Models for Clustered Data

The Rat Pup Example

The data come from a study in which 30 female rats were randomly assigned to receive one of three doses of an experimental compound (variable **treat** with levels: high, low or control). Although 10 female rats were initially assigned to receive each treatment dose, three of the female rats in the high-dose group died, so there are no data for their litters. In addition, litter sizes (variable **lts**) varied widely, ranging from 2 to 18 pups. The sex of the pups was also recorded (variable **sex** taking value zero for males)

Objective of the study: To compare the birth weights (variable **w**) of pups from litters born to female rats that received the high- and low-dose treatments to the birth weights of pups from litters that received the control treatment.

Jose Pinheiro and Doug Bates, (2000) Mixed-Effects Models in S and S-PLUS.

The Rat Pup Example

- Two-level clustered data from a cluster randomized trial
- Each litter (cluster) was randomly assigned to a specific level of treatment
- Rat pups (units of analysis) nested within litters
- Birth weights of rat pups within the same litter are likely to be correlated because the pups shared the same maternal environment

Exploring the data in R

```
> ## Reading the data
> ratpup <- read.table("rat_pup.dat", h = T)
> ratpup$sex1[ratpup$sex == "Female"] <- 1
> ratpup$sex1[ratpup$sex == "Male"] <- 0
> attach(ratpup)
>
> ## Table describing the  data
> g <- function(x)c(N=length(x),Mean=mean(x,na.rm=TRUE),
+ SD=sd(x,na.rm=TRUE), Min=min(x,na.rm=TRUE),Max=max(x,na.rm=TRUE))
> summarize(weight,by=llist(treatment,sex),g)
>
  treatment    sex weight     Mean        SD  Min  Max
1   Control Female     54 6.116111 0.6851179 3.68 7.57
2   Control   Male     77 6.471039 0.7537880 4.57 8.33
3       Low Female     65 5.837538 0.4504964 4.75 7.73
4       Low   Male     61 6.025082 0.3803403 5.25 7.13
5      High Female     32 5.851562 0.6001887 4.48 7.68
6      High   Male     33 5.918485 0.6909058 5.01 7.70
>
```


Exploring the data in R

Treatment	Sex	N obs	Mean	SD	Minimum	Maximum
Control	Female	54.00	6.12	0.69	3.68	7.57
Control	Male	77.00	6.47	0.75	4.57	8.33
Low	Female	65.00	5.84	0.45	4.75	7.73
Low	Male	61.00	6.03	0.38	5.25	7.13
High	Female	32.00	5.85	0.60	4.48	7.68
High	Male	33.00	5.92	0.69	5.01	7.70

- The experimental treatments appear to have a negative effect on mean birth weight for males and females
- Sample mean birth weight of males are consistently higher than those of females within all levels of treatment

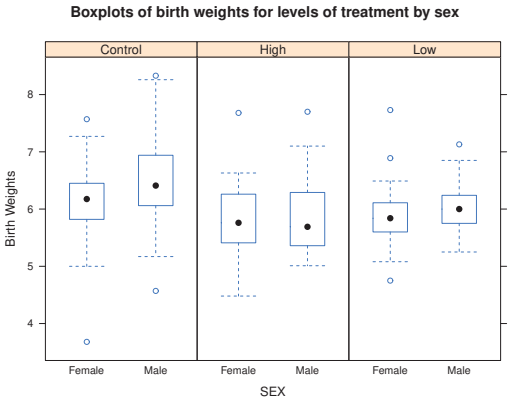
Exploring the data in R

```
> ## Comparing the distributions of birth weights
> ## for each treatment by sex combination
>
> library(lattice)  # trellis graphics
> library(grid)
>
> bwplot(weight ~ sex|treatment, data=ratpup,aspect = 2,
+  ylab="Birth Weights", xlab="SEX",
+  main = "Boxplots of birth weights for levels of treatment by sex")
>
```


Birth weights for levels of treatment by sex

- Males appear to have a higher median birth weight than females in the low and control groups, but not in the high group
- The distribution of birth weight appears to be roughly symmetric at each level of treatment and sex

