Bayes Risk as an Alternative to Fisher Information in Determining Experimental Designs for Nonparametric Models

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Methods of Optimal Design

- **D-optimality** (traditional) maximizes the determinant of the Fisher Information Matrix (Fedorov 1972 [20], Silvey 1980 [19])
  - Intended for parameter estimation problems [11][12]
  - Modifications for robustness: ED, EID, API, etc.

- **Multiple Model Optimal (MMOpt) Design** (new) minimizes an overbound on the Bayes risk
  - Can be evaluated without numerical integration or Monte Carlo simulation/stochastic analysis
  - Intended for multiple model (MM) parametrizations which form the basis of the USC *BestDose* software
    - The multiple model representation corresponds to the support points in the nonparametric population model
  - Based on recent theoretical overbound on Bayes Risk (Blackmore et. al. 2008 [4])

- **Dynamic Model and Measurements**

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

  $\eta_i = h(x(t_i), \theta)$, System output at time t_i

  $y_i = \eta_i + \sigma_i n_i$, Noisy measurement at time t_i

  $n_i \sim N(0, 1)$, Gaussian measurement noise

  $\xi = \{t_1, ..., t_m\}$, Experiment design (optimal sampling)

- **D-Optimal Design**

  $\max_\xi \left|M\right|$

  where the Fisher Information Matrix M is given by,

  $$M(\theta, \xi) = \sum_{i=1}^{m} \frac{1}{\sigma_i^2} \left[\frac{\partial \eta_i}{\partial \theta} \frac{\partial \eta_i}{\partial \theta^T} \right] \Bigg|_{\theta = \overline{\theta}}$$

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

  (i.e., nonlinear problems)

D-Optimal Design for Nonlinear Problems

- D-Optimal design tells you where to place samples so that they are most sensitive to small changes in model parameter values
  - max |M|, where M is Fisher Information Matrix, and |(.)| is determinant
  - Useful tool has become standard in design of clinical experiments
- Problem with D-optimal design - Circular reasoning (Silvey 1980):
  - You need to know the true patient’s parameters before D-optimal design can be used to compute the best experiment to find these same parameters

- To robustify D-optimal design, an expectation is taken with respect to prior information (c.f., Chaloner [13]), Pronzato [14][15], Tod [16], D’Argenio [17]),

  ED: max E{ |M| }

  EID: min E{ 1/|M| }

  ELD (or API): max E{ log|M| }

- MMopt comparison will be made here relative to ED, EID and API. Not exhaustive - other experiment design criteria are possible (cf., Chaloner [13], Merle and Mentre [18])

Definition of ED, EID, API

- **Robust D-Optimal Designs**

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

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

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

  where,

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

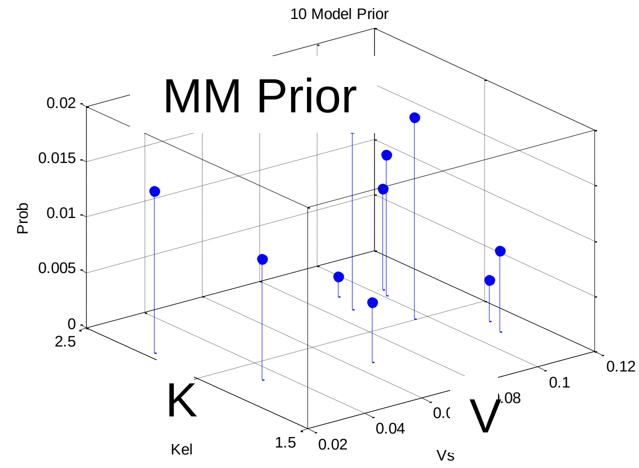
  $\eta = \{t_1, ..., t_m\}$ - Experiment design

  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 nonparametric population 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]).



- Experiment design for MM (i.e., discrete) models is a subject found in classification theory
  - 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 minimizing Bayes risk (Duda et. al. [21])

Multiple Model Optimal Design (MMOpt)

- **Bayes Rule**

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

  H_i - Hypothesis that model i corresponds to true subject

  u - Experiment design variable (to be optimized over)

- **Design Rule for MM Classifier**

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

  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 N regions $R_i,\ i = 1, ..., N$
  such that H_j is classifed as TRUE when $y \in R_j$.

Multiple Model Experiment Design (MMED) (Cont'd)

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

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

  $= \sum_i^N \sum_{j \neq i}^N P(y \in R_j | H_i) p(H_i)$

  $= \sum_i^N \sum_{j \neq i}^N \int_{R_j} P(y \in R_j | H_i) p(H_i) dy$

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

  When performing hypothesis selection between an arbitrary number of hypotheses, for Gaussian observation distributions such that $p(Y|H_i) = N(\mu(i), \Sigma(i)),\ i = 1, ..., N$, the Bayes Risk is upper bounded as follows:

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

  where,

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

- In short, the MMED experiment design maximizes the probability that the true subject will be correctly identified (classified) among competing models

Simple 2-Model Example

- **Simple 2-Model Example**

$$y_i = \eta(t_i, a) + \sigma n_i$$
$$\eta(t, a) = e^{-at}$$
$$a = a_1 = 2 \text{ (fast model)}$$
$$a = a_2 = 0.25 \text{ (slow model)}$$
$$\sigma = 0.3$$
Prior: $p_1 = .5$, $p_2 = .5$

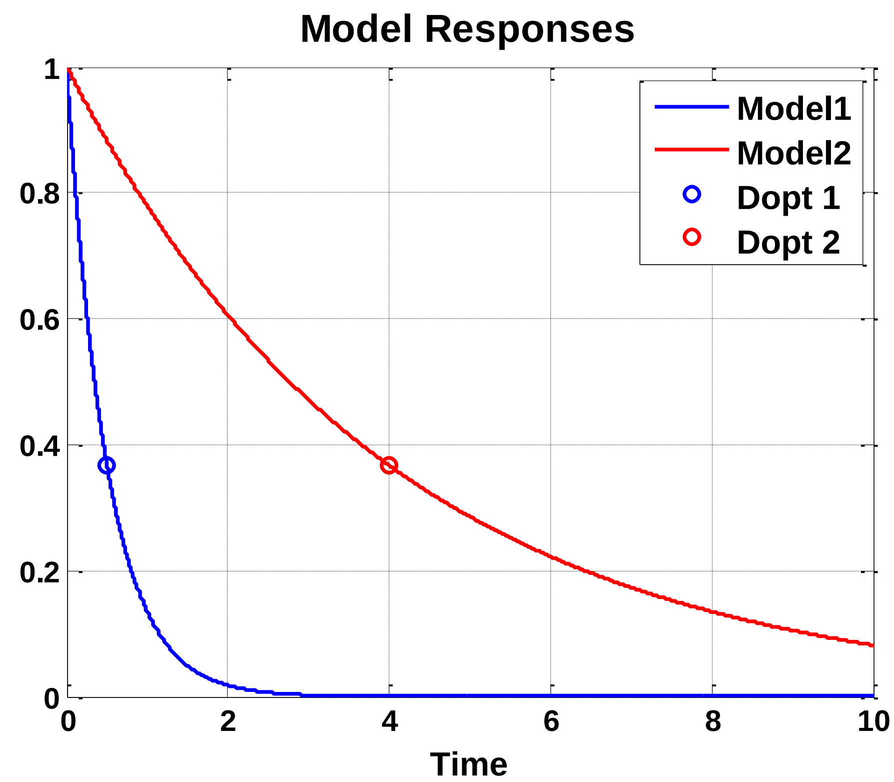
- **Fisher Information Matrix** M

$$\frac{\partial \eta}{\partial a} = -te^{-at}$$
$$M(a) = \frac{1}{\sigma^2}(te^{-at})^2$$
$$|M(a)| = t^2 e^{-2at}/\sigma^2$$

