Optimal Design for Hill Model

SCT 2013

Boston, MA, USA

D-optimal; adaptive design; personalized design

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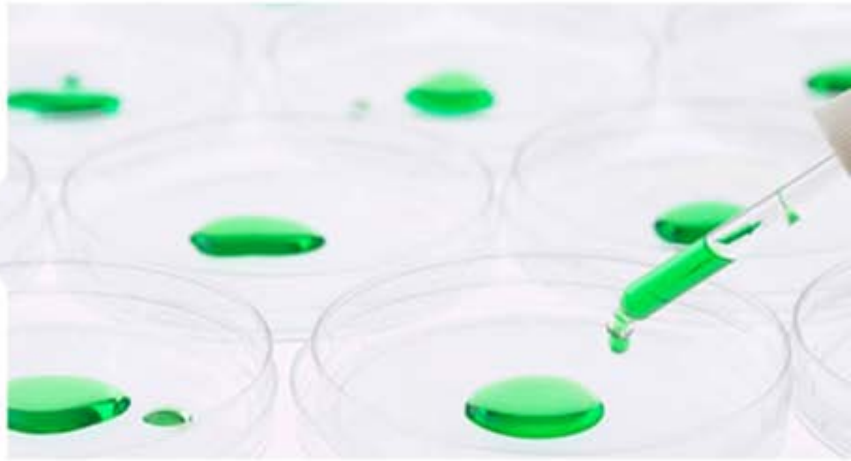
Navigating the new health



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clinical | commercial | consulting | capital

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

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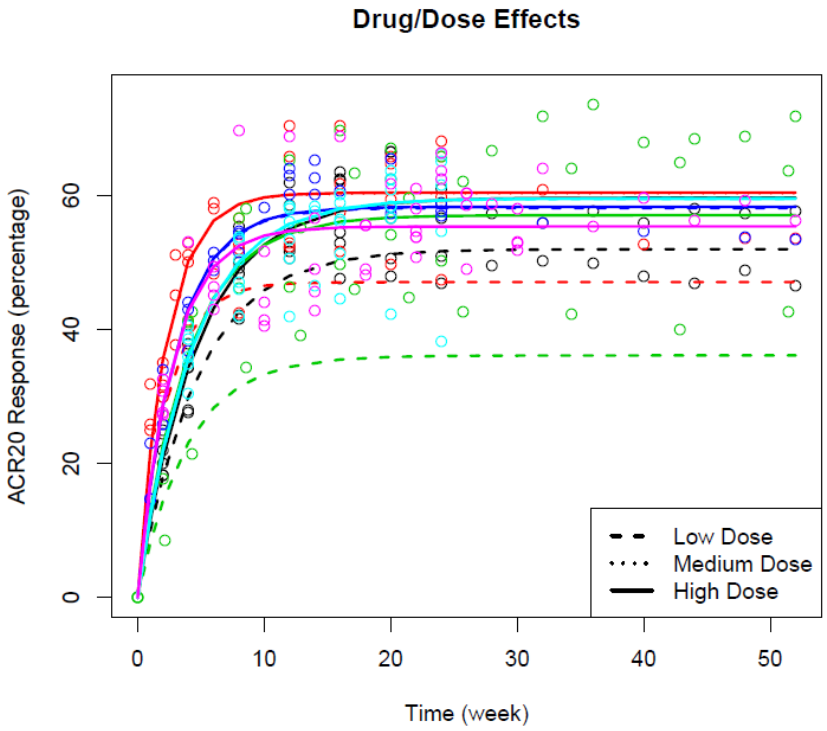
- From North Carolina State University
  - > Wei Xiao
  - > Bradley Ferguson

