Practical Application and Interpretation of Normal Mixed Models

We will now look in-depth into some points relating to the practical application of mixed models and interpretation of some circumstances that might arise.

Negative Variance Component Estimates

Variances by their definition have to be non-negative. Some methods of estimation produce negative variance component estimates. These are underestimates of the true variance component. This may happen when

- when the ratio of the true variance component to the residual is small
- the number of random effects categories is small
- the number of observations per random effect category is small

If a variance component is negative

- remove the random effect from the model
- set the negative variance component to zero (SAS PROC MIXED default)

Either lead to same parameter estimated for fixed and random effects, but df for significance tests will differ.

Situations where you set the negative variance component to zero

- In a cross-over trial, because it is designed to allow for patient effects, the df for patient effects might be retained, even if the variance component is zero
- In a multi-center trial, with both random center and treatment*center effects. If the center effect variance estimate is set to zero and the treatment*center effects variance estimate is positive might retain the center effect

Situations where you would drop the random effect from the model

- When the random effect is not part of the study design.

Negative variance components sometimes can indicate a negative correlation between observations within the same random effect category.

Unlikely in clinical trials, however feasible in trials where animals may be housed together.

For example, if one animal in one cage eats more than the other animals, the variability within the cage might be greater than variability between the cages, leading to a negative variance component estimate for cage.

This negative correlation between animal weights within a cage can be modeled

Go back to our treatment and pasture example. The pasture effect was fit as random, so the variance **V=ZGZ'+R**

$$V = \begin{bmatrix}
\sigma_p^2+\sigma^2 & \sigma_p^2 & \sigma_p^2 & \sigma_p^2 & \sigma_p^2 & \sigma_p^2 & \sigma_p^2 & 0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 \\
\sigma_p^2 & \sigma_p^2+\sigma^2 & \sigma_p^2 & \sigma_p^2 & \sigma_p^2 & \sigma_p^2 & \sigma_p^2 & 0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 \\
\sigma_p^2 & \sigma_p^2 & \sigma_p^2+\sigma^2 & \sigma_p^2 & \sigma_p^2 & \sigma_p^2 & \sigma_p^2 & 0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 \\
\sigma_p^2 & \sigma_p^2 & \sigma_p^2 & \sigma_p^2+\sigma^2 & \sigma_p^2 & \sigma_p^2 & \sigma_p^2 & 0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 \\
\sigma_p^2 & \sigma_p^2 & \sigma_p^2 & \sigma_p^2 & \sigma_p^2+\sigma^2 & \sigma_p^2 & \sigma_p^2 & 0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 \\
\sigma_p^2 & \sigma_p^2 & \sigma_p^2 & \sigma_p^2 & \sigma_p^2 & \sigma_p^2+\sigma^2 & \sigma_p^2 & 0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 \\
\sigma_p^2 & \sigma_p^2 & \sigma_p^2 & \sigma_p^2 & \sigma_p^2 & \sigma_p^2 & \sigma_p^2+\sigma^2 & 0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 \\
0 & 0 & 0 & 0 & 0 & 0 & 0 & \sigma_p^2+\sigma^2 & \sigma_p^2 & \sigma_p^2 & \sigma_p^2 & \sigma_p^2 & \sigma_p^2 & \sigma_p^2 & \sigma_p^2 & \sigma_p^2 \\
0 & 0 & 0 & 0 & 0 & 0 & 0 & \sigma_p^2 & \sigma_p^2+\sigma^2 & \sigma_p^2 & \sigma_p^2 & \sigma_p^2 & \sigma_p^2 & \sigma_p^2 & \sigma_p^2 & \sigma_p^2 \\
0 & 0 & 0 & 0 & 0 & 0 & 0 & \sigma_p^2 & \sigma_p^2 & \sigma_p^2+\sigma^2 & \sigma_p^2 & \sigma_p^2 & \sigma_p^2 & \sigma_p^2 & \sigma_p^2 & \sigma_p^2 \\
0 & 0 & 0 & 0 & 0 & 0 & 0 & \sigma_p^2 & \sigma_p^2 & \sigma_p^2 & \sigma_p^2+\sigma^2 & \sigma_p^2 & \sigma_p^2 & \sigma_p^2 & \sigma_p^2 & \sigma_p^2 \\
0 & 0 & 0 & 0 & 0 & 0 & 0 & \sigma_p^2 & \sigma_p^2 & \sigma_p^2 & \sigma_p^2 & \sigma_p^2+\sigma^2 & \sigma_p^2 & \sigma_p^2 & \sigma_p^2 & \sigma_p^2 \\
0 & 0 & 0 & 0 & 0 & 0 & 0 & \sigma_p^2 & \sigma_p^2 & \sigma_p^2 & \sigma_p^2 & \sigma_p^2 & \sigma_p^2+\sigma^2 & \sigma_p^2 & \sigma_p^2 & \sigma_p^2 \\
0 & 0 & 0 & 0 & 0 & 0 & 0 & \sigma_p^2 & \sigma_p^2 & \sigma_p^2 & \sigma_p^2 & \sigma_p^2 & \sigma_p^2 & \sigma_p^2+\sigma^2 & \sigma_p^2 & \sigma_p^2 \\
0 & 0 & 0 & 0 & 0 & 0 & 0 & \sigma_p^2 & \sigma_p^2 & \sigma_p^2 & \sigma_p^2 & \sigma_p^2 & \sigma_p^2 & \sigma_p^2 & \sigma_p^2+\sigma^2 & \sigma_p^2 \\
0 & 0 & 0 & 0 & 0 & 0 & 0 & \sigma_p^2 & \sigma_p^2 & \sigma_p^2 & \sigma_p^2 & \sigma_p^2 & \sigma_p^2 & \sigma_p^2 & \sigma_p^2 & \sigma_p^2+\sigma^2
\end{bmatrix}$$

