Estimation of Population PK Measures: Selection of Sampling Grids

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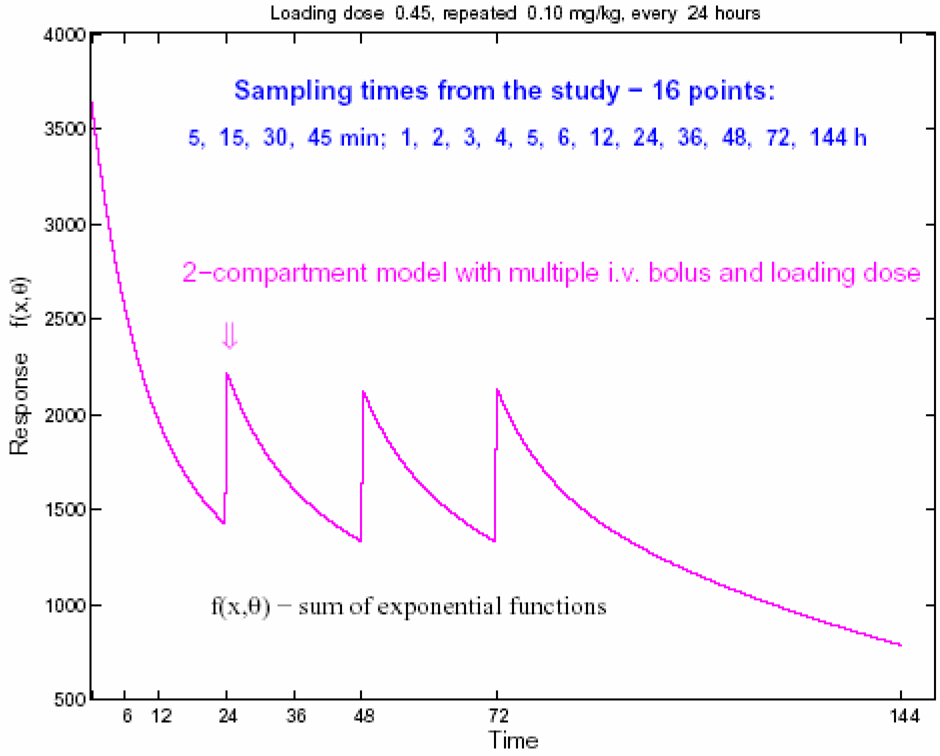
Outline

- Motivation: earlier study, model-based optimal population designs
- Model-based vs empirical (non-compartmental) approaches
- Sampling grids
- Splitting sampling grids
- AUC estimation: mean squared error for empirical approach
- Cost-based designs

Earlier study: Gagnon, Leonov (2005)



Questions

1. How many samples to take?
2. At which times?

"Better" sampling scheme ⇔ better precision of parameter estimates

Information matrix, alternative normalizations

$\mu(\mathbf{x}, \boldsymbol{\vartheta})$ - 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*,

$$\mathbf{M}(\xi, \boldsymbol{\vartheta}) = \sum_{i=1}^{n} p_i \, \boldsymbol{\mu}(\mathbf{x}_i, \boldsymbol{\vartheta}), \quad \xi = \{(\mathbf{x}_i, p_i), \; p_i = \frac{n_i}{N}, \; \mathbf{x}_i \in \mathcal{X}\}$$

ξ - normalized (continuous) design, $\mathcal{X}$ - design region

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

Fedorov, Gagnon, Leonov (2002), Gagnon, Leonov (2005), Retout, Mentré (2003)

Information matrix, cost-based designs

2. Measurements at $\mathrm{x_i}$ associated with cost $c(\mathrm{x_i})$,

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

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

$\tilde{p}_i = n_i c(\mathrm{x_i})/\mathcal{C}$; $\tilde{\boldsymbol{\mu}}(\mathrm{x_i}, \boldsymbol{\vartheta}) = \boldsymbol{\mu}(\mathrm{x_i}, \boldsymbol{\vartheta})/c(\mathrm{x_i})$ $\implies$ same framework,

standard numerical algorithms

Costs in design problems: *Elfving (1952), Cook, Fedorov (1995), Mentré, Mallet, Baccar (1997), Fedorov, Gagnon, Leonov (2002)*

Sampling schemes, earlier results

- Constructed locally D-optimal designs
- No costs: the more samples, the better

  - number of samples may be reduced without significant loss of precision

- Costs introduced (cost of analyzing sample c_s / cost of enrolling patient c_p):

  - sequences with smaller number of samples may become optimal

  - optimal: combination of sequences (different schemes for different cohorts)

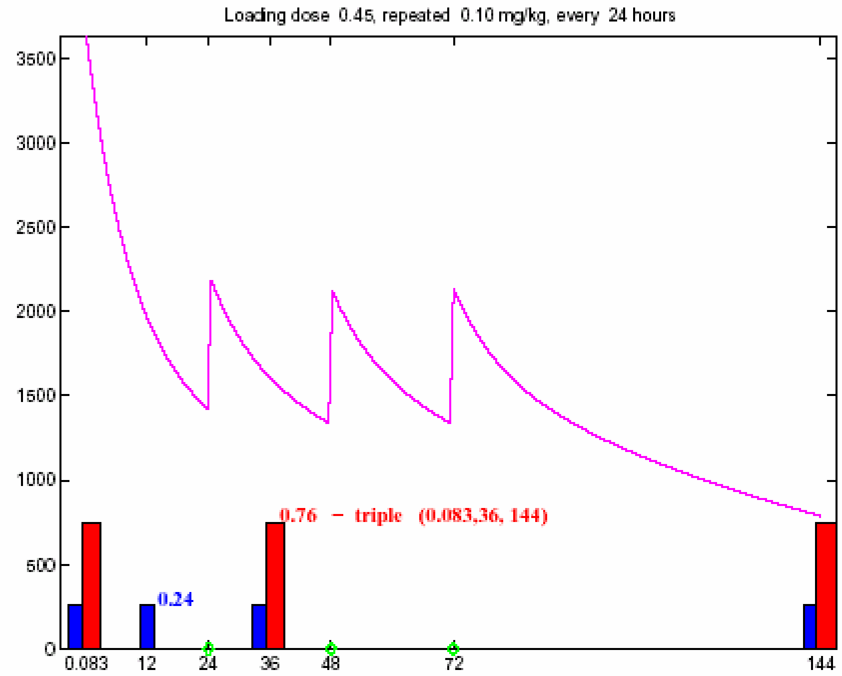
- Software developed: (1) Matlab: stand-alone, GUI-based

