.7025
## period6      -9.50000 11.822442 55 -0.803557  0.4251
##  Correlation:
##         (Intr) perid2 perid3 perid4 perid5
## period2 -0.222
## period3 -0.298  0.672
## period4 -0.347  0.526  0.774
## period5 -0.382  0.441  0.642  0.819
## period6 -0.408  0.385  0.554  0.700  0.844
##
## Standardized Within-Group Residuals:
##        Min         Q1        Med         Q3        Max
## -2.3145023 -0.4535497 -0.1251464  0.4633387  2.0667460
##
## Number of Observations: 72
## Number of Groups: 12
```

```r
anova.lme(Model4, type = "marginal")
```

```
##             numDF denDF  F-value p-value
## (Intercept)     1    55 373.2624  <.0001
## period          5    55   1.0086  0.4215
```

```r
emmeans(Model4, pairwise ~ period)
```

```
## $emmeans
##  period   emmean       SE df lower.CL upper.CL
##  1      279.7500 14.47981 11 247.8801 311.6199
##  2      271.9167 14.47981 11 240.0468 303.7865
```

```
##  3      275.7500 14.47981 11 243.8801 307.6199
##  4      268.0000 14.47981 11 236.1301 299.8699
##  5      275.5000 14.47981 11 243.6301 307.3699
##  6      270.2500 14.47981 11 238.3801 302.1199
##
## Confidence level used: 0.95
##
## $contrasts
##  contrast  estimate        SE df t.ratio p.value
##  1 - 2     7.833333  6.424153 55   1.219  0.8256
##  1 - 3     4.000000  8.628029 55   0.464  0.9972
##  1 - 4    11.750000 10.055240 55   1.169  0.8497
##  1 - 5     4.250000 11.069846 55   0.384  0.9989
##  1 - 6     9.500000 11.822442 55   0.804  0.9657
##  2 - 3    -3.833333  6.424153 55  -0.597  0.9908
##  2 - 4     3.916667  8.628029 55   0.454  0.9975
##  2 - 5    -3.583333 10.055240 55  -0.356  0.9992
##  2 - 6     1.666667 11.069846 55   0.151  1.0000
##  3 - 4     7.750000  6.424153 55   1.206  0.8319
##  3 - 5     0.250000  8.628029 55   0.029  1.0000
##  3 - 6     5.500000 10.055240 55   0.547  0.9939
##  4 - 5    -7.500000  6.424153 55  -1.167  0.8502
##  4 - 6    -2.250000  8.628029 55  -0.261  0.9998
##  5 - 6     5.250000  6.424153 55   0.817  0.9631
##
## P value adjustment: tukey method for comparing a family of 6 estimates
```

```r
getVarCov(Model4, individual = 1, type = "marginal")
```

```
## subject 1
## Marginal variance covariance matrix
##        1      2      3      4      5      6
## 1 2516.0 2268.4 2069.3 1909.3 1780.7 1677.4
## 2 2268.4 2516.0 2268.4 2069.3 1909.3 1780.7
## 3 2069.3 2268.4 2516.0 2268.4 2069.3 1909.3
## 4 1909.3 2069.3 2268.4 2516.0 2268.4 2069.3
## 5 1780.7 1909.3 2069.3 2268.4 2516.0 2268.4
## 6 1677.4 1780.7 1909.3 2069.3 2268.4 2516.0
##   Standard Deviations: 50.16 50.16 50.16 50.16 50.16 50.16
```

Compare Models using AIC

```r
AIC(Model1, Model2, Model3, Model4)
```

```
##        df      AIC
## Model1  8 660.0632
## Model2  8 660.0632
## Model3 23 652.5514
## Model4  9 644.5804
```