Population Pharmacokinetic Measures: Estimation and Selection of Sampling Times

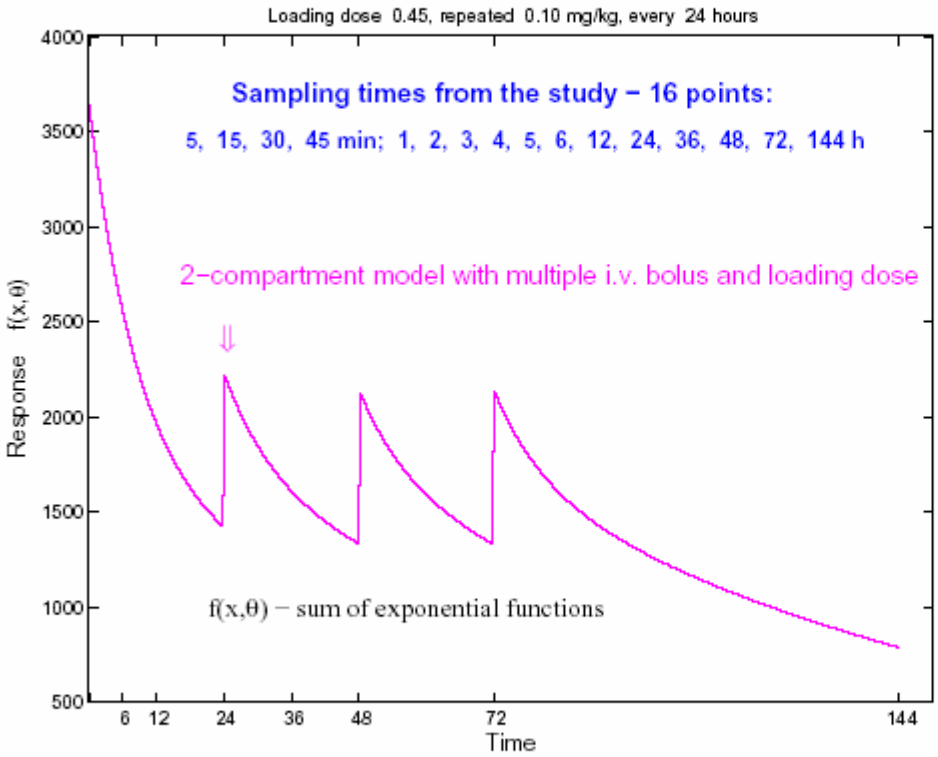
Valerii Fedorov, Sergei Leonov
Research Statistics Unit, Collegeville, PA

Outline

- Motivation: earlier study, model-based optimal population designs
- Parametric (model-based) vs empirical (nonparametric) approaches
- Types of population PK measures (metrics)
- Splitting sampling grids
- Cost-based designs

Details: *Fedorov, Leonov (2007, J. Biopharm. Stat.)*

Earlier study: Gagnon, Leonov (2005)



Questions

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

"Better" sampling scheme $\Leftrightarrow$ 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*, 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 - PODE 2006-08

Information matrix, cost-based designs

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 $\mathcal{C}$,

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

standard numerical algorithms

Costs in design problems: *Elfving (1952), Cook, Fedorov (1995, general setting), 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 (PkStaMp); (2) SAS

Practical issues

- Often interested in 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:

- parametric (model-based, compartmental) as a benchmark
- nonparametric (non-compartmental, empirical)

General 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: $x_{ji} \equiv x_i$, $n_j \equiv 2n$.

One-compartment model (simulations)

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

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

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 $s_i = 0.3\ \theta_i$.

D-optimal designs: from earlier study to current problem

Gagnon, Leonov (2005), candidate sequences: all possible k-point sequences from the set of 16 study sampling times $X = \{x_1, x_2, \ldots, x_{16}\}$.