This model does not model for the negative correlation. This is done by redefining the model as a covariance pattern model which allows for negative covariance parameters. The model no longer includes a center effect, but covariances between observations in the same pasture are allowed. Using a compound symmetry covariance pattern allows us to obtain a constant covariance estimate

$$V = \begin{bmatrix}
\sigma^2 & \rho\sigma_p^2 & \rho\sigma_p^2 & \rho\sigma_p^2 & \rho\sigma_p^2 & \rho\sigma_p^2 & \rho\sigma_p^2 & 0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 \\
\rho\sigma_p^2 & \sigma^2 & \rho\sigma_p^2 & \rho\sigma_p^2 & \rho\sigma_p^2 & \rho\sigma_p^2 & \rho\sigma_p^2 & 0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 \\
\rho\sigma_p^2 & \rho\sigma_p^2 & \sigma^2 & \rho\sigma_p^2 & \rho\sigma_p^2 & \rho\sigma_p^2 & \rho\sigma_p^2 & 0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 \\
\rho\sigma_p^2 & \rho\sigma_p^2 & \rho\sigma_p^2 & \sigma^2 & \rho\sigma_p^2 & \rho\sigma_p^2 & \rho\sigma_p^2 & 0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 \\
\rho\sigma_p^2 & \rho\sigma_p^2 & \rho\sigma_p^2 & \rho\sigma_p^2 & \sigma^2 & \rho\sigma_p^2 & \rho\sigma_p^2 & 0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 \\
\rho\sigma_p^2 & \rho\sigma_p^2 & \rho\sigma_p^2 & \rho\sigma_p^2 & \rho\sigma_p^2 & \sigma^2 & \rho\sigma_p^2 & 0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 \\
\rho\sigma_p^2 & \rho\sigma_p^2 & \rho\sigma_p^2 & \rho\sigma_p^2 & \rho\sigma_p^2 & \rho\sigma_p^2 & \sigma^2 & 0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 \\
0 & 0 & 0 & 0 & 0 & 0 & 0 & \sigma^2 & \rho\sigma_p^2 & \rho\sigma_p^2 & \rho\sigma_p^2 & \rho\sigma_p^2 & \rho\sigma_p^2 & \rho\sigma_p^2 & \rho\sigma_p^2 \\
0 & 0 & 0 & 0 & 0 & 0 & 0 & \rho\sigma_p^2 & \sigma^2 & \rho\sigma_p^2 & \rho\sigma_p^2 & \rho\sigma_p^2 & \rho\sigma_p^2 & \rho\sigma_p^2 & \rho\sigma_p^2 \\
0 & 0 & 0 & 0 & 0 & 0 & 0 & \rho\sigma_p^2 & \rho\sigma_p^2 & \sigma^2 & \rho\sigma_p^2 & \rho\sigma_p^2 & \rho\sigma_p^2 & \rho\sigma_p^2 & \rho\sigma_p^2 \\
0 & 0 & 0 & 0 & 0 & 0 & 0 & \rho\sigma_p^2 & \rho\sigma_p^2 & \rho\sigma_p^2 & \sigma^2 & \rho\sigma_p^2 & \rho\sigma_p^2 & \rho\sigma_p^2 & \rho\sigma_p^2 \\
0 & 0 & 0 & 0 & 0 & 0 & 0 & \rho\sigma_p^2 & \rho\sigma_p^2 & \rho\sigma_p^2 & \rho\sigma_p^2 & \sigma^2 & \rho\sigma_p^2 & \rho\sigma_p^2 & \rho\sigma_p^2 \\
0 & 0 & 0 & 0 & 0 & 0 & 0 & \rho\sigma_p^2 & \rho\sigma_p^2 & \rho\sigma_p^2 & \rho\sigma_p^2 & \rho\sigma_p^2 & \sigma^2 & \rho\sigma_p^2 & \rho\sigma_p^2 \\
0 & 0 & 0 & 0 & 0 & 0 & 0 & \rho\sigma_p^2 & \rho\sigma_p^2 & \rho\sigma_p^2 & \rho\sigma_p^2 & \rho\sigma_p^2 & \rho\sigma_p^2 & \sigma^2 & \rho\sigma_p^2 \\
0 & 0 & 0 & 0 & 0 & 0 & 0 & \rho\sigma_p^2 & \rho\sigma_p^2 & \rho\sigma_p^2 & \rho\sigma_p^2 & \rho\sigma_p^2 & \rho\sigma_p^2 & \rho\sigma_p^2 & \sigma^2
\end{bmatrix}$$

