BIOS6643. L10 Model Building

Exercise involving G and R matrices

Consider a basic science experiment conducted where cell counts are measured at 4 time points for samples taken from individual subjects or animals. A linear mixed model will be fit for the data (perhaps after log transformation), and fixed effects will be included for time, and treatment group as well as their interaction. (To answer this question we do not need to know the specific form of $X\beta$.)

Determine the structure for V_i if a random intercept for subjects will be included, plus an AR(1) structure for the error covariance matrix (R_i). What does the combination of non-simple R and G allow you to do in modeling covariance that using only one cannot do? Discuss in a few sentences.

FEV Study

Description

The data set gives characteristics of children patients with a diagnosis of Cystic Fibrosis (CF) who are patients at the Colorado Children's Hospital. Data pull was conducted in Summer 2020. This dataset may only be used for BIOS6643.

VARIABLE DESCRIPTIONS:
id: patient ID
race: race
Genotypes1: mutation of copy one of the gene that codes for the CFTR protein Genotypes2: mutation of copy two of the gene that codes for the CFTR protein. age: Age in years
gender : gender fev: % of predicted forced expiratory volume in 1 second

- **Objectives** of the study included:
    - Determine if fev values over time are larger on average for males than for females
    - Determine if the rate of change of fev over time is different for males and females.

