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Optimal model-based design, dose ranging, and population PK measures

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Outline

- Dose ranging studies
- Motivation: earlier study, model-based population optimal designs
- Population PK measures/metrics
- Parametric (model-based) vs empirical (nonparametric) approaches
- Splitting sampling grids

Introduction

Dose-ranging study

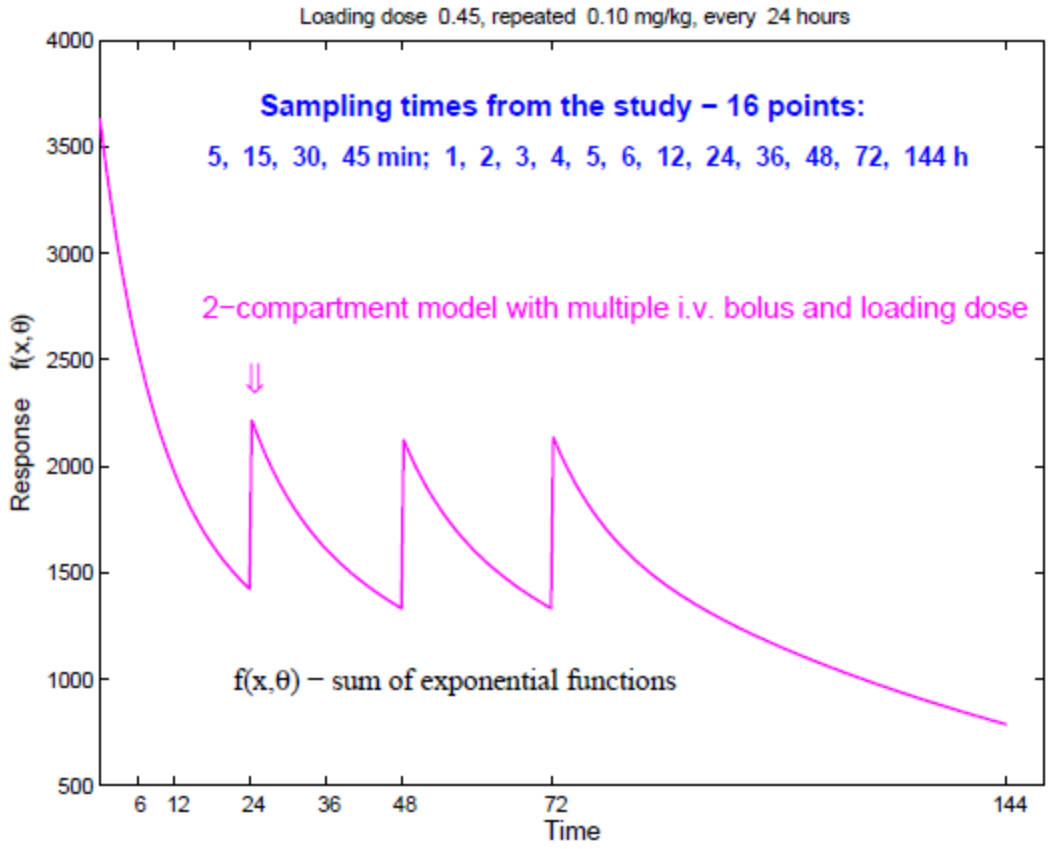
- A clinical trial where different doses of a drug are tested to establish which dose works best and/or is least harmful
- Usually a phase I or early phase II clinical trial
- Typically includes a placebo group of subjects, and a few groups that receive different doses of the test drug
- Main goal: estimate the response vs. dose given (analyze the efficacy and safety of the drug)
- Pharmacokinetic/pharmacodynamic (PK/PD) analysis is critical

Introduction (cont.)

- Pharmacokinetics (PK): how a body affects a drug
  - Modelling how drug amount /concentration changes over time (compartmental vs noncompartmental analyses)
- Pharmacodynamics (PD): how the drug affects the body
  - Concentration – response models
  - Effect of drug concentration on clinically relevant endpoint (blood pressure, number of exacerbations)
- Early phases: dense sampling (plasma drug concentration), small number of subjects
- Later phases: population PK/PD analysis, often sparse sampling with large number of subjects

Motivation

$$\begin{cases} \dot{q}_1(x,\gamma) = & -(K_{12}+K_{10})q_1(x,\gamma) & + K_{21}q_2(x,\gamma), \\ \dot{q}_2(x,\gamma) = & K_{12}q_1(x,\gamma) & - K_{21}q_2(x,\gamma), \end{cases}$$



Gagnon, Leonov (2005)

- Rich sampling

Questions

- How many samples to take?
- At which times?

Better sampling scheme → better precision of parameter estimates

Models, information matrix

$\mu(\mathbf{x}, \boldsymbol{\vartheta})$ - information matrix for observations $\mathbf{Y}$ at sequence $\mathbf{x}$,

$\mathbf{x} = (t_1, t_2, \ldots, t_k)$ - sampling times, $\mathbf{Y} = [y(t_1), \ldots, y(t_k)]^T$

If n_i patients on sequence $\mathbf{x}_i$, $\sum_i n_i = N \implies \mathbf{M}_N(\boldsymbol{\vartheta}) = \sum_i n_i \, \boldsymbol{\mu}(\mathbf{x}_i, \boldsymbol{\vartheta})$.

1. Standard normalization: *N - available resource, ξ - normalized design:*

$$\mathbf{M}(\xi, \boldsymbol{\vartheta}) = \frac{\mathbf{M}_N(\boldsymbol{\vartheta})}{N} = \sum_{i=1}^{n} p_i \, \boldsymbol{\mu}(\mathbf{x_i}, \boldsymbol{\vartheta}), \quad \xi = \{(\mathbf{x_i}, p_i), \; p_i = \frac{n_i}{N}, \; \}$$

D-criterion: $|\mathbf{M}^{-1}(\xi, \boldsymbol{\vartheta})| \to \min_{\xi}, \quad \mathbf{x_i} \in \mathcal{X}$ (design region)

Key: derive $\mu(\mathbf{x}, \boldsymbol{\vartheta})$ for population compartmental models

