Lab 2 Longitudinal Models

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ICPSR Summer Program at York University

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```
#
#  Schizophrenia patients were assessed at 6 annual checkups.
#
#  At each checkup, the type of drug currently prescribed by the treating
#  physician was recorded.  There were 3 types of drugs: Typical, Atypical and
#  Clozapine.
#
```

```
#  Researchers are interested in using this observational data to study the
#  effectiveness of the newest drug, Clozapine, particularly comparing it with
#  'Typical' drugs, the established standard.
#
#  There are a number of 'outcome' measures (i.e. measures of the
#  severity of the illness) but only one, 'neg', is of interest
#  for now.
#

library(spida2)   # devtools::install_github('gmonette/spida2')
library(p3d)      # devtools::install_github('gmonette/p3d')
```

```
|   Loading required package: rgl
|
|   Attaching package: 'rgl'
|   The following object is masked from 'package:spida2':
|
|       %>%
|
|   Attaching package: 'p3d'
```

```
|   The following objects are masked from 'package:spida2':
|
|       cell, center, ConjComp, dell, disp, ell, ell.conj, ellbox,
|       ellplus, ellpt, ellptc, ellpts, ellptsc, elltan, elltanc,
|       na.include, uv
```

```
library(car)
```

```
|   Loading required package: carData
```

```
|
|   Attaching package: 'car'
```

```
|   The following object is masked from 'package:p3d':
|
|       Identify3d
```

```
library(lattice)
library(latticeExtra)
```

```
|   Loading required package: RColorBrewer
```

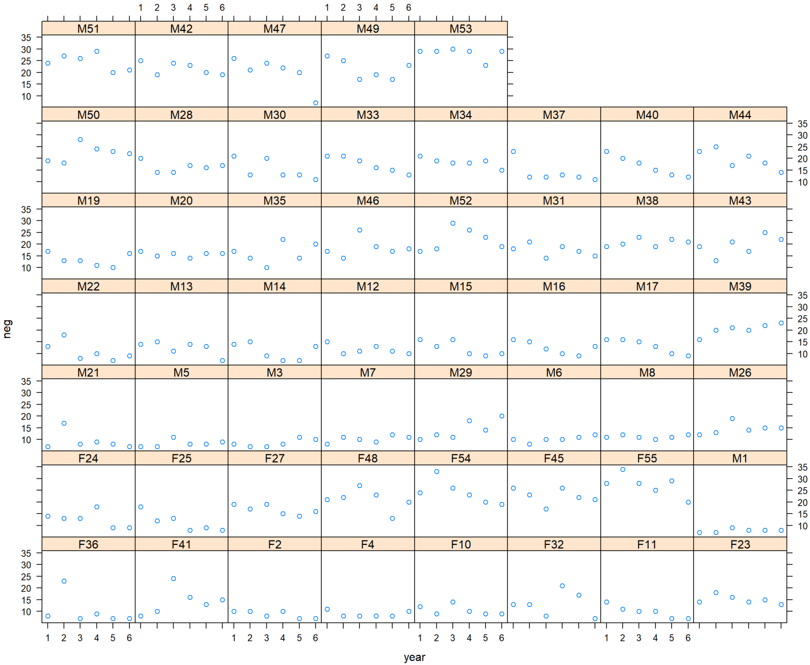
```
interactive <- FALSE

# ?Drugs
```

```
some( Drugs )
```

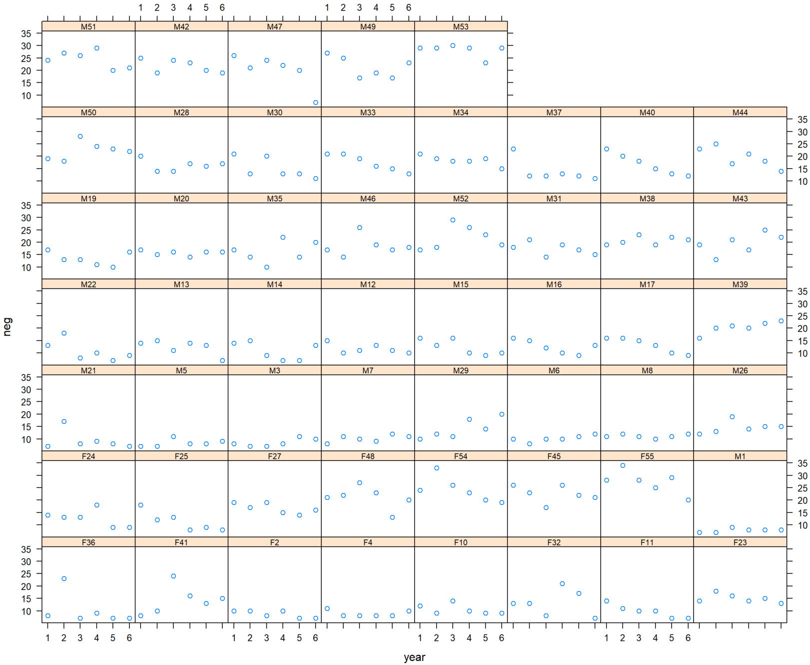
```
|        age1 yrsill1 pos neg gen total year      drug              status Sex
|    22  26.2       9   7  12  25    44    1   Typical             Married   F
|    326 30.5      10  20  19  39    78    6 Clozapine              Single   F
|    330 31.1      12  10  20  33    63    6  Atypical Separated/Divorced   F
|    164 31.8      13   7  11  18    36    3 Clozapine              Single   M
|    188 31.3       6   8  14  42    64    4   Typical              Single   M
|    298 31.3       6   9   7  24    40    6   Typical              Single   M
|    294 33.4      14  13  22  37    72    6  Atypical              Single   M
|    128 31.3      15  17  12  27    56    3   Typical              Single   M
|    238 31.3      15  18  12  28    58    5 Clozapine              Single   M
|    75  37.7      15  26  21  43    90    2 Clozapine              Single   M
|        Subj
|    22   F10
|    326  F54
|    330  F55
|    164  M29
|    188  M13
|    298  M13
|    294  M43
|    128  M37
```

```
|   238  M37
|   75   M47
```

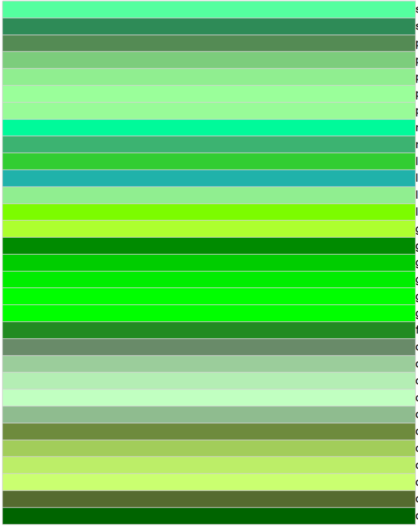
```
# Which drug seems best to reduce 'neg' symptoms
xyplot( neg ~  year | Subj, Drugs)
```


M51
M42
M47
M49
M53
M50
M28
M30
M33
M34
M37
M40
M44
M19
M20
M35
M46
M52
M31
M38
M43
M22
M13
M14
M12
M15
M16
M17
M39
M21
M5
M3
M7
M29
M6
M8
M26
F24
F25
F27
F48
F54
F45
F55
M1
F36
F41
F2
F4
F10
F32
F11
F23
neg
year
1
2
3
4
5
6
10
15
20
25
30
35

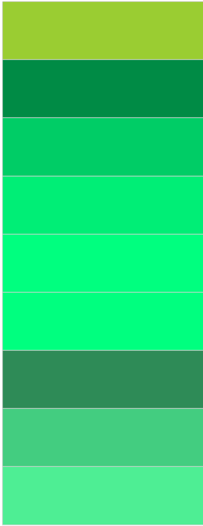
```
# smaller strips
xyplot( neg ~  year | Subj, Drugs,
        par.strip.text = list(cex = .7))
```


M51
M42
M47
M49
M53
M50
M28
M30
M33
M34
M37
M40
M44
M19
M20
M35
M46
M52
M31
M38
M43
M22
M13
M14
M12
M15
M16
M17
M39
M21
M5
M3
M7
M29
M6
M8
M26
F24
F25
F27
F48
F54
F45
F55
M1
F36
F41
F2
F4
F10
F32
F11
F23
neg
year
1
2
3
4
5
6
10
15
20
25
30
35

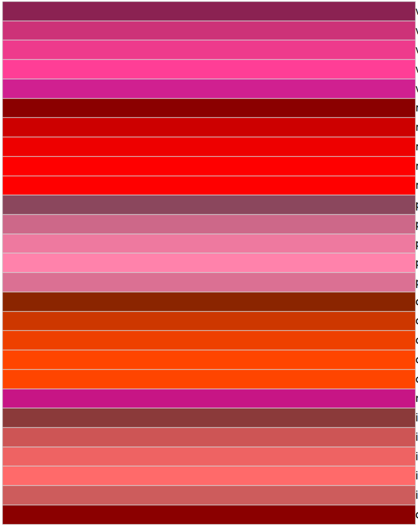
```
dd <- Drugs

dd$id <- reorder( dd$Subj, dd$neg)  # orders ’id’s in order of average ’neg’ sym
# choose nice color
pals(’green’)
```



seagreen1 (84 255 159)
seagreen (46 139 87)
palegreen4 (84 139 84)
palegreen3 (124 205 124)
palegreen2 (144 238 144)
palegreen1 (154 255 154)
palegreen (152 251 152)
mediumspringgreen (0 250 154)
mediumseagreen (60 179 113)
limegreen (50 205 50)
lightseagreen (32 178 170)
lightgreen (144 238 144)
lawngreen (124 252 0)
greenyellow (173 255 47)
green4 (0 139 0)
green3 (0 205 0)
green2 (0 238 0)
green1 (0 255 0)
green (0 255 0)
forestgreen (34 139 34)
darkseagreen4 (105 139 105)
darkseagreen3 (155 205 155)
darkseagreen2 (180 238 180)
darkseagreen1 (193 255 193)
darkseagreen (143 188 143)
darkolivegreen4 (110 139 61)
darkolivegreen3 (162 205 90)
darkolivegreen2 (188 238 104)
darkolivegreen1 (202 255 112)
darkolivegreen (85 107 47)
darkgreen (0 100 0)

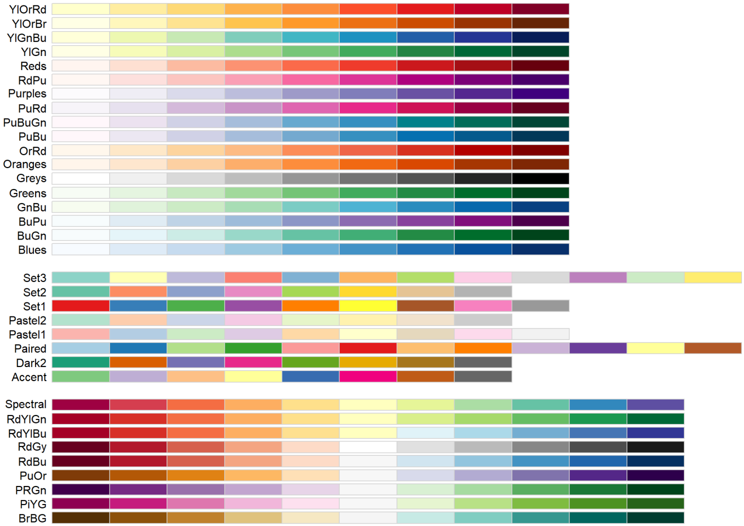


```
pals('red')
```



violetred4 (139 34 82)
violetred3 (205 50 120)
violetred2 (238 58 140)
violetred1 (255 62 150)
violetred (208 32 144)
red4 (139 0 0)
red3 (205 0 0)
red2 (238 0 0)
red1 (255 0 0)
red (255 0 0)
palevioletred4 (139 71 93)
palevioletred3 (205 104 137)
palevioletred2 (238 121 159)
palevioletred1 (255 130 171)
palevioletred (219 112 147)
orangered4 (139 37 0)
orangered3 (205 55 0)
orangered2 (238 64 0)
orangered1 (255 69 0)
orangered (255 69 0)
mediumvioletred (199 21 133)
indianred4 (139 58 58)
indianred3 (205 85 85)
indianred2 (238 99 99)
indianred1 (255 106 106)
indianred (205 92 92)
darkred (139 0 0)

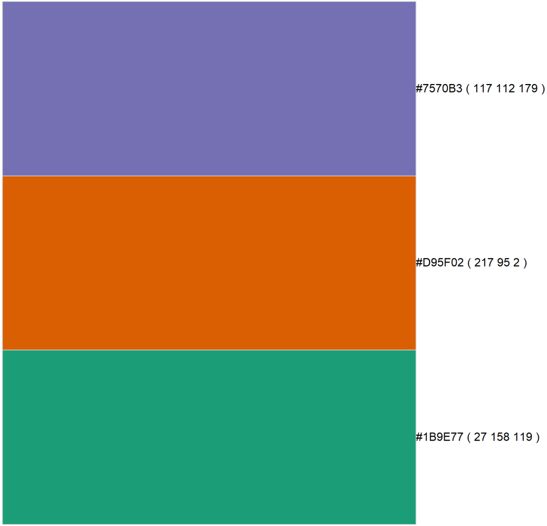
```
display.brewer.all()
```


YlOrRd
YlOrBr
YlGnBu
YlGn
Reds
RdPu
Purples
PuRd
PuBuGn
PuBu
OrRd
Oranges
Greys
Greens
GnBu
BuPu
BuGn
Blues
Set3
Set2
Set1
Pastel2
Pastel1
Paired
Dark2
Accent
Spectral
RdYlGn
RdYlBu
RdGy
RdBu
PuOr
PRGn
PiYG
BrBG

```
cols <- brewer.pal(3,’Dark2’)
cols
```

```
|    [1] "#1B9E77" "#D95F02" "#7570B3"
```

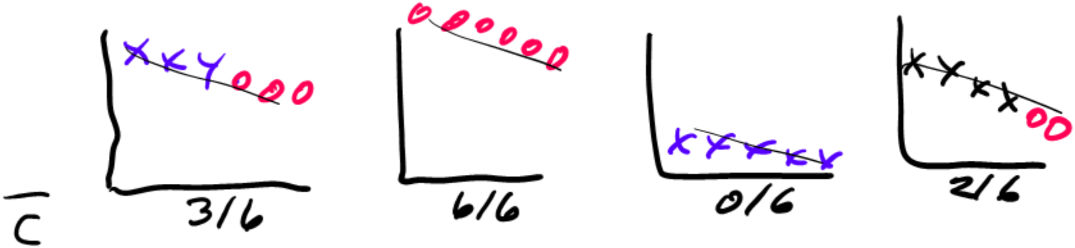
```
pal(cols)
```


#7570B3 (117 112 179)
#D95F02 (217 95 2)
#1B9E77 (27 158 119)

```
|           red green blue
|   #1B9E77  27   158  119
|   #D95F02 217    95    2
|   #7570B3 117   112  179
```

```r
gd(col = cols) # uses ggplot2-like style
gd(pch = c(16,16), cex = 1)
xyplot( neg ~ year | id, dd , groups = drug,
        auto.key = list(columns=3),
        par.strip.text = list(cex = .7))
```


Atypical ●
Clozapine ●
Typical ●
F45
F54
M51
F55
M53
M47
M39
M38
F48
M49
M42
M52
M50
F27
M40
M31
M33
M34
M46
M43
M44
M29
F41
M26
F23
M30
M20
M35
M28
M13
M15
M16
F24
F32
M17
M19
M37
M7
M6
F10
M22
M14
M8
F25
M12
M1
M5
M3
F2
F4
M21
F11
F36
neg
35
30
25
20
15
10
1
2
3
4
5
6
year



Clozapine - Typical   No Control + Bad

"   " $\bar{C}$ + C – Good

"   " $\bar{C}$ + C + Y – N.S.

" + AR(1) – lower Sig.

```
#
# QUESTION:
#
#         Can we perform OLS fits on each cluster?
#         Note that the data are balanced with respect to time
#         but not with respect to drugs.
#
#         Also note that Clozapine is more frequently given later in the study
#

# compare drugs:

# Pooling the data

fit.lm <- lm(neg ~ drug, dd)
summary(fit.lm)
```

```
|
|   Call:
|   lm(formula = neg ~ drug, data = dd)
|
|   Residuals:
```

```
|      Min     1Q Median     3Q    Max
|   -9.299 -5.233 -1.233  3.767 18.767
|
|   Coefficients:
|                 Estimate Std. Error t value Pr(>|t|)
|   (Intercept)   15.27778    0.71557  21.351   <2e-16 ***
|   drugClozapine  1.02107    0.96737   1.056    0.292
|   drugTypical   -0.04507    0.86250  -0.052    0.958
|   ---
|   Signif. codes:  0 ’***’ 0.001 ’**’ 0.01 ’*’ 0.05 ’.’ 0.1 ’ ’ 1
|
|   Residual standard error: 6.072 on 315 degrees of freedom
|   Multiple R-squared:  0.005996,  Adjusted R-squared:  -0.0003149
|   F-statistic: 0.9501 on 2 and 315 DF,  p-value: 0.3878
```

```
Ld <- Ldiff(fit.lm, ’drug’)
wald(fit.lm, Ld)
```

```
|     numDF denDF   F.value p.value
|   1     2   315 0.9501109  0.3878
|
|                          Estimate Std.Error  DF   t-value p-value Lower 0.95
```

```
|     Clozapine - <ref>    1.021073  0.967366 315  1.055519 0.29200  -0.882243
|     Typical - <ref>     -0.045073  0.862500 315 -0.052259 0.95836  -1.742063
|     Typical - Clozapine -1.066146  0.809706 315 -1.316707 0.18889  -2.659262
|
|                         Upper 0.95
|     Clozapine - <ref>     2.924388
|     Typical - <ref>       1.651917
|     Typical - Clozapine   0.526970
```

```r
Ld <- Ldiff(fit.lm, ’drug’, ref = "Atypical")
wald(fit.lm, Ld)
```

```
|     numDF denDF   F.value p.value
|   1     2   315 0.9501109  0.3878
|
|                           Estimate Std.Error  DF   t-value p-value
|     Clozapine - Atypical  1.021073  0.967366 315  1.055519 0.29200
|     Typical - Atypical   -0.045073  0.862500 315 -0.052259 0.95836
|     Typical - Clozapine  -1.066146  0.809706 315 -1.316707 0.18889
|
|                          Lower 0.95 Upper 0.95
|     Clozapine - Atypical  -0.882243   2.924388
```

```
|      Typical - Atypical    -1.742063   1.651917
|      Typical - Clozapine   -2.659262   0.526970
```

```
# Which looks better: Clozapine or Typical? Remember that a higher response mean
# more severe symptoms.

#
# LME model
#

library(nlme)
```

```
|
|   Attaching package: 'nlme'
```

```
|   The following object is masked from 'package:spida2':
|
|       getData
```

```
fit <- lme( neg ~ drug, dd, random = ~ 1 | id )
summary(fit)
```

```
|   Linear mixed-effects model fit by REML
|    Data: dd
```

```
|          AIC      BIC    logLik
|     1829.011 1847.773 -909.5053
|
|    Random effects:
|     Formula: ~1 | id
|            (Intercept) Residual
|    StdDev:    5.240588 3.399672
|
|    Fixed effects: neg ~ drug
|                      Value Std.Error  DF   t-value p-value
|    (Intercept)   15.482816 0.8783362 263 17.627437  0.0000
|    drugClozapine -1.300272 0.7980602 263 -1.629290  0.1044
|    drugTypical    0.815021 0.6140648 263  1.327255  0.1856
|     Correlation:
|                  (Intr) drgClz
|    drugClozapine -0.444
|    drugTypical   -0.489  0.559
|
|    Standardized Within-Group Residuals:
|            Min          Q1         Med          Q3         Max
|    -3.71174345 -0.59155383 -0.05454849  0.47584480  3.47145299
```

```
|
|   Number of Observations: 318
|   Number of Groups: 53
```

```
wald(fit, -1)
```

```
|     numDF denDF  F.value p.value
|   1     2   263 4.974805 0.00757
|
|                  Estimate Std.Error  DF   t-value p-value Lower 0.95
|     drugClozapine -1.300272  0.798060 263 -1.629290 0.10445  -2.871672
|     drugTypical    0.815021  0.614065 263  1.327255 0.18558  -0.394089
|
|                  Upper 0.95
|     drugClozapine   0.271129
|     drugTypical     2.024130
```

```
# Note: overall significance although individual p-values were not

# Now, Clozapine looks best

Ld <- Ldiff ( fit, "drug")   # hypothesis matrix to test differences between dru
Ld
```

```
|                       [,1] [,2] [,3]
|   Clozapine - <ref>      0    1    0
|   Typical - <ref>        0    0    1
|   Typical - Clozapine    0   -1    1
```

```
wald( fit, Ld )
```

```
|     numDF denDF  F.value p.value
|   1     2   263 4.974805 0.00757
|
|                          Estimate Std.Error  DF   t-value p-value Lower 0.95
|     Clozapine - <ref>   -1.300272  0.798060 263 -1.629290 0.10445  -2.871672
|     Typical - <ref>      0.815021  0.614065 263  1.327255 0.18558  -0.394089
|     Typical - Clozapine  2.115292  0.682395 263  3.099806 0.00215   0.771639
|
|                         Upper 0.95
|     Clozapine - <ref>     0.271129
|     Typical - <ref>       2.024130
|     Typical - Clozapine   3.458945
```

```
Ld <- Ldiff ( fit,  "drug", ref = "Atypical")
wald( fit, Ld )
```

```
|      numDF denDF  F.value p.value
|    1     2   263 4.974805 0.00757
|
|                             Estimate Std.Error  DF   t-value p-value
|      Clozapine - Atypical -1.300272  0.798060 263 -1.629290 0.10445
|      Typical - Atypical    0.815021  0.614065 263  1.327255 0.18558
|      Typical - Clozapine   2.115292  0.682395 263  3.099806 0.00215
|
|                            Lower 0.95 Upper 0.95
|      Clozapine - Atypical  -2.871672   0.271129
|      Typical - Atypical    -0.394089   2.024130
|      Typical - Clozapine    0.771639   3.458945
# Other ways



# QUESTIONS:
#       1) Can you explain why 'drug' is significant overall although
#          neither p-value is significant in the summary output. Note that
#          this illustrates the danger in dropping multiple terms on the
#          basis of individual p-values.
#
```

```
#       2) How is clozapine doing ?
#          Is it better than the others as expected?
#          What explanation can you think of for the results?
#

#
# Hausman test: test whether contextual variables have a significant effect.
#


fit2 <- update( fit, . ~ . + cvar( drug, id))
summary( fit2 )
```

```
|   Linear mixed-effects model fit by REML
|    Data: dd
|          AIC      BIC    logLik
|     1818.357 1844.581 -902.1785
|
|   Random effects:
|    Formula: ~1 | id
|           (Intercept) Residual
|   StdDev:    4.984062  3.39656
```

```
|
|   Fixed effects: neg ~ drug + cvar(drug, id)
|                               Value Std.Error  DF   t-value p-value
|   (Intercept)             15.838657  2.121548 263  7.465614  0.0000
|   drugClozapine           -1.782102  0.834395 263 -2.135802  0.0336
|   drugTypical              0.896756  0.627306 263  1.429535  0.1540
|   cvar(drug, id)Clozapine  3.813141  2.872332  50  1.327542  0.1904
|   cvar(drug, id)Typical   -2.616211  2.891131  50 -0.904909  0.3699
|    Correlation:
|                           (Intr) drgClz drgTyp c(,i)C
|   drugClozapine            0.000
|   drugTypical              0.000  0.552
|   cvar(drug, id)Clozapine -0.771 -0.290 -0.160
|   cvar(drug, id)Typical   -0.884 -0.120 -0.217  0.668
|
|   Standardized Within-Group Residuals:
|           Min          Q1         Med          Q3         Max
|   -3.78234220 -0.60736018 -0.06230846  0.49922986  3.32999988
|
|   Number of Observations: 318
|   Number of Groups: 53
```

```
wald( fit2, 'cvar')
```

```
|          numDF denDF  F.value p.value
|   cvar     2    50 3.783136 0.02952
|
|   Coefficients                     Estimate Std.Error DF   t-value p-value
|     cvar(drug, id)Clozapine  3.813141  2.872332 50  1.327542 0.19036
|     cvar(drug, id)Typical   -2.616211  2.891131 50 -0.904909 0.36985
|
|   Coefficients                    Lower 0.95 Upper 0.95
|     cvar(drug, id)Clozapine  -1.956108   9.582391
|     cvar(drug, id)Typical    -8.423218   3.190796
```

```
#
# QUESTIONS:
#   1) What is the interpretation of the contextual variable for a
#      categorical effect:
```

```
head( cbind( dd['id'], getX( fit2) ), 18 )
```

```
|          id (Intercept) drugClozapine drugTypical cvar(drug, id)Clozapine
|   17   F36           1             0           1               0.6666667
|   72   F36           1             0           0               0.6666667
```

```
|   127 F36           1             1           0               0.6666667
|   182 F36           1             1           0               0.6666667
|   237 F36           1             1           0               0.6666667
|   292 F36           1             1           0               0.6666667
|   38  F41           1             0           1               0.6666667
|   93  F41           1             0           0               0.6666667
|   148 F41           1             1           0               0.6666667
|   203 F41           1             1           0               0.6666667
|   258 F41           1             1           0               0.6666667
|   313 F41           1             1           0               0.6666667
|   14   F2           1             0           1               0.0000000
|   69   F2           1             0           1               0.0000000
|   124  F2           1             0           1               0.0000000
|   179  F2           1             0           1               0.0000000
|   234  F2           1             0           1               0.0000000
|   289  F2           1             0           1               0.0000000
|       cvar(drug, id)Typical
|   17              0.1666667
|   72              0.1666667
|   127             0.1666667
|   182             0.1666667
```

```
|    237                0.1666667
|    292                0.1666667
|    38                 0.1666667
|    93                 0.1666667
|    148                0.1666667
|    203                0.1666667
|    258                0.1666667
|    313                0.1666667
|    14                 1.0000000
|    69                 1.0000000
|    124                1.0000000
|    179                1.0000000
|    234                1.0000000
|    289                1.0000000

#
#   2) Compare results with and without cvar's
#
#   3) Compare cvar effect with corresponding raw var: what does this suggest??
#      E.g. 'Typical' and cvar(Typical)?
#
```