Birth weights for levels of treatment by sex

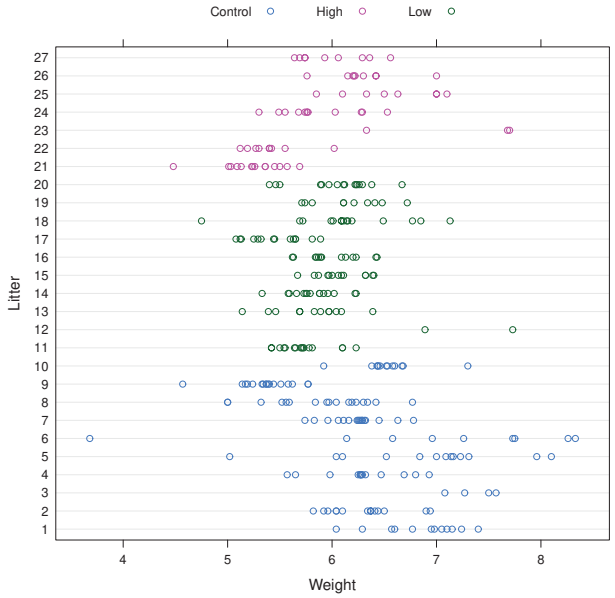


- Lower birth weight for the high- and low-dose treatments compared to the control group
- Variance of the birth weight is similar for males and females within each treatment but appears to differ across treatments

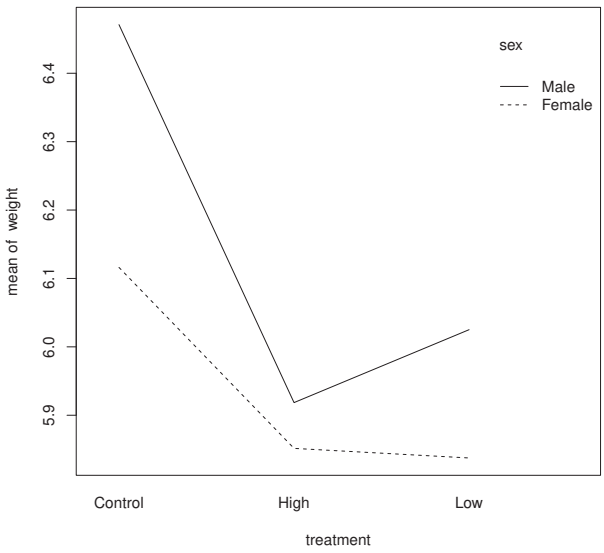
Exploring the data in R

```
> ## Comparing the distributions of birth weights for each treatment
>
> dotplot(litterid ~ weight,group=treatment, data =ratpup,
+ xlab="Weight", ylab="Litter",
+ auto.key=list(space="top", column=3, cex=.8, title="",
+                cex.title=1, lines=FALSE, points=TRUE) )
> with(ratpup, interaction.plot(treatment,sex,weight))
>
```

Exploring the data in R



Exploring the data in R



Hierarchical model interpretation

Level 1: ANOVA type model

$$w_{ij} = \pi_{0i} + \pi_{1i} sex_{ij} + \varepsilon_{ij}, \text{ with } \varepsilon_{ij} \sim N(0, \sigma^2_\varepsilon)$$

Level 2:

$$\begin{cases} \pi_{0i} = \gamma_{00} + \gamma_{01} treat_{1i} + \gamma_{02} treat_{2i} + \gamma_{03} ls_i + b_{0i} \\ \pi_{1i} = \gamma_{10} + \gamma_{20} treat_{1i} + \gamma_{30} treat_{2i} \end{cases}$$

where $treat_{1i}$ and $treat_{2i}$ are level 2 indicator variables for high and low treatment levels, ls_i is the litter size and $b_{0i} \sim N\left(0, \sigma^2_b\right)$

$\Rightarrow$ Birth weights of pups vary **within** litter due to differences in gender and in other unaccounted factors (ε_{ij})

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where $treat_{1i}$ and $treat_{2i}$ are level 2 indicator variables for high and low treatment levels, ls_i is the litter size and $b_{0i} \sim N\left(0, \sigma^2_b\right)$

$\Rightarrow$ Birth weights vary **between** litters due to differences in treatment, litter size and other litter-specific characteristics unaccounted for by the model (b_{0i})

$\Rightarrow$ Notice that treatment may affect males and females pups differently

