Class Notes for Thursday March 20th

Reminder: Please don't forget Homework 5, due next week!

- We can assess interaction (synergy or antagonism) using either one of the Finney models or the SR model
- The Finney models combine two x's (e.g., doses of two drugs) in the effective dose formula (Equation 6.10) first, and then relates this z (effective dose) to the response variable using either Equation 6.11 or 6.12 or some variant of these
- θ_5 is the key (so-called coefficient of synergy) parameter, with
  - **$\theta_5 > 0$ indicating synergy**
  - **$\theta_5 < 0$ indicating antagonism**
  - **$\theta_5 = 0$ indicating independent action**
- As noted last class, Equation 6.12 is the binary logistic model function using the ***log-dose scale*** – in practice, one needs to determine which exact scale to use and modify accordingly
- **Example 6.6.** Gerig 2 phenolic acids (ferulic and vanilic acids) in 3 chambers (blocks). Chosen design in graph on p.16 (six support points, only one of which is an interior point). NLIN output on p.16 indicates significant ***antagonism***, but Likelihood (Full and Reduced test) gives marginal proof: p-value = 0.0254. Clearly need a better study! See the ***isobole*** on p.16.
- **Example 6.7.** Upjohn drugs A and B binomial example – design in graph on p.18 (plus additional support points). n_k mice given a given combination of A and B, and y_k = number that die is counted; log-scale is indicated (output not shown). These data indicate significant ***synergy*** between drugs A and B (p.18).
- **Example 6.8.** Carter ethanol and chloral hydrate binomial; checkerboard design on p.19. Maybe a "Ray Design" would be better. Evidence here of synergy ($p = 0.0151$).
- **Example 6.9.** Machado & Robinson. Y = RT activity (counts). Drugs are AZT and ddI. Ray design on p.20 with ***3 interior rays***.

Normal fit produces conclusion of independent action and the residual plot on p.20 – Yikes! Refit using Poisson distribution and modelling variance – got similar results, so former is on p.21. Conclude significant synergy between these two drugs.

- **Example 6.10.** Chou and Talalay example shows the need for the Box-Cox scale parameter (θ_6) since it's estimate is neither zero (log-dose) nor one (dose) here. Also, response variable here is a fraction, so we take logit transformation to (hopefully) achieve Normality. Then, we observe significant synergy.
- Sometimes the Finney models are not rich enough and we need a larger model such as the Separate Ray (SR) model. The SR model allows for e.g. synergy for one ray, independent action for another, and antagonism for yet a third. Note for example that the for the Finney model to fit, the slopes must be equal and the LD_{50}'s must line up on an ***isobole*** as on p.16 or p.18 – the point being that it is a rather 'narrow' or restrictive model (that said, it does fit in many cases).
- Lots of notation in the SR model, but the big picture is graph on p.24. Point C is the LD_{50} for Drug B and point E is LD_{50} for Drug A. Rays 3 … J … R are ***interior rays*** – corresponding to different proportions of drugs A and B (with "***slopes***" $\mathbf{c_k}$ in Equation 6.15). For Ray J, if the LD_{50} is at the point D, then we have independent action. If it's closer to the origin, we have synergy (further from the origin → antagonism). A measure of the actual LD_{50} to the one expected under independent action is the **combination index** (κ_r) for each interior ray. The SR model simultaneously fits separate logistic (or otherwise) curves along each of the rays, and calculates the κ_r's.

$\kappa_r = 1$ → **independent action**
$\kappa_r < 1$ → **synergy**
$\kappa_r > 1$ → **antagonism**

- It can be shown that if all the ***slope parameters*** (θ_3's) are equal and the κ_r's follow a specific algebraic relation, then the SR reduces to the Finney model.
- **Example 6.11.** Martin. On p.26, just one interior ray. Six design points on the interior ray, and 5 on the two exterior rays. Point A is the LD_{50} for Deguelin, point B is LD_{50} for Rotenone, point C is intersection with interior ray, and point F (filled circle) is the actual LD_{50} along the interior ray, so $\hat{\kappa}_3$ = **0.6615** (***make corrections in text!***). Note that Output 6.10a here is better than 6.10b (equal slopes) for these data (p = 0.0042). Wald test of H_0: $\kappa = 1$ is on p.27 – better yet, using the program near the bottom of p.27, likelihood –2ΔLL test gives $\chi_1^2 = 14.3$, p = 0.0002. Finally, since RP estimate is $\hat{\rho}$ = 2.6405, the interior ray corresponds to the effective fraction f = 0.6053 (Equation 6.19).
- **Example 6.12.** Additional Binomial examples with one interior ray. Hewlett and Plackett DDT and γ-BHC again. Output 6.11a shows that log-dose and dose scales are wrong for these data – see Equations 6.13 and 6.14. Stay on this new scale for these data. Then, can accept equal slopes ($\chi_2^2 = 0.8$), but not independent action – synergy detected here too; $\hat{\kappa}_3$ = 0.4555.
- **Example 6.13.** Shelton data: response variable here is a fraction, and transformed to Normality with the logit transformation – one interior ray here. Cannot accept common slopes – see Full & Reduced F on p.30, so the Finney model will not fit these data. Synergy detect here $\hat{\kappa}_3$ = 0.4286 and c = ¼ → f = 0.2605, which may be too low. See Equation 6.17 on p.23. This example points out that we need a good estimate of ρ = relative potency before we choose the slope of the ray(s), c.
- **Example 6.9 continued.** Finney model even with the Poisson distribution doesn't fit well – residual plot on p.31 looks wavy. Separate Ray model fits better – see p.32. This dataset has 3 interior rays with slopes c = 10, 5, and 1. Synergy is detected

along each ray, and we accept a common combination index; test that it equals 1 is rejected ($\chi_1^2 = 218.9$, $p < 0.0001$). Relative potency estimate is such that these interior rays correspond to the effective fractions f = 0.1588, 0.2741, and 0.6537.

- **Example 6.14 (not 6.15).** Goldin cancer example – three interior rays with slopes c = 7.5, 1, and 1/7.5. Graph on p.33. Independent action along first ray, marginal story along the central ray, and strong synergy along gentle-sloped ray. Combination indices can be related to effective fractions as in plot on p.35.

Homework due this Friday; Exam next Thursday

Next Classes – Chapter 7: Analyzing Repeated Measures Data.