PODE 2008

Optimization of sampling times for a combined PK/PD model: optimal design as a reference point

Sergei Leonov
(*Research Statistics Unit, GSK*)

Joint work with Mindy Magee and Brian McHugh (*CPK M&S, GSK*)

Paris, June 23

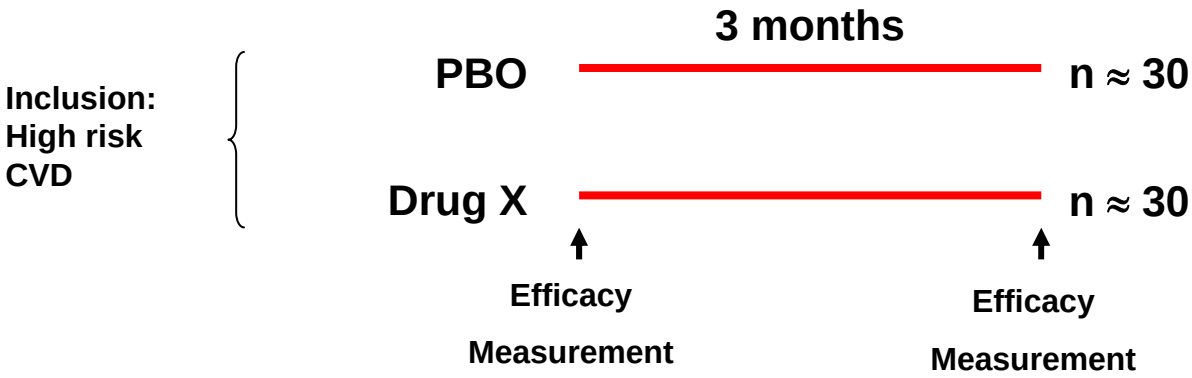
RSU Research Statistics Unit

gsk

Outline

- Background: clinical problem
- Original sampling design
- Optimization of sampling times
- Comparison options