```
wald( fit2, -1)

|      numDF denDF  F.value p.value
|   1     4    50 4.294531  0.0046
|
|                              Estimate Std.Error  DF   t-value p-value
|      drugClozapine          -1.782102  0.834395 263 -2.135802 0.03362
|      drugTypical             0.896756  0.627306 263  1.429535 0.15404
|      cvar(drug, id)Clozapine  3.813141  2.872332  50  1.327542 0.19036
|      cvar(drug, id)Typical  -2.616211  2.891131  50 -0.904909 0.36985
|
|                             Lower 0.95 Upper 0.95
|      drugClozapine           -3.425047  -0.139158
|      drugTypical             -0.338425   2.131937
|      cvar(drug, id)Clozapine -1.956108   9.582391
|      cvar(drug, id)Typical   -8.423218   3.190796
wald( fit , -1)

|      numDF denDF  F.value p.value
|   1     2   263 4.974805 0.00757
|
|                    Estimate Std.Error  DF   t-value p-value Lower 0.95
```

```
|     drugClozapine -1.300272  0.798060 263 -1.629290 0.10445  -2.871672
|     drugTypical    0.815021  0.614065 263  1.327255 0.18558  -0.394089
|
|                   Upper 0.95
|     drugClozapine   0.271129
|     drugTypical     2.024130

Ld <- Ldiff( fit2, "drug", ref = "Atypical")

wald( fit2, Ld )  # compare Clozapine with Typical

|     numDF denDF  F.value p.value
|   1     2   263 7.174332 0.00093
|
|                            Estimate Std.Error  DF   t-value p-value
|     Clozapine - Atypical -1.782102  0.834395 263 -2.135802 0.03362
|     Typical - Atypical    0.896756  0.627306 263  1.429535 0.15404
|     Typical - Clozapine   2.678858  0.715431 263  3.744397 0.00022
|
|                          Lower 0.95 Upper 0.95
|     Clozapine - Atypical  -3.425047  -0.139158
|     Typical - Atypical    -0.338425   2.131937
```

```
|     Typical - Clozapine    1.270156   4.087560

#
# QUESTIONS:
#
#  1) Would it ever be appropriate to include a contextual variable even
#         though it isn't significant?  e.g. In this case if the p-value were
#         0.06, what would be the consequence of including it or excluding it?
#
#  2) Compare the SEs for the raw variables and for the contextual variable.
#         What could explain the difference?
#
# === EXERCISE: ===
#
#  1) Estimate the between-patient differences (compositional effects)
#      in these three drugs. Note that there are at least two ways of
#      doing this.
#
#  2) Carry out a similar analysis for general symptoms: 'gen'
#

#
```

```
# Taking time into account
#
# When the range of time is compact and similar for all subjects
# and when time is not expected to have a very different effect
# as time progresses, simple models for time are generally adequate
#
# In the next session, we will see much richer functions of
# time: splines, asymptotic models, Fourier analysis, etc.
#

fit2l <- update(fit2, . ~ . + year)
summary( fit2l )
```

```
|   Linear mixed-effects model fit by REML
|    Data: dd
|         AIC      BIC    logLik
|     1810.39 1840.334 -897.1952
|
|   Random effects:
|    Formula: ~1 | id
|           (Intercept) Residual
|   StdDev:    4.992041 3.325507
```

```
|
|  Fixed effects: neg ~ drug + cvar(drug, id) + year
|                              Value Std.Error  DF   t-value p-value
|  (Intercept)             17.511006 2.1742271 262  8.053899  0.0000
|  drugClozapine           -1.153198 0.8362982 262 -1.378931  0.1691
|  drugTypical             -0.117037 0.6785156 262 -0.172489  0.8632
|  cvar(drug, id)Clozapine  3.184237 2.8728859  50  1.108376  0.2730
|  cvar(drug, id)Typical   -1.602418 2.9026725  50 -0.552049  0.5834
|  year                    -0.477814 0.1359168 262 -3.515489  0.0005
|   Correlation:
|                          (Intr) drgClz drgTyp c(,i)C c(,i)T
|  drugClozapine            0.047
|  drugTypical             -0.093  0.397
|  cvar(drug, id)Clozapine -0.766 -0.291 -0.116
|  cvar(drug, id)Typical   -0.837 -0.093 -0.234  0.658
|  year                    -0.219 -0.214  0.425  0.062 -0.099
|
|  Standardized Within-Group Residuals:
|          Min          Q1         Med          Q3         Max
|  -3.50585771 -0.61471185 -0.09486059  0.56161475  3.26692262
|
```

```
|   Number of Observations: 318
|   Number of Groups: 53
```

```
ww <-wald( fit2l )
wald( fit2l, 'cvar' )
```

```
|         numDF denDF  F.value p.value
|   cvar      2    50 2.061446 0.13795
|
|   Coefficients                   Estimate Std.Error DF   t-value p-value
|     cvar(drug, id)Clozapine  3.184237  2.872886 50  1.108376 0.27300
|     cvar(drug, id)Typical   -1.602418  2.902672 50 -0.552049 0.58337
|
|   Coefficients                  Lower 0.95 Upper 0.95
|     cvar(drug, id)Clozapine  -2.586125   8.954598
|     cvar(drug, id)Typical    -7.432608   4.227771
```

```
wald( fit2l, 'drug' )
```

```
|         numDF denDF  F.value p.value
|   drug      4    50 1.224521 0.31232
|
|   Coefficients                   Estimate Std.Error  DF   t-value p-value
```

```
|     drugClozapine            -1.153198  0.836298 262 -1.378931 0.16909
|     drugTypical              -0.117037  0.678516 262 -0.172489 0.86319
|     cvar(drug, id)Clozapine   3.184237  2.872886  50  1.108376 0.27300
|     cvar(drug, id)Typical    -1.602418  2.902672  50 -0.552049 0.58337
|
|   Coefficients               Lower 0.95 Upper 0.95
|     drugClozapine             -2.799919   0.493524
|     drugTypical               -1.453074   1.219001
|     cvar(drug, id)Clozapine   -2.586125   8.954598
|     cvar(drug, id)Typical     -7.432608   4.227771
```

```
Ld <- Ldiff( fit2l, "drug", ref = "Atypical")
wald ( fit2l, Ld )     # What does this say about Clozapine ?
```

```
|     numDF denDF  F.value p.value
|   1     2   262 1.034312 0.35692
|
|                              Estimate Std.Error  DF   t-value p-value
|     Clozapine - Atypical -1.153198  0.836298 262 -1.378931 0.16909
|     Typical - Atypical   -0.117037  0.678516 262 -0.172489 0.86319
|     Typical - Clozapine   1.036161  0.842019 262  1.230567 0.21959
|
```

```
|                          Lower 0.95 Upper 0.95
|     Clozapine - Atypical  -2.799919   0.493524
|     Typical - Atypical    -1.453074   1.219001
|     Typical - Clozapine   -0.621825   2.694147
```

```
# Q: How do you explain the differences in the estimation of the Typical - Cloza
#    comparison in the 4 analyses:
#
lapply(
  list("pooled" = fit.lm, "no ctx" = fit,"ctx"= fit2,"ctx+year" = fit2l),
  function( fit ) wald( fit , Ldiff( fit,'drug', ref = "Atypical"))
)
```

```
|   $pooled
|     numDF denDF   F.value p.value
|   1     2   315 0.9501109  0.3878
|
|                           Estimate Std.Error  DF   t-value p-value
|     Clozapine - Atypical  1.021073  0.967366 315  1.055519 0.29200
|     Typical - Atypical   -0.045073  0.862500 315 -0.052259 0.95836
|     Typical - Clozapine  -1.066146  0.809706 315 -1.316707 0.18889
|
```

```
|                          Lower 0.95 Upper 0.95
|     Clozapine - Atypical  -0.882243   2.924388
|     Typical - Atypical    -1.742063   1.651917
|     Typical - Clozapine   -2.659262   0.526970
|
|
|   $`no ctx`
|     numDF denDF  F.value p.value
|   1     2   263 4.974805 0.00757
|
|                           Estimate Std.Error  DF   t-value p-value
|     Clozapine - Atypical -1.300272  0.798060 263 -1.629290 0.10445
|     Typical - Atypical    0.815021  0.614065 263  1.327255 0.18558
|     Typical - Clozapine   2.115292  0.682395 263  3.099806 0.00215
|
|                          Lower 0.95 Upper 0.95
|     Clozapine - Atypical  -2.871672   0.271129
|     Typical - Atypical    -0.394089   2.024130
|     Typical - Clozapine    0.771639   3.458945
|
|
```

```
|   $ctx
|     numDF denDF  F.value p.value
|   1     2   263 7.174332 0.00093
|
|                           Estimate Std.Error  DF   t-value p-value
|     Clozapine - Atypical -1.782102  0.834395 263 -2.135802 0.03362
|     Typical - Atypical    0.896756  0.627306 263  1.429535 0.15404
|     Typical - Clozapine   2.678858  0.715431 263  3.744397 0.00022
|
|                          Lower 0.95 Upper 0.95
|     Clozapine - Atypical  -3.425047  -0.139158
|     Typical - Atypical    -0.338425   2.131937
|     Typical - Clozapine    1.270156   4.087560
|
|
|   $‘ctx+year‘
|     numDF denDF  F.value p.value
|   1     2   262 1.034312 0.35692
|
|                           Estimate Std.Error  DF   t-value p-value
|     Clozapine - Atypical -1.153198  0.836298 262 -1.378931 0.16909
```

```
|     Typical - Atypical   -0.117037  0.678516 262 -0.172489 0.86319
|     Typical - Clozapine   1.036161  0.842019 262  1.230567 0.21959
|
|                          Lower 0.95 Upper 0.95
|     Clozapine - Atypical  -2.799919   0.493524
|     Typical - Atypical    -1.453074   1.219001
|     Typical - Clozapine   -0.621825   2.694147
```

```
clist <- lapply(
  list("pooled" = fit.lm, "no ctx" = fit,"ctx"= fit2,"ctx+year" = fit2l),
  function( fit ) wald( fit , Ldiff( fit,'drug', ref = "Atypical"))
)
clist
```

```
|   $pooled
|     numDF denDF   F.value p.value
|   1     2   315 0.9501109  0.3878
|
|                           Estimate Std.Error  DF   t-value p-value
|     Clozapine - Atypical  1.021073  0.967366 315  1.055519 0.29200
|     Typical - Atypical   -0.045073  0.862500 315 -0.052259 0.95836
|     Typical - Clozapine  -1.066146  0.809706 315 -1.316707 0.18889
```

```
|
|                          Lower 0.95 Upper 0.95
|     Clozapine - Atypical  -0.882243   2.924388
|     Typical - Atypical    -1.742063   1.651917
|     Typical - Clozapine   -2.659262   0.526970
|
|
|   $`no ctx`
|     numDF denDF  F.value p.value
|   1     2   263 4.974805 0.00757
|
|                           Estimate Std.Error  DF   t-value p-value
|     Clozapine - Atypical -1.300272  0.798060 263 -1.629290 0.10445
|     Typical - Atypical    0.815021  0.614065 263  1.327255 0.18558
|     Typical - Clozapine   2.115292  0.682395 263  3.099806 0.00215
|
|                          Lower 0.95 Upper 0.95
|     Clozapine - Atypical  -2.871672   0.271129
|     Typical - Atypical    -0.394089   2.024130
|     Typical - Clozapine    0.771639   3.458945
|
```

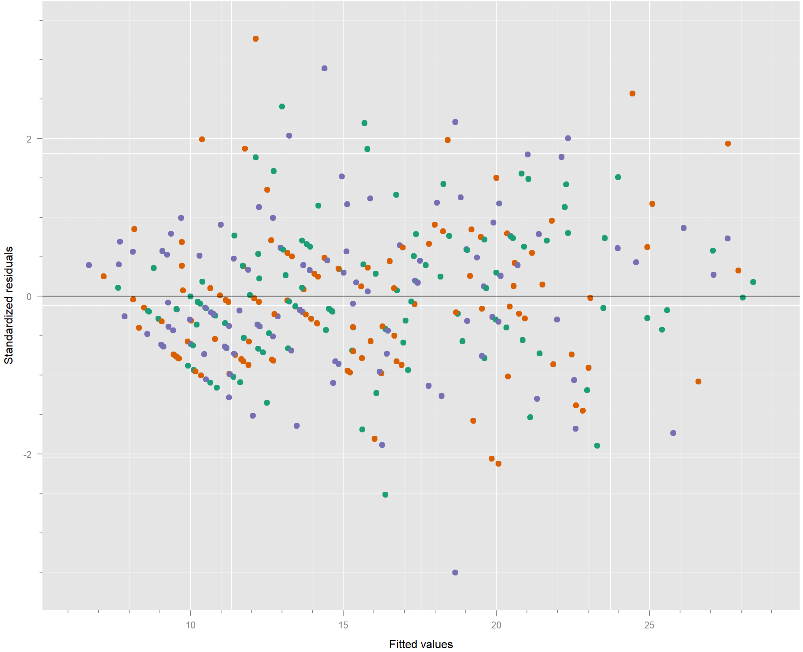
```
|
|  $ctx
|    numDF denDF  F.value p.value
|  1     2   263 7.174332 0.00093
|
|                             Estimate Std.Error  DF   t-value p-value
|    Clozapine - Atypical -1.782102  0.834395 263 -2.135802 0.03362
|    Typical - Atypical    0.896756  0.627306 263  1.429535 0.15404
|    Typical - Clozapine   2.678858  0.715431 263  3.744397 0.00022
|
|                            Lower 0.95 Upper 0.95
|    Clozapine - Atypical  -3.425047  -0.139158
|    Typical - Atypical    -0.338425   2.131937
|    Typical - Clozapine    1.270156   4.087560
|
|
|  $‘ctx+year‘
|    numDF denDF  F.value p.value
|  1     2   262 1.034312 0.35692
|
|                             Estimate Std.Error  DF   t-value p-value
```

```
|     Clozapine - Atypical -1.153198  0.836298 262 -1.378931 0.16909
|     Typical - Atypical   -0.117037  0.678516 262 -0.172489 0.86319
|     Typical - Clozapine   1.036161  0.842019 262  1.230567 0.21959
|
|                          Lower 0.95 Upper 0.95
|     Clozapine - Atypical  -2.799919   0.493524
|     Typical - Atypical    -1.453074   1.219001
|     Typical - Clozapine   -0.621825   2.694147
```

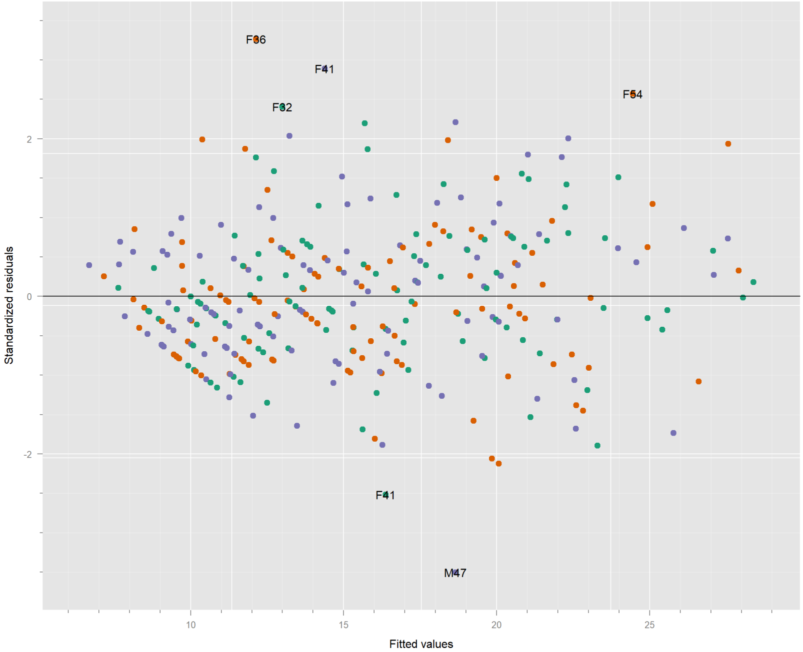
```
do.call( rbind, lapply(clist, function(x) x[[1]][[2]][3,]))
```

```
|
|               Estimate Std.Error  DF   t-value      p-value Lower 0.95
|     pooled   -1.066146 0.8097063 315 -1.316707 0.1888939025 -2.6592623
|     no ctx    2.115292 0.6823951 263  3.099806 0.0021468358  0.7716393
|     ctx       2.678858 0.7154312 263  3.744397 0.0002221581  1.2701563
|     ctx+year  1.036161 0.8420192 262  1.230567 0.2195885901 -0.6218253
|
|              Upper 0.95
|     pooled     0.526970
|     no ctx     3.458945
|     ctx        4.087560
```

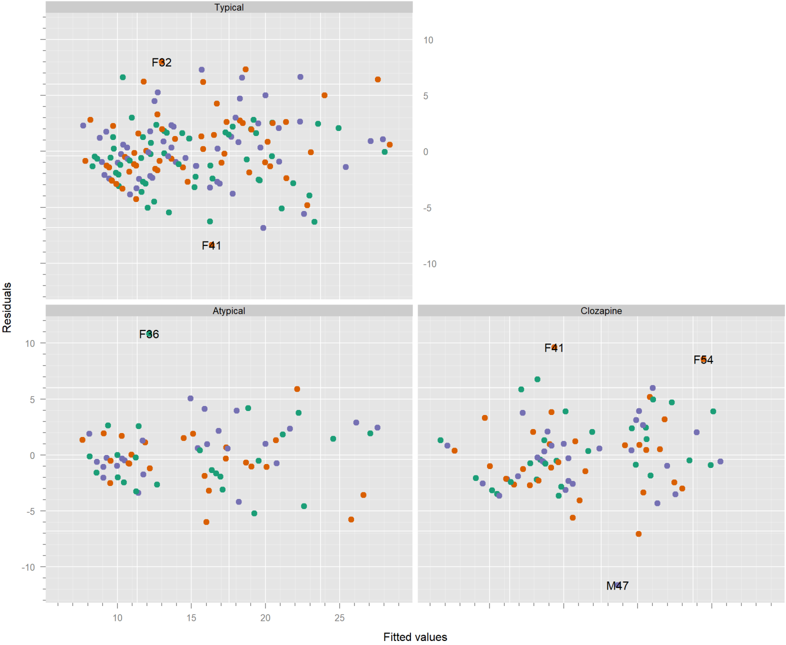
```
|      ctx+year   2.694147

#
# Can you think of explanations consistent with these results?
#

#
#  EXERCISE:
#      Is there evidence that there is curvature in the effect of time?
#
# Level 1 and Level 2 diagnostics
#
#
# Level 1
#

plot( fit2l )
```


Standardized residuals
2
0
-2
10
15
20
25
Fitted values

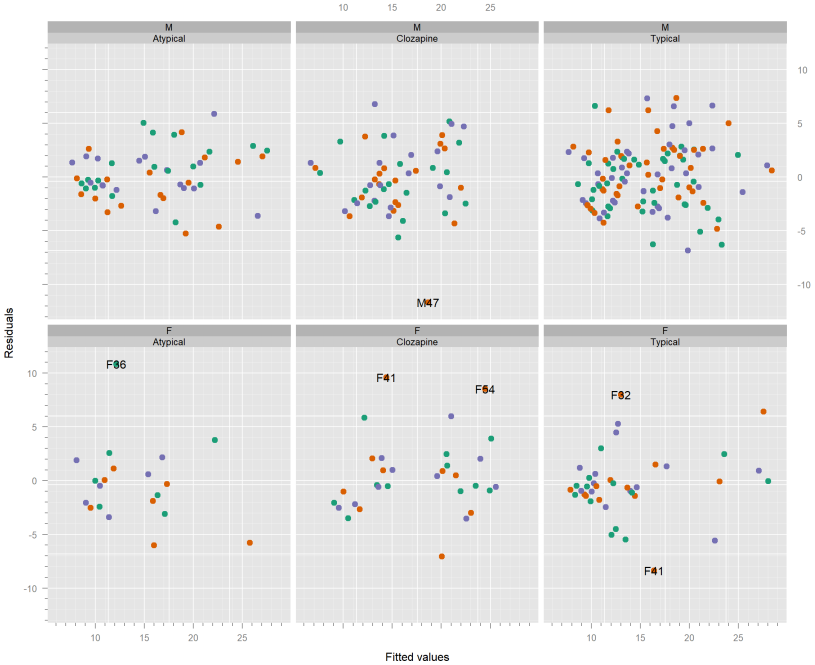
```
plot( fit2l, id = .02)
```


F36
F41
F32
F54
F41
M47
Standardized residuals
2
0
-2
Fitted values
10
15
20
25

```r
plot( fit2l, resid(.) ~ fitted(.) | drug, id = .02)
```


Typical
Atypical
Clozapine
F32
F41
F36
F41
F54
M47
10
5
0
-5
-10
Residuals
10
15
20
25
Fitted values

```
plot( fit2l, resid(.) ~ fitted(.) | drug * Sex, id = .02)
```


M
Atypical
M
Clozapine
M
Typical
F
Atypical
F
Clozapine
F
Typical
M47
F36
F41
F54
F32
F41
10
15
20
25
10
5
0
-5
-10
Residuals
Fitted values

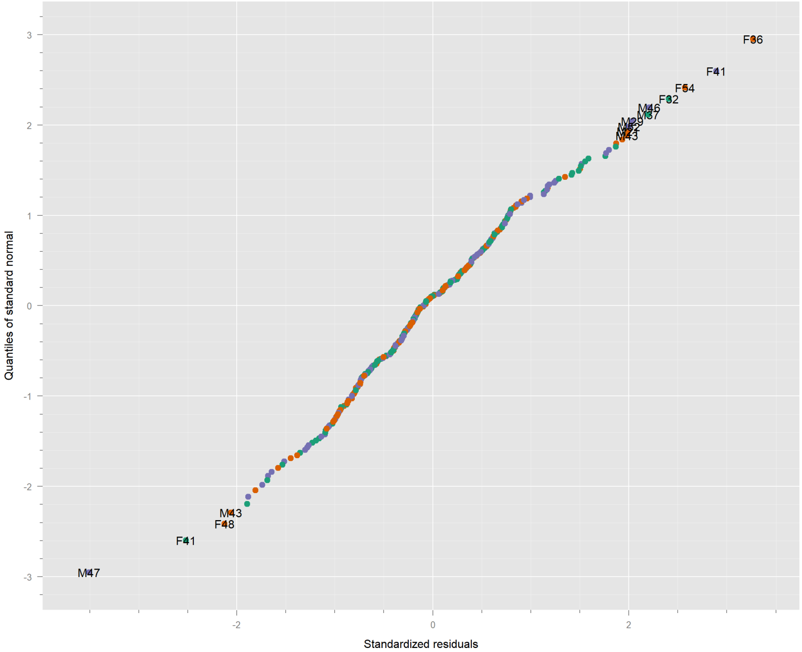
```
#
# Diagnostic for heteroskedasticity
#

plot( fit2l, sqrt( abs( resid(.))) ~ fitted(.), id = .02) # exploratory version
```


M47
F36
F41
F41
F54
F32
Residuals
3
2
1
0
10
15
20
25
Fitted values

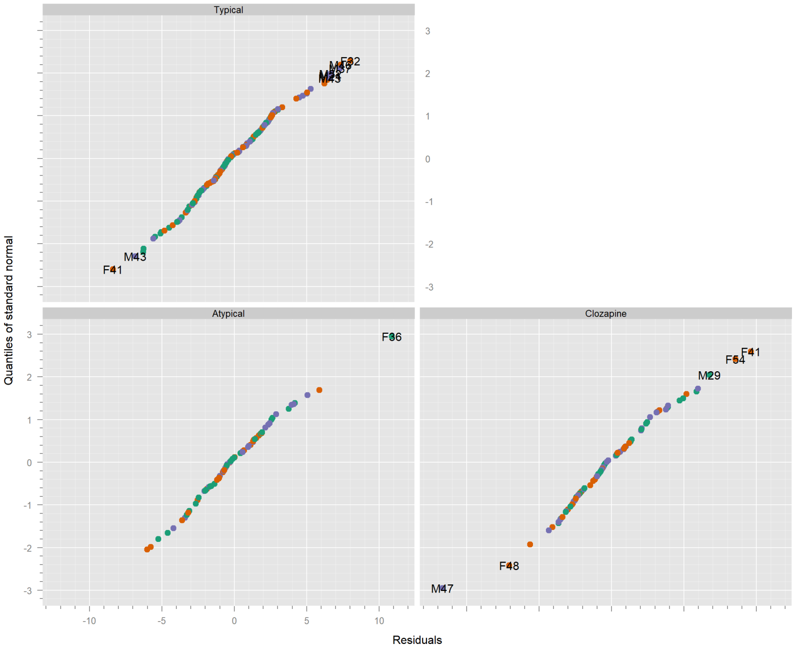
```
# fancy version
plot( fit2l, sqrt( abs( resid(.))) ~ fitted(.), id = .02, sub = "scale-location
      ylab = expression( sqrt(abs(" resid "))),
      panel = function(x, y, ...){
        panel.xyplot( x, y, ...)
        panel.loess(x ,y, ...)
      })
```

scale-location plot

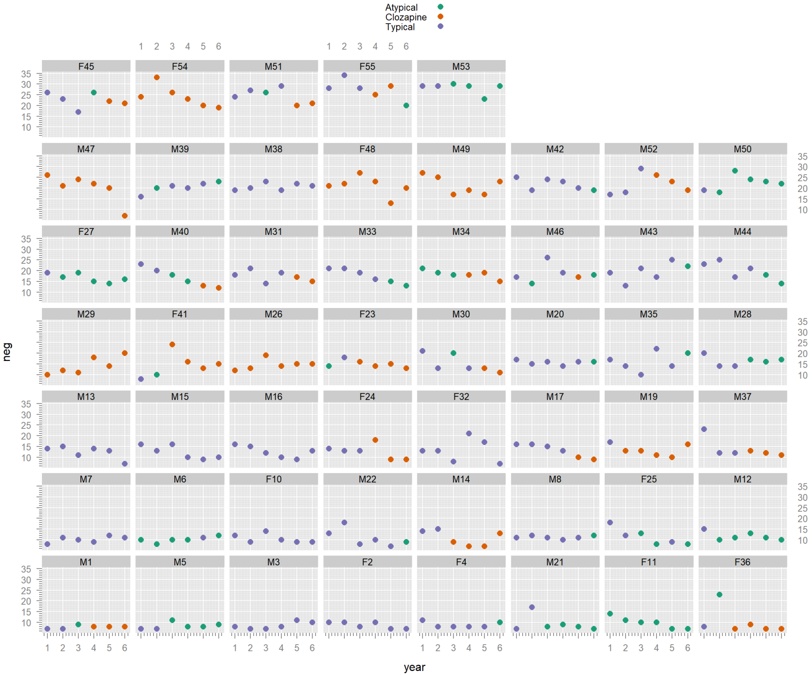
```
# id didn't work so we do it manually
#
if(interactive) {
  trellis.focus()            # trellis = lattice ?!? (the archaeology should be
  panel.identify(labels = dd$id)
  trellis.unfocus()
}
# no strong pattern here so we wait until later to see what to do about it.


