Repeated Mixed Model

```
#rm(list = ls()) # Clean the workspace
#install.packages("nlme")  # If necesary install the library
library(lsmeans)           # Call the library to the workspace
library(nlme)              # Call the library to the workspace

# Read the data
myfile<-"C:/Users/toledo/Dropbox/UNIPD/Biostatistics Curse  R Spring 2018/curso STAT phD 2018 Mixed Models/dat
mydata<-read.table(file=myfile,stringsAsFactors = TRUE,header = TRUE,sep = "\t")
options(contrasts = c("contr.SAS","contr.poly")) # Change contrast options
mydata$animal<-as.factor(mydata$animal)   # Set as factor
mydata$age<-as.factor(mydata$age)         # Set as factor

# Different covariance Structures
# Model Unstructured
model.un<-gls(bw ~  group + age + group*age, data = mydata,     # Model
              correlation = corSymm(form = ~ 1|group/animal),  # General correlation matrix, unstructure.
              weights = varIdent(form = ~ 1|age))              # Constant variance(s), used to allow different
                                                               # variances according to the levels of a classi

model.un               # Model fitted
```

```
## Generalized least squares fit by REML
##   Model: bw ~ group + age + group * age
##   Data: mydata
##   Log-restricted-likelihood: -670.3923
##
## Coefficients:
##  (Intercept)       groupA       groupB       groupC         age1
##  295.6666667  -18.6666667  -40.1666667   40.6190476 -219.3333333
##         age2         age3         age4         age5         age6
## -188.1666667 -169.3333333 -142.1666667 -105.3333333  -74.3333333
##         age7  groupA:age1  groupB:age1  groupC:age1  groupA:age2
##  -45.0000000   10.9047619   16.0833333  -60.2380952   -0.9761905
##  groupB:age2  groupC:age2  groupA:age3  groupB:age3  groupC:age3
##    4.7916667  -48.6904762    8.3333333    9.2083333  -29.3809524
##  groupA:age4  groupB:age4  groupC:age4  groupA:age5  groupB:age5
##   13.1666667   17.2916667  -22.9761905    0.6190476   12.7083333
##  groupC:age5  groupA:age6  groupB:age6  groupC:age6  groupA:age7
##  -10.5238095    4.3333333   17.9583333    9.3333333   -3.1428571
##  groupB:age7  groupC:age7
##   21.5000000   15.8571429
##
## Correlation Structure: General
##  Formula: ~1 | group/animal
##  Parameter estimate(s):
##  Correlation:
##   1     2     3     4     5     6     7
## 2 0.497
## 3 0.244 0.755
## 4 0.254 0.425 0.709
## 5 0.197 0.389 0.744 0.944
## 6 0.045 0.239 0.669 0.895 0.963
## 7 0.075 0.271 0.678 0.892 0.962 0.989
## 8 0.069 0.197 0.632 0.858 0.919 0.964 0.977
## Variance function:
##  Structure: Different standard deviations per stratum
```

```
##  Formula: ~1 | age
##  Parameter estimates:
##        1        2        3        4        5        6        7        8
## 1.000000 1.546902 1.730297 2.234001 2.801870 2.891596 3.275352 3.353758
## Degrees of freedom: 224 total; 192 residual
## Residual standard error: 7.916225
```

```
anova(model.un)        # ANOVA
```

```
## Denom. DF: 192
##             numDF  F-value p-value
## (Intercept)     1 5283.275  <.0001
## group           3   21.487  <.0001
## age             7  549.657  <.0001
## group:age      21   14.102  <.0001
```

