Class Notes for Chapter 7

Class One:

- **Now we consider repeated measures (correlated) data**
- **First: Linear mixed models methods (in Section 7.2):**
  - **multivariate approach (often too conservative)**
  - **split-plot approach (often not correct)**
  - **proc mixed approach (usually a good idea)**

  Next: mixed linear and nonlinear models, hierarchical models. Finally: time series models
- **If four measurements are made on each person over time – denoted y_1, y_2, y_3, y_4, - these measurements are probably correlated. Not really sure of the structure of this correlation without looking at the data: every dataset will differ. Worse case setting is to have 10 variance components (variance parameters) as in Equation 7.1; this is the multivariate approach or UN structure**
- **CS (Compound Symmetry) structure is as in 7.2, and this is what the split plot design assumes. CS has only 2 variance parameters. HF structure in 7.3 has 5 variance parameters. AR(1), called the first-order autoregressive, structure in 7.4 has only 2 parameters. TOEP structure in 7.5 has 4 parameters.**
- **What does the *independence/constant variance* structure look like?**
- **Which of these structures are *nested* in others (and in which)?**
- **Appreciate the difference between the CS and AR(1) structures in terms of the *covariances*: between y_1 and y_2, between y_1 and y_3, and between y_1 and y_4.**
- **Example 7.1. Rabbits. 4 measurements at times 0, 30, 60 and 90 minutes. Profiles (p.4) do not look the same. GLM procedure used here at first. Sphericity test (Output 7.1b) indicates HF structure is accepted for these data. Regardless, Wilks (likelihood) test of**

time*trt **interaction is NS (p = 0.1134). Can then look at *time* test: p = 0.0082 imply average profile is not flat over time. Nonetheless, Output 7.1d indicates that the *linear aspect of the time*trt profiles* (i.e., the slopes) are not the same (p = 0.0247), but not the quadratic nor cubic (p = 0.6084 and 0.1842 resp.) Bottom line: profiles differ in terms of slopes, but wait …**

- **Rabbits. Analysis of these data using the SP approach indicate significant *time*trt* interaction (p = 0.0207), but SP approach is only rarely appropriate**
- **Rabbits. Both of the above are special cases of the MIXED approach (p.8), obtained by running this program and cycling through different choices for "type = ___" structures. *Nested* structures can be tested against one another using –2ΔLL test; otherwise, use AIC or BIC (lowest value). Output 7.3 on p.9 corresponds to AR(1), indicates significant *time*trt* interaction (p = 0.0253). Table on p.10 helps sort things out. AIC indicates AR(1) is best; -2ΔLL approach comparing AR(1) and INDEP (write down H_0 and H_A) give some pause for thought, but since interaction p-values are close, let's use AR(1). How is it the case that the AR(1) structure "sees" a significant *time*trt* interaction here whereas UN (MULT) does not? Conclusion: slopes are not the same, but need to follow up. A better approach may be as used in the next example.**

Class Two:

- **Example 7.2. Intracellular Li+ accumulation in 3 types of cells. 4 measurements at times 15, 30, 45 and 60 minutes. Turns out (lots of trial and error!) that UN(1) in 7.6 is best here – clearly explain in words what this structure means. Then, Output 7.4a gives intercept (7.36, 6.10, 1.81) and slope estimates (0.12, 0.09, 0.06) – uses the "noint" and "s" options. Then, Output 7.4b is useful to help us test**

for parallelism of the trt*time profiles. Conclusion: we accept parallelism (no linear interaction).

