Effective Application of Modeling, Simulation and Knowledge Sharing in Drug Development

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JOHNS HOPKINS MEDICINE | THE SIDNEY KIMMEL COMPREHENSIVE CANCER CENTER

The Talks

- Michael Heathman: Integration of Pharmacometrics and Statistics to Support Study Design Optimization
- Neal Thomas: Meta-Data and Software for Bayesian Emax Dose Response Models
- Chyi-Hung Hsu: Adaptive Borrowing of Adult Data for Pediatric Trials
- John Gibbs: Trial Simulations to Support Proof of Concept Study Design: Application to Immunology

Some General Questions Considered

- How incorporate prior information?
- How much does incorporating prior information help?
- How much to borrow?
- How determine degree of borrowing?
- Does it matter which method we use to borrow info?
- Is there software we can use?

What Do We Want from Studies?

- Evidence one trt is superior to the other?
  - Estimation with precision?
- Decision rule regarding hypothesis?
  - “Yes” reject? “No” do not reject?
- Decision rule regarding next step?
  - Continue to next phase of study?
  - Approve the treatment for indication?

Sheiner: Two Major Learn-Confirm Cycles in Clinical Drug Development

- 1st cycle: *Clin Pharmacol Ther* 61:275-91, 1997
  - Phase 1: Learn what dose is tolerated
  - Phase 2: Confirm dose has promise of efficacy
    - Make decision based on this learn-confirm cycle
- 2nd cycle:
  - Phase 2B: Learn how to use the drug in patients
  - Phase 3: Confirm in large representative pt pop'n that therapy achieves acceptable benefit:risk ratio
    - If acceptable, approval is granted

Sheiner (cont'd)

- Learning & confirming are distinct
  - Different goals, designs, methods of analysis
    - Analysis choice: Hypothesis testing or estimation?
      - Learning involves estimation
        - "The [B]ayesian view is well suited to this task because it provides a theoretical basis for learning from experience; that is, for updating prior beliefs in the light of new evidence."

          Clin Pharmacol Ther 61:275-91, 1997
      - Confirming involves hypothesis testing

Decision Theory & Clinical Trials

- Why decision theory?
  - Clinical trials: Purpose is to lead to decisions
    - What dose(s) to use?
    - How best to apply the therapy?
    - What is the next step for evaluating therapy?
    - Should patients receive this therapy from now on?
    - Which patients receive the most benefit?

Why not make decisions explicit and coherent?

  - Put results in context via formal decision analysis

Decision Theory & Clinical Trials

- Clinical trial design involves decisions, too
  - Sample size
  - PK and/or PD sampling times
  - Duration of follow-up
  - Stopping rules
  - Whether to run the study in the 1st place

Why not make these decisions explicit and coherent?

SUNDAY REVIEW The New York Times

How to Make a Big Decision

Have no fear. An emerging science can now help you choose.

By Steven Johnson
Mr. Johnson writes about science and the history of innovation.

Sept. 1, 2018

- "Value model"
  - Weight each "value" (utility for each outcome)
  - Develop scenarios (simulate the trial)
  - "Multiply each grade by the weight of each value and add up the numbers for each scenario. The scenario with the highest score wins."

Bayesian Optimal Design

- "Bayes" action maximizes expected utility
  - Expectation to account for sources of uncertainty
    - Uncertainty in parameters $p(\theta)$
    - Variation in data resulting from action $p_a(y \mid \theta)$

$$\mathcal{U}(a) = \int_{\mathbf{Y}} \int_{\mathbf{\Theta}} u(y) p_a(y \mid \theta) p(\theta) d\theta dy$$

- Choose: $a^* = \arg\max \mathcal{U}(a)$

Application

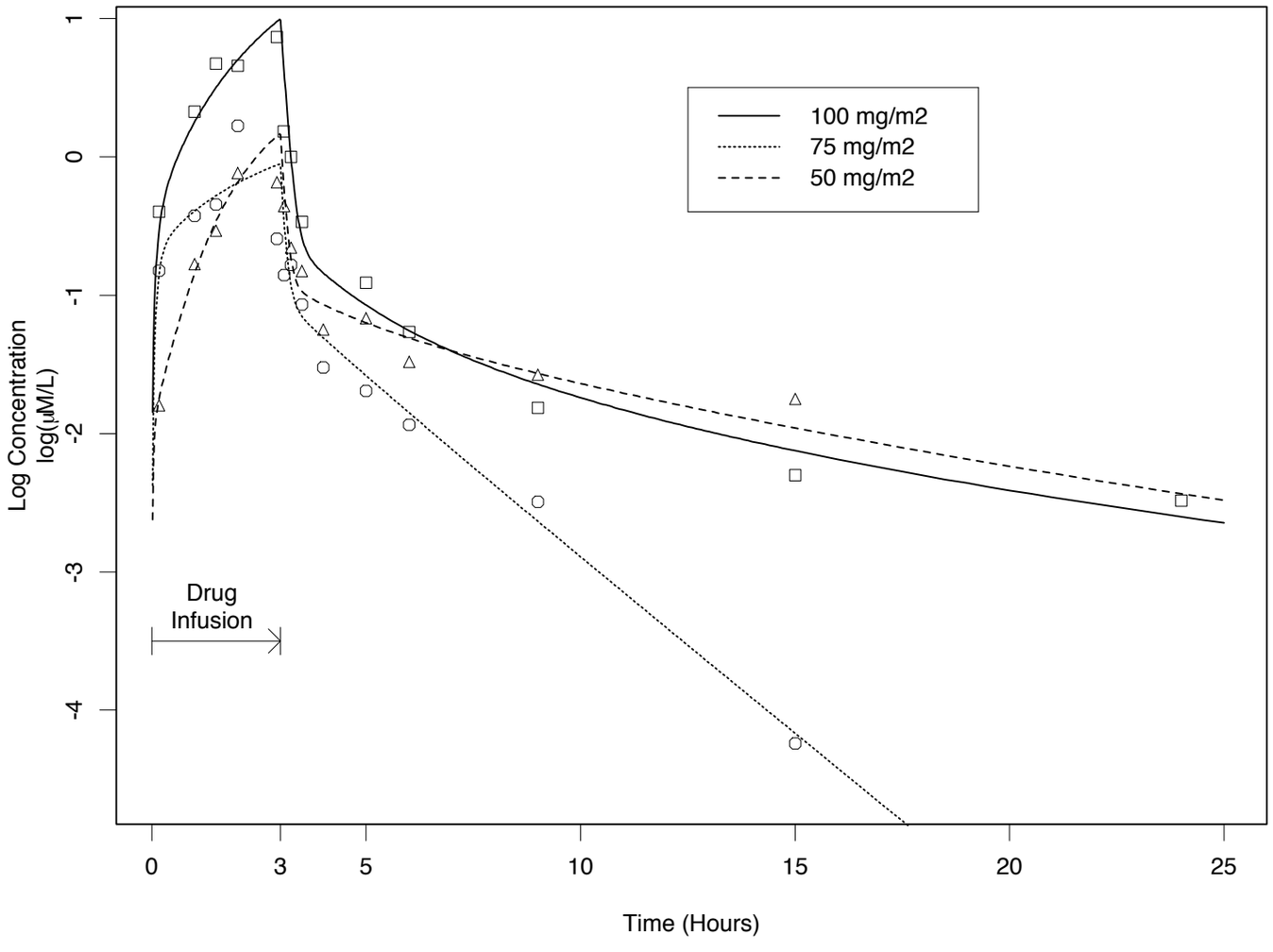
- Cancer & Leukemia Group B wanted to study Taxol
  - Large population of women
  - 3-hour infusion
  - Many participating hospitals
  - Outpatient

