Experiment Design Based on Bayes Risk and Weighted Bayes Risk with Application to Pharmacokinetic Systems

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Introduction

- **Multiple Model Optimal (MMOpt) Design**
  - Captures essential elements of Bayesian Experiment Design without the excessive computation
  - Minimizes a recent theoretical overbound on the Bayes Risk (Blackmore et. al. 2008 [4])
  - Intended for multiple model (MM) parametrizations which form the basis of the USC BestDose software (corresponds to the support points in a nonparametric population model)
  - Has several advantages relative to D-optimality and other criteria based on the asymptotic Fisher Information matrix for <u>nonlinear problems</u>
- **Contribution of present paper, since the last PODE, is to generalize MMOpt by introducing a weighting into the Bayes Risk Cost**
  - New result shows that simple analytical overbound of [4] is preserved in the weighted case
  - Weights allow MMOpt experiment design to address many problems of practical interest (AUC estimation, what best future dose to give, etc.)
- **Numerical examples demonstrate MMOpt on several relevant PK problems**

- **Dynamic Model and Measurements**

$$\dot{x}(t) = f(x(t), d(t), \theta) \quad \text{State } x, \text{ Input } d, \text{ Parameter } \theta \in R^p$$

$$\eta_k = h(x(t_k), \theta), \quad \text{System output at time } t_k$$

$$y_k = \eta_k + \sigma_k n_k, \quad \text{Noisy measurement at time } t_k$$

$$n_k \sim N(0, 1), \quad \text{Gaussian measurement noise}$$

$$\xi = \{t_1, ..., t_n\}, \quad \text{Experiment design (optimal sampling)}$$

- **D-Optimal Design**

$$\max_\xi |M|$$

where the Fisher Information Matrix M is given by,

$$M(\theta, \xi) = \sum_{k=1}^n \frac{1}{\sigma_k^2} \left[\frac{\partial \eta_k}{\partial \theta} \frac{\partial \eta_k}{\partial \theta^T} \right] \Bigg|_{\theta = \bar{\theta}}$$

- Herein, $M(\theta, \xi)$ is assumed to be a function of θ

  (i.e., nonlinear problems)

D-Optimal Design for Nonlinear Problems

- **D-optimality** (traditional) maximizes the determinant of the Fisher Information Matrix (Fedorov 1972 [20], Silvey 1980 [19])
  - max |M|, where M is Fisher Information Matrix, and |(.)| is determinant
  - Useful tool has become standard in design of clinical experiments
- For nonlinear problems, **MMOpt** offers several advantages relative to D-optimality and other criteria based on the asymptotic Fisher Information matrix
  - Avoids **circular reasoning** associated with having to know a patient's true parameters in order to design an experiment
  - Avoids using an **asymptotic information measure** when placing only a small number of samples

- **To robustify D-optimal design**, an expectation is taken with respect to certain functions of prior information giving rise to ED, EID, and ELD (or API) optimal designs
  - Chaloner [13], Pronzato [14][15], Tod [16], D'Argenio [17]

Definition of ED, EID, API

- **Robust D-Optimal Designs**

    ED: $\arg\max_\xi \; E_\theta\left(\;|M|\;\right)$

    EID: $\arg\min_\xi \; E_\theta\left(\frac{1}{|M|}\right)$

    API: $\arg\max_\xi \; E_\theta\left(\; log|M|\;\right)$

    where,

 $\theta \in R^p$ - Parameter Vector

    $\eta = \{t_1, ..., t_n\}$ - Experiment design

    M - Fisher Information Matrix

• All above design metrics require Fisher Matrix M to be nonsingular, and hence **require at least p samples to be taken**, where p=# parameters

Multiple Model Optimal Design

- USC *BestDose* software [3] is based on a multiple model (MM) parametrization of the Bayesian prior (i.e., discrete support points in the <u>nonparametric population</u> model)

  - Nonparametric Maximum Likelihood (NPML) estimation of a population model has the form of a MM prior (Mallet [5], Lindsay [6]).
  - Software for population NPML modeling is available, e.g., NPEM (Schumitzky [7][11]), NPAG (Leary [8], Baek [9]), USC*PACK (Jelliffe [10], and **Pmetrics** in Bestdose [3].