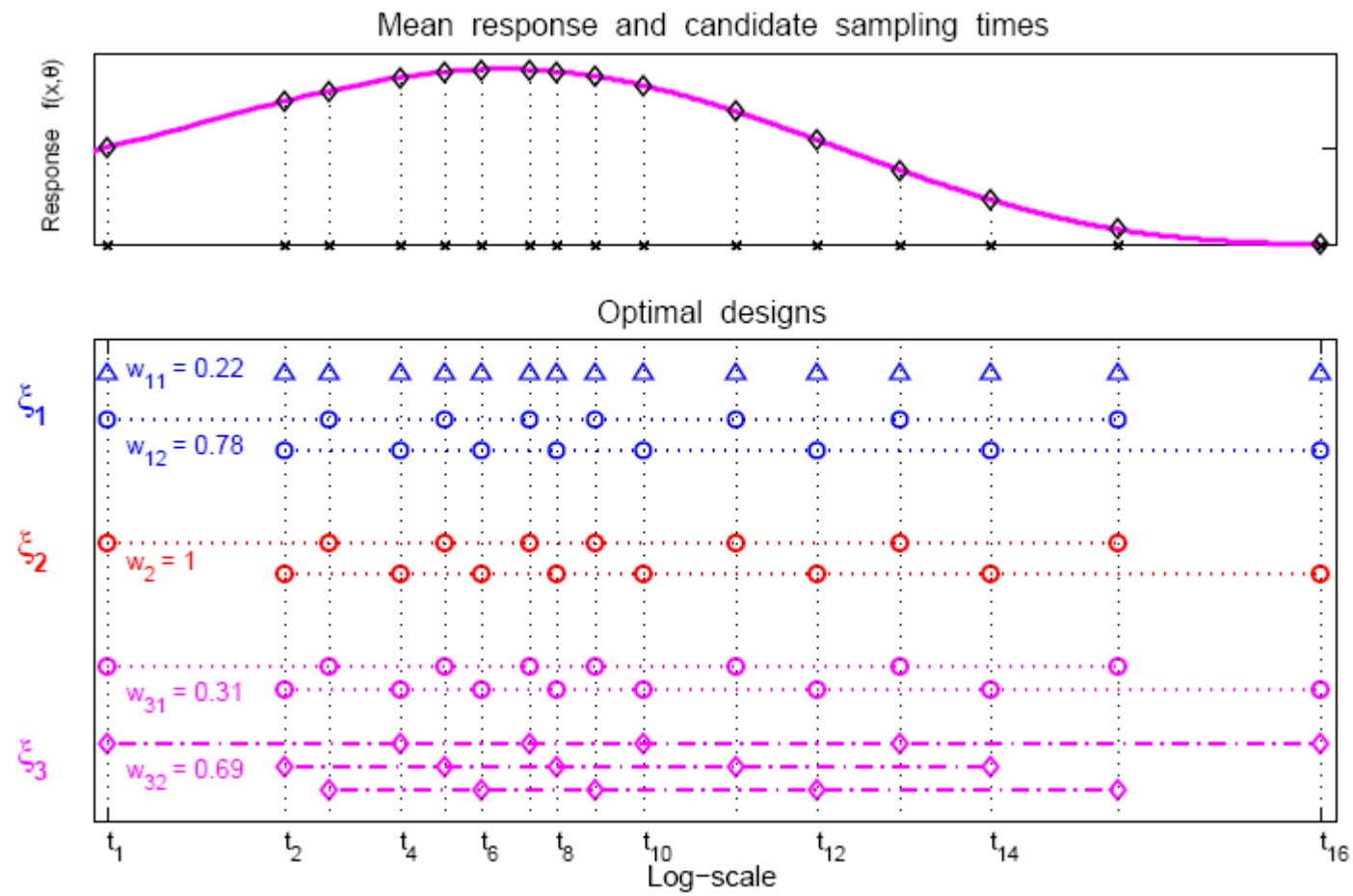
New example: use S-order splits of X, $N = n_1 + n_2 + n_3$

- n_1 patients on $\mathbf{x}_1$: use all n sampling times
- n_2 patients on $\mathbf{x}_2$: times $\mathbf{x}_{21} = \{x_1, x_3, x_5, \ldots\}$ for $n_2/2$ patients,
  $\mathbf{x}_{22} = \{x_2, x_4, x_6, \ldots\}$ 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 $(n_3/3)$
  $\mathbf{x}_{33} = \{x_3, x_6, x_9, \ldots\}$, 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 cost-based designs, one-compartment model