Rheumatoid Arthritis

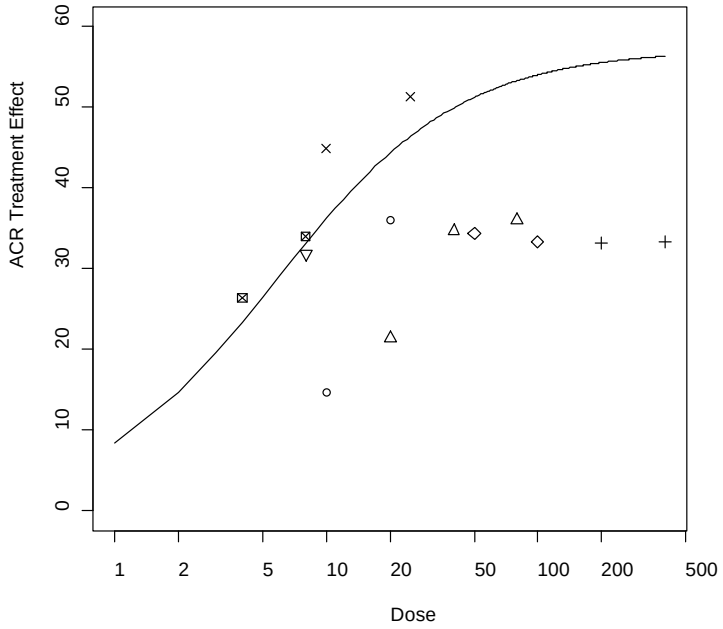
- Progressive disease
- Large proportion of the population
- Very large market (> $25 billion/yr)

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



Dose Response

Multiplied on top of time-response model



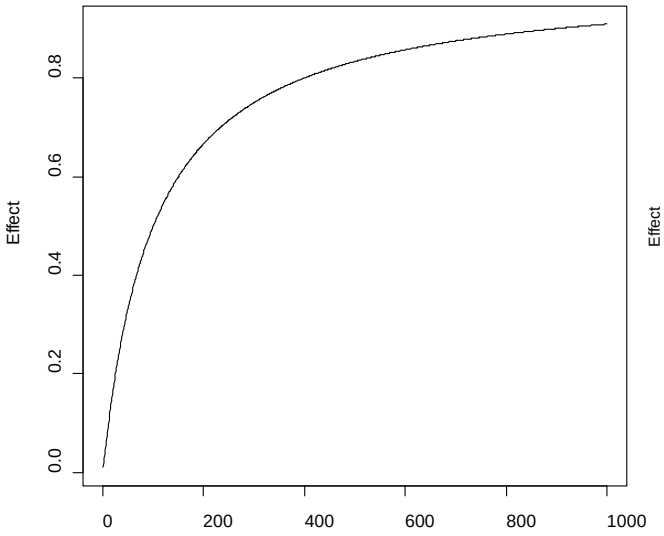
Forms of Hill Model

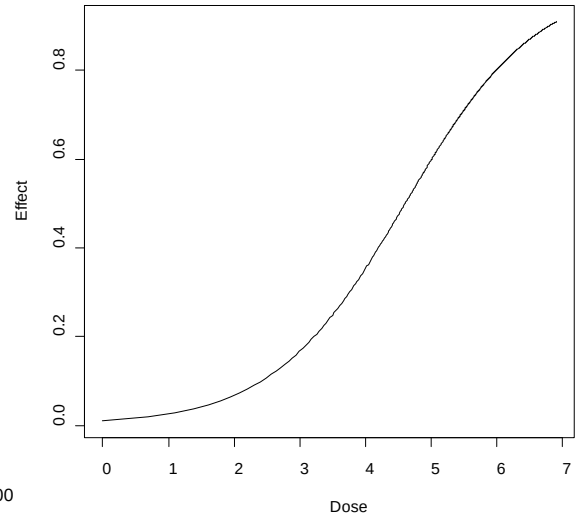
Many forms available, all equivalent

- Hill model was first developed around 1903

- $E = a + Emax\ d^h/(ED_{50}^h + d^h)$
- $E = \mu + (E_{range} - ½)/(1 + \exp(-h(\log x - \log ED_{50})))$

