

# An Adaptive Dose Exploration Design for the Estimation of Human Colonizing Dose 50 (HCD<sub>50</sub>) and 90 (HCD<sub>90</sub>)

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January 27, 2009

# Outline

- 1 Motivating example - H-Flu design
- 2 Bayesian design
- 3 Simulation and comparison
- 4 Conclusion

## H-Flu (*Haemophilus influenzae*) Study

- Healthy volunteers were inoculated with one of 8 different doses of NTHi 2019 StrR #1
- Nasal washes and nasopharyngeal swabs were taken and analyzed for recovery for this pathogen. This is the response of primary interest in a dose response model.
- Other responses: symptoms and immunoblobulin response

# H-Flu Design

- Two-stage study:
  - **Stage 1:** to develop a colonization model and understand the dose response relationship. Subjects entered the study sequentially: one at a time. The next dose allocation was determined by the outcomes from previous subjects. A total of 6 subjects were enrolled, resulting 64 possible outcome-dose allocations.
  - **Stage 2:** to gain additional experience at the dose above, below and closest to  $HCD_{90}$ , and to further refine the estimates of the dose response relationship. Nine additional subjects were included.
- Outcome:
  - Success (1): subject was colonized
  - Failure (0): subject was not colonized

# H-Flu Design

## Stage 1

- Potential doses ( $\log_{10}(\text{dose})$ ) range from 1.5 to 5.0, starting from 3.0, with increment/decrement of 0.5
- Starting dose of 3.0 was chosen by consensus as safe, and based on other pathogens
- The design was modified from Up-and-Down Method (Dixon & Mood, 1948; Wu, 1985):

$$x_{i+1} = \begin{cases} x_i + 0.5 & \text{if } y_i = 0 \\ x_i - 0.5 & \text{if } y_i = 1 \end{cases}$$

- Using Up-and-Down Method with dose range [1.5, 5.0], there may be more than two subjects with the same dose
- The Up-and-Down design was modified so that no more than two subjects were inoculated with the same dose

# H-Flu Design

## Stage 1

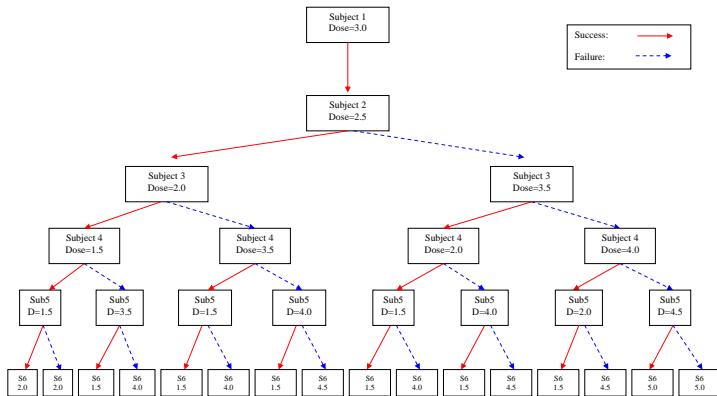


Figure: Diagram for H-Flu Design (Stage 1)

# H-Flu Design

## Stage 1

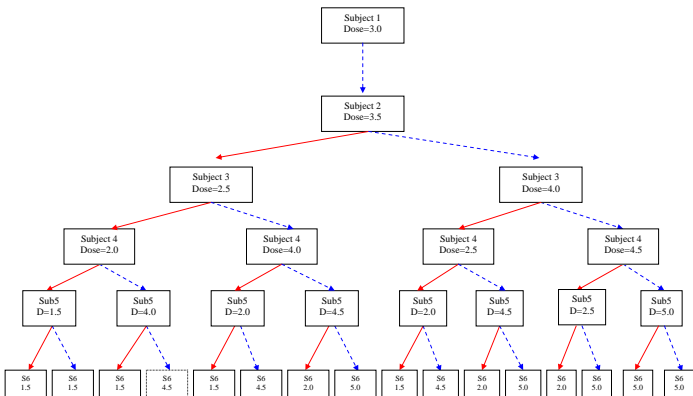


Figure: Diagram for H-Flu Design (Stage 1)

