A comparison of sequential design procedures for discriminating enzyme kinetic models

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Overview

- Introduction
  - Why sequential designs?

- Methodologies for sequential designs
  - Hunter and Reiner
  - Ds
  - Linearized distance (δ)

- Application
  - Enzyme kinetic models

- Results
  - Sequential designs
  - Precision in estimation
  - Comparison of (normalized) criterion values

- Discussion

Why sequential?

- Many optimal design procedures for discrimination (including T) depend on true model and its parameters (locally optimum).
- Sequential procedure: one option to tackle this dependence.
- Use the information provided in the observations.
- Cost is an important factor.

- Investigated sequential design strategies based on:
  - Hunter and Reiner [6] (adapted T).
  - D_s; Atkinson and Cox [3] .
  - Linearized distance (δ-)criterion; Harman and Müller [5].

Rival models

- $y_i = \eta_0(\boldsymbol{\theta}_0, \mathbf{x}_i) + \epsilon_i, \qquad i = 1, \ldots, N$
- $y_i = \eta_1(\boldsymbol{\theta}_1, \mathbf{x}_i) + \epsilon_i, \qquad i = 1, \ldots, N$

  - $\boldsymbol{\theta} = (\theta_1, \ldots, \theta_m)^T$
  - $\boldsymbol{\theta} \in \boldsymbol{\Theta} \subseteq \mathbb{R}^m$
  - $\mathbf{x}_i = (x_{1i}, x_{2i})^T$
  - $\mathfrak{X} = [x_1] \times [x_2]$
  - $0 \leq [x_1]_{\min} \leq [x_1] \leq [x_1]_{\max}$
  - $0 \leq [x_2]_{\min} \leq [x_2] \leq [x_2]_{\max}$
  - $\eta(\boldsymbol{\theta}, \mathbf{x}_i)$, expected response
  - $\eta : \boldsymbol{\Theta} \times \mathfrak{X} \to \mathbb{R}$
  - $\epsilon \sim \mathcal{N}(0, \sigma^2)$

Hunter and Reiner [6] (adapted T) sequential procedure:

1. Let an initial design ξ_{N_0} with N_0 observations $y_i, i = 1, \ldots, N_0$ be given.
   Find the nonlinear least square parameter estimates of the models $(\hat{\boldsymbol{\theta}}_{0N_0}, \hat{\boldsymbol{\theta}}_{1N_0})$

$$\sum_{i=1}^{N_0} \left(y_i - \widehat{y_{ji}}\right)^2 = \inf_{\boldsymbol{\theta}_j \in \boldsymbol{\Theta}_j} \sum_{i=1}^{N_0} (y_i - \eta_j(\boldsymbol{\theta}_j, \mathbf{x}_i))^2 \quad (\widehat{y_{ji}} = \eta_j(\hat{\boldsymbol{\theta}}_{jN_0}, \mathbf{x}_i), j = 0, 1).$$

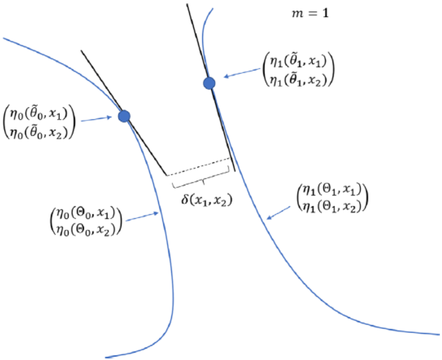
2. The next point $\mathbf{x}_{N_0+1}$ is chosen as
   $\mathbf{x}_{N_0+1} = \arg\max_{\mathbf{x} \in \mathfrak{X}} \left\{\eta_0(\hat{\boldsymbol{\theta}}_{0N_0}, \mathbf{x}) - \eta_1(\hat{\boldsymbol{\theta}}_{1N_0}, \mathbf{x})\right\}^2.$
3. The $(N_0 + 1)$th observation is taken at $\mathbf{x}_{N_0+1}$.
4. Steps 1 to 3 are repeated.

- This will lead to an asymptotically T-optimal design.

Ds [Atkinson and Cox [3]] sequential procedure:

