Design of experiments in nonlinear models

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Outline I

1. DoE: objectives & examples
2. DoE based on asymptotic normality
3. Construction of (locally) optimal designs
4. Problems with nonlinear models
5. Small-sample properties
6. Nonlocal optimum design

1 DoE: objectives & examples

A/ Parameter estimation

<u>Ex1</u>: Weighing with a two-pan balance

☞ Determine the weights of 8 objets, with mass m_i, $i = 1, \ldots, 8$

i.i.d. errors $\varepsilon_i \sim \mathcal{N}(0, \sigma^2)$

1 DoE: objectives & examples

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i.i.d. errors $\varepsilon_i \sim \mathcal{N}(0, \sigma^2)$

Method a: weigh each objet successively

$\rightarrow y(i) = m_i + \varepsilon_i,\ i = 1, \ldots, 8$

$\rightarrow$ estimated weights : $\hat{m}_i = y_i \sim \mathcal{N}(m_i, \sigma^2)$

Repeat 8 times, average the results: $\hat{\hat{m}}_i \sim \mathcal{N}(m_i, \sigma^2/8)$ (<u>with 64 observations</u>. . .)

Method b: more sophisticated...

$$
\begin{aligned}
y_1 &= m_1 + m_2 + m_3 + m_4 + m_5 + m_6 + m_7 + m_8 + \varepsilon_1 \\
y_2 &= m_1 + m_2 + m_3 - m_4 - m_5 - m_6 - m_7 + m_8 + \varepsilon_2 \\
y_3 &= m_1 - m_2 - m_3 + m_4 + m_5 - m_6 - m_7 + m_8 + \varepsilon_3 \\
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y_8 &= -m_1 - m_2 + m_3 - m_4 + m_5 + m_6 - m_7 + m_8 + \varepsilon_8
\end{aligned}
$$

$$
\begin{aligned}
\to \quad \hat{m}_8 &= \frac{1}{8}\sum_{i=1}^{8} y_i \\
&= m_8 + \frac{\varepsilon_1 + \varepsilon_2 + \varepsilon_3 + \varepsilon_4 + \varepsilon_5 + \varepsilon_6 + \varepsilon_7 + \varepsilon_8}{8} \\
&\sim \mathcal{N}(m_8, \sigma^2/8) \quad \text{(idem for all } m_j,\ j \leq 7)
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➠ **8 observations only, against 64 with method a!**

Here, selection of a good design = combinatorial problem

$y_k = \sum_{i=1}^{8} \mathbf{f}_{k\,i} m_i + \varepsilon_k = \mathbf{f}_k^\top \mathbf{m} + \varepsilon_k$,

(e.g., in Method b $\mathbf{f}_2 = [1\ 1\ 1\ -1\ -1\ -1\ -1\ 1]^\top$)

$\mathbf{y} = \mathbf{F}\mathbf{m} + \varepsilon$ with

method a: $\mathbf{F}_a = \mathbf{I}_8$

method b: $\mathbf{F}_b = 8 \times 8$ Hadamard matrix, $\mathbf{F}_b^\top \mathbf{F}_b = 8\,\mathbf{I}_8$

(= fractional factorial design with 2 levels)

$$\text{LS estimator } \hat{\mathbf{m}} = \arg\min_{\mathbf{m}} \sum_{k=1}^{n} [y_k - \mathbf{f}_k^\top \mathbf{m}]^2$$

$$= \left(\sum_{k=1}^{n} \mathbf{f}_k \mathbf{f}_k^\top \right)^{-1} \sum_{k=1}^{n} y_k \mathbf{f}_k = (\mathbf{F}^\top \mathbf{F})^{-1} \mathbf{F}^\top \mathbf{y}$$

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$\Longrightarrow$ Choose the $\mathbf{f}_k$'s such that $\mathbf{M}_n = \frac{1}{n} \sum_{k=1}^{n} \mathbf{f}_k \mathbf{f}_k^\top = \frac{1}{n} \mathbf{F}^\top \mathbf{F}$ is nonsingular

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$\mathrm{E}\{\hat{\mathbf{m}}\} = \mathbf{m}$ (no bias)

$\mathrm{E}\{(\hat{\mathbf{m}} - \mathbf{m})(\hat{\mathbf{m}} - \mathbf{m})^\top\} = \frac{\sigma^2}{n} \mathbf{M}_n^{-1}$

$\Longrightarrow$ **minimize a scalar function of $\mathbf{M}_n^{-1}$**

In this particular situation: combinatorial problem (since $\mathbf{f}_{k\,i} \in \{-1, 0, 1\}$) [Fisher 1925 . . .]

More generally, when the design variables (*inputs*) are real numbers, optimum design for parameter estimation is obtained by optimization of a scalar function of the (asymptotic) covariance matrix of the estimator

Ex2: [D'Argenio 1981]: two-compartment model in pharmacokinetics
A product x is injected in blood ($\rightarrow$ input $u(t)$),
$x_C(t)$ (product in blood) moves to another tissue $\rightarrow x_P(t)$

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$\rightarrow$ Linear differential equations:

$$\left\{ \begin{array}{rcl} \frac{dx_C(t)}{dt} & = & (-K_{EL} - K_{CP})x_C(t) + K_{PC}x_P(t) + u(t) \\ \frac{dx_P(t)}{dt} & = & K_{CP}x_C(t) - K_{PC}x_P(t) \end{array} \right.$$

we observe the concentration of x in blood: $y(t) = x_C(t)/V + \varepsilon(t)$,
the errors $\epsilon(t_i)$'s are i.i.d. $\mathcal{N}(0, \sigma^2)$, $\sigma = 0.2\mu$g/ml

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There are 4 unknown parameters $\theta = (K_{CP}, K_{PC}, K_{EL}, V)$
The profile of the input $u(t)$ is given (fast infusion 75 mg/min for 1 min, then 1.45 mg/min)

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☞ **simulated experiments** with «true» parameter values

$$\bar{\theta} = (0.066\,\text{min}^{-1},\ 0.038\,\text{min}^{-1},\ 0.0242\,\text{min}^{-1},\ 30\,\text{l})$$

Experimental variables = sampling times t_i, $1 \leq t_i \leq 720$ min

- «conventional» design :

$$\mathbf{t} = (5, 10, 30, 60, 120, 180, 360, 720) \text{ (in min)}$$

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- «optimal» design (for $\bar{\theta}$) :

$$\mathbf{t} = (1, 1, 10, 10, 74, 74, 720, 720) \text{ (in min)}$$

(assumes that independent measurements at the same time are possible)

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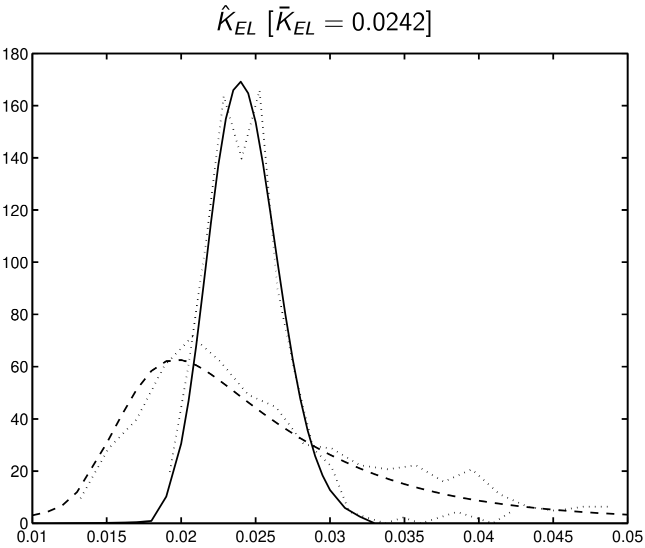
(assumes that independent measurements at the same time are possible)
→ 400 simulations
→ 400 sets of 8 observations each, for each design
→ 400 parameter estimates (LS) for each design . . .
➔ histograms of $\hat{\theta}_i$
(and approximated marginals [Pázman & P 1996])

➠ «optimal» design gives more precise estimation



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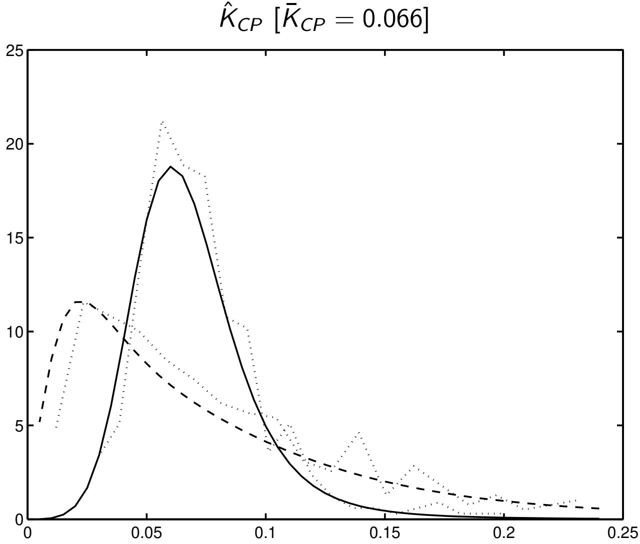

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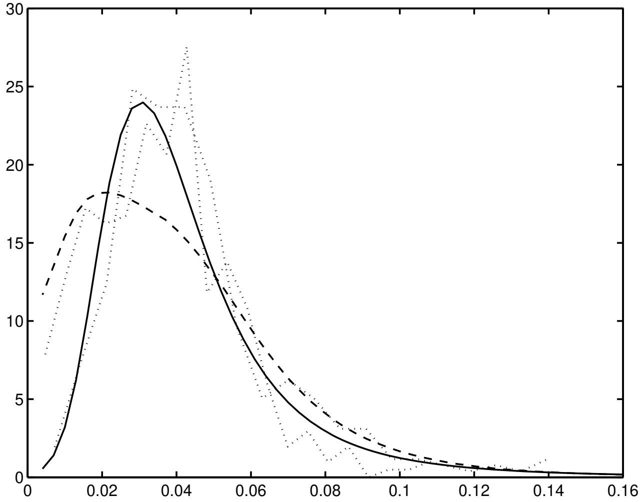
$\hat{K}_{PC}$ [$\bar{K}_{PC} = 0.038$]