where ρ is the correlation between animals in the same pasture.

Accuracy of variance parameters

The accuracy of the variance parameters dependent on the number of degrees of freedom used to estimate them.

Rule of thumb: don't fit an effect as random if less than 5 df available for estimation.

Instead of treating as fixed effect, could use variance parameter estimates from a previous study. PROC MIXED will allow you to fix the variance parameter estimates. Alternative would be to use both the previous and current information (Bayesian analysis, which we won't cover).

Bias in fixed and random effects standard errors

Standard errors for fixed and random effects calculated based on known **V**

For example $\text{var}(\hat{\beta}) = (XV^{-1}X)^{-1}$ for fixed effects.

Because **V** is estimated, even when data are balanced, standard errors will still be biased.

When data are unbalanced, greater bias will occur. The bias will be relevant when

- variance parameters are imprecise
- ratio of the variance parameter to the residual variance is small
- large degree of imbalance in the data

Variance adjustment for bias has been suggested. Won't worry about it at this point.

Significance testing

A test can be defined using a contrast:

for fixed effects:

$$C = L'\hat{\beta} = 0$$

for random effects

$$C = L'\hat{\mu} = 0$$

For example, trial with Treatments A, B, and C, want to compare B and C:

$$L'\hat{\beta} = \begin{pmatrix} 0 & 0 & 1 & -1 \end{pmatrix} \hat{\beta} = \hat{\beta}_B - \hat{\beta}_C$$

To look at the equality of the three treatments

$$L'\hat{\beta} = \begin{pmatrix} 0 & 1 & 0 & -1 \\ 0 & 0 & 1 & -1 \end{pmatrix} \hat{\beta} = \begin{pmatrix} \hat{\beta}_A - \hat{\beta}_C \\ \hat{\beta}_B - \hat{\beta}_C \end{pmatrix}$$

Use the Wald F statistic to test the null hypothesis that the contrast is zero

$$W = (L'\hat{\beta})'(\text{var}(L'\hat{\beta}))^{-1}(L'\hat{\beta}) = (L'\hat{\beta})'(L'\text{var}(\hat{\beta})L)^{-1}(L'\hat{\beta})$$

For random effects, substitute $\hat{\mu}$ and $\text{var}(\hat{\mu})$ for $\hat{\beta}$ and $\text{var}(\hat{\beta})$.

For single comparison, use a Wald z statistic

$$z = (L'\hat{\beta})' / SE(L\hat{\beta})$$

W is the square of the contrast divided by its variance. The Wald F and t tests are produced by default in PROC MIXED.

Testing variance parameters

Significance of a variance parameter can be tested using a likelihood ratio test. The likelihood ratio test compares the likelihoods of the model including the parameter (L_1) with the model excluding the parameter (L_0). The differences in the log-likelihoods are distributed as ½ χ^2_1.

$$2(\log(L_1) - \log(L_0)) \sim \chi^2_1$$

In nested models, where the difference in the number of parameters between the two models is more than one, then the χ^2 distribution degrees of freedom will be that difference. We will go into more detail on this later.

Model checking

So far, in the random effects model we assume that the random effects estimates are normally distributed and uncorrelated. With the random coefficient and covariance pattern models we know that the residuals and random coefficients are correlated. When we discuss these models more in depth later, we will cover model checking methods.

Model checking methods for mixed models

- not developed in depth
- consequences of violating assumptions not fully known

Go over some simple visual checks based on plots of the residuals.