Best intention sequential designs in clinical trial studies

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Response is given by

$$y = \theta_0 + \theta_1 x + \theta_2 x^2 + \varepsilon, \quad x \in [-1, 1]$$

Our aim is to estimate $x^* = -\frac{\theta_1}{2\theta_2}$

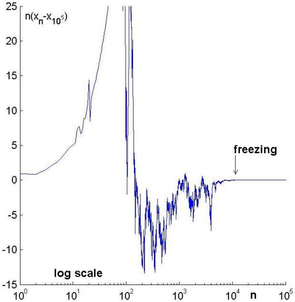
Best intention design procedure

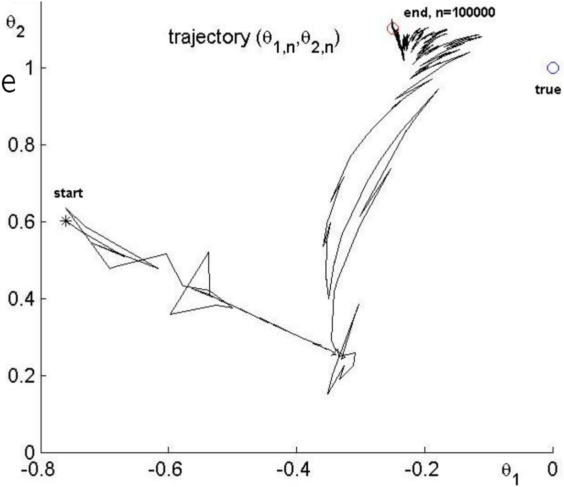
- initial (equidistant) design $x_1, \ldots, x_k$, k is small
- in the loop $n = k, k+1, \ldots$
  - $\theta_n = (X_n^T X_n)^{-1} X_n^T Y_n$ is LSE of θ, $Y_n = (y_1, \ldots, y_n)^T$
  - $x_{n+1} = -\frac{\theta_{1,n}}{2\theta_{2,n}}$ is the next design point

Trajectories for model $\theta_0 + \theta_1 x + \theta_2 x^2$

$x_n \to x_0 \neq x^*$
with rate $\frac{1}{n}$ and freeze

$\theta_{i,n} \xrightarrow{\frac{1}{n}} \theta_{i,0} \neq \theta_i^*$





Consider two parameter model

$$y = \theta_1 x + \theta_2 x^2 + \varepsilon, \quad x \in [-1, 1]$$

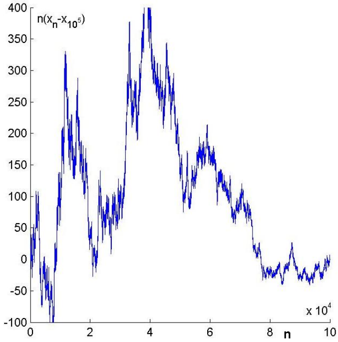
Best intention design procedure

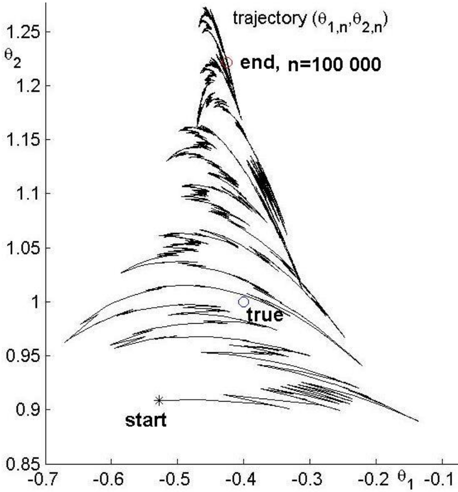
- $x_n \to x^*$ if $\theta_1^* = 0$
- $x_n \to x_0 \neq x^*$ if $\theta_1^* \neq 0$