- Experiment design for MM (i.e., discrete) models is a subject found in <u>classification theory</u>

  - How do we sample the patient to find out which support point he best corresponds to?
  - Classifying patients is fundamentally different from trying to estimate patient's parameters

- Treating MM experiment design in the context of classification theory leads to the mathematical problem of <u>minimizing Bayes risk</u> (Duda et. al. [21])
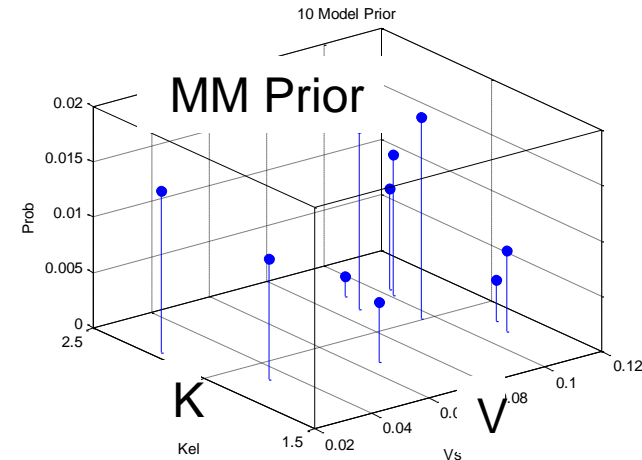
Multiple Model Optimal Design (MMOpt)

- **Bayes Rule**

  $$p(H_i|y,u) = \frac{p(y|H_i,u)p(H_i)}{p(y|u)}, \quad i = 1, ..., m$$

  H_i - Hypothesis that model i corresponds to true subject

  u - Experiment design variable (to be optimized over)

- **Design Rule for MM Classifier**

  If $p(H_j|y,u) = \max_i\{p(H_i|y,u)\}$, then

  1. H_j is classified as TRUE

     (i.e., j'th model is classified as true subject)
  2. H_i for $i \neq j$ is classified as FALSE

- **Design Regions**

  MM classifier breaks y into m regions $R_i, \ i = 1, ..., m$

  such that H_j is classifed as TRUE when $y \in R_j$.

Multiple Model Optimal Design (Cont'd)

- **Bayes Risk (i.e., Probability of MM Classifier Being Wrong)**

  $P(error) = \sum_i^m \sum_{j \neq i}^m P(y \in R_j, H_i | u)$

  (Sum of probabilities over all possible ways of making a mistake)

- **Bayes Risk represents a cost function to be minimized**

  - Consistent with a Bayesian experiment design philosophy

- **Result: (Blackmore et. al. 2008)**

  The Bayes Risk is upper bounded as follows:

  $$P(error) \leq \sum_i^m \sum_{j>i}^m P(H_i)^{\frac{1}{2}} P(H_j)^{\frac{1}{2}} e^{-k(i,j)} \tag{1}$$

  where,

  $$k(i,j) = \frac{1}{4}(\mu(j) - \mu(i))^T \left(\Sigma(i) + \Sigma(j) \right)^{-1} (\mu(j) - \mu(i)) + \frac{1}{2} \ln \frac{|\frac{1}{2}(\Sigma(i) + \Sigma(j))|}{\sqrt{|\Sigma(i)||\Sigma(j)|}}$$

- **MMOpt minimizes upper bound (1) on the probability that the true subject will be incorrectly classified**
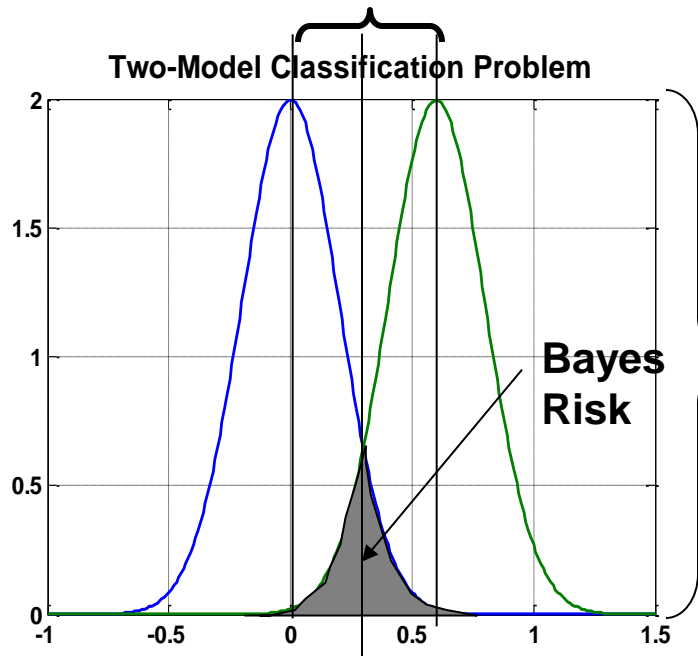
Model Response Separation r(t)