  (2) SAS *(Fedorov et al. (2006))*

Earlier study: cost-based design (compartmental model)

Allowed: 3-,4- and 5-sample sequences (candidate times - from original study)

Optimal population design: two sequences (3-sample, 76% of patients; 4-sample, 24%)



Practical issues

- Often interested in certain PK measures (not parameters):

  area under the curve (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

$$\Downarrow$$

We compare two approaches:

- model-based (compartmental) as a benchmark

- empirical (non-compartmental or nonparametric)

General model

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

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)

$N = \#\{\text{enrolled patients}\}$, $n_j = \#\{\text{sampling times for patient } j\}$,

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

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

One-compartment model (simulations)

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

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 $s_i = 0.15\ \theta_i$.

Model-based (compartmental) approach

Method 1: start with individual estimates of PK measures

- For each patient, parameters $\bar{\boldsymbol{\theta}}_j$ are estimated (MLE, NLS), then

$$AUC_j = \int_a^b f(x, \bar{\boldsymbol{\theta}}_j) dx, \quad C_{max,j} = \max_x f(x, \bar{\boldsymbol{\theta}}_j), \quad T_{max,j} = \arg\max_x f(x, \bar{\boldsymbol{\theta}}_j).$$

- Individual estimates are averaged across population:

$$AUC_{M1} = \frac{1}{N} \sum_{j=1}^{N} AUC_j, \quad \text{same for } T_{max,M1} \text{ and } C_{max,M1}.$$

Method 2: average individual parameter estimates $\hat{\boldsymbol{\theta}} = \sum_j \bar{\boldsymbol{\theta}}_j / N$,

- Use $\hat{\boldsymbol{\theta}}$ to obtain population estimates

$$AUC_{M2} = \int_a^b f(x, \hat{\boldsymbol{\theta}}) dx, \quad C_{max,M2} = \max_x f(x, \hat{\boldsymbol{\theta}}), \quad T_{max,M2} = \arg\max_x f(x, \hat{\boldsymbol{\theta}}).$$

Empirical (non-compartmental) approach

Method 1: for each patient, get individual $T_{max,j}$, $C_{max,j}$, AUC_j

- Average individual estimates to obtain population estimates

$$T_{max,E1} = \frac{1}{N}\sum_{j=1}^{N} T_{max,j}, \quad \text{same for } C_{max,E1} \text{ and } AUC_{E1}$$

Sparse sampling: method 1 cannot be used

Method 2: responses at each time point are averaged across patients,

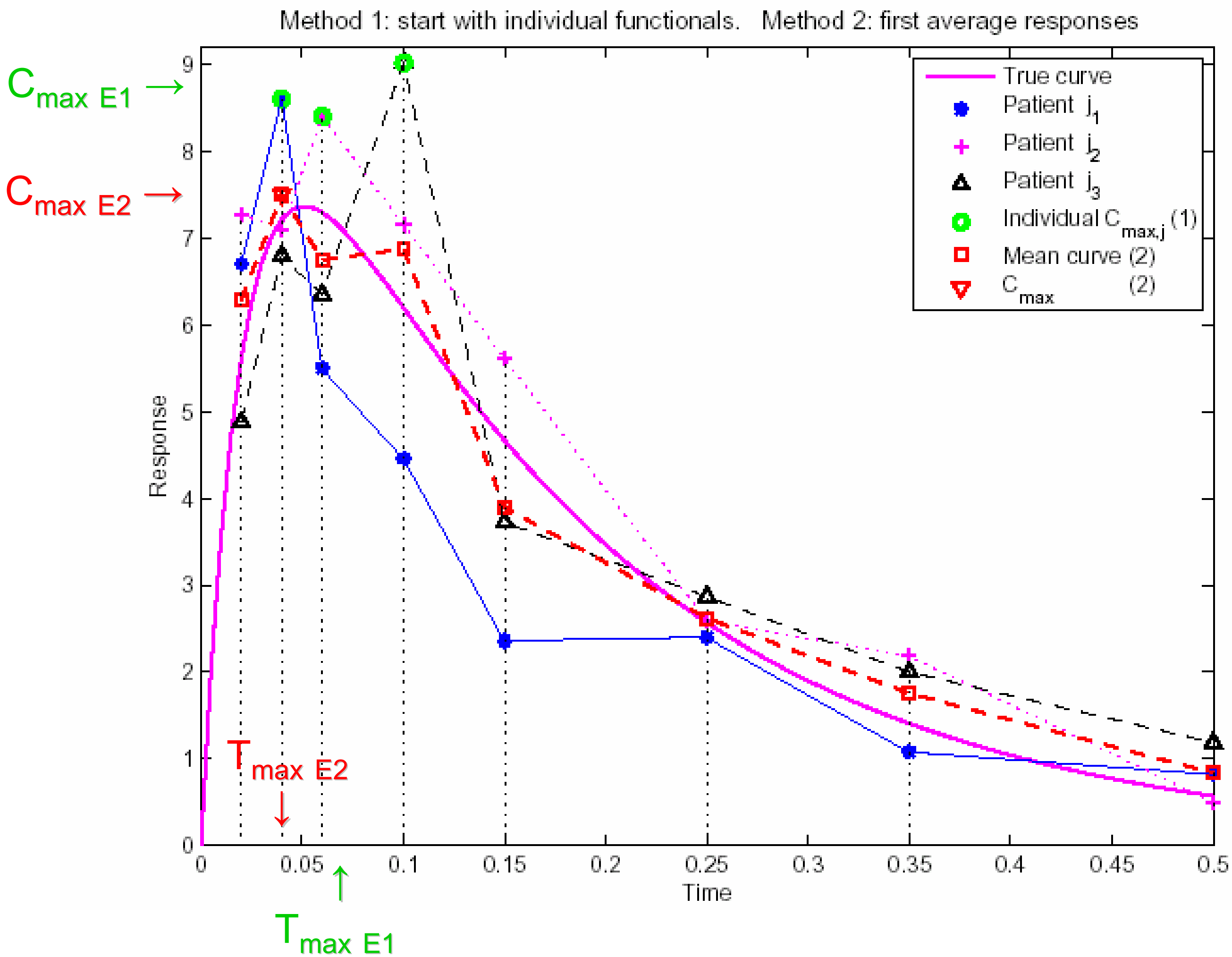
$$\hat{f}_i = \frac{1}{N}\sum_{j=1}^{N} y_{ij}, \quad i = 0, \ldots, n.$$