Study Design



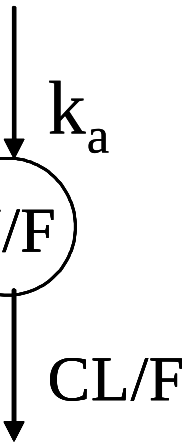
Endpoints

- Safety
- Efficacy
- PK
- PK/PD

Drug X PK/PD Modeling & Simulation

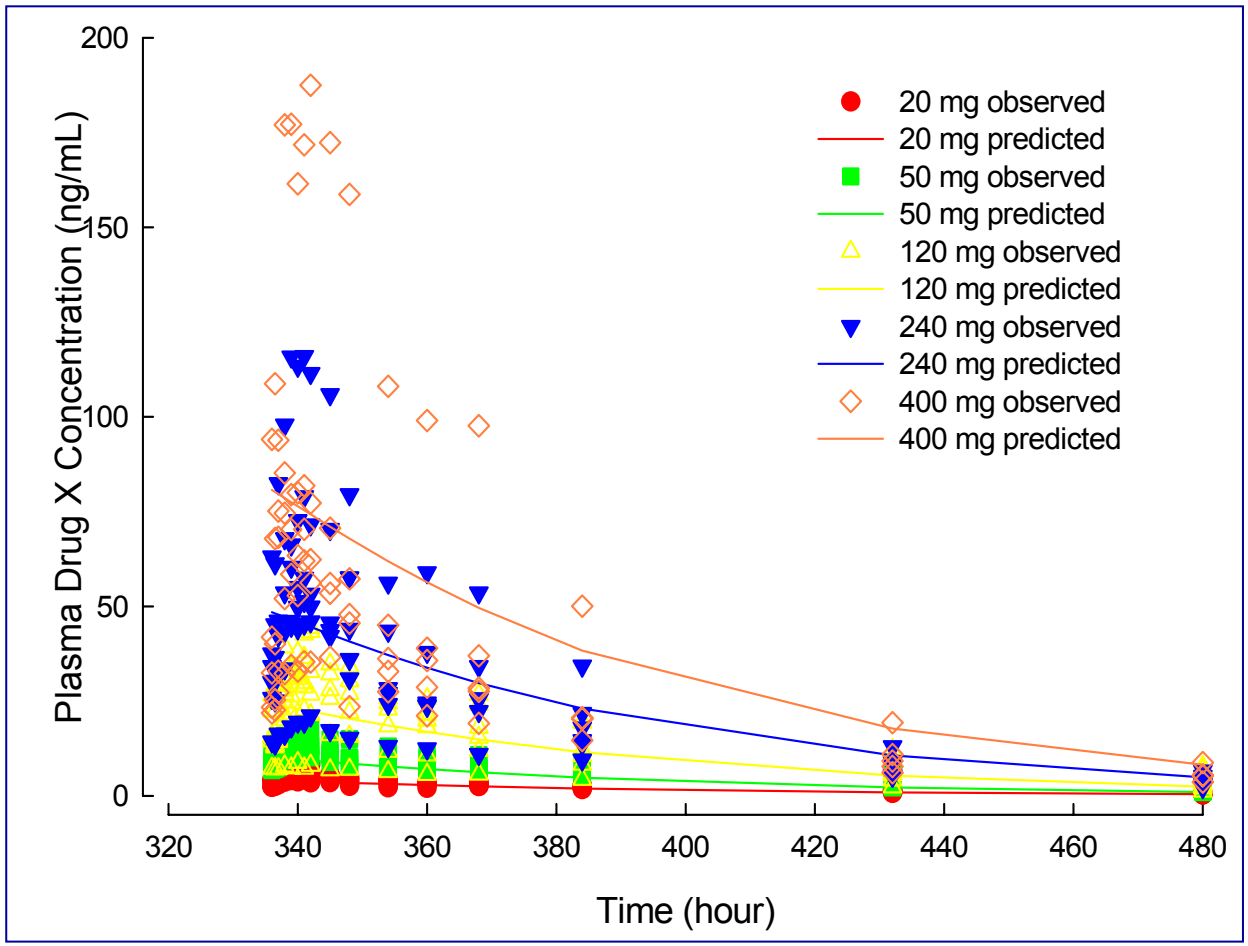
Final PK/PD Model

$$E = E_o \cdot \left(1 - \frac{C_p}{IC_{50} + C_p}\right)$$

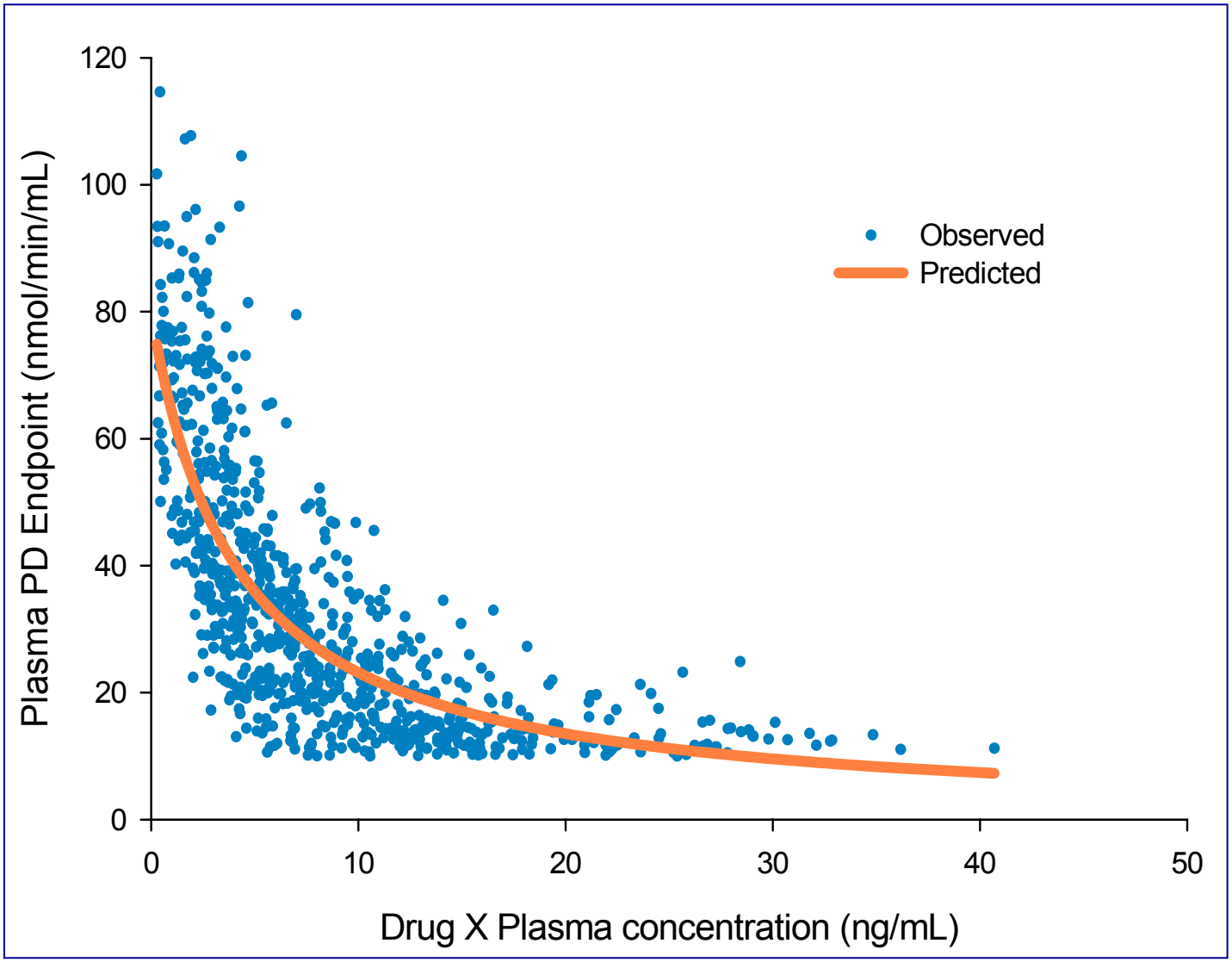


k_a: first-order absorption rate constant (h^{-1})
V/F: apparent volume of distribution (L)
CL/F: apparent systemic clearance (L/h)
E_o: PD endpoint at baseline (nM/min/mL)
IC_{50}: Drug X plasma concentration causing 50% inhibition of PD endpoint (ng/mL)

PK


Plasma Drug X Concentration (ng/mL)
200
150
100
50
0
320
340
360
380
400
420
440
460
480
Time (hour)
20 mg observed
20 mg predicted
50 mg observed
50 mg predicted
120 mg observed
120 mg predicted
240 mg observed
240 mg predicted
400 mg observed
400 mg predicted

PK/PD


Plasma PD Endpoint (nmol/min/mL)
120
100
80
60
40
20
0
0
10
20
30
40
50
Drug X Plasma concentration (ng/mL)
Observed
Predicted

Final PK/PD Sampling Scheme

	Treatment				
Sample Collection Timepoint[1, 2]	Baseline / Randomization	Week 4	Week 6	Week 8	Week 10
Pre-dose (Trough concentration)	X	X		X	
0.5-5 hours after dose (Absorption phase)		X		X	
5-9 hours after dose (Peak concentration)					X
9-22 hours after dose (Elimination phase)			X[3]		

