Class Notes for Tuesday April 8th

Reminder: Don't forget Homework 6 due this Friday!

- In Section 7.3 (pp.13-21), 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 (σ²) 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.14. That makes 4 variance terms in total; another is added since the intercept variability appears to differ by treatment.
- Full model on p.15 and Output 7.6a. Wald test of whether the covariance term 'sb01' can be dropped says 'yes' but Likelihood test says 'no'. Reduced model on p.15 bottom and Output 7.6b shows we can retain equal slopes. Interpretation of Output 7.6b is key and on p.16.
- Example 7.5 fits the Normal Logistic (LOG3) model on p.17 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_1 s) as in Output 7.7a. 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 some parameters are skewed, so we use the *Log-Normal distribution* as in Equations 7.16-7.18. Key output in 7.8; retain the claim that 'sab' = 0, so it is dropped in Output 7.8. *Interpretations* on p.21 are key! Aside: the program on p.21 fits the additive Normal (not Log-Normal) distribution: since these models are <u>not nested</u>, comparisons must use AIC instead of –2LL; the AIC also shows preference for Log-Normal case so we use Output 7.8 for these data.
- 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. Phi (φ) is between -1 and 1. Time series analysis is more common in economics 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 at the bottom of p.22: modified LL2. Residual plot is on the top of p.23. 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 at the bottom of p.23. Kind of see a sine pattern, but these data are not rich enough to fit the AR(1) error pattern.
- Example 7.9. Sredni gives chloride ion transport through blood cell walls data. Measurements on the same unit (person?) over time, so they are correlated; measurements are taken every 0.1 minutes (every 6 seconds). We fit the LL3 model in Equation 7.23: θ₁ is the UA, θ₂ is the LA, θ₃ is the LD₅₀. NLIN and Output 7.9a at bottom of p.24 ignores the problem; when we take the

associated residuals and plot residuals versus the laggedresiduals, we get the plot at the top of p.25. Think in terms of

$$\varepsilon_t = \phi \varepsilon_{t-1} + a_t \quad (7.21)$$

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.25 is wrong provided just for comparison with correct analysis.
- Equation at top of p.26 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 φ is given at the bottom of p.26 does not look parabolic so Wald and Likelihood results will differ. It hits its minimum at φ̂ = 0.0282681.
- Comparing the SE's in Output 7.9c with those in 7.9b, notice the *increase!* For LD50 from 0.577008 to 1.13469. This runs counter to Example 7.5 results above. But, from our knowledge of the results for time series methods, it is not unexpected.