Models, information matrix, costs

2. Measurements at $\mathbf{x_i}$ associated with cost $c(\mathbf{x_i})$ $\quad [c(\mathbf{x_i}) = c_p + kc_s]$

$$\sum_i n_i c(\mathbf{x_i}) \le \mathcal{C} \Longrightarrow \mathbf{M}_C(\boldsymbol{\vartheta}) = \sum_{i=1}^{n} \frac{n_i}{\mathcal{C}} \boldsymbol{\mu}(\mathbf{x_i}, \boldsymbol{\vartheta}) = \sum_i \tilde{p}_i \, \tilde{\boldsymbol{\mu}}(\mathbf{x_i}, \boldsymbol{\vartheta}),$$

Information matrix normalized by total cost $\mathcal{C}$,

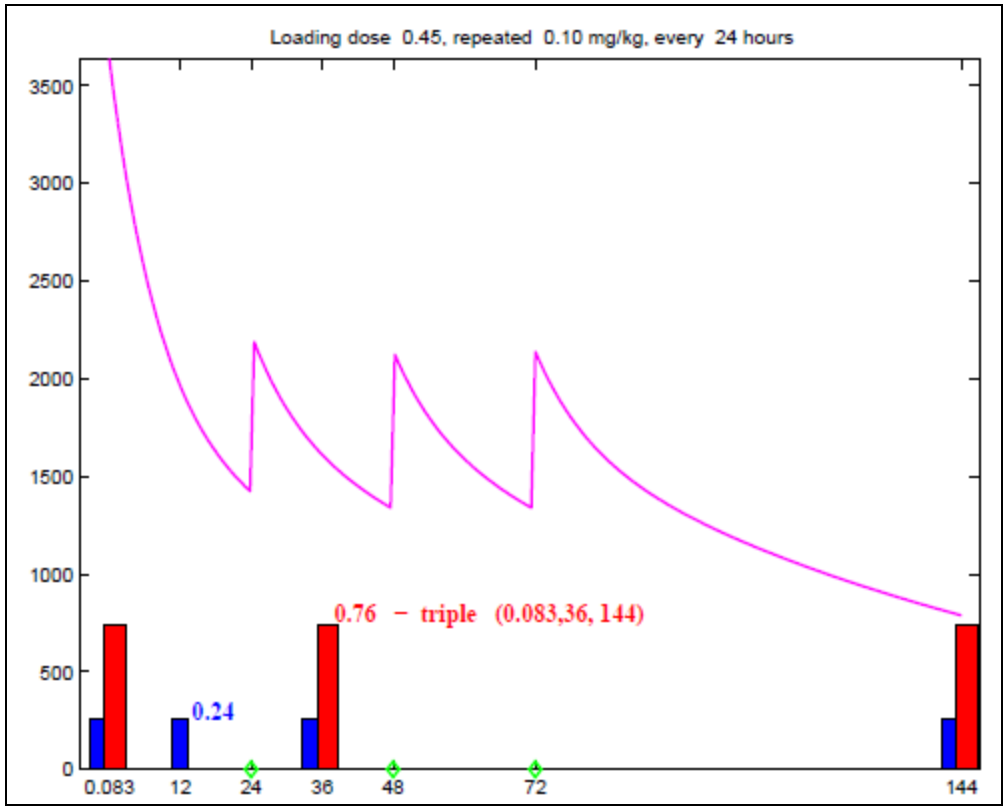
$$\tilde{p}_i = n_i c(\mathbf{x_i})/\mathcal{C}; \quad \tilde{\boldsymbol{\mu}}(\mathbf{x_i}, \boldsymbol{\vartheta}) = \boldsymbol{\mu}(\mathbf{x_i}, \boldsymbol{\vartheta})/c(\mathbf{x_i}) \Longrightarrow \text{same framework},$$

standard numerical algorithms

Costs/constraints in design problems: Elfving (1952); Cook, Wong (1994); Cook, Fedorov (1995, general setting)

PK/PD: Mentré et al. (1997); Fedorov et al. (2002); Fedorov, Leonov (2013, Ch. 4, 7)

Motivation (cont.)



No costs: the more samples, the better

- # of samples can be reduced (small loss of precision)

Costs introduced

- Sequences with smaller number of samples may become optimal
- Optimal design: combination of sequences (distinct sampling schemes for different cohorts)
- OD, up to 5-point sequences: **3-point** and **4-point** sequences selected

Background: population model

$$y_{ji} = f(x_{ji}, \boldsymbol{\theta}_j) + \varepsilon_{ji}, \quad i = 1, \ldots, k_j, \quad j = 1, \ldots, N,$$

x_{ji}: i-th sampling time for patient j, $x_{ji} \in [a, b]$,

y_{ji}: measurement at time x_{ji} for patient j;

$f(x, \boldsymbol{\theta})$: response function which depends on time x and parameters $\boldsymbol{\theta}$,

$\boldsymbol{\theta}_j$: parameters of patient j, $\boldsymbol{\theta}_j \sim \mathcal{N}(\boldsymbol{\theta}^0, \mathbf{U})$ (population distribution)

N: no. of enrolled patients; k_j: no. of sampling times for patient j,

ε_{ji}: measurement errors $\sim \mathcal{N}(0, \sigma^2)$.

Simplest case: same sampling times for all patients: $x_{ji} \equiv x_i$, $n_j \equiv 2n$.

$$f(x, \boldsymbol{\theta}) = \frac{K_a}{V(K_a - K_{el})} \left(e^{-K_{el}x} - e^{-K_a x}\right), \quad \boldsymbol{\theta} = (K_a, K_{el}, V)^T$$

Practical considerations

- Often interested in PK measures, not parameters:
  - Area under the curve (time-concentration), *AUC*
  - Maximal concentration, C_{max}
  - Time to maximal concentration, T_{max}
- Optimal design for PK measures: Atkinson et al. (1993)
- Regulatory agencies require non-compartmental analysis
- We compare two approaches (MSE as a metric):
  - Model-based (compartmental) as a benchmark
  - Nonparametric (non-compartmental, empirical)

Example: one-compartment model

$$f(x,\boldsymbol{\theta}) \;=\; \frac{K_a}{V(K_a-K_{el})}\left(e^{-K_{el}x}-e^{-K_a x}\right), \quad \boldsymbol{\theta}=(K_a,K_{el},V)^T,$$

K_a, K_{el} - absorption and elimination rate constants;

V - volume of distribution; $x \in [0,1]$ (normalized time scale),

$$AUC=\int_0^1 f(x,\boldsymbol{\theta}^0)dx, \quad T_{max}=\frac{\ln(K_a/K_{el})}{K_a-K_{el}}, \quad C_{max}=\frac{1}{V}\left(\frac{K_a}{K_{el}}\right)^{-K_{el}/(K_a-K_{el})}$$

Mean vector $\boldsymbol{\theta}^0=(46,6,0.1)$ (mimics data from an earlier clinical study)

Variance parameters: $\sigma=0.5$, $\mathbf{U}=Var(\boldsymbol{\theta})=\mathrm{diag}(s_i^2)$ with $s_i=0.3\,\theta_i$.