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

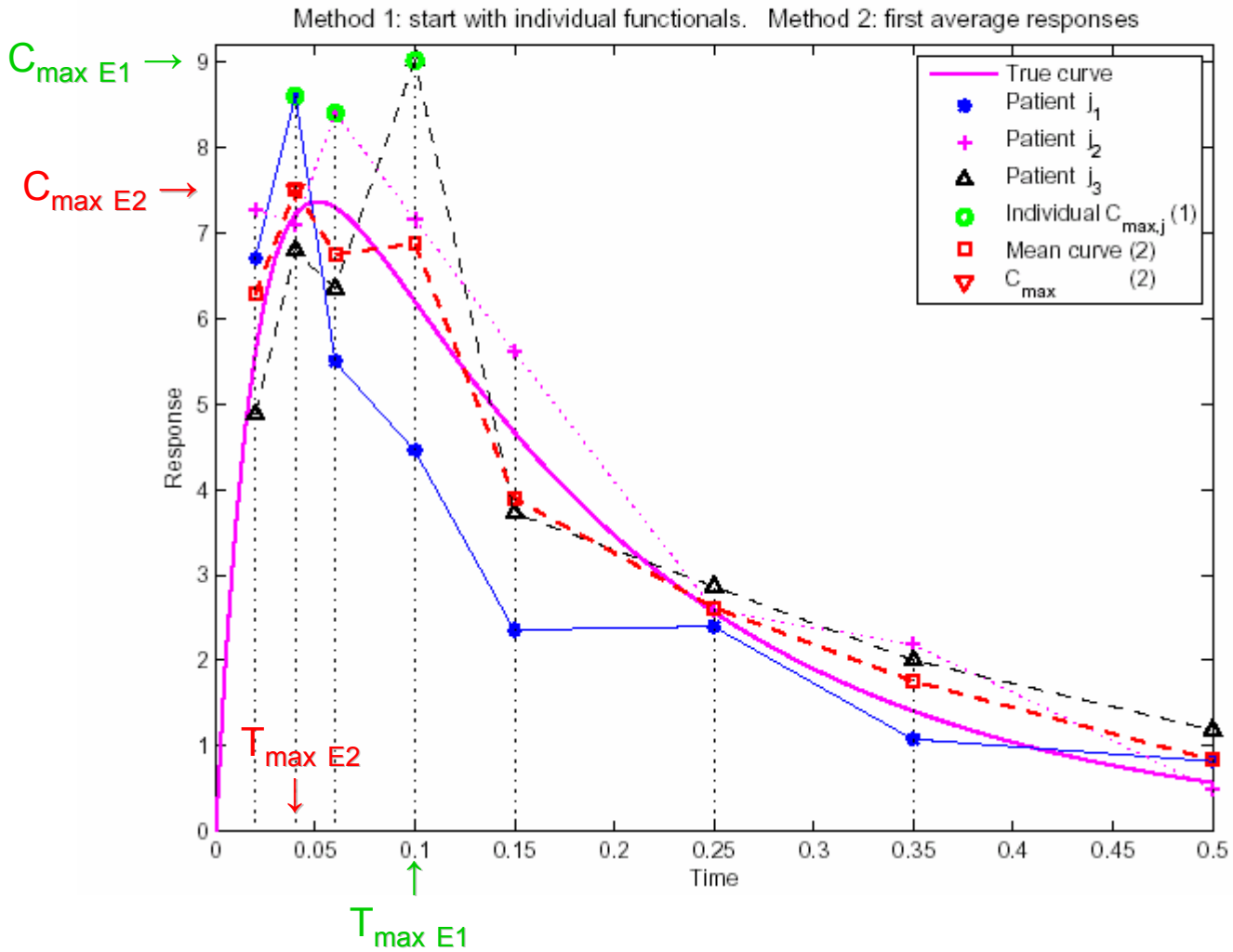


Today: population measures, MSE as criterion, nonparametric approach

Potential approaches

	Model-based	Empirical
	Info used: specific $f(x, \boldsymbol{\theta})$ and y_{ji}	Info used: measurements y_{ji} only
I	(0) Estimate individual $\hat{\boldsymbol{\theta}}_j$ (a) Compute individual PK estimates: $\widehat{AUC}_j = \int_a^b f(x, \hat{\boldsymbol{\theta}}_j) dx$, $\widehat{C}_{max,j} = \max_x f(x, \hat{\boldsymbol{\theta}}_j)$, $\widehat{T}_{max,j} = \arg\max_x f(x, \hat{\boldsymbol{\theta}}_j)$ (b) Then average across population: $\widehat{AUC}_I = \frac{1}{N} \sum_{j=1}^N \widehat{AUC}_j$ etc.	(a) Use sample estimates: $\widehat{AUC}_j$ - numerical integration, $\widehat{C}_{max,j} = \max_i y_{ji} = y_{ji^*}$, $\widehat{T}_{max,j} = x_{i^*}$ (b) Do averaging: $\Leftarrow$ exactly the same
II	(0) Estimate individual $\hat{\boldsymbol{\theta}}_j$ (a) Average parameter values: $\widehat{\boldsymbol{\theta}} = \sum_j \widehat{\boldsymbol{\theta}}_j / N,$ (b) Then get population measures: $\widehat{AUC}_{II} = \int_a^b f(x, \widehat{\boldsymbol{\theta}}) \, dx, \; \widehat{C}_{II}, \; \widehat{T}_{II}$	(a) Get "population" curve $\hat{f}_i = \frac{1}{N} \sum_{j=1}^N y_{ji}, \; i = 0, \ldots, n$ (b) Get empirical estimates for "population curve" $\{\hat{f}_i\}$: $\widehat{AUC}_{II}, \; \widehat{T}_{II}, \; \widehat{C}_{II}$

Averaging methods, population PK measures



Model-based (compartmental) approach

All methods start with individual parameter estimates $\boldsymbol{\theta}_j$ (MLE, nonlinear LS)

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) approach (cont.)

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) approach (cont.)

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) approach

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) approach (cont.)