- Redo step one for the more general model only, to get the $\hat{\boldsymbol{\theta}}_{2N_0}$.
- Alter the second step as:
  - $$M(\xi_{N_0}, \hat{\boldsymbol{\theta}}_{2N_0}) = \begin{pmatrix} M_{11}(\xi_{N_0}, \hat{\boldsymbol{\theta}}_{2N_0}) & M_{12}(\xi_{N_0}, \hat{\boldsymbol{\theta}}_{2N_0}) \\ M_{21}(\xi_{N_0}, \hat{\boldsymbol{\theta}}_{2N_0}) & M_{22}(\xi_{N_0}, \hat{\boldsymbol{\theta}}_{2N_0}) \end{pmatrix}$$
  - $M_{11}(\xi_{N_0}, \hat{\boldsymbol{\theta}}_{2N_0}) = \sum_{i=1}^{N_0} f_1(\xi_{N_0 i}, \hat{\boldsymbol{\theta}}_{2N_0}) f_1^T(\xi_{N_0 i}, \hat{\boldsymbol{\theta}}_{2N_0})$ (for nuisance pars).
  - Nuisance part of $\hat{\boldsymbol{\theta}}_{2N_0}$ contributes in f_1 and M_{11}.
  - $M_{22}(\xi_{N_0}, \hat{\boldsymbol{\theta}}_{2N_0})$ (for pars of interest)
  - $A^{-1} = \left\{ M_{22} - M_{21} M_{11}^{-1} M_{12} \right\}^{-1}$
  - $\Phi_s(\xi_{N_0}, \hat{\boldsymbol{\theta}}_{2N_0}) = \dfrac{|M(\xi_{N_0}, \hat{\boldsymbol{\theta}}_{2N_0})|}{|M_{11}(\xi_{N_0}, \hat{\boldsymbol{\theta}}_{2N_0}|}$.
  - $$\mathbf{x}_{N_0+1} = \arg\max_{\mathbf{x} \in \mathfrak{X}} \Big\{ f^T(\mathbf{x}, \hat{\boldsymbol{\theta}}_{2N_0}) M^{-1}(\xi_{N_0}, \hat{\boldsymbol{\theta}}_{2N_0}) f(\mathbf{x}, \hat{\boldsymbol{\theta}}_{2N_0}) - f_1^T(\mathbf{x}, \hat{\boldsymbol{\theta}}_{2N_0}) M_{11}^{-1}(\xi_{N_0}, \hat{\boldsymbol{\theta}}_{2N_0}) f_1(\mathbf{x}, \hat{\boldsymbol{\theta}}_{2N_0}) \Big\}.$$

- Linearized distance (δ) [Harman and Müller [5]]



Definition of $\delta(\mathcal{D})$. The line segments correspond to the sets $\{\mathbf{a}_0(\mathcal{D}) + \mathbf{F}_0(\mathcal{D})\boldsymbol{\theta}_0\}$ and $\{\mathbf{a}_1(\mathcal{D}) + \mathbf{F}_1(\mathcal{D})\boldsymbol{\theta}_1\}$ for some flexible nominal sets.

The linearized distance (δ) as a sequential procedure:

- The second step is altered as:
  - $$(y_i)_{i=1}^{N_0+1} \approx \mathbf{F}_u(\mathcal{D})\boldsymbol{\theta}_u + \mathbf{a}_u(\mathcal{D}) + \epsilon.$$
    $$\mathbf{a}_u(\mathcal{D}) = (\eta_u(\hat{\boldsymbol{\theta}}_{uN_0}, \mathbf{x}_i))_{i=1}^{N_0+1} - \mathbf{F}_u(\mathcal{D})\hat{\boldsymbol{\theta}}_{uN_0}, u = 0, 1.$$
  - $\mathcal{D} = (\mathbf{x}_1, \ldots, \mathbf{x}_{N_0+1})$ is an exact design of size $N_0 + 1$.
  - $\mathbf{F}_u(\mathcal{D})$ is the $(N_0 + 1) \times m$ matrix of partial derivatives at $\hat{\boldsymbol{\theta}}_{uN_0}$.
  - $$\delta_r(\mathcal{D}) = \inf_{\boldsymbol{\theta}_0 \in \widehat{\boldsymbol{\Theta}}_0^{(r)}, \boldsymbol{\theta}_1 \in \widehat{\boldsymbol{\Theta}}_1^{(r)}} \delta(\mathcal{D} \mid \boldsymbol{\theta}_0, \boldsymbol{\theta}_1). \quad (1)$$
    $$\delta(\mathcal{D} \mid \boldsymbol{\theta}_0, \boldsymbol{\theta}_1) = \|\mathbf{a}_0(\mathcal{D}) + \mathbf{F}_0(\mathcal{D})\boldsymbol{\theta}_0 - \{\mathbf{a}_1(\mathcal{D}) + \mathbf{F}_1(\mathcal{D})\boldsymbol{\theta}_1\}\|$$
  - A design is called δ-optimal if
    $$\mathcal{D}^* \in \arg\max_{\mathcal{D} \in \mathfrak{D}} \delta_r(\mathcal{D}). \quad (2)$$
  - Eq. (1) is computed for all designs of size $N_0 + 1$ (design of size N_0 so far plus 1 candidate point), then done for all points on the grid. Finally the best is chosen.