Motivation (cont.)

Hypothetical example, several options for a PK study

- Option 1: 20 patients, sequences of 6 samples for each
- Option 2: 24 patients, sequences of 5 samples for each,
- ……
- 120 samples per option: which option to choose?

Key factors

- Sources of variability (population/observational)
- Costs
- $\boldsymbol{\mu}(\mathbf{x},\boldsymbol{\theta})$ – individual information matrix of a *k*-dimensional predictor **x** (sequence of sampling times): how to compute it?

PODE workshops (**P**opulation **O**ptimum **D**esign of **E**xperiments, 2006-2017)

Software developed/compared: Nyberg et al. (2015, *Brit. J. Clin. Pharm*.)

Numerics

- Optimization: in general, a difficult step
- Design region
  - $t \in [0,T]$, continuous variable - ?
  - X = $\{x_1, x_2, \ldots, x_s\}$ – set of preselected times
    - $\mathcal{X}$ = { **x** = [sequences of *k* times from X] } – finite set
    - $\boldsymbol{\mu}(\mathbf{x},\boldsymbol{\theta})$ can be precomputed
    - Optimization step is easy (e.g., 1st order/Fedorov-Wynn)

- Designs with n < m support points may be non-singular
  - By design, $\boldsymbol{\mu}(\mathbf{x},\boldsymbol{\theta})$ will have rank >= 1
  - Var(ε_{ji}) may depend on $\boldsymbol{\theta}$ $\rightarrow$ $\boldsymbol{\mu}(\mathbf{x},\boldsymbol{\theta})$ is the sum of two terms $\rightarrow$ its rank >= 1

Technical details , OD for population PK/PD models (NLME):
Fedorov, Leonov (2013, Chapter 7)

Motivation (cont.)

Earlier work, candidate sequences: all possible k-point sequences from the set of 16 study sampling times $X = \{x_1, x_2, \ldots, x_{16}\}$.

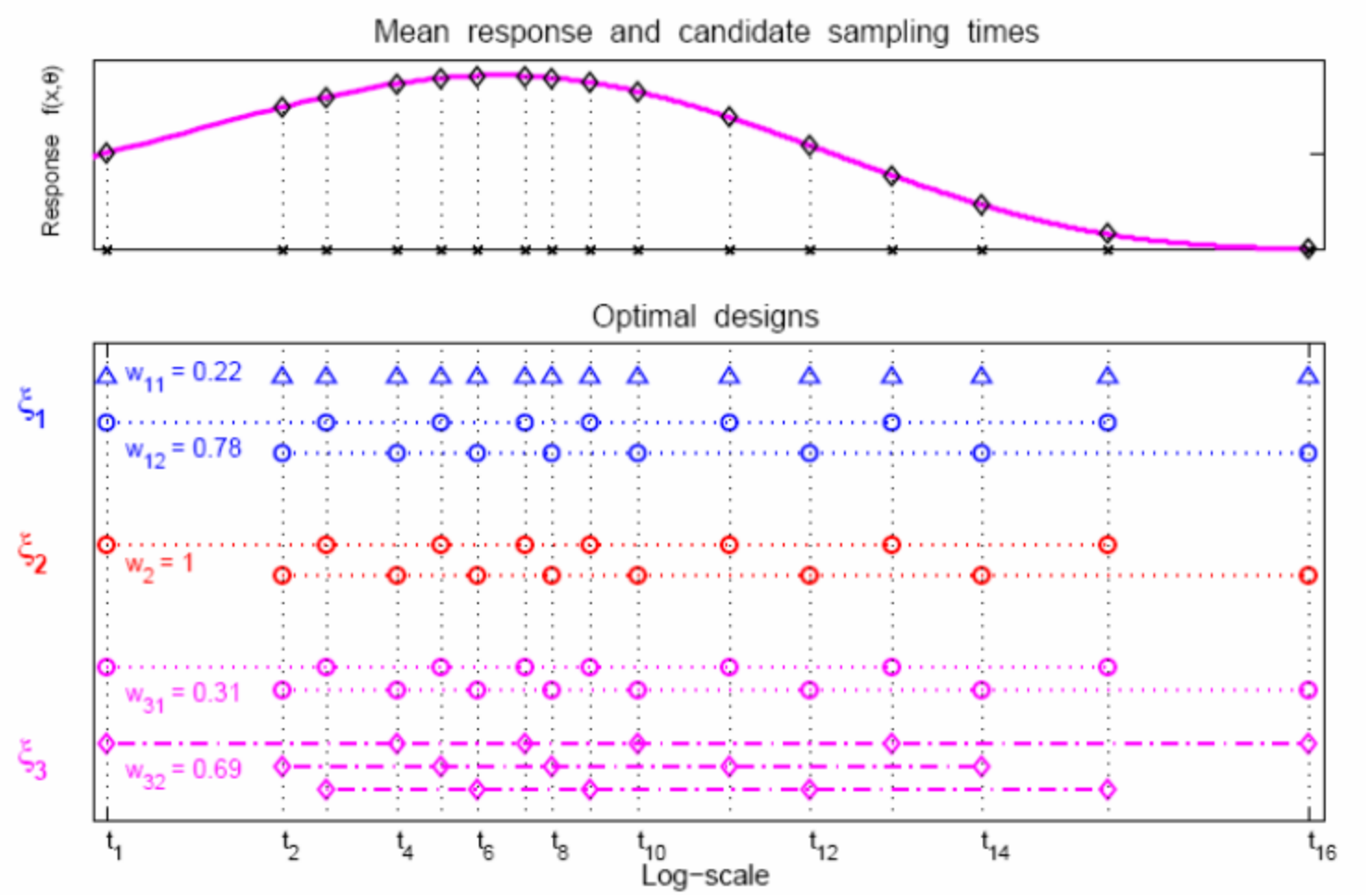
New example: use s-order splits of X, $N = \sum_s n_s$

- n_1 patients on $\mathbf{x}_1$: use all n sampling times ← p_1
- n_2 patients on $\mathbf{x}_2$: times $\mathbf{x}_{21} = \{x_1, x_3, x_5, \ldots\}$ for $n_2/2$ patients, ← p_2
  $\mathbf{x}_{22} = \{x_2, x_4, x_6, \ldots\}$ for remaining "half"
- n_3 patients on $\mathbf{x}_3$: times $\mathbf{x}_{31} = \{x_1, x_4, x_7, \ldots\}$, first $n_3/3$ patients,
  $\mathbf{x}_{32} = \{x_2, x_5, x_8, \ldots\}$, second subgroup $(n_3/3)$ ← p_3
  $\mathbf{x}_{33} = \{x_3, x_6, x_9, \ldots\}$, third subgroup etc.