1. If the subject is withdrawn early, a blood sample for PK and PD should be collected prior to discharge from the study, if possible
2. For each PK sample, a PD sample will be drawn at the same time to assess the plasma PD endpoint
3. Subjects should be reminded to take their study medication around lunch time for the 2 days prior to clinic visit

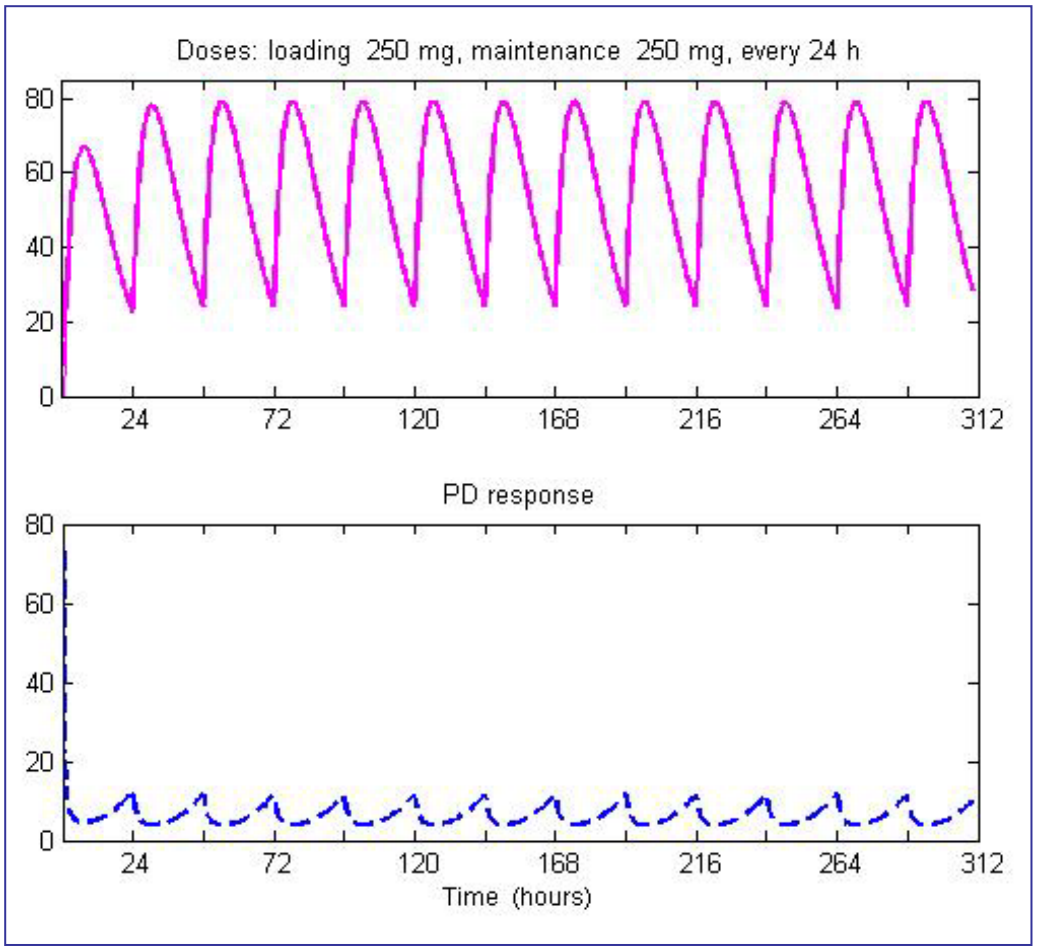
4 samples to be selected

- Week 4, between [0.5, 5] h
- Week 6, between [9, 22] h
- Week 8, between [0.5, 5] h
- Week 10, between [5, 9] h

Forced samples:

- PD trough (0 h)
- Trough PK/PD, weeks 4 and 8

PK/PD curves



Main goal: validate proposed design

- 4 “flexible” candidate times
- Given frequency e.g. every 30 min

1. Day 4, [0.5, 5] h: 10 points
2. Day 6, [0.5, 5] h: 10 points
3. Day 6, [5, 9] h: 9 points
4. Day 6, [9, 22]h: 17 points

Nonlinear models, multiple responses

- Predictor $\mathbf{x} = (x_1, x_2, \ldots, x_k)$ - sequence of sampling times,
- Measurements $\mathbf{Y} = [y(x_1), \ldots, y(x_k)]$ - vector,
- Response $\boldsymbol{\eta}(\mathbf{x}, \boldsymbol{\theta}) = [\eta(x_1, \boldsymbol{\theta}), \ldots, \eta(x_k, \boldsymbol{\theta})]$ - vector

Key: $\boldsymbol{\mu}(\mathbf{x}, \boldsymbol{\theta})$ - information matrix of a k-dimensional sequence $\mathbf{x}$

Optimal design

Information matrix : n_i patients on seq. $\mathbf{x}_i \Longrightarrow \mathbf{M}_N(\boldsymbol{\theta}) = \sum_{i=1}^{N} n_i \, \boldsymbol{\mu}(\mathbf{x}_i, \boldsymbol{\theta})$

Variance of the MLE: $\mathbf{Var}(\hat{\boldsymbol{\theta}}) \approx \mathbf{M}_N^{-1}(\boldsymbol{\theta})$

$\mathbf{M}(\xi, \boldsymbol{\theta}) = \dfrac{\mathbf{M}_N(\boldsymbol{\theta})}{N} = \sum_i w_i \boldsymbol{\mu}(\mathbf{x}_i, \boldsymbol{\theta})$ - normalized information, per observation

$\xi = \{w_i, \mathbf{x}_i\}$ - normalized design; $w_i = n_i/N$ - weights

$\mathbf{D}(\xi, \boldsymbol{\theta}) = \mathbf{M}^{-1}(\xi, \boldsymbol{\theta})$ - normalized variance-covariance matrix

Restrictions on the number of optimal sequences: NONE

Optimal design (cont.)