- Get estimates $T_{max,E2}$, $C_{max,E2}$ for 'population curve' $\{\hat{f}_i\}$,

  use numerical integration to estimate AUC_{E2}:

$$AUC_{E2} = \sum_{i=1}^{2n} \int_{x_{i-1}}^{x_i} g(x, \mathbf{a}_i)dx \quad (g - \text{interpolant passing through } \hat{f}_{i-1} \text{ and } \hat{f}_i)$$

Averaging methods, population PK measures



Numerical integration

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

(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} (descending portion)

(4) Cubic splines: piecewise cubic polynomial (join in the knots $\{x_i\}$, obeying continuity conditions for f and its first two derivatives)

Sampling schemes

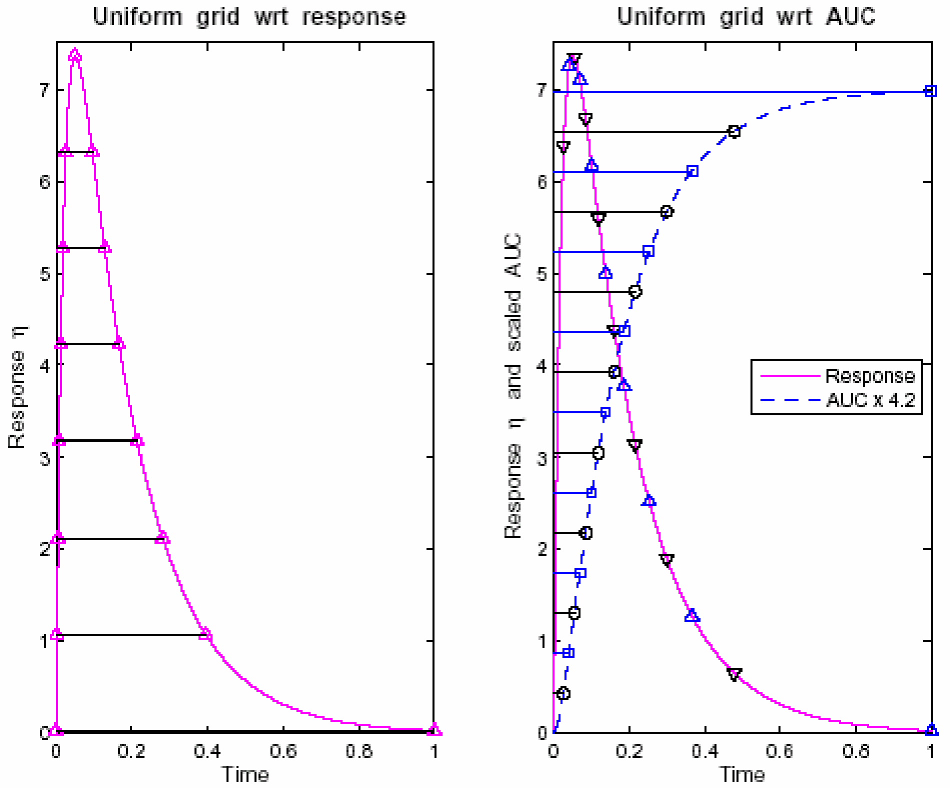
PK studies: more samples at the left end (immediately after administering the drug), then more sparse sampling (after 'anticipated' T_{max})

Alternative sampling 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 (next slide, left panel)
- Take a uniform grid on the Y-axis with respect to values of AUC (next slide, right panel)

Simulations: 16 sampling times, N=20 (patients)

Sampling schemes (cont.)

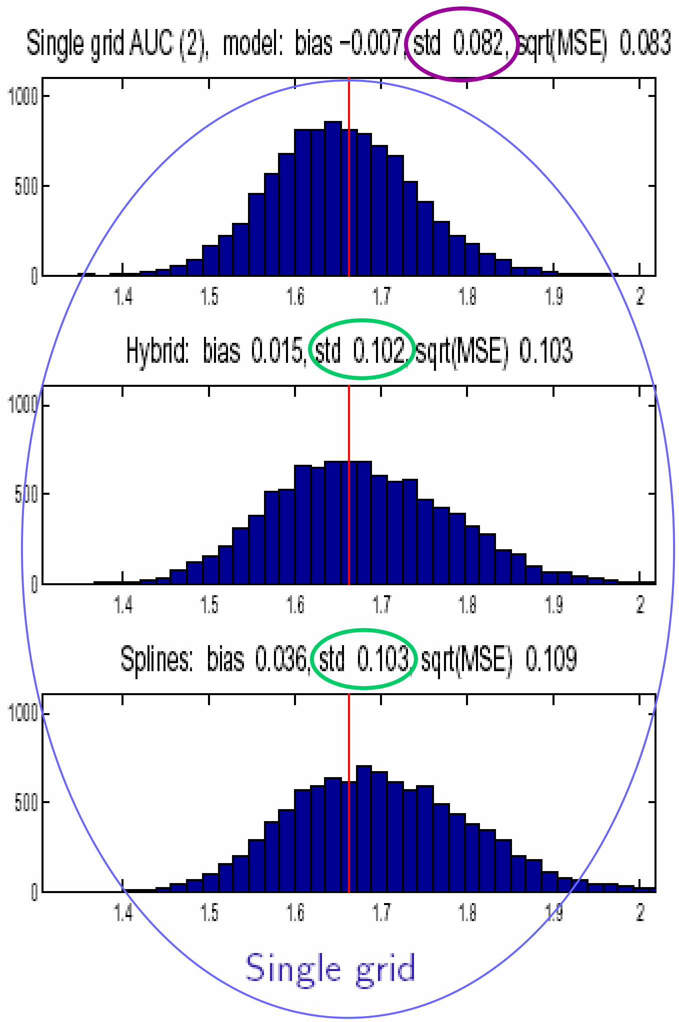


Uniform grid with respect to values of response (left panel) and AUC(right panel).