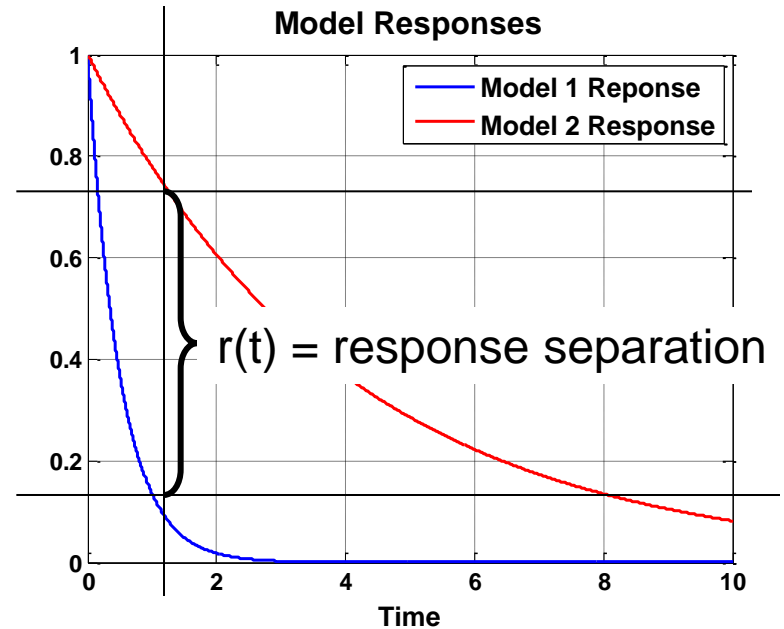• **Model Response Separation r(t) is the separation between two model responses at a given time t**

$$r(t) = |\eta(t, a_1) - \eta(t, a_2)|$$

•**Defines natural statistic for discriminating between two models**

• **Bayes Risk is shown in gray area**

r(t)=response separation

Two-Model Classification Problem

Bayes Risk

Pull Gaussians apart to minimize gray area

Model Responses

r(t) = response separation

• Bayes Risk (gray area) decreases as response separation r(t) increases

• Models are best discriminated by sampling at a time t that maximizes r(t)

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MMOpt Example: 4-Models (1/2)

- Two-Parameters a, b
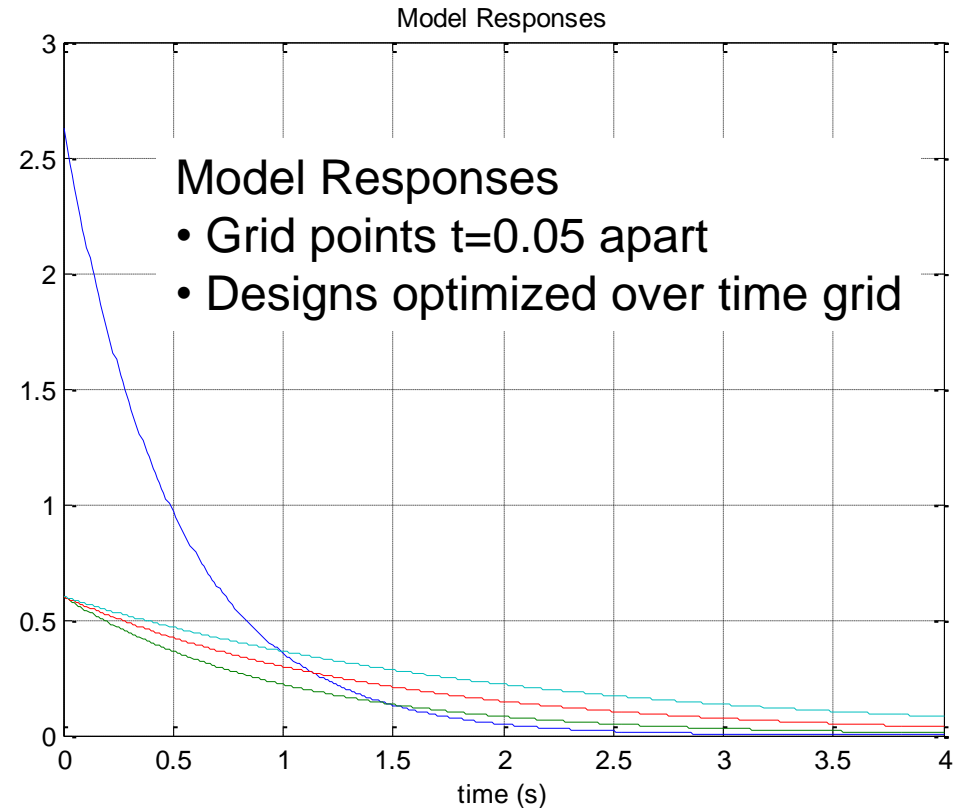
$$y_i = \eta(t_i, a, b) + \sigma n_i$$

