OPTIMAL DESIGN FOR POPULATION PK/PD MODELS

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OUTLINE

1. Introduction
2. Population design evaluation and optimisation
3. Models with IOV and covariates with application to enoxaparine PK
4. Prediction of power with application to viral load dynamics
5. PK/PD models with evaluation by simulation
6. Conclusion

1. INTRODUCTION

Population PK/PD

- Population PK/PD studies increasingly performed during drug development
- Several methods/software for maximum likelihood estimation of population parameters using nonlinear mixed effects models
  - NONMEM
  - Splus/R: nmle, SAS: Proc NLINMIX
  - MCMC estimation methods: SAEM (MONOLIX), MC-PEM,…
- Problem beforehand: choice of population design
  - number of patients?
  - number of sampling times?
  - sampling times?

Population Design

- N subjects i
- Elementary design ξ_i in subject i
  - number of samples n_i and sampling times: $t_{i1} \ldots t_{in_i}$
  - may differ between subjects and may lead to non-identifiability of individual experiment
- Population design
  - set of elementary designs $\Xi = \{\xi_1, \ldots, \xi_N\}$
  - number of observations $n_{tot} = \Sigma n_i$
- Often few elementary designs
  - Q groups of N_q subjects
  - same design ξ_q of n_q sampling times
  - $n_{tot} = \Sigma N_q n_q$

Statistical estimation (1)

Statistics:

1. Inference
2. Planning

1. Inference
   - hypothesis testing
   - estimation
   - prediction
2. Planning = find « optimal » design given
   - objective (ex: estimation)
   - statistical method (ex: maximum likelihood)
   - experimental constraints
   - some prior knowledge on expected results

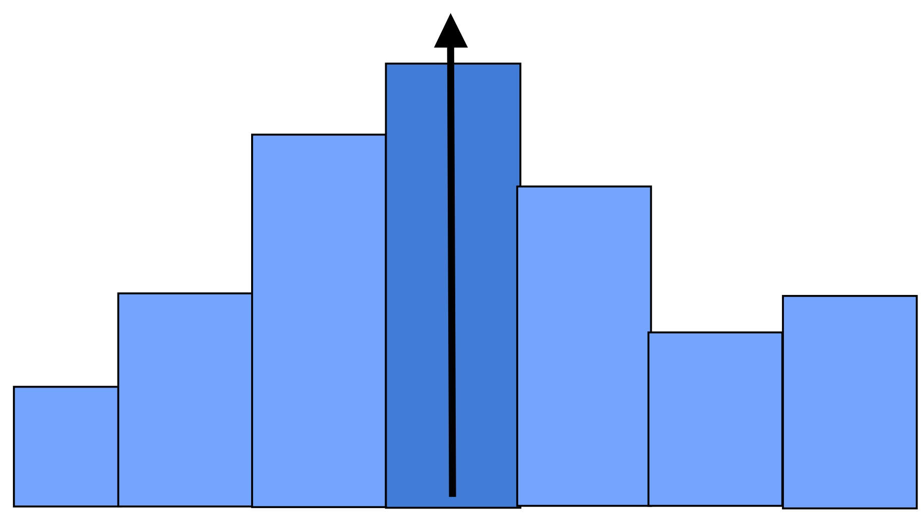
Statistical estimation (2)

Same design

- Data set 1 → Estimate θ_1
- Data set 2 → Estimate θ_2
- …
- Data set K → Estimate θ_K

Histogram of estimates

Estimation variance: Var $(\hat{\theta})$



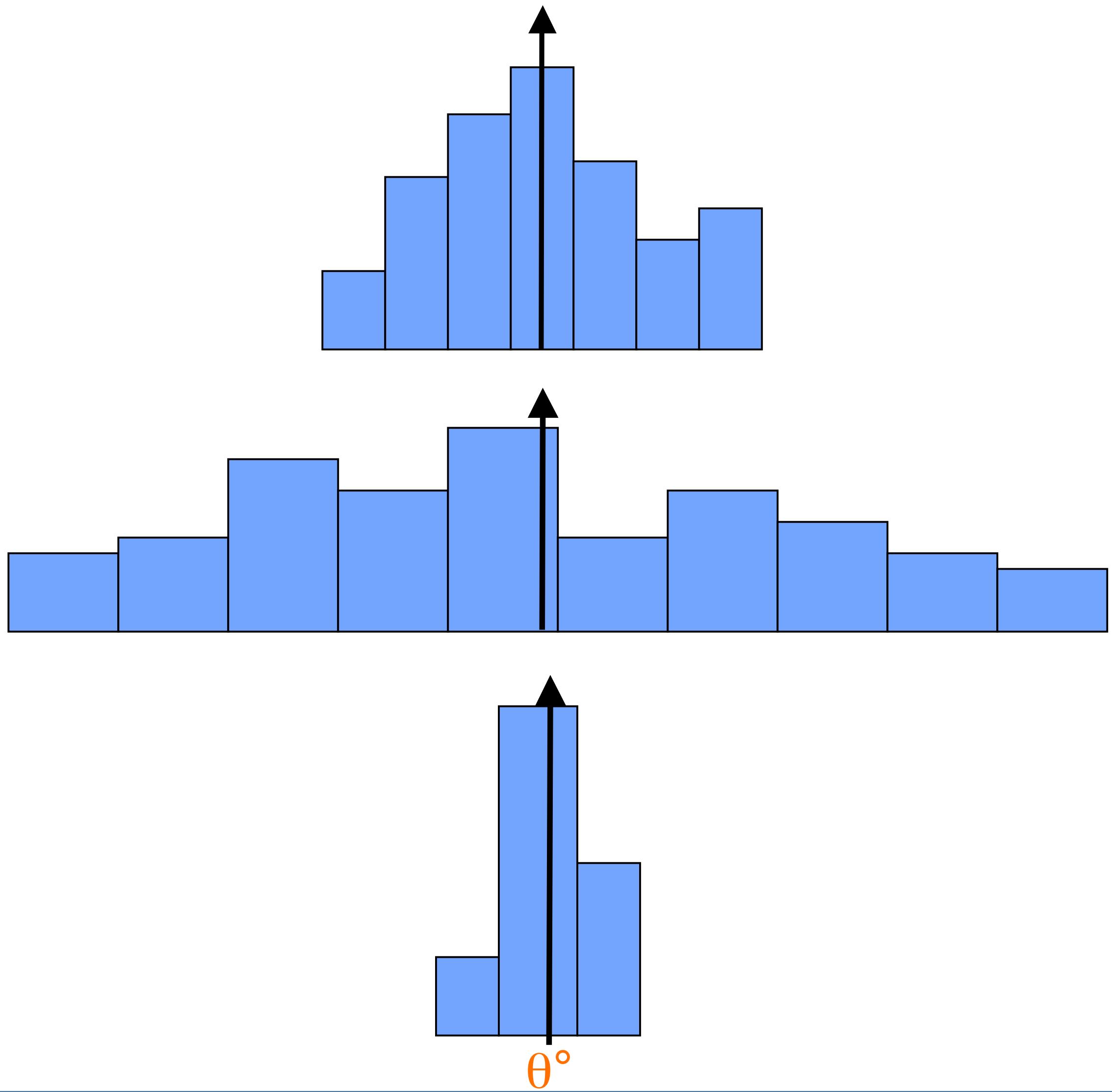
Real value of parameters: $\theta°$

Statistical estimation (4)