- **Individual D-Optimal Designs**

Fast Model: $t = 1/a_1 = .5$

Slow Model: $t = 1/a_2 = 4$



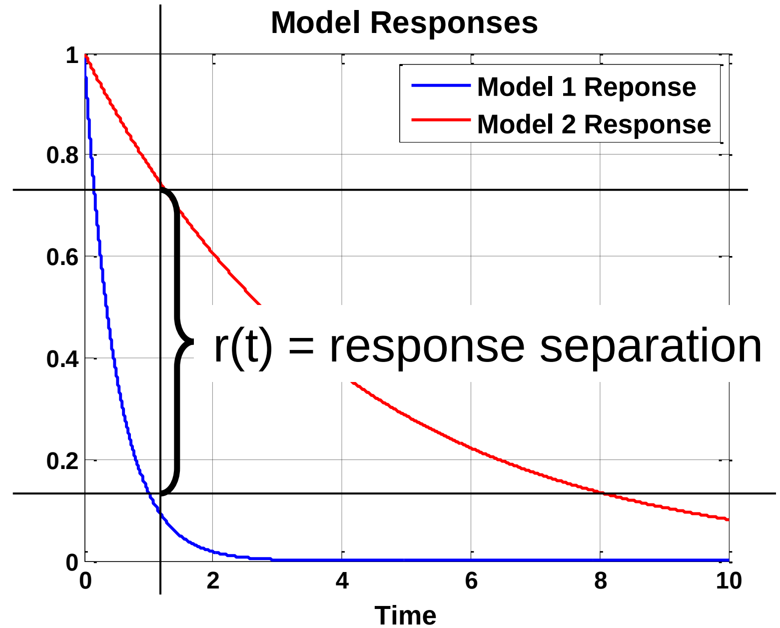
Model Response Separation r(t)

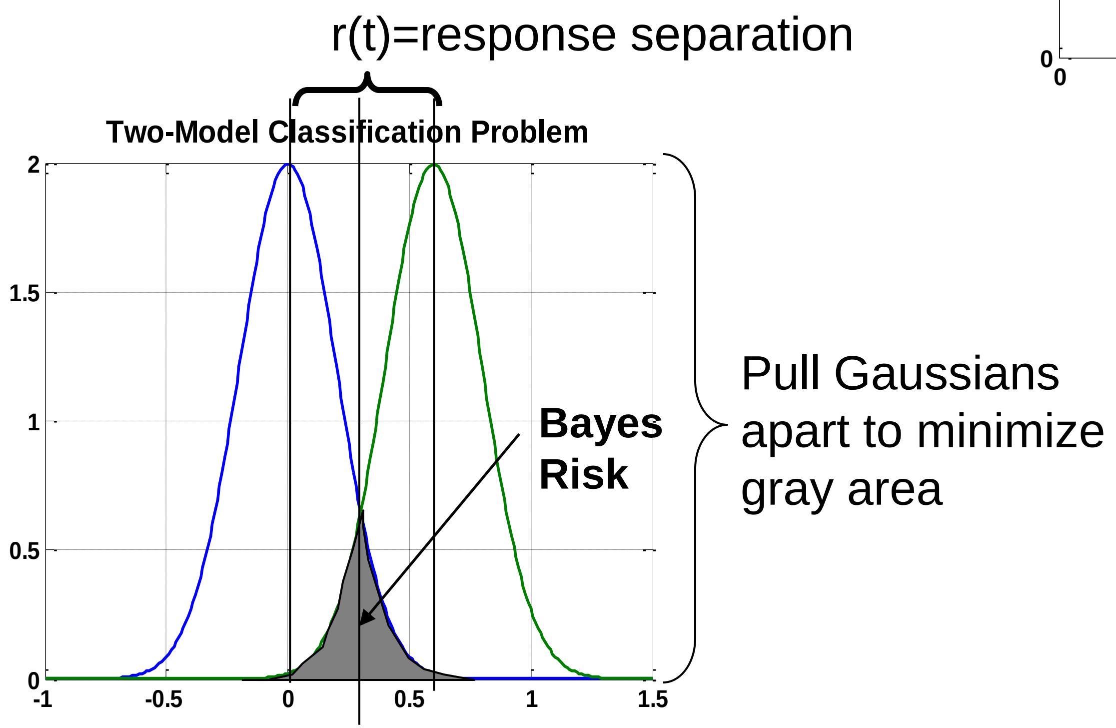
• **Model Response Separation r(t) is the separation between two model responses at a given time t**

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

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

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





• 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)

Bayes Optimal Design

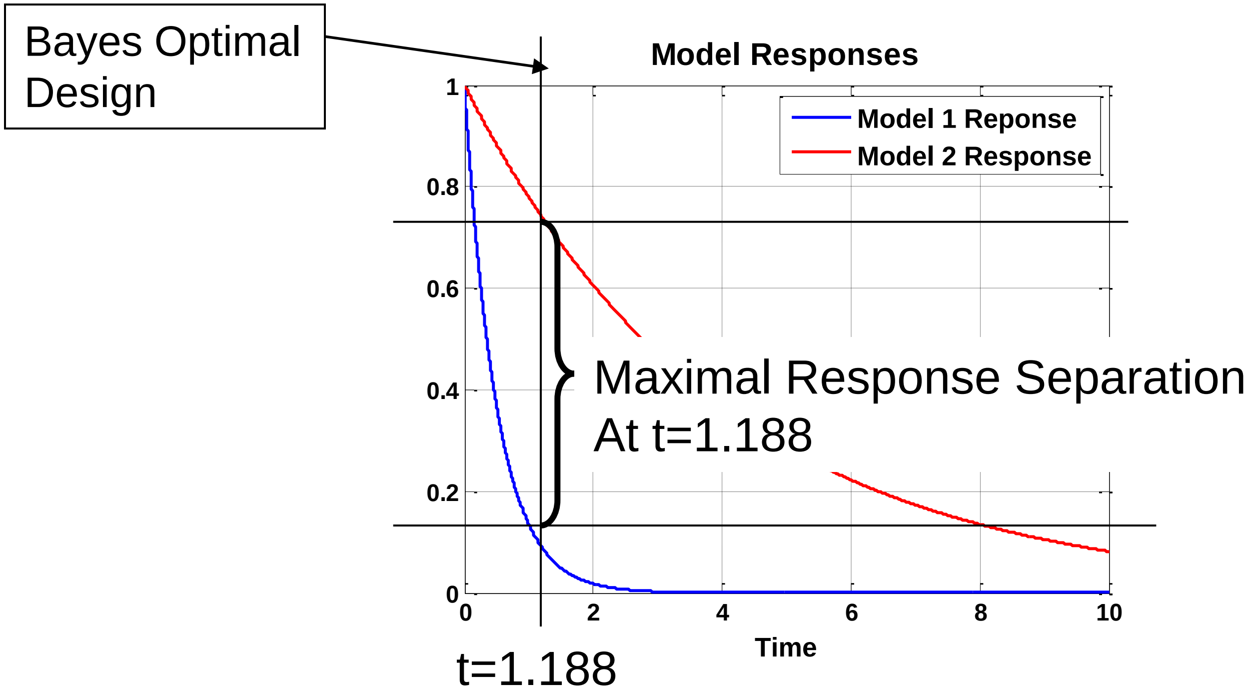
- Bayes Optimal Design minimizes Bayes Risk
- Bayes Risk = Prob(Type I error)+ Prob(Type II error)

