Inference in mixed models in R - beyond the usual asymptotic likelihood ratio test

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Outline and take-home message

- Mixed models (random effects, random regression etc.) models handled by `lme4` package in R.
- Tests are based on χ^2 approximation of LR test statistic.
  - Works fine with "large samples" / "large dataset"
  - But a dataset can be large with respect to some aspect of a model while small with respect to other.
- Package `pbkrtest` provides some remedies:
  - Base test on F-statistic, where denominator degrees of freedom are estimated from data.
  - Base test of parametric bootstrap where data are simulated under the model.
  - Parametric bootstrap carries over to e.g. generalized linear mixed models.
- Look at simulated and real data
- Shortcomings of `pbkrtest`

History: The degree-of-freedom police

- Years ago, Ulrich Halekoh and SH colleagues at “Danish Institute for Agricultural Sciences”
  - Main concern: Help protect researcher colleagues from reporting effects to be “more significant than they really are”.
  - Many studies called for random effects models - and for `PROC MIXED` (from SAS)
  - `PROC MIXED` reports (by default) p–values from asymptotic likelihood ratio test.
  - Common advice: Account for uncertainty in estimate of variance by doing F-test instead. Use Satterthwaite or Kenward-Roger approximation of denominator degrees of freedom in F-test – in an attempt not to get things “too wrong”.
- Then R became popular;
  - Mixed models fitted with nlme and lme4 package
  - No Satterthwaite or Kenward-Roger approximation, so our common advice fell apart.

- SH raised the issue on R-help - 2006: `[R] how calculation degrees freedom` see:
  - SH: Along similar lines . . . probably in recognition of the degree of freedom problem. It could be nice, however, if anova() produced . . .
  - Doug Bates: I don't think the "degrees of freedom police" would find that to be a suitable compromise. :-)
- In reply to related question:
  - Doug Bates: I will defer to any of the "degrees of freedom police" who post to this list to give you an explanation of why there should be different degrees of freedom.
- The point being:
  - Quite different views on whether the degree-of-freedom issue really is an issue or not.

Example: Double registration in labs

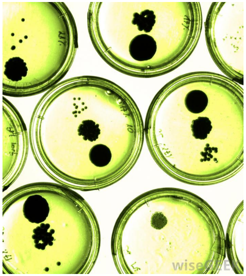


Figure 1

Clustered data:

- Compare two groups (treatment with a control);
- M units (petri plates, persons, animals. . .) per group;
- Each unit is measured R times. Measurements on same unit are positively correlated.

Simulated data: $N = 3$ subjects per group, $R = 2$ replicated measurements per subject.

```
dub
```

```
##      y1 y2  grp  subj
## 1  1.70  0 ctrl subj1
## 2  2.01  0 ctrl subj1
## 3  0.65  0 ctrl subj2
## 4  1.39  2 ctrl subj2
## 5  0.31  1 ctrl subj3
## 6  0.94  0 ctrl subj3
## 7  0.55  0 trt1 subj4
## 8  1.20  2 trt1 subj4
## 9  4.49  4 trt1 subj5
## 10 4.53  5 trt1 subj5
## 11 3.94  2 trt1 subj6
## 12 4.02  0 trt1 subj6
```

Problem/issues: If we ignore clustering/positive correlation:

- pretending to have more information than we have
- standard errors of estimates become too small
- *p* values become too small
- effects appear stronger than they really are.

Notice:

- Measuring the same unit many many times will make the dataset larger, but will not really add many more chunks of information (depending on the size of the within-subject correlation, of course).
- Instead, more units are needed.

```r
lg1 <- lm(y1 ~ grp, data=dub)
lg1 %>% summary %>% coef %>% as.data.frame -> tb1
tb1$"Pr(>|X^2|)" = 1 - pchisq(tb1[,3]^2, df=1)
tb1
```

```
##             Estimate Std. Error t value Pr(>|t|) Pr(>|X^2|)
## (Intercept)    1.167     0.5437   2.146  0.05747    0.03189
## grptrt1        1.955     0.7689   2.543  0.02923    0.01100
```

Notice: the *t*-test "accounts for" the uncertainty in the estimate of the standard error.