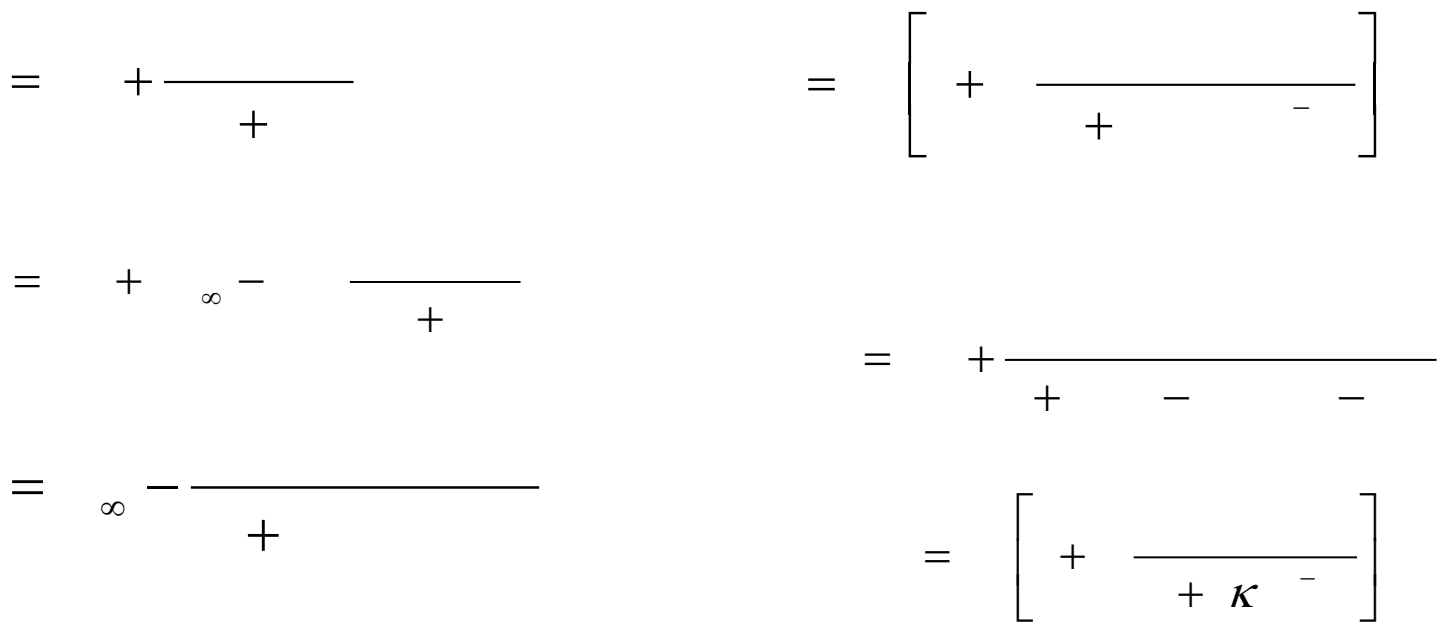
- Aliases
  - > Michaelis-Menten
  - > Emax
  - > 4-parameter Logistic





Hill Model Forms

All are equivalent functions of the dose d



$$= \quad + \frac{}{+}$$

$$= \left[+ \frac{}{+ \qquad -} \right]$$

$$= \quad + \quad \infty - \frac{}{+}$$

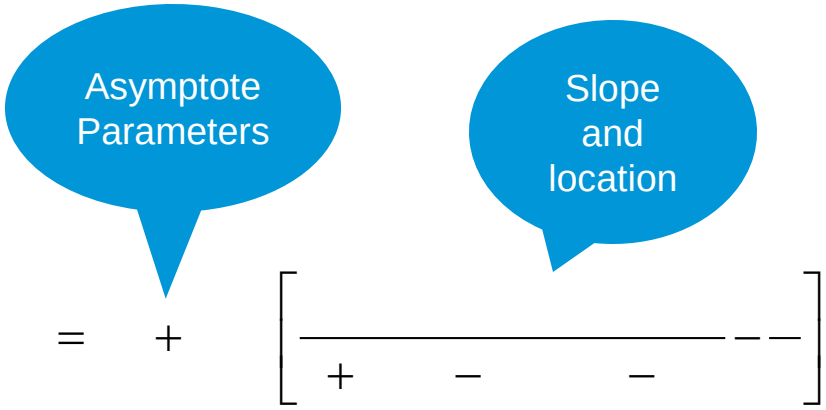
$$= \quad + \frac{}{+ \qquad - \qquad -}$$

