Kenward-Roger modification of the F-statistic for some linear mixed models fitted with lmer

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- Dependence of sugar percentage of sugar beets on harvest time and sowing time is investigated.
- Five sowing times (s) and two harvesting times (h).
- Experiment was laid out in three blocks (b).

```
Experimental plan for sugar beets experiment

Sowing times:
  1: 4/4, 2: 12/4, 3: 21/4, 4: 29/4, 5: 18/5

Harvest times:
  1: 2/10, 2: 21/10

Plot allocation:
      |  Block 1           |  Block 2           |  Block 3           |
      +--------------------|--------------------|--------------------+
Plot  | h1  h1  h1  h1  h1 | h2  h2  h2  h2  h2 | h1  h1  h1  h1  h1 | Harvest time
 1-15 | s3  s4  s5  s2  s1 | s3  s2  s4  s5  s1 | s5  s2  s3  s4  s1 | Sowing time
      |--------------------|--------------------|--------------------|
Plot  | h2  h2  h2  h2  h2 | h1  h1  h1  h1  h1 | h2  h2  h2  h2  h2 | Harvest time
16-30 | s2  s1  s5  s4  s3 | s4  s1  s3  s2  s5 | s1  s4  s3  s2  s5 | Sowing time
      +--------------------|--------------------|--------------------+
```

- For simplicity we assume that there is no interaction between sowing and harvesting times.
- A typical model for such an experiment would be:

$$y_{hbs} = \mu + \alpha_h + \beta_b + \gamma_s + U_{hb} + \epsilon_{hbs}, \quad (1)$$

where $U_{hb} \sim N(0, \omega^2)$ and $\epsilon_{hbs} \sim N(0, \sigma^2)$.

- Notice that U_{hb} describes the random variation between whole–plots (within blocks).

As the design is balanced we may make F–tests for each of the effects as:

R-code

```
> beets$bh <- with(beets, interaction(block, harvest))
> summary(aov(sugpct~block+sow+harvest+Error(bh), beets))

Error: bh
          Df Sum Sq Mean Sq F value Pr(>F)
block      2 0.0327  0.0163    2.58   0.28
harvest    1 0.0963  0.0963   15.21   0.06
Residuals  2 0.0127  0.0063

Error: Within
          Df Sum Sq Mean Sq F value  Pr(>F)
sow        4   1.01  0.2525     101 5.7e-13
Residuals 20   0.05  0.0025
```

Notice: the F–statistics are $F_{1,2}$ for harvest time and $F_{4,20}$ for sowing time.

Using `lmer()` from `lme4` we can fit the models and test for no effect of sowing and harvest time as follows:

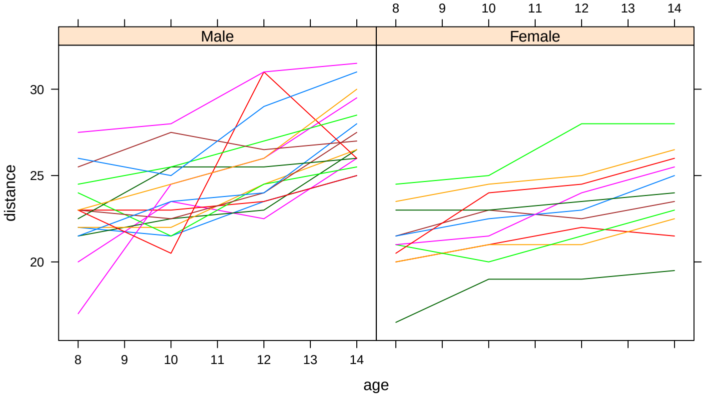
R-code

```
> beetLarge<-lmer(sugpct~block+sow+harvest+(1|block:harvest),
+             data=beets, REML=FALSE)
> beet_no.harv <- update(beetLarge, .~.-harvest)
> beet_no.sow  <- update(beetLarge, .~.-sow)
> as.data.frame(anova(beetLarge, beet_no.sow))

            Df     AIC     BIC logLik deviance Chisq Chi Df Pr(>Chisq)
beet_no.sow  6  -2.795   5.612  7.398    -14.8    NA     NA         NA
beetLarge   10 -79.998 -65.986 49.999   -100.0  85.2      4  1.374e-17

> as.data.frame(anova(beetLarge, beet_no.harv))

             Df    AIC    BIC logLik deviance Chisq Chi Df Pr(>Chisq)
beet_no.harv  9 -69.08 -56.47  43.54   -87.08    NA     NA         NA
beetLarge    10 -80.00 -65.99  50.00  -100.00 12.91      1  0.0003261
```

The LRT based p–values are anti–conservative: the effect of harvest appears stronger than it is.

Random coefficient model

The change with age of the distance between two cranial distances was observed for 16 boys and 11 girls from age 8 until age 14.



Random coefficient model

Plot suggests:

$$dist_{[i]} = \alpha_{sex[i]} + \beta_{sex[i]} age_{[i]} + A_{Subj[i]} + B_{Subj[i]} age_{[i]} + e_{[i]}$$

with $(A, B) \sim N(0, \mathbf{S})$.