One single model

Model

$$\begin{aligned} w_{ij} = \quad & \gamma_{00} + \gamma_{01} treat_{1i} + \gamma_{02} treat_{2i} + \gamma_{03} ls_i + \\ & \gamma_{10} sex_{ij} + \gamma_{20} treat_{1i} sex_{ij} + \gamma_{30} treat_{2i} sex_{ij} + \\ & b_{0i} + \varepsilon_{ij} \end{aligned}$$

Distributional Assumptions

$$b_{0i} \sim N\left(0, \sigma_b^2\right) \text{ and } \varepsilon_{ij} \sim N(0, \sigma_\varepsilon^2)$$

Fitting the homocedastic model in R

Model 1

```
> ## Fitting the model
>
> library(nlme)
>
> meanfull.hom <- lme(weight ~ treatment + sex1 + litsize + treatment:sex1,
+                     random = ~1 | litterid, ratpup, method = "REML")
>
```

- The factor() function is not necessary for treatment, because the original treatment variable has string values High, Low, and Control, and will therefore be considered as a factor automatically
- We also do not need to declare sex1 as a factor, because it is an indicator variable having only values of 0 and 1

Fitting the homocedastic model in R

Model 1

```
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>
> library(nlme)
>
> meanfull.hom <- lme(weight ~ treatment + sex1 + litsize + treatment:sex1,
+                     random = ~1 | litterid, ratpup, method = "REML")
>
```

- lme() treats the lowest level (alphabetically or numerically) of a factor as the reference category. This means that "Control" will be the reference category of treatment. The reference level can be changed using

  `treatment=relevel(treatment,ref="High")`

Fitting the homocedastic model in R

Model 1

```
> ## Fitting the model
>
> library(nlme)
>
> meanfull.hom <- lme(weight ~ treatment + sex1 + litsize + treatment:sex1,
+                     random = ~1 | litterid, ratpup, method = "REML")
>
```

- `random = 1 | litterid`, includes a random effect (intercept) for each level of litter in the model
- `method = "REML"`, specifies that the default REML estimation method is to be used

Fitting the homocedastic model in R

```
> summary(meanfull.hom)
>
Linear mixed-effects model fit by REML
 Data: ratpup
       AIC      BIC    logLik
  419.1043 452.8775 -200.5522

Random effects:
 Formula: ~1 | litterid
        (Intercept) Residual
StdDev:   0.3106722 0.404337

Fixed effects: weight ~ treatment + sex1 + litsize + treatment:sex1
                      Value  Std.Error  DF   t-value p-value
(Intercept)         8.323340 0.27333009 292 30.451605  0.0000
treatmentHigh      -0.906057 0.19154238  23 -4.730320  0.0001
treatmentLow       -0.467040 0.15818328  23 -2.952521  0.0071
sex1               -0.411688 0.07315410 292 -5.627679  0.0000
litsize            -0.128382 0.01875336  23 -6.845819  0.0000
treatmentHigh:sex1  0.107023 0.13176318 292  0.812239  0.4173
treatmentLow:sex1   0.083866 0.10568189 292  0.793568  0.4281

.............................................................

Standardized Within-Group Residuals:
        Min          Q1         Med          Q3         Max
-7.47250744 -0.50014749  0.02911668  0.57348178  3.00962055

Number of Observations: 322
Number of Groups: 27
>
```


Fitting the homocedastic model in R

```
> anova(meanfull.hom)
>
                numDF denDF  F-value p-value
(Intercept)         1   292 9093.772  <.0001
treatment           2    23    5.082  0.0149
sex1                1   292   52.602  <.0001
litsize             1    23   47.374  <.0001
treatment:sex1      2   292    0.466  0.6282
>
```

- The anova() function performs a series of Type I (or sequential) F-tests for the fixed effects in the model, each of which are conditional on the preceding terms in the model specification
- For example, the F-test for sex1 is conditional on the treatment effects, but the F-test for treatment is not conditional on the sex1 effect

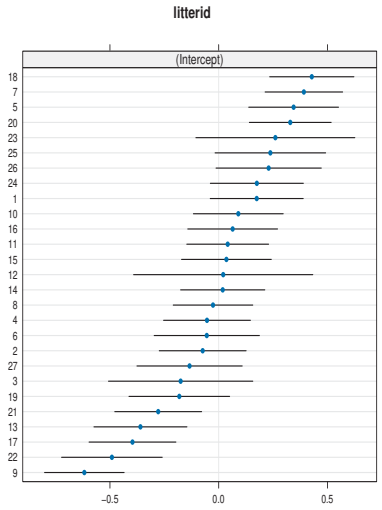
Fitting the homocedastic model in R

```
> anova(meanfull.hom)
>
                numDF denDF  F-value p-value
(Intercept)         1   292 9093.772  <.0001
treatment           2    23    5.082  0.0149
sex1                1   292   52.602  <.0001
litsize             1    23   47.374  <.0001
treatment:sex1      2   292    0.466  0.6282
>
```