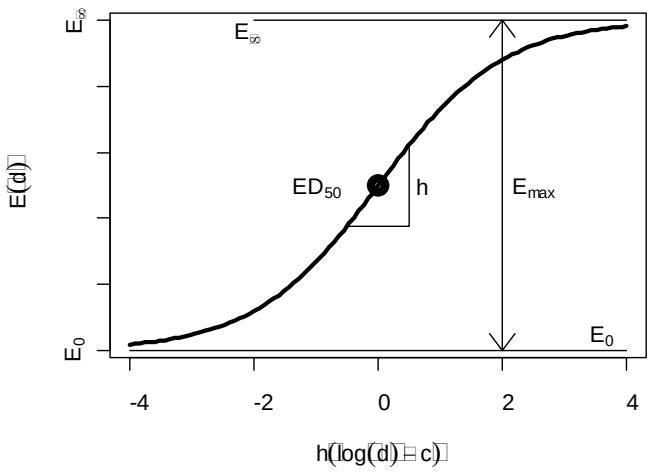
$$= \quad \infty - \frac{}{+}$$

$$= \left[+ \frac{}{+ \; \kappa \; -} \right]$$

$$= \quad + \left[\frac{}{+ \qquad - \qquad -} - - \right]$$

Parameter Interpretation





Define

Binary Responses

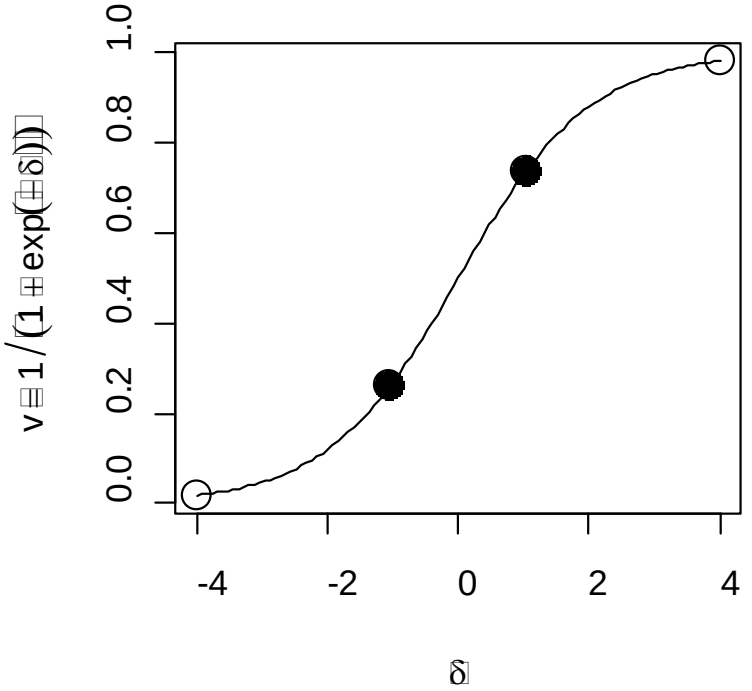
- Logistic Regression uses a Hill model (logit) with asymptotes of 0 and 1
- $P(Y=1) = a + d/\{1 + \exp[-b(\log x - c)]\}$
- 4-parameter version used in mycophenolate mofetil RCCT (1992)
  - > x = log AUC
  - > Y = organ rejection status
  - > Patients randomized to AUC levels
  - > Doses adjusted to get patients onto target using Bayesian updating of exposure-response relationship
    - AUC = $\gamma_1 + \gamma_2$ dose
    - Prior for γ_1 was based on variability in patient population
    - Distribution of γ_1 was updated after each dose, and used to adjust the next dose