$$\eta(t, a, b) = be^{-at}$$

$$n_i \sim N(0, \sigma^2)$$

$$\sigma = 0.1$$

- Prior: $p_i = .25, \quad i = 1, ..., 4$

Model Parameters		
#	**a**	**b**
1	2	2.625
2	1	0.6
3	0.7	0.6
4	0.5	0.6

Model Responses

Model Responses
- Grid points t=0.05 apart
- Designs optimized over time grid

MMOpt Example: 4-Models (2/2)

Design Metric	2-Sample Times		Bayes Risk	Bayes Risk 99%Conf *
MMOpt	0.45	1.4	0.32839	+/- 0.00070
ED	0	0.8	0.37028	+/- 0.00070
EID	0	1	0.36044	+/- 0.00072
API	0	0.95	0.36234	+/- 0.00072

Design Metric	3-Sample Times			Bayes Risk	Bayes Risk 99% Conf *
MMOpt	0.45	1.4	1.4	0.28065	+/- 0.00067
ED	0	0.7	0.9	0.32048	+/- 0.00067
EID	0	0	1	0.36034	+/- 0.00072
API	0	0.85	0.105	0.3099	+/- 0.00069

- MMOpt has smallest Bayes Risk of all designs studied

* evaluated based on Monte Carlo analysis using 1,400,000 runs per estimate

Comparison Table

	ED	EID	API	MMOpt
Invariant under regular <u>linear</u> reparametrization*	Yes	Yes	Yes	Yes
Invariant under regular <u>nonlinear</u> reparametrization*	No	No	Yes	Yes
Allows taking fewer than p samples, p= # of parameters	No	No	No	Yes
Can handle heterogeneous model structures	No	No	No	Yes
Gives known optimal solution to 2-model example*	No	No	No	Yes
Captures main elements of minimizing Bayes risk	No	No	No	Yes

*Proved in Bayard et. al., PODE 2013 [23]

Weighted MMOpt

- Introduce weights $\{c_{ij}\}$ to specify a cost for each type of classification error

- Assign c_{ij} as the cost of mistaking truth subject i for subject j $(j \neq i)$