Type II, Method E2: *averaging responses*

- Get average curve

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

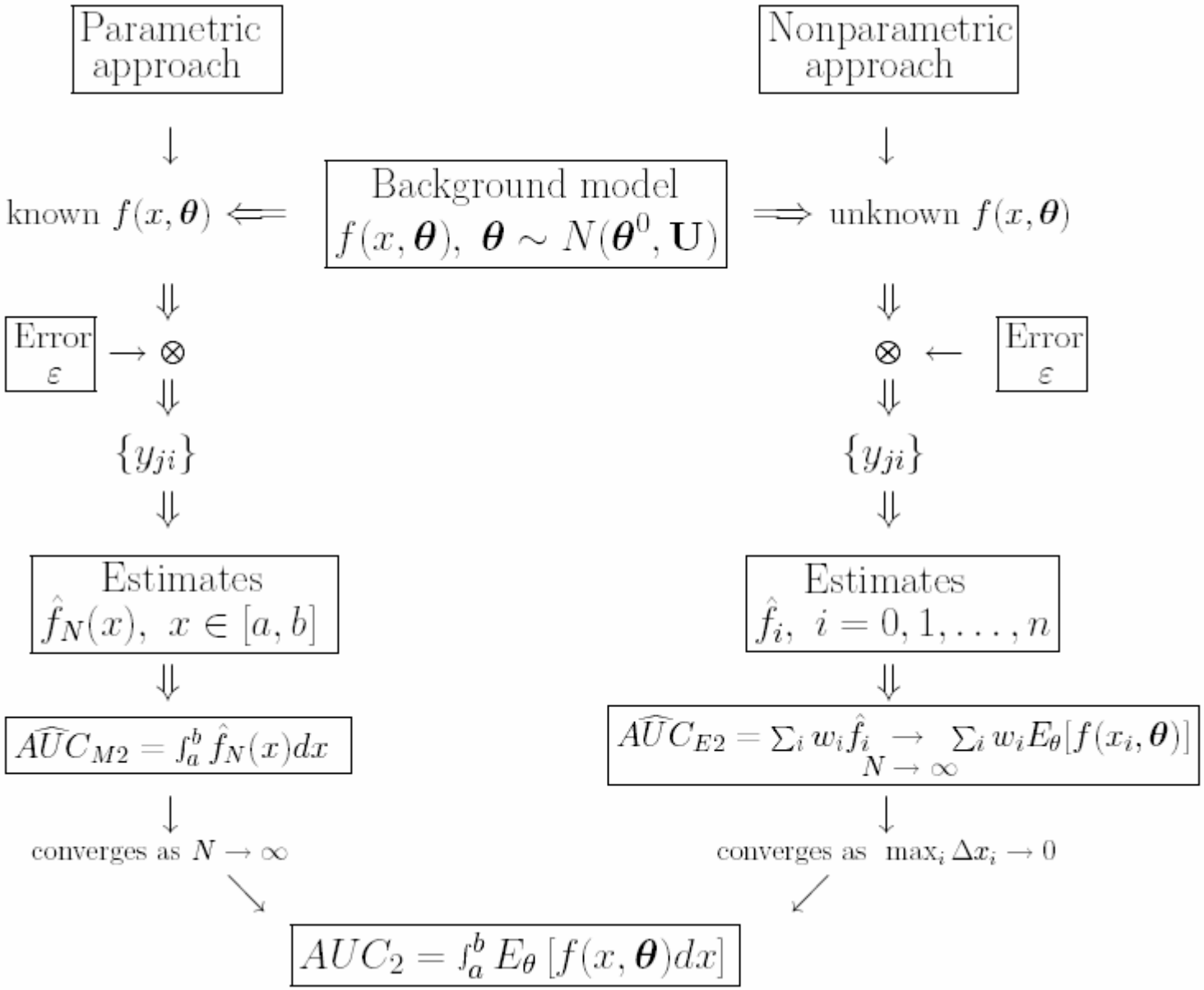
- Get empirical estimates $\widehat{T}_{E2},\ \widehat{C}_{E2}$ for "population curve" $\{\hat{f}_i\}$,

  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 (data combined in the "population curve")


Parametric approach
Nonparametric approach
known $f(x,\boldsymbol{\theta})$
Background model $f(x,\boldsymbol{\theta}),\ \boldsymbol{\theta} \sim N(\boldsymbol{\theta}^0, \mathbf{U})$
unknown $f(x,\boldsymbol{\theta})$
Error ε
Error ε
$\{y_{ji}\}$
$\{y_{ji}\}$
Estimates $\hat{f}_N(x),\ x \in [a,b]$
Estimates $\hat{f}_i,\ i = 0, 1, \ldots, n$
$\widehat{AUC}_{M2} = \int_a^b \hat{f}_N(x)dx$
$\widehat{AUC}_{E2} = \sum_i w_i \hat{f}_i \underset{N\to\infty}{\to} \sum_i w_i E_\theta[f(x_i,\boldsymbol{\theta})]$
converges as $N \to \infty$
converges as $\max_i \Delta x_i \to 0$
$AUC_2 = \int_a^b E_\theta\,[f(x,\boldsymbol{\theta})dx]$