D_{22} Optimal

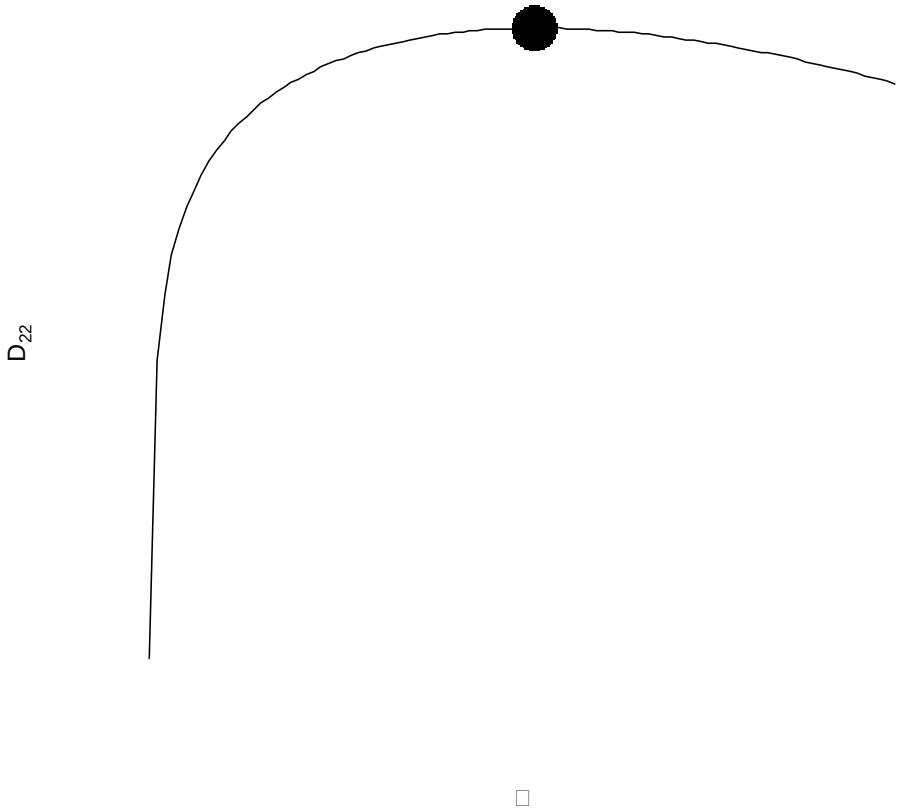
- D-optimal design has points at

$$\delta_{\text{opt}} \approx 4(3 + 2e)/(3 + e)^2.$$

- This implies ≈ .



Robustness of Optimal Location



Bayesian D-optimal

- Put prior on parameters

$$= \int \quad \phi \qquad \tau \qquad = \int \; {}^{\omega\ \delta} \quad \phi \qquad \tau$$

- 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
  - > $E_0 = 40$, $E_{max} = -5$, $h = 1.5$, $\sigma = 1$, $c \in \{1, 1.1, \ldots, 1.9, 2.0\}$
  - > 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 θ
  - > K = 120, M = 20

- Look at ability to accurate and precisely estimate log ED_{50}, log ED_{70}, and log ED_{90}.

Comparison of Performance

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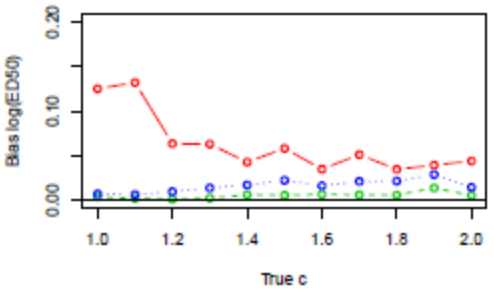
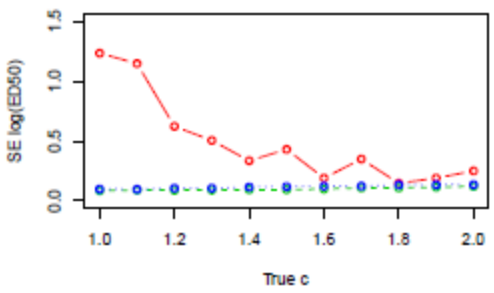
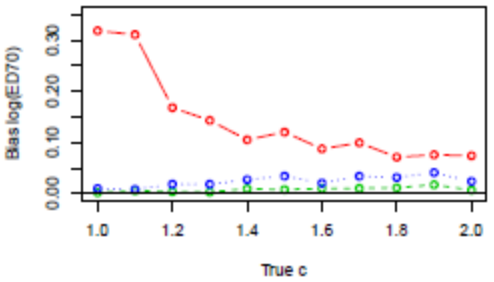
Bias | SD