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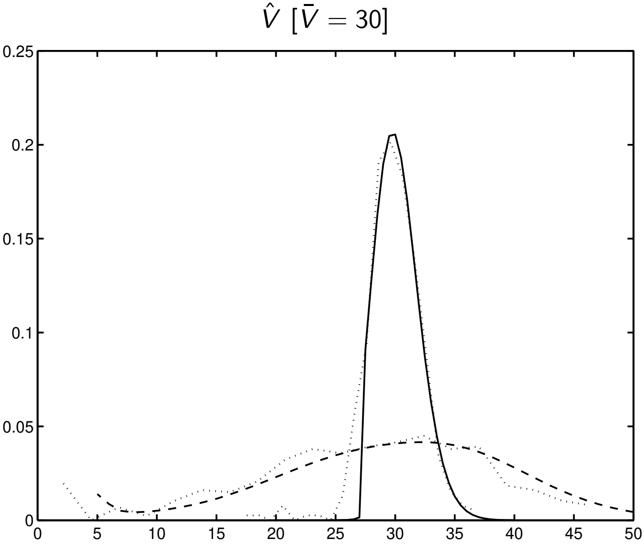

B/ Model discrimination

Ex3: [Box & Hill 1967] Chemical reaction $A \to B$
2 design variables: $\mathbf{x} = (\text{time } t, \text{ temperature } T)$
reaction of 1st, 2nd, 3rd ou 4th order?
$\to$ 4 model structures are candidate:

$$\begin{aligned}
\eta^{(1)}(\mathbf{x}, \theta_1) &= \exp[-\theta_{11} t \exp(-\theta_{12}/T)] \\
\eta^{(2)}(\mathbf{x}, \theta_2) &= \frac{1}{1 + \theta_{21} t \exp(-\theta_{22}/T)} \\
\eta^{(3)}(\mathbf{x}, \theta_3) &= \frac{1}{[1 + 2\theta_{31} t \exp(-\theta_{32}/T)]^{1/2}} \\
\eta^{(4)}(\mathbf{x}, \theta_4) &= \frac{1}{[1 + 3\theta_{41} t \exp(-\theta_{42}/T)]^{1/3}}
\end{aligned}$$

Simulated experiment

Observations with 2nd structure («true»): $y(\mathbf{x}_j) = \eta^{(2)}(\mathbf{x}_j, \bar{\theta}_2) + \varepsilon_j$, with

➤ $\bar{\theta}_2 = (400, 5000)^\top$ the «true» value (unknown) of parameters in model 2

➤ (ϵ_j) i.i.d. $\mathcal{N}(0, \sigma^2)$, $\sigma = 0.05$

Admissible experimental domain: $0 \leq t \leq 150$, $450 \leq T \leq 600$

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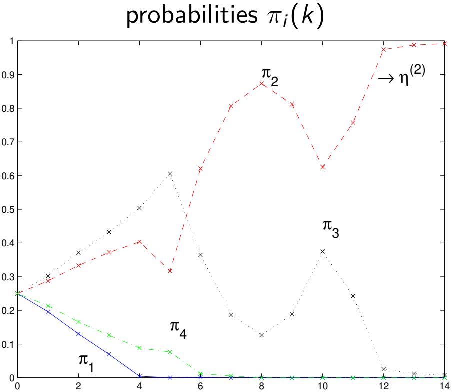
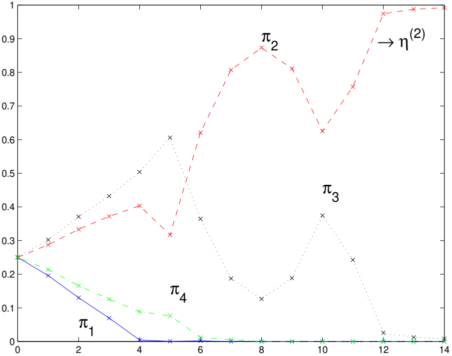
Sequential design: after the observation of $y(\mathbf{x}_j)$, $j = 1, \ldots, k$,

- estimate $\hat{\theta}_i^k$ (LS) for $i = 1, 2, 3, 4$
- compute posterior probability $\pi_i(k)$ that model i is correct for $i = 1, 2, 3, 4$

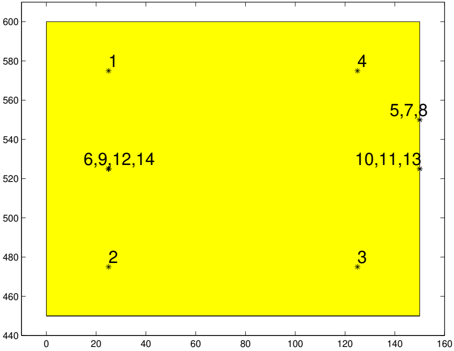
Initialization: $\pi_i(0) = 1/4$, $i = 1, \ldots, 4$ and $\mathbf{x}_1, \ldots, \mathbf{x}_4$ are given


probabilities $\pi_i(k)$
π_1
π_2
π_3
π_4
$\rightarrow \eta^{(2)}$
0
0.1
0.2
0.3
0.4
0.5
0.6
0.7
0.8
0.9
1
0
2
4
6
8
10
12
14

probabilities $\pi_i(k)$



design points $\mathbf{x}_k$



Design for discrimination is not considered in the following

A simple sequential method for discriminating between two structures $\eta^{(1)}(\mathbf{x}, \theta_1)$, $\eta^{(2)}(\mathbf{x}, \theta_2)$ [Atkinson & Fedorov 1975]

- After observation of $y(\mathbf{x}_1), \ldots, y(\mathbf{x}_k)$ estimate $\hat{\theta}_1^k$ and $\hat{\theta}_2^k$ for both models
- place next point $\mathbf{x}_{k+1}$ where $[\eta^{(1)}(\mathbf{x}, \hat{\theta}_1^k) - \eta^{(2)}(\mathbf{x}, \hat{\theta}_2^k)]^2$ is maximum
- $k \rightarrow k+1$, repeat

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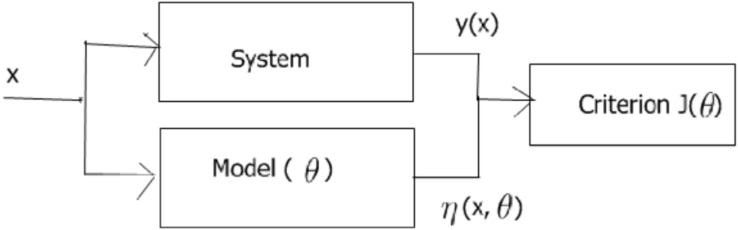
- $k \rightarrow k + 1$, repeat

If more than two models: estimate $\hat{\theta}_i^k$ for all of them, place next point using the two models with best and second best fitting
(see [Atkinson & Cox 1974; Hill 1978] for surveys)

2 DoE based on asymptotic normality

A/ Regression models

$y_i = y(x_i) = \eta(x_i, \theta) + \varepsilon_i$



- System: physical experimental device, experimental conditions x_i, $i = 1, 2, \ldots, n$
- Model(θ): mathematical equations, parameters $\theta = (\theta_1, \ldots, \theta_p)^\top$ (response $\eta(x, \theta)$ known explicitly or result of simulation of ODEs or PDEs)
- Criterion: similarity between $y_i = y(x_i)$ and $\eta(x_i, \theta)$, $i = 1, 2, \ldots, n$, e.g., $J(\theta) = \frac{1}{n} \sum_{i=1}^{n} [y_i - \eta(x_i, \theta)]^2$ (LS)

Remarks:

- Model(θ) also provides derivatives $\partial\eta(x,\theta)/\partial\theta = (\partial\eta(x,\theta)/\partial\theta_1, \ldots, \partial\eta(x,\theta)/\partial\theta_p)^\top$
  — plus higher-order derivatives if necessary—
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- Criterion: other criteria than LS can be used, e.g., $J(\theta) = \frac{1}{n}\sum_{i=1}^{n} |y_i - \eta(x_i,\theta)|$ ($\rightarrow$ robust estimation), including Maximum-Likelihood (ML) estimation in more general settings ($J(\theta) = \frac{1}{n}\sum_{i=1}^{n} \log\pi(y_i|\theta) \rightarrow$ max!)

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Most of the following can be found in [P & Pázman: Design of Experiments in Nonlinear Models, Springer, 2013]

B/ LS estimation

$$\hat{\theta}^n = \arg\min_\theta \frac{1}{n} \sum_{i=1}^{n} [y_i - \eta(x_i, \theta)]^2$$

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Linear model: $\eta(x,\theta) = \mathbf{f}^\top(x)\theta \rightarrow \boxed{\hat{\theta}^n = (\mathbf{F}^\top\mathbf{F})^{-1}\mathbf{F}^\top\mathbf{y}}$,
with $\mathbf{y} = (y_1,\ldots,y_n)^\top$ and $\mathbf{F}^\top = (\mathbf{f}(x_1),\ldots,\mathbf{f}(x_n))^\top$

$\Longrightarrow$ choose the x_i such that $\mathbf{M}_n = \frac{1}{n}\mathbf{F}^\top\mathbf{F}$ has full rank
($\mathbf{M}_n$ = normalized information matrix)

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Since $y_i = \mathbf{f}^\top(x_i)\bar{\theta} + \varepsilon_i$ for some $\bar{\theta}$ and $\mathrm{E}\{\varepsilon_i\} = 0$ for all i, $\mathrm{E}\{\mathbf{y}\} = \mathbf{F}\bar{\theta}$
and $\mathrm{E}\{\hat{\theta}^n\} = \bar{\theta}$
Also, $\mathrm{Var}(\hat{\theta}^n) = \mathrm{E}\{(\hat{\theta}^n - \bar{\theta})(\hat{\theta}^n - \bar{\theta})^\top\} = \sigma^2(\mathbf{F}^\top\mathbf{F})^{-1} = \frac{\sigma^2}{n}\mathbf{M}_n^{-1}$ when the ε_i are i.i.d. with finite variance σ^2
$\Longrightarrow$ choose the x_i to minimize a scalar function of $\mathbf{M}_n^{-1}$
(see Example 1: weighing with a two-pan balance)

Nonlinear model: $\eta(x, \theta)$
Under «standard» assumptions ($\theta \in \Theta$ compact, $\eta(x, \theta)$ continuous in θ for all $x \ldots$) and for a suitable sequence (x_i)

$\boxed{\hat{\theta}^n \stackrel{\text{a.s.}}{\to} \bar{\theta} \text{ as } n \to \infty}$ (strong consistency)