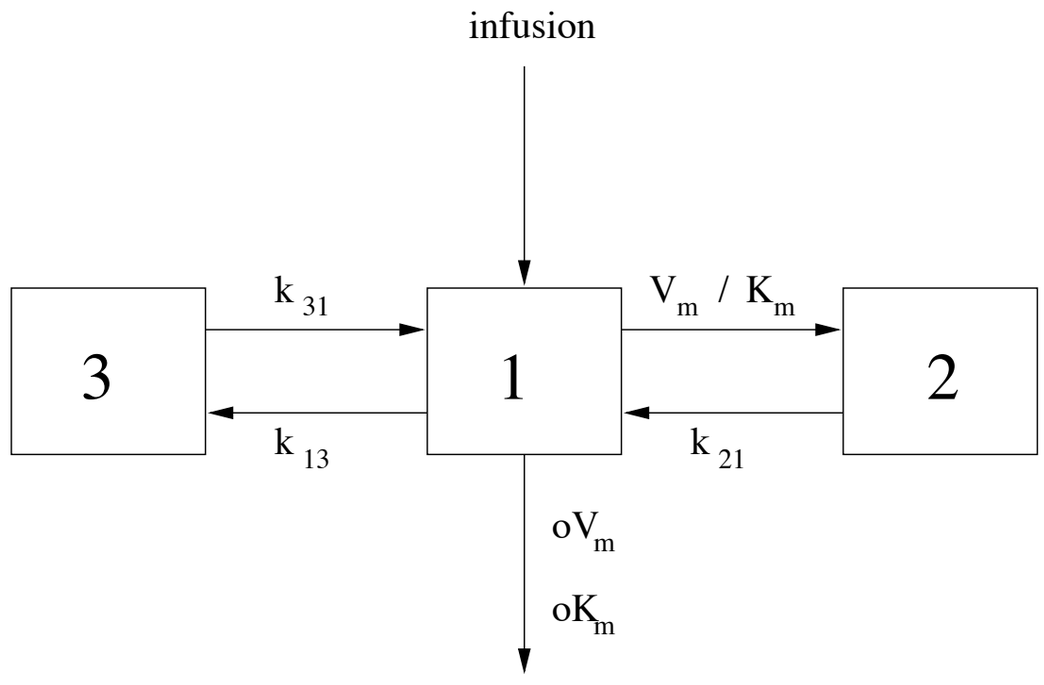
Problem

- Cannot carry out extensive sampling
  - Large study
  - Many institutions
- Devise limited-sampling scheme
  - Optimal sampling times

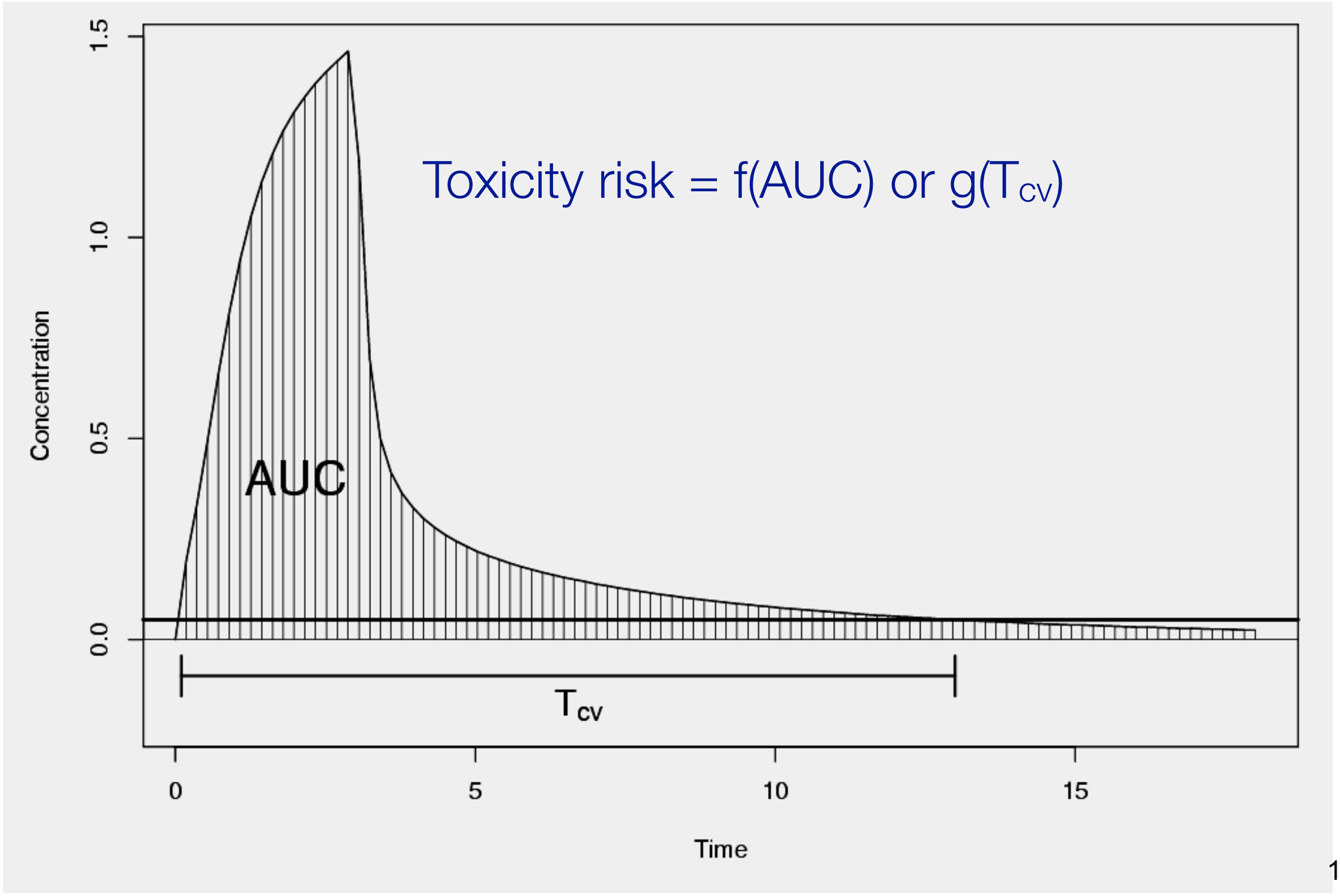
Stroud JR, Müller P, Rosner GL. Optimal sampling times in population pharmacokinetic studies. Applied Statistics. 2001;50(3):345-59.