Information matrix for s-order split: $\mu(\mathbf{x}_s, \boldsymbol{\theta}) = \sum_{k=1}^{s} \mu(\mathbf{x}_{sk}, \boldsymbol{\theta})/s$

D-optimal designs, cost-based

Cost function $c(\mathbf{x}_S) = c_p + c_s n/S\ , \quad c_p = 5$



Model-based/compartmental, Type I

Model-based methods start with individual parameter estimates $\hat{\boldsymbol{\theta}}_j$

Type I, Method M1: *averaging measures*

- Estimate individual measures:

$$\widehat{AUC}_j = \int_a^b f(x, \hat{\boldsymbol{\theta}}_j)dx, \quad \widehat{C}_{max,j} = \max_x f(x, \hat{\boldsymbol{\theta}}_j), \quad \widehat{T}_{max,j} = \arg\max_x f(x, \hat{\boldsymbol{\theta}}_j).$$

- Individual measures are averaged across population:

$$\widehat{AUC}_{M1} = \sum_{j=1}^{N} w_j \, \widehat{AUC}_j, \; w_j = \frac{1}{N}, \quad \text{same for } \widehat{T}_{max,M1} \text{ and } \widehat{C}_{max,M1}.$$

- Metrics of interest:

$$AUC_1 = E_\theta \left[\int_a^b f(x, \boldsymbol{\theta})dx \right], \; T_1 = E_\theta \left[\arg\max_x f(x, \boldsymbol{\theta}) \right], \; C_1 = E_\theta \left[\max_x f(x, \boldsymbol{\theta}) \right].$$

Model-based/compartmental, Type II

Type II, Method M2: *averaging responses*

- Get "average" PK curve, $\widehat{f}_N(x) = \sum_j f(x, \hat{\boldsymbol{\theta}}_j)/N$,
- Estimate PK measures for the "average" curve:

$$\widehat{AUC}_{M2} = \int_a^b \widehat{f}_N(x)dx,\ \widehat{T}_{M2} = \arg\max_x \widehat{f}_N(x),\ \widehat{C}_{M2} = \max_x \widehat{f}_N(x),$$

- Metrics of interest:

$$AUC_2 = \int_a^b \bar{f}(x)dx,\ T_2 = \arg\max_x \bar{f}(x),\ C_2 = \max_x \bar{f}(x),\ \text{with } \bar{f}(x) = E_\theta\left[f(x, \boldsymbol{\theta})\right]$$

Note that $\widehat{AUC}_{M1} = \widehat{AUC}_{M2}$, $AUC_1 = AUC_2$, but

$$\widehat{C}_{M1} \neq \widehat{C}_{M2},\quad \widehat{T}_{M1} \neq \widehat{T}_{M2}$$

Model-based/compartmental, Type III

Type III, Method M3: *averaging parameters*

- Get average parameter values, $\widehat{\boldsymbol{\theta}} = \sum_j \widehat{\boldsymbol{\theta}}_j / N,$
- Get PK measures for $\widehat{\boldsymbol{\theta}}$:

$$\widehat{AUC}_{M3} = \int_a^b f(x, \widehat{\boldsymbol{\theta}})\, dx,\ \widehat{T}_{M3} = \arg\max_x f(x, \widehat{\boldsymbol{\theta}}),\ \widehat{C}_{M3} = \max_x f(x, \widehat{\boldsymbol{\theta}}),$$

- Metrics of interest:

$$AUC_3 = \int_a^b f(x, E\boldsymbol{\theta})dx,\ T_3 = \arg\max_x f(x, \mathbf{E}\boldsymbol{\theta}),\ C_3 = \max_x f(x, E\boldsymbol{\theta}).$$

Empirical/non-compartmental, Type I

Type I, Method E1: *averaging measures*

- For each patient, get empirical $\widehat{T}_{max,j}$, $\widehat{C}_{max,j}$ and $\widehat{AUC}_j$ (numerical integration),

$$\widehat{AUC}_j = \sum_{i=1}^{n} \int_{x_{i-1}}^{x_i} g(x, \mathbf{a}_i)dx \quad (g - \text{interpolant passing through } y_{j,i-1} \text{ and } y_{j,i})$$

- Average individual measures as for M1:

$$\widehat{AUC}_{E1} = \frac{1}{N} \sum_{j=1}^{N} \widehat{AUC}_j, \quad \text{same for } \widehat{T}_{max,E1} \text{ and } \widehat{C}_{max,E1}.$$

- Metrics: AUC_1, T_1, C_1 (for dense grids $\{x_i\}$ and large N)
- Sparse sampling: problems with method E1

Empirical/non-compartmental, Type II

Type II, Method E2: *averaging responses*

- Get average curve

$$\hat{f}_i = \hat{f}_{iN} = \frac{1}{N}\sum_{j=1}^{N} y_{ji}, \quad i = 0, \ldots, n.$$

