An effective approach for obtaining optimal sampling windows for population pharmacokinetic experiments

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Introduction

- Population pharmacokinetics involves collection of blood samples
- Sample collection at specific times may not be feasible – less informative
  - Size of the trial (Phase III)
  - Delays in seeing the medical personnel
  - Poor patient compliance with respect to dosing times
  - More immediate medical procedure
- Sampling windows – controlling sampling times
  - Sampling within some time intervals
  - Gives flexibility, informative data and satisfactory parameter estimation

Population PK modelling

Level 1 – Individual level

$$y_{ij} = f(\theta_i, t_{ij}) + \varepsilon_{ij} \quad j = 1,...,n_i, i = 1,...,N$$

$$\varepsilon_{ij} \sim N\left(0, \sigma_1^2 + \sigma_2^2 f^2(\theta_i, t_{ij})\right)$$

Level 2 – Population level

$$\theta_i = g(\theta, b_i) \qquad b_i \sim N(0, \Omega) \qquad \Omega = \begin{bmatrix} \omega_{11} & \omega_{12} & . \\ \omega_{12} & \omega_{22} & . \\ . & . & \omega_{pp} \end{bmatrix}$$

Parameters

$$\Psi = \left[\theta_1,...,\theta_p, \omega_{11},...,\omega_{1p}, \omega_{22},...,\omega_{2p},...,\omega_{pp}, \sigma_1^2, \sigma_2^2\right]$$

Sampling Times

$$\xi_i = \left[t_{i1},...,t_{in_i}\right]$$

Population Fisher information Matrix

○ Expressions for PFIM based on mixed effects modelling by maximum likelihood method

Log-likelihood of observations

$$F(\Psi, \xi_i) = E\left(-\frac{\partial^2 l(\Psi; y_i)}{\partial\Psi\partial\Psi^T} \right)$$

○ Approximations based on linearization of the model

$$F(\Psi, \xi_i)_{az} = J_a V^{-1} J_z^T + \frac{1}{2} tr\left(\frac{\partial V}{\partial\Psi_a} V^{-1} \frac{\partial V}{\partial\Psi_z} V^{-1} \right)$$

○ Population design

$$\Xi = \left\{ \begin{array}{c} \xi_1,...,\xi_Q \\ N_1,...,N_Q \end{array} \right\} \qquad F(\Psi, \Xi) = \sum_{q=1}^{Q} \sum_{i_q=1}^{N_q} F(\Psi, \xi_{i_q}) = \sum_{q=1}^{Q} N_q F(\Psi, \xi_q)$$

Optimal Design

- Optimality criteria - D-optimality
- Population D-optimal design

$$\Xi^D = \arg\max_{\chi} \left| F(\Psi, \Xi) \right|$$

- D-Efficiency

$$eff_D(\Psi, \Xi, \Xi^D) = \left[\frac{\left| F(\Psi, \Xi) \right|}{\left| F(\Psi, \Xi^D) \right|} \right]^{1/\dim(\Psi)}$$

Sampling windows determination - approaches

- Duffull et al. (*Pharmaceutical Research* **2001**)
  - Sampling windows design obtained as marginal windows associated with each time points – varying one sampling time at a time until determinant is reduced by 5%
- Graham and Aarons (*Statistics in Medicine* **2006)**
  - Two stage approach and a quadratic loss function
  - Sampling windows design result in specified loss of efficiency compared to fixed D-optimal time points
- Patan and Bogacka (*Advances in Model-Oriented Design and analysis* **2007**)
  - Based on equivalence theorem for D-optimal continuous designs using the variance function

Sampling windows determination - approaches

Summary of attributes

Attribute		Duffull	G&A	P&B
Parameter Sensitivities		Yes	No	Yes
Assessment of Sampling Windows Efficiency		No	Yes	Yes
Design	Exact	Yes	Yes	No
	Continuous	Yes	Yes	Yes

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Sampling windows determination – new approach

- Main features
  - Very efficient and effective
  - Can be applied to different types of design
    - Exact
    - Continuous
  - Reflects parameter sensitivities
    - Less flexibility (narrow window) for high parameter sensitivities (important to sample close to optimal time point)
    - More flexibility (wide window) for low parameter sensitivities (less important to sample close to optimal time point)
  - The efficiency of the sampling windows design can be assessed jointly