Alternative: Analyze average

```r
duba <- aggregate(y1 ~ grp + subj, FUN=mean, data=dub)
lm(y1 ~ grp, data=duba) %>% summary %>% coef
```

```
##             Estimate Std. Error t value Pr(>|t|)
## (Intercept)    1.167     0.8416   1.386   0.2380
## grptrt1        1.955     1.1903   1.642   0.1758
```

- Works fine (gives the correct test) in (nearly) balanced cases.
- Does not provide estimate of between and within subject variation (not necessarily severe problem here).
- Analyzing-the-average is often not a feasible strategy.

Alternative: Random effects model

```r
lg2 <- lmer(y1 ~ grp + (1|subj), data=dub)
tidy(lg2)
```

```
## Warning in bind_rows_(x, .id): binding factor and character vector,
## coercing into character vector

## Warning in bind_rows_(x, .id): binding character and factor vector,
## coercing into character vector

## # A tibble: 4 x 5
##   term                     estimate std.error statistic group
##   <chr>                       <dbl>     <dbl>     <dbl> <chr>
## 1 (Intercept)                 1.17      0.842      1.39 fixed
## 2 grptrt1                     1.96      1.19       1.64 fixed
## 3 sd_(Intercept).subj         1.44     NA         NA    subj
## 4 sd_Observation.Residual     0.350    NA         NA    Residual
```

```r
sm2 <- update(lg2, .~. -grp)
as.data.frame(anova(lg2, sm2))
```

```
##     Df   AIC   BIC logLik deviance Chisq Chi Df Pr(>Chisq)
## sm2  3 36.80 38.26 -15.40    30.80    NA     NA         NA
## lg2  4 35.71 37.65 -13.86    27.71 3.093      1    0.07864
```

Notice: Test is based in the χ^2 distribution (i.e. that the variance is

Alternatives in the pbkrtest package:

```
KRmodcomp(lg2, sm2)
```

```
## F-test with Kenward-Roger approximation; time: 0.13 sec
## large : y1 ~ grp + (1 | subj)
## small : y1 ~ (1 | subj)
##       stat ndf ddf F.scaling p.value
## Ftest  2.7 1.0 4.0         1    0.18
```

```
PBmodcomp(lg2, sm2)
```

```
## Bootstrap test; time: 7.19 sec;samples: 1000; extremes: 186;
## large : y1 ~ grp + (1 | subj)
## small : y1 ~ (1 | subj)
##        stat df p.value
## LRT     2.9  1   0.089
## PBtest  2.9      0.187
```

Notice: Same *p*-value as when analyzing average.

The Kenward–Roger approach

The Kenward–Roger modification of the F–statistic

For multivariate normal data

$$Y_{n\times 1} \sim N(X_{n\times p}\beta_{p\times 1}, \Sigma)$$

we consider the test of the hypothesis

$$L_{d\times p}(\beta - \beta_0) = 0$$

With $\hat{\beta} \sim N_d(\beta, \Phi)$, a Wald statistic is

$$W = [L(\hat{\beta} - \beta_0)]^\top [L\Phi L^\top]^{-1} [L(\hat{\beta} - \beta_0)]$$

which is asymptotically $W \sim \chi^2_d$ under the null hypothesis.

A scaled version of W is

$$F = \frac{1}{d} W$$

- Asymptotically $F \sim \frac{1}{d}\chi^2_d$ under the null hypothesis
- Think of as the limiting distribution of an $F_{d,m}$–distribution as $m \to \infty$
- To account for the fact that $\Phi = \mathbb{V}ar(\hat{\beta})$ is estimated from data, we must come up with a better estimate of the denominator degrees of freedom m (better than $m = \infty$).
- That was what Kenward and Roger worked on. . .

The linear hypothesis $L\beta = \beta_0$ can be tested via the Wald-type statistic

$$F = \frac{1}{r}(\hat{\beta} - \beta_0)^\top L^\top (L^\top \Phi(\hat{\sigma}) L)^{-1} L(\hat{\beta} - \beta_0)$$

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

Kenward and Roger (1997)

- replaced Φ by an improved small sample approximation Φ_A
- scaled F by a factor λ
- determined denominator degrees of freedom m by matching moments of F/λ with an $F_{d,m}$ distribution.