Paclitaxel PK Sampling Times





Objective: Maximize Precision

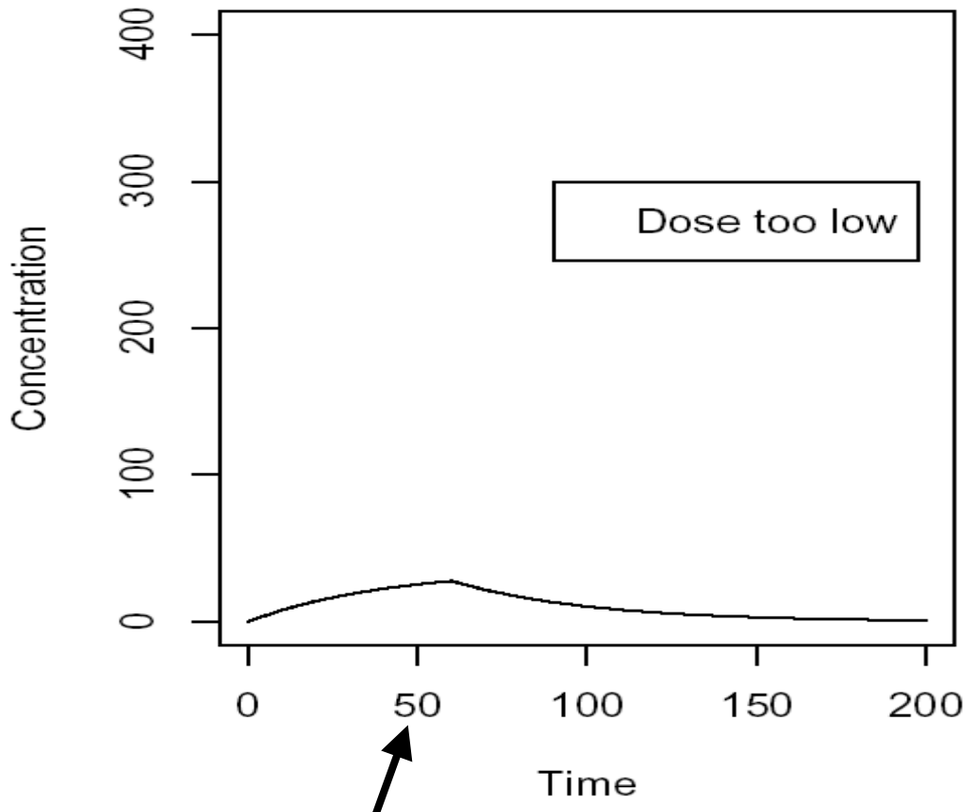


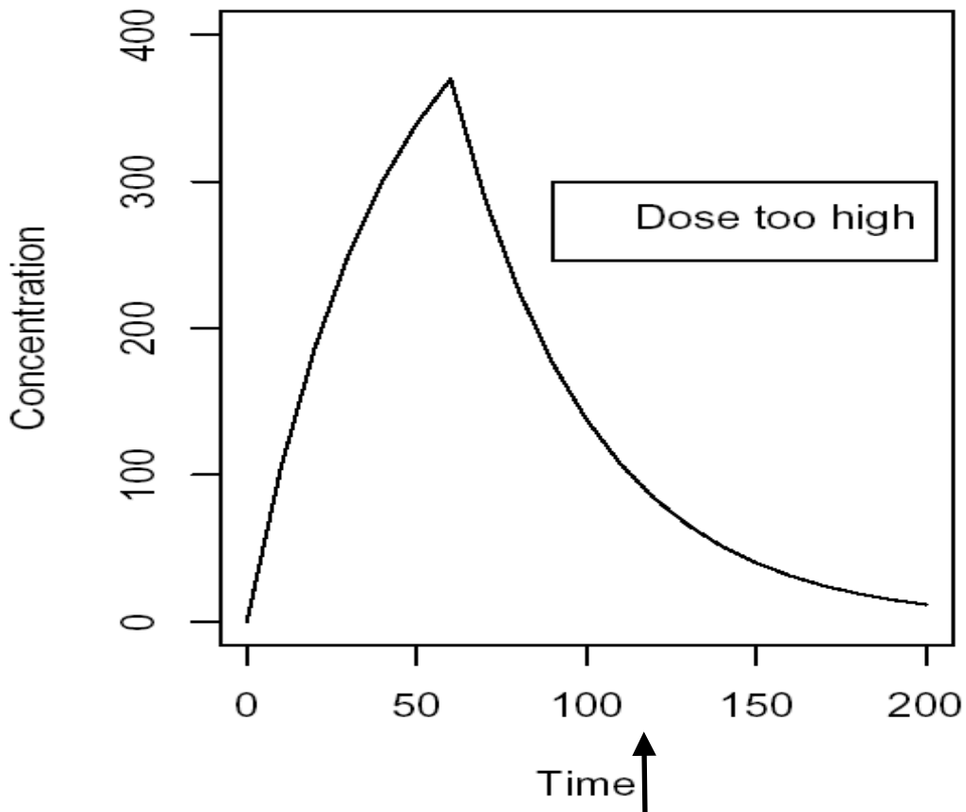
Optimal Sampling Times for AUC

$$u(t,y) = \left[\int \{\phi(\theta) - E\left[\phi(\theta) \mid y, Y, t\right]\}^2 p(\theta \mid