Design ξ_1

Design ξ_2

Design ξ_k



Finding optimal design

- From
  - maximum cost (number of samples)
  - experimental constraints
  - a priori values of parameters
- Find best design
  - smallest variance of estimation
  - greatest information in the data
- Two approaches
  - simulation studies
  - mathematical derivation of the Fisher Information matrix (MF)
    - Cramer-Rao inequality: MF^{-1} is the lower bound of the estimation variance

2. POPULATION DESIGN EVALUATION AND OPTIMISATION

Guidance for Industry

Population Pharmacokinetics

U.S. Department of Health and Human Services
Food and Drug Administration
Center for Drug Evaluation and Research (CDER)
Center for Biologics Evaluation and Research (CBER)
February 1999
CP 1

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V. STUDY DESIGN AND EXECUTION

Because it will determine the study design, the objective of a population PK study should be defined clearly from the outset. When designing a population PK study, practical design limitations, such as sampling times, number of samples per subject, and number of subjects, should be considered. Obtaining preliminary information on variability from pilot studies makes possible through simulation (see section C, below) to anticipate certain fatal study designs, and recognize informative ones. Optimizing the sampling design becomes particularly important wh severe limitations exist on the number of subjects and/or samples per subject (e.g., in pediatric patients or the elderly) (15). Use of informative designs for population PK studies is encourage (15-20). Such designs should include enough patients in important subgroups to ensure accura and precise parameter estimation and the detection of any subgroup differences.

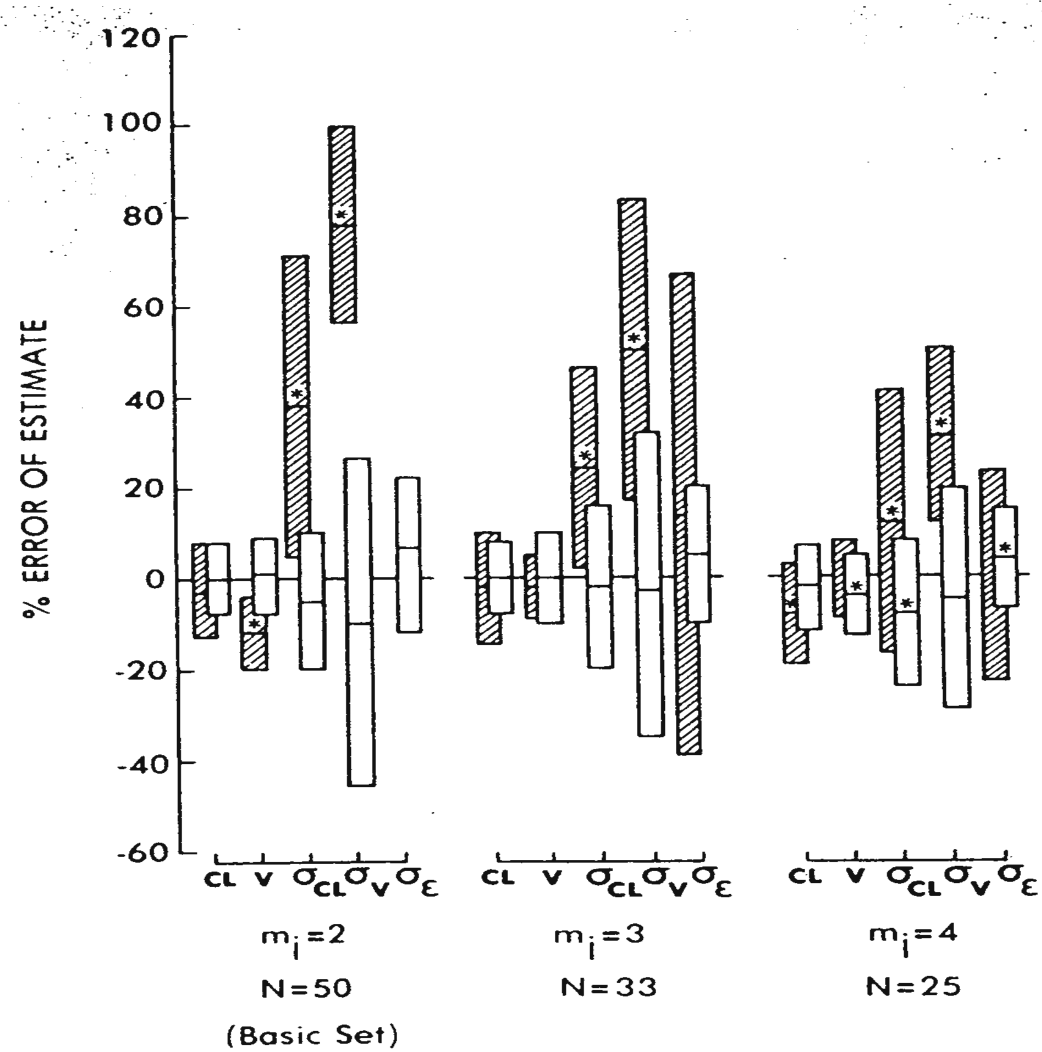
Evaluation of designs by simulation

- Several published studies
  - Hashimoto & Sheiner, *J Pharmacokin Biopharm*, 1991
  - Jonsson, Wade & Karlsson, *J Pharmacokin Biopharm*, 1996
- Evaluation of population designs with respect to
  - number of patients (N), number of samples per patient (n)
  - sampling times
  - number of occasions per patient, number of samples per occasion
- Main limitation
  - very time consuming
  - only limiter number of designs evaluated

→ approach for design evaluation without simulation based on Fisher Information matrix

Comparison of STS (shaded blocks) and NONMEM (white blocks) on simulated data sets

Sheiner & Beal, *J Pharmacokinet Biopharm*, 1983



3 population designs

Fisher information matrix (1)

- Vector of population parameters: ψ (size P)
  - θ (fixed effects)
  - unknowns in Ω (variance of random effects)
  - σ_{inter} and/or σ_{slope} (error variance)

- Information Matrix for population design $\Xi = \{\xi^1, ..., \xi^N\}$

$$MF(\Xi, \Psi) = \sum_{i=1}^{N} MF(\xi^i, \Psi)$$

- Information Matrix for elementary design ξ^i

$$MF(\xi^i, \Psi) = E\left\{ \frac{\partial \log l(y;\Psi)}{\partial \psi} \frac{\partial \log l(y;\Psi)'}{\partial \psi} \right\}$$

Fisher information matrix (2)