Application: definitions of models

- Competitive inhibition model:
$$y = \frac{\theta_{01} x_1}{\theta_{02}\left(1 + \frac{x_2}{\theta_{03}}\right) + x_1} + \epsilon$$
- Non-competitive inhibition model:
$$y = \frac{\theta_{11} x_1}{(\theta_{12} + x_1)\left(1 + \frac{x_2}{\theta_{13}}\right)} + \epsilon$$
- Encompassing model (Atkinson [1]):
$$y = \frac{\theta_{21} x_1}{\theta_{22}\left(1 + \frac{x_2}{\theta_{23}}\right) + x_1\left(1 + \frac{(1-\lambda)x_2}{\theta_{23}}\right)} + \epsilon$$

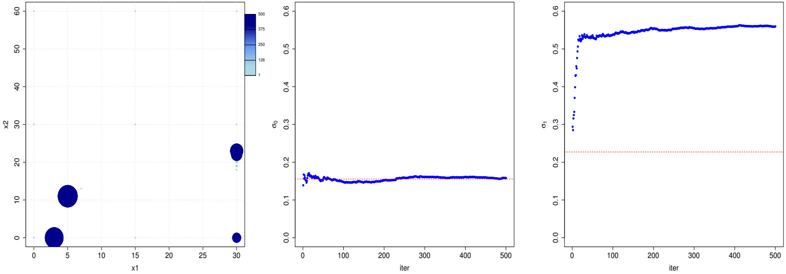
- $x_1 \geq 0$, substrate concentration
- $x_2 \geq 0$, inhibition concentration
- θ_{01}, maximum velocity
- θ_{02}, substrate constant
- θ_{03}, inhibition constant
- $\epsilon \sim \mathcal{N}(0, \sigma^2)$

- $0 \leq \lambda \leq 1$
- $\lambda = 1$: competitive inhibition
- $\lambda = 0$: non-competitive inhibition

Competitive model ($\hat{\sigma} = 0.1553$)			Non-competitive model ($\hat{\sigma} = 0.2272$)		
	Estimate $\hat{\boldsymbol{\theta}}$	SE $\hat{\boldsymbol{\sigma}}$		Estimate $\hat{\boldsymbol{\theta}}$	SE $\hat{\boldsymbol{\sigma}}$
θ_{01}	7.2976	0.1143	θ_{11}	8.6957	0.2227
θ_{02}	4.3860	0.2333	θ_{12}	8.0664	0.4880
θ_{03}	2.5821	0.1454	θ_{13}	12.0566	0.6709

Standard case ($\hat{\sigma} = 0.1526$)		
	Estimate $\hat{\boldsymbol{\theta}}$	SE $\hat{\boldsymbol{\sigma}}$
θ_{21}	7.4253	0.1298
θ_{22}	4.6808	0.2724
θ_{23}	3.0581	0.2815
λ	0.9636	0.0191

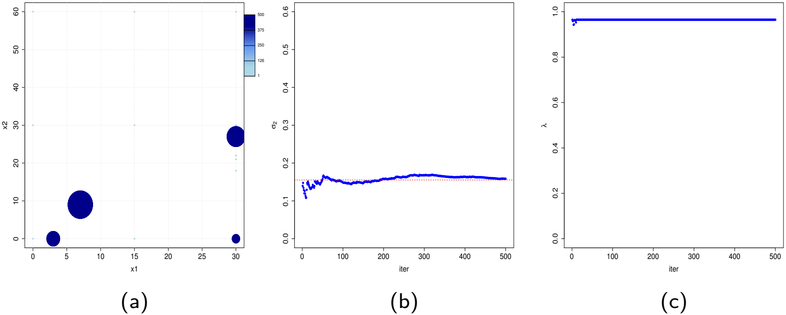
- Initial estimates: $N = 120$ triple observations from Bogacka et al. [4]
- Design region: $\mathfrak{X} = [0, 30] \times [0, 60]$.
- Parameter space: $\boldsymbol{\theta} \in (0, \infty)$
- Estimates of λ is in favor of the competitive model.



(a) (b) (c)

T-sequential procedure, the competitive model is the data generator. (a): sequentially constructed designs, (b) and (c): residual standard error estimates of the competitive and noncompetitive models, respectively.

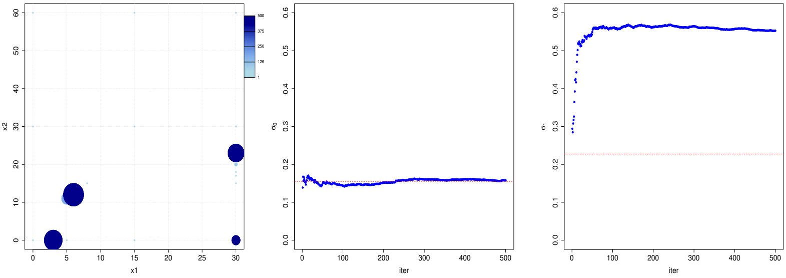
- Compare to approximate designs in Atkinson [2], Yousefi and Müller [7].