y, Y, t) d\theta\right]^{-1} - k\sum_{i=1}^{p} t_i^2 I_{\{t_i > 8\}}$$

Cost Coeff	n=1		n=2	
k	t^*	U^*	t^*	U^*
0.00000	(3)	0.53	(3,25)	0.90
0.00004	(3)	0.53	(3,10)	0.74
0.00008	(3)	0.53	(3,7)	0.70

Dose Optimization





AUC too low!

TARGET

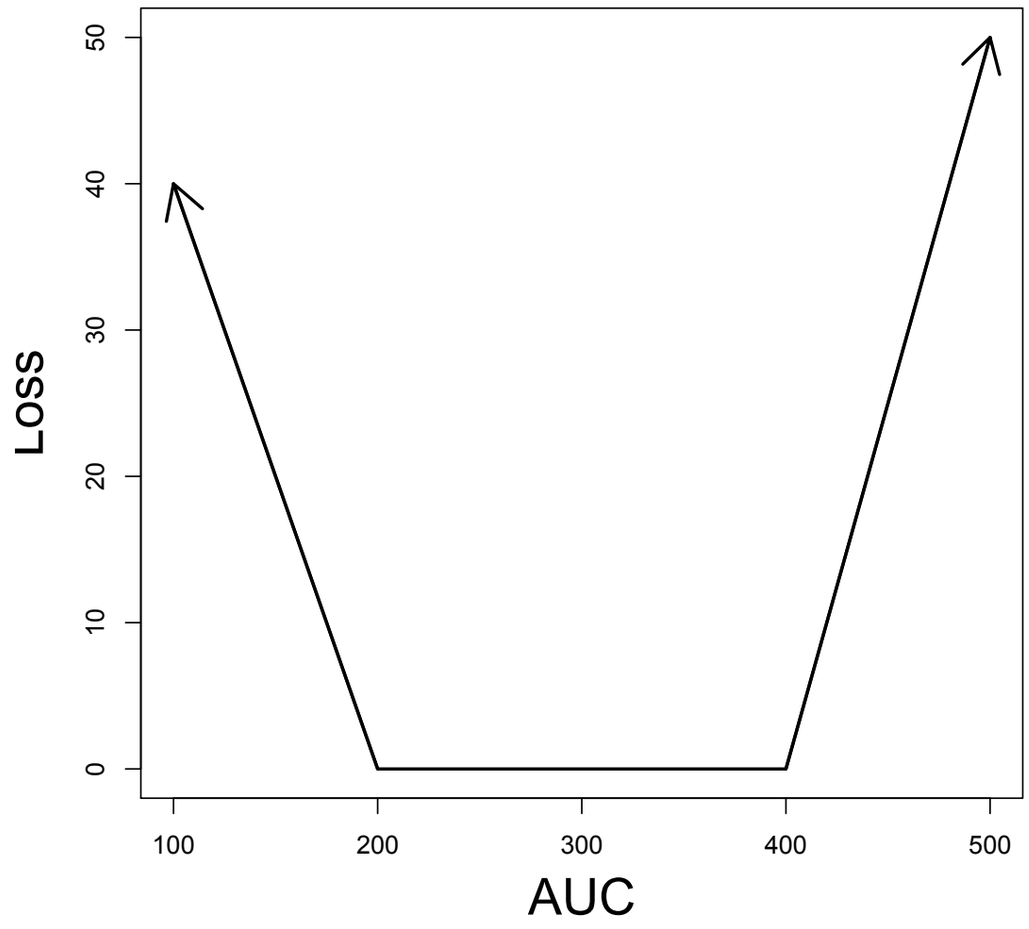
AUC too high!