Nonlinear model: $\eta(x,\theta)$

Under «standard» assumptions ($\theta \in \Theta$ compact, $\eta(x,\theta)$ continuous in θ for all $x \ldots$) and for a suitable sequence (x_i)

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$\Longrightarrow$ choose the x_i (design) to minimize a scalar function of $\mathbf{M}^{-1}$,
or maximize a function $\Phi(\mathbf{M})$

= **classical approach for DoE**
(see Example 2 with a two-compartment model)

Remarks:

- Weighted LS: suppose heteroscedastic errors
  $\mathrm{var}\{\varepsilon_i\} = \mathrm{E}\{\varepsilon_i^2\} = \mathrm{E}\{\varepsilon^2(x_i)\} = \sigma^2(x_i)$

Weighted LS estimator $\hat{\theta}^n_{WLS}$ minimizes $J_{WLS}(\theta) = \frac{1}{n}\sum_{i=1}^n w(x_i)\,[y_i - \eta(x_i,\theta)]^2$

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  Strong consistency and asymptotic normality $\sqrt{n}(\hat{\theta}^n_{WLS} - \bar{\theta}) \xrightarrow{\mathrm{d}} \mathcal{N}(\mathbf{0}, \mathbf{C})$ as $n \to \infty$, where
  $\mathbf{C} = \mathbf{M}_a^{-1}\mathbf{M}_b\mathbf{M}_a^{-1}$ and
  $\mathbf{M}_a = \lim_{n\to\infty} \frac{1}{n}\sum_{i=1}^n w(x_i)\, \frac{\partial\eta(x_i,\theta)}{\partial\theta}\Big|_{\bar{\theta}} \frac{\partial\eta(x_i,\theta)}{\partial\theta^\top}\Big|_{\bar{\theta}}$
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  ➠ $\mathbf{C} \succeq \mathbf{M}^{-1}$
  $\mathbf{M} = \lim_{n\to\infty} \frac{1}{n}\sum_{i=1}^n \frac{1}{\sigma^2(x_i)}\, \frac{\partial\eta(x_i,\theta)}{\partial\theta}\Big|_{\bar{\theta}} \frac{\partial\eta(x_i,\theta)}{\partial\theta^\top}\Big|_{\bar{\theta}}$

  ➠ $\mathbf{C} = \mathbf{M}^{-1}$ when $w(x) \propto \sigma^{-2}(x)$

$\Longrightarrow$ choose the best estimator, then the best design

Remarks (continued):

- One may also consider the case $\text{var}\{\varepsilon_i\} = \sigma^2(x_i, \theta)$ (errors with parameterized variance)

  ➠ Use two-stage LS: 1/ use $w(x) \equiv 1 \rightarrow \hat{\theta}^n_{(1)}$; 2/ use $w(x) = \sigma^{-2}(x, \hat{\theta}^n_{(1)})$
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- Similar asymptotic results for ML estimation $\sqrt{n}(\hat{\theta}^n_{ML} - \bar{\theta}) \xrightarrow{\text{d}} \mathcal{N}(\mathbf{0}, \sigma^2 \, \mathbf{M}_F^{-1})$ as $n \rightarrow \infty$, with $\mathbf{M}_F$ = Fisher information matrix

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- Model(θ) = linear ODE, experimental design = system input $u(t)$
  ➠ ($\approx$ simple) analytic expression for $\mathbf{M}$
  ➠ optimal input design $\Leftrightarrow$ optimal control problem (frequency domain $\rightarrow$ optimal combination of sinusoidal signals) [Goodwin & Payne 1977; Zarrop 1979; Ljung 1987; Walter & P 1994, 1997]

C/ Design based on the information matrix

Maximize $\Phi(\mathbf{M})$, but which $\Phi(\cdot)$?

➠ There are many possibilities!

LS estimation in linear regression with i.i.d. errors $\mathcal{N}(0, \sigma^2)$

$$\mathcal{R}(\hat{\theta}^n, \alpha) = \{\theta \in \mathbb{R}^p : (\theta - \hat{\theta}^n)^\top \mathbf{M}_n(\theta - \hat{\theta}^n) \leq \frac{\sigma^2}{n} \chi^2_p(1-\alpha)\}$$

$=$ confidence region (ellipsoid) at level α: $\text{Prob}\{\bar{\theta} \in \mathcal{R}(\hat{\theta}^n, \alpha)\} = \alpha$

(**asymptotically true** in nonlinear situations — e.g., nonlinear regression)

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➠ Nonlinear model $\Longrightarrow$ $\mathbf{M} = \mathbf{M}(\theta)$ depends on the θ where $\eta(x,\theta)$ is linearized:

for the moment use a nominal value θ^0

➠ **locally optimum design**

A few choices for $\Phi(\cdot)$

- *A*-optimality: maximize $-\mathrm{trace}[\mathbf{M}^{-1}] \Leftrightarrow$ maximize $1/\mathrm{trace}[\mathbf{M}^{-1}]$
$\Leftrightarrow$ minimize the sum of lengths^2 of axes of (asymptotic) confidence ellipsoids $\mathcal{R}(\hat{\theta}^n, \alpha)$

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- *D*-optimality: maximize $\log\det\mathbf{M}$
  $\Leftrightarrow$ minimize volume of $\mathcal{R}(\hat{\theta}^n, \alpha)$ (proportional to $1/\sqrt{\det\mathbf{M}}$)
  Very much used:
  - a *D*-optimum design is invariant by reparametrization

$$\det\mathbf{M}'(\beta(\theta)) = \det\mathbf{M}(\theta)\det{}^{-2}\left(\frac{\partial\beta}{\partial\theta^\top}\right)$$

  - often leads to repeat the same experimental conditions (replications)
    (remember Ex2: $\dim(\theta) = 4 \rightarrow 4$ different sampling times, several observations at each)

- D_s-optimality: only $s < p$ parameters of interest (and $p - s$ «nuisance» parameters) $\rightarrow \theta^\top = (\theta_1^\top, \theta_2^\top)$, with θ_1 the vector of s parameters of interest

$$\mathbf{M}(\theta) = \begin{pmatrix} \mathbf{M}_{11} & \mathbf{M}_{12} \\ \mathbf{M}_{21} & \mathbf{M}_{22} \end{pmatrix}, \ \mathbf{M}^{-1}(\theta) = \begin{pmatrix} \mathbf{A}_{11} & \mathbf{A}_{12} \\ \mathbf{A}_{21} & \mathbf{A}_{22} \end{pmatrix}$$

with

$$\begin{aligned} \mathbf{A}_{11} &= [\mathbf{M}_{11} - \mathbf{M}_{12}\mathbf{M}_{22}^{-1}\mathbf{M}_{21}]^{-1} \\ \mathbf{A}_{12} &= -[\mathbf{M}_{11} - \mathbf{M}_{12}\mathbf{M}_{22}^{-1}\mathbf{M}_{21}]^{-1}\mathbf{M}_{12}\mathbf{M}_{22}^{-1} \\ \mathbf{A}_{21} &= -\mathbf{M}_{22}^{-1}\mathbf{M}_{21}[\mathbf{M}_{11} - \mathbf{M}_{12}\mathbf{M}_{22}^{-1}\mathbf{M}_{21}]^{-1} \\ \mathbf{A}_{22} &= \mathbf{M}_{22}^{-1} + \mathbf{M}_{22}^{-1}\mathbf{M}_{21}[\mathbf{M}_{11} - \mathbf{M}_{12}\mathbf{M}_{22}^{-1}\mathbf{M}_{21}]^{-1}\mathbf{M}_{12}\mathbf{M}_{22}^{-1} \end{aligned}$$

$\rightarrow$ maximize $\Phi_{D_s}[\mathbf{M}] = \det[\mathbf{M}_{11} - \mathbf{M}_{12}\mathbf{M}_{22}^{-1}\mathbf{M}_{21}]$

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➠ Useful for **model discrimination**:
if $\eta^{(2)}(x, \theta_2) = \eta^{(1)}(x, \theta_1) + \delta(x, \theta_{2\setminus 1})$ (nested models),
estimate $\theta_{2\setminus 1}$ in $\eta^{(2)}$ to decide whether $\eta^{(1)}$ or $\eta^{(2)}$ is more appropriate, see [Atkinson & Cox 1974]

3 Construction of (locally) optimal designs

A/ Exact design

n observations at $X_n = (x_1, \ldots, x_n)$ in a regression model (for simplicity)
Each design point x_i can be anything, e.g. a point in a subset $\mathscr{X}$ of $\mathbb{R}^d$

☞ maximize $\Phi(\mathbf{M}_n)$ w.r.t. X_n with $\mathbf{M}_n = \mathbf{M}(X_n, \theta^0) = \frac{1}{n} \sum_{i=1}^{n} \frac{\partial \eta(x_i, \theta)}{\partial \theta}\Big|_{\theta^0} \frac{\partial \eta(x_i, \theta)}{\partial \theta^\top}\Big|_{\theta^0}$

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- If problem dimension $n \times d$ not too large → standard algorithm (but with constraints, local optimas. . .)
- Otherwise, use an algorithm that takes the particular form of the problem into account

Exchange methods: at iteration k, exchange **one** *support point* x_j with a better one x^* in $\mathscr{X}$ (design space) — better for $\Phi(\cdot)$

$$X_n^k = (x_1, \ldots, \boxed{x_j \updownarrow x^*}, \ldots, x_n)$$

- [Fedorov 1972]: consider all n possible exchanges successively, each time starting from X_n^k, retain the «best» one among these $n \rightarrow X_n^{k+1}$

$$X_n^k = \begin{pmatrix} x_1 & ,\ldots, & x_j & ,\ldots, & x_n \\ \updownarrow & & \updownarrow & & \updownarrow \\ x_1^* & & x_j^* & & x_n^* \end{pmatrix}$$

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One iteration $\to$ n optimizations of dimension d followed by ranking n criterion values

- [Mitchell, 1974]: DETMAX algorithm
  If one additional observation were allowed $\rightarrow$ optimal choice

$$X_n^{k+} = (x_1, \ldots, x_j, \ldots, x_n, x_{n+1}^*)$$

Then, remove one support point to return to a n-points design:

➔ consider all $n+1$ possible cancellations,
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➔ consider all $n+1$ possible cancellations,
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➔ globally, exchange some x_j with x_{n+1}^*
[= excursion of length 1, longer excursions are possible. . .]
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- Other methods:
  - Branch and bound: guaranteed convergence, but complicated [Welch 1982]
  - Rounding an optimal design measure (support points x_i and associated weights w_i^*, $i = 1, \ldots, m$, presented next in B/):
    choose n integers r_i (r_i= nb. of replications of observations at x_i) such that $\sum_{i=1}^m r_i = n$ and $r_i/n \approx w_i^*$
    (e.g., maximize $\min_{i=1,\ldots,m} r_i/w_i^*$ = Adams apportionment, see [Pukelsheim & Reider 1992])

B/ Design measures: approximate design theory

[Chernoff 1953; Kiefer & Wolfowitz 1960, Fedorov 1972; Silvey 1980, Pázman 1986, Pukelsheim 1993, Fedorov & Leonov 2014...]
(nonlinear) regression, n observations at $X_n = (x_1, \ldots, x_n)$ with i.i.d. errors:

$$\mathbf{M}(X_n, \theta^0) = \frac{1}{n} \sum_{i=1}^{n} \frac{\partial \eta(x_i, \theta)}{\partial \theta}\Big|_{\theta^0} \frac{\partial \eta(x_i, \theta)}{\partial \theta^\top}\Big|_{\theta^0}$$

(the additive form is essential — related to the independence of observations)

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(the additive form is essential — related to the independence of observations)

Suppose that several x_i's coincide (replications): only $m < n$ different x_i's

$$\mathbf{M}(X_n, \theta^0) = \sum_{i=1}^{m} \frac{r_i}{n} \frac{\partial \eta(x_i, \theta)}{\partial \theta}\Big|_{\theta^0} \frac{\partial \eta(x_i, \theta)}{\partial \theta^\top}\Big|_{\theta^0}$$

$\frac{r_i}{n}$ = proportion of observations collected at x_i

= «percentage of experimental effort» at x_i

= weight w_i of support point x_i

$$\mathbf{M}(X_n,\theta^0) = \sum_{i=1}^{m} w_i \frac{\partial\eta(x_i,\theta)}{\partial\theta}\Big|_{\theta^0} \frac{\partial\eta(x_i,\theta)}{\partial\theta^\top}\Big|_{\theta^0}$$

➔ design $X_n \Leftrightarrow \left\{ \begin{array}{ccc} x_1 & \cdots & x_m \\ w_1 & \cdots & w_m \end{array} \right\}$ with $\sum_{i=1}^m w_i = 1$

➔ normalized discrete distribution on the x_i,

with $\boxed{\text{constraints } r_i/n = w_i}$

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➠ Release the constraints: only enforce $w_i \geq 0$ with $\sum_{i=1}^m w_i = 1$

➔ ξ = discrete probability measure on $\mathscr{X}$ (= design space)
support points x_i and associated weights w_i
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More general expression: ξ = any probability measure on $\mathscr{X}$

$$\mathbf{M}(\xi) = \mathbf{M}(\xi,\theta^0) = \int_{\mathscr{X}} \frac{\partial\eta(x,\theta)}{\partial\theta}\Big|_{\theta^0} \frac{\partial\eta(x,\theta)}{\partial\theta^\top}\Big|_{\theta^0} \xi(\mathrm{d}x)\,,\ \int_{\mathscr{X}} \xi(\mathrm{d}x) = 1$$

$\mathbf{M}(\xi) \in$ convex closure of $\mathcal{M}$= set of rank 1 matrices

$$\mathbf{M}(\delta_x) = \frac{\partial \eta(x,\theta)}{\partial \theta}\Big|_{\theta^0} \frac{\partial \eta(x,\theta)}{\partial \theta^\top}\Big|_{\theta^0}$$

$\mathbf{M}(\xi)$ is symmetric $p \times p$: $\in$ q-dimensional space, $q = \frac{p(p+1)}{2}$

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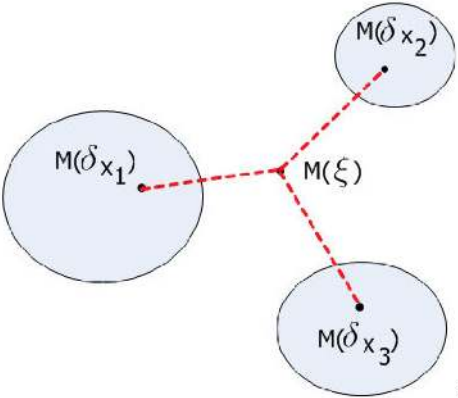

$\xi = w_1\delta_{x_1} + w_2\delta_{x_2} + w_3\delta_{x_3}$
(3 points are enough for $q = 2$)

Caratheodory Theorem:
$\mathbf{M}(\xi)$ can be written as the linear combination of at most $q+1$ elements of $\mathcal{M}$:

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Why design measures are interesting?
How does it simplify the optimization problem?

C/ Optimal design measures

➠ Maximize $\Phi(\cdot)$ concave w.r.t. $\mathbf{M}(\xi)$ in a convex set

Ex: D-optimality: $\forall\ \mathbf{M}_1 \succ \mathbf{O}$, $\mathbf{M}_2 \succeq \mathbf{O}$, with $\mathbf{M}_2 \not\propto \mathbf{M}_2$, $\forall \alpha$, $0 < \alpha < 1$,

$$\log\det[(1-\alpha)\mathbf{M}_1 + \alpha\mathbf{M}_2] > (1-\alpha)\log\det\mathbf{M}_1 + \alpha\log\det\mathbf{M}_2$$

$\Rightarrow \log\det[\cdot]$ is (strictly) concave

convex set + concave criterion $\Rightarrow$ one unique optimum!

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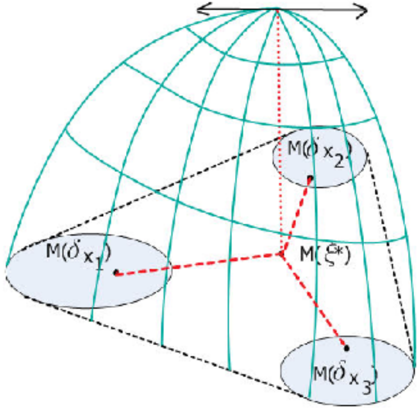

ξ^* is optimal $\Leftrightarrow$ directional derivative ≤ 0 in all directions

$\Longrightarrow$ "Equivalence Theorem" [Kiefer & Wolfowitz 1960]

Ξ = set of probability measures on $\mathscr{X}$, $\Phi(\cdot)$ concave, $\phi(\xi) = \Phi[\mathbf{M}(\xi)]$

$F_\phi(\xi;\nu) = \lim_{\alpha\to 0^+} \frac{\phi[(1-\alpha)\xi+\alpha\nu]-\phi(\xi)}{\alpha}$
= directional derivative of $\phi(\cdot)$ at ξ in direction ν

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Ex: D-optimal design

- ξ_D^* maximizes $\log\det[\mathbf{M}(\xi)]$ w.r.t. $\xi \in \Xi$
- $\Leftrightarrow \max_{x\in\mathscr{X}} d(\xi_D^*, x) \leq p$
- $\Leftrightarrow \xi_D^*$ minimizes $\max_{x\in\mathscr{X}} d(\xi, x)$ w.r.t. $\xi \in \Xi$

where $d(\xi, x) = \frac{\partial\eta(x,\theta)}{\partial\theta^\top}\Big|_{\theta^0} \mathbf{M}^{-1}(\xi) \frac{\partial\eta(x,\theta)}{\partial\theta}\Big|_{\theta^0}$

Moreover, $d(\xi_D^*, x_i) = p = \dim(\theta)$ for any x_i = support point of ξ_D^*

Ex: $\eta(x,\theta) = \theta_1 \exp(-\theta_2 x)$ ($p = 2$) i.i.d. errors, $\mathscr{X} = \mathbb{R}^+$
$[\theta_2^0 = 2]$

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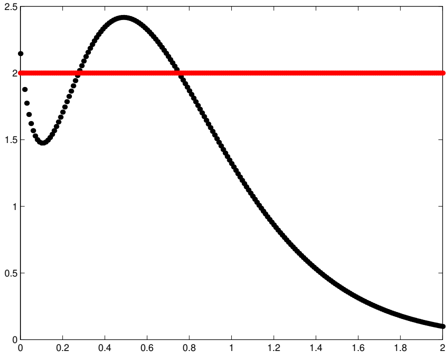
$$\xi_2 = \left\{ \begin{array}{cc} 0.01 & 0.75 \\ 1/2 & 1/2 \end{array} \right\}$$



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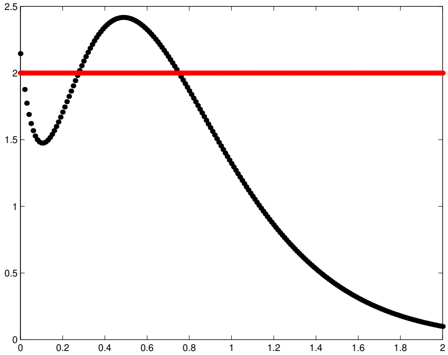
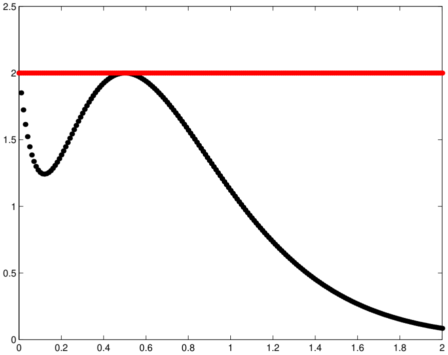
$$\xi_2 = \left\{ \begin{array}{cc} 0.01 & 0.75 \\ 1/2 & 1/2 \end{array} \right\} \qquad \xi_D^* = \left\{ \begin{array}{cc} 0 & 1/\theta_2 = 0.5 \\ 1/2 & 1/2 \end{array} \right\}$$





KW Eq. Th. relates optimality in θ space to optimality in y space (i.i.d. errors)

$$n\,\text{var}[\eta(x,\hat{\theta}^n)] \to \sigma^2 \, \frac{\partial\eta(x,\theta)}{\partial\theta^\top}\Big|_{\bar{\theta}} \mathbf{M}^{-1}(\xi,\bar{\theta}) \frac{\partial\eta(x,\theta)}{\partial\theta}\Big|_{\bar{\theta}} = \sigma^2 \, d(\xi,x)\Big|_{\bar{\theta}},\ n\to\infty$$

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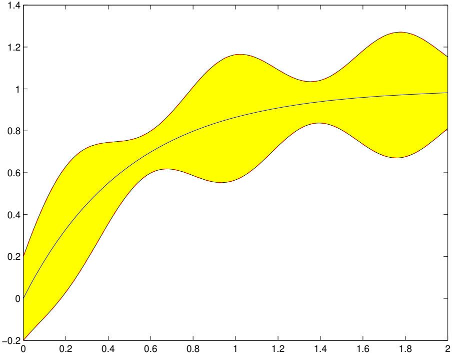
$\eta(x,\bar{\theta})$, $\eta(x,\bar{\theta}) \pm$ 2 st.d.