Selecting the mean structure

```
#  Read in the data

##  Read in the data
dat <- read.csv("/Users/juarezce/Documents/OneDrive - The University of Colorado Denver/BIOS6643/BIOS664
                header=TRUE)
length(unique(dat$id)) ## number of individuals
```

```
## [1] 723
```

```
head(dat,3)
```

```
##   id      Race Genotypes1 Genotypes2   age gender      fev
## 1  1 Caucasian       F508      R553X 10.32      m 55.45775
```

```
## 2  1 Caucasian       F508       R553X 10.47       m 53.48924
## 3  1 Caucasian       F508       R553X 10.72       m 49.62416
```

```
summary(dat$age) ## age in years
```

```
##    Min. 1st Qu.  Median    Mean 3rd Qu.    Max.
##    6.01    9.83   13.50   13.73   17.29   25.00
```

```
summary(dat$fev)
```

```
##    Min. 1st Qu.  Median    Mean 3rd Qu.    Max.
##   10.99   66.72   85.53   81.90   99.31  160.10
```
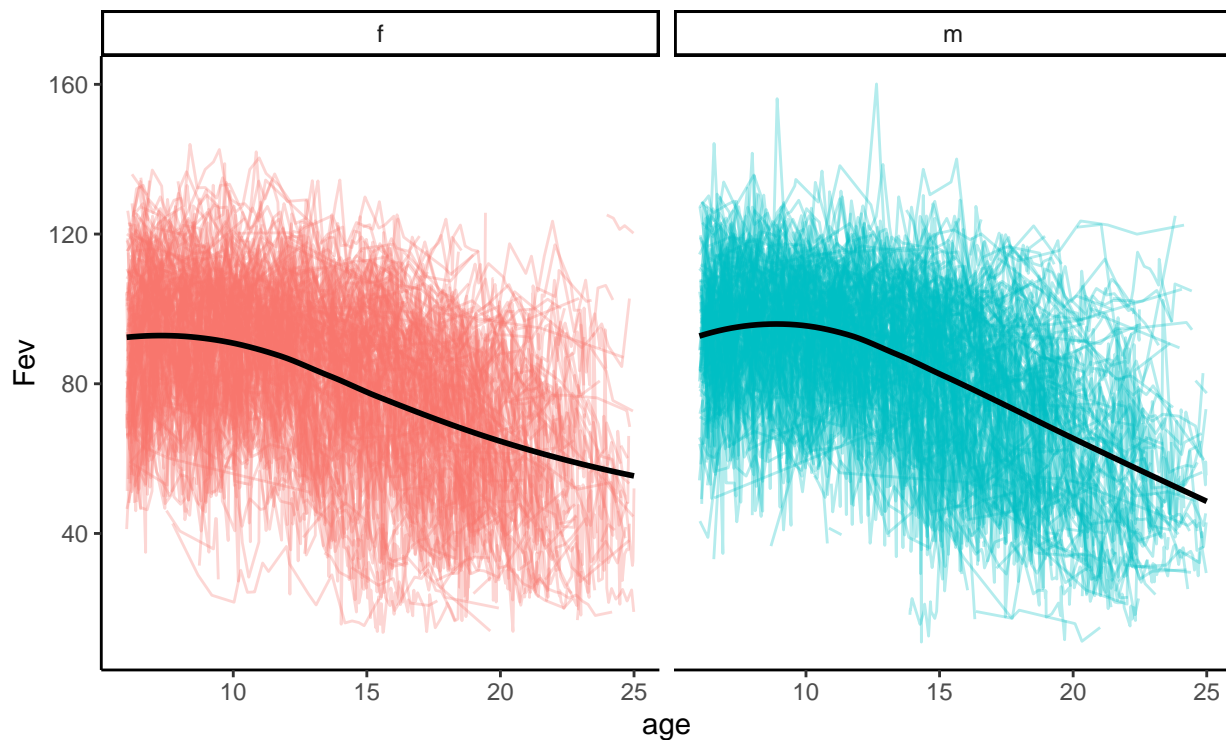
```
######
########################################################################################
### selecting the mean form
## -----------------------------------------------------------------------------------
```

```
ggplot(dat, aes(x = age, y = fev, group = id)) +
    facet_wrap(~gender) +
    geom_line(aes(color = gender), alpha = 0.3) +
    geom_smooth(aes(group = 1), method="loess", color="black", se=FALSE) +
    theme_classic() +
    theme(legend.position = "top") +
    ylab("Fev")
```

```
## `geom_smooth()` using formula 'y ~ x'
```



```
## age as linear
fit.lme.0 <- lme(fev ~ -1 + gender + age:gender, data=dat,
```

```
                        random = ~ 1 | id,method="ML")
summary(fit.lme.0)
```

```
## Linear mixed-effects model fit by maximum likelihood
##   Data: dat
##        AIC       BIC    logLik
##   145661.2 145708.1 -72824.58
##
## Random effects:
##  Formula: ~1 | id
##         (Intercept) Residual
## StdDev:    17.76981 11.57677
##
## Fixed effects:  fev ~ -1 + gender + age:gender
##                 Value Std.Error    DF   t-value p-value
## genderf      106.70242 1.0952620   721  97.42182       0
## genderm      107.72595 1.0864343   721  99.15550       0
## genderf:age   -1.76779 0.0370579 17770 -47.70342       0
## genderm:age   -1.79357 0.0409169 17770 -43.83454       0
##  Correlation:
##             gendrf gendrm gndrf:
## genderm      0.000
## genderf:age -0.439  0.000
## genderm:age  0.000 -0.499  0.000
##
## Standardized Within-Group Residuals:
##         Min          Q1         Med          Q3         Max
## -7.07828572 -0.53190983  0.05024462  0.60213684  5.64679392
##
## Number of Observations: 18494
## Number of Groups: 723
```

```
## adding quadratic terms of age
fit.lme.1 <- lme(fev ~ -1 + gender  + age:gender + I(age*age):gender,
               data=dat,
                  random = ~ 1 | id,method="ML")
summary(fit.lme.1)
```

```
## Linear mixed-effects model fit by maximum likelihood
##   Data: dat
##        AIC       BIC    logLik
##   145213.8 145276.4 -72598.92
##
## Random effects:
##  Formula: ~1 | id
##         (Intercept) Residual
## StdDev:    17.67878 11.43327
##
## Fixed effects:  fev ~ -1 + gender + age:gender + I(age * age):gender
##                     Value Std.Error    DF   t-value p-value
## genderf            93.62488 1.5128318   721  61.88717  0.0000
## genderm            87.90149 1.5695259   721  56.00512  0.0000
## genderf:age         0.41730 0.1794696 17768   2.32517  0.0201
## genderm:age         1.49555 0.1934694 17768   7.73017  0.0000
```

```
## genderf:I(age * age) -0.07836 0.0063016 17768 -12.43528  0.0000
## genderm:I(age * age) -0.11718 0.0067410 17768 -17.38287  0.0000
##  Correlation:
##                        gendrf gendrm gndrf: gndrm: gndrf:I(*a)
## genderm                 0.000
## genderf:age            -0.744  0.000
## genderm:age             0.000 -0.782  0.000
## genderf:I(age * age)    0.695  0.000 -0.979  0.000
## genderm:I(age * age)    0.000  0.726  0.000 -0.978  0.000
##
## Standardized Within-Group Residuals:
##          Min          Q1         Med          Q3         Max
## -7.24451152 -0.53995990  0.04787477  0.60276234  5.76966302
##
## Number of Observations: 18494
## Number of Groups: 723
```