(Mentré, Mallet & Baccar, *Biometrika*, 1997;
Retout, Mentré & Bruno, *Stat Med*, 2002)

- Nonlinear structural models
  - no analytical expression for MF(ξ, Ψ)
  - first order expansion of f about random effects taken at 0

(+ further assumption on independence between Var(b_i) and fixed effects)

$$MF(\xi, \Psi) = \begin{pmatrix} MF(\xi,\mu) & 0 \\ 0 & MF(\xi,\Omega,\sigma) \end{pmatrix}$$

  - analytical expressions for MF(ξ, μ) and MF(ξ, Ω, σ)

Population design evaluation and comparison

- Evaluation of MF for nonlinear mixed effects models implemented in software
  - PFIM in R and Splus (Retout & Mentré)
  - WinPOPT in MATLAB (Duffull)
  - …

- Comparison of designs
  - for a given model and a given Ψ
  - for each Ξ
    - predict MF and efficiency criterion = $\det(MF)^{1/P}$
    - predict SE or RSE (%) for each population parameter

Population design optimisation

- Find design which maximises $\det(MF)^{1/P}$
- Exact design
  - Fixed design structure (Q, N_q, number of samples in ξ_q)
  - Optimization of the sampling times in ξ_q, q = 1, …, Q
  - General algorithms: simplex, simulated annealing, NARS, …
    (Duffull, Retout & Mentré, *Comput Methods Programs Biomed*, 2002;
    Retout & Mentré, *J Pharmacokin Pharmacodyn*, 2003)
- Statistical design
  - α_q (≈ N_q/N) proportions of subjects in ξ_q
  - Fedorov-Wynn algorithm for optimization of
    - design structure (Q, α_q, n_q)
    - sampling times in ξ_q among a given set (discrete times)
      (Mentré, Mallet & Baccar, *Biometrika*, 1997;
      Retout, Comets, Samson & Mentré, *PAGE,* 2005)

3. Models with IOV and covariates with application to PK of enoxaparine

(Retout & Mentré, *J Biopharm Stat*, 2003;
Retout & Mentré, *J Pharmacokin Pharmacodyn*, 2003)

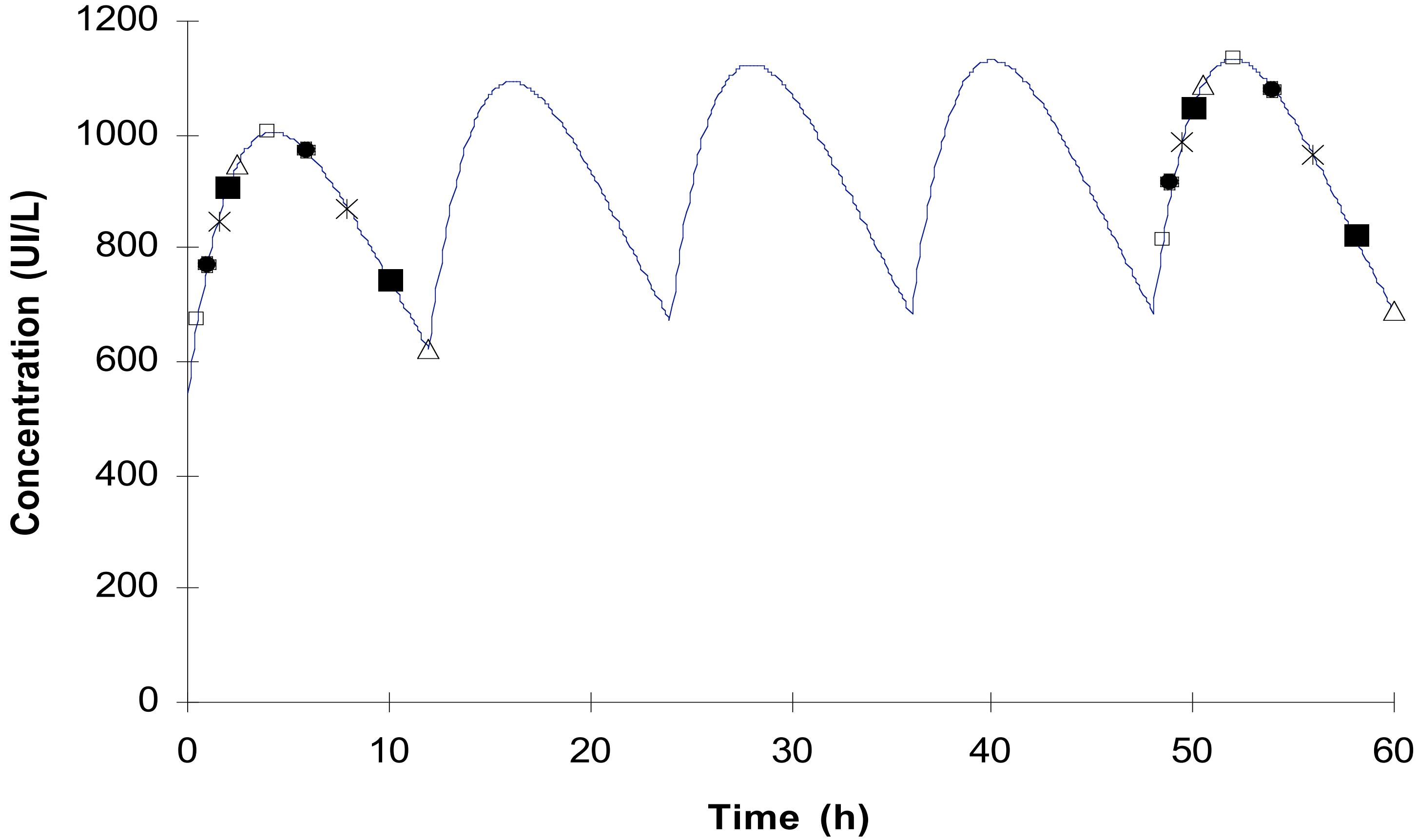
Material

(Retout, Mentré & Bruno, *Stat Med*, 2002)

- Enoxaparin administration
  - 30 mg by IV bolus at t = 0
  - 1 mg/kg/12h by subcutaneous injection
- Population model (from prior study)
  - one cp model, first order absorption and elimination
  - exponential random effects, constant CV residual error
  - estimation of Ψ using NONMEM FOCE
- Basic model
  - CL, V, KA, ω_{CL}, ω_V, σ^2
- Rich model
  - two covariates (weight and CLCr) and IOV on CL
  - CL, β_{WT}, β_{CLCR}, V, KA, ω_{CL}, ω_{IOV}, ω_V, σ^2

Empirical design

– 200 patients: 2 samples at D1 replicated at D3 (5 designs)
– 20 patients: 4 samples at D3



Empirical design for the basic model

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Design	Q	Elementary designs			Criterion
		ξ_q (h)		N_q	
		D1	D3		
Empirical	6	(0.5, 4)	(0.5, 4)	40	1295.2
		(1, 6)	(1, 6)	40	
		(1.5, 8)	(1.5, 8)	40	
		(2, 10)	(2, 10)	40	
		(2.5,12)	(2.5, 12)	40	
		-	(1, 2, 6, 12)	20	