Criterion of optimality $\Psi(\xi, \boldsymbol{\theta}) \rightarrow \min_{\xi}$: minimization with respect to

- weights w_i, $0 \leq w_i \leq 1$, $\Sigma_i w_i = 1$
- admissible sampling sequences $\mathbf{x}_i \in \mathbf{X}$ - design region.

Locally optimal designs:

D-criterion: $\Psi = |\mathbf{D}(\xi, \boldsymbol{\theta})|$; A-criterion: $\Psi = \mathrm{tr}\,[\mathbf{A}\mathbf{D}(\xi, \boldsymbol{\theta})]$

Equivalence Theorem: *Kiefer, Wolfowitz (1960), Fedorov (1972)* - background for algorithms

Information matrix for sequence **x**

Gaussian $\mathbf{Y}$: $\mathbf{E}[\mathbf{Y}|\mathbf{x}] = \boldsymbol{\eta}(\mathbf{x}, \boldsymbol{\theta})$, $\mathbf{Var}[\mathbf{Y}|\mathbf{x}] = \mathbf{S}(\mathbf{x}, \boldsymbol{\theta})$

$\boldsymbol{\mu}(\mathbf{x}, \boldsymbol{\theta})$ - information matrix of a single (k-dimensional) sequence $\mathbf{x}$:

$$\mu_{\alpha\beta}(\mathbf{x}, \boldsymbol{\theta}) = \frac{\partial \boldsymbol{\eta}}{\partial \theta_\alpha} \mathbf{S}^{-1} \frac{\partial \boldsymbol{\eta}}{\partial \theta_\beta} + \frac{1}{2} \operatorname{tr}\left[\mathbf{S}^{-1} \frac{\partial \mathbf{S}}{\partial \theta_\alpha} \mathbf{S}^{-1} \frac{\partial \mathbf{S}}{\partial \theta_\beta}\right],$$

$\mathbf{S} = \mathbf{S}(\mathbf{x}, \boldsymbol{\theta})$, $\boldsymbol{\eta} = \boldsymbol{\eta}(\mathbf{x}, \boldsymbol{\theta})$ [*Muirhead (1982), Magnus and Neudecker (1988)*]

If $\boldsymbol{\eta}$, $\mathbf{S}$ defined (approximated) $\Rightarrow$ get $\boldsymbol{\mu}$ $\Rightarrow$ run the algorithm

Vector **Y** combines PK and PD responses

Information matrix for sequence **x** (cont.)

- Data $y(x_{ij}) = \eta(x_{ij}, \boldsymbol{\gamma}_i)\left[1 + \varepsilon_{ij}^p\right] + \varepsilon_{ij}^a, \quad j = 1, \ldots, k_i.$ (1)

$\varepsilon_{ij}^a \sim N(0, \sigma_a^2), \quad \varepsilon_{ij}^p \sim N(0, \sigma_p^2)$

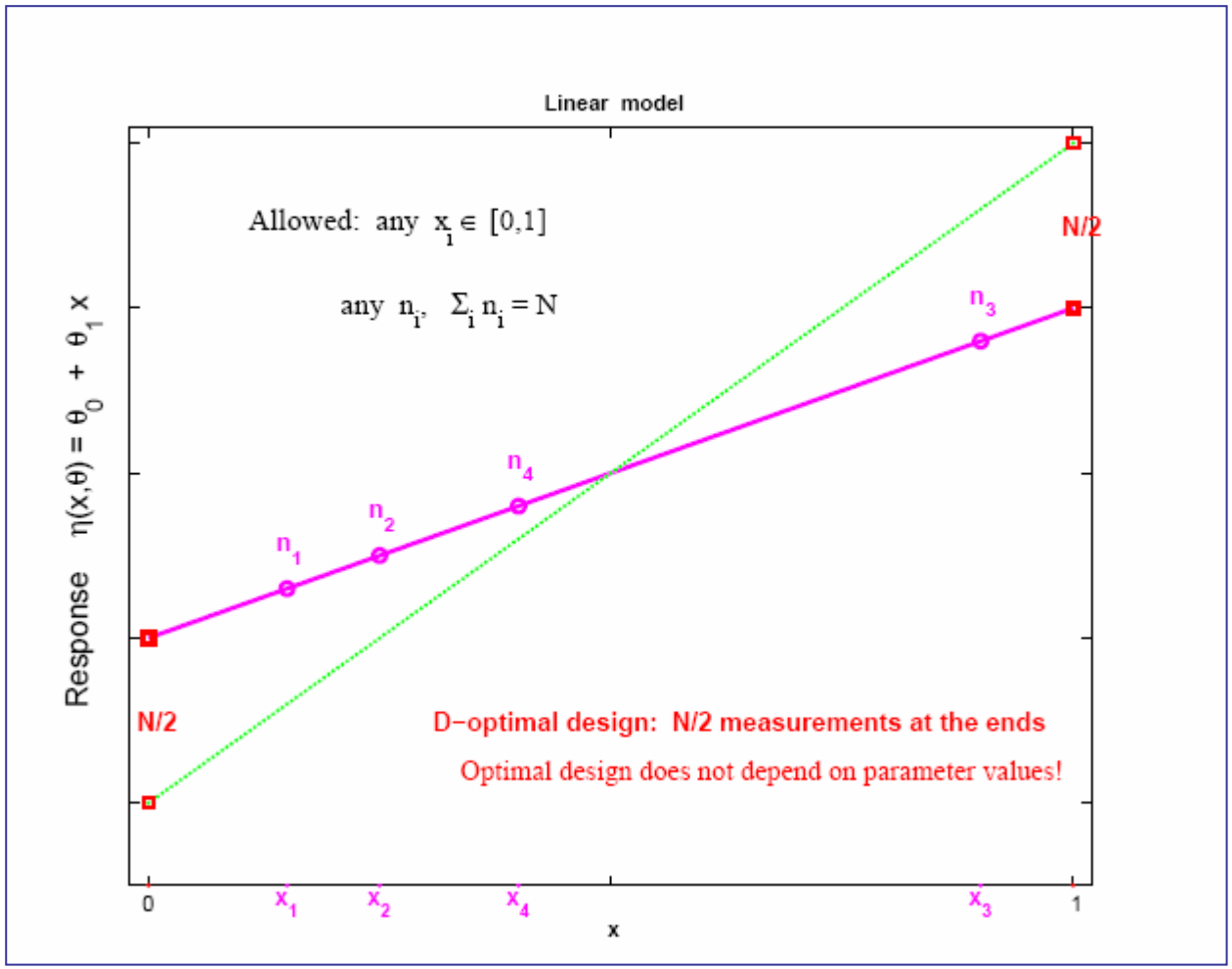
First-order approximation of variance matrix **S**, model (1): for normal $\boldsymbol{\gamma}$