adding cubic terms of age

```
fit.lme.2 <- lme(fev ~ -1 + gender  + age:gender + I(age*age):gender +
                 I(age*age*age):gender, data=dat,
                 random = ~ 1 | id,method="ML")
summary(fit.lme.2)
```

```
## Linear mixed-effects model fit by maximum likelihood
##   Data: dat
##        AIC      BIC    logLik
##   144944.3 145022.6 -72462.17
##
## Random effects:
##  Formula: ~1 | id
##         (Intercept) Residual
## StdDev:     17.7227 11.34474
##
## Fixed effects:  fev ~ -1 + gender + age:gender + I(age * age):gender + I(age *        age * age):gende:
##                            Value Std.Error    DF   t-value p-value
## genderf                 64.45107  3.298411   721  19.540039       0
## genderm                 46.67971  3.472294   721  13.443478       0
## genderf:age              7.49048  0.733378 17766  10.213667       0
## genderm:age             11.46857  0.774428 17766  14.809086       0
## genderf:I(age * age)    -0.60229  0.053070 17766 -11.348941       0
## genderm:I(age * age)    -0.85428  0.055854 17766 -15.294934       0
## genderf:I(age * age * age)  0.01204  0.001211 17766   9.941387       0
## genderm:I(age * age * age)  0.01687  0.001269 17766  13.292823       0
##  Correlation:
##                            gendrf gendrm gndrf: gndrm: gndrf:I(*a) gndrm:I(*a)
## genderm                     0.000
## genderf:age                -0.945  0.000
## genderm:age                 0.000 -0.952  0.000
## genderf:I(age * age)        0.921  0.000 -0.991  0.000
## genderm:I(age * age)        0.000  0.926  0.000 -0.991  0.000
## genderf:I(age * age * age) -0.889  0.000  0.970  0.000 -0.993       0.000
## genderm:I(age * age * age)  0.000 -0.893  0.000  0.969  0.000      -0.993
##                            gndrf:I(*a*a)
## genderm
## genderf:age
```

```
## genderm:age
## genderf:I(age * age)
## genderm:I(age * age)
## genderf:I(age * age * age)
## genderm:I(age * age * age)  0.000
##
## Standardized Within-Group Residuals:
##        Min          Q1         Med          Q3         Max
## -7.40275579 -0.54663718  0.04382553  0.60320809  5.72214673
##
## Number of Observations: 18494
## Number of Groups: 723
```

```
## updating model - same as above
## fit.lme.2 <- update(fit.lme.1, fev ~ -1 + gender  + age:gender + I(age*age):gender +
##               I(age*age*age):gender)

anova(fit.lme.0, fit.lme.1, fit.lme.2)
```

```
##            Model df      AIC      BIC    logLik   Test  L.Ratio p-value
## fit.lme.0      1  6 145661.2 145708.1 -72824.58
## fit.lme.1      2  8 145213.8 145276.4 -72598.92 1 vs 2 451.3298  <.0001
## fit.lme.2      3 10 144944.4 145022.6 -72462.17 2 vs 3 273.4885  <.0001
```