Asymmetric Loss Function

- Want AUC in "optimal" range

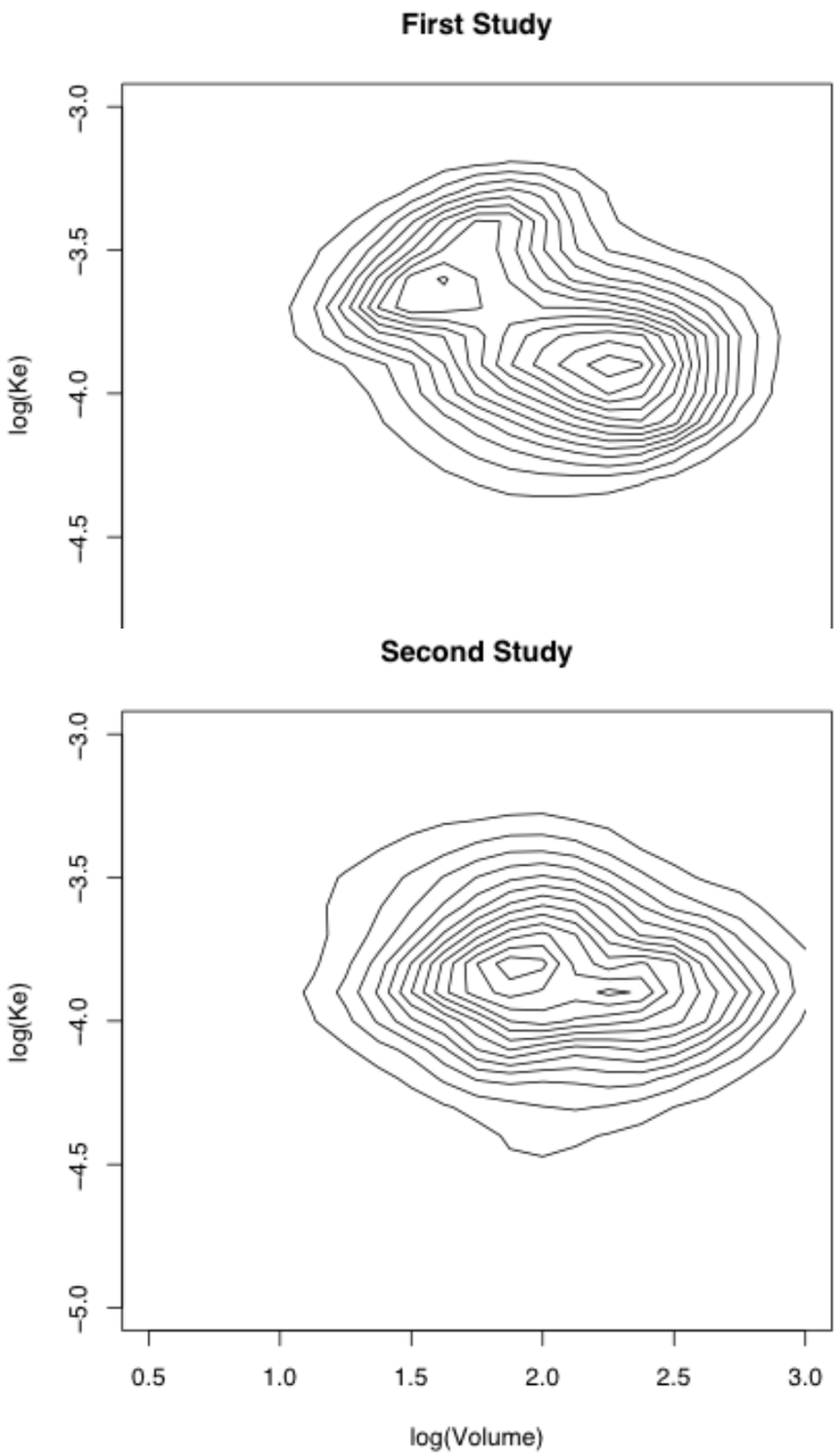
$$AUC_{ll} \leq AUC \leq AUC_{ul}$$

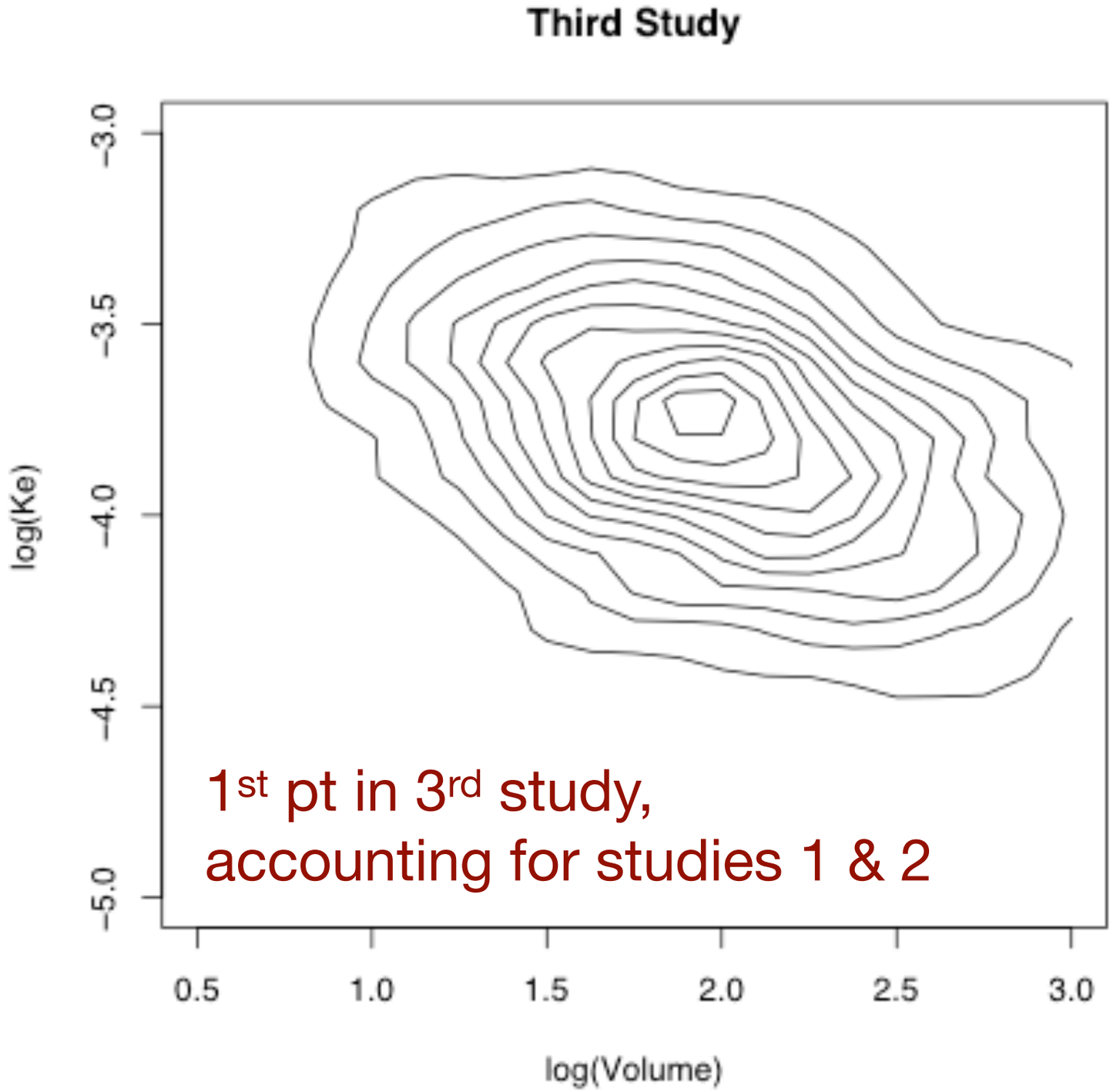
- Loss function



$$L(auc) = \begin{cases} L^{-}(auc, \mathrm{AUC}_{ll}) & \text{if } auc < \mathrm{AUC}_{ll} \\ 0 & \text{if } \mathrm{AUC}_{ll} \leq auc \leq \mathrm{AUC}_{ul} \\ L^{+}(auc, \mathrm{AUC}_{ul}) & \text{if } auc > \mathrm{AUC}_{ul} \end{cases}$$