$$S(\mathbf{x}, \boldsymbol{\theta}) \simeq \mathbf{F}\,\boldsymbol{\Lambda}\,\mathbf{F}^T + \sigma_P^2\,\mathrm{Diag}[\boldsymbol{\eta}(\mathbf{x}, \boldsymbol{\theta})\,\boldsymbol{\eta}^T(\mathbf{x}, \boldsymbol{\theta}) + \mathbf{F}\,\boldsymbol{\Lambda}\,\mathbf{F}^T] + \sigma_A^2 \mathbf{I}_k,$$

$$\mathbf{F} = \mathbf{F}(\mathbf{x}, \boldsymbol{\gamma}^0) = \left[\frac{\partial \boldsymbol{\eta}(\mathbf{x}, \boldsymbol{\theta})}{\partial \boldsymbol{\gamma}_\alpha}\right]\Bigg|_{\boldsymbol{\gamma}=\boldsymbol{\gamma}^0} - (k \times m_\gamma) \text{ matrix}$$

Retout, Mentré (2003), Gagnon and Leonov (2005)

Optimal designs: not necessarily practical

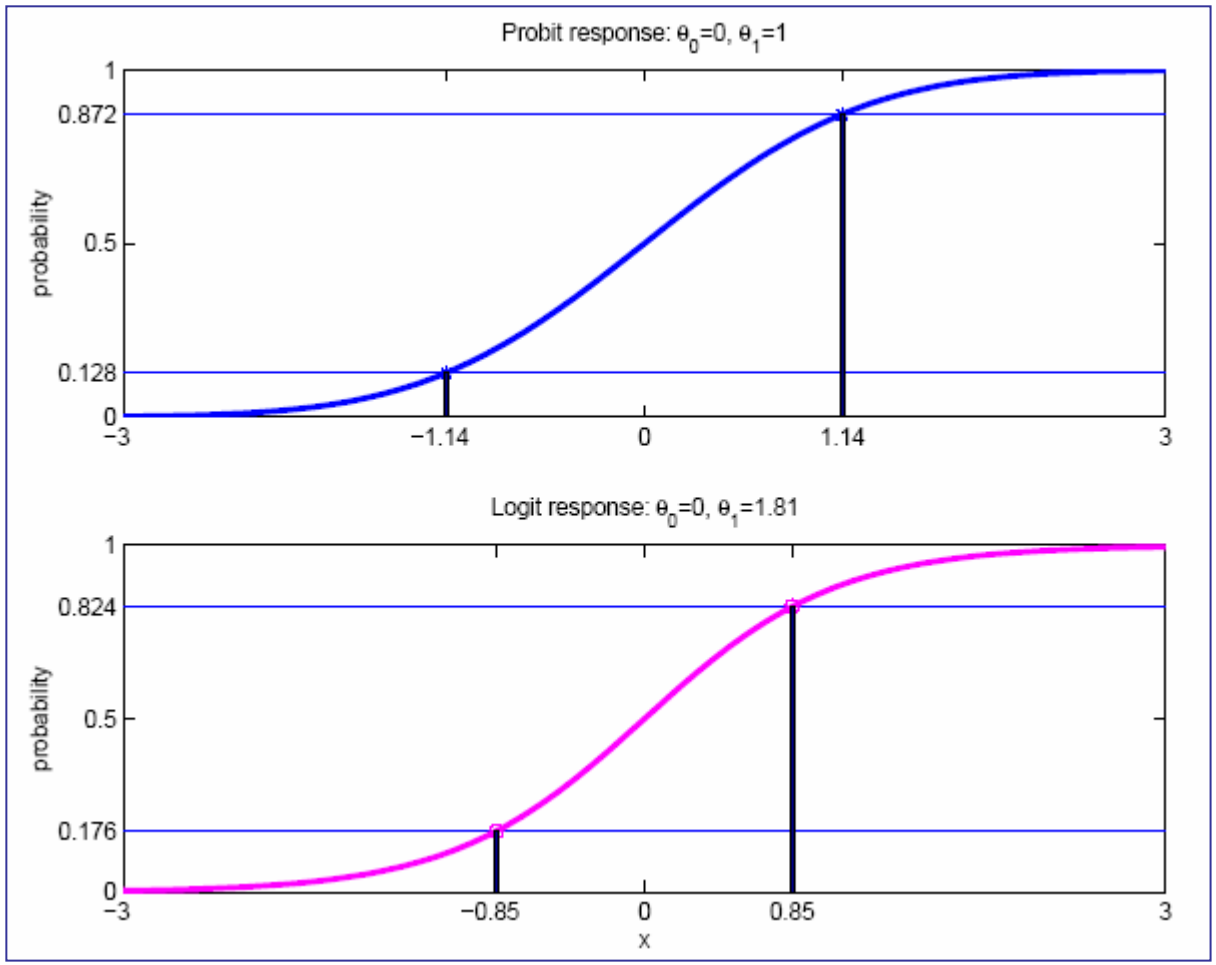


Optimal designs: not necessarily practical

Binary logistic model: $P(\text{response}|\theta) = \exp(\theta_0+\theta_1 x) / [1+ \exp(\theta_0+\theta_1 x)]$

Two optimal doses with equal weights on z-scale: $z= \theta_0+\theta_1 x$ *White (1975)*

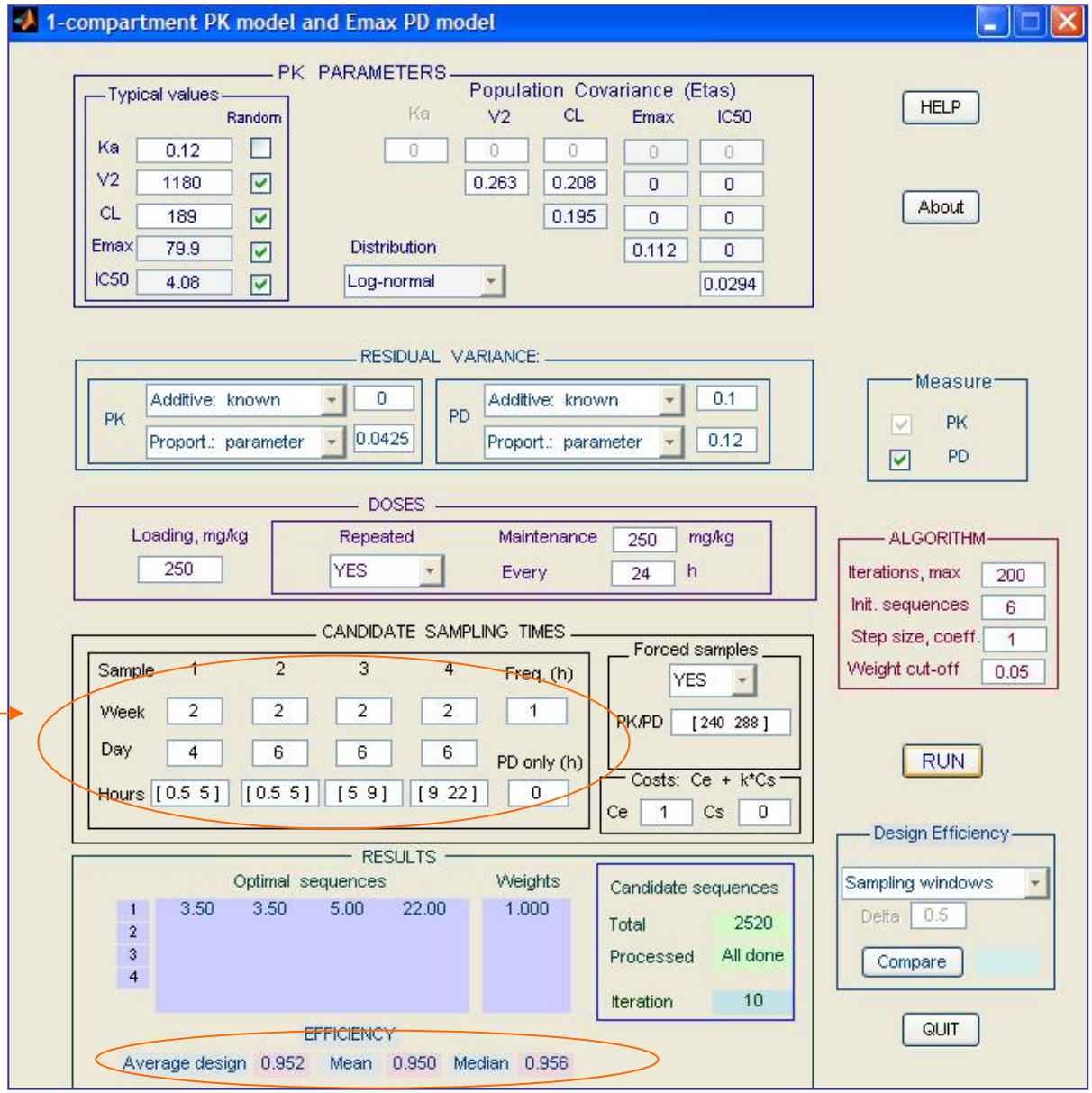
$$z^* = \pm 1.54 \ \text{(Logit)}, \quad z^* = \pm 1.14 \ \text{(Probit)}$$