Preliminary covariance structure G

```
################################################################################
###


################################################################################
### preliminary covariance G
## --------------------------------------------------------------------------------
```

```
fit.lm.0 <- lm(fev ~ -1 + gender  + age:gender + I(age*age):gender +
               I(age*age*age):gender, data=dat)
summary(fit.lm.0)
```

```
##
## Call:
## lm(formula = fev ~ -1 + gender + age:gender + I(age * age):gender +
##     I(age * age * age):gender, data = dat)
##
## Residuals:
##     Min      1Q  Median      3Q     Max
## -74.375 -13.618   1.711  14.295  71.351
##
## Coefficients:
##                          Estimate Std. Error t value Pr(>|t|)
## genderf                 69.493830   5.047281  13.769  < 2e-16 ***
## genderm                 54.768689   5.313181  10.308  < 2e-16 ***
## genderf:age              7.209947   1.166087   6.183 6.42e-10 ***
## genderm:age             10.670168   1.224638   8.713  < 2e-16 ***
## genderf:I(age * age)    -0.644283   0.083694  -7.698 1.45e-14 ***
```

```
## genderm:I(age * age)      -0.815717   0.087642  -9.307  < 2e-16 ***
## genderf:I(age * age * age)  0.013504   0.001889   7.147 9.19e-13 ***
## genderm:I(age * age * age)  0.015347   0.001969   7.795 6.75e-15 ***
## ---
## Signif. codes:  0 '***' 0.001 '**' 0.01 '*' 0.05 '.' 0.1 ' ' 1
##
## Residual standard error: 20.28 on 18486 degrees of freedom
## Multiple R-squared:  0.9434, Adjusted R-squared:  0.9433
## F-statistic: 3.849e+04 on 8 and 18486 DF,  p-value: < 2.2e-16
```