Design optimisation

- Constraints
  - 220 patients, 4 samples per patient
  - two at D1 (first dose), two at D3 (fifth dose)

- Extension of MF for models
  1. with IOV
  2. with fixed effects for covariates
     - specificy the expected distribution of covariates
     - evaluation of the expected (mean) MF
     - prediction of the expected SE of β

- Optimisation with Federov Wynn algorithm
  - 10 available sampling times:
    {0.5, 1, 1.5, 2, 2.5, 4, 6, 8, 10, 12}

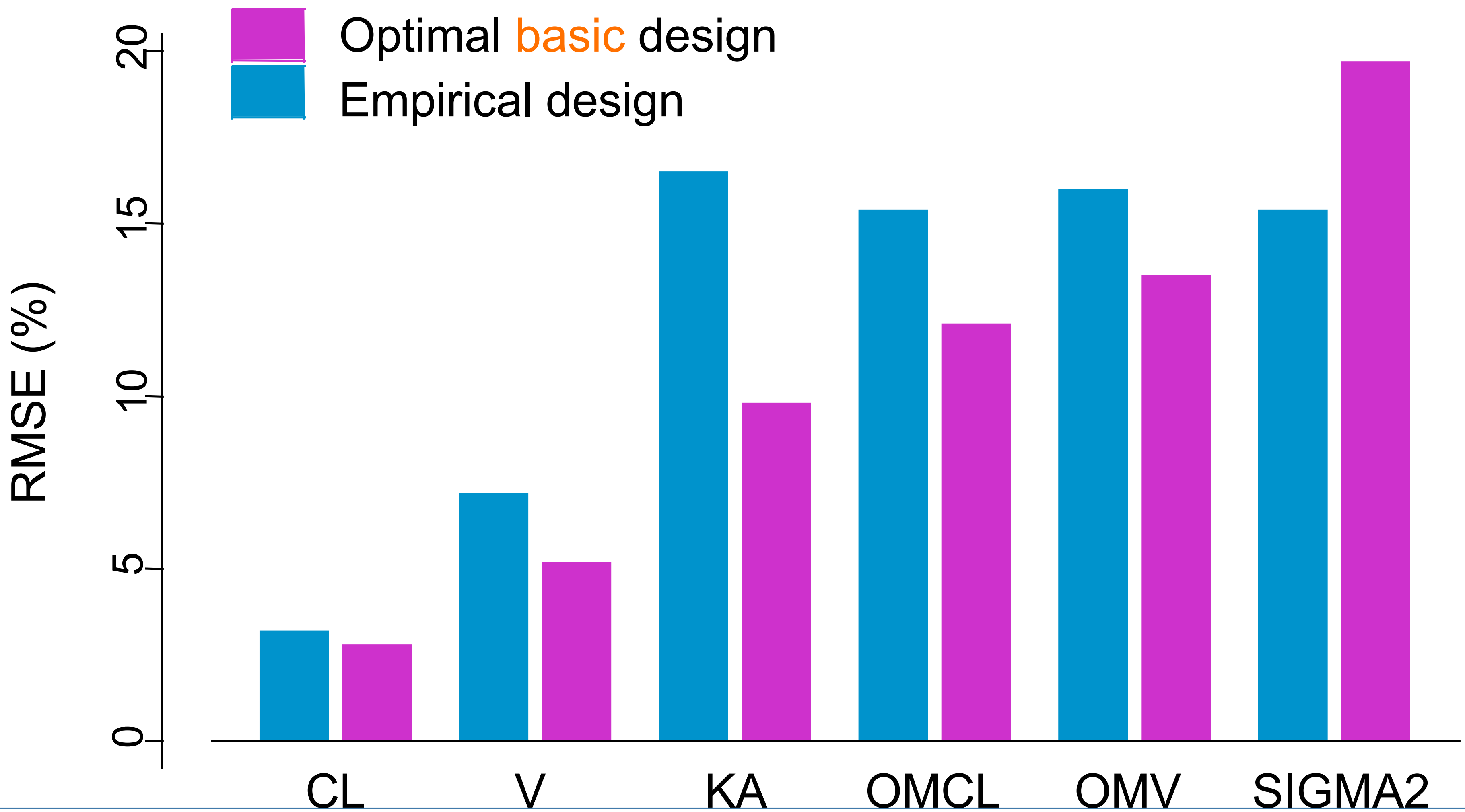
Optimal design for the basic model

Design	Q	Elementary designs			Criterion
		?$_q$ (h)		N_q	
		D1	D3		
Empirical	6	(0.5, 4)	(0.5, 4)	40	1295.2
		(1, 6)	(1, 6)	40	
		(1.5, 8)	(1.5, 8)	40	
		(2, 10)	(2, 10)	40	
		(2.5,12)	(2.5, 12)	40	
		-	(1, 2, 6, 12)	20	
Optimal design	1	(0.5, 4)	(2.5, 12)	220	1742.8