$\to$ put next observation where $d(\xi,x)$ is large

Remark:

Eq. Th. $=$ stationarity condition $=$ NS condition for optimality

$\neq$ duality property!

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Dual problem to D-optimum design:

Define $\mathcal{S} = \left\{ \frac{\partial \eta(x,\theta)}{\partial \theta}\Big|_{\theta^0} ,\ x \in \mathscr{X} \right\}$ [$\mathcal{S} \cup -\mathcal{S} =$ Elfving's set]

$\mathcal{E}^* =$ minimum-volume ellipsoid centered at $\mathbf{0}$ that contains $\mathcal{S}$

Lagrangian theory $\Rightarrow \mathcal{E}^* = \{\mathbf{z} \in \mathbb{R}^p : \mathbf{z}^\top \mathbf{M}_F^{-1}(\xi_D^*)\mathbf{z} \leq p\}$ where ξ_D^* is D-optimum
support points of $\xi_D^* =$ contact between $\mathcal{E}^*$ and $\mathcal{S}$

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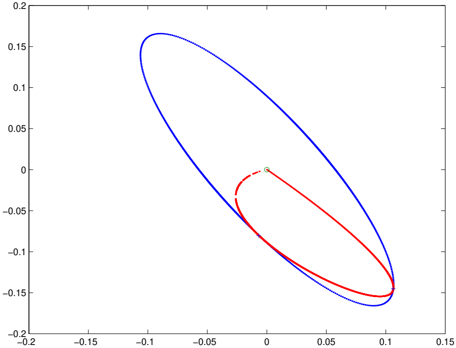
In general, few contact points $\rightarrow$ repeat observations at the same place (see [Yang 2010, Dette & Melas 2011])

There exist dual problems for other criteria $\Phi(\cdot)$
($=$ one of the main topics in [Pukelsheim 1993])

Ex: $\eta(x,\theta) = \frac{\theta_1}{\theta_1-\theta_2}[\exp(-\theta_2 x) - \exp(-\theta_1 x)]$
$\theta = (1,5)$, $\mathscr{X} = \mathbb{R}^+$



$\mathcal{E}^*$ and $\mathcal{S}$

$\Rightarrow$ D optimum design ξ_D^* supported on two points

D/ Construction of an optimal design measure

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Fedorov–Wynn Algorithm: sort of steepest ascent

- 1 : Choose ξ^1 not degenerate ($\det \mathbf{M}(\xi^1) > 0$)
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Step-size α_k?

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➔ monotone convergence

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➠ $\alpha_k > 0$, $\lim_{k\to\infty}\alpha_k = 0$, $\sum_{i=1}^{\infty}\alpha_k = \infty$ [[Wynn 1970] for D-optimal design]

Remarks:

- Consider sequential design, one x_i at a time enters $\mathbf{M}(X)$
$$\mathbf{M}(X_{k+1}) = \frac{k}{k+1}\,\mathbf{M}(X_k) + \frac{1}{k+1}\,\frac{\partial\eta(x_{k+1},\theta)}{\partial\theta}\Big|_{\theta^0}\frac{\partial\eta(x_{k+1},\theta)}{\partial\theta^\top}\Big|_{\theta^0}$$
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- **Guaranteed convergence to the optimum**
- There exist faster methods:
  - remove support points from ξ^k ($\approx$ allow α_k to be < 0) [Atwood 1973; Böhning 1985, 1986]
  - combine with gradient projection (or a second-order method) [Wu 1978]
  - use a multiplicative algorithm [Titterington 1976; Torsney 1983–2009; Yu 2010] [for D or A optimal design, far from the optimum]
  - combine different methods [Yu 2011]
  - Still an active topic. . .

Remarks: Usually, $\mathscr{X}$ = compact subset of $\mathbb{R}^d$ (e.g., the probability simplex for mixture experiments)

$\rightarrow$ discretized into $\mathscr{X}_\ell$ with ℓ elements (a grid — or better, a low-discrepancy sequence, see [Niederreiter 1992])

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➠ Combine continuous search for support points in $\mathscr{X}$ with optimization of a design measure with few support points, say $m \ll \ell$

➠ Exploit guaranteed (and fast) convergence of algorithms for m small
+ use Eq. Th. to check optimality [Yang *et al.*, 2013, P & Zhigljavsky, 2014]

Ex: *D*-optimal design for

$$\eta(x,\theta) = \theta_0 + \theta_1 \exp(-\theta_2 x_1) + \frac{\theta_3}{\theta_3 - \theta_4} [\exp(-\theta_4 x_2) - \exp(-\theta_3 x_2)]$$

with $x = (x_1, x_2) \in \mathscr{X} = [0,2] \times [0,10]$ (and $p = 5$, $\theta_2^0 = 2$, $\theta_3^0 = 0.7$, $\theta_4^0 = 0.2$)

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and

$$\beta_0^{(2)} + \beta_1^{(2)} [\exp(-\beta_2^{(2)} x_2) - \exp(-\beta_1^{(2)} x_2)]/(\beta_1^{(2)} - \beta_2^{(2)})$$

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Use the Equivalence Th. to construct ξ_D^* (with arbitrary precision — Maple)
[weight 1/9 at (0, 0.46268527927, 2) $\otimes$ (0, 1.22947139883, 6.85768905493)]

➡ 7 iterations of the algorithm in [P & Zhigljavsky, 2014] yield ξ such that $\max_{x \in \mathscr{X}} F_\phi(\xi; \delta_x) < 10^{-5}$

What if $\Phi(\cdot)$ not differentiable? (e.g., maximize $\Phi(\mathbf{M}) = \lambda_{\min}(\mathbf{M})$)

$\Phi(\cdot)$ concave, $\mathscr{X}$ discretized into $\mathscr{X}_\ell$, ℓ not too large

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$w_i \geq 0$, $\sum_{i=1}^{\ell} w_i = 1$

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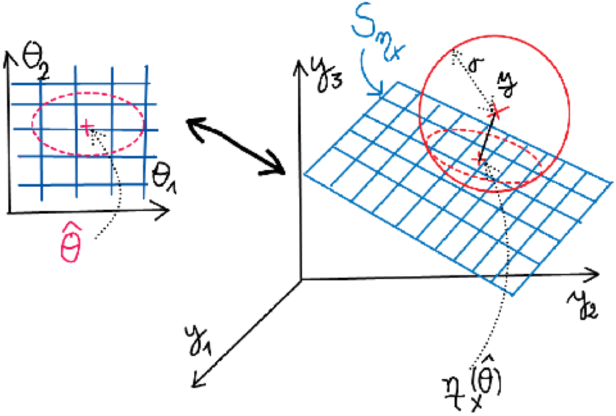
- subgradients ($\leftrightarrow$ directional derivatives)

What if $\Phi(\cdot)$ not differentiable? (e.g., maximize $\Phi(\mathbf{M}) = \lambda_{\min}(\mathbf{M})$)
$\Phi(\cdot)$ concave, $\mathscr{X}$ discretized into $\mathscr{X}_\ell$, ℓ not too large
➔ optimal design $\Longleftrightarrow$ optimal vector of weights $\mathbf{w} \in \mathbb{R}^\ell$
$w_i \geq 0$, $\sum_{i=1}^{\ell} w_i = 1$

- subgradients ($\leftrightarrow$ directional derivatives)
- general method for non-differentiable optimization (cutting plane method [Kelley 1960], level method [Nesterov 2004]), see Chap. 9 of [P & Pázman 2013]

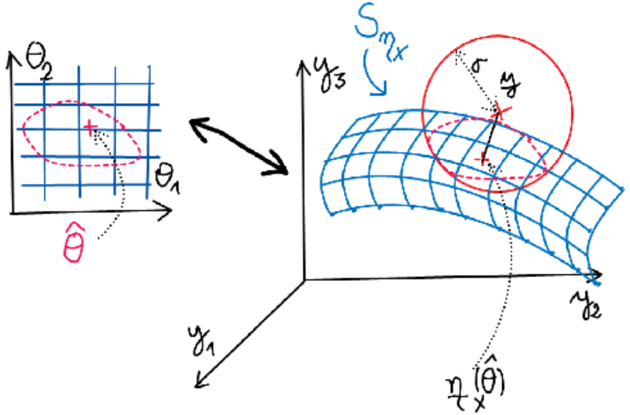
4 Problems with nonlinear models

Linear regression: easy



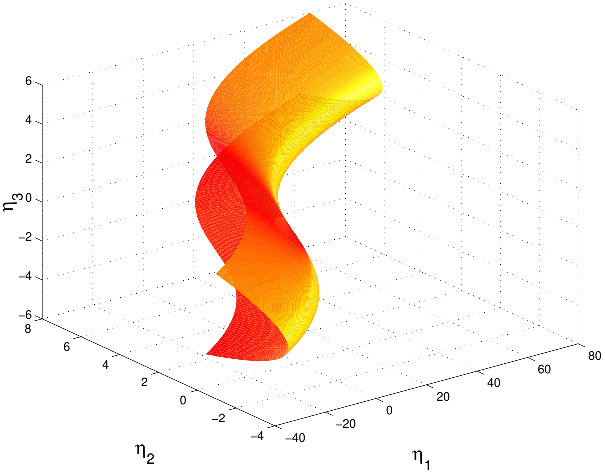
The expectation surface $\mathbb{S}_\eta = \{\eta(\theta) = (\eta(x_1,\theta),\ldots,\eta(x_n,\theta))^\top : \theta \in \mathbb{R}^p\}$ is flat and linearly parameterized

Nonlinear regression: may be a bit tricky



$\mathbb{S}_\eta$ is curved (intrinsic curvature) and nonlinearly parameterized (parametric curvature) [Bates & Watts 1980]