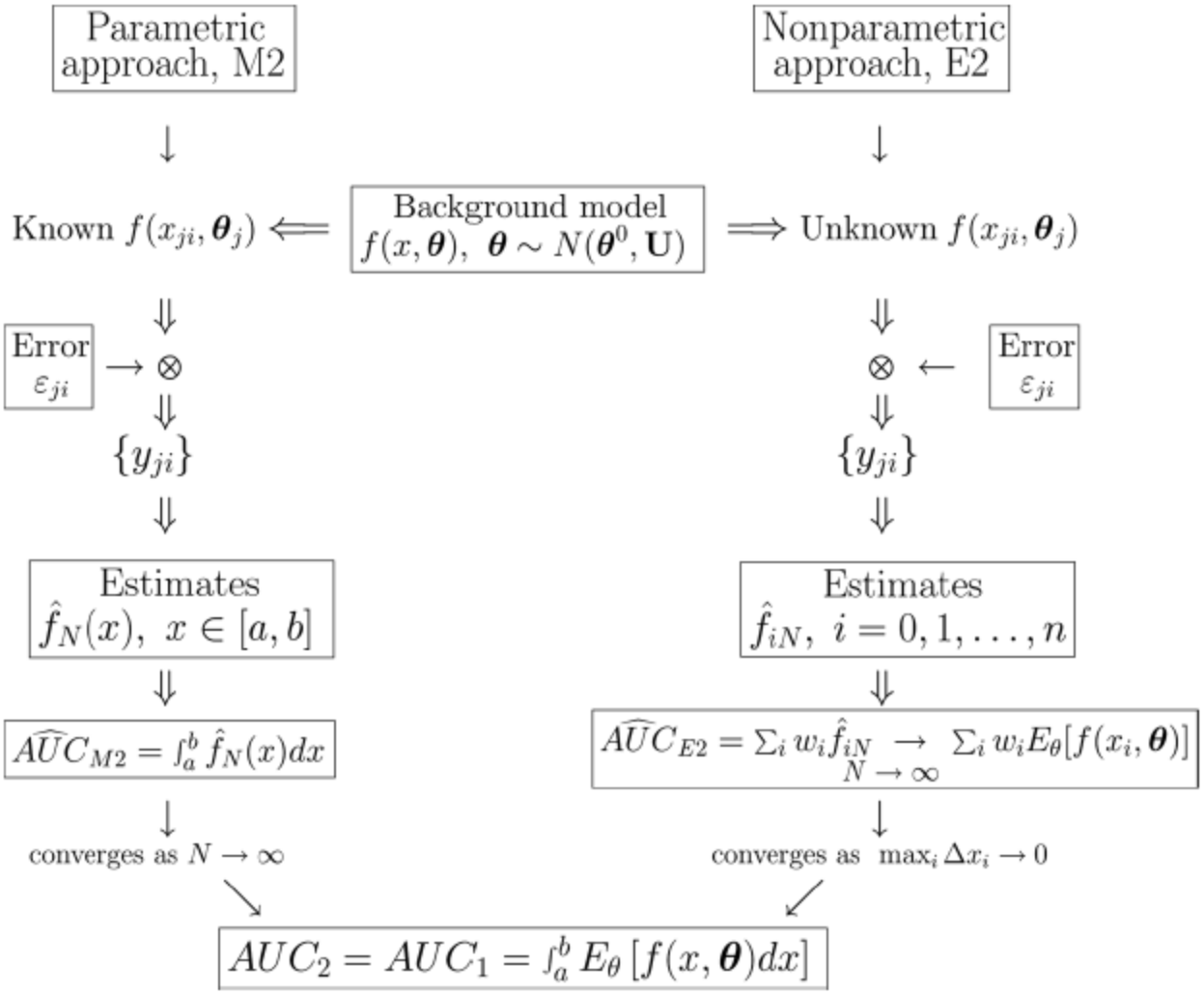
- Get empirical estimates $\widehat{T}_{E2}$, $\widehat{C}_{E2}$ for "population curve" $\{\hat{f}_i\}$, use numerical integration to estimate AUC:

$$\widehat{AUC}_{E2} = \sum_{i=1}^{n} \int_{x_{i-1}}^{x_i} g(x, \mathbf{a}_i)dx \quad (g - \text{interpolant passing through } \hat{f}_{i-1} \text{ and } \hat{f}_i)$$

- Metrics: AUC_2, T_2, C_2
- Sparse sampling: E2 - method of choice

Approaches: model-based vs. nonparametric

MSE as a metric



Numerical integration

(1) Trapezoidal rule : $I_i = \int_{x_{i-1}}^{x_i} g(x, \mathbf{a}_i)dx = \Delta x_i \frac{\hat{f}_{i-1} + \hat{f}_i}{2}$

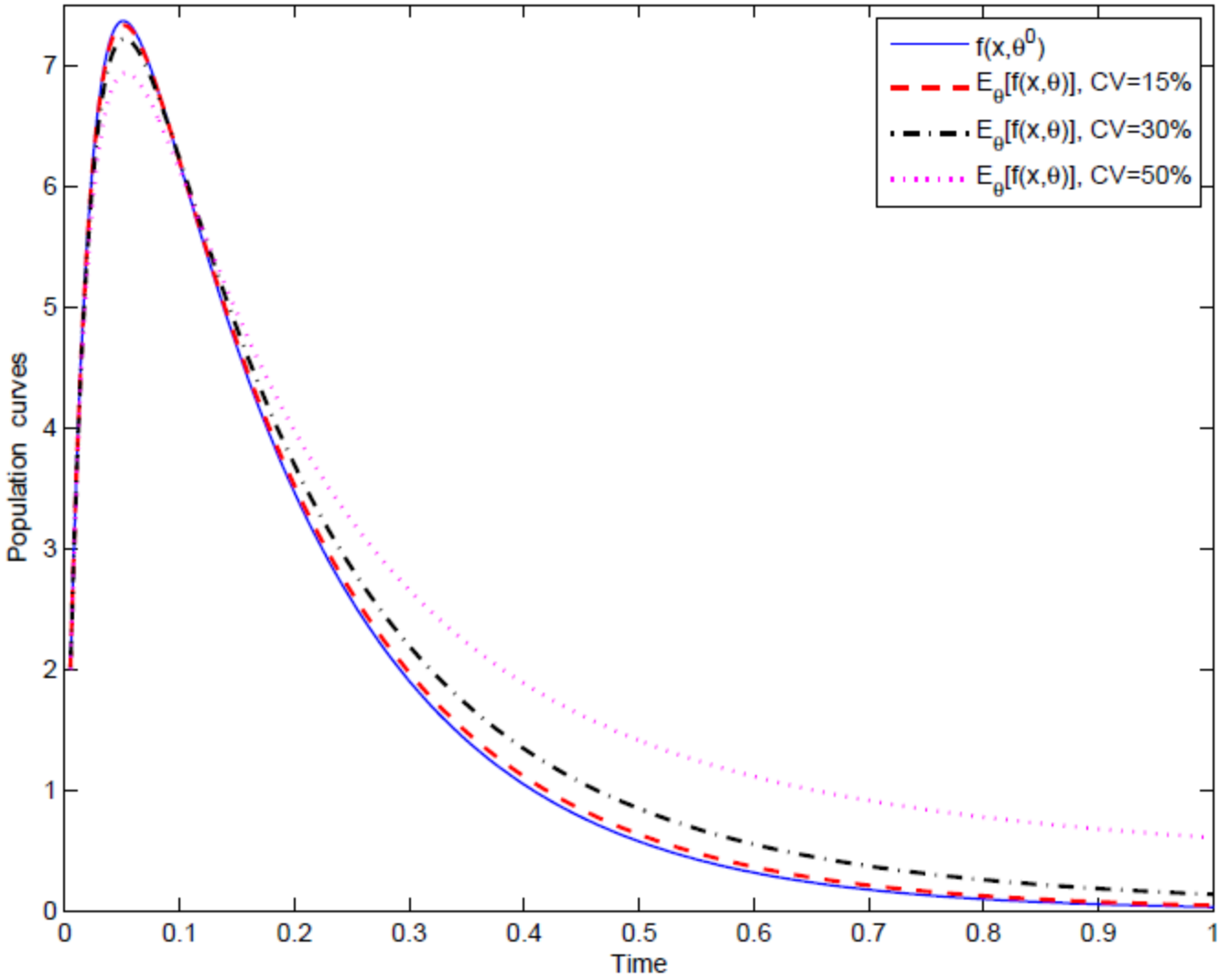
(2) Log-trapezoidal rule : $I_i = \Delta x_i \frac{\hat{f}_i - \hat{f}_{i-1}}{\log(\hat{f}_i / \hat{f}_{i-1})}$ (exact for exponential)