Sampling windows determination

- Fixed time population D-optimal design

$$\Xi^D = \left\{ \begin{array}{c} \xi^D \\ N \end{array} \right\} \qquad \Xi^D = \left[t_1^D, ..., t_n^D \right]$$

- Sampling windows population design

$$\Xi^W = \left\{ \begin{array}{c} t_1^U, ..., t_n^U \\ t_1^L, ..., t_n^L \end{array} \right\}$$

$$t_j^U = t_j^D + \delta_j \qquad t_j^L = t_j^D - \delta_j$$

$$\Delta = \left[\delta_1, ..., \delta_n \right]$$

Sampling windows determination

○ Efficiency functions – conditional and joint
  - Uniform or loguniform distribution

$$eff_D(\Psi, \Xi_j^W(\delta_j)) = \frac{E\left[\left|F(\Psi, \Xi_j^W(\delta_j))\right|^{1/\dim(\Psi)}\right]}{\left|F(\Psi, \Xi^D)\right|^{1/\dim(\Psi)}}$$

$$eff_D(\Psi, \Xi^W(\Delta)) = \frac{E\left[\left|F(\Psi, \Xi^W(\Delta))\right|^{1/\dim(\Psi)}\right]}{\left|F(\Psi, \Xi^D)\right|^{1/\dim(\Psi)}}$$

Sampling windows determination – 3 stage approach

- ○ **Stage 1:**
  - • Optimisation of fixed D-optimal time points

- ○ **Stage 2:**
  - • Assuming a distribution – uniform or loguniform
  - • Define a target mean efficiency level, eff_0
  - • Optimise one window length at a time using a quadratic function

$$\delta_j = arg\left\{\min_{\delta \in \Delta}\left[\left(\mathit{eff}_D(\Psi, \Xi_j^W(\delta_j)) - \mathit{eff}_0\right)^2\right]\right\}$$

Sampling windows determination

- **Stage 3:**
  - Evaluate the efficiency of the joint sampling windows

$$eff_D(\Psi, \Xi^W(\Delta))$$

  - Check if eff_D is greater than eff_0 if not (ideally) reduce the window lengths by equal percentage, 1% and obtain a new vector for the lengths of the sampling windows

$$\delta_{j(new)} = \delta_{j(old)} - \left(\delta_{j(old)} * 0.01\right)$$

  - Repeat Stage 3 until the required efficiency level is obtained
  - Take the last vector of sampling windows lengths as the optimal sampling windows lengths

Sampling windows determination

○ Apart from mean efficiency level, percentiles can also be used - mean efficiency can produce variation in the realized design depending on distribution of samples within the windows

- Sampling at or close to boundaries – less efficient design
- Sampling at or close to fixed D-optimal time points – more efficient design

○ Constraints during optimisation – especially if any of the fixed D-optimal time points is at the boundary or near the boundary

- Ensure sampling windows do not extend outside the design space (sampling at negative time points)

Sampling windows determination – Example 1

○ Individual continuous design

○ One compartment IV bolus model (proportional residual)

$$y_j = \frac{Dose}{V} e^{-(Cl/V)t_j}$$

$$\Psi = \left[Cl, V, \sigma_2^2 \right] = \left[3,30,0.04 \right] \quad Dose = 450mg$$

○ Design region 0 and 24 hrs

○ Sampling windows – P&B and new approach

• 95% and 90% efficiency levels

• Mean, 5th and 10th percentile efficiency criteria

• Uniform and loguniform sample distributions

Sampling windows determination – Example 1

○ Fixed D-optimal time points = 0 and 24 hr (0.5,0.5)

Efficiency level	Criteria	Uniform		Loguniform	
		P&B	New Approach	P&B	New Approach
90%	Mean	0 – 3.48 20.52 - 24	0 – 3.48 20.53 - 24	0 – 5.66 18.34 - 24	0 – 5.49 18.35 - 24
	10th	0 – 2.30 21.70 - 24	0 – 2.31 21.70 - 24	0 – 3.50 20.50 - 24	0 – 3.72 20.47 - 24
	5th	0 – 2.12 21.88 - 24	0 – 2.14 21.85 - 24	0 – 3.08 20.92 - 24	0 – 2.15 20.65 - 24
95%	Mean	0 – 1.76 22.24 - 24	0 – 1.77 22.23 – 24	0 – 2.90 21.10 - 24	0 – 3.45 21.25 - 24
	10th	0 – 1.19 22.81 - 24	0 – 1.18 22.82 - 24	0 – 1.80 22.21 - 24	0 – 1.97 22.20 - 24
	5th	0 – 1.06 22.94 - 24	0 – 1.05 22.96 - 24	0 – 1.68 22.32 - 24	0 – 1.80 22.30 - 24