qqnorm( fit2l, id = .05 )
```


F36
F41
F54
F32
M46
M37
M29
M52
M43
M43
F48
F41
M47
Quantiles of standard normal
3
2
1
0
-1
-2
-3
-2
0
2
Standardized residuals

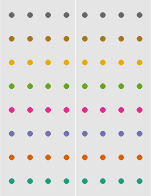
```
qqnorm( fit2l, ~ resid(.) | drug, id = .05 )
```

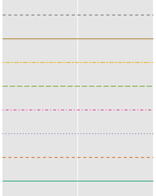

Typical
Atypical
Clozapine
Quantiles of standard normal
Residuals
3
2
1
0
-1
-2
-3
-10
-5
0
5
10
F32
M46
M37
M24
M43
M43
F41
F36
F41
F54
M29
F48
M47

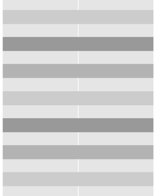
```
# We note 'M47', 'F36', 'F41' as suspicious cases

xyplot( neg ~ year | id, dd, groups = drug, auto.key = T)   # not clear for lect
```

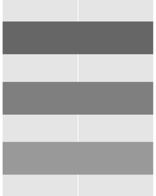

Atypical ●
Clozapine ●
Typical ●
F45
F54
M51
F55
M53
M47
M39
M38
F48
M49
M42
M52
M50
F27
M40
M31
M33
M34
M46
M43
M44
M29
F41
M26
F23
M30
M20
M35
M28
M13
M15
M16
F24
F32
M17
M19
M37
M7
M6
F10
M22
M14
M8
F25
M12
M1
M5
M3
F2
F4
M21
F11
F36
35
30
25
20
15
10
1
2
3
4
5
6
neg
year

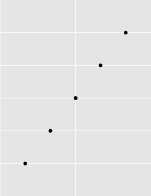
```
show.settings()
```

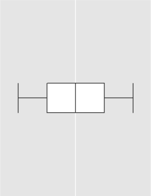

superpose.symbol

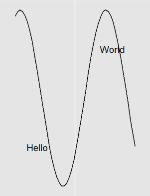

superpose.line


strip.background

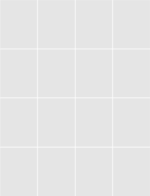

strip.shingle

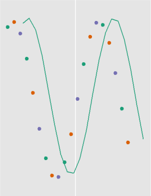

dot.[symbol, line]

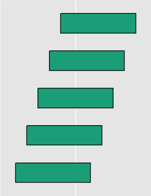

box.[dot, rectangle, umbrella]

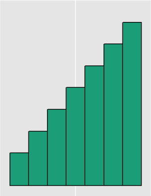


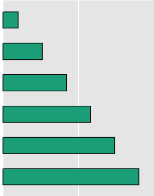
add.[line, text]

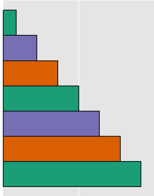

reference.line


plot.[symbol, line]


plot.shingle[plot.polygon]

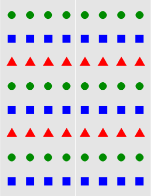

histogram[plot.polygon]


barchart[plot.polygon]

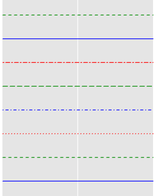

superpose.polygon


regions

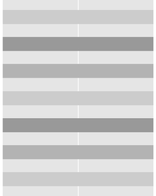
```
gd( pch = 15:17, col = c('blue','green4','red'))
show.settings()
```



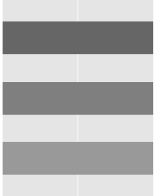
superpose.symbol



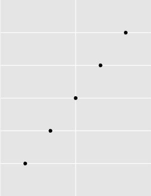
superpose.line



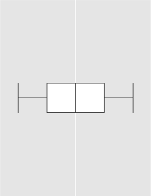
strip.background



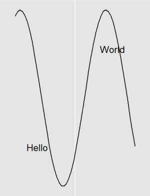
strip.shingle



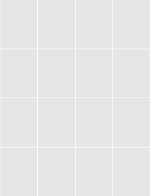
dot.[symbol, line]



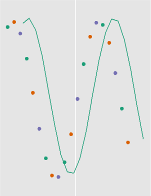
box.[dot, rectangle, umbrella]



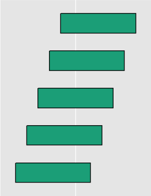
add.[line, text]



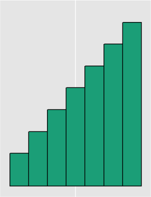
reference.line



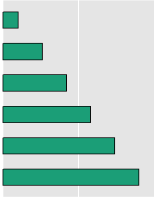
plot.[symbol, line]



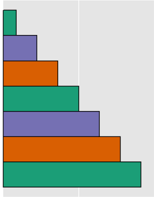
plot.shingle[plot.polygon]



histogram[plot.polygon]



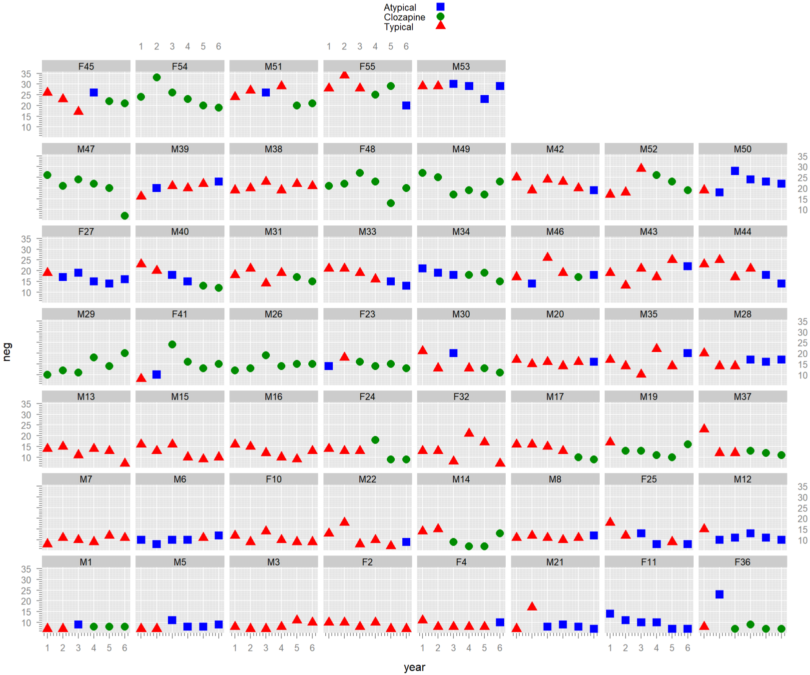
barchart[plot.polygon]



superpose.polygon

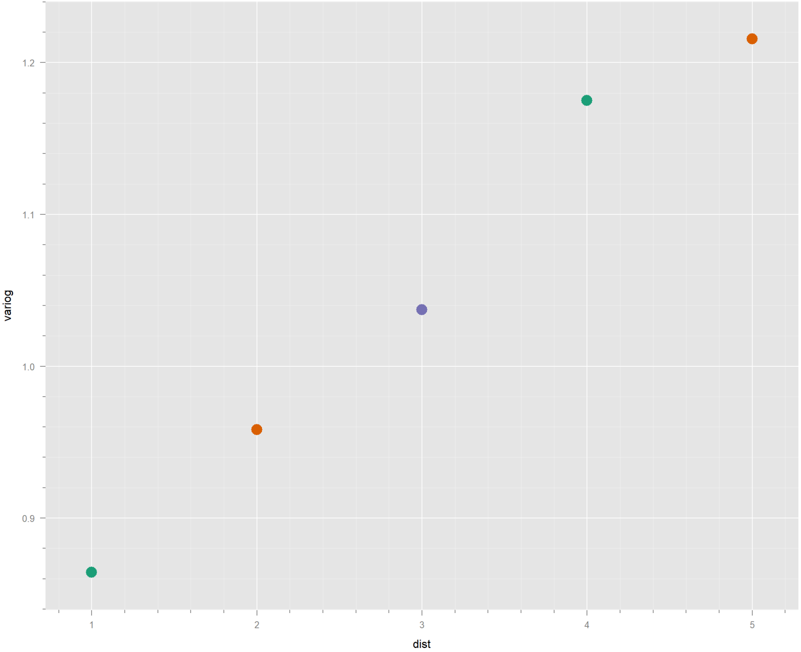
regions

```
xyplot( neg ~ year | id, dd, groups = drug, auto.key = T) # look for M47, F36 an
```


Atypical
Clozapine
Typical
F45
F54
M51
F55
M53
M47
M39
M38
F48
M49
M42
M52
M50
F27
M40
M31
M33
M34
M46
M43
M44
M29
F41
M26
F23
M30
M20
M35
M28
M13
M15
M16
F24
F32
M17
M19
M37
M7
M6
F10
M22
M14
M8
F25
M12
M1
M5
M3
F2
F4
M21
F11
F36
neg
35
30
25
20
15
10
1
2
3
4
5
6
year

```
#
#  Variogram: diagnostics for autocorrelation
#  New level 1 diagnostic for longitudinal data
#

vv <- Variogram( fit2l , form = ~ year | id, maxdist = .7)
vv         # variance of differences between pairs as a function of distance in

|        variog dist n.pairs
|   1 0.8641087    1     265
|   2 0.9580987    2     212
|   3 1.0372402    3     159
|   4 1.1749621    4     106
|   5 1.2156057    5      53

str(vv)

|   Classes 'Variogram' and 'data.frame':   5 obs. of  3 variables:
|    $ variog : num  0.864 0.958 1.037 1.175 1.216
|    $ dist   : num  1 2 3 4 5
|    $ n.pairs: int  265 212 159 106 53
|    - attr(*, "collapse")= logi TRUE
```

```
# plot(vv) # produceds an error
xyplot(variog ~ dist, vv, pch = 16, cex =2)
```


1.2
1.1
1.0
0.9
variog
1
2
3
4
5
dist

```
# Shows that differences between pairs of residuals that are close have smaller
# variance than between those that are far apart

#
#  Level 2 diagnostics
#

ranef(fit2l)   # Level 2 residuals BLUPS for u_is
```

```
|        (Intercept)
|    M1   -7.8659136
|    M5   -6.4547653
|    M3   -5.2322173
|    F2   -5.0770287
|    F4   -5.1886799
|    M21  -5.5236336
|    F11  -5.5917474
|    F36  -6.2753069
|    M7   -3.6803311
|    M6   -5.0145303
|    F10  -3.3699539
|    M22  -3.3264165
```

```
|    M14  -5.3877126
|    M8   -3.0160392
|    F25  -3.3945303
|    M12  -3.6178327
|    M13  -1.6628790
|    M15  -1.6628790
|    M16  -1.5076904
|    F24  -3.0986038
|    F32  -0.8869359
|    M17  -2.0510039
|    M19  -3.6419172
|    M37  -2.0122834
|    M29  -3.4480081
|    F41  -2.3955914
|    M26  -2.9824423
|    F23  -1.7748369
|    M30  -0.4555803
|    M20   1.1740535
|    M35   1.6396194
|    M28   1.2611283
|    F27   1.0378258
```

```
|    M40   0.8294660
|    M31   1.8287116
|    M33   2.6142885
|    M34   1.3772898
|    M46   2.9633862
|    M43   4.7433918
|    M44   4.6317405
|    M47   1.9835936
|    M39   5.2524950
|    M38   6.0965519
|    F48   2.9147253
|    M49   3.2251025
|    M42   6.7608438
|    M52   5.5919589
|    M50   6.3142389
|    F45   6.3727189
|    F54   5.8633090
|    M51   8.2349824
|    F55  10.8731889
|    M53  12.0126804
```

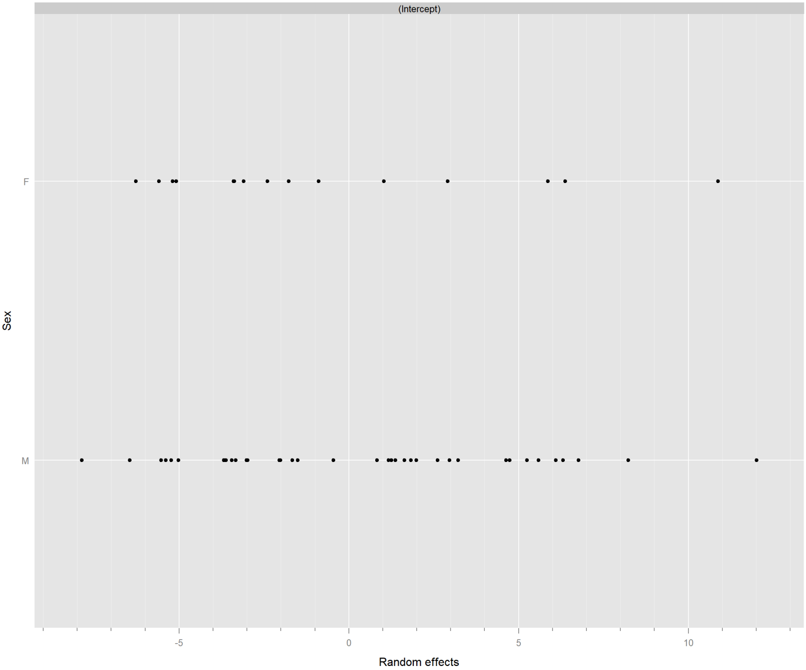
```
class(ranef(fit2l))
```

```
|   [1] "ranef.lme"  "data.frame"
```

```
methods(class = 'ranef.lme')
```

```
|   [1] plot  print
|   see '?methods' for accessing help and source code
```

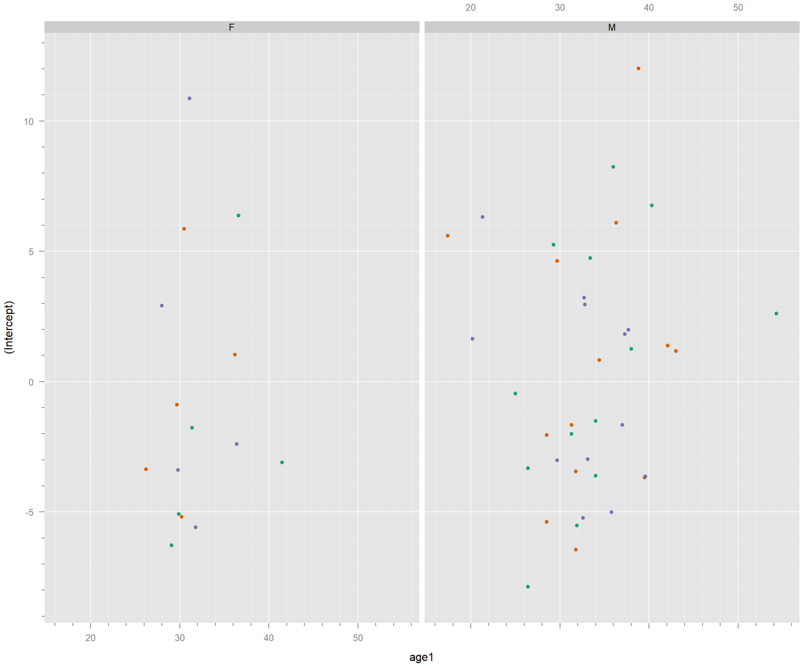
```
plot( ranef( fit2l, aug = T ), form =  ~ Sex)
```


(Intercept)
Sex
F
M
-5
0
5
10
Random effects

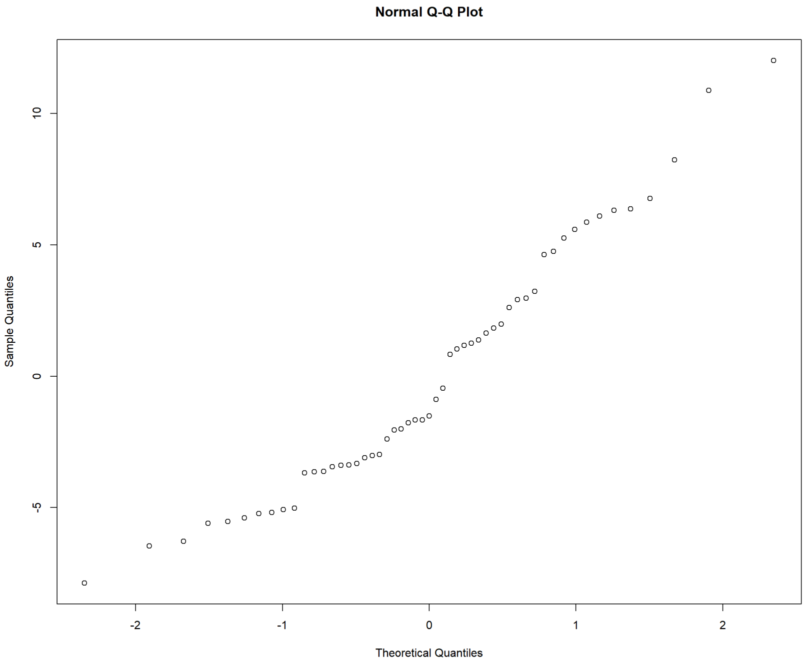
```
# note ranef( fit2l, aug = T) has a ’bug’ and doesn’t work if there’s a matrix i

# To plot BLUPS
RE <- cbind( ranef( fit2l), up( dd, ~ id))
head( RE )
```

```
|       (Intercept) age1 yrsill1 status Sex Subj  id
|   M1    -7.865914 26.4       8 Single   M   M1  M1
|   M5    -6.454765 31.8      13 Single   M   M5  M5
|   M3    -5.232217 32.6      14 Single   M   M3  M3
|   F2    -5.077029 29.9      10 Single   F   F2  F2
|   F4    -5.188680 30.2       8 Single   F   F4  F4
|   M21   -5.523634 31.9      12 Single   M  M21 M21
```

```
xyplot( ‘(Intercept)‘ ~ age1 | Sex , RE)
```


F
M
(Intercept)
10
5
0
-5
20
30
40
50
age1

```
qqnorm( RE[[1]])
```


Normal Q-Q Plot
Sample Quantiles
10
5
0
-5
-2
-1
0
1
2
Theoretical Quantiles

```
#
# Acting on diagnostics
# Should we drop some observations
#

fit2l.d <- update( fit2l, data = subset(dd, !(id %in% c("M47","F36","F41")) ))

# or

fit2l.d <- update( fit2l, subset = !(id %in% c("M47","F36","F41")) )
summary (fit2l.d)
```

```
|   Linear mixed-effects model fit by REML
|    Data: dd
|     Subset: !(id %in% c("M47", "F36", "F41"))
|          AIC      BIC    logLik
|     1669.854 1699.323 -826.9271
|
|   Random effects:
|    Formula: ~1 | id
|           (Intercept) Residual
|   StdDev:    5.064185 3.075854
```

```
|
|   Fixed effects: neg ~ drug + cvar(drug, id) + year
|                              Value Std.Error  DF   t-value p-value
|   (Intercept)             17.337154 2.1910795 247  7.912608  0.0000
|   drugClozapine           -1.402456 0.8165726 247 -1.717491  0.0871
|   drugTypical              0.358380 0.6441458 247  0.556365  0.5785
|   cvar(drug, id)Clozapine  3.708741 2.9771527  47  1.245734  0.2190
|   cvar(drug, id)Typical   -2.286751 2.9236816  47 -0.782148  0.4381
|   year                    -0.375001 0.1289879 247 -2.907255  0.0040
|    Correlation:
|                           (Intr) drgClz drgTyp c(,i)C c(,i)T
|   drugClozapine            0.039
|   drugTypical             -0.090  0.406
|   cvar(drug, id)Clozapine -0.738 -0.274 -0.111
|   cvar(drug, id)Typical   -0.844 -0.089 -0.220  0.629
|   year                    -0.206 -0.189  0.436  0.052 -0.096
|
|   Standardized Within-Group Residuals:
|          Min          Q1         Med          Q3         Max
|   -2.36776534 -0.63680435 -0.09251977  0.55370236  2.79884975
|
```

```
|   Number of Observations: 300
|   Number of Groups: 50

#
# Note: a problem with this approach: a cluster or observation could have high
# influence even though it does not have a large residual. So we could miss
# some influential points.
#
# There was a package 'influence.ME' that was being developed to produce
# influence diagnostics for 'lme' object but the version eventually released
# on CRAN only work for 'lmer' objects.
#
#
#
# EXERCISE:
#     Compare results with fit2l.d and fit2l. Any substantial differences?
#
# In the following analysis, we keep the original data but this does not
# imply that this is the best course. If some outliers prove to have
# uncorrectable measurement errors, or if they are not in scope (some other
# diagnosis) then it would be appropriate to drop them.
#
```

```
#
#
#  Incorporation of possible autocorrelation
#

#
#  Add a correlation structure to the R side.
#  Most common:
#      corAR1:    autoregressive of order 1 for evenly spaced data
#      corCAR1:   continuous autoregressive of order 1 for
#                 unevenly spaced data
#      corARMA:   autoregressive moving average of variable order
#      -- other classes are mainly for spatial correlation
#      -- you can write your own but it's challenging
#  See: ?corClasses for a complete list
#

# Auto-regressive process of order 1

fit2lc <- update( fit2l, correlation = corAR1( form = ~ year | id))
summary( fit2lc)
```

```
|   Linear mixed-effects model fit by REML
|    Data: dd
|          AIC      BIC    logLik
|     1806.119 1839.806 -894.0595
|
|   Random effects:
|    Formula: ~1 | id
|           (Intercept) Residual
|   StdDev:    4.863878 3.477444
|
|   Correlation Structure: AR(1)
|    Formula: ~year | id
|    Parameter estimate(s):
|         Phi
|   0.2045159
|   Fixed effects: neg ~ drug + cvar(drug, id) + year
|                               Value Std.Error  DF   t-value p-value
|   (Intercept)             17.551586 2.1753872 262  8.068258  0.0000
|   drugClozapine           -1.198927 0.8940467 262 -1.341011  0.1811
|   drugTypical             -0.241801 0.6875520 262 -0.351684  0.7254
|   cvar(drug, id)Clozapine  3.164622 2.8743291  50  1.100995  0.2762
```

```
|   cvar(drug, id)Typical   -1.494575 2.8857604  50 -0.517914  0.6068
|   year                    -0.485736 0.1503674 262 -3.230327  0.0014
|    Correlation:
|                           (Intr) drgClz drgTyp c(,i)C c(,i)T
|   drugClozapine            0.050
|   drugTypical             -0.102  0.375
|   cvar(drug, id)Clozapine -0.758 -0.309 -0.115
|   cvar(drug, id)Typical   -0.831 -0.088 -0.233  0.654
|   year                    -0.244 -0.211  0.403  0.066 -0.094
|
|   Standardized Within-Group Residuals:
|          Min         Q1        Med         Q3        Max
|   -3.2515034 -0.6100687 -0.1129732  0.5311779  3.0912181
|
|   Number of Observations: 318
|   Number of Groups: 53
```

```
# do we need the autocorrelation?

intervals( fit2lc )    # look at CI for Phi (correlation)
```

```
|   Approximate 95% confidence intervals
```

```
|
|    Fixed effects:
|                                 lower       est.      upper
|   (Intercept)             13.2681190 17.5515864 21.8350537
|   drugClozapine           -2.9593580 -1.1989267  0.5615045
|   drugTypical             -1.5956322 -0.2418011  1.1120299
|   cvar(drug, id)Clozapine -2.6086379  3.1646220  8.9378819
|   cvar(drug, id)Typical   -7.2907957 -1.4945753  4.3016451
|   year                    -0.7818181 -0.4857358 -0.1896535
|   attr(,"label")
|   [1] "Fixed effects:"
|
|    Random Effects:
|     Level: id
|                      lower     est.    upper
|   sd((Intercept)) 3.897772 4.863878 6.069445
|
|    Correlation structure:
|            lower      est.     upper
|   Phi 0.03372634 0.2045159 0.3636998
|   attr(,"label")
```

```
|   [1] "Correlation structure:"
|
|    Within-group standard error:
|      lower     est.    upper
|   3.125207 3.477444 3.869381

# or

anova( fit2l, fit2lc ) # this test can be ok because there is no boundary at 0 f

|          Model df      AIC      BIC    logLik   Test  L.Ratio p-value
|   fit2l      1  8 1810.390 1840.334 -897.1952
|   fit2lc     2  9 1806.119 1839.806 -894.0595 1 vs 2 6.271422  0.0123

# but there is when using corCAR1.
# plot( simulate( fit2l, nsim = 1000, m2 = fit2lc))  # out of luck with fancier
wald( fit2l )

|    numDF denDF  F.value p.value
|        6    50 84.67485 <.00001
|
|   Coefficients               Estimate Std.Error  DF   t-value p-value
|     (Intercept)             17.511006  2.174227 262  8.053899 <.00001
```

```
|     drugClozapine                -1.153198  0.836298 262 -1.378931 0.16909
|     drugTypical                  -0.117037  0.678516 262 -0.172489 0.86319
|     cvar(drug, id)Clozapine       3.184237  2.872886  50  1.108376 0.27300
|     cvar(drug, id)Typical        -1.602418  2.902672  50 -0.552049 0.58337
|     year                         -0.477814  0.135917 262 -3.515489 0.00052
|
|   Coefficients                   Lower 0.95 Upper 0.95
|     (Intercept)                   13.229823  21.792190
|     drugClozapine                 -2.799919   0.493524
|     drugTypical                   -1.453074   1.219001
|     cvar(drug, id)Clozapine       -2.586125   8.954598
|     cvar(drug, id)Typical         -7.432608   4.227771
|     year                          -0.745442  -0.210186
```

```r
wald( fit2lc )
```

```
|    numDF denDF  F.value p.value
|        6    50 84.33179 <.00001
|
|   Coefficients                    Estimate Std.Error  DF   t-value p-value
|     (Intercept)                  17.551586  2.175387 262  8.068258 <.00001
|     drugClozapine                -1.198927  0.894047 262 -1.341011 0.18108
```

```
|      drugTypical               -0.241801  0.687552 262 -0.351684 0.72536
|      cvar(drug, id)Clozapine    3.164622  2.874329  50  1.100995 0.27617
|      cvar(drug, id)Typical     -1.494575  2.885760  50 -0.517914 0.60680
|      year                      -0.485736  0.150367 262 -3.230327 0.00139
|
|    Coefficients                Lower 0.95 Upper 0.95
|      (Intercept)                13.268119  21.835054
|      drugClozapine              -2.959358   0.561505
|      drugTypical                -1.595632   1.112030
|      cvar(drug, id)Clozapine    -2.608638   8.937882
|      cvar(drug, id)Typical      -7.290796   4.301645
|      year                       -0.781818  -0.189654
```

