Optimal Design for Hill Model

SCT 2013
Boston, MA, USA

D-optimal; adaptive design; personalized design

Russell Reeve, PhD
Quintiles
Durham, NC, USA
Outline

- Motivating problem, from rheumatoid arthritis
- Hill model
- D-optimal design for Hill model
- D-Bayes optimal design for Hill model
- Adaptive design based on D-Bayes design
- Personalized design for RA

- Implementation challenges and solutions
Co-authors on work presented herein

• From North Carolina State University
  > Wei Xiao
  > Bradley Ferguson
Rheumatoid Arthritis

- Progressive disease
- Large proportion of the population
- Very large market (> $25 billion/yr)

- Clinical trials
  > Endpoints: ACR20, DAS28
- Time model can be modeled as exponential
  > $ACR20 = a(1 - e^{-bt})$
- Also have dose-response
Dose Response

*Multipled on top of time-response model*
Forms of Hill Model

Many forms available, all equivalent

• Hill model was first developed around 1903

• \( E = a + E_{\text{max}} \frac{d^h}{(E_{D_{50}}^h + d^h)} \)

• \( E = \mu + (E_{\text{range}} - \frac{1}{2})/\left(1 + \exp(-h(\log x - \log E_{D_{50}}))\right) \)

• Aliases
  > Michaelis-Menten
  > Emax
  > 4-parameter Logistic
Hill Model Forms

All are equivalent functions of the dose $d$

\[
= + \quad +
\]

\[
= + \quad \infty - \quad +
\]

\[
= \infty - \quad +
\]

\[
= \quad + \quad \left[ \begin{array}{c}
+ \\
+ - \\
+ - \\
+ - \\
\end{array} \right]
\]

\[
= \quad + \quad \left[ \begin{array}{c}
+ \\
+ \kappa - \\
+ \\
+ - \\
\end{array} \right]
\]

\[
= \quad + \quad \left[ \begin{array}{c}
+ \\
+ - \\
+ - \\
\end{array} \right]
\]
Parameter Interpretation

Asymptote Parameters and Slope and location

\[
E = \frac{E_D}{h} + \frac{E_0}{h(c + d)}
\]

Define
Binary Responses

- Logistic Regression uses a Hill model (logit) with asymptotes of 0 and 1

\[ P(Y=1) = a + \frac{d}{1 + \exp[-b(\log x - c)]} \]

- 4-parameter version used in mycophenolate mofetil RCCT (1992)
  - \( x = \log \text{AUC} \)
  - \( Y = \text{organ rejection status} \)
  - Patients randomized to AUC levels
  - Doses adjusted to get patients onto target using Bayesian updating of exposure-response relationship
    - \( \text{AUC} = \gamma_1 + \gamma_2 \text{ dose} \)
    - Prior for \( \gamma_1 \) was based on variability in patient population
    - Distribution of \( \gamma_1 \) was updated after each dose, and used to adjust the next dose
$D_{22}$ Optimal

- D-optimal design has points at
  \[ \delta_{\text{opt}} \approx \frac{4(3 + 2e)}{(3 + e)^2}. \]
- This implies
Robustness of Optimal Location
Bayesian D-optimal

• Put prior on parameters

\[ = \int \phi \tau = \int^{\omega} \delta \phi \tau \]

• Difficult to get expressions to solve this
• Widens up the location of the maximum, but not as much as you might think
Adaptive Design

- Start with optimal design for first $K$ subjects
- Update distributions of parameters
- Use D-Bayes design to pick next set of $M$ subjects
- Repeat process

- Should beat fixed design
Simulation Study

• Truth
  > $E_0 = 40$, $E_{\text{max}} = -5$, $h = 1.5$, $\sigma = 1$, $c \in \{1, 1.1, \ldots, 1.9, 2.0\}$
  > This model based on actual experience in clinical trial
  > Sample size $N = 300$

• Fixed design
  > Doses = 0, 20/3, 40/3, and 4 (equal allocation of patients)

• D-optimal design
  > 4 doses (equal allocation of patients)

• D-Bayes optimal design
  > Use uniform prior for $\theta$
  > $K = 120$, $M = 20$

• Look at ability to accurately and precisely estimate log ED$_{50}$, log ED$_{70}$, and log ED$_{90}$. 
Comparison of Performance

Red = fixed design
Blue = Bayes adaptive
Green = D optimal
Within Patient Adapting

- Back to RA motivating example
- We have several options
  - Fixed design
    - Ad hoc
    - D-optimal
  - Bayesian adaptive design
  - Within patient adaptive
- Endpoint is ACR20
  - Binary
  - If a patient achieve $\geq 20\%$ reduction in symptoms, then set to 1; otherwise set to 0
Personalized Design

- ACR20 is binary
- $P(ACR20 = 1)$ follows Hill model

- Can we estimate ED70 better than with Bayesian design or fixed design?

- Patients are seen at baseline, weeks 4, 8, 12, 16, and 24
- If ACR20 = 0 for 3 consecutive visits, increase dose
- If ACR20 = 1 for 3 consecutive visits, decrease dose
Simulation Results

Comparison of design options for bias and precision of $ED_{50}$ estimates (lower is better on these graphs)

Personalized wins
Conclusion

• Developed expression for D-optimal design for Hill models
• Used D-Bayes to construct adaptive trial
• D-Bayes adaptive trial significantly outperformed fixed trial
• Personalized trial beat again D-Bayes adaptive trial

• Take away: Faster you can utilize information, the better
Sticking Points to Implementation

• **Time to set up:** Can take several months more than fixed design, will get the time back in the form of a smaller trial later, or another trial avoided

• **Drug supply:** More challenging to provide a wide assortment of doses, especially in PO products
  > Can manufacture large tablets and smaller “adjustment” tablets
  > Simulation can help optimize the manufacturing load
  > Mycophenolate example
    - Drug administered in morning
    - Blood samples collected for AUC (abbreviated collection times)
    - Blood samples analyzed overnight for concentrations
    - Data uploaded into program that generated next dose level, and package ID (package ID randomly coded to preserve blinding)
      » Packages had large tablets of several sizes, but we also manufactured smaller tablets for fine tuning of doses
    - Next day subjects given updated dose
  > For RA, adjustment would be based on ACR20 or DAS28, doses updated instantly using eDC technologies
Adaptive Data Management

• Data Flow for Interims
• IVRS holds probabilities for treatment assignment
• Interims are scary thoughts for a trial that has a number of adjustments
  > Monitoring of data to clean
  > Do we suspend enrollment during process?
  > TLF generation

Clean only that which is needed for dose updating, don’t need 100% review
Call this a probability adjustment event (PAE), not an interim
Automate data flow and analysis

Using push technology works well
Monitor continually instead of batches
Conclusion

• Adaptive designs are more efficient at extracting information than fixed designs
• Personalized designs better yet

• Not hard to set up operationally, but does not some time to plan
• Communication among team members during trial is key

• Thanks for your time

• Russell Reeve
• russell.reeve@quintiles.com
• 919-760-0035 (cell)