(3) Hybrid method: use (1) before T_{max} and (2) - after T_{max}

(4) Cubic splines: piecewise cubic polynomial

Comparison of population curves

Type III curve $f(x, \theta^0)$ and Type II curves $\bar{f}(x) = E_\theta [f(x, \theta)]$



Sampling schemes

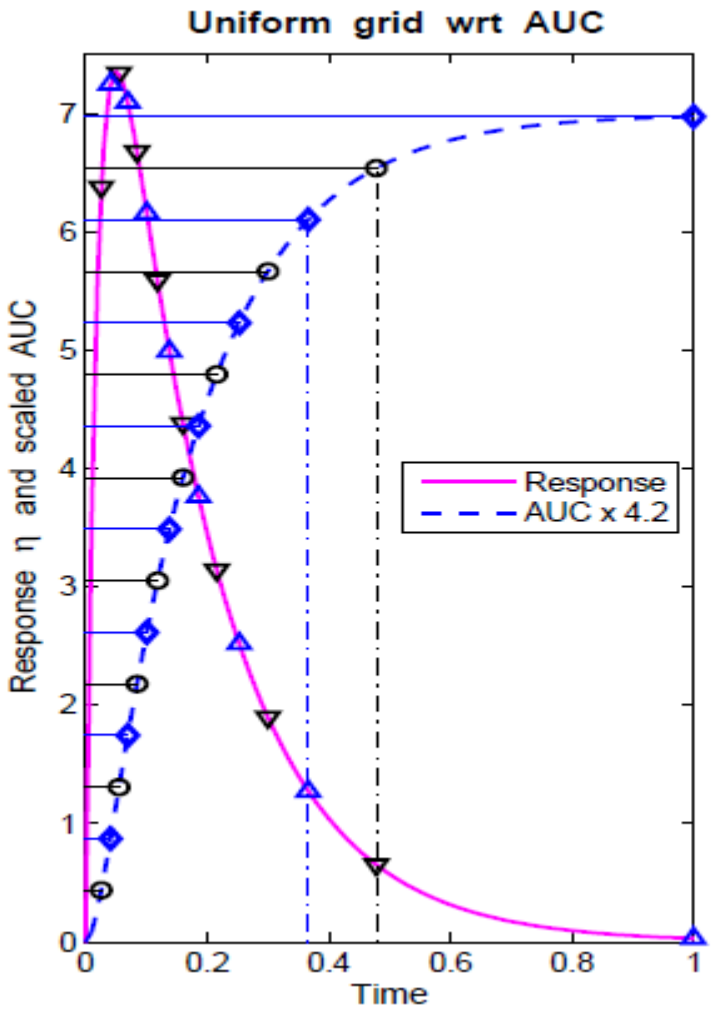
PK studies

- Dense sampling at the left end (after administering the drug),
- Sparse sampling after T_{max}

Alternative schemes

- Take a uniform grid on the *Y*-axis with respect to values of response and project points on the response curve to the *X*-axis
- Take a uniform grid on the *Y*-axis with respect to values of *AUC*
- López-Fidalgo, Wong (2002): “inverse linear” designs

Sampling schemes (cont.)