- Choice of weights tailors experiment design to desired applications of interest
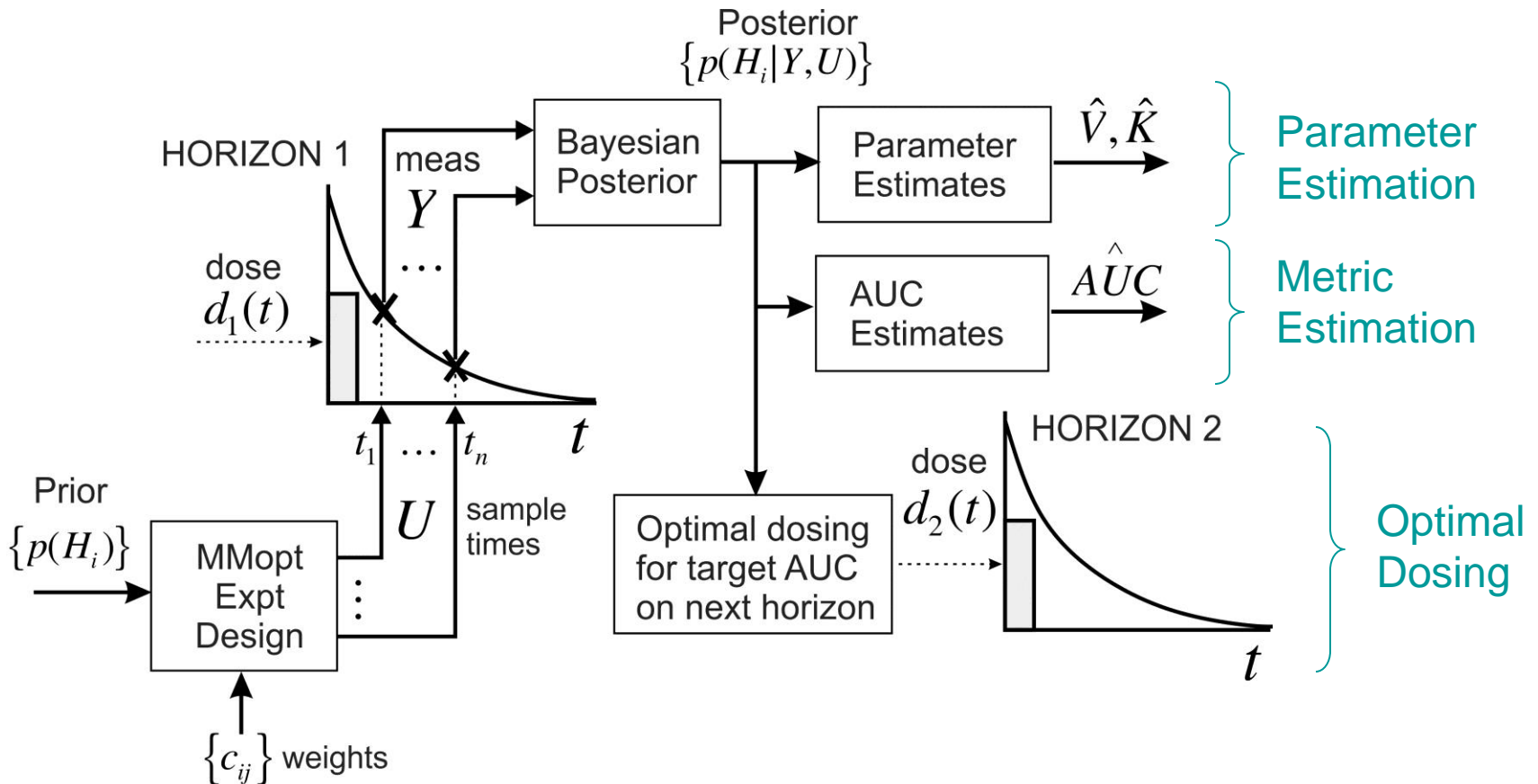
Weighted MMOpt

- **Weighted Bayes Risk (i.e., Expected Cost of MM Classifier Being Wrong)**

  $C(error) = \sum_i^m \sum_{j \neq i}^m c_{ij} P(y \in R_j, H_i | u)$

  (Sum of costs over all possible ways of making a mistake)

  Here, c_{ij} is the cost of mistaking subject i for subject j $(j \neq i)$

- **Useful Result (new)**

  The Weighted Bayes Risk is upper bounded as follows:

  $$C(error) \leq \sum_i^m \sum_{j \neq i}^m \overline{c}_{ij} P(H_i)^{\frac{1}{2}} P(H_j)^{\frac{1}{2}} e^{-k(i,j)} \tag{2}$$

  where,

  $$k(i,j) = \tfrac{1}{4}(\mu(j) - \mu(i))^T \left(\Sigma(i) + \Sigma(j) \right)^{-1} (\mu(j) - \mu(i)) + \tfrac{1}{2} \ln \frac{|\frac{1}{2}(\Sigma(i)+\Sigma(j))|}{\sqrt{|\Sigma(i)||\Sigma(j)|}}$$

  $$\overline{c}_{ij} = \max(c_{ij}, c_{ji})$$

- Result allows weighted bound-optimal designs to be systematically calculated as in the unweighted MMopt case

- *Weighted* **MMOpt minimizes upper bound (2) on the expected cost associated with the true subject being incorrectly classified**