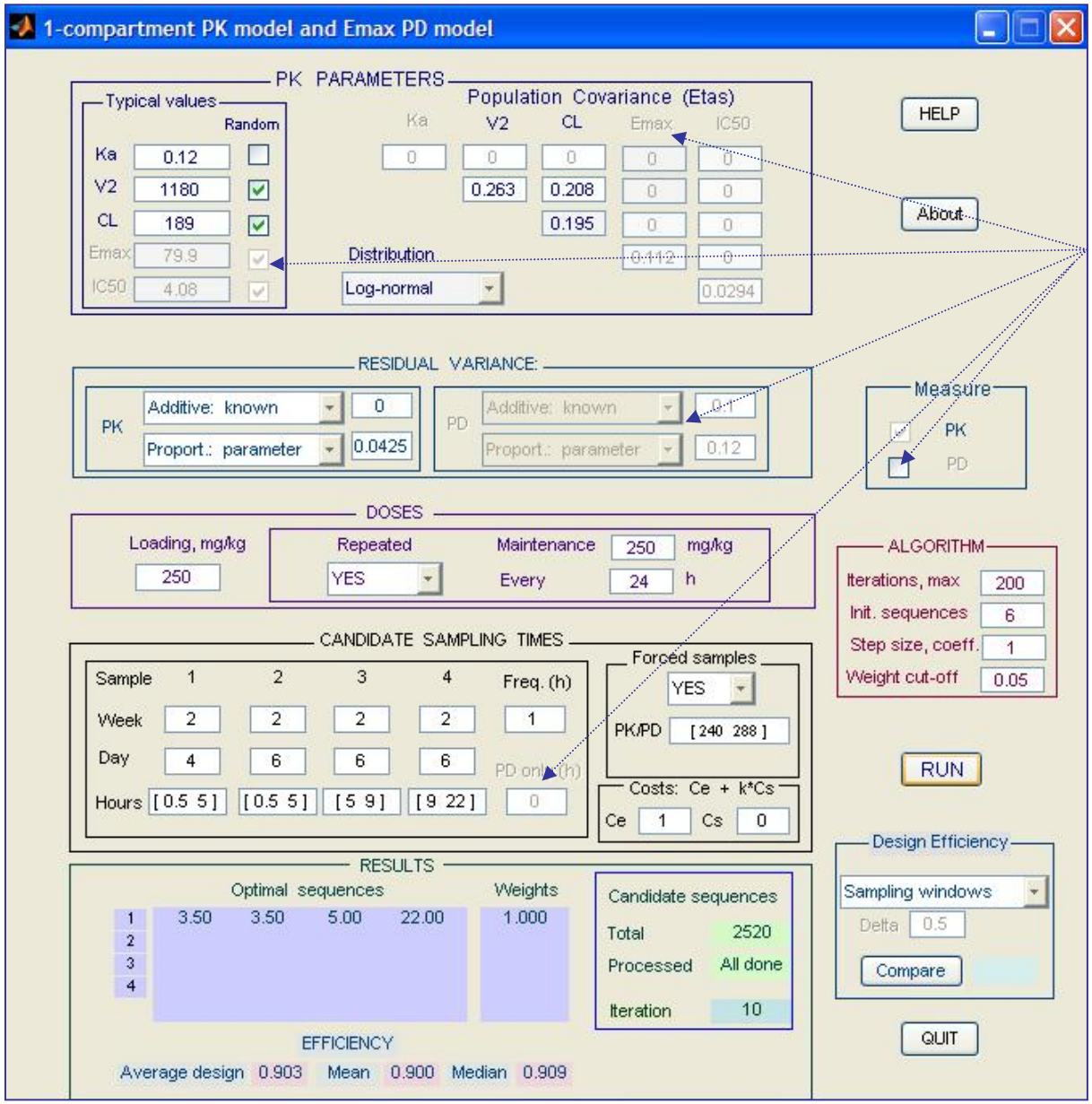
One-compartment PK and E_{max} PD

Parameters:
K_a,V/F, CL/F (PK)
E_{max}, IC_{50} (PD)