- **Example 7.3. Physical Exercise. 4 measurements at days 2, 6, 10, and 14 days. AR(1) structure turns out to be best here. Four time points means that we can fit cubic polynomials for each of the three treatments (12 total parms): these also correspond to intercept + (2df for the 3 treatments) + (3df for the 4 time points) + (6df = 2*3 for the interaction). Output 7.5a shows that the cubic terms are NS: this corresponds to the graph on p.13 too. Quadratics in Equation (7.7) are fit in Output 7.5b (looks like quadratic term is only necessary for the "reps" program). When we compare with Output 7.5c, we appreciate the true statement of H_A (at least one of the β_2's is not zero). Curves are plotted with data on p.13. For Rep's program, taking the derivative of the fitted quadratic, setting to zero, and solving gives maximum strength at about 11 days. It turns out that Control curve is essentially flat, and that Weight program keeps climbing over the range of these data.**
- **In Section 7.3 (pp.15-28), we fit a population (linear or nonlinear) model, and then allow the individual subjects to deviate from it in a hierarchical manner by letting the parameters themselves vary.**
- **So, we now have two levels of variability – variability around one's curve (σ^2) and individual variability in the parameters (with additional variances); often, we assume that the parameters have a Normal distribution, although this is hard to verify in practice.**
- **Example 7.4 fits two population lines – one for each of two treatments – with individual variation in one's intercept and slope, assumed to have the MVR Normal distribution on p.17 (top). That makes 5 variance terms in total; another is added since the intercept variability appears to differ by treatment.**
- **Full model on p.17 and Output 7.6a. Wald test of whether the covariance term 'var_01' can be dropped says 'yes' but Likelihood**

test says 'no'. Reduced model on p.18 bottom and Output 7.6b shows we can retain equal slopes. Interpretation of Output 7.6c is key and on p.20.

Class Three:

- **Example 7.5 fits the Normal Logistic (LOG3) model on p.21 top. Homoskedastic fit is way off (table at bottom of page and graph). Could model variances but that too is off (table) and doesn't take account of repeated measurements. As in last e.g., we model the upper asymptotes (θ_1s) as in Output 7.7b. Can test this model (and modeled variance model) vs. homoskedastic one with –2LL's since nested, but must compare last 2 models with AIC since neither is nested. Winner is this hierarchical one. Comparing Outputs 7.7a and 7.7b, note the large reduction in the SE of the LD50 parameter (θ_2).**
- **Example 7.6 (*PK of theophylline*) – 12 subjects; fit population model function in Equation 7.12 reparameterized as in 7.14 … 7.15. Parameters have important interpretations: clearance, absorption, elimination, AUC, t_{max}, c_{max}. The twist here is distributions of one parameter is skewed, so we use the *Log-Normal distribution* as in Equations 7.16-7.18. Key output in 7.8; retain the claim that 'var_uw' = 0, so it is dropped in Output 7.8. *Interpretations* on pp.27-8 are key!**
- **Time Series Errors. AR(1) structure is given in Equation 7.21: it relates the residual from one day to the residual from the previous day. Rho (ρ) is between –1 and 1. Time series analysis is more common in econometrics than other fields.**
- **Example 7.7. 4000 plastic beads placed into a sheep, and counting how many remain in the sheep over time. The model function is on p.29: modified LL2. Residual plot is also on p.29. Notice the sine pattern – this demonstrates the AR(1) structure. But, the non-constant variance presents a big problem called *nonstationarity*.**

- **Example 7.8. Atkinson gives PK/theophylline data for a single horse. When we fit the IP3 model in Equation 7.12, we get the residual plot on p.30. Kind of see a sine pattern, but these data are not rich enough to fit the AR(1) error pattern, so we move on to:**
- **Example 7.9. Sredni gives chloride ion transport through blood cell walls data. Measurements on the same unit (person?) over time, so they are probably correlated; measurements are taken every 0.1 minutes (i.e., every 6 seconds). We fit the LL3 model in Equation 7.23: θ_1 is the UA, θ_2 is the LA, θ_3 is the LD_{50}. NLIN and Output 7.9a on p.31 ignores the problem; when we take the associated residuals and plot residuals versus the lagged-residuals, we get the plot at the top of p.32. Think in terms of**