Applications of MMOpt

- **Three Numerical Examples**
  - PK Estimation (unweighted MMOpt)
  - AUC Estimation (weighted MMOpt)
  - AUC Control (weighted MMOpt)
- **Results will be compared to ED optimal design EDopt**
  - Also compared to Bayes optimal design Bopt when computationally feasible to do so

PK Population Model with 10 Multiple Model Points - First-Order PK Model
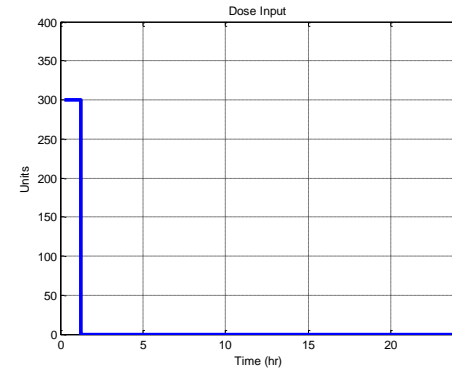
- **First-Order Model**

$$\dot{x} = -Kx + d$$

$$\eta_i = \frac{x(t_i)}{V}$$
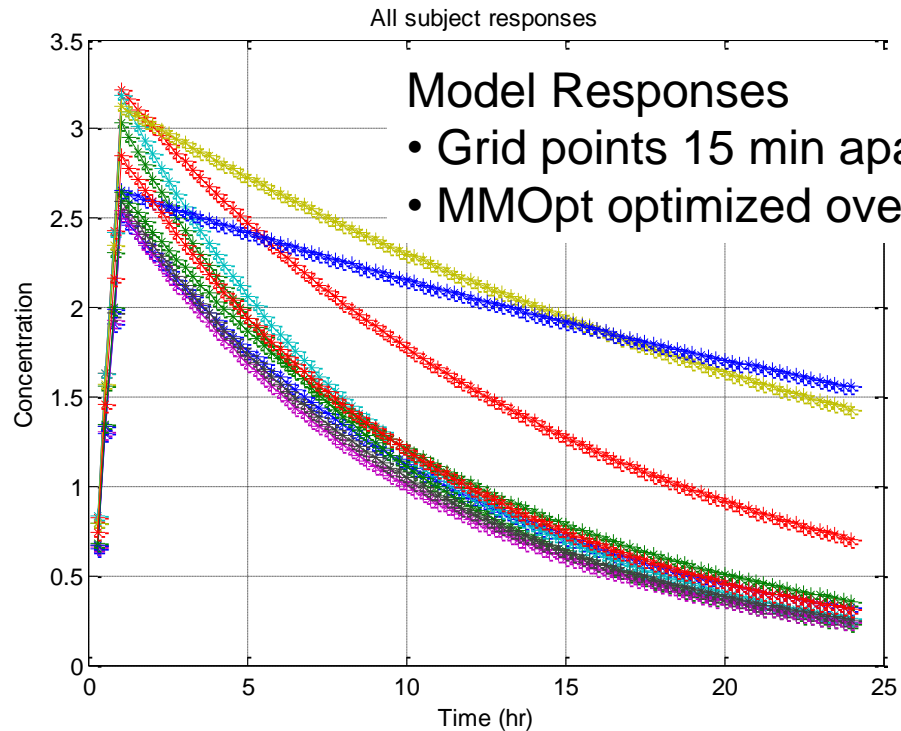
$$y_i = \eta_i + \sigma_i n_i$$

$$n_i \sim N(0,1)$$

$$\sigma_i = 0.1$$

Dose input = 300 units for 1 hour, starting at time 0

Dose Input

Model Parameters		
#	**K**	**V**
1	0.090088	113.7451
2	0.111611	93.4326
3	0.066074	90.2832
4	0.108604	89.2334
5	0.103047	112.1093
6	0.033965	94.3847
7	0.100859	109.8633
8	0.023174	111.7920
9	0.087041	108.6670
10	0.095996	100.3418

All subject responses

Model Responses
- Grid points 15 min apart
- MMOpt optimized over time grid

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Unweighted MMOpt for PK Estimation