$$= p_1 \int_{t_{cross}}^{\infty} p(y|a_1)dy + p_2 \int_{-\infty}^{t_{cross}} p(y|a_2)dy = 1 - \int_{-\infty}^{r(t)/2} N(0,\sigma^2)dy$$

where $r(t) = |\eta(t,a_1) - \eta(t,a_2)|$ is <u>response separation</u>

- Bayes Risk decreases monotonically with increasing $r(t)$
  - Minimized at time of maximal response separation $r(t)$

$$\arg\max_t \; r(t) = |\eta(t,a_1) - \eta(t,a_1)| = 1.188$$



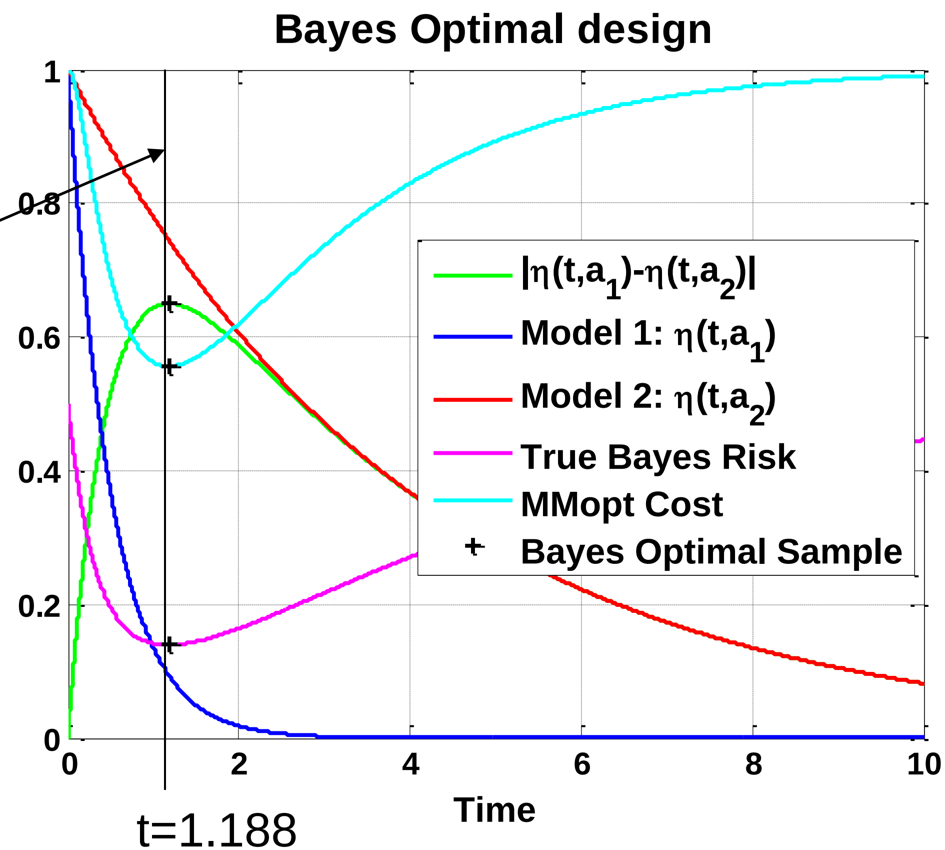
MMopt for 2-Model Example

$$\text{MMopt} = \arg\min_t \; p_1^{\frac{1}{2}} p_2^{\frac{1}{2}} e^{-k(1,2)} + p_2^{\frac{1}{2}} p_1^{\frac{1}{2}} e^{-k(2,1)} = \arg\min_t \; e^{-(\eta(t,a_1)-\eta(t,a_2))^2/(8\sigma^2)}$$

- Take negative-log since monotonic: $\text{MMopt} = \arg\max_t |\eta(t,a_1) - \eta(t,a_2)|$
- MMopt directly maximizes $r(t) = |\eta(t,a_1) - \eta(t,a_1)|$ response separation
- Hence, MMopt sample is at $t = 1.188$ which is same as Bayes Optimal Design

For 2-Model problem, MMopt gives identical solution as Bayes Optimal Design at t=1.188

Both designs maximize response separation (green curve)



ED Design for 2-Model Example

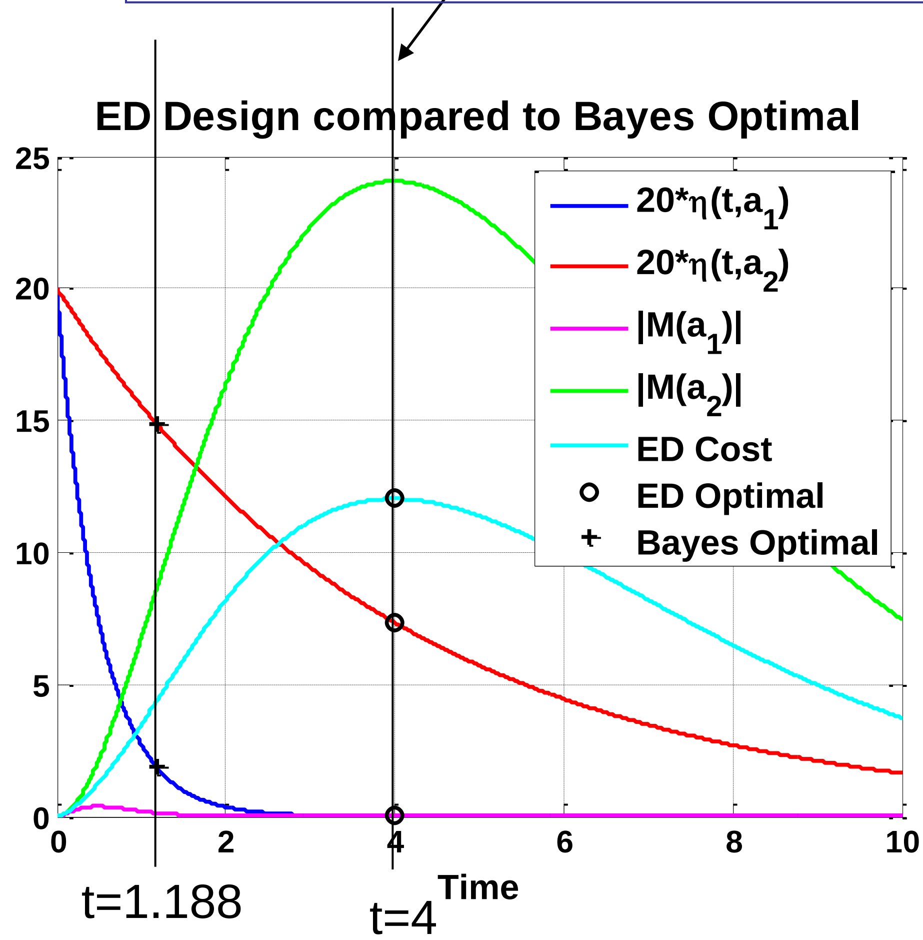
- **ED Optimal Design**

$$\text{ED information} = E[|M|]$$
$$= .5|M(a_1)| + .5|M(a_2)|$$
$$= .5\left(\frac{t^2 e^{-2a_1 t}}{\sigma^2}\right) + .5\left(\frac{t^2 e^{-2a_2 t}}{\sigma^2}\right)$$

ED Criterion is blind to model response separation:

$$\eta(t, a_1) - \eta(t, a_2)$$
$$= e^{-a_1 t} - e^{-a_2 t}$$

ED design at t=4 sec is very different from Bayes optimal design of t=1.188



Note: model responses have been rescaled to enable showing everything on one plot