```
Ld
```

```
|                          [,1] [,2] [,3] [,4] [,5] [,6]
|    Clozapine - Atypical     0    1    0    0    0    0
|    Typical - Atypical       0    0    1    0    0    0
|    Typical - Clozapine      0   -1    1    0    0    0
```

```
wald( fit2l, Ld )
```

```
|      numDF denDF  F.value p.value
```

```
|    1     2   262 1.034312 0.35692
|
|                            Estimate Std.Error   DF   t-value p-value
|     Clozapine - Atypical -1.153198  0.836298 262 -1.378931 0.16909
|     Typical - Atypical   -0.117037  0.678516 262 -0.172489 0.86319
|     Typical - Clozapine   1.036161  0.842019 262  1.230567 0.21959
|
|                           Lower 0.95 Upper 0.95
|     Clozapine - Atypical  -2.799919   0.493524
|     Typical - Atypical    -1.453074   1.219001
|     Typical - Clozapine   -0.621825   2.694147
```

```
wald( fit2lc, Ld )
```

```
|     numDF denDF   F.value p.value
|    1     2   262 0.9123941 0.40283
|
|                            Estimate Std.Error   DF   t-value p-value
|     Clozapine - Atypical -1.198927  0.894047 262 -1.341011 0.18108
|     Typical - Atypical   -0.241801  0.687552 262 -0.351684 0.72536
|     Typical - Clozapine   0.957126  0.900737 262  1.062602 0.28894
|
```

```
|                          Lower 0.95 Upper 0.95
|     Clozapine - Atypical  -2.959358   0.561505
|     Typical - Atypical    -1.595632   1.112030
|     Typical - Clozapine   -0.816480   2.730731

# QUESTION: When would you expect results to be affected by
#        including AR in the model?
#
#    Note: AR (with positive autocorrelation) implies we expect obs.
#    close in time to be closer than expected under the assumption
#    of independence and observations that are far in time
#    to be farther.
#
#    Therefore a treatment difference between
#    adjoining times gets more weight
#    than one between distant times.
#
#    That explains why including autocorrelation can change estimated
#    differences and p-values.
#
#
#  EXERCISE:
```

```
#    Look at diagnostics for models predicting 'gen' instead of 'neg'
#
#

#
# Heteroscedasticiy revisited
#

fitg <- lme( gen ~ drug + cvar(drug,id) , dd, random = ~ 1 | id)
summary( fitg )
```

```
|   Linear mixed-effects model fit by REML
|    Data: dd
|          AIC      BIC    logLik
|     2161.396 2187.62 -1073.698
|
|   Random effects:
|    Formula: ~1 | id
|           (Intercept) Residual
|   StdDev:    5.771655 6.277779
|
|   Fixed effects: gen ~ drug + cvar(drug, id)
```

```
|                               Value Std.Error  DF   t-value p-value
|   (Intercept)             30.074931  2.589763 263 11.613004  0.0000
|   drugClozapine           -2.900413  1.542192 263 -1.880709  0.0611
|   drugTypical              4.278485  1.159434 263  3.690148  0.0003
|   cvar(drug, id)Clozapine  9.931334  3.692515  50  2.689585  0.0097
|   cvar(drug, id)Typical   -3.457844  3.634982  50 -0.951268  0.3460
|    Correlation:
|                           (Intr) drgClz drgTyp c(,i)C
|   drugClozapine            0.000
|   drugTypical              0.000  0.552
|   cvar(drug, id)Clozapine -0.732 -0.418 -0.231
|   cvar(drug, id)Typical   -0.858 -0.176 -0.319  0.658
|
|   Standardized Within-Group Residuals:
|           Min          Q1         Med          Q3         Max
|   -2.18006804 -0.62712129 -0.08655213  0.52664934  4.25622647
|
|   Number of Observations: 318
|   Number of Groups: 53
fitgl <- lme( gen ~ drug + cvar(drug,id) + year, dd, random = ~ 1 | id)
summary( fitgl )
```

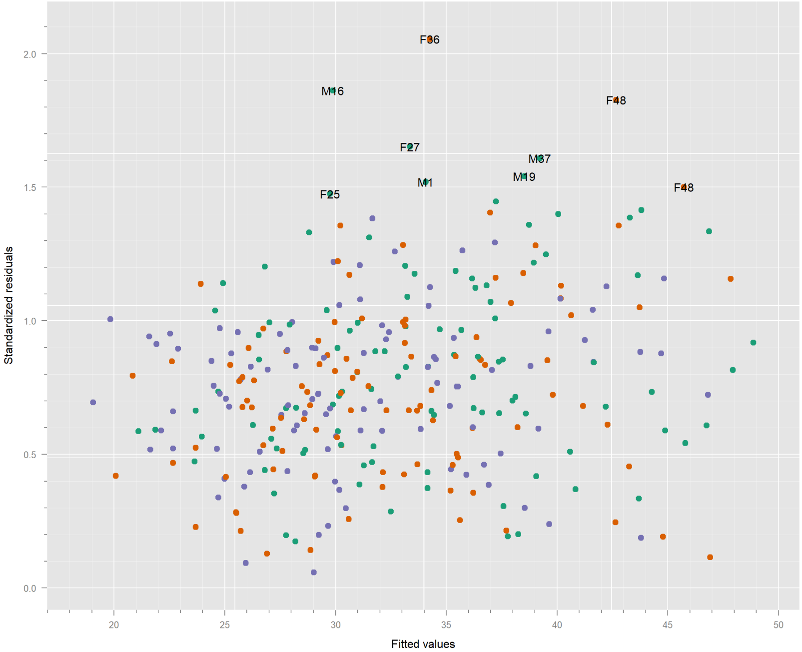
```
|   Linear mixed-effects model fit by REML
|    Data: dd
|         AIC      BIC   logLik
|     2148.02 2177.964 -1066.01
|
|   Random effects:
|    Formula: ~1 | id
|           (Intercept) Residual
|   StdDev:    5.803759 6.097606
|
|   Fixed effects: gen ~ drug + cvar(drug, id) + year
|                              Value Std.Error  DF   t-value p-value
|   (Intercept)             33.64712  2.732709 262 12.312733  0.0000
|   drugClozapine           -1.55705  1.533425 262 -1.015409  0.3108
|   drugTypical              2.11299  1.244117 262  1.698387  0.0906
|   cvar(drug, id)Clozapine  8.58797  3.688862  50  2.328082  0.0240
|   cvar(drug, id)Typical   -1.29235  3.662873  50 -0.352825  0.7257
|   year                    -1.02063  0.249215 262 -4.095356  0.0001
|    Correlation:
|                           (Intr) drgClz drgTyp c(,i)C c(,i)T
|   drugClozapine            0.068
```

```
|   drugTypical             -0.136  0.397
|   cvar(drug, id)Clozapine -0.723 -0.416 -0.165
|   cvar(drug, id)Typical   -0.761 -0.135 -0.340  0.636
|   year                    -0.319 -0.214  0.425  0.089 -0.144
|
|   Standardized Within-Group Residuals:
|          Min         Q1        Med         Q3        Max
|   -2.3078278 -0.5731915 -0.1464905  0.5223173  4.2237955
|
|   Number of Observations: 318
|   Number of Groups: 53
```

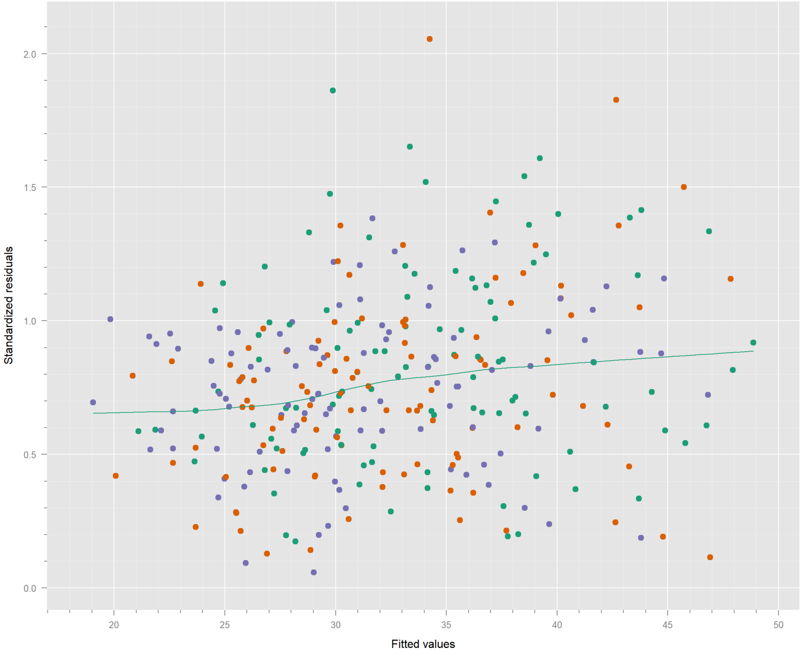
```
wald( fitgl, Ld)
```

```
|     numDF denDF  F.value p.value
|   1     2   262 3.137857 0.04501
|
|                           Estimate Std.Error  DF   t-value p-value
|     Clozapine - Atypical -1.557054  1.533425 262 -1.015409 0.31085
|     Typical - Atypical    2.112993  1.244117 262  1.698387 0.09062
|     Typical - Clozapine   3.670046  1.543915 262  2.377103 0.01817
|
```

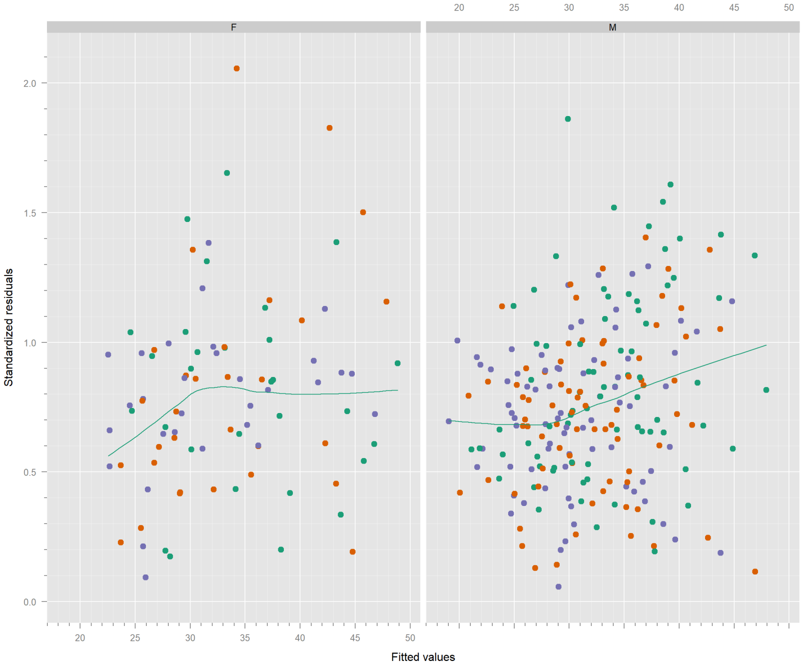
```
|                               Lower 0.95 Upper 0.95
|     Clozapine - Atypical  -4.576460   1.462353
|     Typical - Atypical    -0.336749   4.562734
|     Typical - Clozapine    0.629985   6.710108

# ... many diagnostics later ....
# Note: I believe there is an error in documentation and the default
# for resid is type = 'r' for 'raw' or 'response'. We prefer the
# standardized, 'pearson' residuals here.

plot( fitgl, sqrt( abs( resid(., type = 'p'))) ~ fitted(.), id = .03)
```


F36
M16
F48
F27
M37
M19
M1
F25
F48
2.0
1.5
1.0
0.5
0.0
Standardized residuals
20
25
30
35
40
45
50
Fitted values

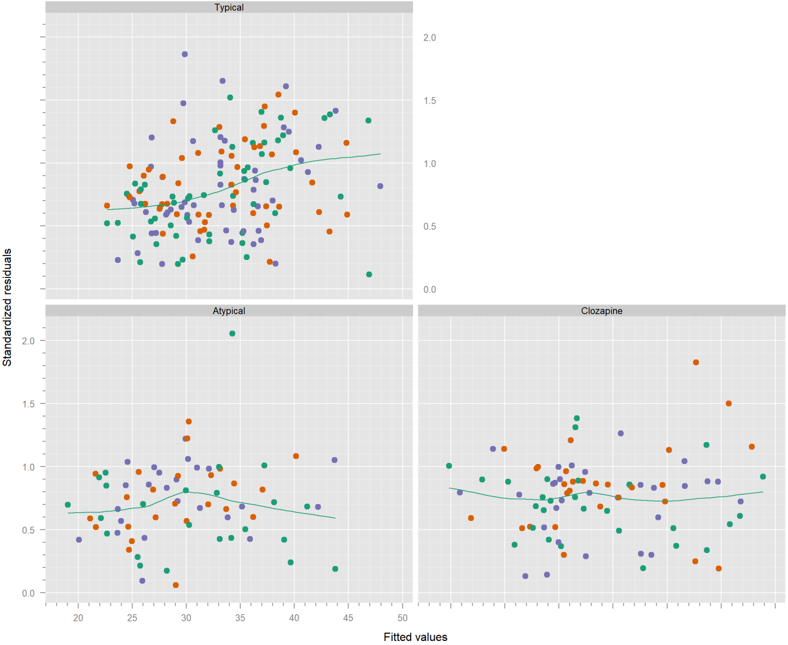
```
plot( fitgl, sqrt( abs( resid(., type = 'p'))) ~ fitted(.), id = .03,
      panel = function(x, y, ...) {
        panel.xyplot( x, y, ...)
        panel.loess( x, y,...)
      })
```


Standardized residuals
0.0
0.5
1.0
1.5
2.0
20
25
30
35
40
45
50
Fitted values

```
plot( fitgl, sqrt( abs( resid(., type = 'p'))) ~ fitted(.) | Sex, id = .03,
      panel = function(x, y, ...) {
        panel.xyplot( x, y, ...)
        panel.loess( x, y,...)
      })
```


F
M
Standardized residuals
Fitted values
0.0
0.5
1.0
1.5
2.0
20
25
30
35
40
45
50

```
plot( fitgl, sqrt( abs( resid(., type = 'p'))) ~ fitted(.) | drug, id = .03,
      panel = function(x, y, ...) {
        panel.xyplot( x, y, ...)
        panel.loess( x, y,...)
      })
```


Typical
Atypical
Clozapine
Standardized residuals
Fitted values
0.0
0.5
1.0
1.5
2.0
20
25
30
35
40
45
50

```
#
# Perhaps: increased variability with increase in predicted value
#    In practice, I wouldn't be too disturbed by this plot but
#    for pedagogical purposes, let's see what we could do to address this.
#

#
# Accounting for heteroskedasticity
#


#
#  We assume that the SD of residuals changes with the fitted value (variance co
#
#  Common assumptions are that:
#
#     1) variance is proportional to an unknown power of the variance covariate
#
#         or
#
#     2) a unknown constant plus an unknown power of the covariate
```

```
#

# To see the full set of methods, available (you can also create your own):

?varClasses

|   starting httpd help server ... done

# Here we illustrate varConstPower

fitglh <- update( fitgl, weights = varConstPower( form =  ~fitted(.)| drug) )

summary(fitglh)

|   Linear mixed-effects model fit by REML
|    Data: dd
|          AIC      BIC   logLik
|     2131.661 2184.063 -1051.83
|
|   Random effects:
|    Formula: ~1 | id
|           (Intercept)   Residual
|   StdDev:    5.813634 0.03365691
```

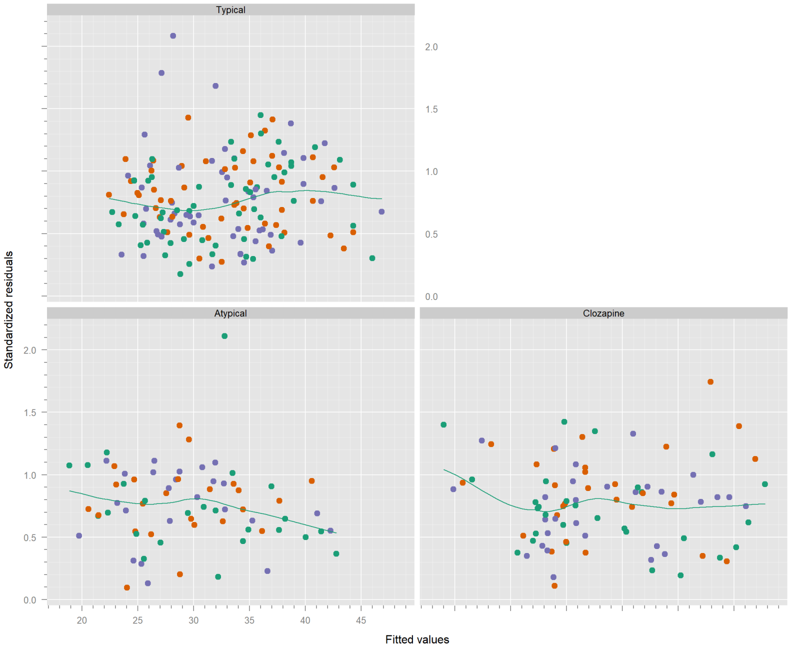
```
|
|   Variance function:
|    Structure: Constant plus power of variance covariate, different strata
|    Formula: ~fitted(.) | drug
|    Parameter estimates:
|             Typical    Atypical Clozapine
|   const 0.000895613 0.001125126 58.502605
|   power 1.513026811 1.489908517  1.310149
|   Fixed effects: gen ~ drug + cvar(drug, id) + year
|                                Value Std.Error  DF   t-value p-value
|   (Intercept)               32.80306  2.662644 262 12.319732  0.0000
|   drugClozapine             -2.13808  1.508406 262 -1.417441  0.1575
|   drugTypical                2.37355  1.142420 262  2.077649  0.0387
|   cvar(drug, id)Clozapine  9.14154  3.712537  50  2.462343  0.0173
|   cvar(drug, id)Typical   -1.66796  3.581094  50 -0.465769  0.6434
|   year                      -0.85033  0.215380 262 -3.948066  0.0001
|    Correlation:
|                             (Intr) drgClz drgTyp c(,i)C c(,i)T
|   drugClozapine              0.064
|   drugTypical               -0.091  0.349
|   cvar(drug, id)Clozapine -0.709 -0.457 -0.163
```

```
|   cvar(drug, id)Typical   -0.785 -0.128 -0.328  0.625
|   year                    -0.299 -0.174  0.420  0.081 -0.132
|
|   Standardized Within-Group Residuals:
|           Min          Q1         Med          Q3         Max
|   -2.10072756 -0.55449512 -0.09397095  0.58046097  4.45778160
|
|   Number of Observations: 318
|   Number of Groups: 53
```

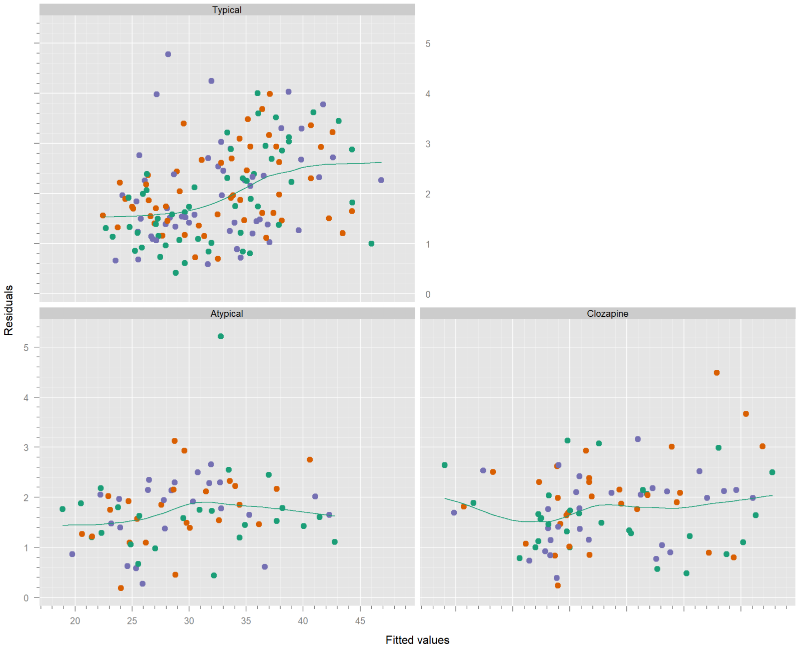
```
anova( fitgl, fitglh )
```

```
|           Model df      AIC      BIC   logLik   Test L.Ratio p-value
|   fitgl       1  8 2148.020 2177.964 -1066.01
|   fitglh      2 14 2131.661 2184.063 -1051.83 1 vs 2 28.3594   1e-04
```

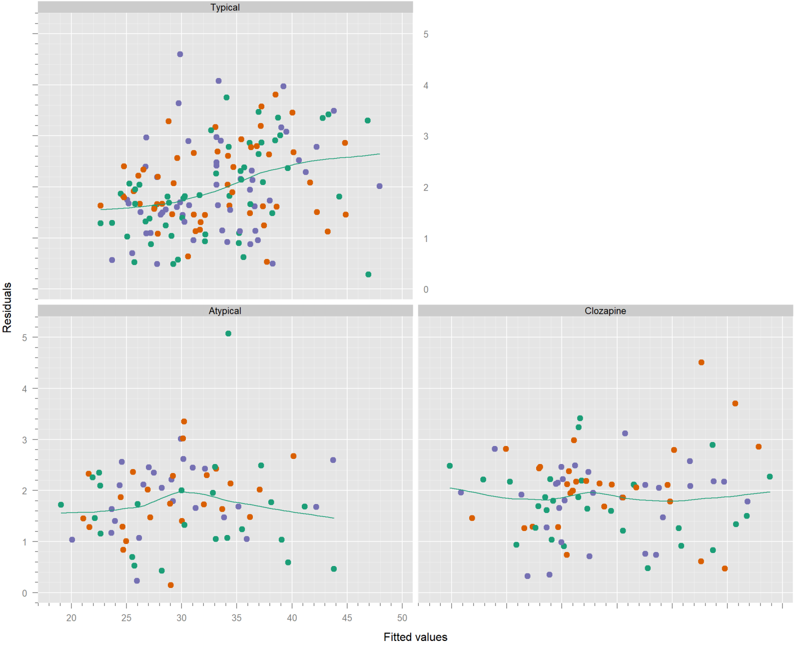
```
plot( fitglh, sqrt( abs( resid(.,type = 'p'))) ~ fitted(.) | drug, id = .03,
      panel = function(x, y, ...) {
        panel.xyplot( x, y, ...)
        panel.loess( x, y,...)
      })
```


Typical
Atypical
Clozapine
Standardized residuals
0.0
0.5
1.0
1.5
2.0
Fitted values
20
25
30
35
40
45

```
# note that 'pearson residuals' are plotted so that
# high variance residuals will be shrunk.
# with raw residuals we expect heteroskedasticity to look
# even worse because the high variance observations have
# less influence on the fit
# raw residuals:
plot( fitglh, sqrt( abs( resid(., type = 'r'))) ~ fitted(.) | drug, id = .03,
      panel = function(x, y, ...) {
        panel.xyplot( x, y, ...)
        panel.loess( x, y,...)
      })
```


Typical
Atypical
Clozapine
Residuals
Fitted values
0
1
2
3
4
5
20
25
30
35
40
45

```
plot( fitgl, sqrt( abs( resid(., type = ’r’))) ~ fitted(.) | drug, id = .03,
      panel = function(x, y, ...) {
        panel.xyplot( x, y, ...)
        panel.loess( x, y,...)
      })
```

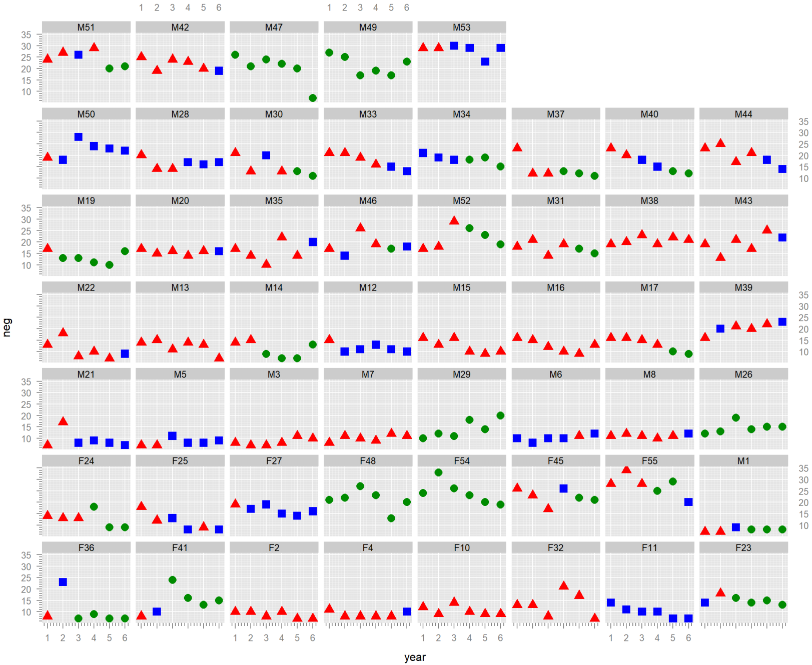

Typical
Atypical
Clozapine
Residuals
Fitted values
0
1
2
3
4
5
20
25
30
35
40
45
50