Sampling windows determination – Example 2

- Individual continuous design
- One compartment first order absorption model at steady state (the data and the model are log transformed)

$$\log(y_j) = \log\left\{\frac{FDka}{Vka - Cl}\left(\frac{e^{-Clt_j/V}}{1 - e^{-Cl\tau/V}} - \frac{e^{-kat_j}}{1 - e^{-ka\tau}}\right)\right\} + \varepsilon_j(\sigma_1^2)$$

$$\Psi = \left[Cl, V, ka, \sigma_1^2\right] = \left[11.55, 100, 2.08, 0.0225\right]$$

$$F = 1, D = 1mg, \tau = 12hr$$

- Design region 0.1 and 12 hr
- Sampling windows – P&B and new approach
  - 95% and 90% efficiency levels
  - Mean, 5th and 10th percentile efficiency criteria
 - Uniform and loguniform sample distributions

Sampling windows determination – Example 2

○ Fixed D-optimal time points = 0.29,2.46,12 hr (0.33,0.33,0.33)

Efficiency level	Criteria	Uniform		Loguniform	
		P&B	New Approach	P&B	New Approach
90%	Mean	0.12 - 0.63 1.33 - 4.37 10.73 - 12	0.05 - 0.57 1.55 - 3.37 10.47 - 12	0.12 - 0.64 1.32 - 4.41 10.70 - 12	0.14 - 0.59 1.41 - 4.31 10.17 - 12
	10th	0.14 - 0.54 1.52 - 3.93 11.14 - 12	0.11 - 0.47 1.69 - 3.23 10.91 - 12	0.14 - 0.54 1.50 - 3.96 11.11 - 12	0.16 - 0.52 1.58 - 3.83 10.71 - 12
	5th	0.15 - 0.52 1.56 - 3.84 11.22 - 12	0.11 - 0.47 1.93 - 2.99 11.20 - 12	0.15 - 0.52 1.55 - 3.84 11.21 - 12	0.17 - 0.48 1.62 - 3.74 10.79 - 12
95%	Mean	0.15 - 0.50 1.61 - 3.72 11.32 - 12	0.14 - 0.44 1.64 - 3.29 11.08 - 12	0.15 - 0.50 1.61 - 3.73 11.31 - 12	0.18 - 0.48 1.66 - 3.64 11.06 - 12
	10th	0.17 - 0.45 1.75 - 3.43 11.55 - 12	0.18 - 0.40 1.78 - 3.14 11.35 - 12	0.18 - 0.44 1.77 - 3.41 11.57 - 12	0.19 - 0.43 1.81 - 3.34 11.35 - 12
	5th	0.18 - 0.43 1.81 - 3.34 11.62 - 12	0.18 - 0.39 1.81 - 3.11 11.34 - 12	0.18 - 0.44 1.79 - 3.37 11.60 - 12	0.20 - 0.42 1.83 - 3.30 11.38 - 12

Sampling windows determination – Example 2 (95% Efficiency, Mean criteria and Uniform distribution)