2-Model Results

Design Metric	Sample Time	Bayes Risk
Bayes Optimal	1.188	0.1393
MMOpt	1.188	0.1393
ED	4.000	0.2701
EID	0.5600	0.1827
API	0.8890	0.1462

- MMopt has smallest Bayes Risk of all designs studied
- *Observation:* ED metric is blind to the underlying classification problem
  - Misses importance of maximizing the response difference $|\eta(t, a_1) - \eta(t, a_2)|$, which requires analyzing model responses jointly.
- Above observation applies to ED, EID, ELD, and any other information metric that simply takes an expectation over individual model information.
- As desired for classification, MMopt directly maximizes response difference $|\eta(t, a_1) - \eta(t, a_2)|$ and agrees exactly with Bayes optimal design for this problem

2-Models with Close Parameters

- **2-Model with Close Dynamics**

  $y_i = \eta(t_i, a) + \sigma n_i$

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

  $a = a_1 = 1.1$ (fast model)

  $a = a_2 = 1$ (slow model)

  $\sigma = 0.3$

  Prior: $p_1 = .5$, $p_2 = .5$

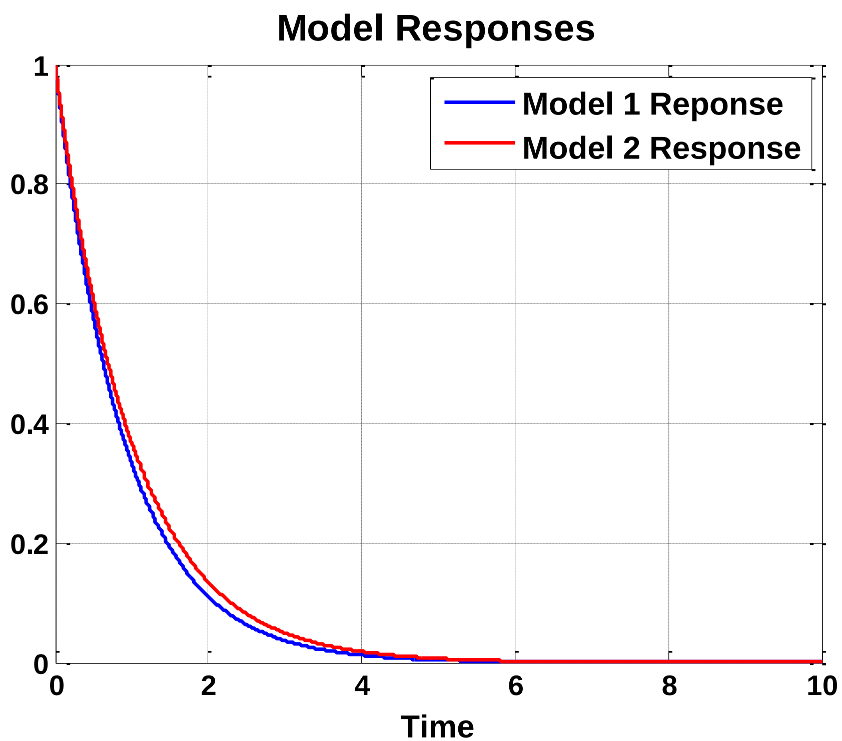
- **Individual D-Optimal Designs**

  Fast Model: $t = 1/a_1 = 0.9091$

  Slow Model: $t = 1/a_2 = 1$

  A-prior Mean Model: $t = 1/\overline{a} = 0.9524$

  $\overline{a} = (a_1 + a_2)/2$



Results for 2-Models with Close Parameters

Design Metric	Sample Time	Bayes Risk
Bayes Optimal	**0.9530**	**0.4767**
MMOpt	**0.9530**	**0.4767**
ED	**0.9570**	**0.4767**
EID	**0.9480**	**0.4767**
API	**0.9520**	**0.4767**
D-Optimal	**0.9524**	**0.4767**

- MMopt agrees exactly with Bayes optimal design for this problem
- Designs (ED, EID, API, D-Optimal) are close to Bayes Optimal design
- Not coincidence: for two model responses close enough to differ by a first-order approximation in a Taylor expansion:
  - Maximizing Model response separation is similar to maximizing Fisher information
  - Goals of classification and parameter estimation are very similar

- Result (see Appendix): For the 2-Model example, the D-Optimal design (designed for *a-prior* mean $\overline{a} = (a_1 + a_2)/2$) approaches the MMopt design (and Bayes Optimal Design) asymptotically as the *a-prior* parameter uncertainty $\Delta a = a_2 - a_1$ becomes small

4-Model Example

- Example where Bayes Optimal Design is too difficult to compute
- Demonstrates usefulness of MMopt design

- Two-Parameters a, b

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

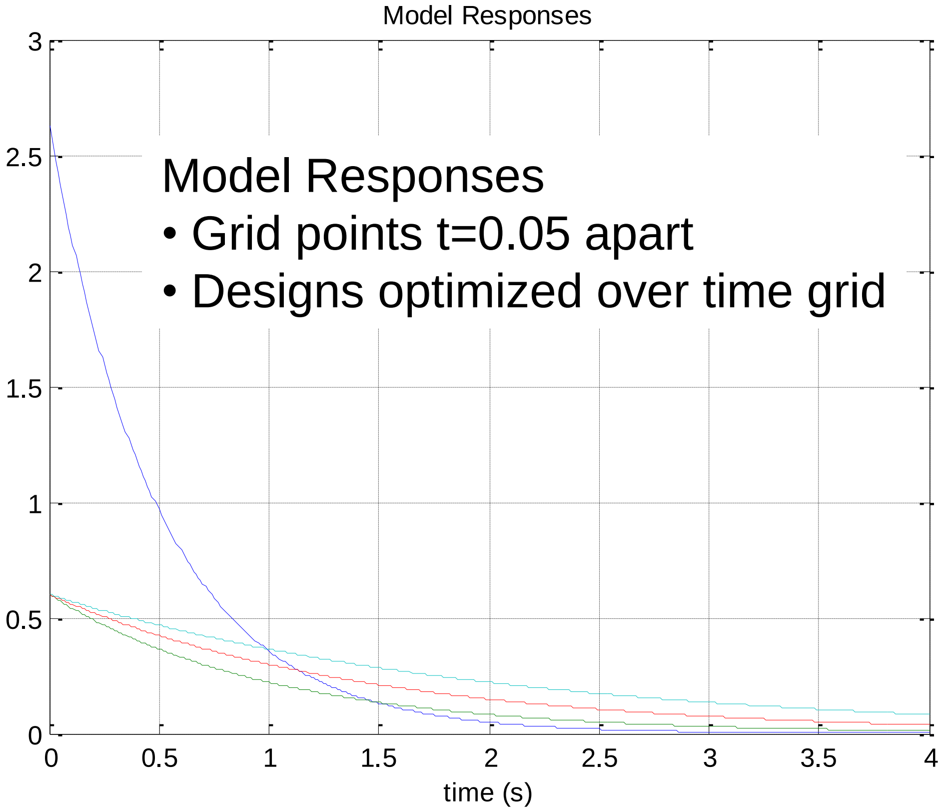
$$\eta(t, a, b) = be^{-at}$$

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

$$\sigma = 0.1$$

- 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



4-Model Results

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
- Bayes optimal design is too difficult to compute for this problem

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

Experiment Design under Reparametrization

- **Typical PK Parameters**

  V - Volume of Distribution

  K - Elimination Rate

  C - Clearance ($C = VK$)