Model fitted using REML

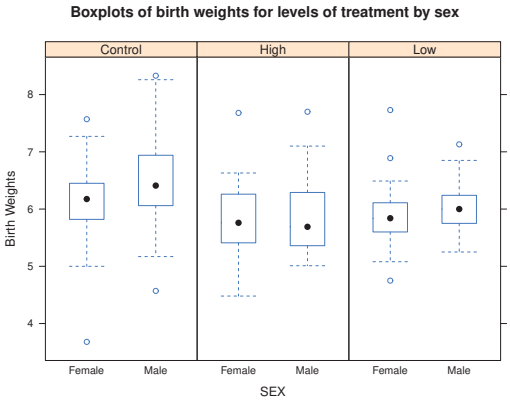
The model was fitted using REML and, therefore, different mean structures cannot be compare!

Effect of early dietary intervention on children IQ




```
> ## Display the random effects (EBLUPs) from the model.
>
> random.effects(meanfull.hom)
>
   (Intercept)       (Intercept)
1   0.17480024    17 -0.39636862
2  -0.07362296    18  0.42802095
3  -0.17490203    19 -0.18110865
4  -0.05376249    20  0.32903707
5   0.34446954    21 -0.27813901
6  -0.05480208    22 -0.49096620
7   0.39153638    23  0.26053476
8  -0.02616704    24  0.17537803
9  -0.61772106    25  0.23748827
10  0.09017150    26  0.22966911
11  0.04136696    27 -0.13396497
12  0.02072931
13 -0.35981737
14  0.01847368
15  0.03549783
16  0.06416884
>
```

Modeling the covariance structure



- Previous model assumes that the within litter variability σ^2_ε is constant across treatment
- The variances of the birth weights are similar for males and females within each treatment but appear to differ across treatments

Covariance structure: Testing homoscedasticity

Hence, one wants to test if the variance of the residuals (σ^2_ε) is the same (homogeneous) for the three treatment groups (high, low, and control)

$$H_0 : \sigma^2_{high} = \sigma^2_{low} = \sigma^2_{control} = \sigma^2_\varepsilon$$

- REML-based likelihood ratio test to compare two models (mean structure stays the same):

  Model 1: All three variances equal (meanfull.hom)

  Model 2: All three variances different (meanfull.het)

- The asymptotic null distribution of this test statistic is a χ^2 with 2 degrees of freedom

Covariance structure: Testing homoscedasticity

- At this moment the lmer() function does not allow users to fit models with heterogeneous error variance structures
- Therefore, we will work with the function lme() from the package nlme
- lme() and lmer() are similar but there are some differences in syntax and output that will be explained in the following

Fitting the heterocedastic model in R

Model 2

```
> ## Fitting a heterocedastic model
>
> meanfull.het <- lme(weight ~ treatment + sex1 + litsize + treatment:sex1,
+                     random = ~1 | litterid, ratpup, method = "REML",
+                     weights = varIdent(form = ~1 | treatment))
>
```

- The arguments of the lme() function are the same as those used to fit Model 1, with the addition of the weights argument
- The argument

  `weights = varIdent(form = ~ 1 |treatment)`

  sets up a heterogeneous residual variance structure, with observations at different levels of treatment having different residual variance parameters

Fitting the heterocedastic model in R

```
> summary(meanfull.het)
>
Linear mixed-effects model fit by REML
 Data: ratpup
       AIC     BIC    logLik
  381.8847 423.163 -179.9423

Random effects:
 Formula: ~1 | litterid
        (Intercept)  Residual
StdDev:   0.3134846 0.5147948

Variance function:
 Structure: Different standard deviations per stratum
 Formula: ~1 | treatment
 Parameter estimates:
  Control       Low      High
1.0000000 0.5649830 0.6394383

Fixed effects: weight ~ treatment + sex1 + litsize + treatment:sex1
                      Value  Std.Error  DF   t-value p-value
(Intercept)         8.345294 0.27464753 292 30.385468  0.0000
treatmentHigh      -0.903277 0.19215903  23 -4.700672  0.0001
treatmentLow       -0.466292 0.15908908  23 -2.931013  0.0075
sex1               -0.408131 0.09303486 292 -4.386865  0.0000
litsize            -0.130007 0.01848708  23 -7.032332  0.0000
treatmentHigh:sex1  0.094666 0.12919527 292  0.732737  0.4643
treatmentLow:sex1   0.076013 0.10811858 292  0.703053  0.4826

.............................................................
```