ML-test of $\beta_{boy} = \beta_{girl}$:

R-code

```
> ort1ML<- lmer(distance ~ age + Sex + age:Sex + (1 + age | Subject),
+                     REML = FALSE, data=Orthodont)
> ort2ML<- update(ort1ML, .~.-age:Sex)
> as.data.frame(anova(ort1ML, ort2ML))

       Df   AIC   BIC logLik deviance Chisq Chi Df Pr(>Chisq)
ort2ML  7 446.8 465.6 -216.4    432.8    NA     NA         NA
ort1ML  8 443.8 465.3 -213.9    427.8 5.029      1    0.02492
```

Our goal...

Our goal is to extend the tests provided by `lmer()`.

There are two issues here:

- The choice of test statistic and
- The reference distribution in which the test statistic is evaluated.

Setting the scene

For multivariate normal data

$$Y_{n\times 1} \sim N(\mathbf{X}_{n\times p}\boldsymbol{\beta}_{p\times 1}, \boldsymbol{\Sigma})$$

we consider the test of the hypothesis

$$\mathbf{L}_{l\times p}\boldsymbol{\beta} = \boldsymbol{\beta}_0$$

where $\mathbf{L}$ is a regular matrix of estimable functions of $\boldsymbol{\beta}$.

The linear hypothesis can be tested via the Wald-type statistic

$$F = \frac{1}{l}(\hat{\boldsymbol{\beta}} - \boldsymbol{\beta}_0)^\top \mathbf{L}^\top (\mathbf{L}^\top \boldsymbol{\Phi}(\hat{\boldsymbol{\sigma}})\mathbf{L})^{-1}\mathbf{L}(\hat{\boldsymbol{\beta}} - \boldsymbol{\beta}_0)$$

- $\boldsymbol{\Phi}(\boldsymbol{\sigma}) = (\mathbf{X}^\top \boldsymbol{\Sigma}(\boldsymbol{\sigma})\mathbf{X})^{-1} \approx \mathbb{C}\mathrm{ov}(\hat{\boldsymbol{\beta}})$, $\hat{\boldsymbol{\beta}}$ REML estimate of $\boldsymbol{\beta}$
- $\hat{\boldsymbol{\sigma}}$: vector of REML estimates of the elements of $\boldsymbol{\Sigma}$

Kenward and Roger's modification

Kenward and Roger (1997) modify the test statistic

- $\mathbf{\Phi}$ is replaced by an improved small sample approximation $\mathbf{\Phi}_A$

Furthermore

- the statistic F is scaled by a factor λ,
- denominator degrees of freedom m are determined

such that the approximate expectation and variance are those of a $F_{l,m}$ distribution.

Restriction on covariance

- Consider only situations where

$$\mathbf{\Sigma} = \sum_i \sigma_i \mathbf{G}_i, \quad \mathbf{G}_i \text{ known matrices}$$

- Variance component and random coefficient models satisfy this restriction.
- $\Phi_A(\hat{\boldsymbol{\sigma}})$ depends now only on the first partial derivatives of $\mathbf{\Sigma}^{-1}$:

$$\frac{\partial \mathbf{\Sigma}^{-1}}{\partial \sigma_i} = -\mathbf{\Sigma}^{-1} \frac{\partial \mathbf{\Sigma}}{\partial \sigma_i} \mathbf{\Sigma}^{-1}.$$

- $\Phi_A(\hat{\boldsymbol{\sigma}})$ depends also on $\mathbb{V}\mathrm{ar}(\hat{\boldsymbol{\sigma}})$.
- Kenward and Roger propose to estimate $\mathbb{V}\mathrm{ar}(\hat{\boldsymbol{\sigma}})$ via the inverse expected information matrix.

Properties of the Kenward–Roger adjustment

The modification of the F-statistic by Kenward and Roger

- yields the exact F-statistic for balanced mixed classification nested models or balanced split plot models (Alnosaier, 2007).
- Simulation studies (e.g. Spilke, J. et al.(2003)) indicate that the Kenward-Roger approach perform mostly better than alternatives (like Satterthwaite or containment method) for blocked experiments even with missing data.

R package `lme4`

The R package lme4 (Bates, D., Maechler, M, Bolker, B., 2011) provides efficient estimation of linear mixed models.

The package provides all necessary matrices and estimates to implement the Kenward-Roger approach.

1. The implementation uses a straightforward transcription of the description in the article of Kenward and Roger, 1997.
2. Matrix operations use sparse matrices representation.
3. Matrices are extracted from `lmer` objects via their slots (using `@`).