- **PK Parametrization 1: Volume and Elimination** (V, K)

  $\dot{x} = -Kx + d,$ Drug amount x, Dose d

  $\eta_i = \frac{x(t_i)}{V},$ Drug concentration at time t_i

- **PK Parametrization 2: Volume and Clearance** (V, C)

  $\dot{x} = -(C/V)x + d,$ Drug amount x, Dose d

  $\eta_i = \frac{x(t_i)}{V},$ Drug concentration at time t_i

- **Experiment Design under Nonlinear Reparametrization**

- ED and EID designs <u>are NOT invariant</u> under nonlinear reparametrization (see Appendix)

  - In PK example above, ED and EID give <u>different designs</u> depending on whether the (V, K) or (V, C) parametrization is used

- API and MMopt designs are <u>invariant</u> under nonlinear reparametrization (see Appendix)

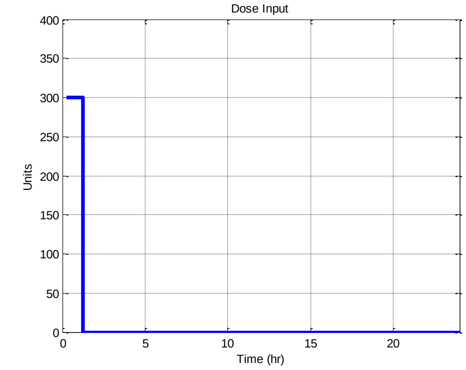
  - "log" in API metric enables invariance (decouples expectation of product into sum)
  - MMopt uses model responses directly rather than forming Fisher Matrix

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

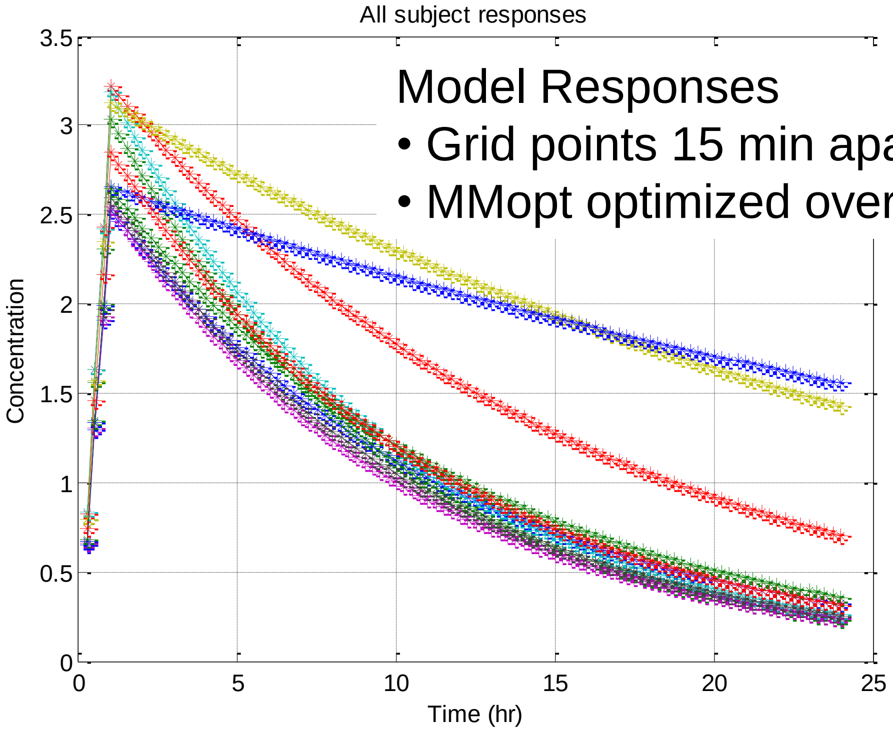
- **First-Order Model**

$$\dot{x} = -Kx + d$$
$$\eta_i = \frac{x(t_i)}{V}$$
$$y_i = \eta_i + \sigma_i n_i$$
$$n_i \sim N(0,1)$$
$$\sigma_i = 0.1$$

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



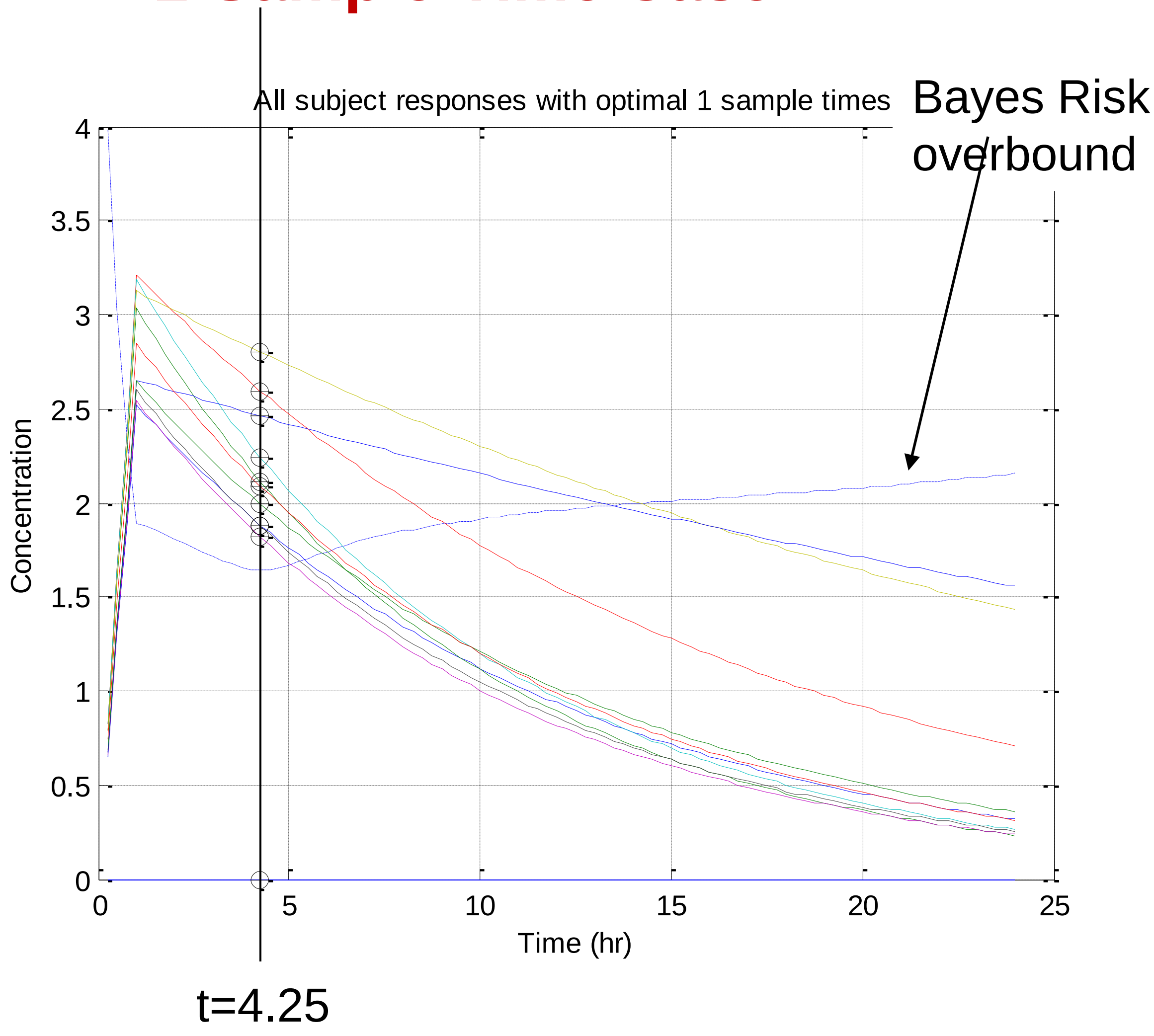
Model Parameters		
#	K	V
1	0.090088	113.7451
2	0.111611	93.4326
3	0.066074	90.2832
4	0.108604	89.2334
5	0.103047	112.1093
6	0.033965	94.3847
7	0.100859	109.8633
8	0.023174	111.7920
9	0.087041	108.6670
10	0.095996	100.3418



