Class Notes for Thursday March 13th

Reminder: Please don't forget Homework 4, due tomorrow!

- Relative potency (ratio of two Normal or otherwise means) is a nonlinear model – need to use techniques of Chapter 5 here
- ***Direct Assay*** (pp. 1-8) versus ***Indirect Assay*** (pp. 8-13)
- Direct Assay examples (6.1, 6.2, and 6.3); Indirect Assay examples (6.4 and 6.5)
- Next week: Assessing ***synergy*** and ***antagonism*** using two models: the Finney model and the Separate Ray model
- **Example 6.1** (pp.1-4): y = sodium excretion rate (assumed Gaussian with constant variances) for two treatment groups, NORMAL ($n_1 = 7$) and B10AE ($n_2 = 7$); relative potency is estimated to be 0.426 (top of p.2).
- To get a CI (Wald or Likelihood), use NLIN approach with mean = μ_2 for NORMAL group and mean = $\mu_1 = \rho\mu_2$ for B10AE group (using dummy variables in Eqns. 6.2 and 6.3)
- So mean = μ_2*NORTRT + $\rho\mu_2$*B10TRT
- NLIN on p.3 assumes Normality and Constant Variances
- Gives RP 95% WCI (-0.0177,0.8697) – we're 95% confident that the true RP (of B10AE to NORMAL) lies between –0.02 and 0.87. Since one is not in the CI, we're confident that they're not equally potent.
- Left endpoint of CI and skewness in p.2 plot makes us doubt our assumptions and return to theory. If $Y_1 = \rho Y_2$, then $\log(Y_1) = \log(\rho) + \log(Y_2)$. Y_1 is conc. of substance 1, etc. Now, let $Z_1 = \log(Y_1)$, and assume $Z_1 \sim \text{Normal}(\nu_1,\sigma^2)$, etc. for substance 2. Plots of Z's given on p.3 look more Normal with constant variance.
- New mean relationship is in Eqn. 6.6 and fit in the NLIN which produces Output 6.1c. Now, 95% WCI for true RP is (0.0803,0.6843). Good to see interval doesn't go into negative

values (impossible). The 95% PLCI is (0.1735,0.8424), and this is the one we should use since Likelihood is best.

- **Example 6.2** – ratio of two independent Poisson means (since these are COUNT data) using NLMIXED procedure (p.5). RP of SOAP ($n_1 = 8$) to CONTROL ($n_2 = 6$) is estimated to be 0.6028 and Wald TS testing equal potency is on the top line of p.6. SAS implies this TS ~ t_{14} (most would argue ~ t_{12}). Likelihood test REDUCED model is fit after line 7 on p.6 (is this right?). Results aren't shown but reported: $\chi_1^2 = 28.2$, $p < 0.0001$. What is our conclusion here?
- **Example 6.3** – Y = prostate size for $n_1 = 5$ CONTROL and $n_2 = 5$ ESTRIADIOL animals. Plot on p.6: data look Normal (symmetric) but variance is not constant – see NLIN residual plot on p.7. Let's model variances too! If $Y_1 = \rho Y_2$, then $\mu_1 = \rho\mu_2$ and $\sigma_1^2 = \rho^2\sigma_2^2$ for. This is kind of like the Seefeldt example (5.8) from last class. See NLMIXED program on p.7 – why can we ***not*** use NLIN here? 95% WCI for RP is (1.84,5.00). Profile likelihood curve is on p.8 with cut-lines at 90% (bottom line), 95% (middle) and 99% (top). From 95% cut line and really good eyes, 95% PLCI is (2.19,5.34). Conclusion: we're 95% confident that Estriadiol is at least 2.19 times as potent as Control; since 1 is not in the PLCI, Estriadiol is significantly more potent than Control.
- For **Indirect Assays**, we cannot measure amounts directly, but must make inferences indirectly. We'll fit dose-response curves such as the Binary Logistic or other nonlinear model function. When we do, we usually assess RP (relative potency) by the ratio of the LD_{50}'s for the two treatments.
- **Example 6.4** compares two peptides, Neurotensin (N) and Somatostatin (S) using Binary Logistic models. Note the chosen design here: either 0.01 and then multiplied by 10^k or 0.03 and then multiplied by 10^k. Looking at the graph on p.9, looks like the doses don't go high enough.

- First step: Had to decide which scale to use – jump forward to Box-Cox transformation Eqn. 6.14 on p.21: when θ_6 is near 0 (asi is the case here), then use log-dose.
- Now look at the program on p.10, and write down the explicit formula for π (success probability).
- The first NLMIXED here has unequal slope parameters (θ_3) and the second one (Reduced one) has a common slope: -2LL's are given in table on p.11. Here, we retain the assumption of common slopes (p=0.1213).
- Then, RP is estimated to be 5.66. Which peptide is more potent?
- As to CI's look at Reduced model output (Output 6.4) on p.10: 95% WCI, (-1.89,13.2) looks weird. Why?
- Profile likelihood plot on p.11. Really good eyesight confirms that 95% PLCI for ρ is (1.59,19.59). Interpretation is at bottom of the page. Consequence/ramification are …?
- Example 6.5 on p.12 gives a Normal example with the modified MM2 model function in Eqn. 6.9, where θ_1 is the upper asymptote but what is θ_2? Testing for common upper asymptotes – programs on top of p.13, and here we do the Full-and-Reduced F test on bottom of p.12 (accept same upper asymptote).
- Reduced model is in Output 6.5, and RP is estimated to be 0.0420 $\approx$ 0.04 = 1/25, so standard insulin is approximately 25 times more potent than the A1-B29 insulin variety.

Next Time – Assessing Synergy and Antagonism (Interaction) of Two Drugs