```r
## calculating residuals
dat$resid <- residuals(fit.lm.0)
head(dat)
```

```
##   id      Race Genotypes1 Genotypes2   age gender      fev       resid
## 1  1 Caucasian       F508      R553X 10.32      m 55.45775 -39.419474
## 2  1 Caucasian       F508      R553X 10.47      m 53.48924 -41.190974
## 3  1 Caucasian       F508      R553X 10.72      m 49.62416 -44.694488
## 4  1 Caucasian       F508      R553X 10.97      m 61.13242 -32.784394
## 5  1 Caucasian       F508      R553X 11.12      m 87.86685  -5.790132
## 6  2 Caucasian       F508       F508 14.04      m 52.75725 -33.500000
```

```r
ggplot(dat, aes(x = age, y = resid, group = id)) +
    facet_wrap(~gender) +
    geom_line(aes(color = gender), alpha = 0.3) +
    geom_smooth(aes(group = 1), method="loess", color="black", se=FALSE) +
    theme_classic() +
    theme(legend.position = "top") +
    ylab("residuals")
```
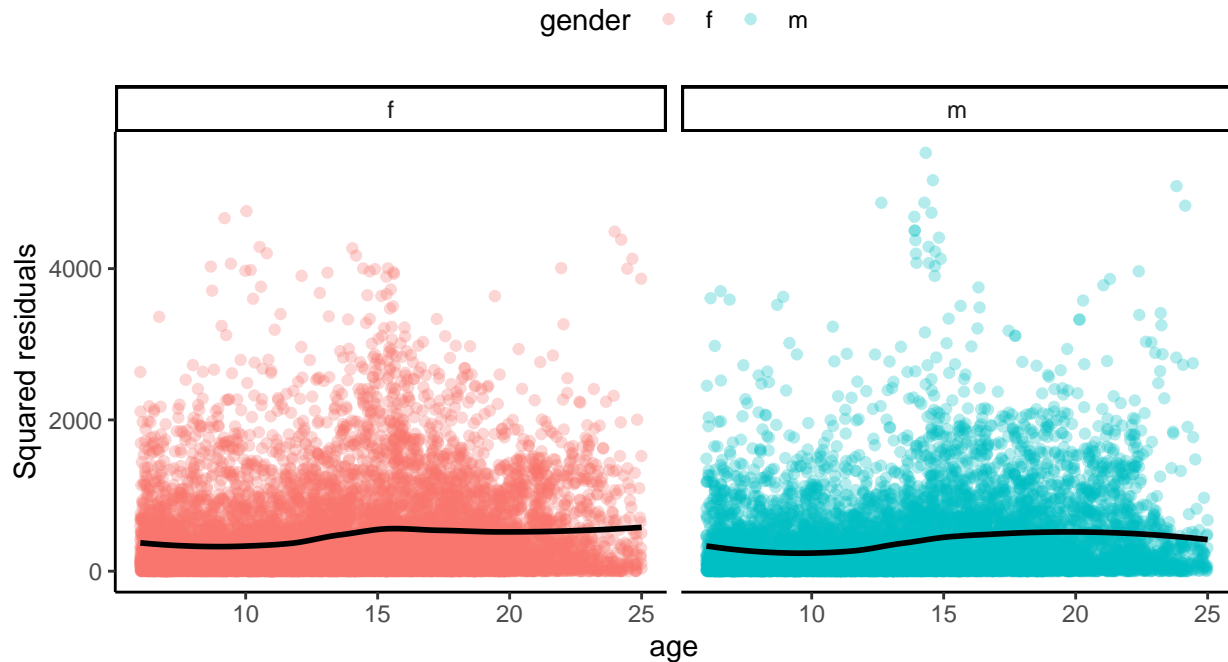
```
## `geom_smooth()` using formula 'y ~ x'
```
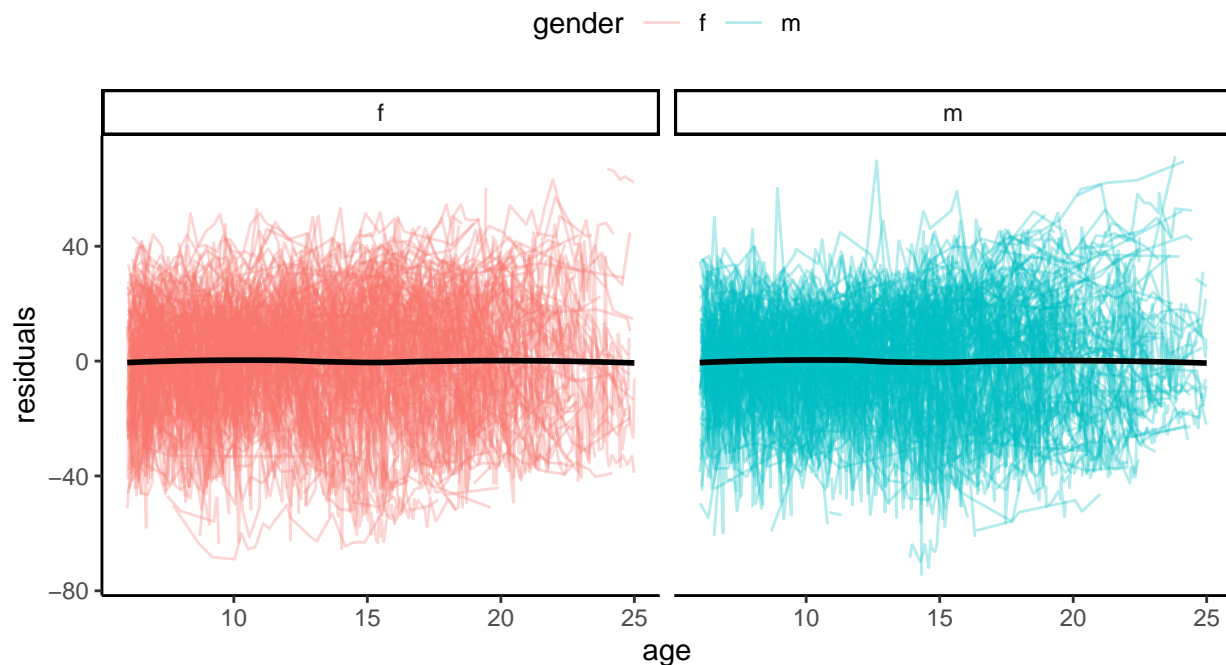


```r
ggplot(dat, aes(x = age, y = resid^2, group = id)) +
    facet_wrap(~gender) +
    geom_point(aes(color = gender), alpha = 0.3) +
```

```
    geom_smooth(aes(group = 1), method="loess", color="black", se=FALSE) +
    theme_classic() +
    theme(legend.position = "top") +
    ylab("Squared residuals")
```