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

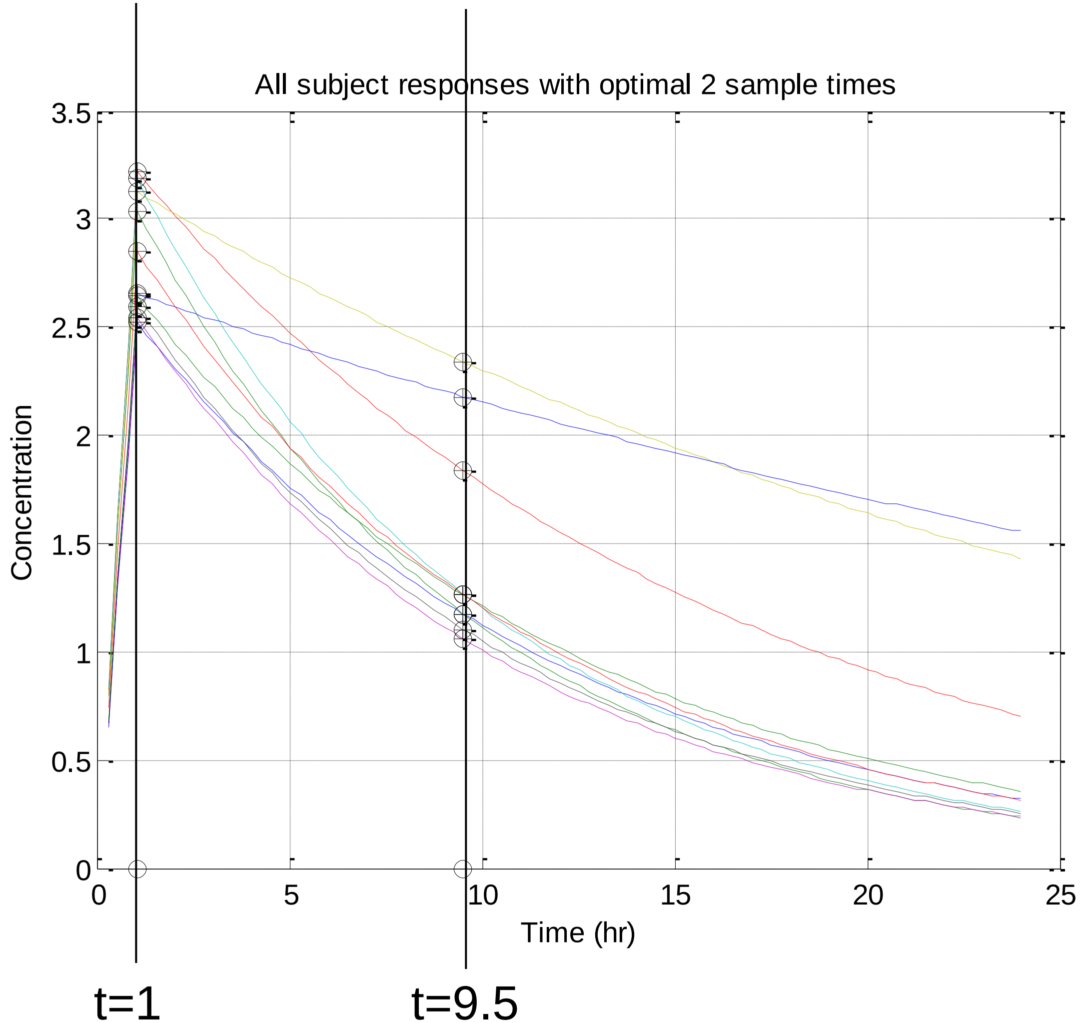
Example of MMopt Design with 10 Models 1-Sample-Time Case

- Optimal Sampling Times (hr)
  4.2500



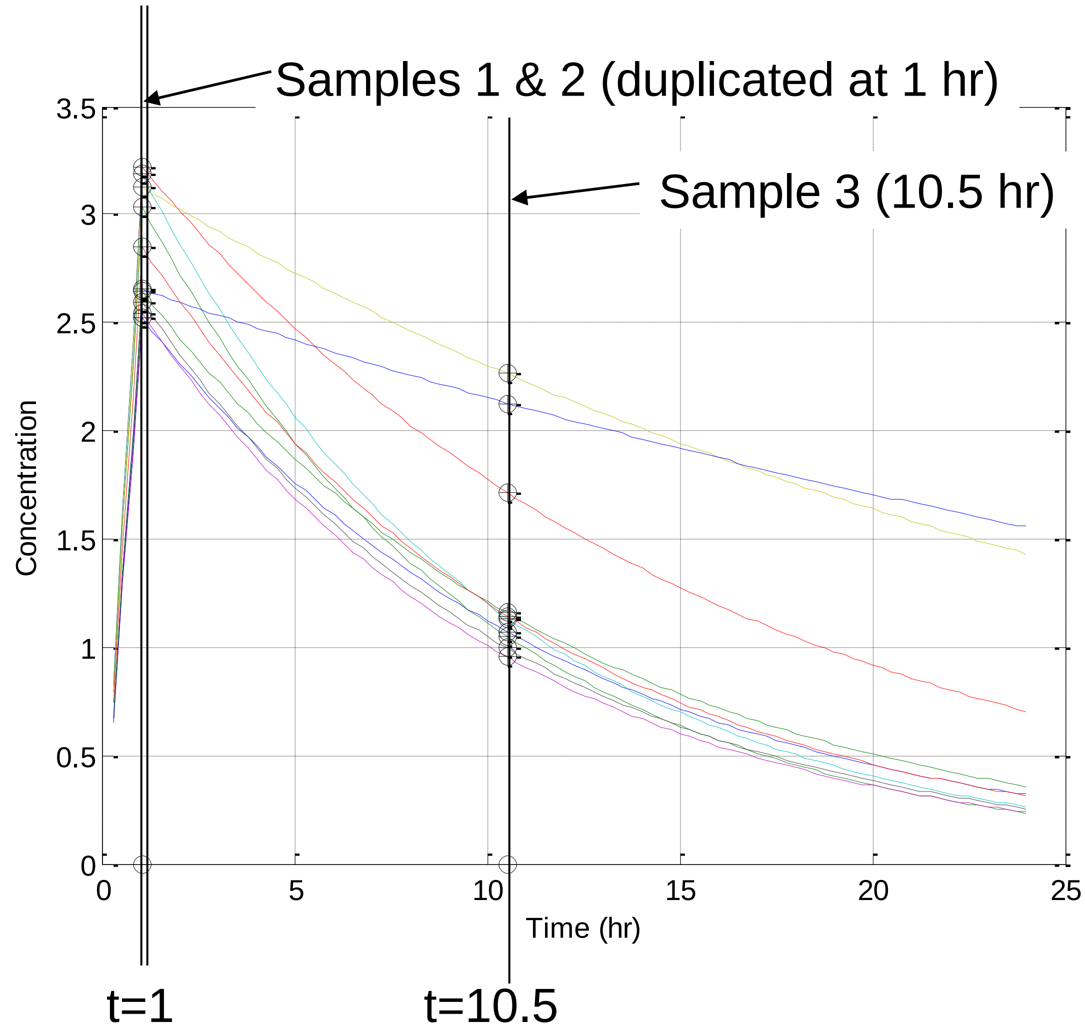
Example of MMopt Design with 10 Models
2-Sample-Time Case