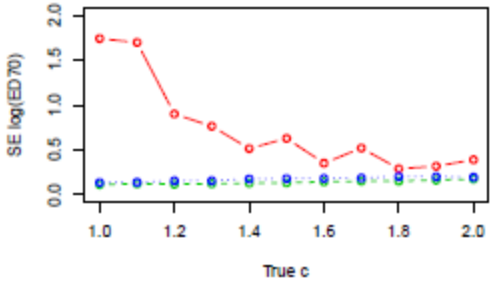
ED_{50}



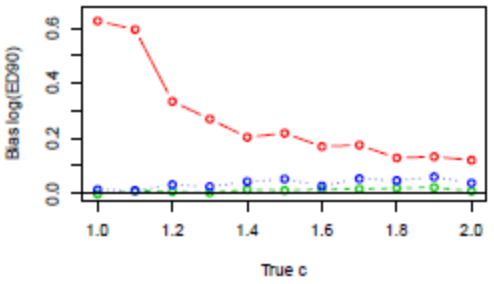


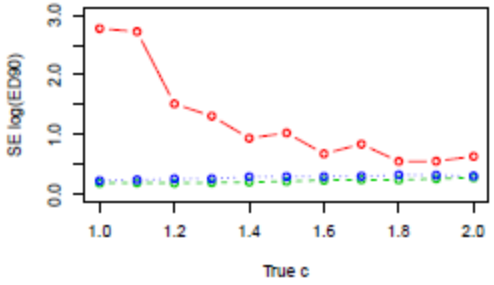
ED_{70}





ED_{90}



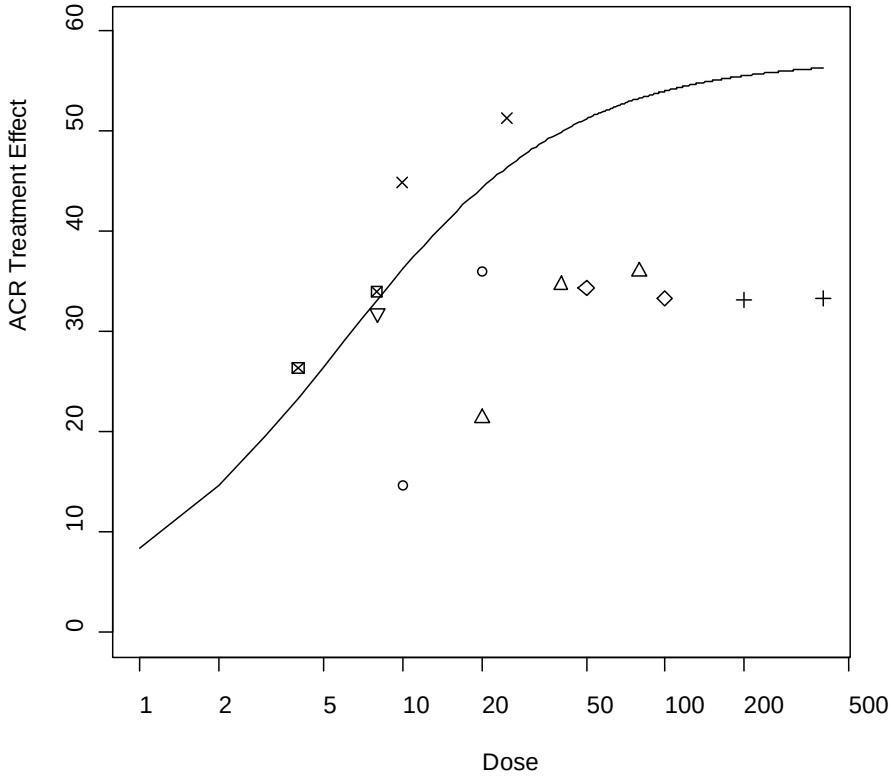


Red = fixed design
Blue = Bayes adaptive
Green = D optimal

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 ≥ 20% reduction in symptoms, then set to 1; otherwise set to 0