## Issues Related to the Design

- Small samples
- Existence of MLE (Sillvapulle, 1981; Wu, 1985; Agin, 1993)

$$(x_{min}^+, x_{max}^+) \cap (x_{min}^-, x_{max}^-) \text{ is nonempty}$$

or

$$x_{min}^+ < x_{min}^- = x_{max}^- < x_{max}^+$$

or

$$x_{min}^- < x_{min}^+ = x_{max}^+ < x_{max}^-$$

- The Up-and-Down design is modified to increase the probability of MLE
- Extremely cautious in dose escalation
- Heuristic

## Notation and Model

Comparison of Bayesian and frequentist analysis (MLE) from a frequentist perspective with this design. For several fixed parameter values, look at sampling distribution of MLE and Bayes estimates.

- Notation:

- Dose:  $x_i, i = 1, \dots, 6$
- Outcome:  $y_i, i = 1, \dots, 6$
- Probability of success (colonization):  $p_i = P(Y_i = 1), i = 1, \dots, 6$

- Logistic regression model:

- $Y_i \sim \text{bin}(1, p_i)$
- $\text{logit}(p_i) = \alpha + \beta x_i; p_i = \frac{\exp(\alpha + \beta x_i)}{1 + \exp(\alpha + \beta x_i)}$
- $HCD_{50} = -\alpha/\beta$
- $HCD_{90} = (\log 9 - \alpha)/\beta = HCD_{50} + \log 9/\beta$

## Frequentist and Bayesian

- Frequentist: MLE of  $\alpha$  and  $\beta$  can be obtained by Newton-Raphson Method
- Bayesian: Define  $\mu = HCD_{50}$ ,  $\delta = HCD_{90} - HCD_{50}$

Prior distribution:

Assume  $\mu \in [1.5, 5]$ ,  $\delta \in [0.1, 5.1]$

Assume  $\frac{\mu-1.5}{3.5} \sim \text{Beta}$  and  $\frac{\delta-0.1}{5} \sim \text{Beta}$ , specifically

$$\frac{\mu - 1.5}{3.5} \sim \text{Beta}(1, 1), \quad \frac{\delta - 0.1}{5} \sim \text{Beta}(0.25, 1)$$

$(\mu, \delta \text{ independent})$

$$\left( \mu = -\frac{\alpha}{\beta}, \delta = \frac{\log 9}{\beta} \right)$$

# Simulation and Results

- Settings for simulation:
  - Nineteen combinations of true  $(HCD_{50}, HCD_{90})$
  - For each combination, simulate 1,000 of  $(x_i, y_i)$ ,  $i = 1, \dots, 6$
  - Compute MLEs and Bayes estimates.
- Results:
  - Normal approximation for MLE does not hold due to small sample size
  - Probability of MLE does not exist is high ( $> 0.4$ )
  - Bayesian method guarantees that estimates exist

# Bayesian Design

- Optimal design uses backward induction (dynamic programming): not practical
- Bayesian myopic procedure:
  - **One-step-look-ahead**: choose the next dose that minimize the expected loss *one* step ahead, assuming there is only *one* step remaining
  - **Two-step-look-ahead**: choose the next dose that minimize the expected loss *two* steps ahead, assuming there are *two* steps remaining (moving window)
  - **Three-step-look-ahead**: choose the next dose that minimize the expected loss *three* steps ahead, assuming there are *three* steps remaining (moving window)
- Also
  - Batch sequential, two subjects at a time (assume two subjects remain, allocate both optimally using best two-step sequential procedure)
- Designs are simulated based on different strategies and different prior distributions

## Settings for Simulation

- Prior distribution:

Denote  $\mu = HCD_{50}$ ,  $\delta = HCD_{90} - HCD_{50}$

$$\frac{\mu - 1.5}{3.5} \sim \text{Beta}(5, 5), \quad \frac{\delta - 0.1}{5} \sim \text{Beta}(1, 6)$$

$(\mu, \delta \text{ independent})$

- Posterior loss:  $\text{Var}(HCD_{50}|Data) + \text{Var}(HCD_{90}|Data)$
- Optimal dose is selected by the dose with minimum expected posterior loss
- Number of subject ranges from 2 to 15