Numerical integration

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

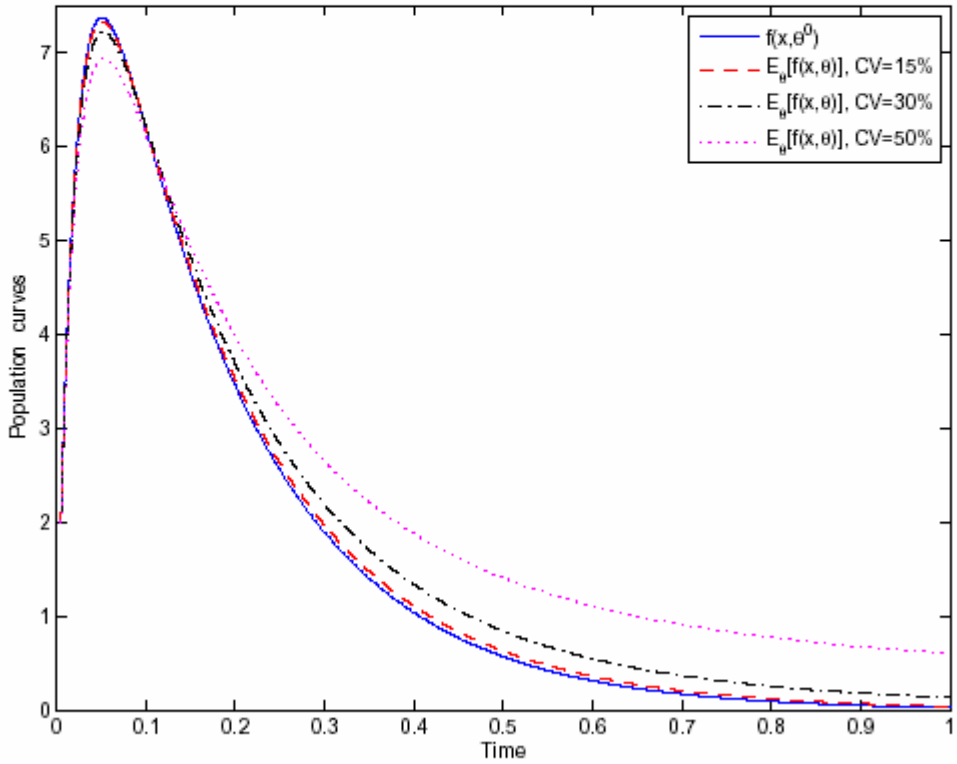
(2) Log-trapezoidal rule : $I_i = \Delta x_i \frac{\hat{f}_i - \hat{f}_{i-1}}{\log(\hat{f}_i / \hat{f}_{i-1})}$ (exact for exponential)

(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)

Comparison of population PK measures

$$AUC_1 = 1.836, \quad T_1 = 0.0546, \quad C_1 = 7.342.$$
$$AUC_1 = AUC_2, \quad T_2 = 0.0521, \quad C_2 = 7.210.$$
$$AUC_3 = 1.662, \quad T_3 = 0.0509, \quad C_3 = 7.367.$$



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), then more sparse sampling (after 'anticipated' T_{max})

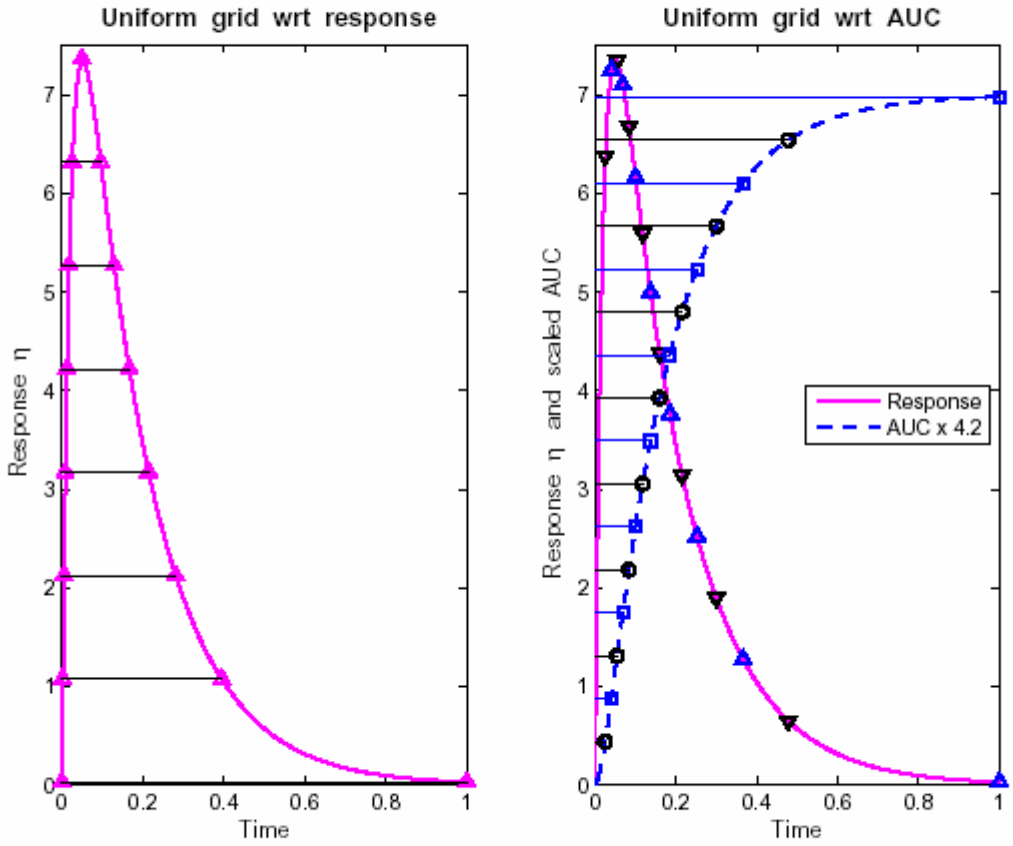
Alternative schemes

- 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 and Wong (2002): "inverse linear" designs