Fitting the heterocedastic model in R

```
Random effects:
 Formula: ~1 | litterid
        (Intercept)  Residual
StdDev:   0.3134846 0.5147948

Variance function:
 Structure: Different standard deviations per stratum
 Formula: ~1 | treatment
 Parameter estimates:
  Control       Low      High
1.0000000 0.5649830 0.6394383
```

- Random effects portion of the output: Estimated residual standard deviation equal to 0.5147948
- Parameter estimates: Values by which the residual standard deviation should be multiplied to obtain the estimated standard deviation of the residuals in each treatment group
- This multiplier is 1.0 for the control group (the reference). Multipliers for the low and high treatment groups are very similar

Heterocedastic versus homocedastic model

The variance of the residuals (σ^2_ε) is the same (homogeneous) for the three treatment groups

$$H_0 : \sigma^2_{high} = \sigma^2_{low} = \sigma^2_{control} = \sigma^2_\varepsilon$$

```
> ## Heterocedastic versus homocedastic model
>
> anova(meanfull.hom,meanfull.het)
>
             Model df      AIC      BIC    logLik   Test  L.Ratio p-value
meanfull.hom     1  9 419.1043 452.8775 -200.5522
meanfull.het     2 11 381.8847 423.1630 -179.9423 1 vs 2 41.21964  <.0001
>
```


Heterocedastic model

```
Random effects:
 Formula: ~1 | litterid
        (Intercept)  Residual
StdDev:   0.3134846 0.5147948

Variance function:
 Structure: Different standard deviations per stratum
 Formula: ~1 | treatment
 Parameter estimates:
  Control       Low      High
1.0000000 0.5649830 0.6394383
```

- $\sigma_{high} = 0.5147948 \cdot 0.6394383$, $\sigma_{low} = 0.5147948 \cdot 0.5649830$ and $\sigma_{control} = 0.5147948 \cdot 1$

Heterocedastic model

```
Random effects:
 Formula: ~1 | litterid
        (Intercept)  Residual
StdDev:   0.3134846 0.5147948

Variance function:
 Structure: Different standard deviations per stratum
 Formula: ~1 | treatment
 Parameter estimates:
  Control       Low      High
1.0000000 0.5649830 0.6394383
```

- $\sigma_{high} = 0.329179$, $\sigma_{low} = 0.290850$ and $\sigma_{control} = 0.5147948$
- Is $\sigma^2_{high} = \sigma^2_{low}$?

High-low dose: Equal residual variance

Hence, one wants to test if the variance of the residuals in the high and low dose groups are the same

$$H_0 : \sigma^2_{high} = \sigma^2_{low}$$

- REML-based likelihood ratio test to compare two models (mean structure stays the same):

  Model 2: All three variances different (meanfull.het)

  Model 3: $\sigma^2_{high} = \sigma^2_{low}$ (meanfull.hilo)

- The asymptotic null distribution of this test statistic is a χ^2 with 1 degrees of freedom

High-low dose: Equal residual variance

```
> ## High-low dose: Equal residual variance
>
> ratpup$trtgrp[treatment=="Control"] <- 1
> ratpup$trtgrp[treatment == "Low" | treatment == "High"] <- 2
>
> meanfull.hilo <- lme(weight ~ treatment + sex1 + litsize + treatment:sex1,
+                      random = ~1 | litterid, ratpup, method = "REML",
+                      weights = varIdent(form = ~1 | trtgrp))
>
> summary(meanfull.hilo)
> anova(meanfull.hilo)
>
```