# Constraints

Some constraints are considered to make dose escalation cautious

- Increase maximum dose slowly by constraining to 0.5 higher than the previous maximum
- The range of the candidate doses for the  $(i + 1)^{th}$  subject is:

$$\left[ 1.5, 2.0, \dots, \max_{j \leq i} \{x_j\} + 0.5 \right]$$

## Comparison

Comparison among prior distributions, recall  $\mu = HCD_{50}$  and  $\delta = HCD_{90} - HCD_{50}$  ( $1.5 \leq \mu \leq 5$ ,  $0.1 \leq \delta \leq 5.1$ )

- “Original” prior distribution:

$$\frac{\mu - 1.5}{3.5} \sim \text{Beta}(5, 5), \quad \frac{\delta - 0.1}{5} \sim \text{Beta}(1, 6)$$

- More precise prior distribution:

$$\frac{\mu - 1.5}{3.5} \sim \text{Beta}(22, 22), \quad \frac{\delta - 0.1}{5} \sim \text{Beta}(4, 26)$$

- Less precise prior distribution:

$$\frac{\mu - 1.5}{3.5} \sim \text{Beta}(7/8, 7/8), \quad \frac{\delta - 0.1}{5} \sim \text{Beta}(0.15, 0.85)$$

# Prior Distribution

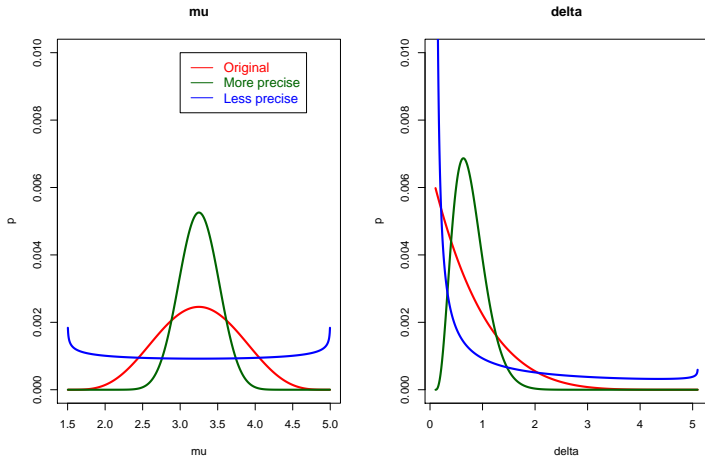


Figure: Prior distribution for  $\mu$  and  $\delta$

# Results

Overall expected loss is the measure of comparison

- Posterior loss:  $\text{Var}(HCD_{50}|Data) + \text{Var}(HCD_{90}|Data)$
- Expected posterior loss:  $E[\text{Var}(HCD_{50}|Data) + \text{Var}(HCD_{90}|Data)]$

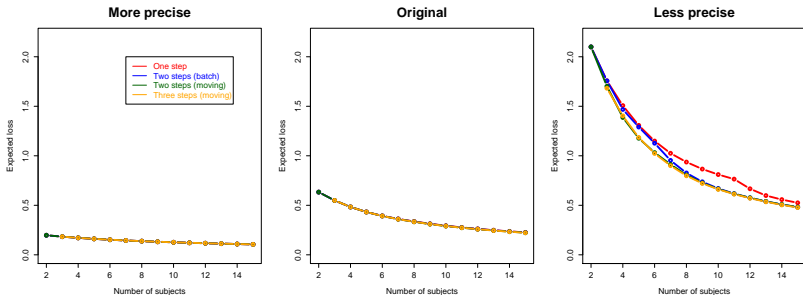


Figure: Overall expected loss for four strategies

## Results

- For comparison within each set of prior distribution, ratio of overall expected loss is computed and one-step-look-ahead serves as benchmark.
  - If ratio  $> 1$ , the strategy performs **worse** than one-step-look-ahead procedure
  - If ratio  $< 1$ , the strategy performs **better** than one-step-look-ahead procedure