```
lsmeans(model.un,"group") # LSM
```

```
##  group   lsmean       SE  df lower.CL upper.CL
##  A     163.1964 6.097614 192 151.1695 175.2233
##  B     149.9844 5.703796 192 138.7342 161.2345
##  C     200.0000 6.097614 192 187.9731 212.0269
##  D     177.7083 6.586176 192 164.7178 190.6989
##
## Results are averaged over the levels of: age
## Confidence level used: 0.95
```

```
cors<-corMatrix(model.un$modelStruct$corStruct)[[1]]  # Extract the Correlation Matrix
cors                                                  # See the Correlation Matrix
```

```
##            [,1]      [,2]      [,3]      [,4]      [,5]      [,6]
## [1,] 1.00000000 0.4969533 0.2435151 0.2544810 0.1972696 0.0447571
## [2,] 0.49695332 1.0000000 0.7546379 0.4254784 0.3885893 0.2393159
## [3,] 0.24351505 0.7546379 1.0000000 0.7092706 0.7444147 0.6688010
## [4,] 0.25448097 0.4254784 0.7092706 1.0000000 0.9439046 0.8945347
## [5,] 0.19726957 0.3885893 0.7444147 0.9439046 1.0000000 0.9633293
## [6,] 0.04475710 0.2393159 0.6688010 0.8945347 0.9633293 1.0000000
## [7,] 0.07521570 0.2714338 0.6776423 0.8916583 0.9615218 0.9892438
## [8,] 0.06923708 0.1973180 0.6324602 0.8580654 0.9187914 0.9642120
##           [,7]       [,8]
## [1,] 0.0752157 0.06923708
## [2,] 0.2714338 0.19731798
## [3,] 0.6776423 0.63246018
## [4,] 0.8916583 0.85806538
## [5,] 0.9615218 0.91879140
## [6,] 0.9892438 0.96421204
## [7,] 1.0000000 0.97650071
## [8,] 0.9765007 1.00000000
```

```
stdev.st<-c(1.000000, 1.546902, 1.730297, 2.234001,
            2.801870, 2.891596, 3.275352, 3.353758)   # Get the stratum SD
vars<-stdev.st*model.un$sigma^2                       # Multiply the stratum SD by the Error Variance
covs<-outer(vars,vars,function(x,y)sqrt(x)*sqrt(y))   # Get the Variance & Covariance Matrix
round(cors*covs,3)                                    # Get the R matrix: Covariance estimate for subjects
```

```
##        [,1]   [,2]    [,3]    [,4]    [,5]    [,6]    [,7]    [,8]
## [1,] 62.667 38.733  20.073  23.836  20.693   4.769   8.530   7.946
## [2,] 38.733 96.939  77.369  49.566  50.697  31.718  38.288  28.164
## [3,] 20.073 77.369 108.432  87.388 102.715  93.748 101.094  95.476
## [4,] 23.836 49.566  87.388 139.997 147.989 142.477 151.149 147.185
## [5,] 20.693 50.697 102.715 147.989 175.584 171.832 182.536 176.499
## [6,]  4.769 31.718  93.748 142.477 171.832 181.207 190.782 188.167
## [7,]  8.530 38.288 101.094 151.149 182.536 190.782 205.255 202.817
```

```
## [8,]  7.946 28.164  95.476 147.185 176.499 188.167 202.817 210.169
```

```
# Model Compound Symmetry Correlation Structure
model.cs<-gls(bw ~  group + age + group*age, data = mydata,    # Model
              correlation = corCompSymm(form = ~ 1|group/animal)) # Compound Symmetry Correlation Structure
model.cs              # Model fitted
```

```