`geom_smooth()` using formula 'y ~ x'


```
## model with quadratic random effects did not converge: adding "+ I(age*age)" to random effects
fit.lme.3 <- lme(fev ~ -1 + gender  + age:gender + I(age*age):gender +
                 I(age*age*age):gender, data=dat,
                 random = ~ age  | id, method="ML")
```

```
summary(fit.lme.2)
```

```
## Linear mixed-effects model fit by maximum likelihood
##   Data: dat
##        AIC      BIC    logLik
##   144944.3 145022.6 -72462.17
##
## Random effects:
##  Formula: ~1 | id
##         (Intercept) Residual
## StdDev:     17.7227 11.34474
##
## Fixed effects:  fev ~ -1 + gender + age:gender + I(age * age):gender + I(age *      age * age):gende
##                           Value Std.Error    DF    t-value p-value
## genderf                64.45107  3.298411   721  19.540039       0
## genderm                46.67971  3.472294   721  13.443478       0
## genderf:age             7.49048  0.733378 17766  10.213667       0
## genderm:age            11.46857  0.774428 17766  14.809086       0
## genderf:I(age * age)   -0.60229  0.053070 17766 -11.348941       0
## genderm:I(age * age)   -0.85428  0.055854 17766 -15.294934       0
## genderf:I(age * age * age)  0.01204  0.001211 17766   9.941387       0
```

```
## genderm:I(age * age * age)  0.01687  0.001269 17766  13.292823        0
##  Correlation:
##                                gendrf gendrm gndrf: gndrm: gndrf:I(*a) gndrm:I(*a)
## genderm                         0.000
## genderf:age                    -0.945  0.000
## genderm:age                     0.000 -0.952  0.000
## genderf:I(age * age)            0.921  0.000 -0.991  0.000
## genderm:I(age * age)            0.000  0.926  0.000 -0.991  0.000
## genderf:I(age * age * age)     -0.889  0.000  0.970  0.000 -0.993       0.000
## genderm:I(age * age * age)      0.000 -0.893  0.000  0.969  0.000      -0.993
##                                gndrf:I(*a*a)
## genderm
## genderf:age
## genderm:age
## genderf:I(age * age)
## genderm:I(age * age)
## genderf:I(age * age * age)
## genderm:I(age * age * age)  0.000
##
## Standardized Within-Group Residuals:
##        Min          Q1         Med          Q3          Max
## -7.40275579 -0.54663718  0.04382553  0.60320809  5.72214673
##
## Number of Observations: 18494
## Number of Groups: 723
```

```
summary(fit.lme.3)
```

```
## Linear mixed-effects model fit by maximum likelihood
##   Data: dat
##        AIC      BIC    logLik
##   141954.7 142048.6 -70965.37
##
## Random effects:
##  Formula: ~age | id
##  Structure: General positive-definite, Log-Cholesky parametrization
##             StdDev    Corr
## (Intercept) 25.051337 (Intr)
## age          1.841479 -0.761
## Residual    10.151809
##
## Fixed effects:  fev ~ -1 + gender + age:gender + I(age * age):gender + I(age *      age * age):gende:
##                              Value Std.Error    DF   t-value p-value
## genderf                   62.69593  3.524726   721  17.787463       0
## genderm                   47.38592  3.838589   721  12.344621       0
## genderf:age                7.67477  0.764109 17766  10.044086       0
## genderm:age               11.24543  0.838210 17766  13.415997       0
## genderf:I(age * age)      -0.60303  0.056200 17766 -10.730110       0
## genderm:I(age * age)      -0.83348  0.060850 17766 -13.697347       0
## genderf:I(age * age * age)  0.01175  0.001306 17766   8.997012       0
## genderm:I(age * age * age)  0.01629  0.001389 17766  11.728614       0
##  Correlation:
##                                gendrf gendrm gndrf: gndrm: gndrf:I(*a) gndrm:I(*a)
## genderm                         0.000
## genderf:age                    -0.924  0.000
```

```
## genderm:age                     0.000 -0.938  0.000
## genderf:I(age * age)            0.842  0.000 -0.975  0.000
## genderm:I(age * age)            0.000  0.867  0.000 -0.979  0.000
## genderf:I(age * age * age) -0.791  0.000  0.941  0.000 -0.989      0.000
## genderm:I(age * age * age)  0.000 -0.816  0.000  0.945  0.000     -0.989
##                                 gndrf:I(*a*a)
## genderm
## genderf:age
## genderm:age
## genderf:I(age * age)
## genderm:I(age * age)
## genderf:I(age * age * age)
## genderm:I(age * age * age)  0.000
##
## Standardized Within-Group Residuals:
##         Min          Q1         Med          Q3         Max
## -8.12207135 -0.51985113  0.04829077  0.58373373  6.63716072
##
## Number of Observations: 18494
## Number of Groups: 723
```