Efficiency = 1.35

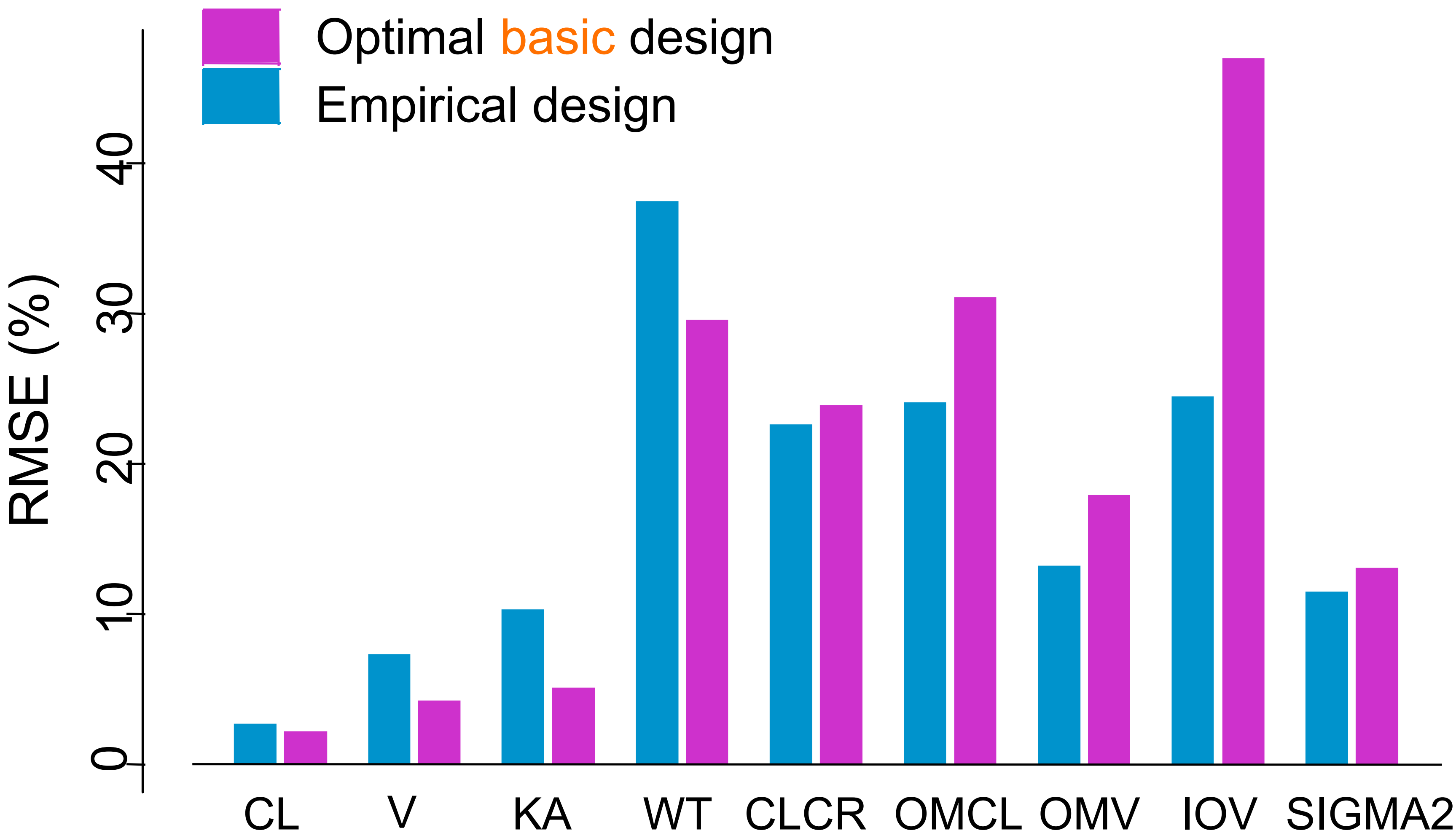
RMSE for 30 simulated data sets: basic model

NONMEM FOCE



RMSE for 30 simulated data sets: rich model

NONMEM FOCE



Optimal design for the rich model

Expected RSE (%) for the rich model

Optimisation	Design	CL	WT	CLCR	OMCL	IOV	SIG	Eff.
Basic	0.5, 4 at D1 2.5, 12 at D3	2.3	23.9	17.3	25.1	39.9	8.8	1
Rich	0.5, 12 at D1 2.5, 12 at D3	2.2	22.4	16.3	15.8	16.7	10.2	1.21

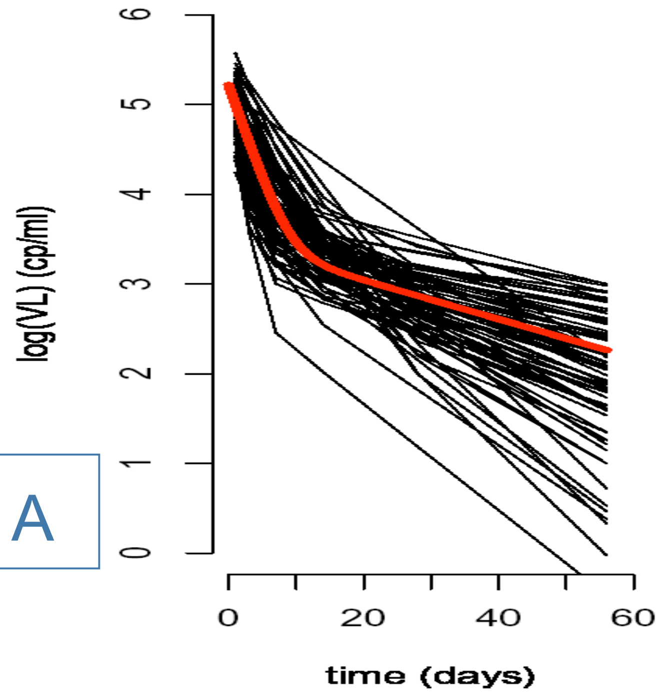
4. Prediction of power with application to viral load dynamics

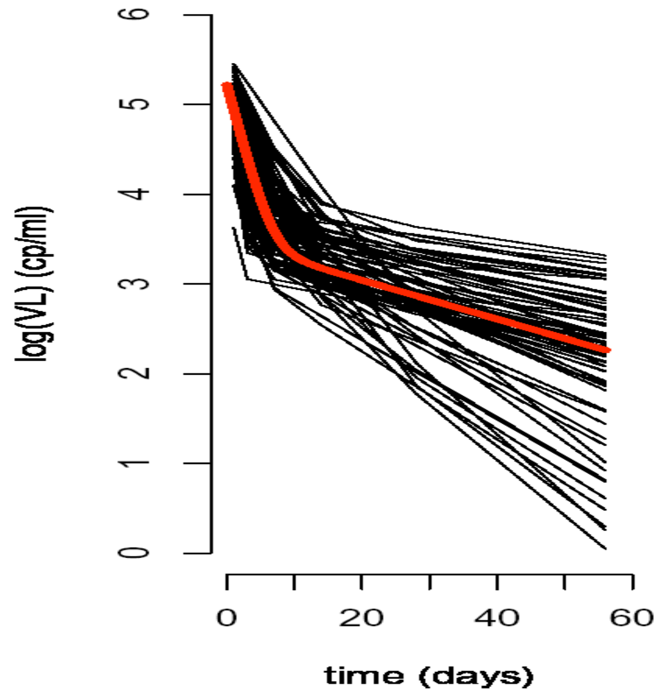
(Retout, Comets, Samson & Mentré, *PAGE,* 2005; *Joint Statistical Meeting,* 2006)

Biexponential model of viral load decrease

(Wu, Ding & de Gruttola, *Stat Med*, 1998; Wu & Ding, *Biometrical J*, 2002)

Group A





Group B

- Fixed effect β for treatment effect on first slope
  - $\log(\lambda_1)^{B} = \log(\lambda_1)^{A} + \beta$
  - Wald test for H_0: $\beta = 0$ (no treatment effect)

Predicted power for test of treatment effect

(Kang, Schwartz &Verotta, *Stat Med,* 2004; *J Pharmacokin Pharmacodyn*, 2005)

- MF to predict SE of β under H_0
- Predict power under H_1

Design $\xi = \{1, 3, 7, 14, 28, 56\}$ in all patients

	H_1: β = 0.262 30% increase	*H_1: β = 0.405* *50% increase*
N = 40 per group	55%	*90%*
N = 100 per group	92%	*99%*

➔ number of subjects needed for a given power

(SE proportional to $N^{1/2}$)