Fitting the heterocedastic model in R

```
> summary(meanfull.hilo)
>
Linear mixed-effects model fit by REML
 Data: ratpup
       AIC      BIC    logLik
  381.0807 418.6065 -180.5404

Random effects:
 Formula: ~1 | litterid
        (Intercept)  Residual
StdDev:   0.3145679 0.5147878

Variance function:
 Structure: Different standard deviations per stratum
 Formula: ~1 | trtgrp
 Parameter estimates:
         1         2
1.0000000 0.5905487

Fixed effects: weight ~ treatment + sex1 + litsize + treatment:sex1
                     Value  Std.Error  DF   t-value p-value
(Intercept)         8.350351 0.27567833 292 30.290196  0.0000
treatmentHigh      -0.901844 0.19140146  23 -4.711793  0.0001
treatmentLow       -0.466596 0.15999337  23 -2.916347  0.0078
sex1               -0.408195 0.09303540 292 -4.387529  0.0000
litsize            -0.130383 0.01856367  23 -7.023574  0.0000
treatmentHigh:sex1  0.092026 0.12461723 292  0.738473  0.4608
treatmentLow:sex1   0.076397 0.10939797 292  0.698337  0.4855
.............................................................
>
```

High-low dose: Equal residual variance

Hence, one wants to test if the variance of the residuals in the high and low dose groups are the same

$$H_0 : \sigma^2_{high} = \sigma^2_{low}$$

```
> ## High-low dose: Equal residual variance
>
> anova(meanfull.het,meanfull.hilo)
>
              Model df      AIC      BIC    logLik   Test  L.Ratio p-value
meanfull.het      1 11 381.8847 423.1630 -179.9423
meanfull.hilo     2 10 381.0807 418.6065 -180.5404 1 vs 2 1.196053  0.2741
>
```


Is there a litter effect?

- Can the random effects (b_{0i}) associated with the litter–specific intercepts be omitted from Model 3?
- One do not directly test the significance of the random litter–specific intercepts, but rather tests a hypothesis related to the variance of the random litter effects.
- The null and alternative hypotheses can be written as follows:

$$H_0 : \sigma^2_b = 0 \text{ versus } H_1 : \sigma^2_b > 0$$

Is there a litter effect?

- Although hypothesis tests are often phrased in terms of parameter restrictions, they basically compare the quality of the fit obtained from two nested models
- Likelihood ratio tests (LRTs) are a valuable tool to compare nested models
- An approximate reference distribution for a LRT is the χ^2_γ where γ, the degrees of freedom, is determined by the difference in the number of parameters for the models H_1 and H_0
- Hence, the LRT for testing $H_0 : \sigma^2_b = 0$ versus $H_1 : \sigma^2_b > 0$ has an approximate reference distribution χ^2_1

Is there a litter effect?

- However, the argument for using a χ^2_1 distribution **does not apply** when the parameter value being tested is on the boundary of the parametric space
- The asymptotic null distribution of the test statistic is a mixture of χ^2 distributions, with 0 and 1 degrees of freedom, and equal weights of 0.5
- As shown in Pinheiro and Bates (2000) Section 2.5, the p-value from the χ^2_1 distribution will be "conservative"in the sense that it is larger than a simulation-based p-value would be
- In the worst-case scenario the χ^2_1-based p-value will be twice as large as it should be

Is there a litter effect?

```
> ## Is there a litter effect?
>
> meanfull.hilo.nolitter <- gls(weight ~ treatment + sex1 + litsize +
+         treatment:sex1, data = ratpup, weights = varIdent(form = ~1 | trtgrp))
>
> summary(meanfull.hilo.nolitter)
>
```


Is there a litter effect?

```
Generalized least squares fit by REML
  Model: weight ~ treatment + sex1 + litsize + treatment:sex1
  Data: ratpup
       AIC      BIC   logLik
  489.6521 523.4252 -235.826

Variance function:
 Structure: Different standard deviations per stratum
 Formula: ~1 | trtgrp
 Parameter estimates:
       1         2
1.0000000 0.7060188

Coefficients:
                     Value  Std.Error   t-value p-value
(Intercept)          8.201712 0.15902776  51.57409  0.0000
treatmentHigh       -0.976414 0.10624042  -9.19060  0.0000
treatmentLow        -0.456018 0.08700180  -5.24147  0.0000
sex1                -0.339911 0.10616682  -3.20167  0.0015
litsize             -0.121478 0.01008518 -12.04524  0.0000
treatmentHigh:sex1   0.180960 0.14941228   1.21114  0.2267
treatmentLow:sex1    0.076386 0.13035758   0.58597  0.5583

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Residual standard error: 0.5980885
Degrees of freedom: 322 total; 315 residual
```

Is there a litter effect?