Residual covariance structure R

```
################################################################################
###

## different variance for males and females
fit.lme.4 <- lme(fev ~ -1 + gender  + age:gender + I(age*age):gender +
                 I(age*age*age):gender, data=dat,
                 random = ~ age  | id, method="ML",
                 weights = varIdent(form = ~ 1 | gender))
summary(fit.lme.4)

## Linear mixed-effects model fit by maximum likelihood
##   Data: dat
##      AIC      BIC    logLik
##   141951 142052.8 -70962.51
##
## Random effects:
##  Formula: ~age | id
##  Structure: General positive-definite, Log-Cholesky parametrization
##             StdDev    Corr
## (Intercept) 25.095132 (Intr)
## age          1.844172 -0.762
## Residual    10.288954
##
## Variance function:
##  Structure: Different standard deviations per stratum
##  Formula: ~1 | gender
##  Parameter estimates:
##         m         f
## 1.0000000 0.9745014
## Fixed effects:  fev ~ -1 + gender + age:gender + I(age * age):gender + I(age *      age * age):gender
```

```
##                              Value Std.Error   DF    t-value p-value
## genderf                   62.62862  3.492402  721  17.932821       0
## genderm                   47.39750  3.880219  721  12.215162       0
## genderf:age                7.68376  0.755558 17766  10.169642       0
## genderm:age               11.24846  0.848374 17766  13.258845       0
## genderf:I(age * age)      -0.60343  0.055565 17766 -10.859823       0
## genderm:I(age * age)      -0.83392  0.061592 17766 -13.539287       0
## genderf:I(age * age * age)  0.01175  0.001291 17766   9.101948       0
## genderm:I(age * age * age)  0.01631  0.001406 17766  11.597094       0
##  Correlation:
##                            gendrf gendrm gndrf: gndrm: gndrf:I(*a) gndrm:I(*a)
## genderm                     0.000
## genderf:age                -0.923  0.000
## genderm:age                 0.000 -0.939  0.000
## genderf:I(age * age)        0.840  0.000 -0.975  0.000
## genderm:I(age * age)        0.000  0.868  0.000 -0.979  0.000
## genderf:I(age * age * age) -0.789  0.000  0.941  0.000 -0.989       0.000
## genderm:I(age * age * age)  0.000 -0.817  0.000  0.946  0.000      -0.989
##                            gndrf:I(*a*a)
## genderm
## genderf:age
## genderm:age
## genderf:I(age * age)
## genderm:I(age * age)
## genderf:I(age * age * age)
## genderm:I(age * age * age)  0.000
##
## Standardized Within-Group Residuals:
##         Min          Q1         Med          Q3         Max
## -8.22395661 -0.51843057  0.04862607  0.58339514  6.72281456
##
## Number of Observations: 18494
## Number of Groups: 723
```

```r
R.b.1 <- getVarCov(fit.lme.4,type="conditional",individual=1)   # R_1; first male
R.b.2 <- getVarCov(fit.lme.4,type="conditional",individual=12)  # R_2; first female
R.b.1
```

```
## id 1
## Conditional variance covariance matrix
##        1      2      3      4      5
## 1 105.86   0.00   0.00   0.00   0.00
## 2   0.00 105.86   0.00   0.00   0.00
## 3   0.00   0.00 105.86   0.00   0.00
## 4   0.00   0.00   0.00 105.86   0.00
## 5   0.00   0.00   0.00   0.00 105.86
##   Standard Deviations: 10.289 10.289 10.289 10.289 10.289
```

```r
R.b.1
```

```
## id 1
## Conditional variance covariance matrix
##        1      2      3      4      5
## 1 105.86   0.00   0.00   0.00   0.00
## 2   0.00 105.86   0.00   0.00   0.00
## 3   0.00   0.00 105.86   0.00   0.00
```

```
## 4    0.00    0.00    0.00 105.86    0.00
## 5    0.00    0.00    0.00    0.00 105.86
##    Standard Deviations: 10.289 10.289 10.289 10.289 10.289
```

```
## allowing for AR(1) exp
fit.lme.5 <- lme(fev ~ -1 + gender  + age:gender + I(age*age):gender +
                   I(age*age*age):gender, data=dat,
                   random = ~ age  | id, method="ML",
                 corExp(form = ~ age | id))
summary(fit.lme.5)
```

```
## Linear mixed-effects model fit by maximum likelihood
##   Data: dat
##        AIC     BIC    logLik
##    141218.2 141320 -70596.12
##
## Random effects:
##  Formula: ~age | id
##  Structure: General positive-definite, Log-Cholesky parametrization
##             StdDev    Corr
## (Intercept) 24.46315 (Intr)
## age          1.79206 -0.751
## Residual    10.16447
##
## Correlation Structure: Exponential spatial correlation
##  Formula: ~age | id
##  Parameter estimate(s):
##     range
## 0.016454
## Fixed effects:  fev ~ -1 + gender + age:gender + I(age * age):gender + I(age *      age * age):gende
##                              Value Std.Error    DF    t-value p-value
## genderf                   63.54202  3.607706   721  17.612858       0
## genderm                   47.80098  3.895726   721  12.270107       0
## genderf:age                7.58913  0.791732 17766   9.585486       0
## genderm:age               11.19460  0.857492 17766  13.055060       0
## genderf:I(age * age)      -0.60329  0.058474 17766 -10.317198       0
## genderm:I(age * age)      -0.83170  0.062426 17766 -13.323083       0
## genderf:I(age * age * age)  0.01189  0.001363 17766   8.729453       0
## genderm:I(age * age * age)  0.01629  0.001428 17766  11.408728       0
##  Correlation:
##                            gendrf gendrm gndrf: gndrm: gndrf:I(*a) gndrm:I(*a)
## genderm                     0.000
## genderf:age                -0.929  0.000
## genderm:age                 0.000 -0.941  0.000
## genderf:I(age * age)        0.851  0.000 -0.977  0.000
## genderm:I(age * age)        0.000  0.873  0.000 -0.979  0.000
## genderf:I(age * age * age) -0.801  0.000  0.943  0.000 -0.989        0.000
## genderm:I(age * age * age)  0.000 -0.822  0.000  0.947  0.000       -0.989
##                            gndrf:I(*a*a)
## genderm
## genderf:age
## genderm:age
## genderf:I(age * age)
## genderm:I(age * age)
## genderf:I(age * age * age)
```

```
## genderm:I(age * age * age)   0.000
##
## Standardized Within-Group Residuals:
##        Min          Q1         Med          Q3         Max
## -8.12800702 -0.52080597  0.04882077  0.58381724  6.36308204
##
## Number of Observations: 18494
## Number of Groups: 723
```

```
anova(fit.lme.3, fit.lme.4, fit.lme.5)
```

```
##            Model df     AIC      BIC    logLik   Test  L.Ratio p-value
## fit.lme.3      1 12 141954.7 142048.6 -70965.37
## fit.lme.4      2 13 141951.0 142052.8 -70962.51 1 vs 2 5.715667  0.0168
## fit.lme.5      3 13 141218.2 141320.0 -70596.12
```