```
wald( fitgl, Ld)

|      numDF denDF  F.value p.value
|   1      2   262 3.137857 0.04501
|
|                              Estimate Std.Error  DF   t-value p-value
|      Clozapine - Atypical -1.557054  1.533425 262 -1.015409 0.31085
|      Typical - Atypical    2.112993  1.244117 262  1.698387 0.09062
|      Typical - Clozapine   3.670046  1.543915 262  2.377103 0.01817
|
|                             Lower 0.95 Upper 0.95
|      Clozapine - Atypical  -4.576460   1.462353
|      Typical - Atypical    -0.336749   4.562734
|      Typical - Clozapine    0.629985   6.710108
wald( fitglh, Ld)

|      numDF denDF  F.value p.value
|   1      2   262 4.774854 0.00919
|
|                              Estimate Std.Error  DF   t-value p-value
|      Clozapine - Atypical -2.138077  1.508406 262 -1.417441 0.15754
|      Typical - Atypical    2.373549  1.142420 262  2.077649 0.03872
```

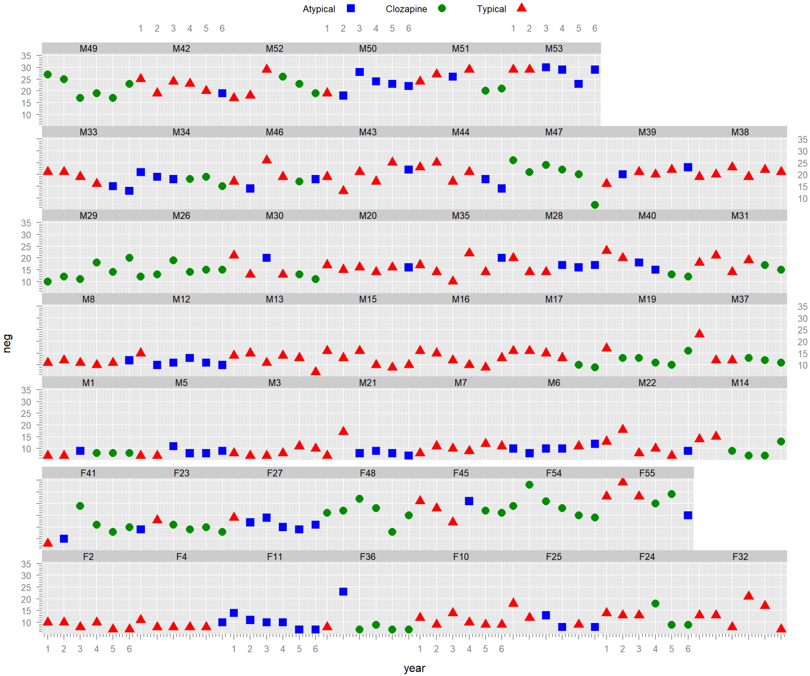
```
|     Typical - Clozapine   4.511625  1.541482 262  2.926810 0.00373
|
|                            Lower 0.95 Upper 0.95
|     Clozapine - Atypical  -5.108219   0.832065
|     Typical - Atypical     0.124055   4.623042
|     Typical - Clozapine    1.476355   7.546896

#
# Note that the impact of accounting for heteroskedasticity is not negligible.
#
# As usual, seeking higher efficiency has an impact on what we're estimating.
# Differences between drugs in patients at lower levels of 'gen' receive
# more weight than those at higher levels. The estimate has lower variance
# and is more precise but it might estimate something slightly different if
# there are differences in drug effects at different levels of severity.
# If this is an important question to address we could reformulate the model
# to attempt to take it into account although we might not have much power
# to detect such an effect.
#

# EXERCISE:
#    Refit 'fitglh' and 'fitgl' dropping a few residual outliers.
```

```
#    Retest the difference between the two models.
#    Does accounting for heteroskedastiticy still improve the fit?
#    Might it be that heteroskedasticity was just accounting for a
#        few outliers instead of capturing a general phenomenon?
#

#  EXERCISE:
#    Enlarge the RE model. How far can you go and what is the impact
#    of doing so.

#
#  Visualizing different models
#

#
# The following code was used to generate graphs for a lecture
# It shows how the different models above fit the data and
# attemps to explain how and why they differ.
#

gd( pch = 15:17, col = c('blue','green4','red'))
```

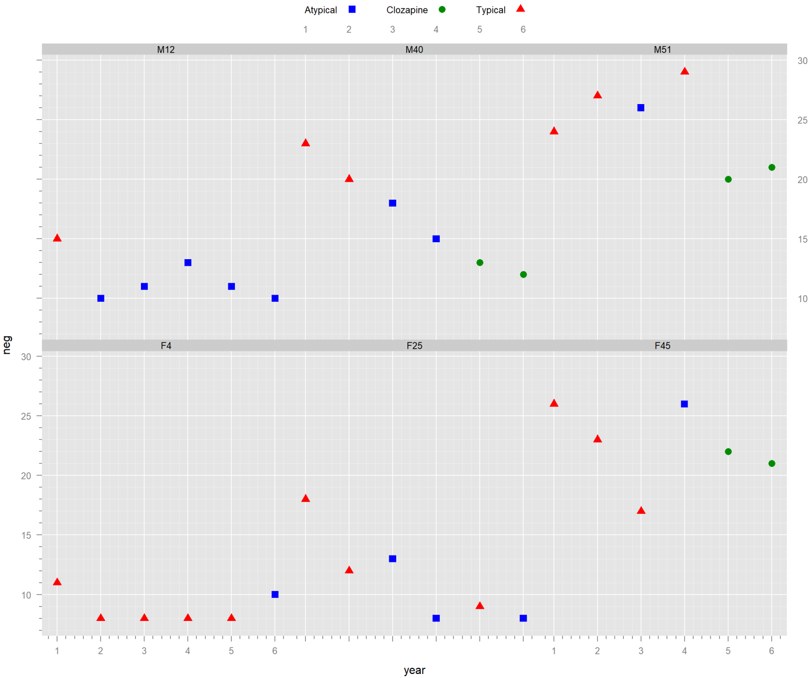
```
xyplot( neg ~ year | Subj, dd, groups = drug )
```


M51
M42
M47
M49
M53
M50
M28
M30
M33
M34
M37
M40
M44
M19
M20
M35
M46
M52
M31
M38
M43
M22
M13
M14
M12
M15
M16
M17
M39
M21
M5
M3
M7
M29
M6
M8
M26
F24
F25
F27
F48
F54
F45
F55
M1
F36
F41
F2
F4
F10
F32
F11
F23
neg
year
10
15
20
25
30
35
1
2
3
4
5
6

```
dd$id <- dd$Subj
dd$id <- reorder( dd$id, 1000*(dd$Sex == "M") + dd$neg )

gd( pch = 15:17, col = c('blue','green4','red'))
xyplot( neg ~ year | id, dd, groups = drug,
        between = list( y = c(0,.5,0,0,0,0,0)) ,
        skip = c( rep(F,15), T, rep(F,30)),
        layout = c( 8,7),
        auto.key = list( columns = 3))
```


Atypical ■
Clozapine ●
Typical ▲
M49
M42
M52
M50
M51
M53
M33
M34
M46
M43
M44
M47
M39
M38
M29
M26
M30
M20
M35
M28
M40
M31
M8
M12
M13
M15
M16
M17
M19
M37
M1
M5
M3
M21
M7
M6
M22
M14
F41
F23
F27
F48
F45
F54
F55
F2
F4
F11
F36
F10
F25
F24
F32
35
30
25
20
15
10
1 2 3 4 5 6
neg
year

```
# select a 'representative' sample of 3 from each sex

sel <- c( "F4","F25","F45","M12","M40","M51")

gd( pch = 15:17, col = c('blue','green4','red'), cex = 1.2)
xyplot( neg ~ year | id, dd, groups = drug,
        between = list( y = c(0,.5,0,0,0,0,0)) ,
        skip = c( rep(F,15), T, rep(F,30)),
        layout = c( 3,2),
        auto.key = list( columns = 3),
        subset = id %in% sel)
```


Atypical
Clozapine
Typical
1
2
3
4
5
6
M12
M40
M51
F4
F25
F45
neg
30
25
20
15
10
year

```r
fit.ols <- lm( neg ~ drug, dd )
summary( fit.ols )
```

```
|
|   Call:
|   lm(formula = neg ~ drug, data = dd)
|
|   Residuals:
|      Min     1Q Median     3Q    Max
|   -9.299 -5.233 -1.233  3.767 18.767
|
|   Coefficients:
|                 Estimate Std. Error t value Pr(>|t|)
|   (Intercept)   15.27778    0.71557  21.351   <2e-16 ***
|   drugClozapine  1.02107    0.96737   1.056    0.292
|   drugTypical   -0.04507    0.86250  -0.052    0.958
|   ---
|   Signif. codes:  0 ’***’ 0.001 ’**’ 0.01 ’*’ 0.05 ’.’ 0.1 ’ ’ 1
|
|   Residual standard error: 6.072 on 315 degrees of freedom
|   Multiple R-squared:  0.005996,  Adjusted R-squared:  -0.0003149
|   F-statistic: 0.9501 on 2 and 315 DF,  p-value: 0.3878
```

```
L <- list(
  'predicted' = cbind( 1, contrasts( dd$drug)),
  'differences' = Ldiff ( fit.ols, 'drug', ref = 'Atypical'))
L
```

```
|   $predicted
|               Clozapine Typical
|   Atypical  1         0       0
|   Clozapine 1         1       0
|   Typical   1         0       1
|
|   $differences
|                         [,1] [,2] [,3]
|   Clozapine - Atypical     0    1    0
|   Typical - Atypical       0    0    1
|   Typical - Clozapine      0   -1    1
```

```
wald( fit.ols, L)
```

```
|              numDF denDF  F.value p.value
|   predicted      3   315 694.4892 <.00001
|
|               Estimate Std.Error  DF  t-value p-value Lower 0.95 Upper 0.95
```

```
|     Atypical  15.27778  0.715570 315 21.35051 <.00001   13.86988   16.68568
|     Clozapine 16.29885  0.650966 315 25.03793 <.00001   15.01806   17.57964
|     Typical   15.23270  0.481526 315 31.63424 <.00001   14.28529   16.18012
|
|               numDF denDF   F.value p.value
|   differences     2   315 0.9501109  0.3878
|
|                           Estimate Std.Error  DF   t-value p-value
|     Clozapine - Atypical  1.021073  0.967366 315  1.055519 0.29200
|     Typical - Atypical   -0.045073  0.862500 315 -0.052259 0.95836
|     Typical - Clozapine  -1.066146  0.809706 315 -1.316707 0.18889
|
|                          Lower 0.95 Upper 0.95
|     Clozapine - Atypical  -0.882243   2.924388
|     Typical - Atypical    -1.742063   1.651917
|     Typical - Clozapine   -2.659262   0.526970
# Clozapine is worst but not significantly so

#
#  Displaying data and fitted values
#
```

```
pred <- expand.grid( year = 1:6, drug = levels( dd$drug), id = levels(dd$id))
head( pred )
```

```
|      year     drug id
|    1    1 Atypical F2
|    2    2 Atypical F2
|    3    3 Atypical F2
|    4    4 Atypical F2
|    5    5 Atypical F2
|    6    6 Atypical F2
```

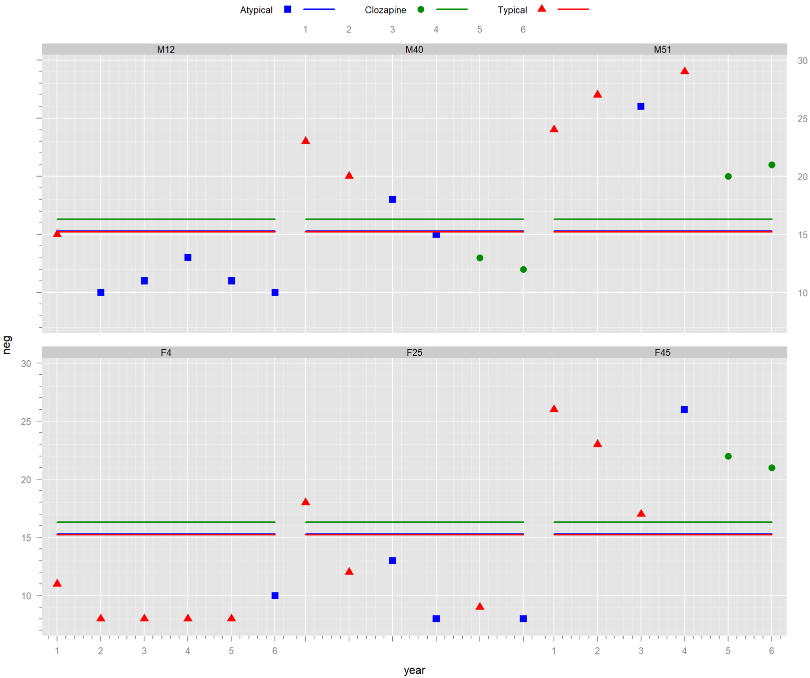
```
some( pred )
```

```
|        year       drug  id
|    38      2  Atypical F11
|    45      3 Clozapine F11
|    132     6  Atypical F32
|    336     6 Clozapine M21
|    365     5  Atypical  M6
|    392     2   Typical M22
|    449     5   Typical M12
|    469     1  Atypical M15
```

```
|   475    1 Clozapine M15
|   735    3   Typical M34
```

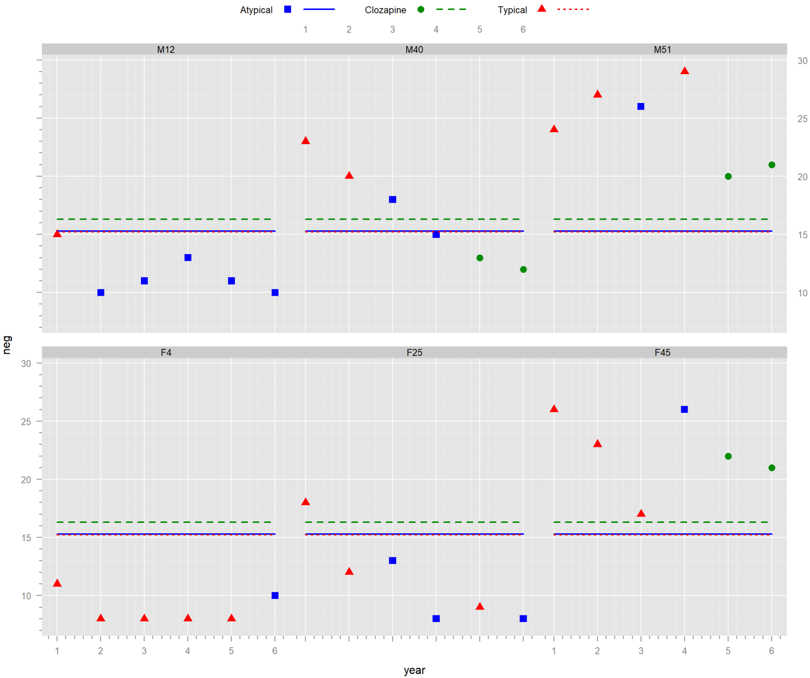
```
pred$neg <- predict( fit.ols, newdata = pred )

# Combine with data for plotting

dd$what <- factor("data")
pred$what <- factor("fit")

gd( pch = 15:17, col = c('blue','green4','red'), cex = 1.2,
    lty = c(1,1,1,1,1,1,2,2,2), lwd = 2)
xyplot( neg ~ year | id, Rbind( dd, pred),  groups = what:drug,
        panel = panel.superpose.2,
        type = c('p','p','p','l','l','l'),
        subset = id %in% sel,
        between = list( y =1 ),
        auto.key = list( text = c("Atypical","Clozapine","Typical"),
                         points = T, lines = T, columns = 3))
```

```
|    [1] "age1"    "yrsill1" "pos"     "neg"     "gen"     "total"   "year"
|    [8] "drug"    "status"  "Sex"     "Subj"    "id"      "what"
```


Atypical
Clozapine
Typical
M12
M40
M51
F4
F25
F45
neg
year
1
2
3
4
5
6
10
15
20
25
30

```
# overplotting problem
#
# make later lines less dense:

gd( pch = 15:17, col = c('blue','green4','red'), cex = 1.2,
    lty = c(1,2,3,1,2,3,1,2,3),lwd = 2)
xyplot( neg ~ year | id, Rbind(dd, pred),  groups = what:drug,
        panel = panel.superpose.2,
        type = c('p','p','p','l','l','l'),
        subset = id %in% sel,
        between = list( y =1 ),
        auto.key = list( text = c("Atypical","Clozapine","Typical"),
                         points = T, lines = T, columns = 3))
```

```
|     [1] "age1"     "yrsill1" "pos"     "neg"     "gen"     "total"   "year"
|     [8] "drug"     "status"  "Sex"     "Subj"    "id"      "what"
```


Atypical
Clozapine
Typical
1
2
3
4
5
6
M12
M40
M51
F4
F25
F45
30
25
20
15
10
neg
year

```
#
# Mixed model: first version
#

fit.mix <- lme( neg ~ drug, dd, random = ~ 1 | id )
summary(fit.mix)
```

```
|   Linear mixed-effects model fit by REML
|    Data: dd
|          AIC      BIC    logLik
|     1829.011 1847.773 -909.5053
|
|   Random effects:
|    Formula: ~1 | id
|           (Intercept) Residual
|   StdDev:    5.240588 3.399672
|
|   Fixed effects: neg ~ drug
|                      Value Std.Error  DF   t-value p-value
|   (Intercept)    15.482816 0.8783362 263 17.627437  0.0000
|   drugClozapine -1.300272 0.7980602 263 -1.629290  0.1044
|   drugTypical    0.815021 0.6140648 263  1.327255  0.1856
```

```
|    Correlation:
|                (Intr) drgClz
|   drugClozapine -0.444
|   drugTypical   -0.489  0.559
|
|   Standardized Within-Group Residuals:
|           Min           Q1          Med           Q3          Max
|   -3.71174345 -0.59155383 -0.05454849  0.47584480  3.47145299
|
|   Number of Observations: 318
|   Number of Groups: 53
```

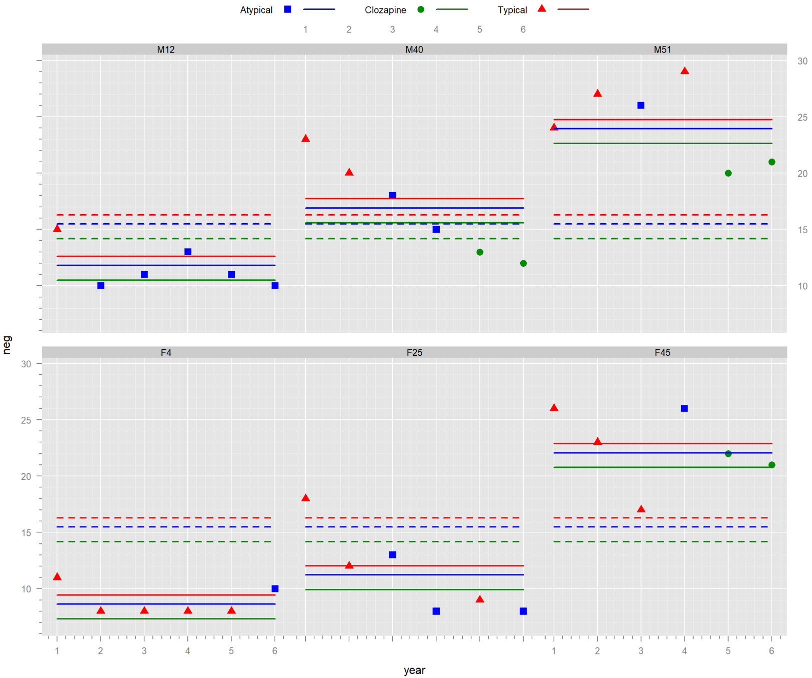
```
wald( fit.mix, L )  # same L as above because same FE model
```

```
|            numDF denDF  F.value p.value
|   predicted     3   263 148.3786 <.00001
|
|               Estimate Std.Error  DF  t-value p-value Lower 0.95 Upper 0.95
|     Atypical  15.48282  0.878336 263 17.62744 <.00001   13.75335   17.21228
|     Clozapine 14.18254  0.886412 263 15.99995 <.00001   12.43718   15.92791
|     Typical   16.29784  0.788330 263 20.67387 <.00001   14.74559   17.85008
|
```

```
|                numDF denDF  F.value p.value
|   differences      2   263 4.974805 0.00757
|
|                            Estimate Std.Error  DF   t-value p-value
|     Clozapine - Atypical -1.300272  0.798060 263 -1.629290 0.10445
|     Typical - Atypical    0.815021  0.614065 263  1.327255 0.18558
|     Typical - Clozapine   2.115292  0.682395 263  3.099806 0.00215
|
|                           Lower 0.95 Upper 0.95
|     Clozapine - Atypical  -2.871672   0.271129
|     Typical - Atypical    -0.394089   2.024130
|     Typical - Clozapine    0.771639   3.458945
# Clozapine is best and sig. diff from Typical

#
# Can use same pred for Popn pred and for BLUPS
#

pred$neg <- predict( fit.mix, pred, level = 0)

# Make a separate data frame for blupss
```

```
pred2 <- pred
pred2$neg <- predict( fit.mix, pred2, level = 1)
pred2$what <- factor("fit2")

# Cut and paste from last, then add 'pred2'

gd( pch = 15:17, col = c('blue','green4','red'), cex = 1.2,
    lty = c(1,1,1,2,2,2,1,1,1),lwd = 2)
xyplot( neg ~ year | id, Rbind( dd, pred, pred2),  groups = what:drug,
        panel = panel.superpose.2,
        lwd = 2,
        type = c(rep('p',3),rep('l',6)),
        subset = id %in% sel,
        between = list( y =1 ),
        auto.key = list( text = c("Atypical","Clozapine","Typical"),
                         points = T, lines = T, columns = 3))
```

```
|    [1] "age1"    "yrsill1" "pos"     "neg"     "gen"     "total"   "year"
|    [8] "drug"    "status"  "Sex"     "Subj"    "id"      "what"
```


Atypical
Clozapine
Typical
M12
M40
M51
F4
F25
F45
neg
year
1
2
3
4
5
6
10
15
20
25
30

```
#
# Hausman test and mixed model with contextual categorical variable
#

dd$drug.m <- cvar( dd$drug, dd$id)           # note that drug.m is matrix
dd$drug.m
```

```
|           Clozapine   Typical
|      [1,] 0.6666667 0.1666667
|      [2,] 0.6666667 0.1666667
|      [3,] 0.6666667 0.1666667
|      [4,] 0.6666667 0.1666667
|      [5,] 0.6666667 0.1666667
|      [6,] 0.6666667 0.1666667
|      [7,] 0.6666667 0.1666667
|      [8,] 0.6666667 0.1666667
|      [9,] 0.6666667 0.1666667
|     [10,] 0.6666667 0.1666667
|     [11,] 0.6666667 0.1666667
|     [12,] 0.6666667 0.1666667
|     [13,] 0.0000000 1.0000000
|     [14,] 0.0000000 1.0000000
```

```
|     [15,] 0.0000000 1.0000000
|     [16,] 0.0000000 1.0000000
|     [17,] 0.0000000 1.0000000
|     [18,] 0.0000000 1.0000000
|     [19,] 0.0000000 0.8333333
|     [20,] 0.0000000 0.8333333
|     [21,] 0.0000000 0.8333333
|     [22,] 0.0000000 0.8333333
|     [23,] 0.0000000 0.8333333
|     [24,] 0.0000000 0.8333333
|     [25,] 0.0000000 1.0000000
|     [26,] 0.0000000 1.0000000
|     [27,] 0.0000000 1.0000000
|     [28,] 0.0000000 1.0000000
|     [29,] 0.0000000 1.0000000
|     [30,] 0.0000000 1.0000000
|     [31,] 0.0000000 1.0000000
|     [32,] 0.0000000 1.0000000
|     [33,] 0.0000000 1.0000000
|     [34,] 0.0000000 1.0000000
|     [35,] 0.0000000 1.0000000
```

```
|    [36,] 0.0000000 1.0000000
|    [37,] 0.0000000 0.0000000
|    [38,] 0.0000000 0.0000000
|    [39,] 0.0000000 0.0000000
|    [40,] 0.0000000 0.0000000
|    [41,] 0.0000000 0.0000000
|    [42,] 0.0000000 0.0000000
|    [43,] 0.6666667 0.1666667
|    [44,] 0.6666667 0.1666667
|    [45,] 0.6666667 0.1666667
|    [46,] 0.6666667 0.1666667
|    [47,] 0.6666667 0.1666667
|    [48,] 0.6666667 0.1666667
|    [49,] 0.5000000 0.5000000
|    [50,] 0.5000000 0.5000000
|    [51,] 0.5000000 0.5000000
|    [52,] 0.5000000 0.5000000
|    [53,] 0.5000000 0.5000000
|    [54,] 0.5000000 0.5000000
|    [55,] 0.0000000 0.5000000
|    [56,] 0.0000000 0.5000000
```

```
|     [57,] 0.0000000 0.5000000
|     [58,] 0.0000000 0.5000000
|     [59,] 0.0000000 0.5000000
|     [60,] 0.0000000 0.5000000
|     [61,] 0.0000000 0.1666667
|     [62,] 0.0000000 0.1666667
|     [63,] 0.0000000 0.1666667
|     [64,] 0.0000000 0.1666667
|     [65,] 0.0000000 0.1666667
|     [66,] 0.0000000 0.1666667
|     [67,] 1.0000000 0.0000000
|     [68,] 1.0000000 0.0000000
|     [69,] 1.0000000 0.0000000
|     [70,] 1.0000000 0.0000000
|     [71,] 1.0000000 0.0000000
|     [72,] 1.0000000 0.0000000
|     [73,] 1.0000000 0.0000000
|     [74,] 1.0000000 0.0000000
|     [75,] 1.0000000 0.0000000
|     [76,] 1.0000000 0.0000000
|     [77,] 1.0000000 0.0000000
```

```
|     [78,] 1.0000000 0.0000000
|     [79,] 0.3333333 0.5000000
|     [80,] 0.3333333 0.5000000
|     [81,] 0.3333333 0.5000000
|     [82,] 0.3333333 0.5000000
|     [83,] 0.3333333 0.5000000
|     [84,] 0.3333333 0.5000000
|     [85,] 0.3333333 0.5000000
|     [86,] 0.3333333 0.5000000
|     [87,] 0.3333333 0.5000000
|     [88,] 0.3333333 0.5000000
|     [89,] 0.3333333 0.5000000
|     [90,] 0.3333333 0.5000000
|     [91,] 0.5000000 0.3333333
|     [92,] 0.5000000 0.3333333
|     [93,] 0.5000000 0.3333333
|     [94,] 0.5000000 0.3333333
|     [95,] 0.5000000 0.3333333
|     [96,] 0.5000000 0.3333333
|     [97,] 0.0000000 0.3333333
|     [98,] 0.0000000 0.3333333
```

```
|     [99,] 0.0000000 0.3333333
|    [100,] 0.0000000 0.3333333
|    [101,] 0.0000000 0.3333333
|    [102,] 0.0000000 0.3333333
|    [103,] 0.0000000 0.3333333
|    [104,] 0.0000000 0.3333333
|    [105,] 0.0000000 0.3333333
|    [106,] 0.0000000 0.3333333
|    [107,] 0.0000000 0.3333333
|    [108,] 0.0000000 0.3333333
|    [109,] 0.0000000 1.0000000
|    [110,] 0.0000000 1.0000000
|    [111,] 0.0000000 1.0000000
|    [112,] 0.0000000 1.0000000
|    [113,] 0.0000000 1.0000000
|    [114,] 0.0000000 1.0000000
|    [115,] 0.0000000 1.0000000
|    [116,] 0.0000000 1.0000000
|    [117,] 0.0000000 1.0000000
|    [118,] 0.0000000 1.0000000
|    [119,] 0.0000000 1.0000000
```