○ Fixed D-optimal time points = 0.29,2.46,12 hr (0.33,0.33,0.33)
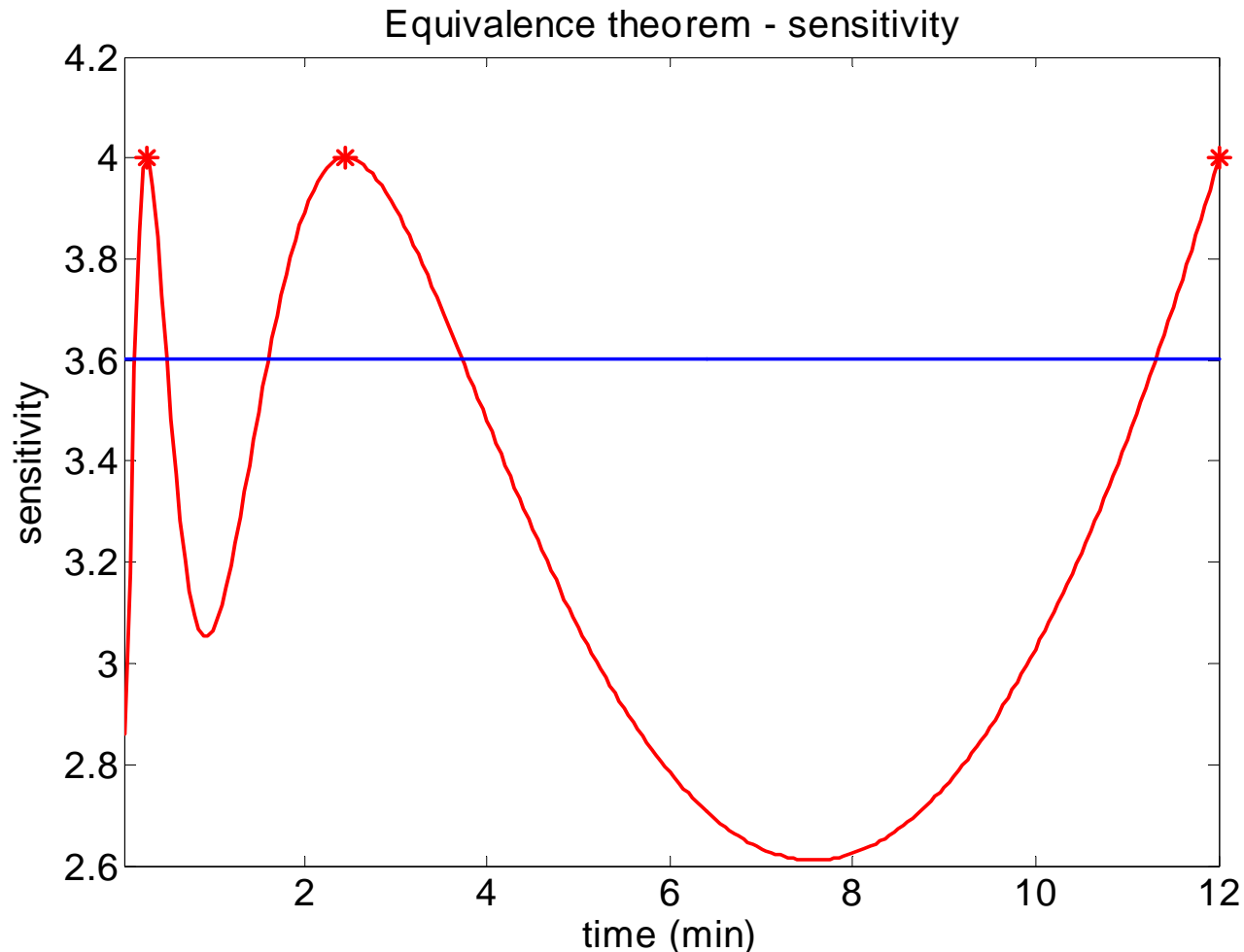
Sampling windows determination – Example 3

- Population exact design
- One compartment first order absorption model at steady state (the data and the model are log transformed)

$$\log(y_{ij}) = \log\left\{\frac{FDka_i}{V_ika_i - Cl_i}\left(\frac{e^{-Cl_it_{ij}/V_i}}{1-e^{-Cl_i\tau/V_i}} - \frac{e^{-ka_it_{ij}}}{1-e^{-ka_i\tau}}\right)\right\} + \varepsilon_{ij}(\sigma_1^2)$$

$$\Psi = \left[Cl, V, ka, \omega_{Cl}, \omega_V, \omega_{ka}, \sigma_1^2\right] = \left[11.55, 100, 2.08, 0.09, 0.09, 0.09, 0.0225\right]$$

$$F = 1, D = 1mg, \tau = 12hr \qquad [a_0, b_0] = [0, 12]$$

- 100 subjects, 1 group and 3 time points
- Sampling windows – G&A, Duffull and new approach
  - 95% and 90% efficiency levels
  - Mean and 10th percentile efficiency criteria
  - Uniform and loguniform sample distributions

Sampling windows determination – Example (Uniform distribution)