Posterior for Pt's PK Parameters

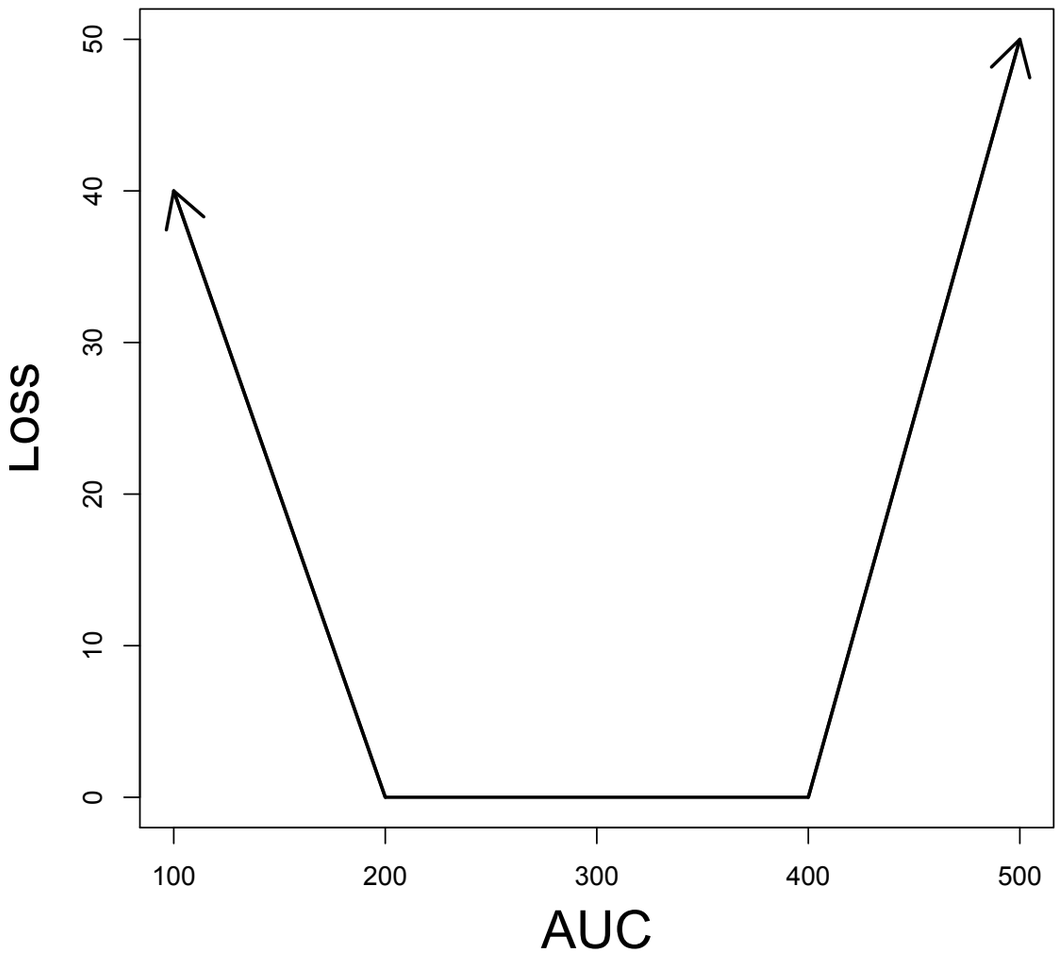




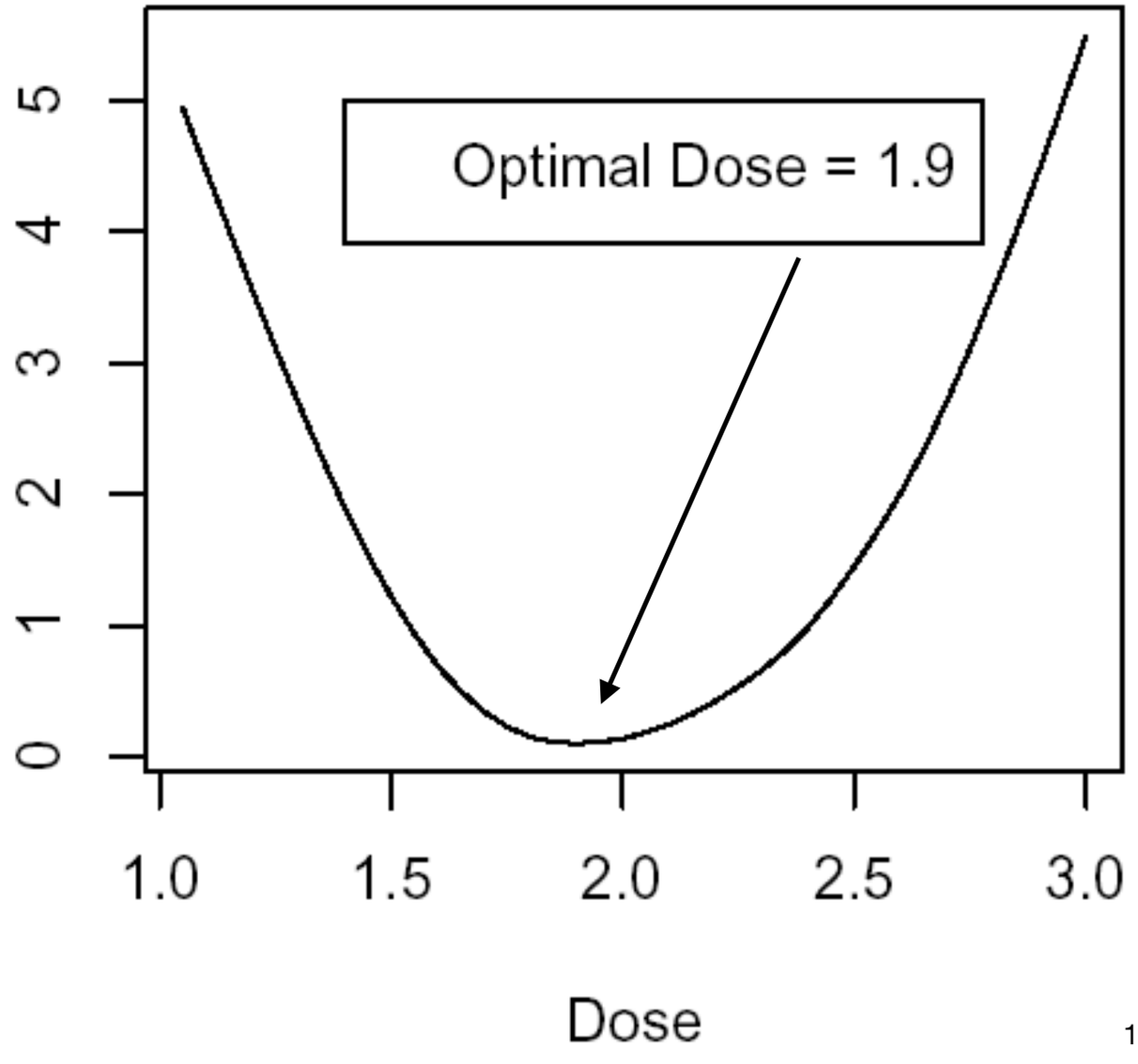
Optimal Dose w.r.t. Posterior

$$E[u(y,d,\theta)] = \int \mathrm{L}\left[AUC(y)\right] p(y \mid d,\theta) p(\theta \mid \mathrm{Data}) dy d\theta$$

Loss Function



Expected Loss



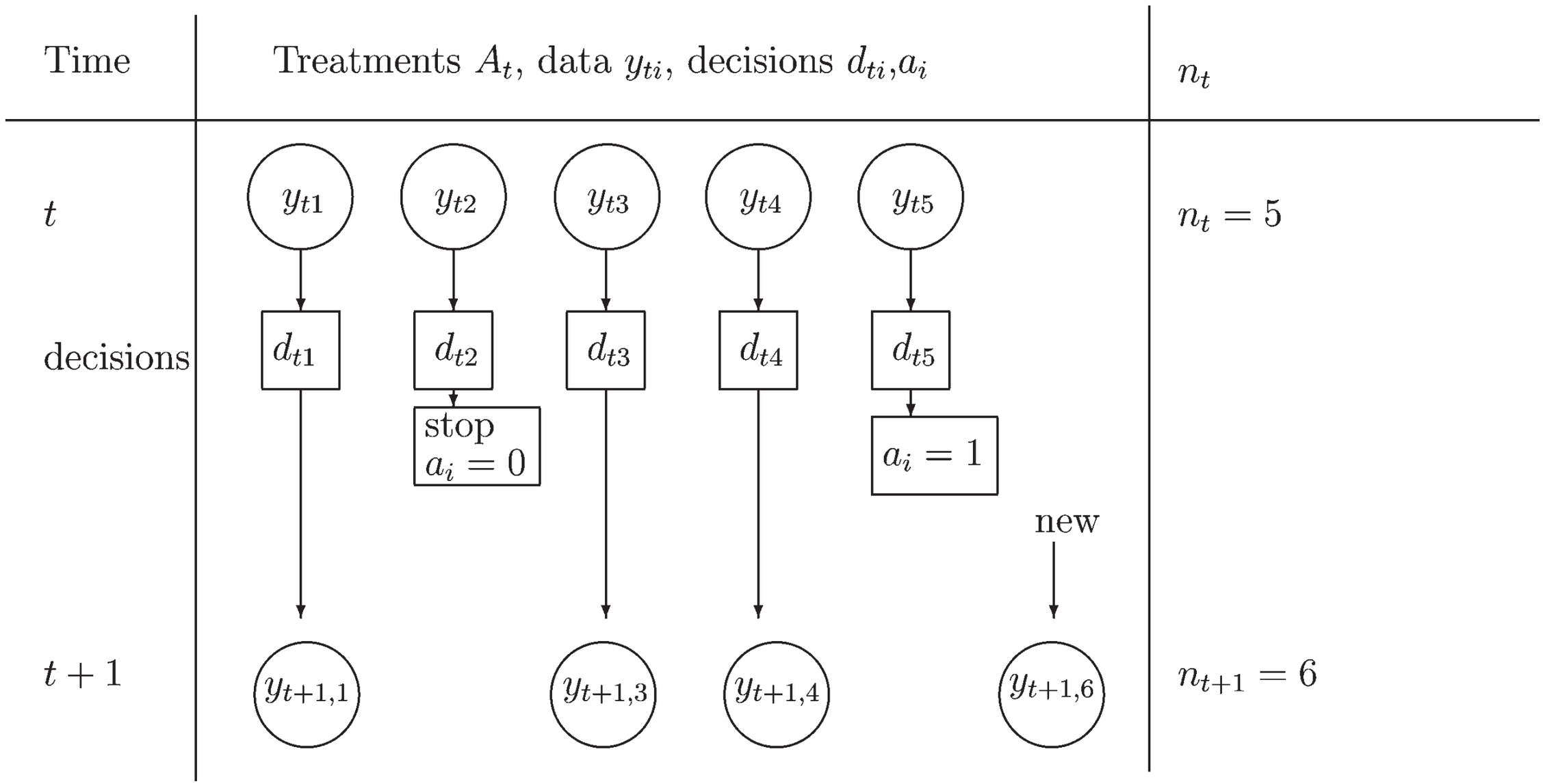
Can Incorporate Frequentist Criteria in Utility Function