- Optimal Sampling Times (hr)
  1.0000
  9.5000



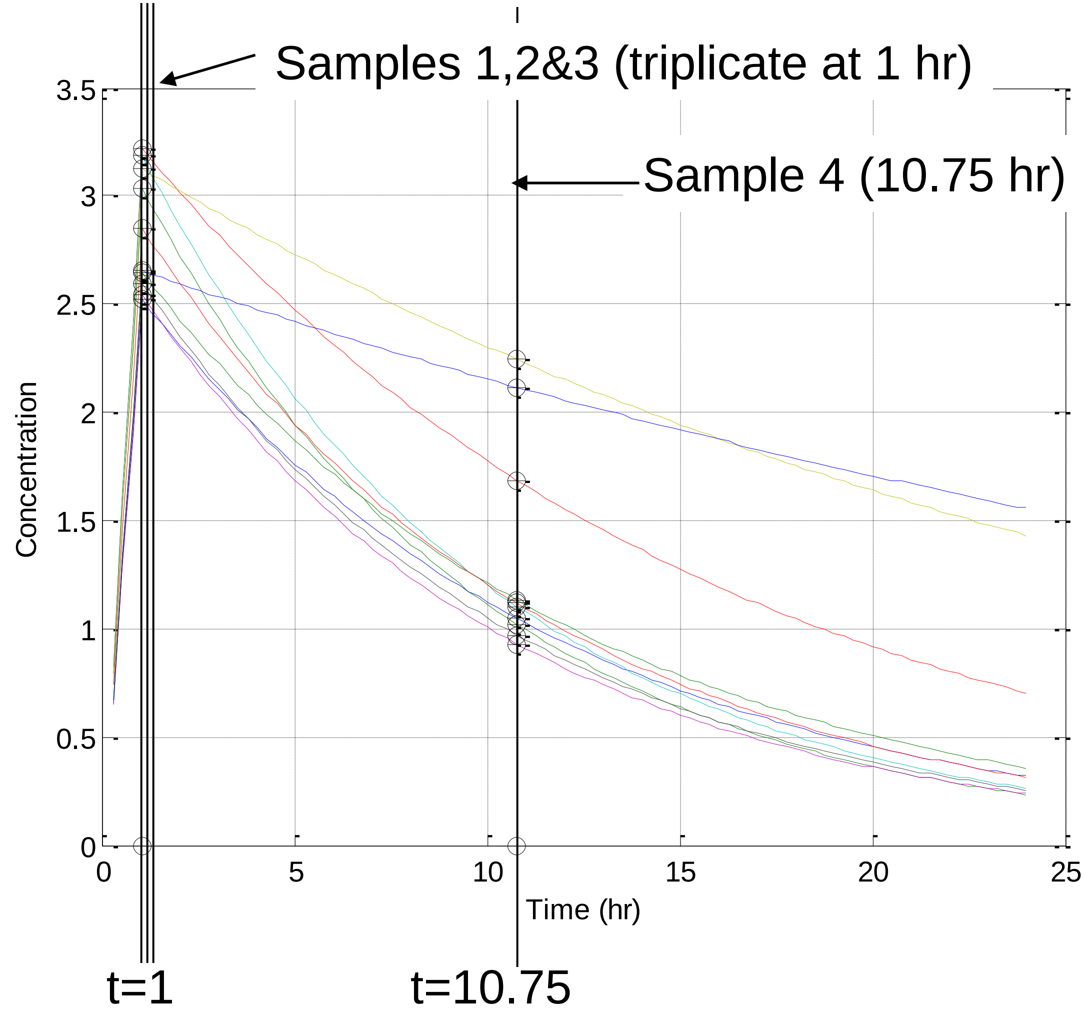
Example of MMopt Design with 10 Models: 3-Sample-Time Case

- Optimal Sampling Times (hr)
  - 1.0000
  - 1.0000
  - 10.5000



Example of MMopt Design with 10 Models: 4-Sample-Time Case

- Optimal Sampling Times (hr)
  1.0000
  1.0000
  1.0000
  10.7500



Comparison Table

	ED	EID	API	MMopt
Invariant under regular linear reparametrization*	**Yes**	**Yes**	**Yes**	**Yes**
Invariant under regular nonlinear 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 Appendix

Summary

- **Multiple Model Optimal Design (MMOpt) provides an alternative to Fisher-Information Matrix based design**
  - Particularly attractive for Nonparametric Models (MM discrete prior)
  - Based on true MM formulation of the problem (i.e., classification theory)
  - Has many advantages relative to ED, EID and API (see Table summary)
  - Based on recent theoretical overbound on Bayes Risk (Blackmore et. al. 2008)

- **Advantages of MMopt shown using simple 2-Model example**
  - Both Bayes Optimal design and MMopt maximize Model Response Separation
  - MMopt identical to Bayes Optimal Sample design for this problem
  - ED, EID and API did not perform well in terms of Bayes Risk unless a-priori parameter uncertainty is chosen small
  - Shown that goals of classification and parameter estimation become asymptotically similar as prior parameter uncertainty becomes vanishingly small

- **ED, EID and API designs do not explicitly consider model response separation**
  - Blind to the underlying classification problem
  - Not as well-suited for nonparametric models

- **MMopt captures essential elements of Bayes Risk minimization without the excessive computation**
  - Targeted to be included in a future release of the USC *BestDose* software

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APPENDIX

Properties of ED-class Designs under Regular* Reparametrization (1/4)

- **Fisher Matrix for Parameter vector a**

$$M_a(a,\xi) = \sum_{i=1}^{m} \frac{1}{\sigma_i(a)^2} \left[\frac{\partial \eta(t_i,a)}{\partial a} \frac{\partial \eta(t_i,a)}{\partial a^T}\right]$$

where,

$y_i = \eta(t_i,a) + \sigma_i(a)n_i$, Noisy measurement at time t_i

$n_i \sim N(0,1)$, Gaussian measurement noise

$\xi = \{t_1, ..., t_m\}$, Experiment design (sampling)

- **Evaluate on $a = a_o$**

$$M_a(a_o,\xi) \triangleq M_a(a,\xi)\Big|_{a=a_o} = \sum_{i=1}^{m} \frac{1}{\sigma_i(a_o)^2} \left[\frac{\partial \eta(t_i,a)}{\partial a} \frac{\partial \eta(t_i,a)}{\partial a^T}\right]\Bigg|_{a=a_o}$$

- **Fisher Matrix for Parameter vector b**

$$M_b(b,\xi) = \sum_{i=1}^{m} \frac{1}{\sigma_i(b)^2} \left[\frac{\partial \eta(t_i,b)}{\partial b} \frac{\partial \eta(t_i,b)}{\partial b^T}\right]$$

- **Under Regular Reparameterization* $a = f(b)$ can show**

$$M_b(b,\xi) = T^T(b)\ M_a(f(b),\xi)\ T(b)$$

$T(b) \triangleq \frac{\partial f(b)}{\partial b^T}$, Differential matrix of transformation