Trajectories for model $\theta_1 x + \theta_2 x^2$

$$x_n \xrightarrow{\frac{1}{n}} x_0 \neq x^*$$

$$\theta_{i,n} \xrightarrow{\frac{1}{n}} \theta_{i,0} \neq \theta_i^*$$

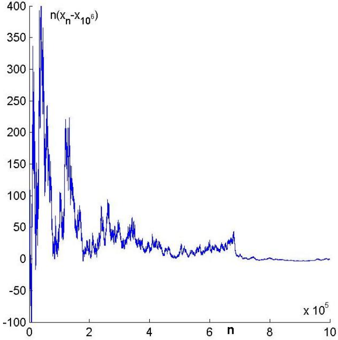


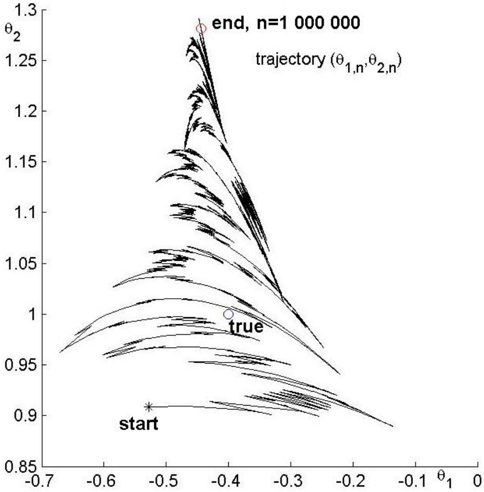


Long trajectories for model $\theta_1 x + \theta_2 x^2$

$$x_n \xrightarrow{\frac{1}{n}} x_0 \neq x^*$$

$$\theta_{i,n} \xrightarrow{\frac{1}{n}} \theta_{i,0} \neq \theta_i^*$$





Estimation of response

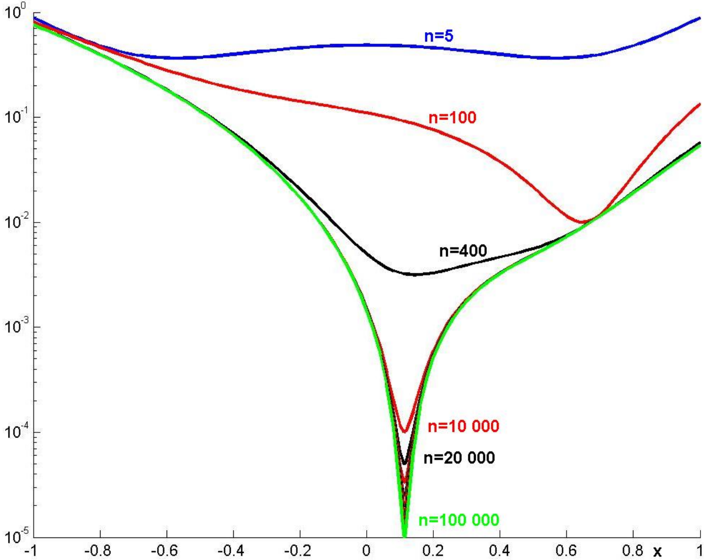
$$\eta(x,\theta) = \theta^T f(x)$$

$$\mathrm{Var}[\eta(x,\hat{\theta})] = d(x,\xi_n) = f^T(x) M^{-1}(\xi_n) f(x)$$

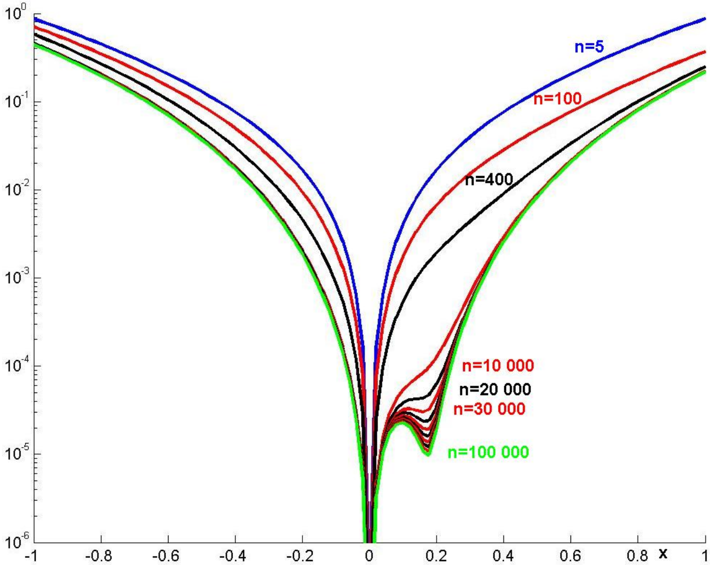
$$M(\xi_n) = \sum_{i=1}^{n} f(x_i) f^T(x_i)$$