Black inverted triangles: odd samples on mean response curve; black circles: odd on AUC curve.

Blue triangles: even samples on mean response curve; blue squares: even on AUC curve.

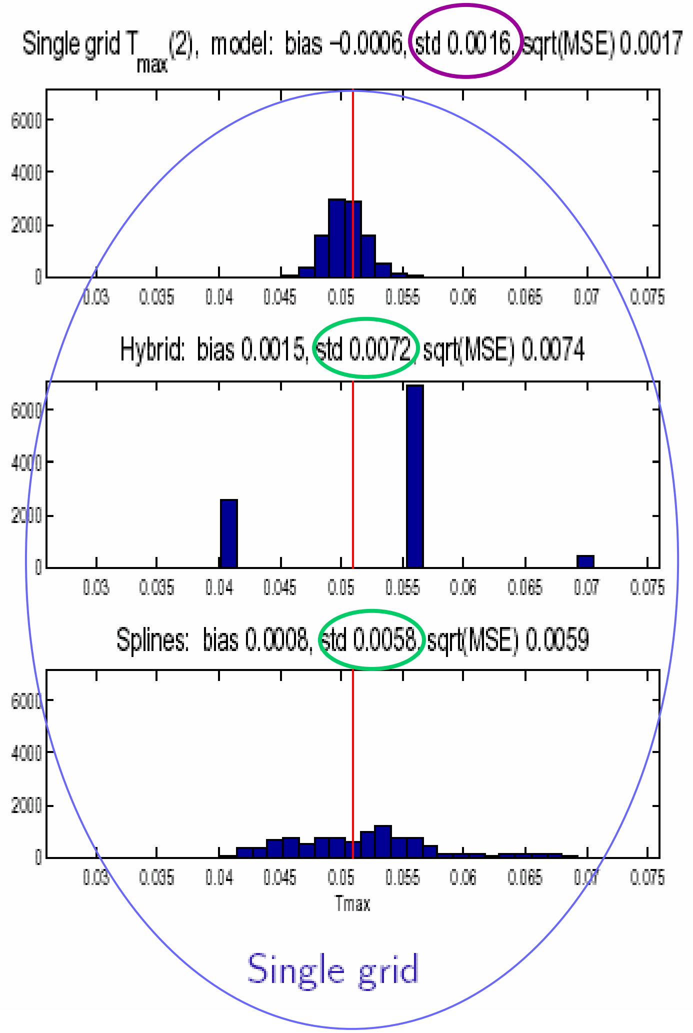
Method 2, AUC: AUC_{true}=1.662



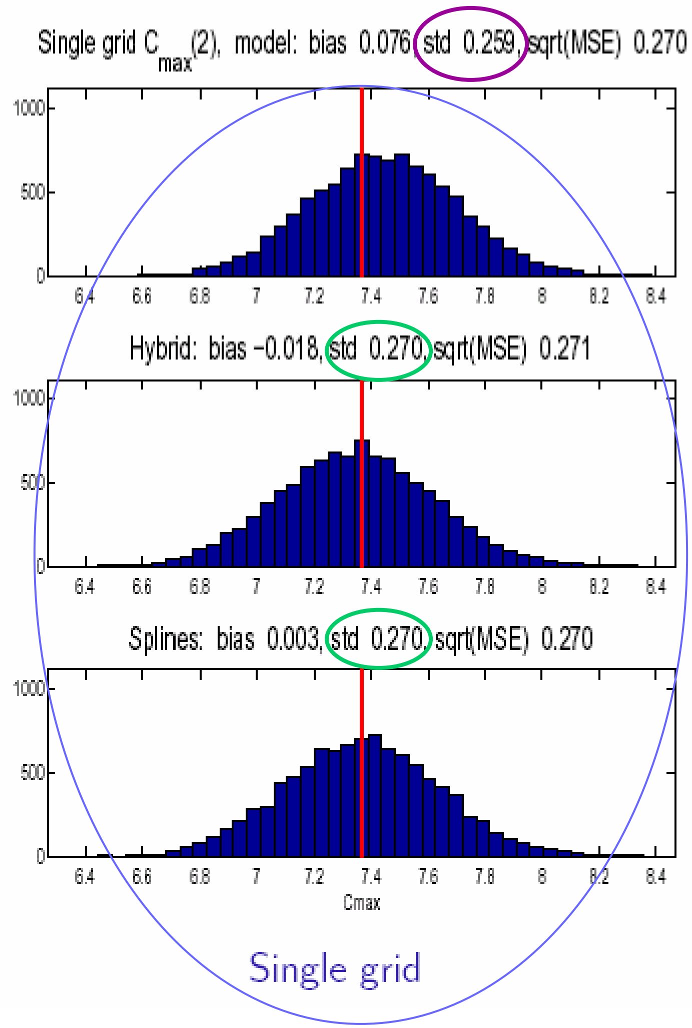
Method 2: first average responses at each x_i