- Summary of optimal 1,2 and 3 sample designs applied to PK Estimation

Design Metric	Samples (hr)			Bayes Risk (prob)	99% conf (prob)
1-Sample Design					
Bopt	4.25			0.5474	±0.0015
MMopt	4.25			0.5474	±0.0015
2-Sample Design					
MMopt	1	9.5		0.2947	±0.0014
EDopt	1	24		0.3272	±0.0014
3-Sample Design					
MMopt	1	1	10.5	0.2325	±0.0013
EDopt	1	1	24	0.2617	±0.0013

- **<u>1 Sample Design</u>: MMOpt performance equals Bayesian optimal design (both have Bayes Risk of 0.5474).**
- **MMOpt performance improves on EDopt design for 2 and 3 sample designs**
  - **<u>2 Sample Design</u>: Bayes Risk of 0.29 versus 0.33**
  - **<u>3 Sample Design</u>: Bayes Risk of 0.23 versus 0.26**
- **All results are statistically significant to $p < 0.0001$**

Weighted MMOpt for AUC Estimation

- **OBJECTIVE:** Design an experiment which is most informative about estimating patient's AUC

  - **In this case MMopt weights are chosen as**

$$c_{ij} = \left(\frac{D}{V_i K_i} - \frac{D}{V_j K_j} \right)^2$$

$$= \text{Squared AUC error incurred if } j\text{'th subject's}$$

$$\text{AUC is used to estimate } i\text{'th subject's AUC}$$

Dose input $D = 300$ (300 units of drug infused over 1 hour)
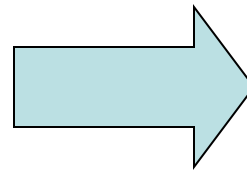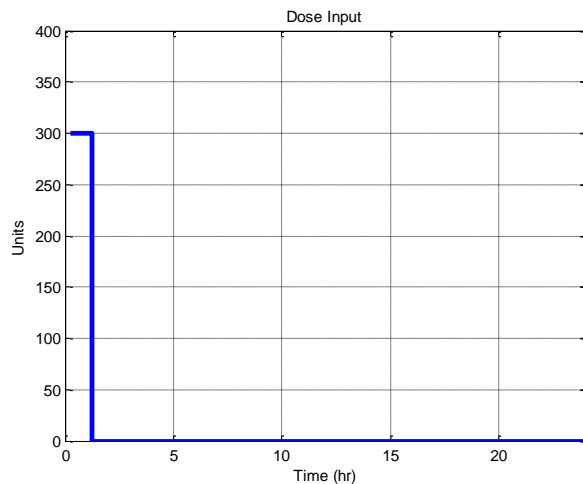
#	AUC Responses
1	29.2767
2	28.7684
3	50.2902
4	30.9562
5	25.9683
6	93.5811
7	27.0741
8	115.8003
9	31.7176
10	31.1448
Mean	46.4578
STD	30.2314

AUC responses to dose D

Weighted MMOpt for AUC Estimation (Cont'd)

- Summary of optimal 1,2 and 3 sample designs applied to AUC estimation

Design Metric	Samples (hr)			RMS Error (AUC units)	99% conf (AUC units)
1-Sample Design					
Bopt_C$_2$	24			5.9059	± 0.0270
MMopt_C$_2$	14			6.9789	± 0.0265
MMopt	4.25			21.6806	± 0.0919
2-Sample Design					
MMopt_C$_2$	1	13		1.8386	± 0.0231
MMopt	1	9.5		2.2346	± 0.0483
EDopt	1	24		2.2079	± 0.0211
3-Sample Design					
MMopt_C$_2$	1	10.25	10.25	1.4042	± 0.0175
MMopt	1	1	10.5	1.7025	± 0.0382
EDopt	1	1	24	1.8949	± 0.0188

- **<u>1 Sample Design</u>: Weighted MMOpt performance approximates that of the Weighted Bayesian optimal design (RMS error of 6.98 versus 5.9 AUC units)**
- **MMOpt performance improves on EDopt design**
  - **<u>2 Sample Design</u>: RMS error of 1.84 versus 2.21 (units of AUC)**
  - **<u>3 Sample Design</u>: RMS error of 1.40 versus 1.89 (units of AUC)**
- **All results are statistically significant to p<0.0001**

Weighted MMOpt for AUC Control

- **OBJECTIVE: Design an experiment most informative about next dose needed for patient to achieve a specified AUC of $\alpha_{des} = 40$**