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

Sampling schemes



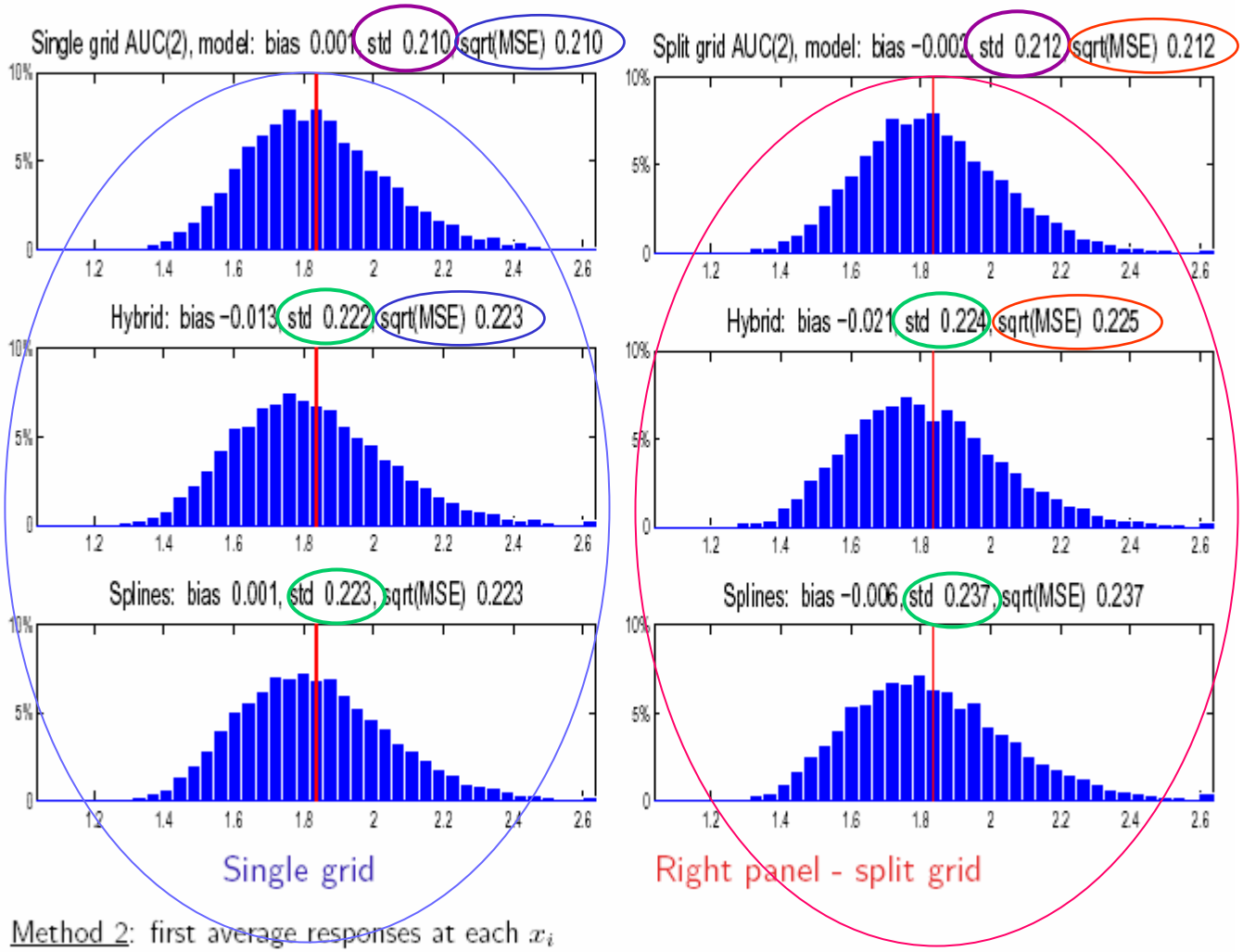
Uniform grid with respect to values of response (left panel) and AUC(right panel).