○ Optimal design (fixed time) – 0.30,1.9 and 12 hrs (det =189.95)

Efficiency	Criterion	G&A	Duffull	New approach
90%	Mean	0.02–0.58 (0.28*) 1.61-2.17 (0.28) 11.72-12.0 (0.28) det** = 170.84 [0.90]	0.02-0.58 (0.28) 0.0-3.82 (1.93) 5.29-12 (6.71) det = 141.3 [0.74]	0.12-0.49 (0.19) 0.75-3.03 (1.14) 7.98-12.0 (4.02) det = 172.29 [0.91]
	10%	0.11-0.49 (0.19) 1.70-2.08 (0.19) 11.81-12.0 (0.19) det = 170.55 [0.90]	0.10-0.50 (0.20) 0.69-3.09 (1.20) 7.63-12 (4.38) det = 148.61 [0.78]	0.16-0.44 (0.14) 1.02-2.76 (0.87) 8.81-12.0 (3.19) det = 171.36 [0.90]
95%	Mean	0.08-0.52 (0.22) 1.67-2.11 (0.22) 11.78-12.0 (0.22) det = 180.65 [0.95]	0.08-0.52 (0.22) 0.44-3.34 (1.45) 7.45-12.0 (4.55) det =159.69 [0.84]	0.16-0.44 (0.14) 1.00-2.78 (0.89) 9.22-12.0 (2.78) det = 180.76 [0.95]
	10%	0.15-0.45 (0.15) 1.74-2.04 (0.15) 11.85-12.0 (0.15) det = 180.74 [0.95]	0.15-0.45 (0.15) 0.93-2.85 (0.96) 9.15-12.0 (2.85) det = 170.71 [0.90]	0.19-0.41 (0.11) 1.21-2.58 (0.69) 10.0-12.0 (2.0) det = 181.27 [0.95]

*Window half lengths in parentheses, **det is the normalised determinant

Sampling windows determination – Example (Loguniform distribution)

○ Optimal design (fixed time) – 0.30, 1.9 and 12 hrs (det =189.95)

| Efficiency	Criterion	G&A	Duffull	New approach
90%	Mean	0.18-0.52 (0.54*) 1.10-3.24 (0.54) 6.99-12.0 (0.54) det** = 171.43 [0.90]	0.09-0.97 (1.18) 0.42-8.49 (1.50) 5.83-12.0 (0.72) det = 129.91 [0.68]	0.16-0.58 (0.66) 0.82-4.37 (0.84) 8.02-12.0 (0.40) det = 172.15 [0.91]
90%	10%	0.20-0.45 (0.40) 1.27-2.82 (0.40) 8.05-12.0 (0.40) det = 170.42 [0.90]	0.14-0.65 (0.77) 0.78-4.57 (0.88) 7.72-12.0 (0.44) det = 145.12 [0.76	0.18-0.51 (0.53) 1.02-3.47 (0.61) 8.85-12.0 (0.30) det = 173.07 [0.91]
95%	Mean	0.21-0.43 9 (0.36) 1.32-2.70 (0.36) 8.40-12.0 (0.36) det = 180.28 [0.95]	0.13-0.70 (0.84) 0.61-5.84 (1.13) 7.69-12.0 (0.44) det = 158.46 [0.83]	0.19-0.48 (0.48) 1.0-3.57 (0.64) 9.34-12.0 (0.25) det = 180.51 [0.95]
95%	10%	0.23-0.38 (0.24) 1.49-2.40 (0.24) 9.44-12.0 (0.24) det = 180.21 [0.95]	0.17-0.52 (0.55) 0.98-3.66 (0.66) 9.20-12 (0.27) det = 168.87 [0.89]	0.21-0.43 (0.35) 1.23-2.90 (0.43) 10.10-12.0 (0.17) det = 180.85 [0.95]

*Window half lengths (on the logarithmic scale) in parentheses, **det is the normalised determinant