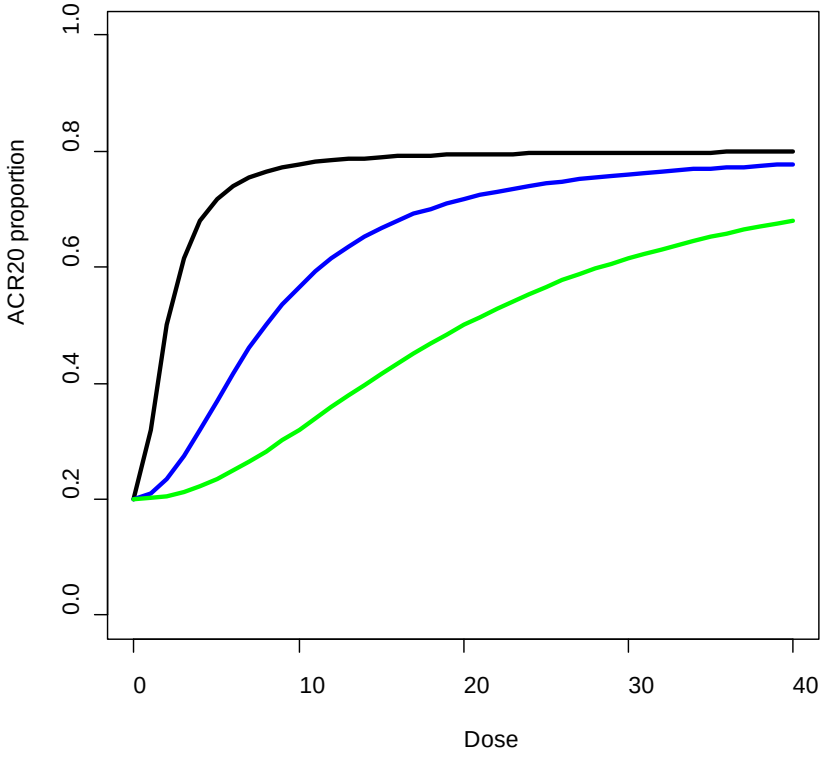


Personalized Design

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

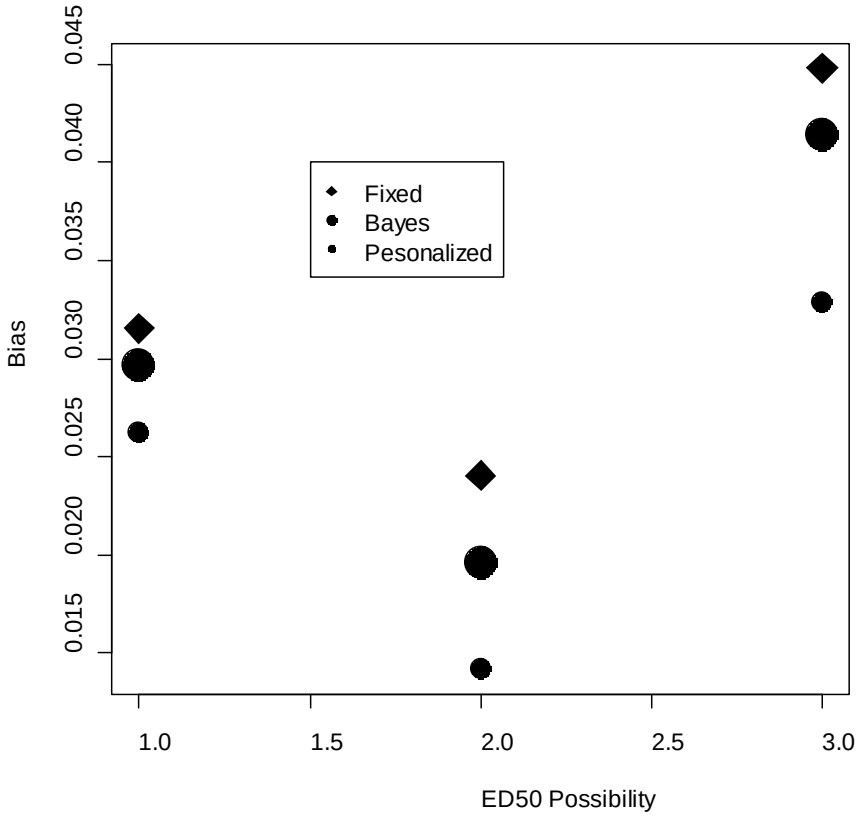
- Can we estimate ED70 better than with Bayesian design or fixed design?