Design optimisation with FW algorithm

Total of 240 samples per group in set {0,1,2,3,5,7,10,14,21,28,42,56}

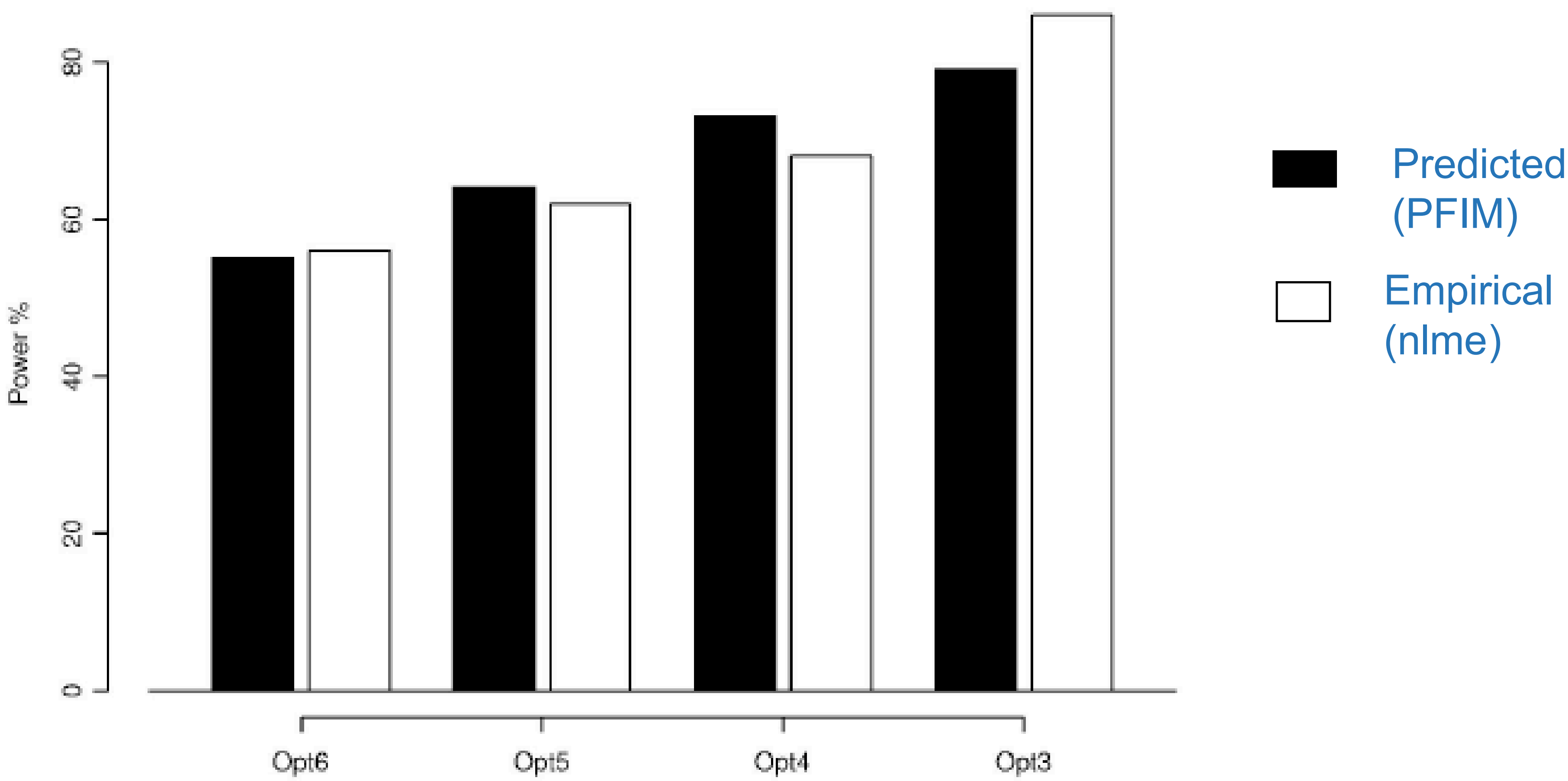
	N per group	n	Design (weeks)	$Det^{1/10}$	**SE (β)**	Power
	40[a]	6	1, 3, 7, 14, 28, 56	458	**0.124**	55%
Opt6	40	6	0, 1, 7, 14, 21, 56	471	**0.124**	55%
Opt5	48	5	0, 7, 14, 21, 56	523	**0.113**	64%
Opt4[b]	60	4	N_1= 40: 0, 5, 14, 56 N_2= 10: 0, 14,21,56 N_3= 10: 0, 1, 2, 3	536	**0.102**	73%
Opt3[b]	80	3	N_1= 35: 7, 14, 56 N_2= 30: 0, 1, 5 N_3= 10: 0, 21, 56 N_4= 5: 0, 5, 56	531	**0.095**	79%

[a] Initial non-optimised design

[b] Rounded optimal statistical design

Predicted / empirical power on 100 simulations under H_1 for several designs

nlme



5. PK/PD models with evaluation by simulation

(Bazzoli, Retout & Mentré, *Master dissertation,* 2006*)*

Model and design

(Hooker & Vincini, *AAPS J*, 2005)

- PK model

$$f_{PK}(\theta^{PK},\xi^{PK}) = \frac{Dose}{V} \times \exp(\frac{-Cl}{V} \times \xi^{PK})$$

- _^{PK}: Cl, V

- constant CV error model

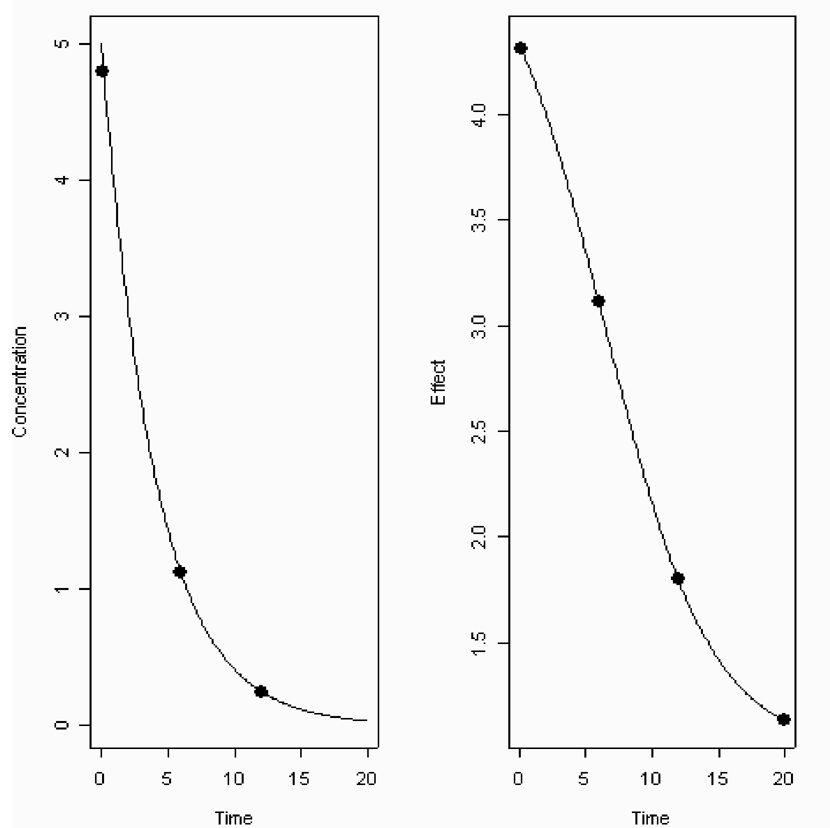
- PD model

$$f_{PD}(\theta^{PK},\theta^{PD},\xi^{PD}) = E_0 + \frac{E_{\max} \times f_{PK}(\theta^{PK},\xi^{PD})}{C_{50} + f_{PK}(\theta^{PK},\xi^{PD})}$$