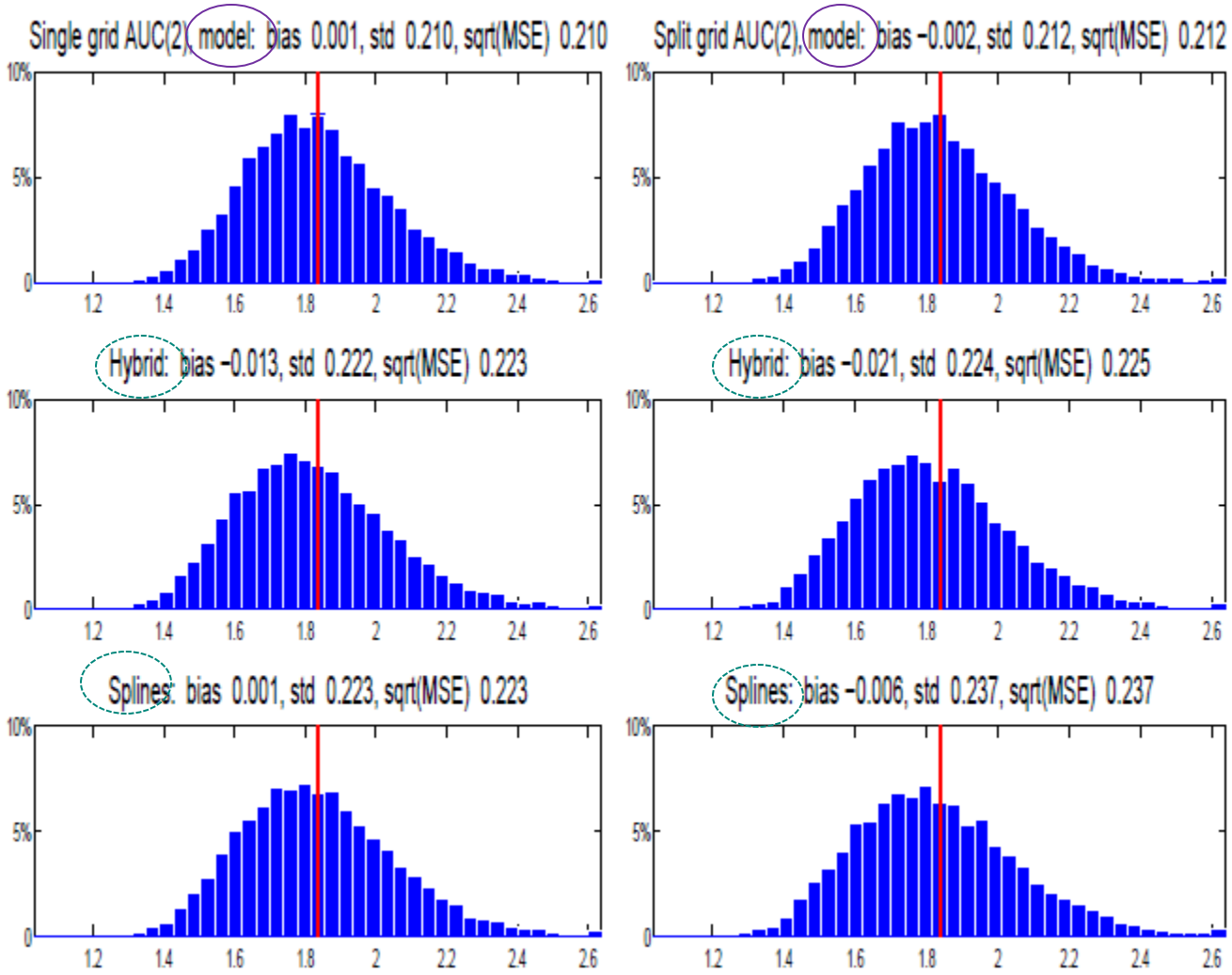
Splitting grids

- Let $\{x_i, \quad i = 1, \ldots, 2n\}$ be a single grid with $2n$ sampling points,
- Take samples at $\{x_{2i-1}, \ i = 1, \ldots, n\}$ for $N/2$ subjects
- Take samples at $\{x_{2i}, \ i = 1, \ldots, n\}$ for the rest half
- Empirical estimate of AUC, method E2: average responses in two series (half-cohorts) separately, then combine two series and get AUC_{E2}.

Total number of samples is reduced by half

Type II measure: *AUC*

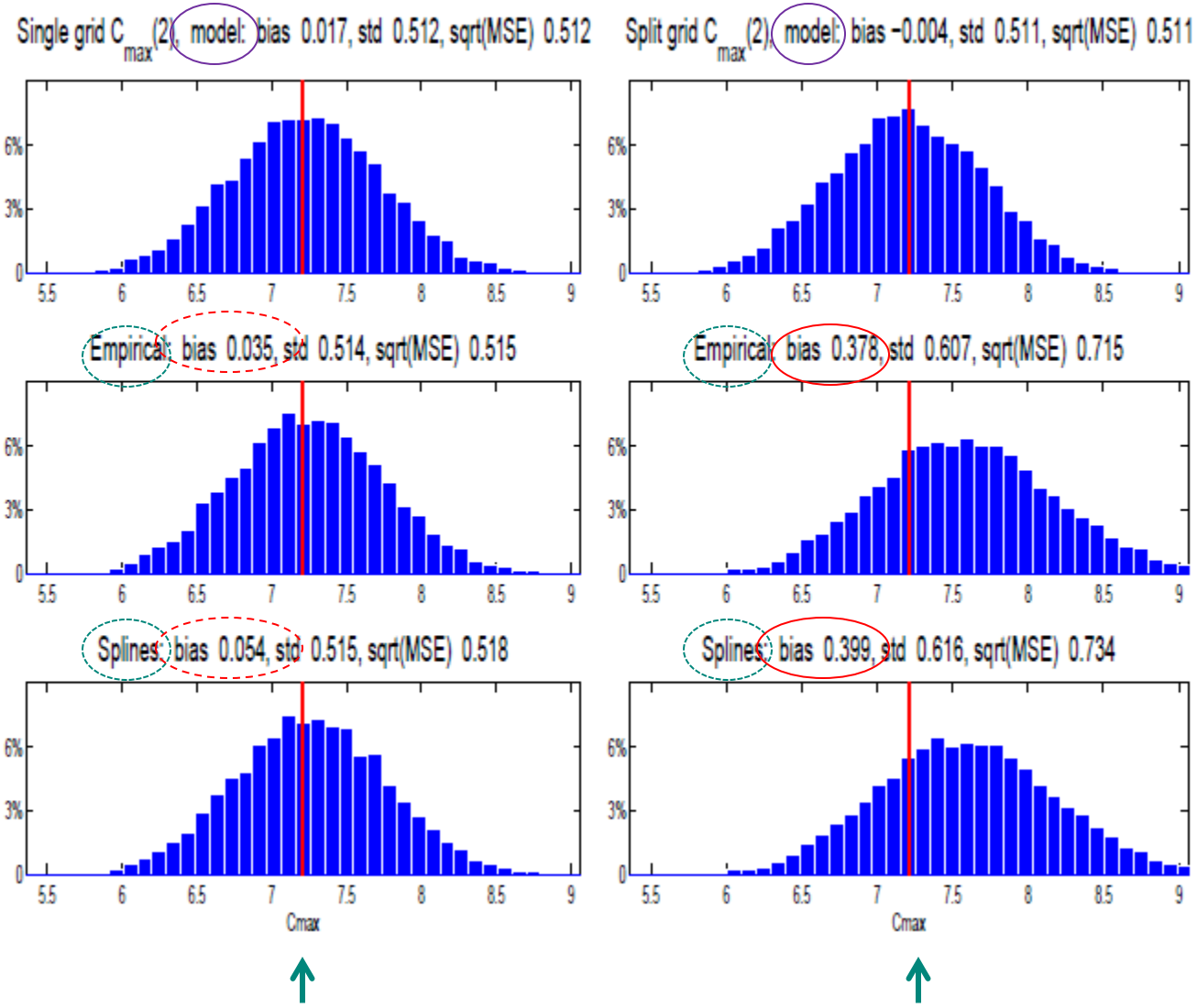
Start with averaging responses at each x_i