```
|    [120,] 0.0000000 1.0000000
|    [121,] 1.0000000 0.0000000
|    [122,] 1.0000000 0.0000000
|    [123,] 1.0000000 0.0000000
|    [124,] 1.0000000 0.0000000
|    [125,] 1.0000000 0.0000000
|    [126,] 1.0000000 0.0000000
|    [127,] 0.0000000 0.1666667
|    [128,] 0.0000000 0.1666667
|    [129,] 0.0000000 0.1666667
|    [130,] 0.0000000 0.1666667
|    [131,] 0.0000000 0.1666667
|    [132,] 0.0000000 0.1666667
|    [133,] 0.0000000 0.8333333
|    [134,] 0.0000000 0.8333333
|    [135,] 0.0000000 0.8333333
|    [136,] 0.0000000 0.8333333
|    [137,] 0.0000000 0.8333333
|    [138,] 0.0000000 0.8333333
|    [139,] 1.0000000 0.0000000
|    [140,] 1.0000000 0.0000000
```

```
|    [141,] 1.0000000 0.0000000
|    [142,] 1.0000000 0.0000000
|    [143,] 1.0000000 0.0000000
|    [144,] 1.0000000 0.0000000
|    [145,] 0.0000000 0.8333333
|    [146,] 0.0000000 0.8333333
|    [147,] 0.0000000 0.8333333
|    [148,] 0.0000000 0.8333333
|    [149,] 0.0000000 0.8333333
|    [150,] 0.0000000 0.8333333
|    [151,] 0.0000000 1.0000000
|    [152,] 0.0000000 1.0000000
|    [153,] 0.0000000 1.0000000
|    [154,] 0.0000000 1.0000000
|    [155,] 0.0000000 1.0000000
|    [156,] 0.0000000 1.0000000
|    [157,] 0.6666667 0.3333333
|    [158,] 0.6666667 0.3333333
|    [159,] 0.6666667 0.3333333
|    [160,] 0.6666667 0.3333333
|    [161,] 0.6666667 0.3333333
```

```
|    [162,] 0.6666667 0.3333333
|    [163,] 0.0000000 0.1666667
|    [164,] 0.0000000 0.1666667
|    [165,] 0.0000000 0.1666667
|    [166,] 0.0000000 0.1666667
|    [167,] 0.0000000 0.1666667
|    [168,] 0.0000000 0.1666667
|    [169,] 0.0000000 1.0000000
|    [170,] 0.0000000 1.0000000
|    [171,] 0.0000000 1.0000000
|    [172,] 0.0000000 1.0000000
|    [173,] 0.0000000 1.0000000
|    [174,] 0.0000000 1.0000000
|    [175,] 0.0000000 1.0000000
|    [176,] 0.0000000 1.0000000
|    [177,] 0.0000000 1.0000000
|    [178,] 0.0000000 1.0000000
|    [179,] 0.0000000 1.0000000
|    [180,] 0.0000000 1.0000000
|    [181,] 0.3333333 0.6666667
|    [182,] 0.3333333 0.6666667
```

```
|    [183,] 0.3333333 0.6666667
|    [184,] 0.3333333 0.6666667
|    [185,] 0.3333333 0.6666667
|    [186,] 0.3333333 0.6666667
|    [187,] 0.0000000 0.6666667
|    [188,] 0.0000000 0.6666667
|    [189,] 0.0000000 0.6666667
|    [190,] 0.0000000 0.6666667
|    [191,] 0.0000000 0.6666667
|    [192,] 0.0000000 0.6666667
|    [193,] 0.8333333 0.1666667
|    [194,] 0.8333333 0.1666667
|    [195,] 0.8333333 0.1666667
|    [196,] 0.8333333 0.1666667
|    [197,] 0.8333333 0.1666667
|    [198,] 0.8333333 0.1666667
|    [199,] 0.0000000 0.8333333
|    [200,] 0.0000000 0.8333333
|    [201,] 0.0000000 0.8333333
|    [202,] 0.0000000 0.8333333
|    [203,] 0.0000000 0.8333333
```

```
|    [204,] 0.0000000 0.8333333
|    [205,] 0.0000000 0.8333333
|    [206,] 0.0000000 0.8333333
|    [207,] 0.0000000 0.8333333
|    [208,] 0.0000000 0.8333333
|    [209,] 0.0000000 0.8333333
|    [210,] 0.0000000 0.8333333
|    [211,] 0.1666667 0.5000000
|    [212,] 0.1666667 0.5000000
|    [213,] 0.1666667 0.5000000
|    [214,] 0.1666667 0.5000000
|    [215,] 0.1666667 0.5000000
|    [216,] 0.1666667 0.5000000
|    [217,] 0.5000000 0.5000000
|    [218,] 0.5000000 0.5000000
|    [219,] 0.5000000 0.5000000
|    [220,] 0.5000000 0.5000000
|    [221,] 0.5000000 0.5000000
|    [222,] 0.5000000 0.5000000
|    [223,] 0.3333333 0.6666667
|    [224,] 0.3333333 0.6666667
```

```
|    [225,] 0.3333333 0.6666667
|    [226,] 0.3333333 0.6666667
|    [227,] 0.3333333 0.6666667
|    [228,] 0.3333333 0.6666667
|    [229,] 0.0000000 1.0000000
|    [230,] 0.0000000 1.0000000
|    [231,] 0.0000000 1.0000000
|    [232,] 0.0000000 1.0000000
|    [233,] 0.0000000 1.0000000
|    [234,] 0.0000000 1.0000000
|    [235,] 0.0000000 0.8333333
|    [236,] 0.0000000 0.8333333
|    [237,] 0.0000000 0.8333333
|    [238,] 0.0000000 0.8333333
|    [239,] 0.0000000 0.8333333
|    [240,] 0.0000000 0.8333333
|    [241,] 0.0000000 0.1666667
|    [242,] 0.0000000 0.1666667
|    [243,] 0.0000000 0.1666667
|    [244,] 0.0000000 0.1666667
|    [245,] 0.0000000 0.1666667
```

```
|    [246,] 0.0000000 0.1666667
|    [247,] 0.0000000 0.5000000
|    [248,] 0.0000000 0.5000000
|    [249,] 0.0000000 0.5000000
|    [250,] 0.0000000 0.5000000
|    [251,] 0.0000000 0.5000000
|    [252,] 0.0000000 0.5000000
|    [253,] 0.3333333 0.5000000
|    [254,] 0.3333333 0.5000000
|    [255,] 0.3333333 0.5000000
|    [256,] 0.3333333 0.5000000
|    [257,] 0.3333333 0.5000000
|    [258,] 0.3333333 0.5000000
|    [259,] 0.0000000 0.6666667
|    [260,] 0.0000000 0.6666667
|    [261,] 0.0000000 0.6666667
|    [262,] 0.0000000 0.6666667
|    [263,] 0.0000000 0.6666667
|    [264,] 0.0000000 0.6666667
|    [265,] 0.5000000 0.0000000
|    [266,] 0.5000000 0.0000000
```

```
|    [267,] 0.5000000 0.0000000
|    [268,] 0.5000000 0.0000000
|    [269,] 0.5000000 0.0000000
|    [270,] 0.5000000 0.0000000
|    [271,] 0.5000000 0.5000000
|    [272,] 0.5000000 0.5000000
|    [273,] 0.5000000 0.5000000
|    [274,] 0.5000000 0.5000000
|    [275,] 0.5000000 0.5000000
|    [276,] 0.5000000 0.5000000
|    [277,] 0.3333333 0.3333333
|    [278,] 0.3333333 0.3333333
|    [279,] 0.3333333 0.3333333
|    [280,] 0.3333333 0.3333333
|    [281,] 0.3333333 0.3333333
|    [282,] 0.3333333 0.3333333
|    [283,] 0.0000000 0.6666667
|    [284,] 0.0000000 0.6666667
|    [285,] 0.0000000 0.6666667
|    [286,] 0.0000000 0.6666667
|    [287,] 0.0000000 0.6666667
```

```
|    [288,] 0.0000000 0.6666667
|    [289,] 0.3333333 0.5000000
|    [290,] 0.3333333 0.5000000
|    [291,] 0.3333333 0.5000000
|    [292,] 0.3333333 0.5000000
|    [293,] 0.3333333 0.5000000
|    [294,] 0.3333333 0.5000000
|    [295,] 0.0000000 0.8333333
|    [296,] 0.0000000 0.8333333
|    [297,] 0.0000000 0.8333333
|    [298,] 0.0000000 0.8333333
|    [299,] 0.0000000 0.8333333
|    [300,] 0.0000000 0.8333333
|    [301,] 1.0000000 0.0000000
|    [302,] 1.0000000 0.0000000
|    [303,] 1.0000000 0.0000000
|    [304,] 1.0000000 0.0000000
|    [305,] 1.0000000 0.0000000
|    [306,] 1.0000000 0.0000000
|    [307,] 1.0000000 0.0000000
|    [308,] 1.0000000 0.0000000
```

```
|    [309,] 1.0000000 0.0000000
|    [310,] 1.0000000 0.0000000
|    [311,] 1.0000000 0.0000000
|    [312,] 1.0000000 0.0000000
|    [313,] 0.0000000 0.3333333
|    [314,] 0.0000000 0.3333333
|    [315,] 0.0000000 0.3333333
|    [316,] 0.0000000 0.3333333
|    [317,] 0.0000000 0.3333333
|    [318,] 0.0000000 0.3333333
```

```
head( dd, 18)
```

```
|        age1 yrsill1 pos neg gen total year      drug               status Sex
|    17  29.1      10  16   8  33    57    1   Typical              Married   F
|    72  29.1      10  21  23  60   104    2  Atypical              Married   F
|    127 29.1      10   9   7  20    36    3 Clozapine              Married   F
|    182 29.1      10   8   9  25    42    4 Clozapine              Married   F
|    237 29.1      10   8   7  25    40    5 Clozapine              Married   F
|    292 29.1      10  12   7  26    45    6 Clozapine              Married   F
|    38  36.4      16  12   8  29    49    1   Typical Separated/Divorced   F
|    93  36.4      16  13  10  31    54    2  Atypical Separated/Divorced   F
```

```
|   148 36.4      16  20  24  40    84    3 Clozapine Separated/Divorced   F
|   203 36.4      16  15  16  35    66    4 Clozapine Separated/Divorced   F
|   258 36.4      16  13  13  28    54    5 Clozapine Separated/Divorced   F
|   313 36.4      16  11  15  22    48    6 Clozapine Separated/Divorced   F
|   14  29.9      10  17  10  28    55    1   Typical             Single   F
|   69  29.9      10  14  10  25    49    2   Typical             Single   F
|   124 29.9      10  10   8  22    40    3   Typical             Single   F
|   179 29.9      10  15  10  28    53    4   Typical             Single   F
|   234 29.9      10   9   7  22    38    5   Typical             Single   F
|   289 29.9      10  11   7  20    38    6   Typical             Single   F
|       Subj  id what drug.m.Clozapine drug.m.Typical
|   17   F36 F36 data        0.6666667      0.1666667
|   72   F36 F36 data        0.6666667      0.1666667
|   127  F36 F36 data        0.6666667      0.1666667
|   182  F36 F36 data        0.6666667      0.1666667
|   237  F36 F36 data        0.6666667      0.1666667
|   292  F36 F36 data        0.6666667      0.1666667
|   38   F41 F41 data        0.6666667      0.1666667
|   93   F41 F41 data        0.6666667      0.1666667
|   148  F41 F41 data        0.6666667      0.1666667
|   203  F41 F41 data        0.6666667      0.1666667
```

```
|   258  F41 F41 data        0.6666667      0.1666667
|   313  F41 F41 data        0.6666667      0.1666667
|   14    F2  F2 data        0.0000000      1.0000000
|   69    F2  F2 data        0.0000000      1.0000000
|   124   F2  F2 data        0.0000000      1.0000000
|   179   F2  F2 data        0.0000000      1.0000000
|   234   F2  F2 data        0.0000000      1.0000000
|   289   F2  F2 data        0.0000000      1.0000000
```

```
some( dd )
```

```
|       age1 yrsill1 pos neg gen total year      drug status Sex Subj  id what
|   59  36.6      20  16  23  40    79    2   Typical Single   F  F45 F45 data
|   139 32.6      14  23   7  26    56    3   Typical Single   M   M3  M3 data
|   231 34.0      12  12   9  23    44    5   Typical Single   M  M16 M16 data
|   319 28.5      11  17   9  25    51    6 Clozapine Single   M  M17 M17 data
|   171 32.8      10  13  19  29    61    4   Typical Single   M  M46 M46 data
|   186 37.3      16  14  19  30    63    4   Typical Single   M  M31 M31 data
|   12  25.0       8  18  21  52    91    1   Typical Single   M  M30 M30 data
|   67  25.0       8  12  13  29    54    2   Typical Single   M  M30 M30 data
|   251 32.7      14  22  17  41    80    5 Clozapine Single   M  M49 M49 data
|   277 38.8      24  10  29  24    63    6  Atypical Single   M  M53 M53 data
```

```
|        drug.m.Clozapine drug.m.Typical
|    59         0.3333333      0.5000000
|    139        0.0000000      1.0000000
|    231        0.0000000      1.0000000
|    319        0.3333333      0.6666667
|    171        0.1666667      0.5000000
|    186        0.3333333      0.6666667
|    12         0.3333333      0.5000000
|    67         0.3333333      0.5000000
|    251        1.0000000      0.0000000
|    277        0.0000000      0.3333333
```

```
# QUESTION:
#  What is the interpretation of drug.m?
#  Why not three columns, one for each drug?

fit.m <- lme( neg ~ drug + drug.m , dd, random = ~ 1 | id )
summary( fit.m )
```

```
|    Linear mixed-effects model fit by REML
|     Data: dd
|           AIC      BIC    logLik
```

```
|     1818.357 1844.581 -902.1785
|
|   Random effects:
|    Formula: ~1 | id
|           (Intercept) Residual
|   StdDev:    4.984062  3.39656
|
|   Fixed effects: neg ~ drug + drug.m
|                      Value Std.Error  DF   t-value p-value
|   (Intercept)      15.838657  2.121548 263  7.465614  0.0000
|   drugClozapine   -1.782102  0.834395 263 -2.135802  0.0336
|   drugTypical      0.896756  0.627306 263  1.429535  0.1540
|   drug.mClozapine  3.813141  2.872332  50  1.327542  0.1904
|   drug.mTypical   -2.616211  2.891131  50 -0.904909  0.3699
|    Correlation:
|                   (Intr) drgClz drgTyp drg.mC
|   drugClozapine    0.000
|   drugTypical      0.000  0.552
|   drug.mClozapine -0.771 -0.290 -0.160
|   drug.mTypical   -0.884 -0.120 -0.217  0.668
|
```

```
|   Standardized Within-Group Residuals:
|           Min          Q1         Med          Q3         Max
|   -3.78234220 -0.60736018 -0.06230846  0.49922986  3.32999988
|
|   Number of Observations: 318
|   Number of Groups: 53
```

```
wald( fit.m , ’drug.m’)   # Should we keep drug.m?
```

```
|          numDF denDF  F.value p.value
|   drug.m     2    50 3.783136 0.02952
|
|   Coefficients       Estimate Std.Error DF   t-value p-value Lower 0.95
|     drug.mClozapine  3.813141  2.872332 50  1.327542 0.19036  -1.956108
|     drug.mTypical   -2.616211  2.891131 50 -0.904909 0.36985  -8.423218
|
|   Coefficients      Upper 0.95
|     drug.mClozapine   9.582391
|     drug.mTypical     3.190796
```

```
wald( fit.m , ’drug’)
```

```
|        numDF denDF  F.value p.value
```

```
|   drug      4    50 4.294531  0.0046
|
|   Coefficients        Estimate Std.Error  DF   t-value p-value Lower 0.95
|     drugClozapine   -1.782102  0.834395 263 -2.135802 0.03362  -3.425047
|     drugTypical      0.896756  0.627306 263  1.429535 0.15404  -0.338425
|     drug.mClozapine  3.813141  2.872332  50  1.327542 0.19036  -1.956108
|     drug.mTypical   -2.616211  2.891131  50 -0.904909 0.36985  -8.423218
|
|   Coefficients       Upper 0.95
|     drugClozapine    -0.139158
|     drugTypical       2.131937
|     drug.mClozapine   9.582391
|     drug.mTypical     3.190796

L

|   $predicted
|               Clozapine Typical
|   Atypical  1         0       0
|   Clozapine 1         1       0
|   Typical   1         0       1
|
```

```
|    $differences
|                         [,1] [,2] [,3]
|    Clozapine - Atypical    0    1    0
|    Typical - Atypical      0    0    1
|    Typical - Clozapine     0   -1    1

Lm <- lapply( L, function(x) cbind( x, 0, 0))
Lm

|    $predicted
|                Clozapine Typical
|    Atypical  1         0       0 0 0
|    Clozapine 1         1       0 0 0
|    Typical   1         0       1 0 0
|
|    $differences
|                         [,1] [,2] [,3] [,4] [,5]
|    Clozapine - Atypical    0    1    0    0    0
|    Typical - Atypical      0    0    1    0    0
|    Typical - Clozapine     0   -1    1    0    0

wald( fit.m , Lm )
```

```
|             numDF denDF  F.value p.value
|   predicted     3   263 23.36135 <.00001
|
|               Estimate Std.Error  DF  t-value p-value Lower 0.95 Upper 0.95
|     Atypical  15.83866  2.121548 263 7.465614 <.00001  11.661277   20.01604
|     Clozapine 14.05655  2.279732 263 6.165879 <.00001   9.567705   18.54540
|     Typical   16.73541  2.212347 263 7.564553 <.00001  12.379247   21.09158
|
|               numDF denDF  F.value p.value
|   differences     2   263 7.174332 0.00093
|
|                           Estimate Std.Error  DF   t-value p-value
|     Clozapine - Atypical -1.782102  0.834395 263 -2.135802 0.03362
|     Typical - Atypical    0.896756  0.627306 263  1.429535 0.15404
|     Typical - Clozapine   2.678858  0.715431 263  3.744397 0.00022
|
|                          Lower 0.95 Upper 0.95
|     Clozapine - Atypical  -3.425047  -0.139158
|     Typical - Atypical    -0.338425   2.131937
|     Typical - Clozapine    1.270156   4.087560
# compare with
```

```
wald( fit.mix, L)

|              numDF denDF  F.value p.value
|   predicted      3   263 148.3786 <.00001
|
|                Estimate Std.Error  DF  t-value p-value Lower 0.95 Upper 0.95
|     Atypical   15.48282  0.878336 263 17.62744 <.00001   13.75335   17.21228
|     Clozapine 14.18254  0.886412 263 15.99995 <.00001   12.43718   15.92791
|     Typical   16.29784  0.788330 263 20.67387 <.00001   14.74559   17.85008
|
|                numDF denDF  F.value p.value
|   differences     2   263 4.974805 0.00757
|
|                            Estimate Std.Error  DF   t-value p-value
|     Clozapine - Atypical -1.300272  0.798060 263 -1.629290 0.10445
|     Typical - Atypical    0.815021  0.614065 263  1.327255 0.18558
|     Typical - Clozapine   2.115292  0.682395 263  3.099806 0.00215
|
|                           Lower 0.95 Upper 0.95
|     Clozapine - Atypical  -2.871672   0.271129
|     Typical - Atypical    -0.394089   2.024130
```

```
|     Typical - Clozapine    0.771639   3.458945

#
# QUESTION:
#    With drug.m in the model, the difference between Typical and Clozapine
#    is larger and more significant. Why?
#


#
#  Plotting fit with Level 2 variables (here the contextual variables)
#


#
#  If you want to show how the response depends on FE variables
#  you need to create a prediction data frame with all the FE variables
#  needed for prediction. (Level 1 or Level 2)
#
#
#  If you want to show predictions for individual clusters ( popn average
#  of BLUPS)
#           AND
#  you have Level 2 variables in your model
```

```
#  you need to construct a data frame with
#      ids and Level 1 variables
#  then you need to merge the data.frame with the matching
#  Level 2 variables.
#
#

pred <- expand.grid( year = 1:6, drug = levels( dd$drug), id = levels(dd$id))
head( pred)
```

```
|      year     drug id
|    1    1 Atypical F2
|    2    2 Atypical F2
|    3    3 Atypical F2
|    4    4 Atypical F2
|    5    5 Atypical F2
|    6    6 Atypical F2
```

```
dim( pred )
```

```
|    [1] 954   3
```

```
# merge pred with specific Level 2 variable2 corresponding to id
```

```
ddu <- up( dd, ~ id)
head(ddu)
```

```
|       age1 yrsill1  status Sex Subj  id what drug.m.Clozapine drug.m.Typical
|   F2  29.9      10  Single   F   F2  F2 data        0.0000000      1.0000000
|   F4  30.2       8  Single   F   F4  F4 data        0.0000000      0.8333333
|   F11 31.8      11  Single   F  F11 F11 data        0.0000000      0.0000000
|   F36 29.1      10 Married   F  F36 F36 data        0.6666667      0.1666667
|   F10 26.2       9 Married   F  F10 F10 data        0.0000000      1.0000000
|   F25 29.8      10  Single   F  F25 F25 data        0.0000000      0.5000000
```

```
predc <- merge( pred, ddu, by = ’id’)
dim( predc )
```

```
|   [1] 954  10
```

```
head( predc )
```

```
|      id year     drug age1 yrsill1  status Sex Subj what drug.m.Clozapine
|   1 F10    1 Atypical 26.2       9 Married   F  F10 data                0
|   2 F10    2 Atypical 26.2       9 Married   F  F10 data                0
|   3 F10    3 Atypical 26.2       9 Married   F  F10 data                0
|   4 F10    4 Atypical 26.2       9 Married   F  F10 data                0
```

```
|   5 F10    5 Atypical 26.2       9 Married   F  F10 data                0
|   6 F10    6 Atypical 26.2       9 Married   F  F10 data                0
|     drug.m.Typical
|   1              1
|   2              1
|   3              1
|   4              1
|   5              1
|   6              1
```

```
names( predc ) # note that drug.m matrix is preserved as a matrix
```

```
|    [1] "id"      "year"    "drug"    "age1"    "yrsill1" "status"  "Sex"
|    [8] "Subj"    "what"    "drug.m"
```

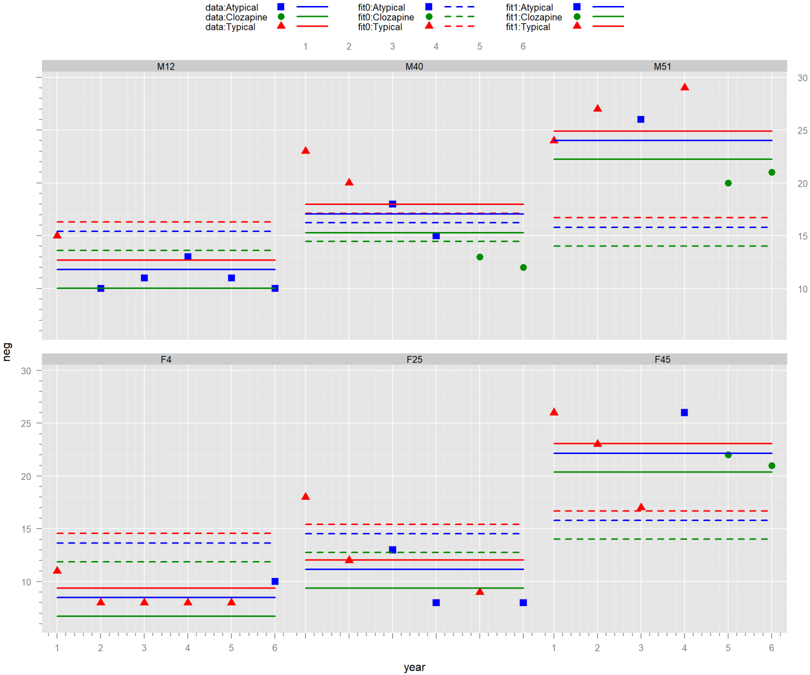
```
# ready to predict popn average:

predc$neg <- predict( fit.m , predc, level = 0)

# predict BLUP

predc.blup <- predc
predc.blup$neg <- predict( fit.m , predc.blup, level = 1)
```

```
# Identify data frames so they can be combined and each plot differently

dd$what <- factor("data")
predc$what <- factor("fit0")
predc.blup$what <- factor('fit1')
comb <- Rbind(dd, predc, predc.blup)
```

```
|    [1] "age1"    "yrsill1" "pos"      "neg"      "gen"      "total"    "year"
|    [8] "drug"    "status"  "Sex"      "Subj"     "id"       "what"     "drug.m"
```

```
# Note: this is all cut and paste except for the first line

gd( pch = 15:17, col = c('blue','green4','red'), cex = 1.2,
    lty = c(1,1,1,2,2,2,1,1,1),lwd = 2)
xyplot( neg ~ year | id , comb,  groups = what:drug,
        panel = panel.superpose.2,
        lwd = 2,
        type = c(rep('p',3),rep('l',6)),
        subset = id %in% sel,
        between = list( y = 1 ),
        #auto.key = list( text = c("Atypical","Clozapine","Typical"),
```

```
auto.key = list(
  points = T, lines = T, columns = 3))
```


data:Atypical
data:Clozapine
data:Typical
fit0:Atypical
fit0:Clozapine
fit0:Typical
fit1:Atypical
fit1:Clozapine
fit1:Typical
M12
M40
M51
F4
F25
F45
neg
year
1
2
3
4
5
6
10
15
20
25
30

```
#
#  Taking time into account
#

fit.my <- update( fit.m, . ~ . + year)

summary( fit.my )   # very significant drop with time
```

```
|   Linear mixed-effects model fit by REML
|    Data: dd
|          AIC      BIC    logLik
|     1810.39 1840.334 -897.1952
|
|   Random effects:
|    Formula: ~1 | id
|           (Intercept) Residual
|   StdDev:    4.992041 3.325507
|
|   Fixed effects: neg ~ drug + drug.m + year
|                      Value Std.Error  DF   t-value p-value
|   (Intercept)    17.511006 2.1742271 262  8.053899  0.0000
|   drugClozapine  -1.153198 0.8362982 262 -1.378931  0.1691
```

```
|   drugTypical      -0.117037 0.6785156 262 -0.172489  0.8632
|   drug.mClozapine   3.184237 2.8728859  50  1.108376  0.2730
|   drug.mTypical    -1.602418 2.9026725  50 -0.552049  0.5834
|   year             -0.477814 0.1359168 262 -3.515489  0.0005
|    Correlation:
|                    (Intr) drgClz drgTyp drg.mC drg.mT
|   drugClozapine     0.047
|   drugTypical      -0.093  0.397
|   drug.mClozapine -0.766 -0.291 -0.116
|   drug.mTypical    -0.837 -0.093 -0.234  0.658
|   year             -0.219 -0.214  0.425  0.062 -0.099
|
|   Standardized Within-Group Residuals:
|           Min          Q1         Med          Q3         Max
|   -3.50585771 -0.61471185 -0.09486059  0.56161475  3.26692262
|
|   Number of Observations: 318
|   Number of Groups: 53
```