  - **In this case MMopt weights are chosen as**

$$
\begin{aligned}
c_{ij} &= (\frac{D_j}{V_i K_i} - \alpha_{des})^2 \\
&= \text{Squared AUC error incurred if } j\text{'th subject's} \\
&\quad \text{ideal dose } D_j \text{ is given to } i\text{'th subject}
\end{aligned}
$$

#	Ideal Dose
1	409.8827
2	417.1242
3	238.6149
4	387.6442
5	462.1011
6	128.2311
7	443.2281
8	103.6267
9	378.3394
10	385.2965
Mean	335.4089
STD	35.8470

	$j=1$	$j=2$	$j=3$	$j=4$	$j=5$	$j=6$	$j=7$	$j=8$	$j=9$	$j=10$
$i=1$	0	0.499	279	4.70	25.9	755	10.5	893	9.47	5.75
$i=2$	0.482	0	293	7.99	18.6	767	6.26	903	13.8	9.31
$i=3$	824	895	0	624	1403	342	1176	512	548	604
$i=4$	5.26	9.25	236	0	59.0	716	32.8	858	0.921	0.0586
$i=5$	20.4	15.1	374	41.5	0	835	2.66	962	52.5	44.2
$i=6$	771	8121	1185	6548	10846	0	9654	58.9	6086	6430
$i=7$	9.05	5.54	340	25.1	2.90	808	0	939	34.2	27.3
$i=8$	13975	14643	2715	12019	19147	90.1	17184	0	11244	11821
$i=9$	11.1	16.8	218	0.967	78.4	699	47.0	843	0	0.541
$i=10$	6.51	10.9	231	0.0594	63.5	712	36.1	855	0.521	0

Ideal Doses $\{D_j\}$ to achieve
desired AUC of $\alpha_{des} = 40$

Matrix of Weights $\{c_{ij}\}$

Weighted MMOpt for AUC Control (Cont'd)

- Summary of optimal 1,2 and 3 sample designs applied to AUC control

Design Metric	Samples (hr)			RMS Error (AUC units)	99% conf (AUC units)
	1-Sample Design				
$Bopt\_C_1$	12.5			3.6194	± 0.0273
$MMopt\_C_1$	14			3.7729	± 0.0166
MMopt	4.25			16.7924	± 0.1145
	2-Sample Design				
$MMopt\_C_1$	1	13		2.1102	± 0.0125
MMopt	1	9.5		2.2575	± 0.0232
EDopt	1	24		2.6159	± 0.0174
	3-Sample Design				
$MMopt\_C_1$	1	10.25	10.25	1.6967	± 0.0078
MMopt	1	1	10.5	1.9991	± 0.0192
EDopt	1	1	24	2.4194	± 0.0174

- **<u>1 Sample Design</u>: weighted MMOpt performance approximates that of the weighted Bayesian optimal design (RMS error of 3.62 versus 3.77 AUC units)**
- **MMOpt performance improves on EDopt design for 2 and 3 sample designs**
  - **<u>2 Sample Design</u>: RMS error of 2.11 versus 2.62 (units of AUC)**
  - **<u>3 Sample Design</u>: RMS error of 1.70 versus 2.42 (units of AUC)**
- **All results are statistically significant to p<0.0001**

Summary

- **Multiple Model Optimal Design (MMOpt) provides an alternative approach to designing experiments**
  - Particularly attractive for Nonparametric Models (MM discrete prior)
  - Based on true MM formulation of the problem (i.e., classification theory)
  - Has several advantages relative to ED, EID and API (last year's PODE [23])
  - Based on recent theoretical overbound on Bayes Risk (Blackmore et. al. 2008 [4])
- **Introduced Weighted version of MMOpt which minimizes upper bound on the Weighted Bayes Risk**
  - Allows specification of costs for each type of classification error
  - Preserves overbound property so that weighted MMOpt designs are as straightforward to compute as unweighted MMOpt designs
  - Examples show that weighted MMOpt performance improves on EDopt, and compares favorably to the theoretically best performance of the weighted Bayes optimal classifier
- **MMOpt captures essential elements of Bayesian Experiment Design without the excessive computation**
  - Bayesian formulation of design problem for multiple model problems
  - Allows approximate pre-posterior analysis "without tears"
  - To be included in a future release of the USC *BestDose* software [3]

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