- _^{PD}: E_0 , E_{max}, C_{50}

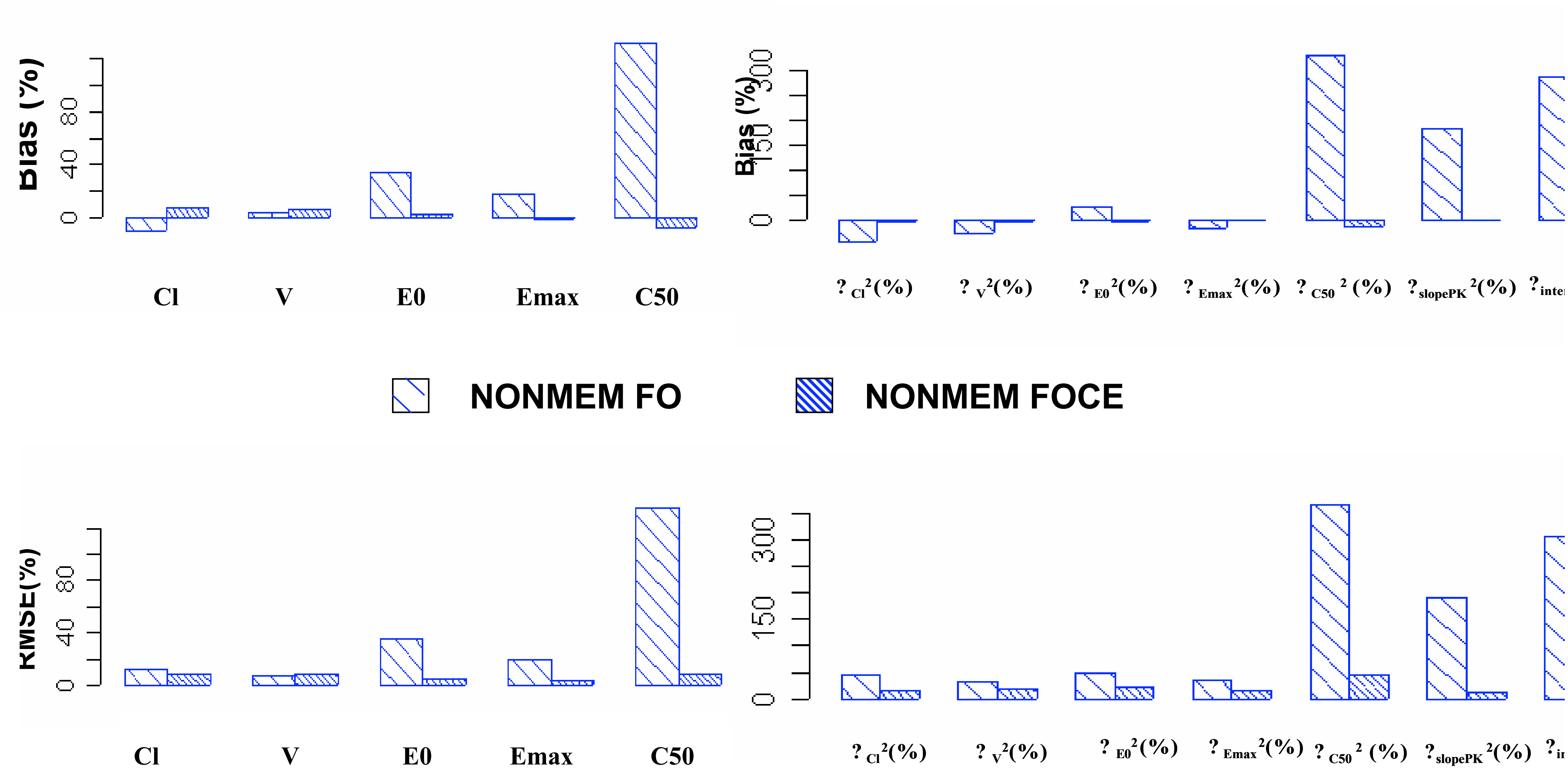
- constant variance error model

- Population design
  - N = 100
  - _^{PK} = {0.167, 6,12}, _^{PD} = {0.167, 6,12, 20}