Ex: $\eta(\mathbf{x},\theta) = \theta_1\{\mathbf{x}\}_1 + \theta_1^3(1-\{\mathbf{x}\}_1) + \theta_2\{\mathbf{x}\}_2 + \theta_2^2(1-\{\mathbf{x}\}_2)$
$X = (\mathbf{x}_1,\mathbf{x}_2,\mathbf{x}_3)$, $\mathbf{x}_1 = (0\ 1)$, $\mathbf{x}_2 = (1\ 0)$, $\mathbf{x}_3 = (1\ 1)$, $\theta \in [-3,4]\times[-2,2]$



Two important difficulties:

❶ Asymptotically ($n \to \infty$) — or if σ^2 small enough — all seems fine
(use linear approximations),

but the distribution of $\hat{\theta}^n$ may be far from normal for small n (or for σ^2 large)
➠ small-sample properties

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➠ small-sample properties

❷ Everything is local (depends on θ): if we linearize, where do we linearize? (choice of a nominal value θ^0)

➠ nonlocal optimum design

5 Small-sample properties

A/ A classification of regression models

Suppose that

$$y_i = y(x_i) = \eta(x_i, \bar{\theta}) + \varepsilon_i \text{ with } \mathsf{E}\{\varepsilon_i\} = 0 \text{ and } \mathsf{E}\{\varepsilon_i^2\} = \sigma^2(x_i) \text{ for all } i$$

Divide y_i and $\eta(x_i, \bar{\theta})$ by $\sigma(x_i)$ ➔ one may suppose that $\sigma^2(x) = \sigma^2$ for all x

Denote

$$\mathbf{y} = (y_1, \ldots, y_n)^\top \text{ and } \eta(\theta) = (\eta(x_i, \theta), \ldots, \eta(x_n, \theta))^\top$$

$$\varepsilon = (\varepsilon_1, \ldots, \varepsilon_n)^\top \text{ so that } \mathsf{E}\{\varepsilon\} = \mathbf{0} \text{ and } \mathsf{Var}(\varepsilon) = \sigma^2 \, \mathbf{I}_n$$

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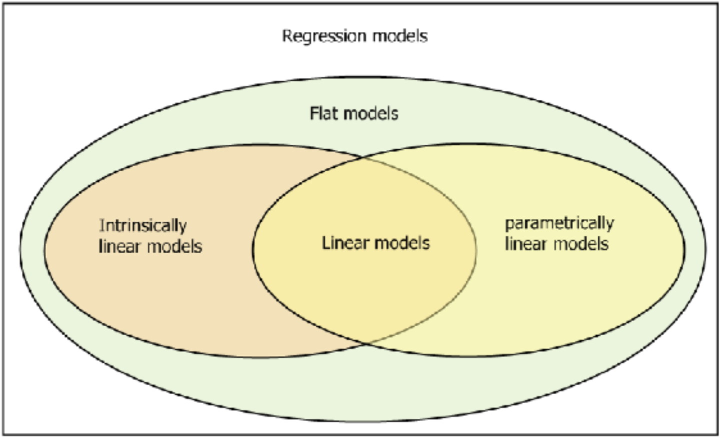
- Expectation surface: $\mathbb{S}_\eta = \{\eta(\theta) : \theta \in \mathbb{R}^p\}$
- Orthogonal projector onto the tangent space to $\mathbb{S}_\eta$ at $\eta(\theta)$:

$$\mathbf{P}_\theta = \frac{1}{n} \frac{\partial \eta(\theta)}{\partial \theta^\top} \mathbf{M}^{-1}(X, \theta) \frac{\partial \eta(\theta)}{\partial \theta} \text{ (a } n \times n \text{ matrix)}$$

(both depend on X)

A classification of regression models [Pázman 1993]



Intrinsically linear models

➤ The expectation surface $\mathbb{S}_\eta = \{\eta(\theta) : \theta \in \mathbb{R}^p\}$ is flat (plane) — intrinsic curvature $\equiv 0$

➤ A reparameterization (continuously differentiable) exists that makes the model linear

➤ $\mathbf{P}_\theta \mathbf{H}_{\cdot ij}(\theta) = \mathbf{H}_{\cdot ij}(\theta)$, where $\mathbf{H}_{\cdot ij}(\theta) = \frac{\partial^2 \eta(\theta)}{\partial \theta_i \partial \theta_j}$

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Observing at p different x_i only (replications) makes the model intrinsically linear

Parametrically linear models

- $\mathbf{M}(X,\theta) = \text{constant}$
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Linear models

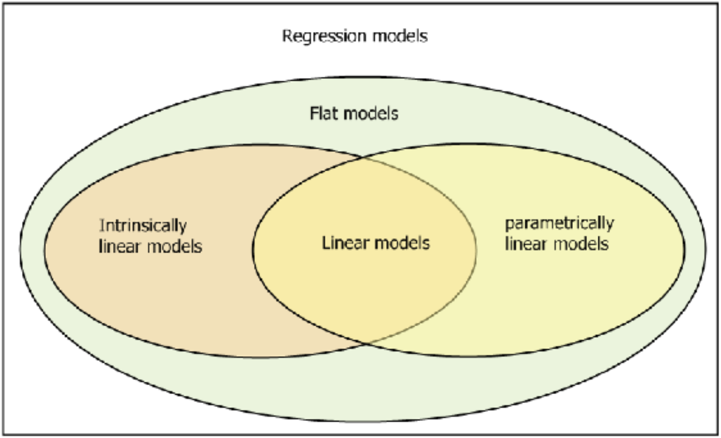
- $\eta(x,\theta) = \mathbf{f}^\top(x)\theta + c(x)$
- the model is intrinsically and parametrically linear

Flat models

- A reparameterization exists that makes the information matrix constant
- Riemannian curvature tensor $\equiv 0$ $R_{hijk}(\theta) = T_{hjik}(\theta) - T_{hkij}(\theta) \equiv 0$ where $T_{hjik}(\theta) = [\mathbf{H}_{hj}^{\cdot}(\theta)]^\top [\mathbf{I}_n - \mathbf{P}_\theta]\mathbf{H}_{ik}^{\cdot}(\theta)$

If all parameters but one appear linearly, then the model is flat

A classification of regression models [Pázman 1993] (bis)



B/ Density of the LS estimator

Suppose $\varepsilon \sim \mathcal{N}(\mathbf{0}, \sigma^2 \mathbf{I}_n)$

Intrinsically linear models (in particular, repetitions at p points):

$\rightarrow$ exact distribution $\boxed{\hat{\theta}^n \sim q(\theta|\bar{\theta}) = \frac{n^{p/2} \det^{1/2} \mathbf{M}(X,\theta)}{(2\pi)^{p/2} \sigma^p} \exp\left\{-\frac{1}{2\sigma^2} \|\eta(\theta) - \eta(\bar{\theta})\|^2\right\}}$

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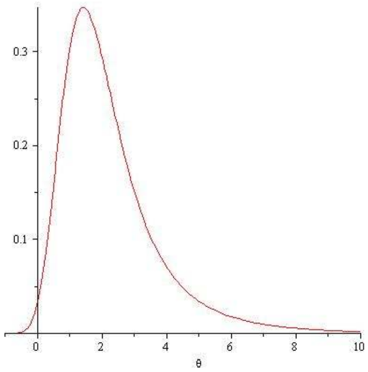
Ex: $\eta(x,\theta) = \exp(-\theta x)$, $\bar{\theta} = 2$, 15 observations at the same $x = 1/2$ ($\sigma^2 = 1$)



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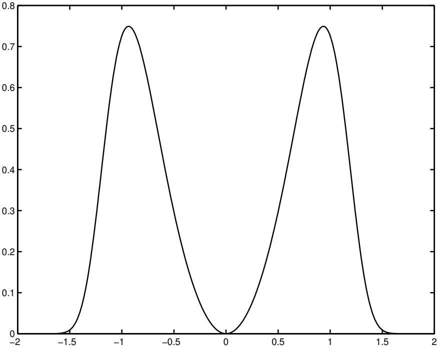
Ex: $\eta(x, \theta) = x\,\theta^3$, $\bar{\theta} = 0$, all observations at the same $x \neq 0$



Flat models: approximate density of $\hat{\theta}^n$

$$q(\theta|\bar{\theta}) = \frac{\det[\mathbf{Q}(\theta,\bar{\theta})]}{(2\pi)^{p/2}\,\sigma^p\, n^{p/2}\, \det^{1/2}\mathbf{M}(X,\theta)} \exp\left\{-\frac{1}{2\sigma^2}\|\mathbf{P}_\theta[\eta(\theta)-\eta(\bar{\theta})]\|^2\right\}$$

where $\{\mathbf{Q}(\theta,\bar{\theta})\}_{ij} = \{n\,\mathbf{M}(X,\theta)\}_{ij} + [\eta(\theta)-\eta(\bar{\theta})]^\top[\mathbf{I}_n - \mathbf{P}_\theta]\mathbf{H}_{:ij}(\theta)$

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Remarks:

- This approximation coincides with the saddle-point approximation of Hougaard (1985)
- Other approximations (more complicated) for models with $R_{hijk}(\theta) \not\equiv 0$ (non-flat)
- An approximation of the density of the penalized LS estimator $\arg\min_{\theta\in\Theta}\left\{\|\mathbf{y}-\eta(\theta)\|^2 + 2w(\theta)\right\}$ (which includes the case of Bayesian estimation) is also available
- We also know the (approximate) marginal densities of the LS estimator $\hat{\theta}^n$ [Pázman & P 1996]

C/ Confidence regions

Suppose $\varepsilon \sim \mathcal{N}(\mathbf{0}, \sigma^2 \mathbf{I}_n)$, define $\mathbf{e}(\theta) = \mathbf{y} - \eta(\theta)$

➔ $\mathbf{e}^\top(\bar{\theta})\, \mathbf{P}_{\bar{\theta}}\, \mathbf{e}(\bar{\theta})/\sigma^2 \sim \chi^2_p$

➔ $\mathbf{e}^\top(\bar{\theta})\, [\mathbf{I}_n - \mathbf{P}_{\bar{\theta}}]\, \mathbf{e}(\bar{\theta})/\sigma^2 \sim \chi^2_{n-p}$

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➠ exact confidence regions at level α

$$\left\{\theta \in \mathbb{R}^p : \mathbf{e}^\top(\theta)\, \mathbf{P}_\theta\, \mathbf{e}(\theta)/\sigma^2 < \chi^2_p[1-\alpha]\right\} \text{ (if } \sigma^2 \text{ known)}$$

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(but they are not of minimum volume, maybe composed of disconnected subsets. . .)