D_s-sequential procedure, the competitive model is used to generate the obs. (a): sequentially constructed designs, (b): residual standard error estimates of the encompassing model, (c): estimates of λ.

- Compare to approximate designs in Atkinson [2], Yousefi and Müller [7].

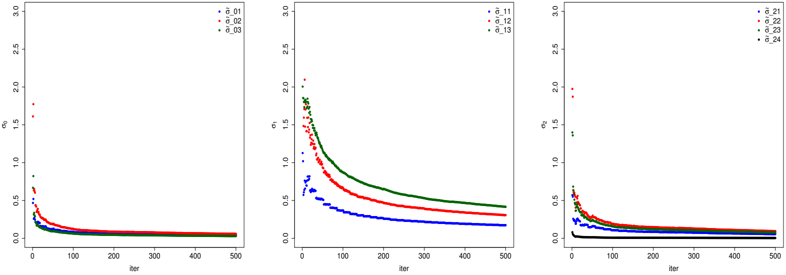
- $\widehat{\boldsymbol{\Theta}}^{(r)} = [\hat{\theta}_{u1} \pm r\hat{\sigma}_{u1}] \times [\hat{\theta}_{u2} \pm r\hat{\sigma}_{u2}] \times [\hat{\theta}_{u3} \pm r\hat{\sigma}_{u3}]_{u=0,1}.$



(a) (b) (c)

δ-sequential procedure, the competitive model is used to generate the obs. (a): sequentially constructed designs, (b) and (c): residual standard error estimates of the competitive and noncompetitive models, respectively.

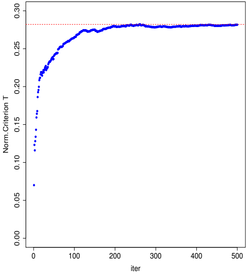
Parameter estimation standard error



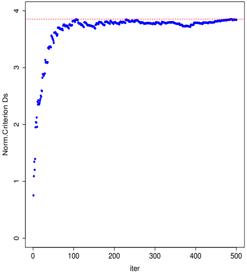
(a) (b) (c)

Parameter estimation standard error for all methods (a),(b): T and δ, (c): D_s

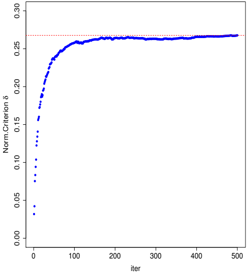
Normalized criterion values



(a)



(b)



(c)

Normalized criterion values for all three methods (a): T, (b): D_s, (c): δ

Minimum number of required observations (Min obs.) to reach different quantiles of the respective maximum for all three methods, left: under competitive and right: under noncompetitive model.

	Min obs. (competitive)				Min obs. (noncompetitive)			
	50%	75%	90%	95%	50%	75%	90%	95%
T	6	16	73	105	5	16	77	97
D_s	6	28	45	61	1	16	65	110
δ	9	26	58	87	22	60	105	138

Discussion and Conclusion

- All T, D_s and δ-sequential procedures behave reasonable.
- D_s-sequential procedure has a relatively higher rate of convergence, by comparing the normalized criterion values.
- Simplicity of computations makes the D_s-sequential procedure even more attractive.
- D_s-procedure: the encompassing (more general) model is not unique.
- Similar results (with slight changes) hold if the noncompetitive model is the data generator.
- Results can help an experimenter with a fixed and limited budget decide on how to proceed sequentially for enzyme kinetic models.

References I

Anthony C Atkinson.
Some optimum designs for building enzyme inhibition kinetic models.
Journal of Statistical Theory and Practice, 10:143–162, 2011.

Anthony C Atkinson.
Optimum experimental designs for choosing between competitive and non competitive models of enzyme inhibition.
Communications in Statistics-Theory and Methods, 41(13-14):2283–2296, 2012.

Anthony C Atkinson and David R Cox.
Planning experiments for discriminating between models.
Journal of the Royal Statistical Society: Series B (Methodological), 36(3):321–334, 1974.

Barbara Bogacka, Maciej Patan, Patrick J Johnson, Kuresh Youdim, and Anthony C Atkinson.
Optimum design of experiments for enzyme inhibition kinetic models.
Journal of Biopharmaceutical Statistics, 21(3):555–572, 2011.

Radoslav Harman and Werner G Müller.
A design criterion for symmetric model discrimination based on flexible nominal sets.
Biometrical Journal, 62(4):1090–1104, 2020.

William G Hunter and Albey M Reiner.
Designs for discriminating between two rival models.
Technometrics, 7(3):307–323, 1965.

Elham Yousefi and Werner G Müller.
Impact of the error structure on the design and analysis of enzyme kinetic models.
arXiv preprint arXiv:2103.09563, 2021.

Thanks for your attention!