Splitting sampling 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

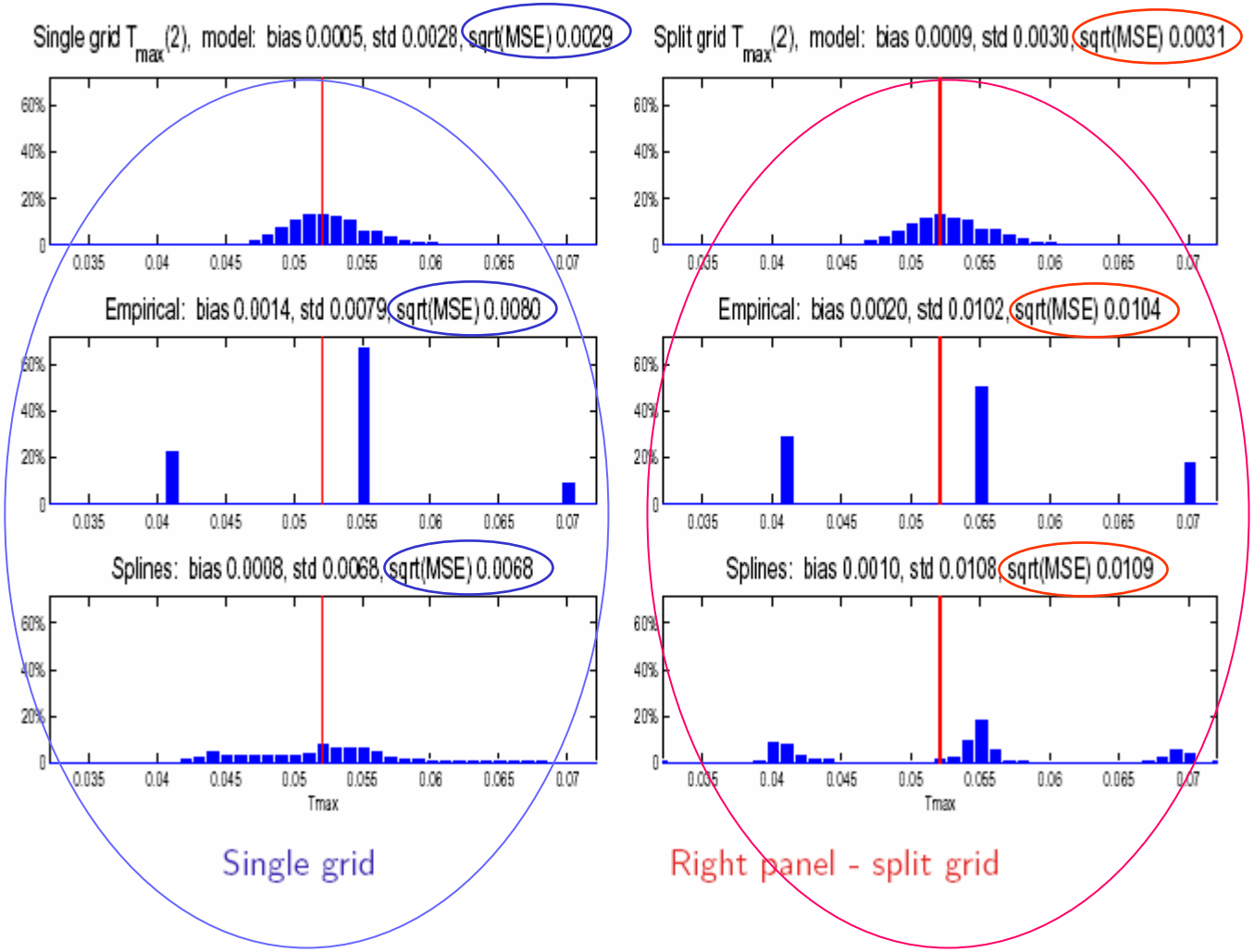
Type II measures: $AUC_2 = 1.833$



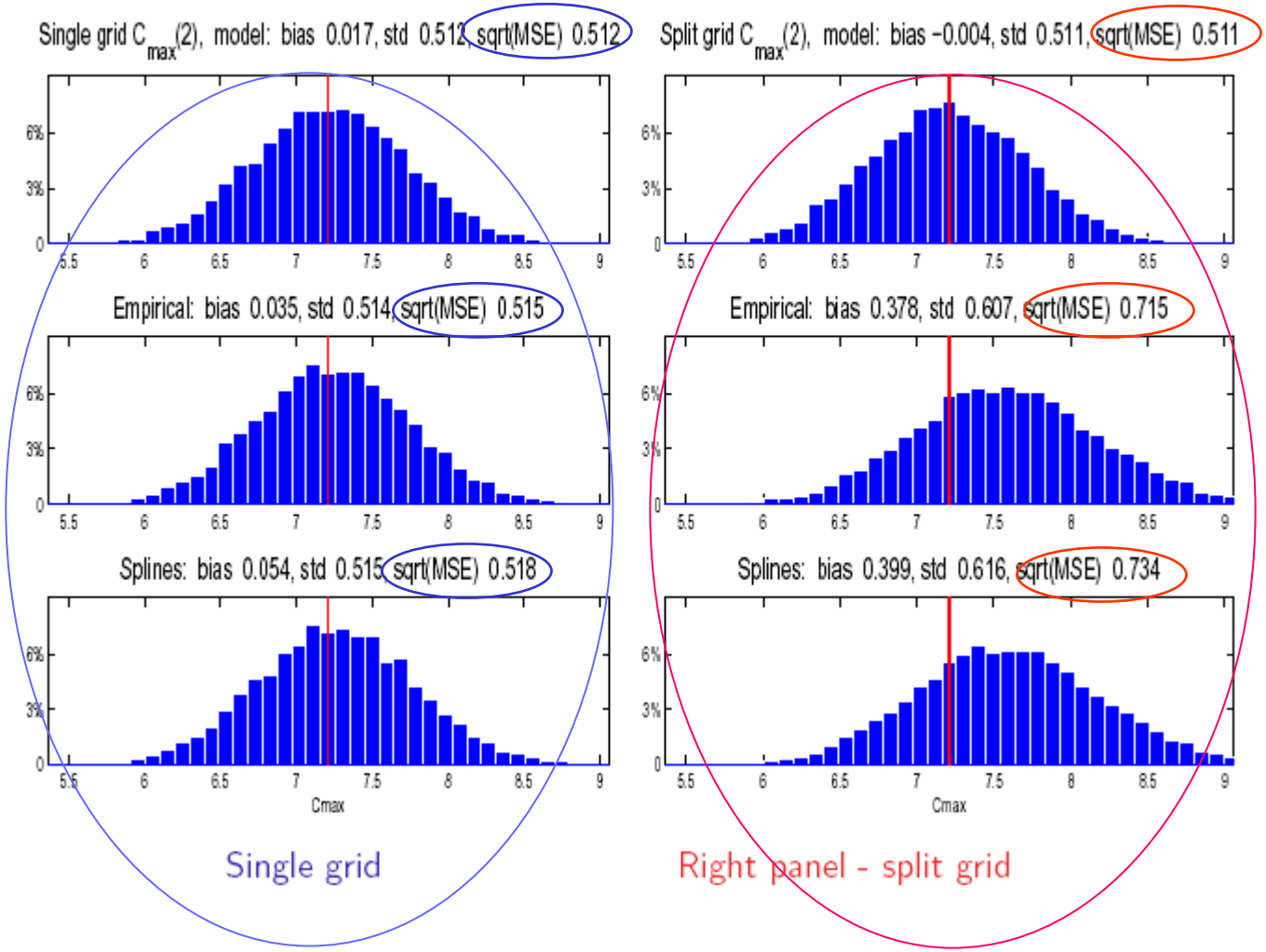
Method 2: first average responses at each x_i