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(but they are not of minimum volume, maybe composed of disconnected subsets. . .)

➠ approximate confidence regions based on likelihood ratio (usually connected):

$$\left\{\theta \in \mathbb{R}^p : \|\mathbf{e}(\theta)\|^2 - \|\mathbf{e}(\hat{\theta})\|^2 < \sigma^2 \chi^2_p[1-\alpha]\right\} \text{ (if } \sigma^2 \text{ known)}$$

$$\left\{\theta \in \mathbb{R}^p : \|\mathbf{e}(\theta)\|^2 / \|\mathbf{e}(\hat{\theta})\|^2 < 1 + \frac{p}{n-p} F_{p,n-p}[1-\alpha]\right\} \text{ (if } \sigma^2 \text{ unknown)}$$

D/ Design based on small-sample properties

3 main ideas (exact design only) based on:

a) (approximate) volume of (approximate) confidence regions (not necessarily of minimum volume) [Hamilton & Watts 1985; Vila 1990; Vila & Gauchi 2007]
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e.g., minimize $\int \|\theta - \bar{\theta}\|^2 q(\theta|\bar{\theta})\, \mathrm{d}\theta$ w.r.t. X (using stochastic approximation, [Pázman & P 1992, Gauchi & Pázman 2006])

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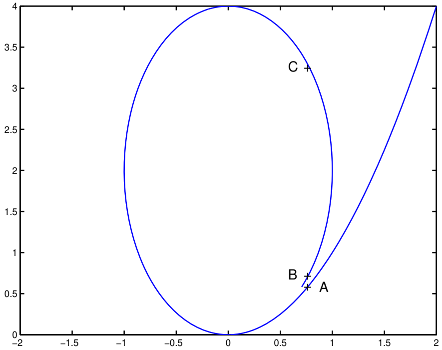
c) higher-order approximation of optimality criteria,
   using $\varphi(\mathbf{y}|X,\bar{\theta}) = \mathcal{N}(\eta(\bar{\theta}), \sigma^2 \mathbf{I}_n)$
   minimize MSE $\int \|\hat{\theta}^n(\mathbf{y}) - \bar{\theta}\|^2 \varphi(\mathbf{y}|X,\bar{\theta})\, \mathrm{d}\mathbf{y}$ [Clarke 1980]
   minimize entropy $-\int \log[q(\hat{\theta}^n(\mathbf{y})|\bar{\theta})] \varphi(\mathbf{y}|X,\bar{\theta})\, \mathrm{d}\mathbf{y}$ [P & Pázman 1994]
   (usual normal approximation for $q(\cdot|\bar{\theta})$ $\rightarrow$ D-optimality)
   $\rightarrow$ explicit (but rather complicated) expressions (depend on 3rd-order derivatives of $\eta(x,\theta)$ w.r.t. θ)

E/ One additional difficulty

Overlapping of $\mathbb{S}_\eta$, local minimizers...



▲ Important and difficult problem, often neglected!

What can we do at the design stage?

➠ extensions of usual optimality criteria, e.g.

$$\text{maximize } \phi_{eE}(X) = \min_{\theta} \frac{\|\eta(\theta) - \eta(\theta^0)\|^2}{\|\theta - \theta^0\|^2}$$

or

$$\text{maximize } \phi_{eE}(\xi) = \min_{\theta} \frac{\int [\eta(x,\theta) - \eta(x,\theta^0)]^2 \, \xi(\mathrm{d}x)}{\|\theta - \theta^0\|^2}$$

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▲ All approaches presented so far are local

(the optimal design depends on $\bar{\theta}$ unknown $\leftarrow \theta^0$)

6 Nonlocal optimum design

Ex: $\eta(x,\theta) = \exp(-\theta x)$, $y_i = \eta(x_i,\bar{\theta}) + \varepsilon_i$, $\theta > 0$, $x \in \mathscr{X} = [0,\infty)$
→ $M(\xi,\theta^0) = \int_{\mathscr{X}} x^2 \exp(-2\theta^0 x)\,\xi(\mathrm{d}x)$
➠ $\xi_D^* = \xi_A^* = \ldots = \delta_{1/\theta^0}$

Objective: remove the dependence in nominal value θ^0

3 main classes of methods (related)

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❸ Sequential design

A/ Average Optimum design

Nothing special: probability measure $\mu(\mathrm{d}\theta)$ on $\Theta \subseteq \mathbb{R}^p$

$$\boxed{\phi(\cdot,\theta^0) \rightarrow \phi_{AO}(\cdot) = \int_\Theta \phi(\cdot,\theta)\,\mu(\mathrm{d}\theta)}$$

No difficulty if $\Theta = \{\theta^{(1)},\ldots\theta^{(M)}\}$ finite and $\mu = \sum_{i=1}^{M} \alpha_i \delta_\theta^{(i)}$ (integral $\rightarrow$ finite sum)

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☛ Exact design: same algorithms as in Section 3

(for continuous distributions μ use stochastic approximation to avoid evaluations of integrals [P & Walter 1985])

A Bayesian interpretation:

Suppose μ=prior distribution has a density $\pi(\theta)$

$\rightarrow$ entropy $-\int_\Theta \pi(\theta)\,\log[\pi(\theta)]\,\mathrm{d}\theta$

Posterior distribution of θ: $\pi(\theta|X,\mathbf{y}) = \frac{\varphi(\mathbf{y}|X,\theta)\pi(\theta)}{\varphi(\mathbf{y}|X)}$

Gain in information = decrease of entropy

Entropy may increase, but expected gain in information $\mathcal{I}(X)$ is always positive [Lindley 1956]

➠ $\mathcal{I}(X) = \mathsf{E}_{\mathbf{y}}\{\int_\Theta(\pi(\theta|X,\mathbf{y})\,\log[\pi(\theta|X,\mathbf{y})] - \pi(\theta)\,\log[\pi(\theta)])\,\mathrm{d}\theta\}$

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If the experiment informative enough (σ^2 small, n large enough):

maximizing $\mathcal{I}(X) \overset{\approx}{\Leftrightarrow}$ maximizing $\int \log\det \mathbf{M}(X, \theta)\, \pi(\theta)\, d\theta$

Which prior $\pi(\theta)$? Expected gain in information maximum when $\pi(\cdot) =$ noninformative prior (Jeffrey) — which depends on ξ

$\pi^*(\theta) = \frac{\det^{1/2} \mathbf{M}(\xi,\theta)}{\int_\Theta \det^{1/2} \mathbf{M}(\xi,\theta)\, d\theta}$ ➠ maximize $\int \det^{1/2} \mathbf{M}(\xi,\theta)\, d\theta$

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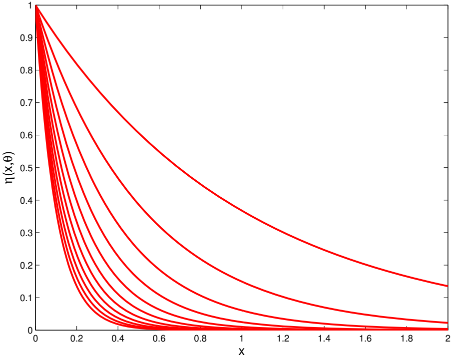
Ex: $\eta(x,\theta) = \exp(-\theta x)$, α-quantiles of $\eta(x,\theta)$ for different π

π uniform on $\Theta = [1, 10]$



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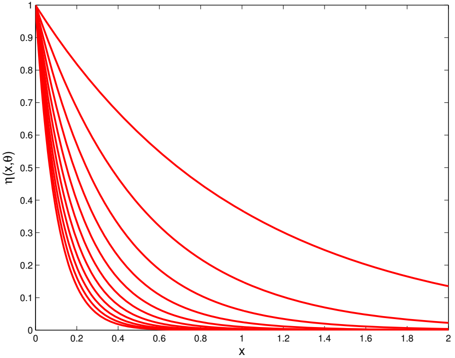
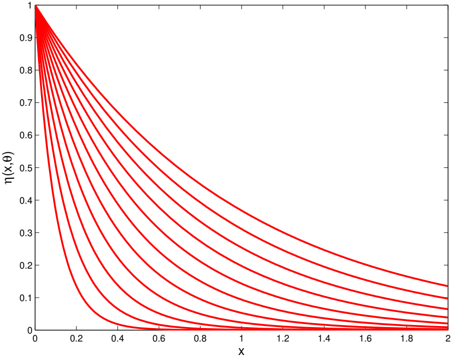


π_ν, ν uniform on $\mathscr{X} = [0, 2]$



B/ Maximin Optimum design

$$\boxed{\phi(\cdot,\theta^0) \rightarrow \phi_{MmO}(\cdot) = \min_{\theta\in\Theta} \phi(\cdot,\theta)}$$

☛ Exact design:

Θ finite $\rightarrow$ same algorithms as in Section 3

Θ compact subset of $\mathbb{R}^p$ $\rightarrow$ relaxation method to solve a sequence of maximin problems with finite (and growing) sets $\Theta^{(k)}$ [P & Walter 1988]

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  - Θ finite $\to$ same algorithms as in Section 3
  - Θ compact subset of $\mathbb{R}^p$ $\to$ relaxation method to solve a sequence of maximin problems with finite (and growing) sets $\Theta^{(k)}$ [P & Walter 1988]
- Approximate design:
  - $\phi_{MmO}(\cdot)$ concave when each $\phi(\cdot, \theta)$ is concave
  - ▲ but $\phi_{MmO}(\cdot)$ is non-differentiable!
  - ➠ maximize $\phi_{MmO}(\xi)$ using a specific algorithm for concave non-differentiable maximization (cutting plane, level method... see Section 3)

How to check optimality of ξ^*?