Upper - model-based, middle-hybrid, lower-splines

Method 2, T_{max}: true T_{max}=0.051



Method 2, C_{max}: true C_{max}=7.367

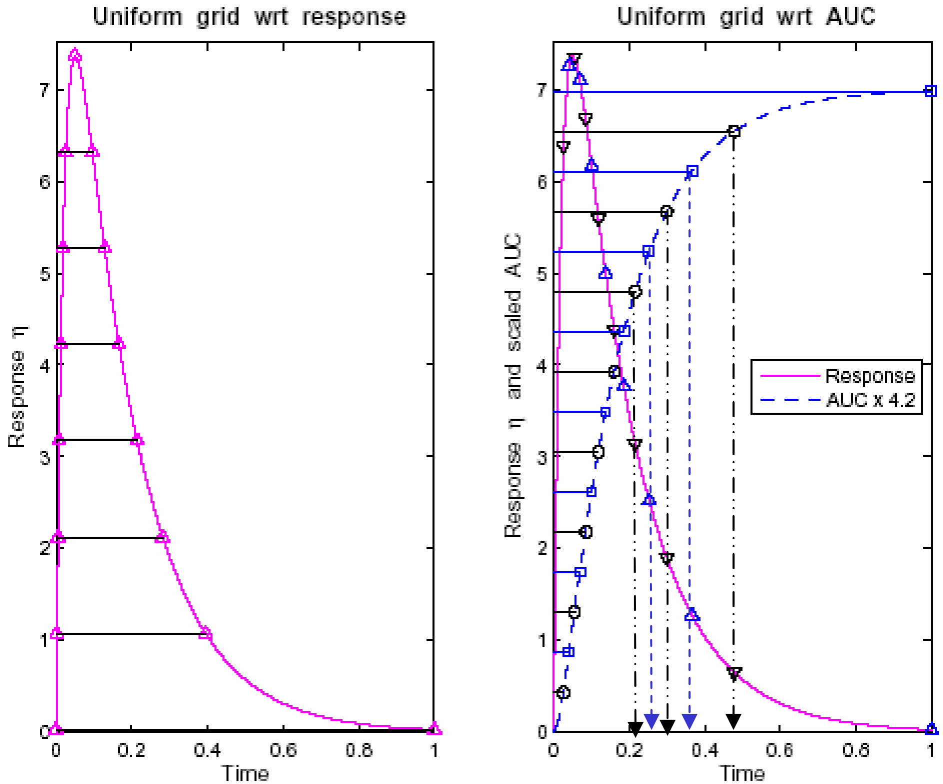


Splitting sampling grids (reducing sampling density)

- Let $\{x_i, \ \ i = 1, \ldots, 2n\}$ be a single grid with $2n$ sampling points,
- Take samples at $\{x_{2i-1}, \ i = 1, \ldots, n\}$ for $N/2$ subjects (black inverted triangles, p.16),
- Take samples at $\{x_{2i}, \ i = 1, \ldots, n\}$ for the rest half (blue triangles, p.16),
- Empirical estimate of AUC, method 2: average responses in two series (half-cohorts) separately, then combine two series and get AUC_{E2}.

Total number of samples is reduced by half - back to histograms

Sampling schemes (cont.)



Uniform grid with respect to values of response (left panel) and AUC(right panel).