Sampling windows determination – Example (uniform distribution, 90% efficiency level and mean criteria)
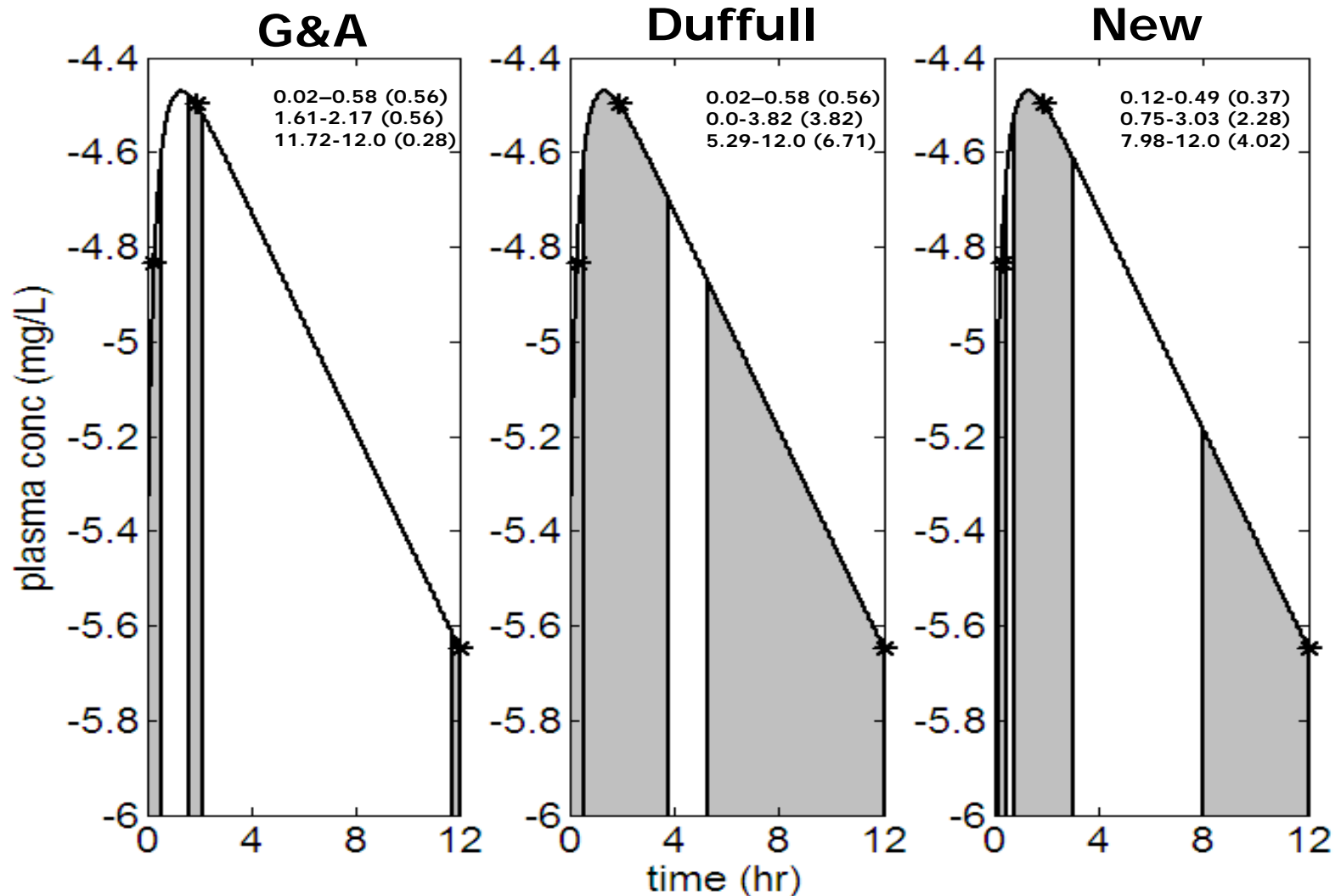
Sampling windows determination – Example (simulations, RE)
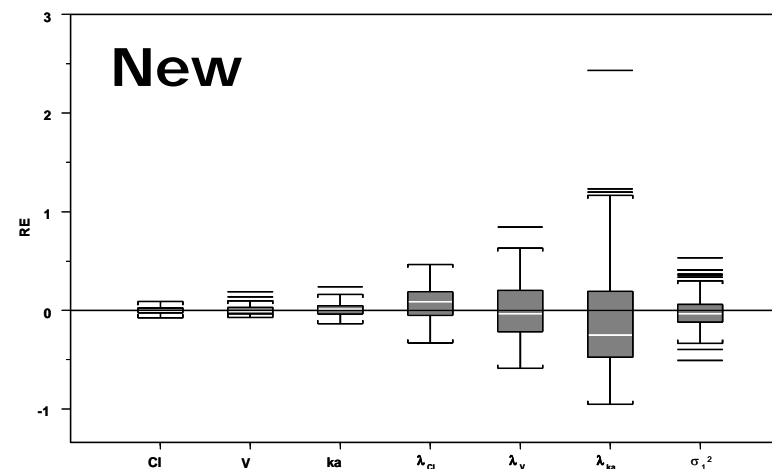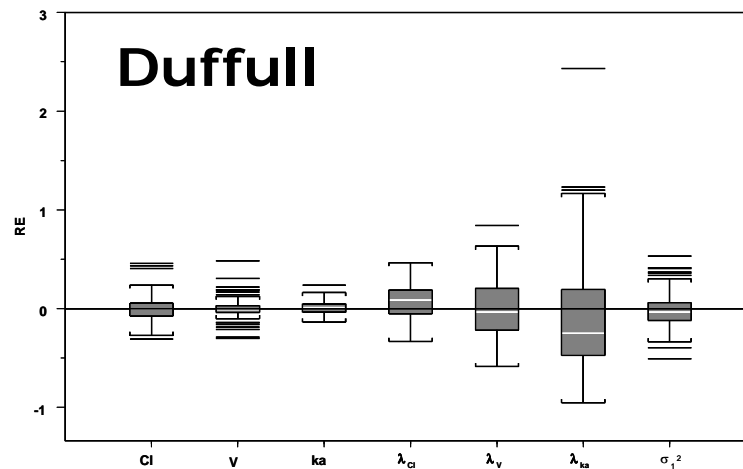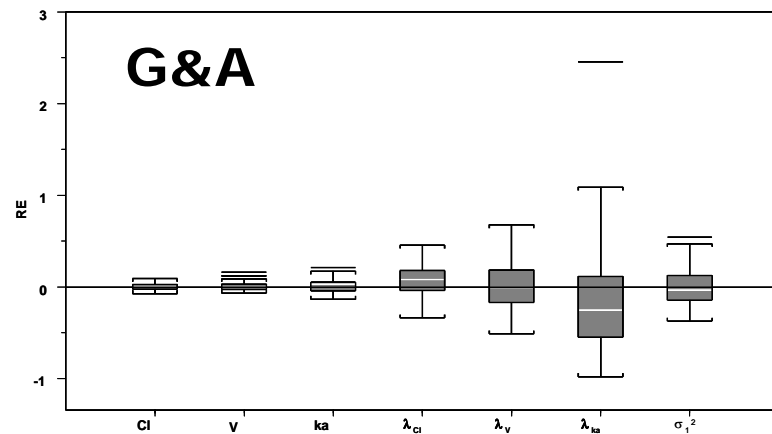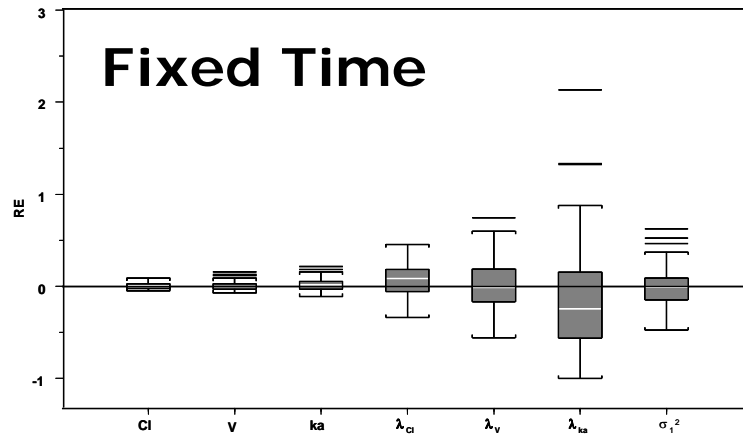
Sampling windows determination – Conclusion

- Sampling windows provide adequate flexibility (controlled flexibility) for sample collection
- The new approach is efficient and reflects parameter sensitivities
- This approach can be applied to both exact and continuous design as well as multiresponse designs
- Choice of efficiency level, criteria function and parameter distribution must be balanced against other design properties
- Efficient population PK experiment can provide improved parameter estimates and can help to reduce cost and time