- Bayesian design optimizes expected utility
  - Utility function can include different considerations
    - Sample size or cost
    - Precision
    - Number of patients who benefit
    - Prediction of future study outcomes
  - E.g., Anscombe (’63), Berry & Ho (’88), Lewis & Berry (’94), Carlin, Kadane, & Gelfand (’98), Stallard, Thall, & Whitehead (’99), Lewis, Lipsky, & Berry (’07), Trippa, Rosner, & Müller (’12), Ventz & Trippa (’15)

Platform or Master Protocols

Rossell, Müller, Rosner (2007) *Biostatistics*
Ding, Rosner, Müller (2008) *Biometrics*

- At any one time, multiple phase II studies



Utility Function

- Utility at decision-time t (for current trt)

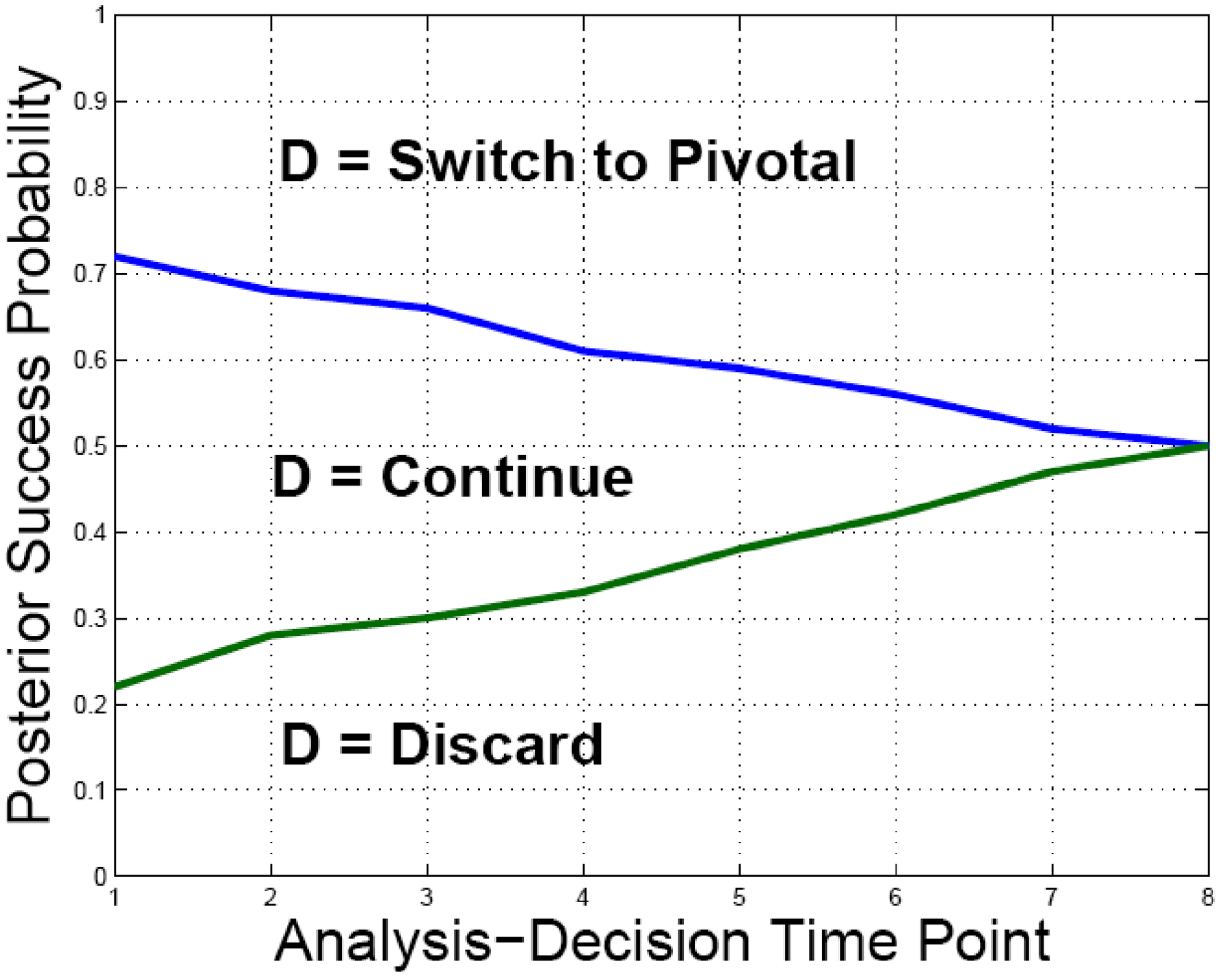
$$u_t(d_t, \theta, Y_t, Y_{III}) = \begin{cases} -c_1 \times n_1 \times t & \textbf{if stop \& discard} \\ -\{c_1 \times n_1 \times t + c_2 \times n_2\} + & \text{Phase 3 sample size \& cost} \\ b \times \{\theta_{new} - \theta_{old}\} I_{[z > z_{1-\alpha}]} & \end{cases}$$

Gain if "significant" phase 3; gain proportional to effect

Predict phase 3 outcome

Stopping Boundaries

$\theta_{old} \sim \text{Beta}(20, 80)$



5 per cohort

$c_1 = 0.14$

$c_2 = 0.7$

$b = 290$

$n_2 = 96$

$\theta_0 = 0.2$

$\theta_A = 0.5$

2000 sims

Opportunities

- Work with colleagues in other fields

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Statistics and Pharmacometrics Interest Group (SxP)

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Conclusions

- Drug development involves learning & confirming
- Bayesian inference has place in drug development
  - Bayesian paradigm corresponds to learning
  - Easier to combine or incorporate external information
    - External information feeds priors
  - Interest in complex designs & decision making
    - Outcome adaptive randomization

Conclusions (cont'd)

- Studies need to meet needs of multiple stakeholders
- Clinical research involves decisions
  - Incorporate statistical decision theory in design
    - Utility function can include many considerations
      - Predicted success of future study
      - Precision of estimation
      - Cost of study
      - Cost to patients

Thank you to our speakers and

Thank you!