$$\varepsilon_t = \rho\varepsilon_{t-1} + a_t$$

Since this plot shows a strong linear association, this encourages us to believe in this AR(1) structure for these data.
- **Equation 7.24 just gives the –2LL function for the independence model. Output at bottom of p.32 is wrong – provided just for comparison with correct analysis.**
- **Equation at top of p.33 is the correct –2LL function for AR(1) case – is slightly modified for the fact that the measurements are not taken at times with step size = 1. Results given in Output 7.9c. Profile Likelihood curve for ρ is given at the top of p.34 – does not look parabolic so Wald and Likelihood results will differ. It hits its minimum at $\hat{\rho}$ = 0.0282681 (take from Output 7.9c).**
- **Comparing the SE's in Output 7.9c with those in 7.9b, notice the *increase!* For LD50 – from 0.816012 to 1.604694. This runs counter to Example 7.5 results above. But, from our knowledge of the results for time series methods, it is not unexpected.**

$$\boldsymbol{\Sigma_{MULT}} = \begin{bmatrix} \sigma_1^2 & \sigma_{12} & \sigma_{13} & \sigma_{14} \\ \sigma_{21} & \sigma_2^2 & \sigma_{23} & \sigma_{24} \\ \sigma_{31} & \sigma_{32} & \sigma_3^2 & \sigma_{34} \\ \sigma_{41} & \sigma_{42} & \sigma_{43} & \sigma_4^2 \end{bmatrix} \boldsymbol{\Sigma_{TOEP}} = \begin{bmatrix} \sigma^2 & \sigma_1^2 & \sigma_2^2 & \sigma_3^2 \\ \sigma_1^2 & \sigma^2 & \sigma_1^2 & \sigma_2^2 \\ \sigma_2^2 & \sigma_1^2 & \sigma^2 & \sigma_1^2 \\ \sigma_3^2 & \sigma_2^2 & \sigma_1^2 & \sigma^2 \end{bmatrix}$$

$$\boldsymbol{\Sigma_{CS}} = \begin{bmatrix} \sigma^2 & \rho\sigma^2 & \rho\sigma^2 & \rho\sigma^2 \\ \rho\sigma^2 & \sigma^2 & \rho\sigma^2 & \rho\sigma^2 \\ \rho\sigma^2 & \rho\sigma^2 & \sigma^2 & \rho\sigma^2 \\ \rho\sigma^2 & \rho\sigma^2 & \rho\sigma^2 & \sigma^2 \end{bmatrix} = \sigma^2 \begin{bmatrix} 1 & \rho & \rho & \rho \\ \rho & 1 & \rho & \rho \\ \rho & \rho & 1 & \rho \\ \rho & \rho & \rho & 1 \end{bmatrix}$$

$$\boldsymbol{\Sigma_{AR1}} = \begin{bmatrix} \sigma^2 & \sigma^2\rho & \sigma^2\rho^2 & \sigma^2\rho^3 \\ \sigma^2\rho & \sigma^2 & \sigma^2\rho & \sigma^2\rho^2 \\ \sigma^2\rho^2 & \sigma^2\rho & \sigma^2 & \sigma^2\rho \\ \sigma^2\rho^3 & \sigma^2\rho^2 & \sigma^2\rho & \sigma^2 \end{bmatrix} = \sigma^2 \begin{bmatrix} 1 & \rho & \rho^2 & \rho^3 \\ \rho & 1 & \rho & \rho^2 \\ \rho^2 & \rho & 1 & \rho \\ \rho^3 & \rho^2 & \rho & 1 \end{bmatrix}$$

$$\boldsymbol{\Sigma_{UN(1)}} = \begin{bmatrix} \sigma_1^2 & 0 & 0 & 0 \\ 0 & \sigma_2^2 & 0 & 0 \\ 0 & 0 & \sigma_3^2 & 0 \\ 0 & 0 & 0 & \sigma_4^2 \end{bmatrix} = diag\{\sigma_1^2, \sigma_2^2, \sigma_3^2, \sigma_4^2\}$$