```
# Previous hypothesis matrix

Lm
```

```
|   $predicted
|               Clozapine Typical
|   Atypical  1         0       0 0 0
|   Clozapine 1         1       0 0 0
|   Typical   1         0       1 0 0
|
|   $differences
|                        [,1] [,2] [,3] [,4] [,5]
|   Clozapine - Atypical    0    1    0    0    0
|   Typical - Atypical      0    0    1    0    0
|   Typical - Clozapine     0   -1    1    0    0
```

```
wald( fit.my )
```

```
|    numDF denDF  F.value p.value
|        6    50 84.67485 <.00001
|
|   Coefficients       Estimate Std.Error  DF   t-value p-value Lower 0.95
|     (Intercept)     17.511006  2.174227 262  8.053899 <.00001  13.229823
|     drugClozapine   -1.153198  0.836298 262 -1.378931 0.16909  -2.799919
|     drugTypical     -0.117037  0.678516 262 -0.172489 0.86319  -1.453074
|     drug.mClozapine  3.184237  2.872886  50  1.108376 0.27300  -2.586125
```

```
|      drug.mTypical   -1.602418  2.902672  50 -0.552049 0.58337  -7.432608
|      year            -0.477814  0.135917 262 -3.515489 0.00052  -0.745442
|
|    Coefficients      Upper 0.95
|      (Intercept)      21.792190
|      drugClozapine     0.493524
|      drugTypical       1.219001
|      drug.mClozapine   8.954598
|      drug.mTypical     4.227771
|      year             -0.210186
```

```
# We only need to add year to Lm

Lmy <- Lm

Lmy <- lapply( Lm , function( x ) cbind(x, 0) )

# let's use the average year for predicted values

Lmy[[1]][,6] <- 3.5

Lmy
```

```
|   $predicted
|               Clozapine Typical
|   Atypical  1         0       0 0 0 3.5
|   Clozapine 1         1       0 0 0 3.5
|   Typical   1         0       1 0 0 3.5
|
|   $differences
|                        [,1] [,2] [,3] [,4] [,5] [,6]
|   Clozapine - Atypical    0    1    0    0    0    0
|   Typical - Atypical      0    0    1    0    0    0
|   Typical - Clozapine     0   -1    1    0    0    0
```

```
#
# QUESTION: Should we do the same thing for the second matrix?
#
#

wald ( fit.my, Lmy )
```

```
|             numDF denDF  F.value p.value
|   predicted     3   262 19.26801 <.00001
|
```

```
|             Estimate Std.Error  DF  t-value p-value Lower 0.95 Upper 0.95
|    Atypical  15.83866  2.121548 262 7.465614 <.00001   11.66120   20.01611
|    Clozapine 14.68546  2.280430 262 6.439777 <.00001   10.19516   19.17576
|    Typical   15.72162  2.227408 262 7.058257 <.00001   11.33572   20.10752
|
|              numDF denDF  F.value p.value
|   differences     2   262 1.034312 0.35692
|
|                         Estimate Std.Error  DF   t-value p-value
|    Clozapine - Atypical -1.153198  0.836298 262 -1.378931 0.16909
|    Typical - Atypical   -0.117037  0.678516 262 -0.172489 0.86319
|    Typical - Clozapine   1.036161  0.842019 262  1.230567 0.21959
|
|                        Lower 0.95 Upper 0.95
|    Clozapine - Atypical  -2.799919   0.493524
|    Typical - Atypical    -1.453074   1.219001
|    Typical - Clozapine   -0.621825   2.694147
#
# QUESTION: What does this say about Clozapine?
#
```

```
# We don't need new pred data.frames

predc$neg <- predict( fit.my, predc, level = 0)
predc.blup$neg <- predict( fit.my, predc.blup, level = 1)

dd$what

|      [1] data data data data data data data data data data data data data data
|     [15] data data data data data data data data data data data data data data
|     [29] data data data data data data data data data data data data data data
|     [43] data data data data data data data data data data data data data data
|     [57] data data data data data data data data data data data data data data
|     [71] data data data data data data data data data data data data data data
|     [85] data data data data data data data data data data data data data data
|     [99] data data data data data data data data data data data data data data
|    [113] data data data data data data data data data data data data data data
|    [127] data data data data data data data data data data data data data data
|    [141] data data data data data data data data data data data data data data
|    [155] data data data data data data data data data data data data data data
|    [169] data data data data data data data data data data data data data data
|    [183] data data data data data data data data data data data data data data
|    [197] data data data data data data data data data data data data data data
```

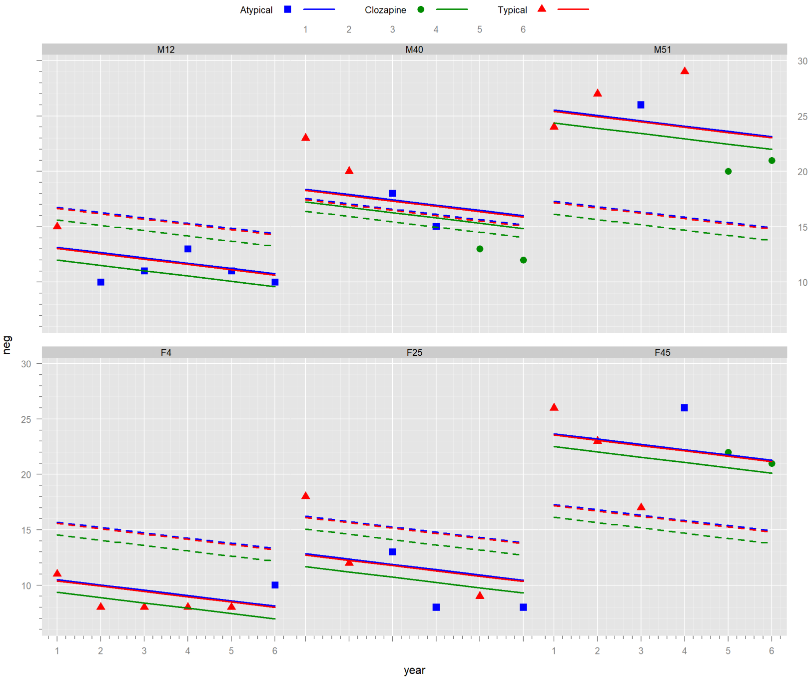
```
|   [211] data data data data data data data data data data data data data data
|   [225] data data data data data data data data data data data data data data
|   [239] data data data data data data data data data data data data data data
|   [253] data data data data data data data data data data data data data data
|   [267] data data data data data data data data data data data data data data
|   [281] data data data data data data data data data data data data data data
|   [295] data data data data data data data data data data data data data data
|   [309] data data data data data data data data data data
|   Levels: data
```

```
predc$what <- factor( 'fit0')
predc.blup$what <- factor( 'fit1')
rb <- Rbind( dd, predc, predc.blup)
```

```
|    [1] "age1"    "yrsill1" "pos"     "neg"     "gen"     "total"   "year"
|    [8] "drug"    "status"  "Sex"     "Subj"    "id"      "what"    "drug.m"
```

```
# Note: this is identical to previous
xyplot( neg ~ year | id , Rbind( dd, predc, predc.blup ),  groups = what:drug,
        panel = panel.superpose.2,
        lwd = 2,
        type = c(rep('p',3),rep('l',6)),
        subset = id %in% sel,
```

```
        between = list( y =1 ),
        auto.key = list( text = c("Atypical","Clozapine","Typical"),
                         points = T, lines = T, columns = 3))

|    [1] "age1"    "yrsill1" "pos"     "neg"     "gen"     "total"   "year"
|    [8] "drug"    "status"  "Sex"     "Subj"    "id"      "what"    "drug.m"
```


Atypical
Clozapine
Typical
1
2
3
4
5
6
M12
M40
M51
F4
F25
F45
neg
30
25
20
15
10
year

```
#
# Adding a possible autocorrelation
#

fit.myc <- update( fit.my, correlation = corAR1( form = ~ year | id ))

summary( fit.myc )   # very significant drop with time

|   Linear mixed-effects model fit by REML
|    Data: dd
|          AIC      BIC    logLik
|     1806.119 1839.806 -894.0595
|
|   Random effects:
|    Formula: ~1 | id
|           (Intercept) Residual
|   StdDev:    4.863878 3.477444
|
|   Correlation Structure: AR(1)
|    Formula: ~year | id
|    Parameter estimate(s):
|         Phi
```

```
|   0.2045159
|   Fixed effects: neg ~ drug + drug.m + year
|                       Value Std.Error  DF   t-value p-value
|   (Intercept)     17.551586 2.1753872 262  8.068258  0.0000
|   drugClozapine   -1.198927 0.8940467 262 -1.341011  0.1811
|   drugTypical     -0.241801 0.6875520 262 -0.351684  0.7254
|   drug.mClozapine  3.164622 2.8743291  50  1.100995  0.2762
|   drug.mTypical   -1.494575 2.8857604  50 -0.517914  0.6068
|   year            -0.485736 0.1503674 262 -3.230327  0.0014
|    Correlation:
|                   (Intr) drgClz drgTyp drg.mC drg.mT
|   drugClozapine    0.050
|   drugTypical     -0.102  0.375
|   drug.mClozapine -0.758 -0.309 -0.115
|   drug.mTypical   -0.831 -0.088 -0.233  0.654
|   year            -0.244 -0.211  0.403  0.066 -0.094
|
|   Standardized Within-Group Residuals:
|          Min          Q1         Med          Q3         Max
|   -3.2515034 -0.6100687 -0.1129732  0.5311779  3.0912181
|
```

```
|   Number of Observations: 318
|   Number of Groups: 53
```

```
wald( fit.myc, 'drug.m')   # what happened to the contextual effect? Why?
```

```
|          numDF denDF F.value p.value
|   drug.m     2    50 1.94558 0.15357
|
|   Coefficients        Estimate Std.Error DF   t-value p-value Lower 0.95
|     drug.mClozapine   3.164622  2.874329 50  1.100995 0.27617  -2.608638
|     drug.mTypical    -1.494575  2.885760 50 -0.517914 0.60680  -7.290796
|
|   Coefficients       Upper 0.95
|     drug.mClozapine   8.937882
|     drug.mTypical     4.301645
```

```
# Hypothesis matrix does not change

wald ( fit.myc, Lmy )
```

```
|             numDF denDF  F.value p.value
|   predicted     3   262 19.41893 <.00001
|
```

```
|                 Estimate Std.Error  DF  t-value p-value Lower 0.95 Upper 0.95
|     Atypical  15.85151  2.109823 262 7.513194 <.00001   11.69714   20.00588
|     Clozapine 14.65258  2.290340 262 6.397560 <.00001   10.14277   19.16240
|     Typical   15.60971  2.216287 262 7.043182 <.00001   11.24571   19.97371
|
|                 numDF denDF   F.value p.value
|   differences     2   262 0.9123941 0.40283
|
|                             Estimate Std.Error  DF   t-value p-value
|     Clozapine - Atypical -1.198927  0.894047 262 -1.341011 0.18108
|     Typical - Atypical   -0.241801  0.687552 262 -0.351684 0.72536
|     Typical - Clozapine   0.957126  0.900737 262  1.062602 0.28894
|
|                            Lower 0.95 Upper 0.95
|     Clozapine - Atypical  -2.959358   0.561505
|     Typical - Atypical    -1.595632   1.112030
|     Typical - Clozapine   -0.816480   2.730731
#
#  Adding random Drug effects
#
```

```
fit.mycr <- update( fit.myc, random = ~ 1 + dvar( drug, id) | id)
```

```
|   Error in lme.formula(fixed = neg ~ drug + drug.m + year, data = dd, random =
|     message = iteration limit reached without convergence (10)
```

```
fit.mycr <- update( fit.myc, random = ~ 1 + dvar( drug, id) | id,
                    control = list( msMaxIter = 200, msVerbose = TRUE   ))
```

```
|      0:     1347.6902: -0.439095 0.104470 0.163370 0.00405209 -0.313548 -1.0571
|      1:     1345.0766: -0.437034 0.134923 0.188122 0.00338929 -0.317594 -1.0663
|      2:     1344.8942: -0.374334 0.145914 0.194446 0.0116358 -0.313973 -1.07546
|      3:     1344.7660: -0.352318 0.247302 0.237992 -0.0241443 -0.393254 -1.1558
|      4:     1344.6270: -0.347783 0.282534 0.300490 0.0236578 -0.427254 -1.29728
|      5:     1344.5999: -0.326152 0.287942 0.277751 0.0332323 -0.448758 -1.35109
|      6:     1344.5505: -0.345930 0.301209 0.266764 0.0542005 -0.468121 -1.40492
|      7:     1344.5190: -0.335589 0.328399 0.259043 0.0892275 -0.481017 -1.45338
|      8:     1344.3794: -0.317595 0.423832 0.255534 0.218433 -0.710795 -1.86481
|      9:     1344.2693: -0.332525 0.600546 0.256183 0.442419 -0.918780 -2.21538
|     10:     1344.2435: -0.304302 0.607110 0.292488 0.476138 -0.993587 -2.32681
|     11:     1344.2190: -0.286623 0.667102 0.313855 0.479519 -1.09430 -2.40992 0
|     12:     1344.1978: -0.281306 0.687068 0.307426 0.542636 -1.18361 -2.50802 0
|     13:     1344.1565: -0.254781 0.763180 0.336230 0.800035 -1.56308 -2.87658 0
|     14:     1344.1309: -0.230403 0.860093 0.305654  1.04580 -1.94885 -3.24176 0
```

```
|    15:     1344.1175: -0.200677 0.955116 0.328173  1.29080 -2.34311 -3.59899 0
|    16:     1344.1083: -0.175381  1.01125 0.346014  1.55846 -2.77199 -3.90521 0
|    17:     1344.1028: -0.150064  1.08022 0.348047  1.82266 -3.19249 -4.20386 0
|    18:     1344.0977: -0.123453  1.12198 0.346923  2.10200 -3.64107 -4.44778 0
|    19:     1344.0953: -0.0945663  1.17102 0.350206  2.37841 -4.08713 -4.69797
|    20:     1344.0926: -0.0664422  1.20335 0.353877  2.66523 -4.55429 -4.89512
|    21:     1344.0907: -0.0370896  1.23723 0.356406  2.95436 -5.02359 -5.08318
|    22:     1344.0876: 0.0188193  1.27182 0.360981  3.47342 -5.87494 -5.32277 0
|    23:     1344.0851: 0.0735086  1.31616 0.362033  3.99704 -6.72242 -5.56489 0
|    24:     1344.0838: 0.122074  1.31827 0.358136  4.44943 -7.45683 -5.58626 0.
|    25:     1344.0799: 0.172725  1.33883 0.360442  4.89420 -8.18267 -5.72482 0.
|    26:     1344.0786: 0.222431  1.35804 0.362186  5.34107 -8.91033 -5.84653 0.
|    27:     1344.0775: 0.237173  1.35287 0.365458  5.44352 -9.07971 -5.82017 0.
|    28:     1344.0751: 0.277163  1.34640 0.368241  5.73547 -9.55361 -5.77370 0.
|    29:     1344.0711: 0.400471  1.33338 0.365608  6.66502 -11.0600 -5.68496 0.
|    30:     1344.0689: 0.452397  1.31052 0.360559  6.99693 -11.5934 -5.53261 0.
|    31:     1344.0680: 0.563252  1.29373 0.353045  7.81897 -12.9217 -5.41781 0.
|    32:     1344.0677: 0.540829  1.29078 0.352286  7.63601 -12.6272 -5.40902 0.
|    33:     1344.0677: 0.553374  1.28930 0.351942  7.73110 -12.7814 -5.39888 0.
|    34:     1344.0677: 0.558589  1.28841 0.351897  7.77049 -12.8456 -5.39307 0.
|    35:     1344.0677: 0.563458  1.28777 0.352000  7.80972 -12.9100 -5.38927 0.
```

```
|    36:     1344.0676: 0.576996  1.28677 0.352471  7.92628 -13.1026 -5.38376 0.
|    37:     1344.0676: 0.593571  1.28683 0.353216  8.08188 -13.3613 -5.38569 0.
|    38:     1344.0674: 0.619875  1.28946 0.354743  8.35504 -13.8185 -5.40543 0.
|    39:     1344.0672: 0.641469  1.29582 0.356721  8.62525 -14.2759 -5.44942 0.
|    40:     1344.0668: 0.660166  1.30852 0.358766  8.94454 -14.8245 -5.53708 0.
|    41:     1344.0668: 0.687453  1.31372 0.358835  9.27042 -15.3746 -5.57681 0.
|    42:     1344.0666: 0.690931  1.31619 0.358227  9.34672 -15.5071 -5.59529 0.
|    43:     1344.0666: 0.711359  1.31937 0.358658  9.59742 -15.9318 -5.61917 0.
|    44:     1344.0665: 0.757395  1.32118 0.359929  10.1220 -16.8187 -5.63908 0.
|    45:     1344.0663: 0.771001  1.31713 0.360429  10.2480 -17.0304 -5.61349 0.
|    46:     1344.0663: 0.816198  1.31473 0.361563  10.7405 -17.8618 -5.60476 0.
|    47:     1344.0662: 0.811773  1.31387 0.361082  10.6910 -17.7782 -5.59889 0.
|    48:     1344.0662: 0.828142  1.31402 0.361355  10.8888 -18.1133 -5.60218 0.
|    49:     1344.0661: 0.847053  1.31517 0.361849  11.1290 -18.5214 -5.61281 0.
|    50:     1344.0661: 0.864558  1.31738 0.362432  11.3688 -18.9296 -5.62999 0.
|    51:     1344.0661: 0.879582  1.32127 0.363119  11.6077 -19.3378 -5.65808 0.
|    52:     1344.0660: 0.897048  1.32241 0.363592  11.8477 -19.7461 -5.66923 0.
|    53:     1344.0660: 0.913854  1.32353 0.364124  12.0882 -20.1542 -5.67902 0.
|    54:     1344.0660: 0.931867  1.32412 0.364585  12.3289 -20.5621 -5.68499 0.
|    55:     1344.0659: 0.950631  1.32343 0.364785  12.5705 -20.9696 -5.68231 0.
|    56:     1344.0659: 0.969734  1.32068 0.364613  12.7998 -21.3528 -5.66493 0.
```

```
|    57:     1344.0659: 0.986369  1.32054 0.364771  13.0280 -21.7372 -5.66560 0.
|    58:     1344.0659:  1.02074  1.32130 0.365114  13.5286 -22.5789 -5.67343 0.
|    59:     1344.0658:  1.03767  1.32322 0.365306  13.8168 -23.0613 -5.68662 0.
|    60:     1344.0658:  1.05586  1.32478 0.365605  14.1044 -23.5442 -5.69778 0.
|    61:     1344.0658:  1.07374  1.32643 0.365897  14.3923 -24.0268 -5.70923 0.
|    62:     1344.0657:  1.07805  1.32824 0.366160  14.4863 -24.1838 -5.72040 0.
|    63:     1344.0657:  1.09577  1.33115 0.366455  14.8085 -24.7204 -5.73961 0.
|    64:     1344.0656:  1.12414  1.33426 0.366503  15.3161 -25.5599 -5.75899 0.
|    65:     1344.0656:  1.13290  1.33485 0.366524  15.4657 -25.8073 -5.76240 0.
|    66:     1344.0656:  1.15016  1.33573 0.366480  15.7658 -26.3015 -5.76684 0.
|    67:     1344.0655:  1.18517  1.33704 0.366238  16.3660 -27.2900 -5.77342 0.
|    68:     1344.0654:  1.21118  1.33576 0.365566  16.8064 -28.0065 -5.76184 0.
|    69:     1344.0654:  1.23582  1.33590 0.365122  17.2462 -28.7235 -5.76009 0.
|    70:     1344.0652:  1.28989  1.33551 0.363645  18.2666 -30.3719 -5.74922 0.
|    71:     1344.0652:  1.30736  1.33596 0.363328  18.5962 -30.9069 -5.75020 0.
|    72:     1344.0651:  1.32242  1.33836 0.363264  18.9261 -31.4415 -5.76309 0.
|    73:     1344.0651:  1.33386  1.34373 0.363616  19.2558 -31.9755 -5.79544 0.
|    74:     1344.0650:  1.33959  1.35226 0.364297  19.5552 -32.4591 -5.84869 0.
|    75:     1344.0650:  1.35258  1.35429 0.364004  19.8565 -32.9444 -5.85988 0.
|    76:     1344.0650:  1.36607  1.35537 0.363530  20.1589 -33.4291 -5.86477 0.
|    77:     1344.0649:  1.39888  1.35524 0.362066  20.8539 -34.5368 -5.85769 0.
```

```
|    78:     1344.0648:  1.41882  1.35237 0.360868  21.2479 -35.1566 -5.83455 0.
|    79:     1344.0648:  1.43641  1.35303 0.360420  21.6392 -35.7787 -5.83399 0.
|    80:     1344.0648:  1.45256  1.35468 0.360253  22.0310 -36.4005 -5.84003 0.
|    81:     1344.0647:  1.46675  1.35776 0.360459  22.4238 -37.0216 -5.85474 0.
|    82:     1344.0647:  1.48045  1.36071 0.360370  22.8171 -37.6424 -5.87008 0.
|    83:     1344.0647:  1.50115  1.36364 0.359496  23.3826 -38.5328 -5.88370 0.
|    84:     1344.0647:  1.51541  1.36592 0.358658  23.8140 -39.2049 -5.89390 0.
|    85:     1344.0646:  1.53162  1.36748 0.357970  24.2427 -39.8787 -5.89977 0.
|    86:     1344.0646:  1.54768  1.36903 0.357357  24.6719 -40.5523 -5.90535 0.
|    87:     1344.0646:  1.54497  1.36788 0.357602  24.5788 -40.4056 -5.89874 0.
|    88:     1344.0646:  1.54803  1.36767 0.357551  24.6498 -40.5164 -5.89642 0.
|    89:     1344.0646:  1.55426  1.36779 0.357369  24.8097 -40.7662 -5.89523 0.
|    90:     1344.0646:  1.55854  1.36820 0.357224  24.9297 -40.9538 -5.89654 0.
|    91:     1344.0646:  1.56344  1.36908 0.357037  25.0803 -41.1894 -5.90085 0.
|    92:     1344.0646:  1.56590  1.36966 0.356942  25.1599 -41.3140 -5.90394 0.
|    93:     1344.0646:  1.56683  1.36987 0.356910  25.1900 -41.3614 -5.90506 0.
```

```
summary( fit.mycr )
```

```
|   Linear mixed-effects model fit by REML
|    Data: dd
|         AIC      BIC   logLik
```

```
|     1809.73 1862.132 -890.865
|
|   Random effects:
|    Formula: ~1 + dvar(drug, id) | id
|    Structure: General positive-definite, Log-Cholesky parametrization
|                           StdDev   Corr
|   (Intercept)             4.874986 (Intr) d(,i)C
|   dvar(drug, id)Clozapine 3.636066 0.132
|   dvar(drug, id)Typical   2.354937 0.359  0.972
|   Residual                3.364987
|
|   Correlation Structure: AR(1)
|    Formula: ~year | id
|    Parameter estimate(s):
|         Phi
|   0.2271199
|   Fixed effects: neg ~ drug + drug.m + year
|                       Value Std.Error  DF   t-value p-value
|   (Intercept)     17.222238 2.1614338 262  7.967969  0.0000
|   drugClozapine   -1.477185 1.0934029 262 -1.350998  0.1779
|   drugTypical     -0.443665 0.7984370 262 -0.555667  0.5789
```

```
|    drug.mClozapine  3.784304 2.9985532  50  1.262043  0.2128
|    drug.mTypical   -0.970400 2.9348551  50 -0.330647  0.7423
|    year            -0.463628 0.1482115 262 -3.128150  0.0020
|     Correlation:
|                    (Intr) drgClz drgTyp drg.mC drg.mT
|    drugClozapine    0.107
|    drugTypical      0.019  0.527
|    drug.mClozapine -0.747 -0.428 -0.257
|    drug.mTypical   -0.838 -0.187 -0.318  0.668
|    year            -0.243 -0.145  0.342  0.059 -0.091
|
|    Standardized Within-Group Residuals:
|            Min          Q1         Med           Q3          Max
|    -3.37154964 -0.55355114 -0.08730445  0.53241624  2.67344088
|
|    Number of Observations: 318
|    Number of Groups: 53
```

```
summary( fit.myc )   # very significant drop with time
```

```
|    Linear mixed-effects model fit by REML
|     Data: dd
```

```
|          AIC      BIC    logLik
|      1806.119 1839.806 -894.0595
|
|   Random effects:
|    Formula: ~1 | id
|           (Intercept) Residual
|   StdDev:    4.863878 3.477444
|
|   Correlation Structure: AR(1)
|    Formula: ~year | id
|    Parameter estimate(s):
|         Phi
|   0.2045159
|   Fixed effects: neg ~ drug + drug.m + year
|                       Value Std.Error  DF   t-value p-value
|   (Intercept)     17.551586 2.1753872 262  8.068258  0.0000
|   drugClozapine   -1.198927 0.8940467 262 -1.341011  0.1811
|   drugTypical     -0.241801 0.6875520 262 -0.351684  0.7254
|   drug.mClozapine  3.164622 2.8743291  50  1.100995  0.2762
|   drug.mTypical   -1.494575 2.8857604  50 -0.517914  0.6068
|   year            -0.485736 0.1503674 262 -3.230327  0.0014
```

```
|    Correlation:
|                   (Intr) drgClz drgTyp drg.mC drg.mT
|   drugClozapine    0.050
|   drugTypical     -0.102  0.375
|   drug.mClozapine -0.758 -0.309 -0.115
|   drug.mTypical   -0.831 -0.088 -0.233  0.654
|   year            -0.244 -0.211  0.403  0.066 -0.094
|
|   Standardized Within-Group Residuals:
|          Min         Q1        Med         Q3        Max
|   -3.2515034 -0.6100687 -0.1129732  0.5311779  3.0912181
|
|   Number of Observations: 318
|   Number of Groups: 53
intervals( fit.myc ) # Beware of interpreting intervals for SDs
|   Approximate 95% confidence intervals
|
|    Fixed effects:
|                        lower       est.      upper
|   (Intercept)     13.2681190 17.5515864 21.8350537
```

```
|   drugClozapine   -2.9593580 -1.1989267  0.5615045
|   drugTypical     -1.5956322 -0.2418011  1.1120299
|   drug.mClozapine -2.6086379  3.1646220  8.9378819
|   drug.mTypical   -7.2907957 -1.4945753  4.3016450
|   year            -0.7818181 -0.4857358 -0.1896535
|   attr(,"label")
|   [1] "Fixed effects:"
|
|    Random Effects:
|     Level: id
|                      lower     est.    upper
|   sd((Intercept)) 3.897864 4.863878 6.069302
|
|    Correlation structure:
|            lower      est.   upper
|   Phi 0.03389873 0.2045159 0.36355
|   attr(,"label")
|   [1] "Correlation structure:"
|
|    Within-group standard error:
|      lower     est.    upper
```