$\phi(\cdot,\theta^0)$ differentiable: $\max_{x\in\mathscr{X}} F_\phi(\xi^*;\delta_x,\theta^0) \leq 0$?
$\rightarrow$ plot $F_\phi(\xi^*;\delta_x,\theta^0)$ as a function of x

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Equivalence Theorem:

ξ^* maximizes $\phi_{MmO}(\xi) \Leftrightarrow \max_{\nu\in\Xi} F_{\phi_{MmO}}(\xi^*;\nu) \leq 0$
$\Leftrightarrow \max_{\nu\in\Xi} \min_{\theta\in\Theta(\xi^*)} F_\phi(\xi^*;\nu,\theta) \leq 0$
with $\Theta(\xi) = \{\theta : \phi(\xi,\theta) = \phi_{MmO}(\xi)\}$
$\Leftrightarrow \max_{x\in\mathscr{X}} \int_{\Theta(\xi^*)} F_\phi(\xi^*;\delta_x,\theta)\mu^*(\mathrm{d}\theta) \leq 0$
for some probability measure μ^* on $\Theta(\xi^*)$

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Once ξ^* is determined, solve a LP problem:
μ^* on $\Theta(\xi^*)$ minimizes $\max_{x\in\mathscr{X}} \int_{\Theta(\xi^*)} F_\phi(\xi^*;\delta_x,\theta)\mu(\mathrm{d}\theta)$
➠ plot $\int_{\Theta(\xi^*)} F_\phi(\xi^*;\delta_x,\theta)\mu^*(\mathrm{d}\theta)$ (should be ≤ 0)

Ex: $\eta(x,\theta) = \theta_1 \exp(-\theta_2 x)$, $p = 2$, $\mathscr{X} = [0,2]$, $\theta_2 \in [0, \theta_{2_{\max}}]$

$$\phi(\xi,\theta) = \frac{\det^{1/p} \mathbf{M}(\xi,\theta)}{\det^{1/p} \mathbf{M}(\xi_D^*,\theta)} \quad (D \text{ efficiency}, \in [0,1])$$

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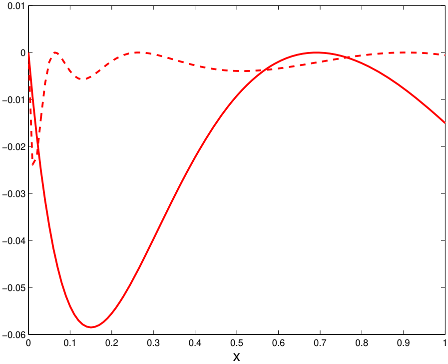
$\int_{\Theta(\xi^*)} F_\phi(\xi^*; \delta_x, \theta)\mu^*(\mathrm{d}\theta)$ for

$\theta_{2_{\max}} = 2$ (solid line, 2 support points) and

$\theta_{2_{\max}} = 20$ (dashed line, 4 support points)



C/ Regularized Maximin Optimum design

Suppose $\phi(\cdot,\theta) > 0$ for all θ; μ a probability measure on $\Theta \subset \mathbb{R}^p$ compact

$\phi_{MmO}(\xi) = \min_{\theta\in\Theta} \phi(\cdot,\theta) \leq \overline{\phi}_q(\xi) = \left[\int_\Theta \phi^{-q}(\xi,\theta)\mu(\mathrm{d}\theta)\right]^{-\frac{1}{q}}$ (differentiable)

with $\overline{\phi}_{-1}(\xi) = \phi_{AO}(\xi)$, $\overline{\phi}_0(\xi) = \exp\left\{\int_\Theta \log[\phi(\xi,\theta)]\mu(\mathrm{d}\theta)\right\}$ and

$\boxed{\overline{\phi}_q(\xi) \to \phi_{MmO}(\xi) \text{ as } q \to \infty}$ (and $\overline{\phi}_q(\cdot)$ concave for $q \geq -1$)

Moreover, $\Theta = \{\theta^{(1)},\ldots,\theta^{(M)}\}$, $\mu = \frac{\sum_i \delta_{\theta^{(i)}}}{M} \implies \frac{\phi_{MmO}(\xi_q^*)}{\phi_{MmO}^*} \geq M^{-1/q}$

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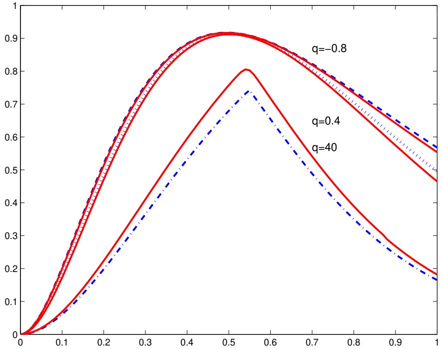
Ex: $\eta = \exp(-\theta x)$

$\phi(\xi,\theta) = \frac{M(\xi,\theta)}{M(\xi^*,\theta)}$ (= efficiency)

Plot of $\overline{\phi}_q(\delta_x)$ function of x



D/ Quantiles and probability level criteria

A/ ξ^*_{AO} good for $\mu(\mathrm{d}\theta)$ on Θ, may be bad for some θ

▲ for $\psi(\cdot) \nearrow$, maximizing $\psi\left[\int_\Theta \phi(\cdot,\theta)\,\mu(\mathrm{d}\theta)\right]$ (AO-opt.)
is different from maximizing $\int_\Theta \psi[\phi(\cdot,\theta)]\,\mu(\mathrm{d}\theta)$

B/ ξ^*_{MmO} often depends on the boundary of Θ
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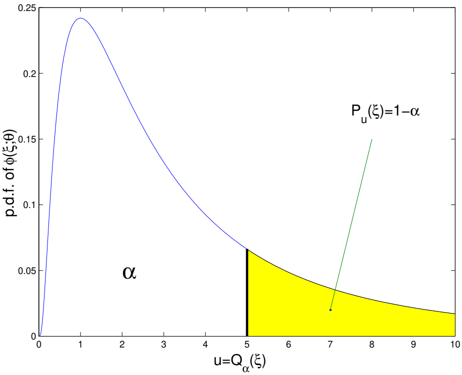
B/ ξ^*_{MmO} often depends on the boundary of Θ
(➔ we often simply replace the dependence on θ^0 by a dependence on $\theta_{\max}$)

u given $\rightarrow$
$P_u(\xi) = \mu\{\phi(\xi,\theta) \geq u\}$

$\alpha \in (0,1)$ given $\rightarrow$
$Q_\alpha(\xi) = \max\{u : P_u(\xi) \geq 1-\alpha\}$



- ➤ maximizing $P_u(\xi) = \mu\{\phi(\xi, \theta) \geq u\}$ is well adapted to
  $\phi(\xi, \theta) =$ efficiency $\in (0, 1)$
- ➤ $Q_\alpha(\xi) \to \phi_{MMO}$ as $\alpha \to 0$
- ➤ for $\psi(\cdot) \nearrow$, using $\psi[\phi(\xi, \theta)]$ does not change $P_u(\xi)$ and $Q_\alpha(\xi)$
- ▲ $P_u(\xi)$ and $Q_\alpha(\xi)$ generally not concave!
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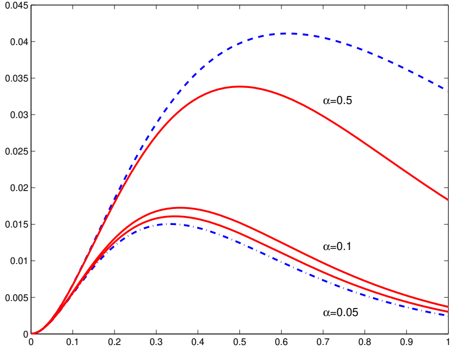
Ex: $\eta = \exp(-\theta x)$
$\phi(\xi,\theta) = M(\xi,\theta)$
Plot of $Q_\alpha(\delta_x)$ function of x
(with $\phi_{AO}(\delta_x)$ and $\phi_{MmO}(\delta_x)$)



Ongoing work: conditional value at risk (also called superquantile)

$$\phi_\alpha(\xi) = \frac{1}{\alpha} \int_{\{\theta:\phi(\xi,\theta)\leq Q_\alpha(\xi)\}} \phi(\xi,\theta)\, \mu(\mathrm{d}\theta)$$

which is concave in ξ when $\phi(\cdot,\theta)$ is concave for all θ, see (Valenzuela et al., 2015; Guerra, 2016)

E/ Sequential design

$\theta^0 \rightarrow$ design: $X^1 = \arg\max_X \phi(X, \theta^0)$

$\rightarrow$ observe: $\mathbf{y}^1 = \mathbf{y}^1(X^1)$

$\rightarrow$ estimate: $\hat{\theta}^1 = \arg\min_\theta J(\theta; \mathbf{y}^1, X^1)$

$\rightarrow$ design: $X^2 = \arg\max_X \phi(\{X^1, X\}, \hat{\theta}^1)$

$\rightarrow$ observe: $\mathbf{y}^2 = \mathbf{y}^2(X^2)$

$\rightarrow$ estimate: $\hat{\theta}^2 = \arg\min_\theta J(\theta; \{\underbrace{\mathbf{y}^1, \mathbf{y}^2}_{\text{growing}}\}, \{\underbrace{X^1, X^2}_{\text{growing}}\})$

$\rightarrow$ design: $X^3 = \arg\max_X \phi(\{X^1, X^2, X\}, \hat{\theta}^2)$

...etc.

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▲ Consistency of $\hat{\theta}^n$?
Asymptotic normality (for design based on **M**)?
(X^k depends on $\mathbf{y}^1, \ldots, \mathbf{y}^{k-1} \Longrightarrow$ independence is lost)

➟ No problem if each X^i has size $\geq p = \dim(\theta)$ (batch sequential design)

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$\rightarrow$ convergence properties difficult to investigate

$$\mathbf{M}(X_{k+1},\hat{\theta}^k) = \frac{k}{k+1}\mathbf{M}(X_k,\hat{\theta}^k) + \frac{1}{k+1}\frac{\partial\eta(x_{k+1},\theta)}{\partial\theta}\Big|_{\hat{\theta}^k}\frac{\partial\eta(x_{k+1},\theta)}{\partial\theta^\top}\Big|_{\hat{\theta}^k}$$

with $x_{k+1} = \arg\max_{\mathscr{X}} F_\phi(\xi^k;\delta_x|\hat{\theta}^k) \Leftrightarrow$ Wynn's algorithm [1970] with $\alpha_k = \frac{1}{k+1}$

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➤ some CV results for Bayesian estimation [Hu 1998]
➤ no general CV results for LS and ML estimation
some results when $\mathscr{X}$ is finite ($\mathscr{X} = \{x^{(1)}, \ldots, x^{(\ell)}\}$) [P 2009, 2010]

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