Take determinant,

$$|M_b(b,\xi)| = J(b)^2 |M_a(f(b),\xi)|$$

$J(b) \triangleq |T(b)|$, Jacobian of transformation

*Mapping $a = f(b)$ is one-to-one and has continuous partial derivatives

Properties of Robust D-Optimal Designs under Regular Reparametrization (2/4)

- **Robust D-Optimal Designs for Parameter Vector a**

  ED: $\xi_a^{ED} \triangleq \arg\max_\xi \; E_a\left(\left|M_a(a,\xi)\right| \right)$

  EID: $\xi_a^{EID} \triangleq \arg\min_\xi \; E_a\left(\frac{1}{|M_a(a,\xi)|}\right)$

  API: $\xi_a^{API} \triangleq \arg\max_\xi \; E_a\left(\, log\left|M_a(a,\xi)\right| \right)$

- **Robust D-Optimal Designs under Regular Reparametrization $a = f(b)$**

- Fisher Matrix M assumed to be non-constant function of a (i.e., nonlinear problems)

- **Case I: Mapping $a = f(b)$ is nonlinear**

  $J(b)$ is non-constant function of b

- **Case II: Mapping $a = f(b) = Fb$ is linear**

  $J(b) = |F| = const$, where $F \in R^{p \times p}$ is a square invertible matrix

- Next slides will prove results in following table:

	ED	EID	ELD
Invariant under regular linear reparametrization	Yes	Yes	Yes
Invariant under regular nonlinear reparametrization	No	No	Yes

Properties of Robust D-Optimal Designs under Regular Reparametrization (3/4)

- **Case I: Mapping $a = f(b)$ is nonlinear**

- **ED Design**

$$\xi_b^{ED} \triangleq \arg\max_\xi \ E_b\left(\left|M_b(b,\xi)\right| \right) = \arg\max_\xi \ E_b\left(J(b)^2 |M_a(f(b),\xi)| \right)$$
$$= \arg\max_\xi \ E_a\left(J(f^{-1}(a))^2 |M_a(a,\xi)| \right) \neq \arg\max_\xi \ E_a\left(\left|M_a(a,\xi)\right| \right) = \xi_a^{ED}$$

Hence, $\xi_b^{ED} \neq \xi_a^{ED}$ and ED design is NOT invariant under regular nonlinear reparametrization

- **ED Design**

$$\xi_b^{EID} \triangleq \arg\min_\xi \ E_b\left(\frac{1}{\left|M_b(b,\xi)\right|} \right) = \arg\min_\xi \ E_b\left(\frac{1}{J(b)^2 |M_a(f(b),\xi)|} \right)$$
$$= \arg\min_\xi \ E_a\left(\frac{1}{J(f^{-1}(a))^2 |M_a(a,\xi)|} \right) \neq \arg\min_\xi \ E_a\left(\frac{1}{\left|M_a(a,\xi)\right|} \right) = \xi_a^{EID}$$

Hence, $\xi_b^{EID} \neq \xi_a^{EID}$ and EID design is NOT invariant under regular nonlinear reparametrization

- **API Design**

$$\xi_b^{API} \triangleq \arg\max_\xi \ E_b\left(log\left|M_b(b,\xi)\right| \right) = \arg\max_\xi \ E_b\left(log\left(J(b)^2 |M_a(f(b),\xi)|\right) \right)$$
$$= \arg\max_\xi \left(2E_b \ log \ J(b) + E_a \ log|M_a(a,\xi)| \right) = \arg\max_\xi \ E_a \ log|M_a(a,\xi)| = \xi_a^{API}$$

Hence, $\xi_b^{API} = \xi_a^{API}$ and API design IS invariant under regular nonlinear reparametrization

Properties of Robust D-Optimal Designs under Regular Reparametrization (4/4)

- **Case II: Mapping $a = f(b) = Fb$ is linear**

- ED Design

$$\xi_b^{ED} \triangleq \arg\max_\xi \ E_b\left(\left|M_b(b,\xi)\right| \right) = \arg\max_\xi \ E_b\left(J(b)^2 |M_a(f(b),\xi)| \right)$$
$$= \arg\max_\xi \ E_a\left(|F|^2 |M_a(a,\xi)| \right) = \arg\max_\xi \ E_a\left(\left|M_a(a,\xi)\right| \right) = \xi_a^{ED}$$

Hence, $\xi_b^{ED} = \xi_a^{ED}$ and ED design IS invariant under regular linear reparametrization

- EID Design

$$\xi_b^{EID} \triangleq \arg\min_\xi \ E_b\left(\frac{1}{\left|M_b(b,\xi)\right|} \right) = \arg\min_\xi \ E_b\left(\frac{1}{J(b)^2|M_a(f(b),\xi)|} \right)$$
$$= \arg\min_\xi \ E_a\left(\frac{1}{|F|^2|M_a(a,\xi)|} \right) = \arg\min_\xi \ E_a\left(\frac{1}{\left|M_a(a,\xi)\right|} \right) = \xi_a^{EID}$$

Hence, $\xi_b^{EID} = \xi_a^{EID}$ and EID design IS invariant under regular linear reparametrization

- API Design

$$\xi_b^{API} \triangleq \arg\max_\xi \ E_b\left(log\left|M_b(b,\xi)\right| \right) = \arg\max_\xi \ E_b\left(log\left(J(b)^2|M_a(f(b),\xi)|\right) \right)$$
$$= \arg\max_\xi \left(2E_b \ log|F| + E_a \ log|M_a(a,\xi)| \right) = \arg\max_\xi \ E_a \ log|M_a(a,\xi)| = \xi_a^{API}$$

Hence, $\xi_b^{API} = \xi_a^{API}$ and API design IS invariant under regular nonlinear reparametrization

Relation Between MMopt and Fisher Matrix in 2-Model Example with Close Parameters

- Assume model responses $\eta(t, a_1)$ and $\eta(t, a_2)$ can be expanded in a Taylor series about the mean parameter $\overline{a} = (a_1 + a_2)/2$

  $$\eta(t, a_2) = \eta(t, \overline{a}) + \frac{\partial \eta(t,a)}{\partial a}|_{a=\overline{a}}(a_2 - \overline{a}) + O(a_2 - \overline{a})^2$$

  $$\eta(t, a_1) = \eta(t, \overline{a}) + \frac{\partial \eta(t,a)}{\partial a}|_{a=\overline{a}}(a_1 - \overline{a}) + O(a_1 - \overline{a})^2$$

- Subtract Taylor expansions and rearrange using $\Delta a = a_2 - a_1$

  $$\eta(t, a_2) - \eta(t, a_1) = \frac{\partial \eta(t,a)}{\partial a}|_{a=\overline{a}}\Delta a + O(\Delta a)^2$$

  $$(\eta(t, a_2) - \eta(t, a_1))^2 = \left(\frac{\partial \eta(t,a)}{\partial a}|_{a=\overline{a}}\right)^2 (\Delta a)^2 + O(\Delta a)^3$$

  $$\frac{(\eta(t,a_2) - \eta(t,a_1))^2}{(\Delta a)^2} = \left(\frac{\partial \eta(t,a)}{\partial a}|_{a=\overline{a}}\right)^2 + O(\Delta a)$$

- Last equation relates MMopt Cost to D-Optimal cost, i.e.,

  $$-log \text{ MMopt Cost} = \text{const } |M(\overline{a})| + O(\Delta a)$$

- Result: For the 2-Model example, the D-Optimal design (designed for *a-prior* mean $\overline{a} = (a_1 + a_2)/2$) approaches the MMopt design (and Bayes Optimal Design) asymptotically as the *a-prior* parameter uncertainty $\Delta a = a_2 - a_1$ becomes small