Shortcommings of Kenward-Roger

- The Kenward–Roger approach is no panacea.
- In the computations of the degrees of freedom we need to compute
$$G_j \Sigma^{-1} G_j$$
where $\Sigma = \sum_i \sigma_i G_i$. Can be space and time consuming!
- An alternative is a Sattherthwaite–kind approximation which is faster to compute. Will come out in next release of `pbkrtest` (code not tested yet). Way faster...
- What to do with generalized linear mixed models – or even with generalized linear models.
- `pbkrtest` also provides the parametric bootstrap *p*-value. Computationally somewhat demanding, but can be parallelized.

Parametric bootstrap

We have two competing models; a large model $f_1(y;\theta)$ and a null model $f_0(y;\theta_0)$; the null model is a submodel of the large model.

- The p value for a composite hypothesis is

$$p = \sup_{\theta \in \Theta_0} Pr_\theta(T \geq t_{obs})$$

  where the sup is taken under the hypothesis.
- We can (usually) not evaluate the sup in practice, so instead we do:

$$p^{PB} = Pr_{\hat{\theta}}(T \geq t_{obs})$$

- In practice we approximate p^{PB} as
  - Draw B parametric bootstrap samples $t^1, \dots, t^B$ under the fitted null model $\hat{\theta}_0$.
  - Fit the large and the null model to each of these datasets;
  - Calculate the LR-test statistic for each simulated data; this gives reference distribution.
  - Calculate how extreme the observed statistic is.

```r
lg2 <- update(lg2, REML=FALSE)
sm2 <- update(sm2, REML=FALSE)
# Observed test statistic:
t.obs <- 2 * (logLik(lg2) - logLik(sm2))
t.obs
```

```
## 'log Lik.' 3.093 (df=4)
```

```r
# Reference distribution
set.seed(121315)
t.sim <- PBrefdist(lg2, sm2, nsim=2000)
# p-value
head(t.sim)
```

```
## [1] 0.35260 2.40216 0.02194 1.20877 1.04064 1.88052
```

```r
sum(t.sim >= t.obs) / length(t.sim)
```

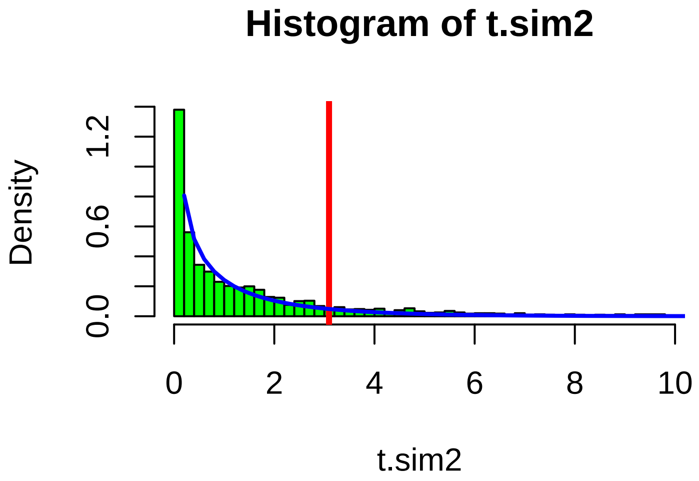
```
## [1] 0.1685
```

```r
# compare with X^2 dist
1 - pchisq(t.obs, df=1)
```

```
## 'log Lik.' 0.07864 (df=4)
```

Interesting to overlay limiting χ_1^2 distribution and simulated reference distribution.

Bootstrap reference distribution has heavier tail giving larger p-value.