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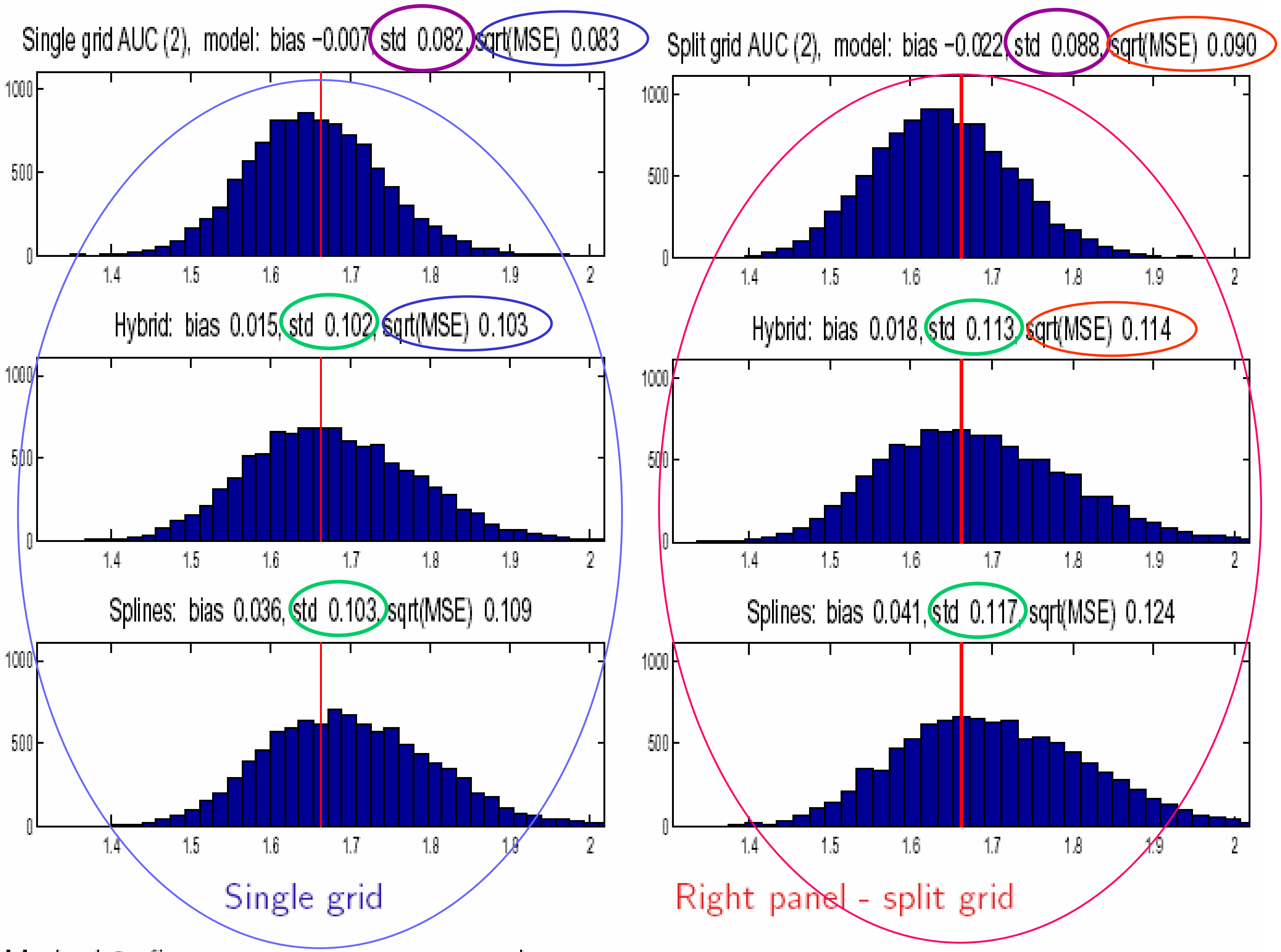
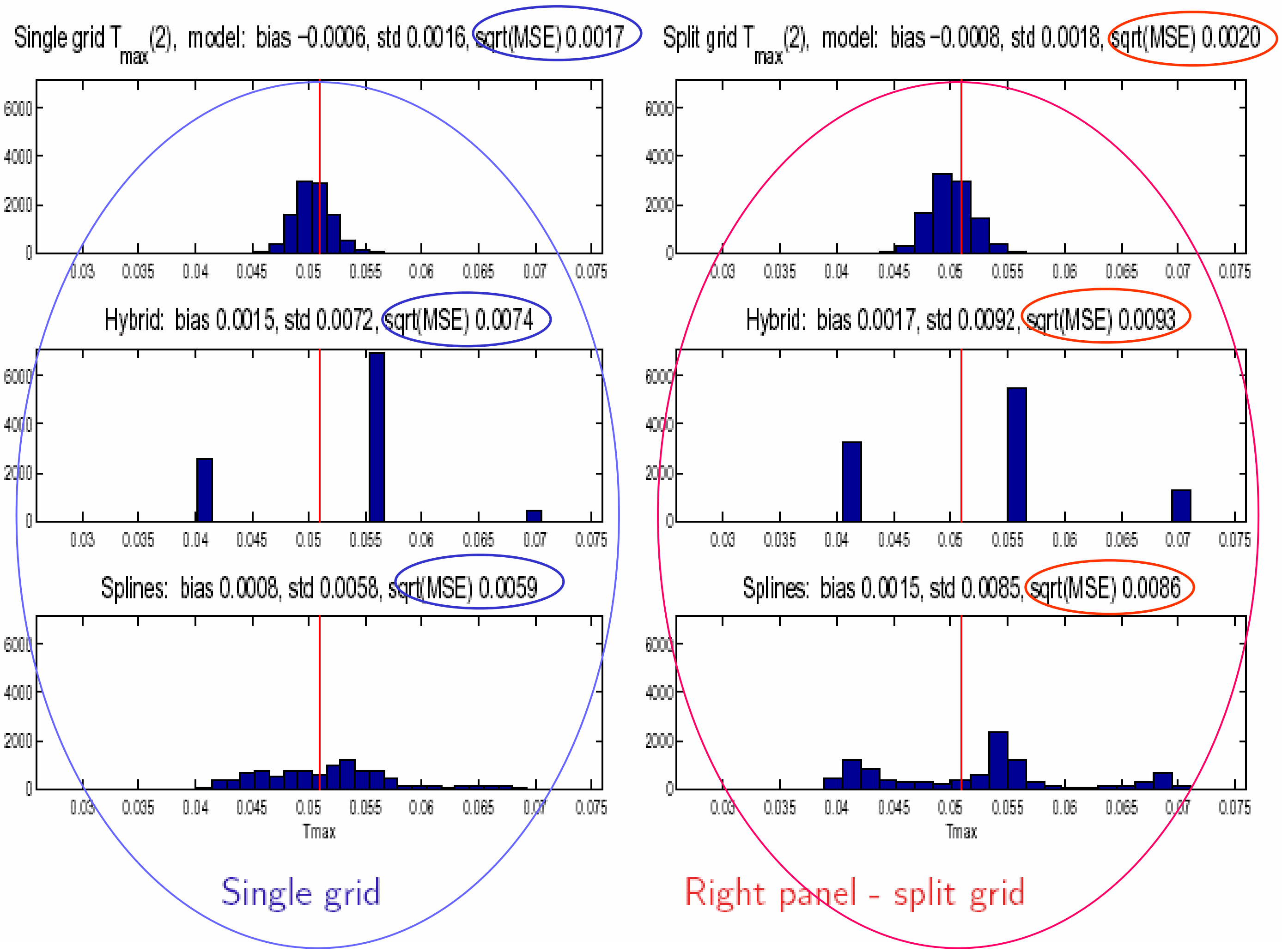
Method 2, AUC: AUC_{true}=1.662