## Generalized least squares fit by REML
##   Model: bw ~ group + age + group * age
##   Data: mydata
##   Log-restricted-likelihood: -813.9656
##
## Coefficients:
##  (Intercept)       groupA       groupB       groupC         age1
##  295.6666667  -18.6666667  -40.1666667   40.6190476 -219.3333333
##         age2         age3         age4         age5         age6
## -188.1666667 -169.3333333 -142.1666667 -105.3333333  -74.3333333
##         age7  groupA:age1  groupB:age1  groupC:age1  groupA:age2
##  -45.0000000   10.9047619   16.0833333  -60.2380952   -0.9761905
##  groupB:age2  groupC:age2  groupA:age3  groupB:age3  groupC:age3
##    4.7916667  -48.6904762    8.3333333    9.2083333  -29.3809524
##  groupA:age4  groupB:age4  groupC:age4  groupA:age5  groupB:age5
##   13.1666667   17.2916667  -22.9761905    0.6190476   12.7083333
##  groupC:age5  groupA:age6  groupB:age6  groupC:age6  groupA:age7
##  -10.5238095    4.3333333   17.9583333    9.3333333   -3.1428571
##  groupB:age7  groupC:age7
##   21.5000000   15.8571429
##
## Correlation Structure: Compound symmetry
##  Formula: ~1 | group/animal
##  Parameter estimate(s):
##       Rho
## 0.6232494
## Degrees of freedom: 224 total; 192 residual
## Residual standard error: 19.70444
```

```
anova(model.cs)       # ANOVA
```

```
## Denom. DF: 192
##             numDF  F-value p-value
## (Intercept)     1 3172.750  <.0001
## group           3   12.937  <.0001
## age             7 1243.995  <.0001
## group:age      21   10.043  <.0001
```

```
lsmeans(model.cs,"group") # LSM
```

```
##  group   lsmean       SE  df lower.CL upper.CL
##  A     163.1964 6.097667 192 151.1694 175.2234
##  B     149.9844 5.703845 192 138.7341 161.2346
##  C     200.0000 6.097667 192 187.9730 212.0270
##  D     177.7083 6.586233 192 164.7177 190.6990
##
## Results are averaged over the levels of: age
## Confidence level used: 0.95
```

```
cors<-corMatrix(model.cs$modelStruct$corStruct)[[1]]  # Extract the Correlation Matrix
cors                                                  # See the Correlation Matrix
```

```
##           [,1]      [,2]      [,3]      [,4]      [,5]      [,6]      [,7]
## [1,] 1.0000000 0.6232494 0.6232494 0.6232494 0.6232494 0.6232494 0.6232494
## [2,] 0.6232494 1.0000000 0.6232494 0.6232494 0.6232494 0.6232494 0.6232494
## [3,] 0.6232494 0.6232494 1.0000000 0.6232494 0.6232494 0.6232494 0.6232494
```

```
## [4,] 0.6232494 0.6232494 0.6232494 1.0000000 0.6232494 0.6232494 0.6232494
## [5,] 0.6232494 0.6232494 0.6232494 0.6232494 1.0000000 0.6232494 0.6232494
## [6,] 0.6232494 0.6232494 0.6232494 0.6232494 0.6232494 1.0000000 0.6232494
## [7,] 0.6232494 0.6232494 0.6232494 0.6232494 0.6232494 0.6232494 1.0000000
## [8,] 0.6232494 0.6232494 0.6232494 0.6232494 0.6232494 0.6232494 0.6232494
##           [,8]
## [1,] 0.6232494
## [2,] 0.6232494
## [3,] 0.6232494
## [4,] 0.6232494
## [5,] 0.6232494
## [6,] 0.6232494
## [7,] 0.6232494
## [8,] 1.0000000
```

```
err.var<-model.cs$sigma^2                          # Err.Variance
round(cors*err.var,3)                              # Get the R matrix: Covariance estimate for subjects
```

```