Speedup I: Sequential p-value

Instead of simulating a fixed number of values $t^1, \dots, t^B$ for determining the reference distribution used for finding p^{PB} we may instead introduce a stopping rule saying *simulate until we have found, say $h = 20$ values t^j larger than t_{obs}*. If J simulations are made then the reported p–value is h/J.

```
spb <- seqPBmodcomp(lg2, sm2)
spb
```

```
## Bootstrap test; time: 1.53 sec;samples: 200; extremes: 34;
## large : y1 ~ grp + (1 | subj)
## small : y1 ~ (1 | subj)
##        stat df p.value
## LRT    3.09  1   0.079
## PBtest 3.09      0.174
```

Speedup II: Parallel computations

Parametric bootstrap is computationally demanding, but multiple cores can be exploited. Done by default on linux / mac platforms.

```
PBmodcomp(lg2, sm2) # Default: Use all cores (4 on my computer)
```

```
## Bootstrap test; time: 9.86 sec;samples: 1000; extremes: 177;
## large : y1 ~ grp + (1 | subj)
## small : y1 ~ (1 | subj)
##        stat df p.value
## LRT    3.09  1   0.079
## PBtest 3.09      0.178
```

```
PBmodcomp(lg2, sm2, cl=1) # Use one core
```

```
## Bootstrap test; time: 15.13 sec;samples: 1000; extremes: 179;
## large : y1 ~ grp + (1 | subj)
## small : y1 ~ (1 | subj)
##        stat df p.value
## LRT    3.09  1   0.079
## PBtest 3.09      0.180
```

On windows (in fact, work on all platforms):

```
set.seed(121315)
library(parallel)
nc <- detectCores(); nc
clus <- makeCluster(rep("localhost", nc))
PBmodcomp(lg2, sm2, cl=clus)
```

Speedup III: Parametric form of reference distribution:

Estimating tail–probabilities will require more samples than estimating the mean (and variance) of the reference distribution.

Suggests to approximate simulated reference distribution with a known distribution so that fewer samples will suffice:

```
pb1 <- PBmodcomp(lg2, sm2, nsim=1000)
pb2 <- PBmodcomp(lg2, sm2, nsim=100)
summary(pb1) %>% as.data.frame
```

```
##           stat df   ddf p.value
## LRT      3.093  1    NA 0.07864
## PBtest   3.093 NA    NA 0.20480
## Gamma    3.093 NA    NA 0.19419
## Bartlett 1.688  1    NA 0.19382
## F        3.093  1 4.404 0.14685
```

```
summary(pb2) %>% as.data.frame
```

```
##           stat df   ddf p.value
## LRT      3.093  1    NA 0.07864
## PBtest   3.093 NA    NA 0.18812
## Gamma    3.093 NA    NA 0.18422
## Bartlett 1.760  1    NA 0.18461
## F        3.093  1 4.641 0.14348
```

Why use parametric bootstrap

- Applies generally; in `pbkrtest` implemented for e.g. generalized linear mixed models (hwere random effects are on the linear predictor scale).
- Kenward-Roger does not readily scale to larger problems because of the computation of

$$G_j \Sigma^{-1} G_j$$

  where $\Sigma = \sum_i \sigma_i G_i$. Can be space and time consuming!
- For example, in random regression models with few relatively long time series. In this case simulation is faster.

Simulation study

```
dub
```

```
##       y1 y2  grp  subj
## 1  1.70  0 ctrl subj1
## 2  2.01  0 ctrl subj1
## 3  0.65  0 ctrl subj2
## 4  1.39  2 ctrl subj2
## 5  0.31  1 ctrl subj3
## 6  0.94  0 ctrl subj3
## 7  0.55  0 trt1 subj4
## 8  1.20  2 trt1 subj4
## 9  4.49  4 trt1 subj5
## 10 4.53  5 trt1 subj5
## 11 3.94  2 trt1 subj6
## 12 4.02  0 trt1 subj6
```

- Task: Test the hypothesis that there is no effect of treatment. How good are the various tests?
- Simulate data 1000 times with divine insight: there is no effect of treatment.
- Test the hypothesis e.g. at level 5%. If test has correct nominal level we shall reject about 50 times.
- If hypothesis is rejected e.g. 100 times then *p* values are anti-conservative: Effects appear more significant than the really are. That is we draw "too strong" conclusions.

	0.010	0.050	0.100
lm+X2	0.178	0.282	0.342
lm+F	0.110	0.240	0.322
mixed+X2	0.044	0.152	0.240
mixed+F-KR	0.012	0.044	0.114
mixed+PB	0.008	0.052	0.108

Motivation: Sugar beets - A split–plot experiment

- Model how sugar percentage in sugar beets depends on harvest time and sowing time.
- Five sowing times (s) and two harvesting times (h).
- Experiment was laid out in three blocks (b).