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

Type II T_{max} measure: T_2=0.0521



Type II C_{max} measure: C_2=7.210



AUC_{E2} : closed-form solution, 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:

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

$Bias_{(2)}$ (no difference!)

$Var_{(2)}$ (no loss in 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 optimization

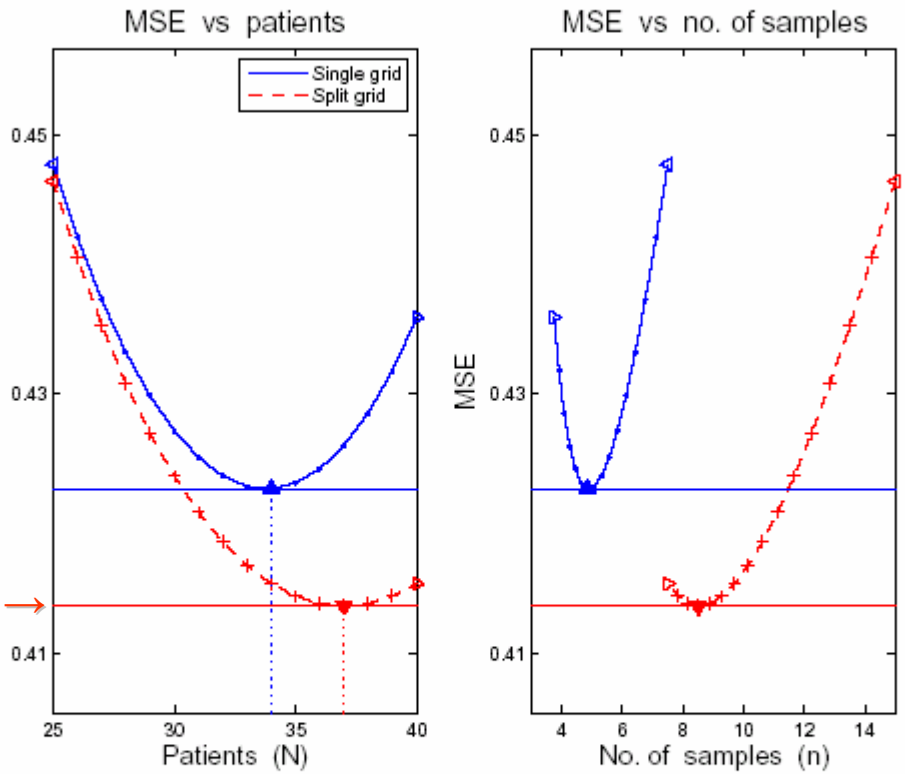
- c_s - cost of analyzing a sample, c_p - cost of patient enrollment,
- C_{total} - budget (resource)
- Overall cost, single grid: $2n\ N\ c_s\ +\ Nc_p\ \leq\ C_{total},$ (C1)
- Overall cost, split grid: $n\ N\ c_s\ +\ Nc_p\ \leq\ C_{total}.$ (C2)

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)

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

- When the model is correctly specified, the model-based approach outperforms the nonparametric one in terms of precision of PK measures' estimation (often not by much).
- Split grids: little effect on the precision of estimation, negligible effect on the bias and terms associated with population variability.
- If costs of analyzing samples and costs of patient's enrollment are taken into account, then sampling schemes with split grids may become optimal

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