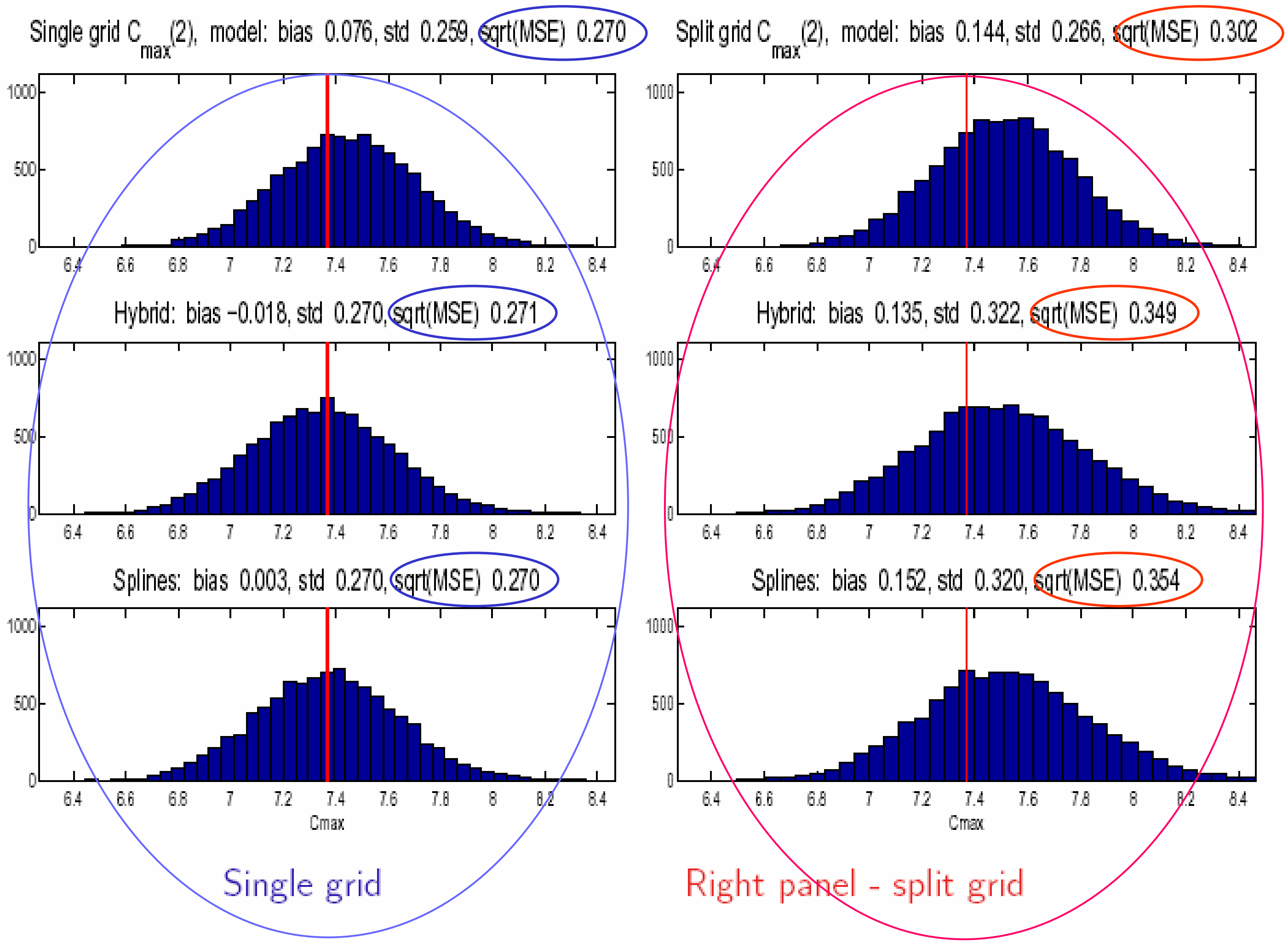
Method 2: first average responses at each x_i

Upper - model-based, middle-hybrid, lower-splines

Method 2, T_{max}: true T_{max}=0.051



Method 2, C_{max}: true C_{max}=7.367



AUC_{E2} : mean squared error for single/split grids

Closed-form solution for a simplified case:

- Response approximated by a 2nd order polynomial:

  $f(x, \theta) = \theta_0 + \theta_1 x + \theta_2 x^2$,

- Population variability: intercept only, $Var(\theta_{0j}) = s^2$,

- Uniform sampling grid

Formulae for MSE

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:

$Bias_{(2)}$ (no difference!) $Var_{(2)}$ (no loss in population term)

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

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

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

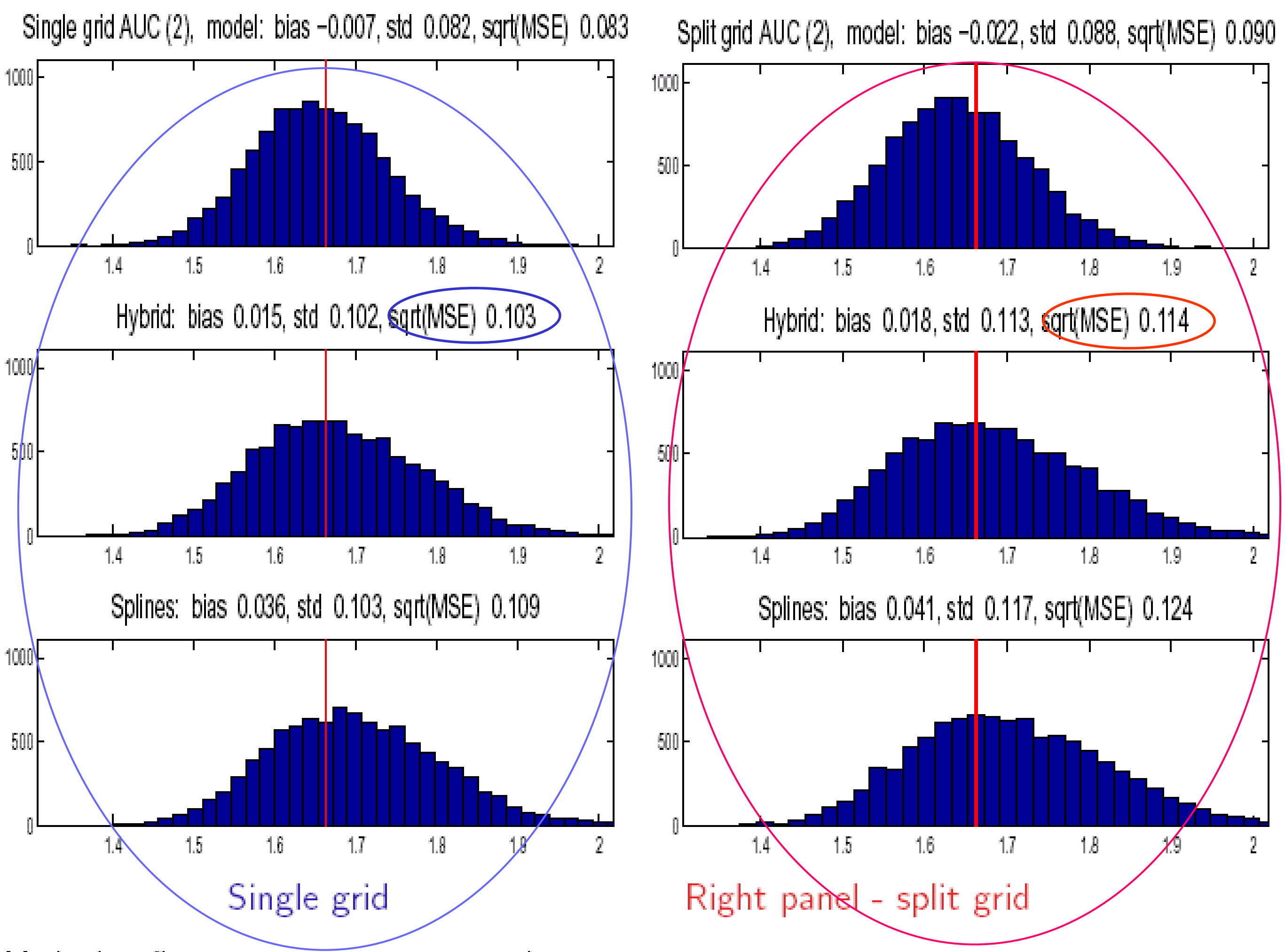
Cost-based optimization

- 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)