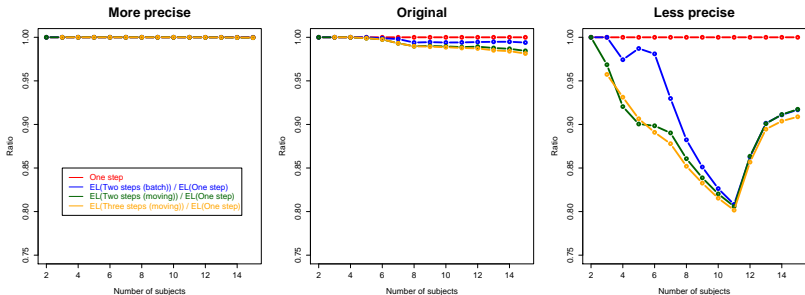


Figure: Ratio of overall expected loss for four strategies

## Conclusion and Future Work

- Comparison between different strategies:

- Overall expected loss:

One-step > Two-step batch > Two-step > Three-step

(usually, but not always)

- As number of subjects increases, the overall expected losses will be similar across strategies
- Comparison between three sets of prior distributions:
  - The more precise the prior distributions, the lower the expected loss, and the strategies give very similar results
- The initial H-Flu study has been completed
- Additional trials are being designed using posterior from initial study as prior for next study
- Two- or three-step-look-ahead procedure is considered in the design of future studies

## References

1. Silvapulle MJ. On the existence of maximum likelihood estimators for the binomial response models. *J. R. Statist. Soc B*, 43: 310-313, 1981.
2. Wu CFJ. Efficient sequential designs with binary data. *JASA*, 80: 974-987, Dec., 1985.
3. DeGroot M. *Optimal statistical decisions*. Wiley, New York, 2004.
4. Agin MA. *Optimal Bayesian design for nonlinear models*. University of Minnesota, School of Statistics, PhD thesis.

# Appendix: Settings for simulation

## Examining the Properties of the Design

- Nineteen combinations of true ( $HCD_{50}$ ,  $HCD_{90}$ )

True HCD50	True HCD90				
	3.0	3.5	4.0	4.5	5.0
1.5	1	2	3	4	5
2.0	6	7	8	9	10
2.5	11	12	13	14	15
3.0		17	18	19	20

## Appendix: H-Flu design

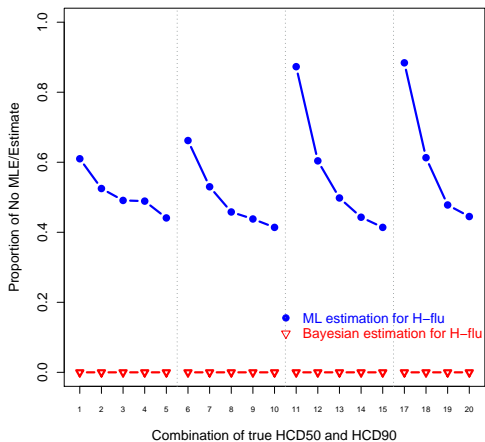


Figure: Proportion of No MLE/Estimate

## Appendix: H-Flu design

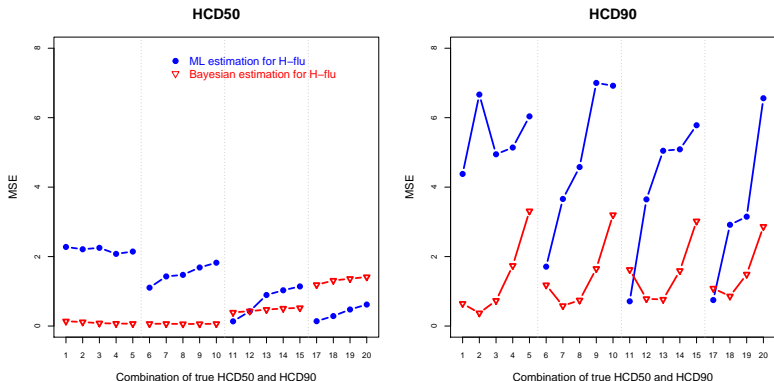


Figure: MSE for  $HCD_{50}$  and  $HCD_{90}$  (MSE for MLE conditional on having MLE well defined)