Model reduction

```
## do we really random slopes? The variance of the random slopes, is not negligible (~1.8^2), so I would
```

```
## testing if the cubic terms are needed in the mean form
fit.lme.5.1 <- lme(fev ~ -1 + gender  + age:gender + I(age*age):gender,
                data=dat,
                random = ~ age  | id, method="ML",
                corExp(form = ~ age | id))
summary(fit.lme.5.1)
```

```
## Linear mixed-effects model fit by maximum likelihood
##   Data: dat
##       AIC      BIC    logLik
##   141418.8 141504.9 -70698.42
##
## Random effects:
##  Formula: ~age | id
##  Structure: General positive-definite, Log-Cholesky parametrization
##             StdDev    Corr
## (Intercept) 25.092200 (Intr)
## age          1.800298 -0.752
## Residual    10.221047
##
## Correlation Structure: Exponential spatial correlation
##  Formula: ~age | id
##  Parameter estimate(s):
##       range
## 0.01674874
## Fixed effects:  fev ~ -1 + gender + age:gender + I(age * age):gender
##                      Value Std.Error    DF   t-value p-value
## genderf            88.58823 2.1959143   721  40.34230       0
## genderm            84.14385 2.2515080   721  37.37222       0
## genderf:age         1.08984 0.2653860 17768   4.10664       0
## genderm:age         1.95814 0.2787764 17768   7.02405       0
## genderf:I(age * age) -0.09911 0.0088488 17768 -11.20084      0
## genderm:I(age * age) -0.12818 0.0093783 17768 -13.66745      0
```

```
##   Correlation:
##                         gendrf gendrm gndrf: gndrm: gndrf:I(*a)
## genderm                  0.000
## genderf:age             -0.869  0.000
## genderm:age              0.000 -0.884  0.000
## genderf:I(age * age)     0.660  0.000 -0.884  0.000
## genderm:I(age * age)     0.000  0.703  0.000 -0.905  0.000
##
## Standardized Within-Group Residuals:
##          Min          Q1         Med          Q3         Max
## -8.00340961 -0.52031162  0.04900868  0.58466303  6.28583914
##
## Number of Observations: 18494
## Number of Groups: 723
```

```
anova(fit.lme.5, fit.lme.5.1) ## we do seem to need cubic terms
```

```
##            Model df      AIC      BIC    logLik   Test  L.Ratio p-value
## fit.lme.5      1 13 141218.2 141320.0 -70596.12
## fit.lme.5.1    2 11 141418.8 141504.9 -70698.42 1 vs 2 204.6105  <.0001
## testing if there is an interaction between age and gender
```

Final model
```