```
|   3.125290 3.477444 3.869279

wald( fit.myc, ’drug.m’)   # what happened to the contextual effect? Why?

|          numDF denDF F.value p.value
|   drug.m     2    50 1.94558 0.15357
|
|   Coefficients       Estimate Std.Error DF   t-value p-value Lower 0.95
|     drug.mClozapine  3.164622  2.874329 50  1.100995 0.27617  -2.608638
|     drug.mTypical   -1.494575  2.885760 50 -0.517914 0.60680  -7.290796
|
|   Coefficients      Upper 0.95
|     drug.mClozapine   8.937882
|     drug.mTypical     4.301645

# Hypothesis matrix does not change

wald ( fit.mycr, Lmy )

|             numDF denDF  F.value p.value
|   predicted     3   262 19.72942 <.00001
|
|               Estimate Std.Error  DF  t-value p-value Lower 0.95 Upper 0.95
```

```
|     Atypical  15.59954  2.096422 262 7.441029 <.00001  11.471560   19.72752
|     Clozapine 14.12236  2.435940 262 5.797498 <.00001   9.325844   18.91887
|     Typical   15.15588  2.319962 262 6.532812 <.00001  10.587732   19.72402
|
|               numDF denDF   F.value p.value
|   differences     2   262 0.9295739 0.39602
|
|                           Estimate Std.Error  DF   t-value p-value
|     Clozapine - Atypical -1.477185  1.093403 262 -1.350998 0.17786
|     Typical - Atypical   -0.443665  0.798437 262 -0.555667 0.57891
|     Typical - Clozapine   1.033520  0.955266 262  1.081919 0.28028
|
|                          Lower 0.95 Upper 0.95
|     Clozapine - Atypical  -3.630161   0.675790
|     Typical - Atypical    -2.015835   1.128505
|     Typical - Clozapine   -0.847456   2.914497
getVarCov( fit.mycr)
|   Random effects variance covariance matrix
|                           (Intercept) dvar(drug, id)Clozapine
|   (Intercept)                 23.7650                  2.3363
```

```
|   dvar(drug, id)Clozapine      2.3363                      13.2210
|   dvar(drug, id)Typical        4.1188                       8.3225
|                           dvar(drug, id)Typical
|   (Intercept)                            4.1188
|   dvar(drug, id)Clozapine                8.3225
|   dvar(drug, id)Typical                  5.5457
|     Standard Deviations: 4.875 3.6361 2.3549
```

```
svd( getVarCov( fit.mycr) )
```

```
|   $d
|   [1] 26.235036428 16.292475767  0.004679905
|
|   $u
|              [,1]       [,2]        [,3]
|   [1,] -0.8756901  0.4731589 -0.09637141
|   [2,] -0.3617502 -0.7750336 -0.51813096
|   [3,] -0.3198494 -0.4188598  0.84985461
|
|   $v
|              [,1]       [,2]        [,3]
|   [1,] -0.8756901  0.4731589 -0.09637141
```

```
|   [2,] -0.3617502 -0.7750336 -0.51813096
|   [3,] -0.3198494 -0.4188598  0.84985461
```

```
coef( fit.mycr )
```

```
|        (Intercept) drugClozapine drugTypical drug.mClozapine drug.mTypical
|   F2     12.258546     -1.477185  -0.4436649         3.784304       -0.9704
|   F4     12.268543     -1.477185  -0.4436649         3.784304       -0.9704
|   F11    12.103318     -1.477185  -0.4436649         3.784304       -0.9704
|   F36    10.737796     -1.477185  -0.4436649         3.784304       -0.9704
|   F10    13.916378     -1.477185  -0.4436649         3.784304       -0.9704
|   F25    14.268775     -1.477185  -0.4436649         3.784304       -0.9704
|   F24    14.069320     -1.477185  -0.4436649         3.784304       -0.9704
|   F32    16.054955     -1.477185  -0.4436649         3.784304       -0.9704
|   F41    14.616743     -1.477185  -0.4436649         3.784304       -0.9704
|   F23    15.501026     -1.477185  -0.4436649         3.784304       -0.9704
|   F27    18.491385     -1.477185  -0.4436649         3.784304       -0.9704
|   F48    19.956942     -1.477185  -0.4436649         3.784304       -0.9704
|   F45    23.301542     -1.477185  -0.4436649         3.784304       -0.9704
|   F54    22.624043     -1.477185  -0.4436649         3.784304       -0.9704
|   F55    27.632965     -1.477185  -0.4436649         3.784304       -0.9704
|   M1      9.585229     -1.477185  -0.4436649         3.784304       -0.9704
```

```
|   M5    11.066035     -1.477185  -0.4436649        3.784304       -0.9704
|   M3    12.162397     -1.477185  -0.4436649        3.784304       -0.9704
|   M21   11.970583     -1.477185  -0.4436649        3.784304       -0.9704
|   M7    13.564028     -1.477185  -0.4436649        3.784304       -0.9704
|   M6    12.676917     -1.477185  -0.4436649        3.784304       -0.9704
|   M22   14.022968     -1.477185  -0.4436649        3.784304       -0.9704
|   M14   12.240517     -1.477185  -0.4436649        3.784304       -0.9704
|   M8    14.266775     -1.477185  -0.4436649        3.784304       -0.9704
|   M12   14.067412     -1.477185  -0.4436649        3.784304       -0.9704
|   M13   15.414158     -1.477185  -0.4436649        3.784304       -0.9704
|   M15   15.614222     -1.477185  -0.4436649        3.784304       -0.9704
|   M16   15.870422     -1.477185  -0.4436649        3.784304       -0.9704
|   M17   15.208013     -1.477185  -0.4436649        3.784304       -0.9704
|   M19   13.927730     -1.477185  -0.4436649        3.784304       -0.9704
|   M37   15.511232     -1.477185  -0.4436649        3.784304       -0.9704
|   M29   13.934164     -1.477185  -0.4436649        3.784304       -0.9704
|   M26   14.222611     -1.477185  -0.4436649        3.784304       -0.9704
|   M30   16.775732     -1.477185  -0.4436649        3.784304       -0.9704
|   M20   18.361869     -1.477185  -0.4436649        3.784304       -0.9704
|   M35   18.781482     -1.477185  -0.4436649        3.784304       -0.9704
|   M28   18.628502     -1.477185  -0.4436649        3.784304       -0.9704
```

```
|    M40   18.275107     -1.477185  -0.4436649        3.784304        -0.9704
|    M31   18.875984     -1.477185  -0.4436649        3.784304        -0.9704
|    M33   19.844552     -1.477185  -0.4436649        3.784304        -0.9704
|    M34   18.620833     -1.477185  -0.4436649        3.784304        -0.9704
|    M46   20.209872     -1.477185  -0.4436649        3.784304        -0.9704
|    M43   21.772251     -1.477185  -0.4436649        3.784304        -0.9704
|    M44   21.751034     -1.477185  -0.4436649        3.784304        -0.9704
|    M47   18.819868     -1.477185  -0.4436649        3.784304        -0.9704
|    M39   22.142500     -1.477185  -0.4436649        3.784304        -0.9704
|    M38   22.982495     -1.477185  -0.4436649        3.784304        -0.9704
|    M49   20.589381     -1.477185  -0.4436649        3.784304        -0.9704
|    M42   23.790315     -1.477185  -0.4436649        3.784304        -0.9704
|    M52   22.187680     -1.477185  -0.4436649        3.784304        -0.9704
|    M50   23.238727     -1.477185  -0.4436649        3.784304        -0.9704
|    M51   25.090523     -1.477185  -0.4436649        3.784304        -0.9704
|    M53   28.912201     -1.477185  -0.4436649        3.784304        -0.9704
|              year dvar(drug, id)Clozapine dvar(drug, id)Typical
|    F2  -0.4636277              -0.48796613          -0.860257908
|    F4  -0.4636277              -1.06065610          -1.208622225
|    F11 -0.4636277              -0.50322608          -0.887160389
|    F36 -0.4636277              -6.94564314          -4.971745231
```

```
|    F10 -0.4636277             -0.32498950           -0.572938923
|    F25 -0.4636277              1.68285053            0.692323493
|    F24 -0.4636277              0.47050360           -0.071775539
|    F32 -0.4636277             -0.11475218           -0.202301890
|    F41 -0.4636277              5.44850075            3.021317777
|    F23 -0.4636277              1.57650131            0.767187831
|    F27 -0.4636277              0.87217103            0.676076885
|    F48 -0.4636277              0.26884080            0.473951809
|    F45 -0.4636277             -1.26353275           -0.083889194
|    F54 -0.4636277              0.53103578            0.936187382
|    F55 -0.4636277              4.25423594            3.775029411
|    M1  -0.4636277              0.26067800           -0.708683863
|    M5  -0.4636277             -1.80920904           -1.801707056
|    M3  -0.4636277             -0.49741826           -0.876921517
|    M21 -0.4636277              2.01387471            0.633916730
|    M7  -0.4636277             -0.35962794           -0.634004617
|    M6  -0.4636277              0.62707650           -0.132369524
|    M22 -0.4636277              0.14756153           -0.272475455
|    M14 -0.4636277             -1.96903346           -1.763056421
|    M8  -0.4636277             -0.82553673           -0.838703711
|    M12 -0.4636277              1.52453012            0.572887265
```

```
|   M13 -0.4636277             -0.17774703          -0.313358413
|   M15 -0.4636277             -0.15807933          -0.278685319
|   M16 -0.4636277             -0.13289303          -0.234283235
|   M17 -0.4636277             -1.49844263          -1.139977803
|   M19 -0.4636277             -1.06218723          -1.019997218
|   M37 -0.4636277             -0.73182373          -0.639315413
|   M29 -0.4636277             -0.32324097          -0.569856352
|   M26 -0.4636277             -0.29488455          -0.519865524
|   M30 -0.4636277             -2.74000190          -1.722303004
|   M20 -0.4636277             -0.42777035          -0.131918198
|   M35 -0.4636277             -2.54597536          -1.377052354
|   M28 -0.4636277             -0.97293608          -0.434404320
|   M40 -0.4636277             -0.19580339           0.003260426
|   M31 -0.4636277              0.30729869           0.374628588
|   M33 -0.4636277              2.07024007           1.560561253
|   M34 -0.4636277              0.55888782           0.499212330
|   M46 -0.4636277              2.36614026           1.783792442
|   M43 -0.4636277             -0.91140621          -0.040617374
|   M44 -0.4636277              2.45098431           2.008953939
|   M47 -0.4636277              0.15705841           0.276885491
|   M39 -0.4636277             -1.30350745          -0.237951006
```

```
|   M38 -0.4636277            0.56627417          0.998310752
|   M49 -0.4636277            0.33101402          0.583559833
|   M42 -0.4636277            0.98448521          1.345072401
|   M52 -0.4636277            2.01118895          1.786846469
|   M50 -0.4636277           -1.34961533         -0.141869333
|   M51 -0.4636277           -0.51883631          0.578305862
|   M53 -0.4636277            0.02480971          1.339799962
```

```
zz <- ranef( fit.mycr )
names(zz) <- c("Int",'Cloz', "Typical")
names(zz)
```

```
|   [1] "Int"     "Cloz"    "Typical"
```

```
if(interactive) {
  library( p3d )
  Init3d()
  Plot3d(Int ~ Cloz +Typical , zz)
  Id3d(pad = 2)
  Ell3d()
}
#
# some of the potential RE variance is accounted for by within-cluster
```

```
# variance.  This is analogous to having an F at or below 1 for blocks
# in a blocked randomized design.
#

fit.mycrd <- update( fit.mycr, subset = !(id %in% c("F41", "F55", "F36", "M53"))

|      0:      1218.2848: -0.350809 0.409399 0.419278 0.0606497 0.197817 -0.929162
|      1:      1214.6465: -0.348493 0.484975 0.456475 0.0664595 0.202482 -0.926218
|      2:      1214.2631: -0.249104 0.531671 0.493657 0.0648044 0.189951 -0.928716
|      3:      1214.0069: -0.289863 0.611199 0.556716 0.0786657 0.188032 -0.935074
|      4:      1213.6081: -0.230851 0.784148 0.693169 0.108721 0.177443 -0.957063
|      5:      1212.9669: -0.245281  1.13922 0.945018 0.227100 0.176893 -1.09821 0
|      6:      1212.8109: -0.175260  1.43672  1.16301 0.400409 0.213672 -1.28302 0
|      7:      1212.6017: -0.225219  1.75511  1.39737 0.555898 0.224998 -1.45494 0
|      8:      1212.5510: -0.225556  1.98982  1.57317 0.705819 0.260614 -1.59721 0
|      9:      1212.5222: -0.223161  2.21568  1.75927 0.855509 0.281178 -1.74432 0
|     10:      1212.5011: -0.222257  2.52465  2.01948  1.06369 0.306900 -1.94779 0
|     11:      1212.4913: -0.223239  2.80790  2.26214  1.25738 0.332138 -2.13482 0
|     12:      1212.4861: -0.224315  3.08885  2.50696  1.45215 0.358484 -2.32121 0
|     13:      1212.4833: -0.225112  3.36799  2.75349  1.64763 0.385423 -2.50725 0
|     14:      1212.4814: -0.225793  3.71203  3.05996  1.89022 0.419445 -2.73723 0
|     15:      1212.4805: -0.226192  4.04391  3.35714  2.12544 0.453042 -2.95951 0
```

```
|    16:     1212.4801: -0.226454  4.37528  3.65469  2.36094 0.486998 -3.18171 0
|    17:     1212.4798: -0.226606  4.70636  3.95242  2.59664 0.521234 -3.40386 0
|    18:     1212.4797: -0.226701  5.03727  4.25024  2.83245 0.555608 -3.62598 0
|    19:     1212.4797: -0.226753  5.36809  4.54811  3.06834 0.590088 -3.84809 0
|    20:     1212.4796: -0.226785  5.69886  4.84600  3.30426 0.624616 -4.07019 0
|    21:     1212.4796: -0.226803  6.02961  5.14389  3.54021 0.659182 -4.29229 0
|    22:     1212.4796: -0.226813  6.36033  5.44180  3.77618 0.693764 -4.51438 0
|    23:     1212.4796: -0.226819  6.69105  5.73971  4.01215 0.728360 -4.73648 0
|    24:     1212.4796: -0.226822  7.02177  6.03761  4.24813 0.762960 -4.95857 0
|    25:     1212.4796: -0.226824  7.35248  6.33552  4.48411 0.797565 -5.18067 0
|    26:     1212.4796: -0.226825  7.68319  6.63343  4.72009 0.832171 -5.40276 0
|    27:     1212.4796: -0.226826  8.01390  6.93134  4.95607 0.866779 -5.62485 0
|    28:     1212.4796: -0.226826  8.34461  7.22925  5.19205 0.901388 -5.84695 0
|    29:     1212.4796: -0.226826  8.67532  7.52716  5.42803 0.935997 -6.06904 0
```

```
summary(fit.mycrd)
```

```
|   Linear mixed-effects model fit by REML
|    Data: dd
|     Subset: !(id %in% c("F41", "F55", "F36", "M53"))
|          AIC      BIC    logLik
|     1639.335 1690.617 -805.6676
```

```
|
|   Random effects:
|    Formula: ~1 + dvar(drug, id) | id
|    Structure: General positive-definite, Log-Cholesky parametrization
|                          StdDev       Corr
|   (Intercept)            4.2162336556 (Intr) d(,i)C
|   dvar(drug, id)Clozapine 0.0005738158 -0.001
|   dvar(drug, id)Typical  0.0018088928 -0.001  0.003
|   Residual               3.3605866597
|
|   Correlation Structure: AR(1)
|    Formula: ~year | id
|    Parameter estimate(s):
|         Phi
|   0.2658394
|   Fixed effects: neg ~ drug + drug.m + year
|                      Value Std.Error  DF   t-value p-value
|   (Intercept)      16.057880 2.0000393 242  8.028782  0.0000
|   drugClozapine   -1.729732 0.9491360 242 -1.822428  0.0696
|   drugTypical     -0.069781 0.6817590 242 -0.102354  0.9186
|   drug.mClozapine  5.463603 2.6625298  46  2.052034  0.0459
```

```
|   drug.mTypical   -0.577079 2.6176684  46 -0.220455  0.8265
|   year            -0.437601 0.1504172 242 -2.909247  0.0040
|    Correlation:
|                   (Intr) drgClz drgTyp drg.mC drg.mT
|   drugClozapine    0.052
|   drugTypical     -0.104  0.387
|   drug.mClozapine -0.738 -0.355 -0.135
|   drug.mTypical   -0.821 -0.098 -0.253  0.647
|   year            -0.265 -0.205  0.374  0.074 -0.094
|
|   Standardized Within-Group Residuals:
|          Min          Q1         Med          Q3         Max
|   -3.3738536 -0.5858574 -0.0880750  0.5438053  2.7528831
|
|   Number of Observations: 294
|   Number of Groups: 49
```

```
wald( fit.mycrd, "drug")
```

```
|        numDF denDF  F.value p.value
|   drug     4    46 2.250855 0.07808
|
```

```
|   Coefficients       Estimate Std.Error  DF   t-value p-value Lower 0.95
|     drugClozapine   -1.729732  0.949136 242 -1.822428 0.06962  -3.599354
|     drugTypical     -0.069781  0.681759 242 -0.102354 0.91856  -1.412720
|     drug.mClozapine  5.463603  2.662530  46  2.052034 0.04588   0.104208
|     drug.mTypical   -0.577079  2.617668  46 -0.220455 0.82649  -5.846172
|
|   Coefficients      Upper 0.95
|     drugClozapine     0.139891
|     drugTypical       1.273158
|     drug.mClozapine  10.822997
|     drug.mTypical     4.692014
```

```
wald( fit.mycrd, Ldiff( fit.mycrd, "drug[^\\.]", ref ="Atypical"))
```

```
|     numDF denDF  F.value p.value
|   1     2   242 1.874021 0.15573
|
|                      Estimate Std.Error  DF   t-value p-value Lower 0.95
|     pine - Atypical -1.729732  0.949136 242 -1.822428 0.06962  -3.599354
|     al - Atypical   -0.069781  0.681759 242 -0.102354 0.91856  -1.412720
|     al - pine        1.659951  0.930129 242  1.784645 0.07557  -0.172232
|
```

```
|                     Upper 0.95
|     pine - Atypical   0.139891
|     al - Atypical     1.273158
|     al - pine         3.492134
```

```
# Finally: random year

fit.mycry <- update( fit.myc, random = ~ 1 + dvar( drug, id) + year | id)

fit.mycry <- update( fit.myc, random = ~ 1 + dvar( drug, id) + year| id,
                     control = list( msMaxIter = 200, msVerbose = TRUE   ))
```

```
|     0:     1342.1088: -0.529535 0.00935858 0.0825324  1.27208 0.0368797 -0.333
|     1:     1342.0089: -0.524417 0.0437405 0.128175  1.28043 0.0395296 -0.34316
|     2:     1341.9801: -0.503277 0.0485775 0.138368  1.29903 0.0375529 -0.34571
|     3:     1341.9793: -0.527049 0.0541661 0.148864  1.31127 0.0217401 -0.35663
|     4:     1341.9560: -0.511187 0.0547405 0.153031  1.31227 0.0292068 -0.35484
|     5:     1341.9415: -0.496887 0.0618125 0.174333  1.32275 0.0323529 -0.36252
|     6:     1341.9090: -0.504847 0.0759527 0.208867  1.33028 0.0358415 -0.38895
|     7:     1341.9055: -0.482569 0.0924420 0.213671  1.32621 0.00899266 -0.4129
|     8:     1341.8769: -0.490251 0.107285 0.213359  1.32996 0.0399562 -0.428768
|     9:     1341.8745: -0.497464 0.105226 0.217439  1.33475 0.0415688 -0.429223
```

```
|     10:     1341.8722: -0.491577 0.104456 0.220498  1.33588 0.0456205 -0.428093
|     11:     1341.8693: -0.495693 0.105681 0.222656  1.33654 0.0446148 -0.429741
|     12:     1341.8230: -0.496765 0.154759 0.258690  1.34041 0.0773498 -0.464767
|     13:     1341.8082: -0.479411 0.158903 0.278163  1.38281 0.141519 -0.582627
|     14:     1341.7612: -0.473119 0.230124 0.275044  1.41117 0.143274 -0.648404
|     15:     1341.7277: -0.456599 0.242358 0.295407  1.37159 0.140966 -0.653899
|     16:     1341.7170: -0.465162 0.235911 0.302909  1.36527 0.152375 -0.666087
|     17:     1341.7128: -0.462066 0.224836 0.303253  1.36551 0.160734 -0.663829
|     18:     1341.7051: -0.466706 0.231688 0.303983  1.37010 0.162482 -0.674659
|     19:     1341.6609: -0.454341 0.291094 0.334134  1.37699 0.229970 -0.808177
|     20:     1341.6356: -0.448586 0.363129 0.355820  1.38311 0.276903 -0.859557
|     21:     1341.6235: -0.427820 0.423566 0.351099  1.42758 0.345425 -0.957342
|     22:     1341.6058: -0.419046 0.470867 0.336768  1.39255 0.402861 -1.07553 -
|     23:     1341.5893: -0.421636 0.488806 0.350097  1.39505 0.417211 -1.07745 -
|     24:     1341.5673: -0.431931 0.553695 0.296058  1.39937 0.464165 -1.04450 -
|     25:     1341.5598: -0.423394 0.585179 0.282630  1.40252 0.509422 -1.10760 -
|     26:     1341.5573: -0.418975 0.615892 0.277159  1.40447 0.537862 -1.15130 -
|     27:     1341.5551: -0.417407 0.637870 0.277960  1.40267 0.565757 -1.19428 -
|     28:     1341.5540: -0.415143 0.658884 0.290562  1.40318 0.586297 -1.24494 -
|     29:     1341.5537: -0.415918 0.660152 0.292820  1.40362 0.590137 -1.25233 -
|     30:     1341.5535: -0.415200 0.664032 0.295138  1.40435 0.598462 -1.26741 -
```

```
|    31:     1341.5533: -0.414202 0.668831 0.295930  1.40503 0.607536 -1.28158 -
|    32:     1341.5528: -0.409593 0.688851 0.297709  1.40738 0.646310 -1.34001 -
|    33:     1341.5523: -0.404595 0.709217 0.298163  1.40912 0.687911 -1.40056 -
|    34:     1341.5517: -0.397108 0.735600 0.297849  1.41069 0.749151 -1.48840 -
|    35:     1341.5512: -0.390327 0.754248 0.297247  1.41126 0.803250 -1.56578 -
|    36:     1341.5506: -0.381999 0.768810 0.297221  1.41125 0.864460 -1.65584 -
|    37:     1341.5500: -0.373075 0.773676 0.298451  1.41074 0.920234 -1.74357 -
|    38:     1341.5495: -0.366772 0.764795 0.300738  1.40999 0.945558 -1.79263 -
|    39:     1341.5493: -0.365842 0.751851 0.302633  1.40956 0.933905 -1.78577 -
|    40:     1341.5493: -0.368244 0.740565 0.303238  1.40926 0.908924 -1.75279 -
|    41:     1341.5493: -0.370239 0.737860 0.303239  1.40923 0.895327 -1.73230 -
|    42:     1341.5493: -0.370687 0.737399 0.303046  1.40917 0.893826 -1.72899 -
|    43:     1341.5493: -0.370650 0.737463 0.303040  1.40915 0.894183 -1.72938 -
```

```
summary(fit.mycry)
```

```
|   Linear mixed-effects model fit by REML
|    Data: dd
|          AIC      BIC    logLik
|     1812.699 1880.073 -888.3496
|
|   Random effects:
```

```
|    Formula: ~1 + dvar(drug, id) + year | id
|    Structure: General positive-definite, Log-Cholesky parametrization
|                           StdDev    Corr
|   (Intercept)             5.7116322 (Intr) d(,i)C d(,i)T
|   dvar(drug, id)Clozapine 4.7831944  0.435
|   dvar(drug, id)Typical   2.2451318  0.199  0.481
|   year                    0.7303589 -0.485 -0.722  0.182
|   Residual                2.9889859
|
|   Correlation Structure: AR(1)
|    Formula: ~year | id
|    Parameter estimate(s):
|          Phi
|   0.07280286
|   Fixed effects: neg ~ drug + drug.m + year
|                      Value Std.Error  DF   t-value p-value
|   (Intercept)     17.373201 2.1886369 262  7.937909  0.0000
|   drugClozapine   -1.561402 1.1228580 262 -1.390560  0.1655
|   drugTypical     -0.582994 0.7728203 262 -0.754372  0.4513
|   drug.mClozapine  3.858564 3.0086968  50  1.282470  0.2056
|   drug.mTypical   -0.827937 2.9391945  50 -0.281688  0.7793
```

```
|   year            -0.504260 0.1670087 262 -3.019364  0.0028
|    Correlation:
|                   (Intr) drgClz drgTyp drg.mC drg.mT
|   drugClozapine    0.153
|   drugTypical      0.006  0.436
|   drug.mClozapine -0.759 -0.426 -0.227
|   drug.mTypical   -0.828 -0.153 -0.312  0.657
|   year            -0.276 -0.312  0.342  0.121 -0.091
|
|   Standardized Within-Group Residuals:
|          Min         Q1        Med          Q3        Max
|   -2.8579153 -0.4981676 -0.1084193  0.4554007  2.6856555
|
|   Number of Observations: 318
|   Number of Groups: 53
```

```
wald( fit.mycry )
```

```
|    numDF denDF  F.value p.value
|        6    50 83.96209 <.00001
|
|   Coefficients       Estimate Std.Error  DF   t-value p-value Lower 0.95
```

```
|      (Intercept)     17.373201  2.188637 262  7.937909 <.00001  13.063644
|      drugClozapine   -1.561402  1.122858 262 -1.390560 0.16554  -3.772376
|      drugTypical     -0.582994  0.772820 262 -0.754372 0.45130  -2.104723
|      drug.mClozapine  3.858564  3.008697  50  1.282470 0.20559  -2.184582
|      drug.mTypical   -0.827937  2.939195  50 -0.281688 0.77935  -6.731483
|      year            -0.504260  0.167009 262 -3.019364 0.00278  -0.833110
|
|    Coefficients      Upper 0.95
|      (Intercept)      21.682758
|      drugClozapine     0.649573
|      drugTypical       0.938736
|      drug.mClozapine   9.901709
|      drug.mTypical     5.075609
|      year             -0.175410

#
#  Please contact Georges Monette <georges@yorku.ca>
#  with any questions or comments.
#
```