##         [,1]    [,2]    [,3]    [,4]    [,5]    [,6]    [,7]    [,8]
## [1,] 388.265 241.986 241.986 241.986 241.986 241.986 241.986 241.986
## [2,] 241.986 388.265 241.986 241.986 241.986 241.986 241.986 241.986
## [3,] 241.986 241.986 388.265 241.986 241.986 241.986 241.986 241.986
## [4,] 241.986 241.986 241.986 388.265 241.986 241.986 241.986 241.986
## [5,] 241.986 241.986 241.986 241.986 388.265 241.986 241.986 241.986
## [6,] 241.986 241.986 241.986 241.986 241.986 388.265 241.986 241.986
## [7,] 241.986 241.986 241.986 241.986 241.986 241.986 388.265 241.986
## [8,] 241.986 241.986 241.986 241.986 241.986 241.986 241.986 388.265
```

```
# A model with No Correlation looks like:
diag(1,8,8)*err.var
```

```
##         [,1]    [,2]    [,3]    [,4]    [,5]    [,6]    [,7]    [,8]
## [1,] 388.265   0.000   0.000   0.000   0.000   0.000   0.000   0.000
## [2,]   0.000 388.265   0.000   0.000   0.000   0.000   0.000   0.000
## [3,]   0.000   0.000 388.265   0.000   0.000   0.000   0.000   0.000
## [4,]   0.000   0.000   0.000 388.265   0.000   0.000   0.000   0.000
## [5,]   0.000   0.000   0.000   0.000 388.265   0.000   0.000   0.000
## [6,]   0.000   0.000   0.000   0.000   0.000 388.265   0.000   0.000
## [7,]   0.000   0.000   0.000   0.000   0.000   0.000 388.265   0.000
## [8,]   0.000   0.000   0.000   0.000   0.000   0.000   0.000 388.265
```

```
# Fit the same model with different types of variance and covariance

model.a<-lme(bw ~  group + age + group*age, data = mydata, # Model
             random = ~ 1|group/animal,                    # Random Effect
             weights = varIdent(form = ~ 1|age),           # Constant variance(s)
             correlation = NULL)                           # No correlation
model.a
```

```
## Linear mixed-effects model fit by REML
##   Data: mydata
##   Log-restricted-likelihood: -782.889
##   Fixed: bw ~ group + age + group * age
##  (Intercept)       groupA       groupB       groupC         age1
##  295.6666667  -18.6666667  -40.1666667   40.6190476 -219.3333333
##         age2         age3         age4         age5         age6
## -188.1666667 -169.3333333 -142.1666667 -105.3333333  -74.3333333
##         age7  groupA:age1  groupB:age1  groupC:age1  groupA:age2
##  -45.0000000   10.9047619   16.0833333  -60.2380952   -0.9761905
##  groupB:age2  groupC:age2  groupA:age3  groupB:age3  groupC:age3
##    4.7916667  -48.6904762    8.3333333    9.2083333  -29.3809524
##  groupA:age4  groupB:age4  groupC:age4  groupA:age5  groupB:age5
```

```
##   13.1666667   17.2916667  -22.9761905    0.6190476   12.7083333
##  groupC:age5  groupA:age6  groupB:age6  groupC:age6  groupA:age7
##  -10.5238095    4.3333333   17.9583333    9.3333333   -3.1428571
##  groupB:age7  groupC:age7
##   21.5000000   15.8571429
##
## Random effects:
##  Formula: ~1 | group
##         (Intercept)
## StdDev:    8.299868
##
##  Formula: ~1 | animal %in% group
##         (Intercept) Residual
## StdDev:     22.5659 23.29137
##
## Variance function:
##  Structure: Different standard deviations per stratum
##  Formula: ~1 | age
##  Parameter estimates:
##         1         2         3         4         5         6         7
## 1.0000000 0.9663973 0.7065238 0.4234375 0.2305685 0.1048387 0.2020408
##         8
## 0.3211019
## Number of Observations: 224
## Number of Groups:
##             group animal %in% group
##                 4                28
```

```
#Doesn't converge ?