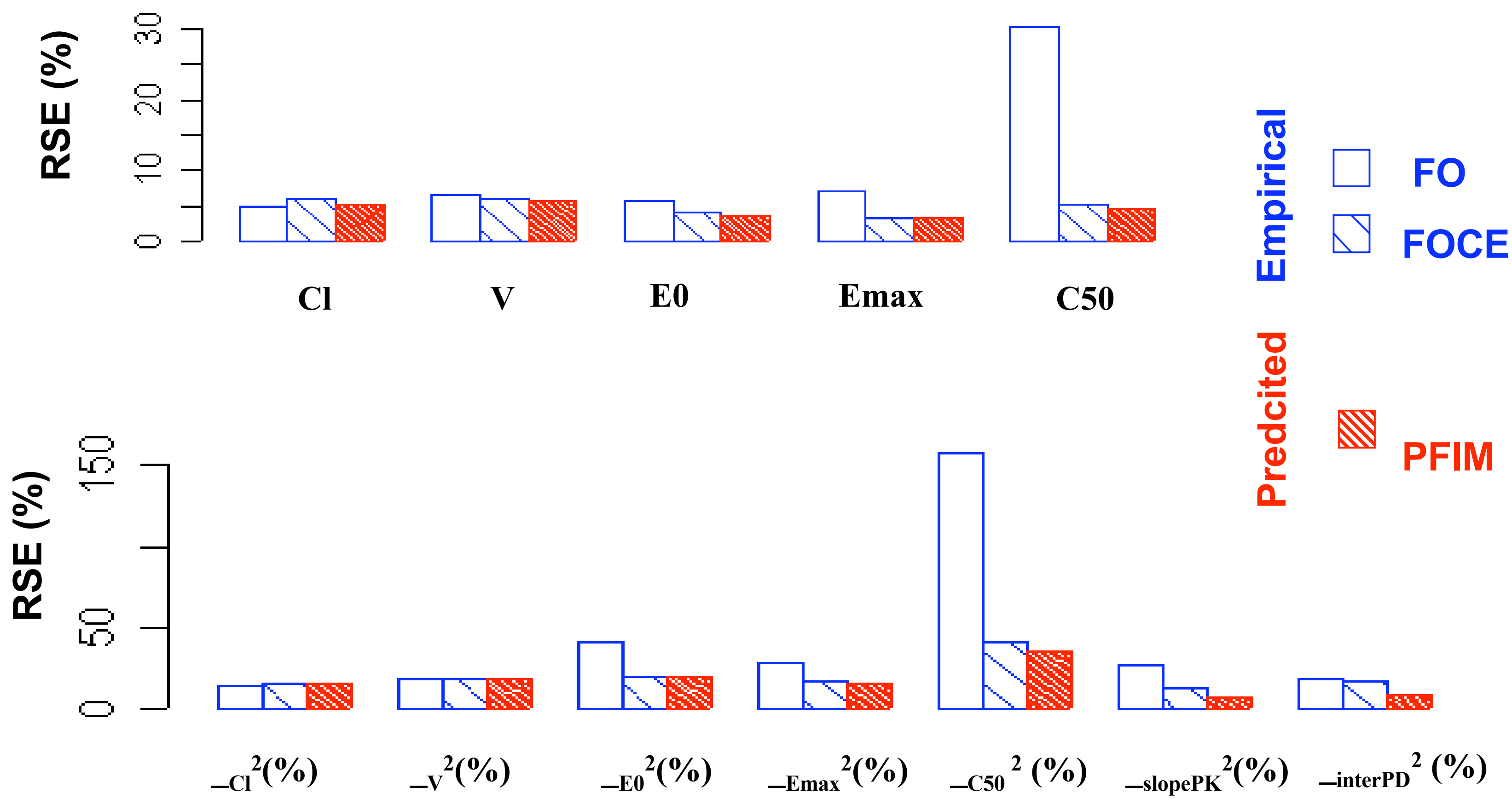


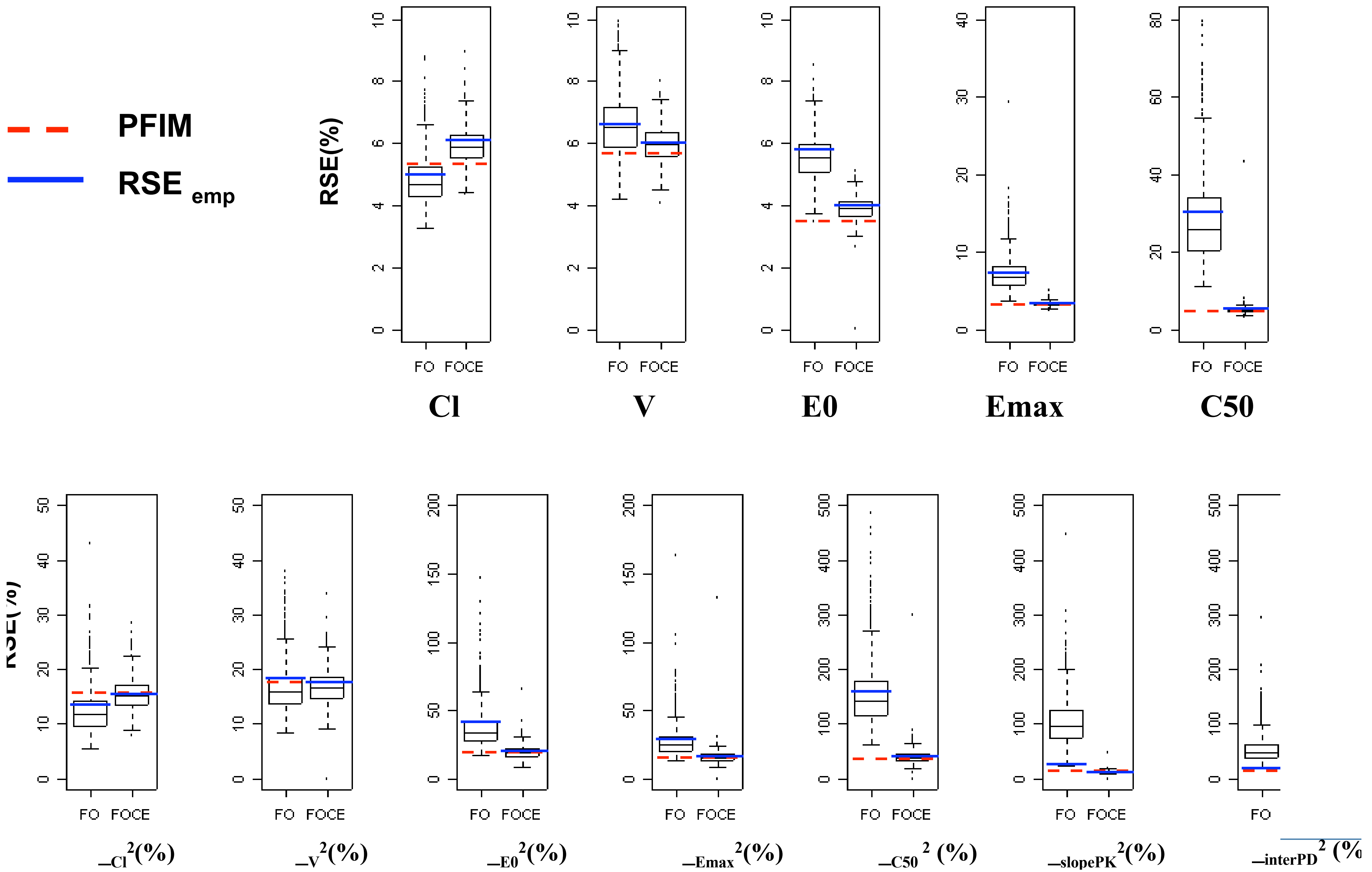
Bias and RMSE on 1000 simulated data sets

(Zhang, Beal & Sheiner, *J Pharmacokin Pharmacodyn*, 2003)



Predicted / empirical RSE on 1000 simulated data sets




PFIM
RSE emp
RSE(%)
FO FOCE
Cl
V
E0
Emax
C50
Cl 2(%)
V 2(%)
E0 2(%)
Emax 2(%)
C50 2 (%)
slopePK 2(%)
interPD 2 (%

6. CONCLUSION

Conclusion (1)

- Results of population PK/PD analyses increasingly used
  - in drug labeling
  - in test of covariates
  - for clinical trial simulation

  ➔ Informative studies with small estimation error

- Evaluation and comparison of population design without simulation using statistical approach

- Results show that design may CONSIDERABLY affects precision of estimation

  SPARSE-SAMPLING DESIGN =

  BEST INFORMATION IS NEEDED

Conclusion (2)

- Several recent extensions
  - optimal allocation of sampling times and group structure
  - expected power of Wald test and number of subjects needed
  - complex multi-responses models (with ODE)
    - different optimal sampling times
  - *other optimisation criteria*
- Optimisation methods are useful tools
  - to define good designs
  - to anticipate some fatal designs
- Then apply more robust or more practical designs
  - with respect to population parameters
  - compromise design
  - sampling windows