Single grid

Split grid

Type II measures: C_{max}



AUC_2: closed-form solution for MSE

- Response - 2nd order polynomial: $f(x, \theta) = \theta_0 + \theta_1 x + \theta_2 x^2$,
- Population variability: intercept only, $Var(\theta_{0j}) = s^2$,

Single grid:

$$MSE_{(1)} = \underbrace{\left[\frac{f''_x(\tilde{x}, \theta)}{12}\frac{1}{4n^2}\right]^2}_{Bias_{(1)}} + \underbrace{\left[\frac{\sigma^2}{2Nn} + \frac{s^2}{N}\right]}_{Var_{(1)}}$$

Split grid:

$$MSE_{(2)} = \underbrace{\left[\frac{f''_x(\tilde{x}, \theta)}{12}\frac{1}{4n^2}\right]^2}_{Bias_{(2)}} + \underbrace{\left[\frac{\sigma^2}{Nn} + \frac{s^2}{N}\right]}_{Var_{(2)}}$$

(no difference!)

(no difference population term)

No costs: - single grid ($2n$ samples/patient) will always be "better"

- how much "better": depends on values of f'', σ^2 and s^2

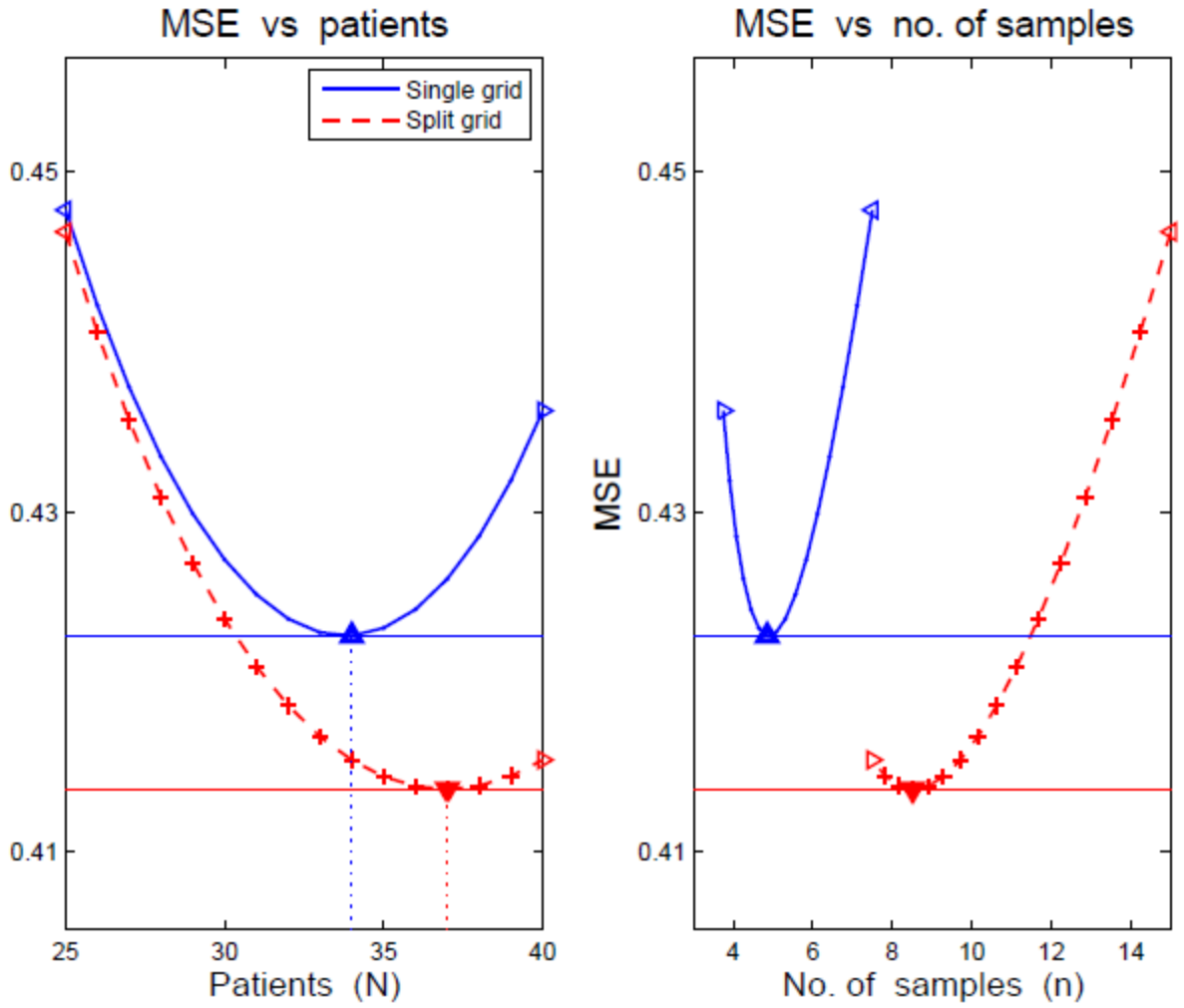
Cost-based designs

- c_s - cost of analyzing a sample, c_p - cost of patient enrollment,
- C_{total} - budget (resource)
- Overall cost, single grid: $2n\ N\ c_s\ +\ Nc_p\ \leq\ C_{total},$ (C1)
- Overall cost, split grid: $n\ N\ c_s\ +\ Nc_p\ \leq\ C_{total}.$ (C2)

Thus, values of n and N are not independent! Given C_{total},

- for a given N, find maximal $n = n(N, C_{total})$ satisfying (C1) or (C2),
- fix n, then find maximal $N = N(n, C_{total})$ satisfying (C1) or (C2)

MSE as function of *N* (left) or *n* (right)



Parameters: $c_s = 100,\ c_p = 500,\ C_{total} = 50000,\ s = 2.4,\ \sigma = 9,\ f'' = 100$

Concluding remarks

- Population PK measures, model-based vs nonparametric: more precise estimation with model-based (*often not by much*)
- No. of samples can be reduced without significant loss of efficiency
  - Design optimality criteria for parameter estimation
  - MSE for nonparametric approach
- Cost-based designs: sampling schemes with smaller number of samples may become optimal
- Alternative types of split grids:
  - Cohort 1: more samples immediately after administering the drug, Cohort 2: more samples in the elimination phase (may reduce study costs)
- Population vs. measurement components of variability
- Software tools available to compare designs and find OD

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Questions:

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