Is there a litter effect?

$$H_0 : \sigma_b^2 = 0 \text{ versus } H_1 : \sigma_b^2 > 0$$

```
> ## Is there a litter effect?
>
> anova(meanfull.hilo.nolitter,meanfull.hilo)
>
                       Model df      AIC      BIC    logLik   Test  L.Ratio p-value
meanfull.hilo.nolitter     1  9 489.6521 523.4252 -235.8260
meanfull.hilo              2 10 381.0807 418.6065 -180.5404 1 vs 2 110.5713  <.0001
>
```


Is there a litter effect?

```
## Simulation based (exact) restricted likelihood ratio test based on
## simulated values from the finite sample distribution for testing
## whether the variance of a random effect is 0 in a linear mixed model
## with  known correlation structure of the tested random
## effect and i.i.d. errors.
>
> require(RLRsim)
> exactRLRT(meanfull.hilo)

        simulated finite sample distribution of RLRT.

        (p-value based on 10000 simulated values)

data:
RLRT = 129.43, p-value < 2.2e-16

>
```

Modeling the mean structure

```
> ## Fitting the final model using ML
>
> meanfull.hilo.ml <- lme(weight ~ treatment + sex1 + litsize + treatment:sex1,
+                         random = ~1 | litterid, ratpup, method = "ML",
+                         weights = varIdent(form = ~1 | trtgrp))
>
> summary(meanfull.hilo.ml)
```


Modeling the mean structure

```
> summary(meanfull.hilo.ml)
>
Linear mixed-effects model fit by maximum likelihood
 Data: ratpup
       AIC      BIC    logLik
  357.1317 394.8773 -168.5659

Random effects:
 Formula: ~1 | litterid
        (Intercept)  Residual
StdDev:   0.2882595 0.5123784

Variance function:
 Structure: Different standard deviations per stratum
 Formula: ~1 | trtgrp
 Parameter estimates:
        1         2
1.0000000 0.5897706
Fixed effects: weight ~ treatment + sex1 + litsize + treatment:sex1
                     Value  Std.Error  DF  t-value p-value
(Intercept)         8.350608 0.26150064 292 31.93341  0.0000
treatmentHigh      -0.904757 0.18092616  23 -5.00070  0.0000
treatmentLow       -0.466869 0.15105108  23 -3.09080  0.0052
sex1               -0.406590 0.09357754 292 -4.34495  0.0000
litsize            -0.130402 0.01755814  23 -7.42689  0.0000
treatmentHigh:sex1  0.093026 0.12521954 292  0.74290  0.4581
treatmentLow:sex1   0.075602 0.10998665 292  0.68737  0.4924
.............................................................

Number of Observations: 322
Number of Groups: 27
```

Modeling the mean structure

```
> anova(meanfull.hilo.ml)
>
               numDF denDF   F-value p-value
(Intercept)        1   292 10274.678  <.0001
treatment          2    23     4.810  0.0180
sex1               1   292    59.906  <.0001
litsize            1    23    55.438  <.0001
treatment:sex1     2   292     0.315  0.7303
>
```


Hierarchical model interpretation

Level 1: ANOVA type model

$$w_{ij} = \pi_{0i} + \pi_{1i} sex_{ij} + \varepsilon_{ij}, \text{ with } \varepsilon_{ij} \sim \begin{cases} N(0, 0.51^2), \text{Control} \\ N(0, 0.30^2), \text{Low/High dose} \end{cases}$$

Level 2:

$$\begin{cases} \pi_{0i} = 8.35 - 0.90 treat_{1i} - 0.47 treat_{2i} - 0.13 ls_i + b_{0i} \\ \pi_{1i} = -0.41 \\ b_{0i} \sim N(0, 0.29^2) \end{cases}$$

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$\Rightarrow$ Birth weights of pups vary **within** litter due to differences in gender and in other unaccounted factors (ε_{ij})

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$\Rightarrow$ Litters in the high/low dose have pups with smaller average birth weights. In addition, litter size has a negative impact on the average birth weight and there is extra variability from other unknown factors

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$\Rightarrow$ Treatment affects males and females pups equally

Missing Data: Problems, risks and solutions

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