$$\xi_n = \{x_1, \ldots, x_n\}$$

$d(x, \xi_n)$ for the model $\theta_0 + \theta_1 x + \theta_2 x^2$

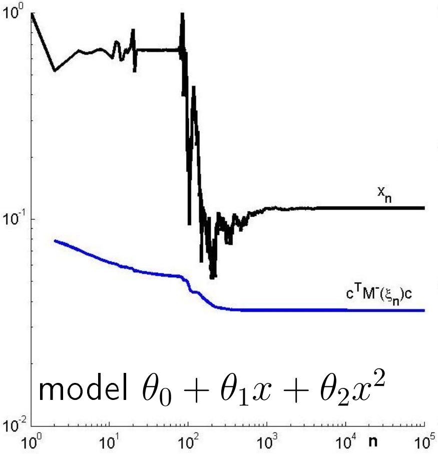


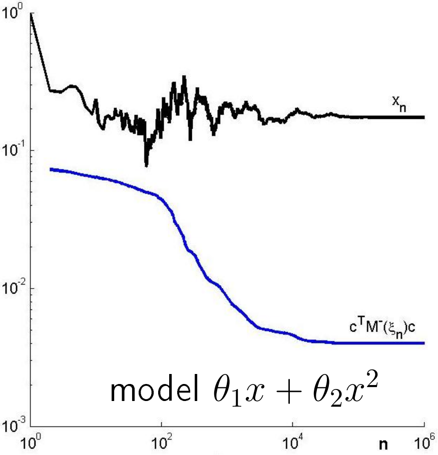
$d(x, \xi_n)$ for the model $\theta_1 x + \theta_2 x^2$



Variance of estimate of x^*

$$\mathrm{Var}[x_n] = c^T M^-(\xi_n)c, \quad c = \frac{\partial f}{\partial x}\Big|_{x=x^*}$$





Recurrent formula for LSE

$M(\xi_n)$ grows linearly as $n \to \infty$
Let $Q_n = (M(\xi_n)/n)^{-1}$

- $x_{n+1} = -\frac{\theta_{1,n}}{2\theta_{2,n}}$ and observe y_{n+1}
- $\theta_{n+1} = \theta_n + \frac{1}{n}\frac{Q_n f(x_{n+1})}{1+f(x_{n+1})Q_n f(x_{n+1})}(y_{n+1} - \theta_n^T f(x_{n+1}))$
- $Q_{n+1} = Q_n + \frac{Q_n}{n} - \frac{1+1/n}{n} \cdot \frac{Q_n f(x_{n+1}) f^T(x_{n+1}) Q_n}{1+f^T(x_{n+1}) Q_n f(x_{n+1})}$

Bozzin-Zarrop approach

Model

$$y(t) = \phi^T(t)\theta^o + \varepsilon(t) = \theta_1^o u(t-1) + \theta_2^o u^2(t-1) + \varepsilon(t)$$

Stochastic approximation, $\gamma(t)$ behaves like $1/t$

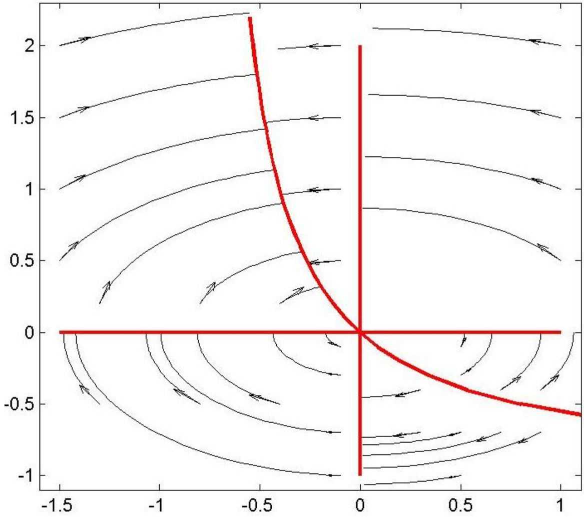
$$\theta(t) = \theta(t-1) + \gamma(t)\phi(t-1)(y(t) - \phi^T(t-1)\theta(t-1))$$