Candidate sampling times

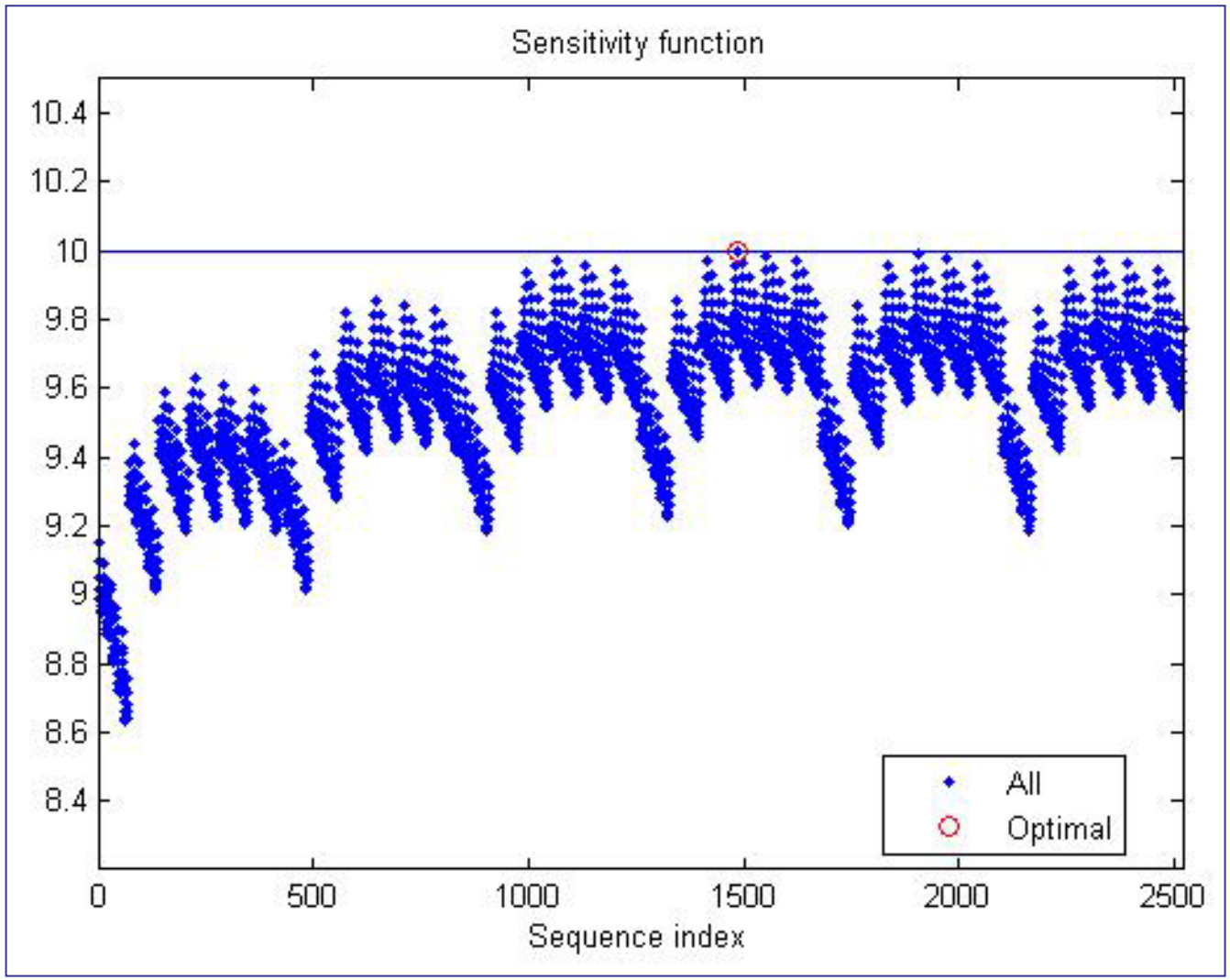


No PD samples option



No PD samples

Sensitivity function



Efficiency analysis: best and worst sequences

- BEST SEQUENCES:

No.	Effic.	Wk 2,D4	Wk 2,D6	Wk 2,D6	Wk 2,D6
1	1.000	3.50	3.50	5.00	22.00
2	0.999	4.50	3.50	5.00	22.00
3	0.999	3.50	4.50	5.00	22.00
4	0.998	4.50	4.50	5.00	22.00
5	0.997	5.00	3.50	5.00	22.00
6	0.997	3.50	5.00	5.00	22.00
7	0.997	2.50	3.50	5.00	22.00
8	0.997	3.50	2.50	5.00	22.00
9	0.996	3.50	3.50	6.00	22.00
10	0.996	5.00	4.50	5.00	22.00

- WORST SEQUENCES:

No.	Effic.	Wk 2,D4	Wk 2,D6	Wk 2,D6	Wk 2,D6
1	0.817	0.50	0.50	9.00	17.00
2	0.818	0.50	0.50	9.00	16.00
3	0.819	0.50	0.50	9.00	18.00
4	0.820	0.50	0.50	9.00	15.00
5	0.822	0.50	0.50	9.00	19.00
6	0.824	0.50	0.50	9.00	14.00
7	0.826	0.50	0.50	9.00	20.00
8	0.829	0.50	0.50	9.00	13.00
9	0.831	0.50	0.50	9.00	21.00
10	0.833	0.50	0.50	8.00	17.00

EFFICIENCY OF INDIVIDUAL SEQUENCES: mean 0.950, median 0.956

EFFICIENCY OF AVERAGE DESIGN 0.952

Sensitivity analysis

- Comparison with "average" design within sampling windows
  - Currently 5 times are selected uniformly in each sampling window (average value across $5^4 = 625$ sequences)
- Comparison with "average" design within Delta-vicinity of D-optimal designs
  - D-optimal times +/- Delta

Conclusions

- Original design: quite efficient
- Optimal design: used as a reference point
  - Serial dilution (bioassays)
  - Dose response modeling (linear, binary logistic models)

References

- Fedorov, V.V., Gagnon, R., Leonov, S., Wu, Y. (2007), Optimal design of experiments in pharmaceutical applications. In: Dmitrienko, A., Chuang-Stein, C., D'Agostino, R. (Eds), *Pharmaceutical Statistics*, SAS Books by Users series, SAS Press, Cary, NC, pp. 151-195.
- Fedorov, V.V., and Hackl, P. (1997), *Model-Oriented Design of Experiments*. Springer, New York.
- Fedorov, V.V., Leonov, S. (2005), Response driven designs in drug development. In: Wong, W.K., Berger, M.P.F. (Eds.), *Applied Optimal Designs*, Wiley, Chichester, pp. 103-136.
- Gagnon, R., and Leonov, S.L. (2005), Optimal population designs for PK models with serial sampling. *J. Biopharm. Stat.*, **15** (1), 143-163.
- Graham, G., Aarons, L. (2006), Optimum blood sampling windows for parameter estimation in population pharmacokinetics experiments. *Stat. Med.*, **25**, 4004 4019.
- Magnus, J.R., Neudecker, H. (1988), *Matrix Differential Calculus with Applications in Statistics and Econometrics*, Wiley, NY.
- Mentrè, F., Mallet, A., Baccar, D. (1997), Optimal design in random-effects regression models, *Biometrika*, **84** (2), 429-442.
- Retout, S., Mentrè, F. (2003), Further developments of the Fisher information matrix in nonlinear mixed effects models with evaluation in population pharmacokinetics. *J. Biopharm. Stat.*, **13** (2), 209-227.