Experimental plan for sugar beets experiment

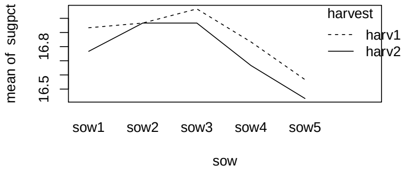
```
# Plot allocation:
#       |  Block 1        |  Block 2        |  Block 3        |
#       +-----------------|-----------------|-----------------+
# Plot  | h1 h1 h1 h1 h1 | h2 h2 h2 h2 h2 | h1 h1 h1 h1 h1 | Harvest time
# 1-15  | s3 s4 s5 s2 s1 | s3 s2 s4 s5 s1 | s5 s2 s3 s4 s1 | Sowing time
# 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

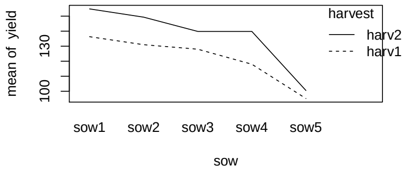
beets data

```r
data(beets, package='pbkrtest')
head(beets)
```

```
##   harvest  block  sow yield sugpct
## 1   harv1 block1 sow3 128.0   17.1
## 2   harv1 block1 sow4 118.0   16.9
## 3   harv1 block1 sow5  95.0   16.6
## 4   harv1 block1 sow2 131.0   17.0
## 5   harv1 block1 sow1 136.5   17.0
## 6   harv2 block2 sow3 136.5   17.0
```

```r
par(mfrow=c(1,2))
with(beets, interaction.plot(sow, harvest, sugpct))
with(beets, interaction.plot(sow, harvest, yield))
```





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

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

  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).

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

```
beet.lg <- lmer(sugpct ~ block + sow + harvest +
                      (1 | block:harvest), data=beets, REML=FALSE)
beet.noh <- update(beet.lg, .~. - harvest)
beet.nos  <- update(beet.lg, .~. - sow)
```

Both factors appear highly significant

```
anova(beet.lg, beet.noh)  %>% as.data.frame
```

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

```
anova(beet.lg, beet.nos)  %>% as.data.frame
```

```
##            Df     AIC     BIC logLik deviance Chisq Chi Df Pr(>Chisq)
## beet.nos  6  -2.795   5.612  7.398    -14.8    NA     NA         NA
## beet.lg  10 -79.998 -65.986 49.999   -100.0  85.2      4  1.374e-17
```

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

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

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

```r
set.seed("260618")
KRmodcomp(beet.lg, beet.noh)
```

```
## F-test with Kenward-Roger approximation; time: 0.13 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
```

```r
PBmodcomp(beet.lg, beet.noh)
```

```
## Bootstrap test; time: 7.94 sec;samples: 1000; extremes: 38;
## large : sugpct ~ block + sow + harvest + (1 | block:harvest)
## small : sugpct ~ block + sow + (1 | block:harvest)
##         stat df p.value
## LRT     12.9  1 0.00033
## PBtest 12.9    0.03896
```

```r
seqPBmodcomp(beet.lg, beet.noh)
```

```
## Bootstrap test; time: 8.30 sec;samples: 1000; extremes: 25;
## large : sugpct ~ block + sow + harvest + (1 | block:harvest)
## small : sugpct ~ block + sow + (1 | block:harvest)
##         stat df p.value
## LRT     12.9  1 0.00033
## PBtest 12.9    0.02597
```

Final remarks

- Satterthwaite approximation of degrees of freedom on its way in `pbkrtest`. Faster to compute than Kenward-Roger scales to larger problems.
- `pbkrtest` available on CRAN `https://cran.r-project.org/package=pbkrtest`
- devel version on github: `devtools::install_github(hojsgaard/pbkrtest)`
- `pbkrtest` described in Ulrich Halekoh and SH (2014) A Kenward-Roger Approximation and Parametric Bootstrap Methods for Tests in Linear Mixed Models The R Package pbkrtest; Journal of Statistical Software, Vol 59.

Thanks for your attention!