Associated differential equation

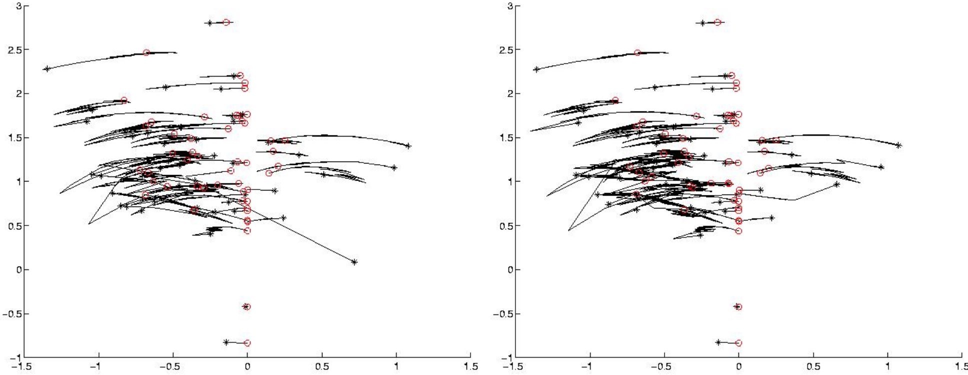
$$\frac{d}{d\tau}\theta_D(\tau) = G(\theta_D(\tau))(\theta^o - \theta_D(\tau))$$

$$G(\theta) = \mathbb{E}(\phi(t)\phi^T(t)) = \begin{pmatrix} u^2 & u^3 \\ u^3 & u^4 \end{pmatrix}$$

Trajectories of differential equation



50 trajectories of LSE (left) and SA (right)



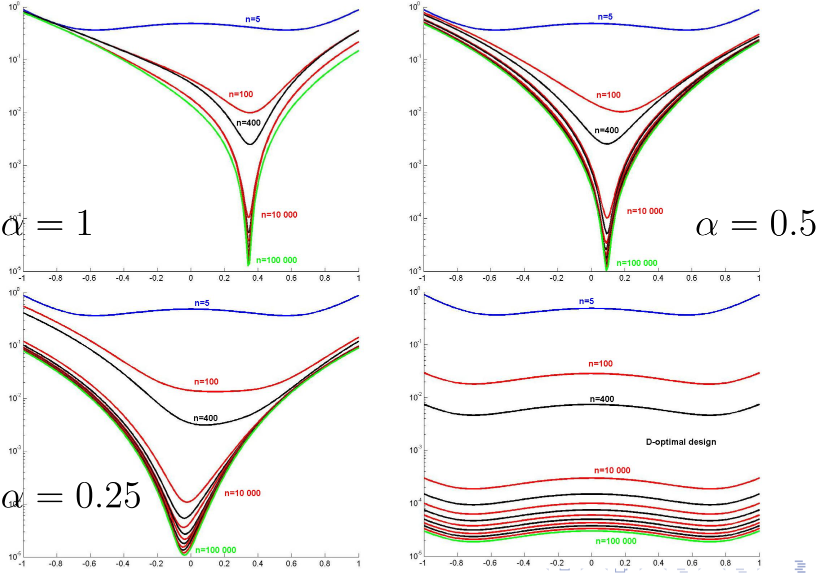
How to modify the procedure to improve

- D-optimal design $\{-1, 0, 1\}$,
  put points at boundary points for large n,
  i.e. try doses with low efficacy or high toxicity
- control the rate of convergence

$$\tilde{x}_k = \begin{cases} x_k & |x_k - \tilde{x}_{k-1}| \geq \frac{1}{k^\alpha} \\ x_k - \frac{1}{k^\alpha} & \tilde{x}_{k-1} - \frac{1}{k^\alpha} < x_k < \tilde{x}_{k-1} \\ x_k + \frac{1}{k^\alpha} & \tilde{x}_{k-1} < x_k < \tilde{x}_{k-1} + \frac{1}{k^\alpha} \end{cases}$$

$\tilde{\xi}_n = \{\tilde{x}_1, \ldots, \tilde{x}_n\}$
consistent if $\alpha < 0.25$

$d(x, \tilde{\xi}_n)$ for the model $\theta_0 + \theta_1 x + \theta_2 x^2$



$c^T M^-(\tilde{\xi}_n)c$ for the model $\theta_0 + \theta_1 x + \theta_2 x^2$