Kenward–Roger: split-plot (sugar-beets)

The Kenward–Roger approach yields the same results as the anova-test:

R-code

```
> beetLarge <- update(beetLarge, REML=TRUE)
> beet_no.harv <- update(beet_no.harv, REML=TRUE)
```

Test for harvest effect:

R-code

```
> KRmodcomp(beetLarge,beet_no.harv)

F-test with Kenward-Roger approximation; computing time: 0.06 sec.
large : sugpct ~ block + sow + harvest + (1 | block:harvest)
small : sugpct ~ block + sow + (1 | block:harvest)
      stat  ndf  ddf F.scaling p.value
Ftest 15.2  1.0  2.0         1    0.06
```

Kenward–Roger: random regression (cranial change)

For the cranial distances data the Kenward and Roger modified F-test yields

R-code

```
> ort1<- update(ort1ML, .~., REML = TRUE)
> ort2<- update(ort2ML, .~., REML = TRUE)
> KRmodcomp(ort1,ort2)

F-test with Kenward-Roger approximation; computing time: 0.13 sec.
large : distance ~ age + Sex + (1 + age | Subject) + age:Sex
small : distance ~ age + Sex + (1 + age | Subject)
       stat   ndf   ddf F.scaling p.value
Ftest  5.12  1.00 25.52         1   0.032
```

The p-value form the ML-test was 0.0249.

Using parametric bootstrap

- The Kenward–Roger approach is no panacea.
- Additionally, we provide the parametric bootstrap p-value $P_{\hat{\theta}_0}(T \geq t_{obs})$ based on the log-LR statistic T.

We draw B parametric bootstrap samples $t^1, \ldots, t^B$ under the estimated null model $\hat{\theta}_0$ and provide three choices to calculate the p-value.

1. directly via the proportion of sampled t_i exceeding t_{obs},
2. approximating the distribution of the scaled statistic $\frac{f}{\bar{t}} \cdot T$ by a χ^2_f distribution (Bartlett type correction) ($\bar{t}$ is the sample average and f the difference in the number of parameters between the null and the alternative model)
3. approximating the bootstrap distribution by a $\Gamma(\alpha, \beta)$ distribution which mean and variance match the moments of the bootstrap sample.

R-code

```
> PBmodcomp(beetLarge,beet_no.harv)

Parametric bootstrap test; time: 20.00 sec; samples: 1000 extremes: 44;
large : sugpct ~ block + sow + harvest + (1 | block:harvest)
small : sugpct ~ block + sow + (1 | block:harvest)
       stat df p.value
LRT    11.8  1 0.00059
PBtest 11.8    0.04496
```

Results from sugar beets:

Table: p-values ($\times$ 100) for removing the harvest or sow effect.

	LRT	KR	ParmBoot	Bartlett	Gamma
harvest	0.03	6	4.1	8.3	4.9
sow	<0.001	<0.001	<0.001	<0.001	<0.001

Results for cranial distance data:

Table: p-values ($\times$ 100) testing $\beta_{boy} = \beta_{girl}$.

LRT	KR	ParmBoot	Bartlett	Gamma
2.5	3.3	4.2	4.0	4.2

Random coefficient model

We consider the simulation from a simple random coefficient model (cf. Kenward and Roger (1997, table 4)):

$$y_{it} = \beta_0 + \beta_1 \cdot t_i + A_i + B_i \cdot t_i + \epsilon_{it}$$

with $cov(A_i, B_i) = \begin{bmatrix} 0.250 & -0.133 \\ -0.133 & 0.250 \end{bmatrix}$ and $var(\epsilon_{it}) = 0.25$.

There are observed $i = 1, \ldots, 24$ subjects divided in groups of 8. For each group observations are at the non overlapping times $t = 0, 1, 2$; $t = 3, 4, 5$ and $t = 6, 7, 8$.

Results from random coefficient model

Table: Observed test sizes ($\times 100$) for $H_0 : \beta_k = 0$ for random coefficient model.

	LR	Wald	ParmBoot	Bartlett	Gamma	KR(R)	KR(SAS)
β_0	6.8	4.6	5.2	5.2	5.4	4.0	5.4
β_1	7.3	5.3	6.0	6.0	5.9	5.4	6.3

Summary

- The functions `KRmodcomp()` and `PBmodcomp()` described here are available in the `pbkrtest` package.
- The Kenward–Roger approach requires fitting by REML; the parametric bootstrap approaches requires fitting by ML.
- The required fitting scheme is set by the relevant functions, so the user needs not worry about this.
- Parametric bootstrap is parallelized using the `snow` package.

Literature

- Alnosaier, W. (2007) *Kenward-Roger Approximate F Test for Fixed Effects in Mixed Linear Models*, Dissertation, Oregon State University
- Bates, D., Maechler, M. and Bolker, B. (2011) *lme4: Linear mixed-effects models using S4 classes*, R package version 0.999375-39.
- Kenward, M. G. and Roger, J. H. (1997) *Small Sample Inference for Fixed Effects from Restricted Maximum Likelihood*, Biometrics, Vol. 53, pp. 983–997
- Spilke J., Piepho, H.-P. and Hu, X. Hu (2005) *A Simulation Study on Tests of Hypotheses and Confidence Intervals for Fixed Effects in Mixed Models for Blocked Experiments With Missing Data* Journal of Agricultural, Biological, and Environmental Statistics, Vol. 10,p. 374-389