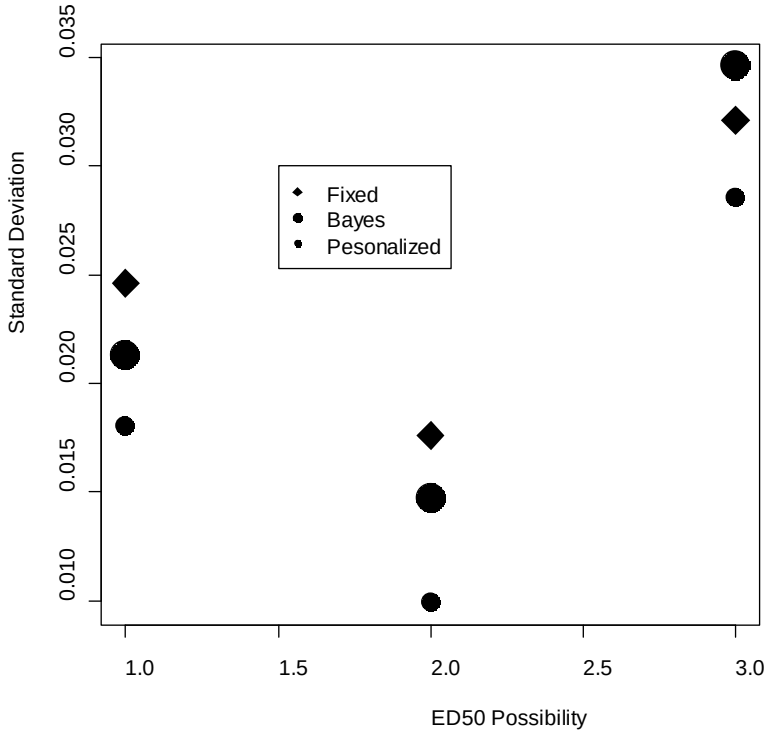
- Patients are seen at baseline, weeks 4, 8, 12, 16, and 24
- If ACR20 = 0 for 3 consecutive visits, increase dose
- If ACR20 = 1 for 3 consecutive visits, decrease dose



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

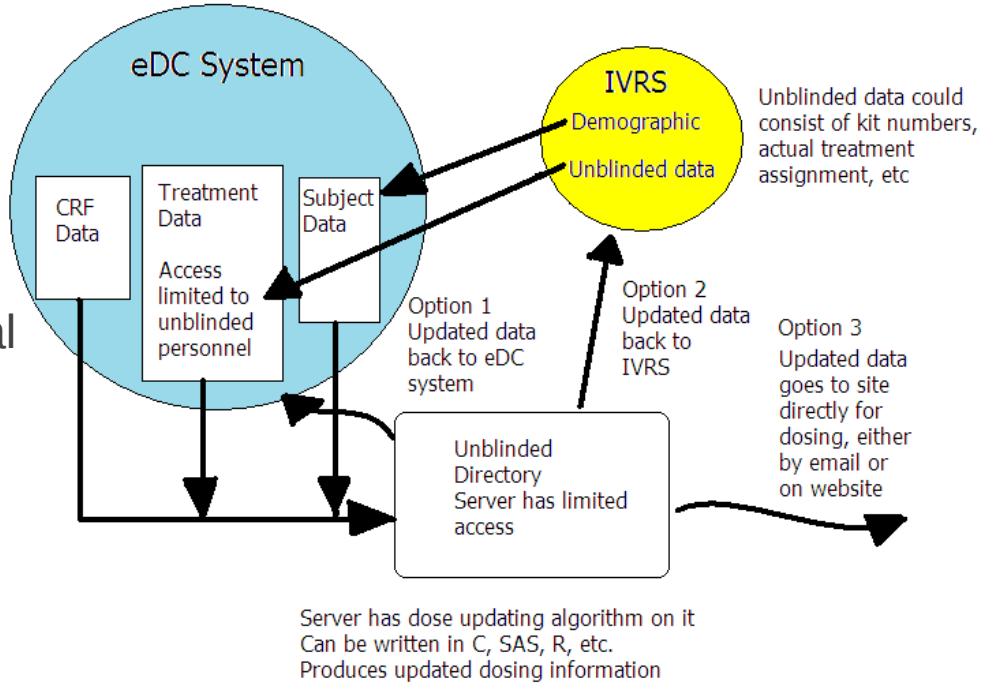
- Take away: Faster you can utilize information, the better

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

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