#model.b<-lme(bw ~  group + age + group*age, data = mydata, # Model
#             random = ~ 1|group/animal,                    # Random Effect
#             weights = varIdent(form = ~ 1|age),           # Constant variance(s)
#             correlation = corSymm())                      # Compound Symmetry Correlation Structure

model.c<-lme(bw ~  group + age + group*age, data = mydata, # Model
             random = ~ 1|group/animal,                    # Random Effect
             weights = varIdent(form = ~ 1|age),           # Constant variance(s)
             correlation = corAR1())                       # autocorrelation structure of order 1
model.c
```

```
## Linear mixed-effects model fit by REML
##   Data: mydata
##   Log-restricted-likelihood: -725.3449
##   Fixed: bw ~ group + age + group * age
##  (Intercept)       groupA       groupB       groupC         age1
##  295.6666667  -18.6666667  -40.1666667   40.6190476 -219.3333333
##         age2         age3         age4         age5         age6
## -188.1666667 -169.3333333 -142.1666667 -105.3333333  -74.3333333
##         age7  groupA:age1  groupB:age1  groupC:age1  groupA:age2
##  -45.0000000   10.9047619   16.0833333  -60.2380952   -0.9761905
##  groupB:age2  groupC:age2  groupA:age3  groupB:age3  groupC:age3
##    4.7916667  -48.6904762    8.3333333    9.2083333  -29.3809524
##  groupA:age4  groupB:age4  groupC:age4  groupA:age5  groupB:age5
##   13.1666667   17.2916667  -22.9761905    0.6190476   12.7083333
##  groupC:age5  groupA:age6  groupB:age6  groupC:age6  groupA:age7
##  -10.5238095    4.3333333   17.9583333    9.3333333   -3.1428571
##  groupB:age7  groupC:age7
##   21.5000000   15.8571429
##
## Random effects:
##  Formula: ~1 | group
```

```
##         (Intercept)
## StdDev:    7.962176
##
##  Formula: ~1 | animal %in% group
##         (Intercept) Residual
## StdDev:    22.58813 22.34425
##
## Correlation Structure: AR(1)
##  Formula: ~1 | group/animal
##  Parameter estimate(s):
##       Phi
## 0.8568647
## Variance function:
##  Structure: Different standard deviations per stratum
##  Formula: ~1 | age
##  Parameter estimates:
##         1         2         3         4         5         6         7
## 1.0000000 1.0049240 0.8437745 0.6594190 0.5226454 0.3214862 0.4282820
##         8
## 0.4803856
## Number of Observations: 224
## Number of Groups:
##             group animal %in% group
##                 4                28
```

```
model.d<-lme(bw ~  group + age + group*age, data = mydata, #  Model
             random = ~ 1|group/animal,                    # Random Effect
             correlation = corCompSymm())                  # Compound Symmetry Correlation Structure
model.d
```

```
## Linear mixed-effects model fit by REML
##   Data: mydata
##   Log-restricted-likelihood: -813.9656
##   Fixed: bw ~ group + age + group * age
##  (Intercept)       groupA       groupB       groupC         age1
##  295.6666667  -18.6666667  -40.1666667   40.6190476 -219.3333333
##         age2         age3         age4         age5         age6
## -188.1666667 -169.3333333 -142.1666667 -105.3333333  -74.3333333
##         age7  groupA:age1  groupB:age1  groupC:age1  groupA:age2
##  -45.0000000   10.9047619   16.0833333  -60.2380952   -0.9761905
##  groupB:age2  groupC:age2  groupA:age3  groupB:age3  groupC:age3
##    4.7916667  -48.6904762    8.3333333    9.2083333  -29.3809524
##  groupA:age4  groupB:age4  groupC:age4  groupA:age5  groupB:age5
##   13.1666667   17.2916667  -22.9761905    0.6190476   12.7083333
##  groupC:age5  groupA:age6  groupB:age6  groupC:age6  groupA:age7
##  -10.5238095    4.3333333   17.9583333    9.3333333   -3.1428571
##  groupB:age7  groupC:age7
##   21.5000000   15.8571429
##
## Random effects:
##  Formula: ~1 | group
##         (Intercept)
## StdDev:    4.309886
##
##  Formula: ~1 | animal %in% group
##         (Intercept) Residual
## StdDev:     15.5559 12.09459
##
## Correlation Structure: Compound symmetry
##  Formula: ~1 | group/animal
##  Parameter estimate(s):
```

```
## Rho
##   0
## Number of Observations: 224
## Number of Groups:
##              group animal %in% group
##                  4                28
```

```
anova(model.a,model.c,model.d)                              # Model Comparisson
```

```
##         Model df      AIC      BIC    logLik   Test  L.Ratio p-value
## model.a     1 42 1649.778 1786.593 -782.8890
## model.c     2 43 1536.690 1676.762 -725.3449 1 vs 2 115.0882  <.0001
## model.d     3 36 1699.931 1817.201 -813.9656 2 vs 3 177.2414  <.0001
```