Method 2, AUC: AUC_{true}=1.662

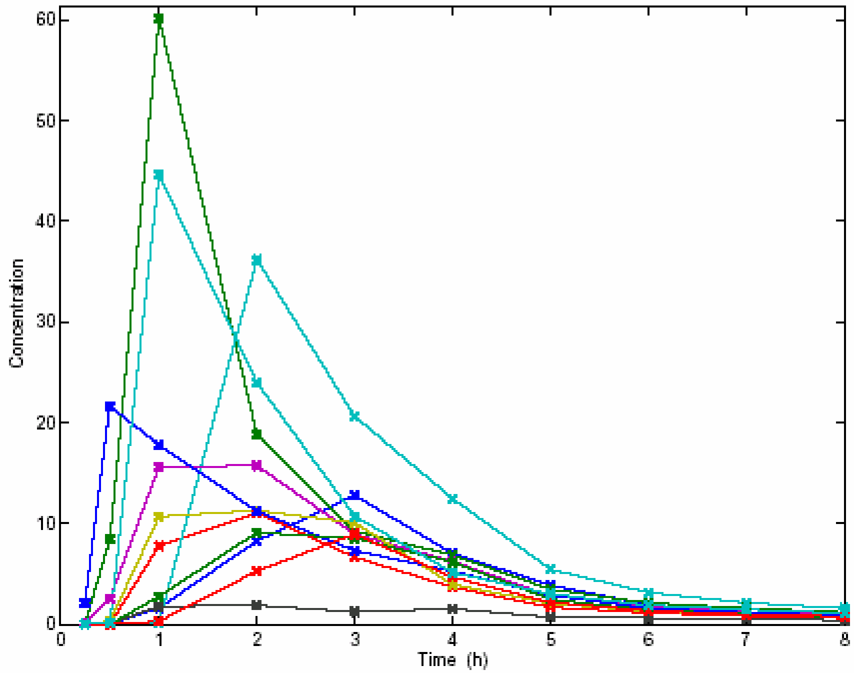


Method 2: first average responses at each x_i

Upper - model-based, middle-hybrid, lower-splines

Costs: $2nNc_s + Nc_p$ $nNc_s + Nc_p$

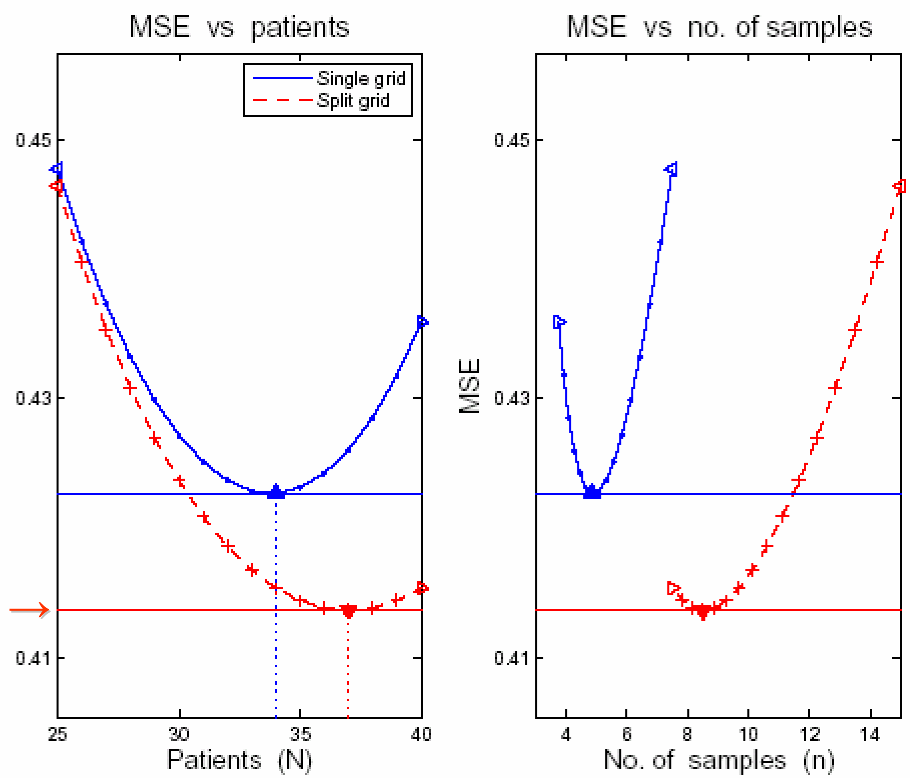
How to select "meaningful" parameters



Concentration-time curves from a real study

- $f(x,\theta) = A - B(x-x_0)^2, \quad \max_x f(x,\theta) = f(x_0,\theta) = A, \quad |f''| \equiv 2B$
- $f(0,\theta) = 0, \ x_0 = 1 \implies A = B.$ From the plot: $x_0 \approx 1, \ \bar{A}_j \sim 40 \implies |f''| \approx 80$
- Range of values: $50 \approx \max_x f(x,\theta_j) - \min_x f(x,\theta_j) \approx 5 \times std \implies$ selected $\sigma + s \sim 10$

MSE as a function of N (left) and n (right), fixed C_{total}



Split grid is better →

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

- Single grid: $N_{opt} = 34,\ n_{opt} = 5,\ MSE_{opt} \approx 0.425$ ($2n_{opt}$=10 samples/subject)
- Split grid: $N_{opt} = 37,\ n_{opt} = 8,\ MSE_{opt} \approx 0.415$

Concluding remarks

- Model-based designs: superior to empirical
- Empirical approach: reasonable performance
- Split grids ("sparse" sampling): may perform quite well (method 2)
- Cost-based designs: more meaningful comparison

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Numerical integration, examples