Importance of model based optimal designs to design successful PKPD clinical trials

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Infection . Antimicrobials . Modelling. Evolution

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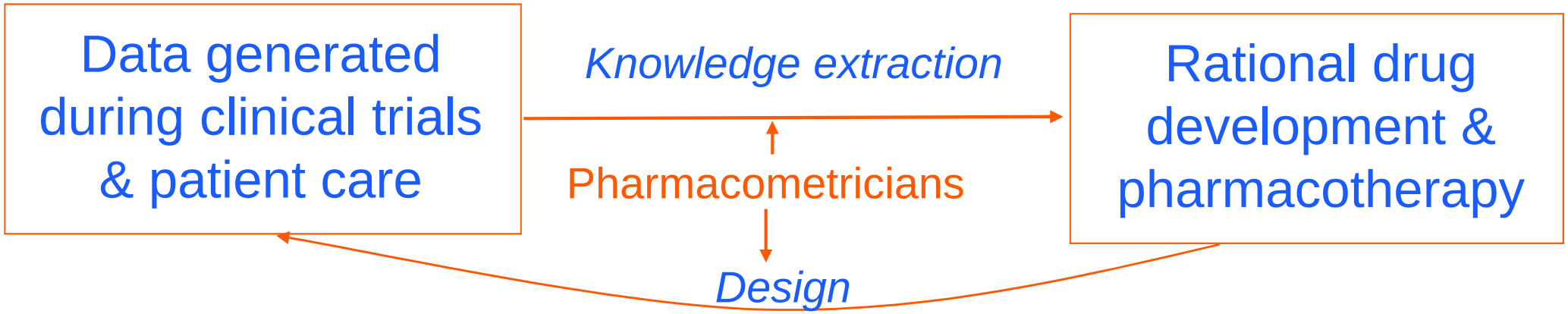
OUTLINE

1. Introduction
2. Design for NLMEM
3. Population PK example: enoxaparin
4. Covariate and power
5. Bayesian estimation and shrinkage
6. Software tools in population design
7. Conclusion

1. INTRODUCTION

PHARMACOMETRICS

The science of quantitative clinical pharmacology



- Clinical pharmacology = PK + PD + Disease models

  - Both during drug development and in clinical care
  - Main statistical tool: Nonlinear Mixed Effect Models (NLMEM)

Population PKPD

- Population PKPD studies increasingly performed for analysis of preclinical or clinical data
- Several methods/software for maximum likelihood estimation of population parameters using nonlinear mixed effects models
  - NONMEM
  - MONOLIX
  - Phoenix NLME
  - Splus/R: nmle, SAS: Proc NLMIXED, …
- Problem beforehand: choice of 'population' design
  - number of individuals?
  - number of sampling times?
  - sampling times?
  - other design variables (doses, etc…)

Design for Population PKPD analyses

- Increasingly important task for pharmacologists/ statisticians
- Importance of the choice
  - influence the precision of parameters estimation and power of tests
  - poor design can lead to unreliable studies especially for complex models
  - all the more important in special population (paediatric studies …)
    - severe limitations on the number of samples to be taken
    - ethical and physiological reasons
- Design considerations for population PK(PD) analyses stress out in FDA and EMEA guidelines

Design in PK/PD

- Individual designs
  - standard nonlinear regression
  - PKPD: define number of samples (n) and sampling times (t_i) or doses
- Population designs
  - nonlinear mixed-effects models
  - define
    - number of patients (N) and number of elementary designs (ξ_i)
    - for each elementary design (ξ_i) : number of samples (n_i) and sampling times (t_{ij})
- Bayesian designs
  - Bayesian individual estimation (from prior pop PKPD)
  - number of samples (n) and sampling times (t_i)

Statistical estimation

Statistics:

1. Inference
2. **Planning**

1. Inference
   - hypothesis testing
   - **estimation**
   - prediction
2. Planning = find ‘optimal’ design given
   - objective (e.g.: estimation)
   - statistical method (e.g.: maximum likelihood)
   - experimental constraints
   - some prior knowledge on expected results (e.g.: models and parameters)

Design evaluation/optimisation for estimation

- From statistical model and a priori values of parameters
  - Local planification
- Evaluate/compare designs
  - Predict standard error for each parameter
- Find optimal design
  - From given cost & experimental constraints
  - Smallest standard errors/ ‘greatest’ information in the data
- Two approaches
  - Simulation studies (‘Clinical trial simulation’)
  - Mathematical derivation of the Fisher Information Matrix

Statistical test

Statistics:

1. Inference
2. **Planning**

1. Inference
   - **hypothesis testing**
   - estimation
   - prediction
2. Planning = find ‘optimal’ design given
   - objective (e.g.: test)
   - statistical method (e.g.: Wald test)
   - experimental constraints
   - some prior knowledge on expected results (e.g.: models and parameters, effect size)

Design evaluation/optimisation for test

- From statistical model and a priori values of parameters (including effect size)
  - Local planification
- Evaluate/compare designs
  - Predict power and/or number of subject needed
- Find optimal design
  - From given cost & experimental constraints
  - Highest power/ ‘greatest’ information in the data
- Two approaches
  - Simulation studies (‘Clinical trial simulation’)
  - Mathematical derivation of power from predicted SE of effect (Wald test) using Fisher information matrix

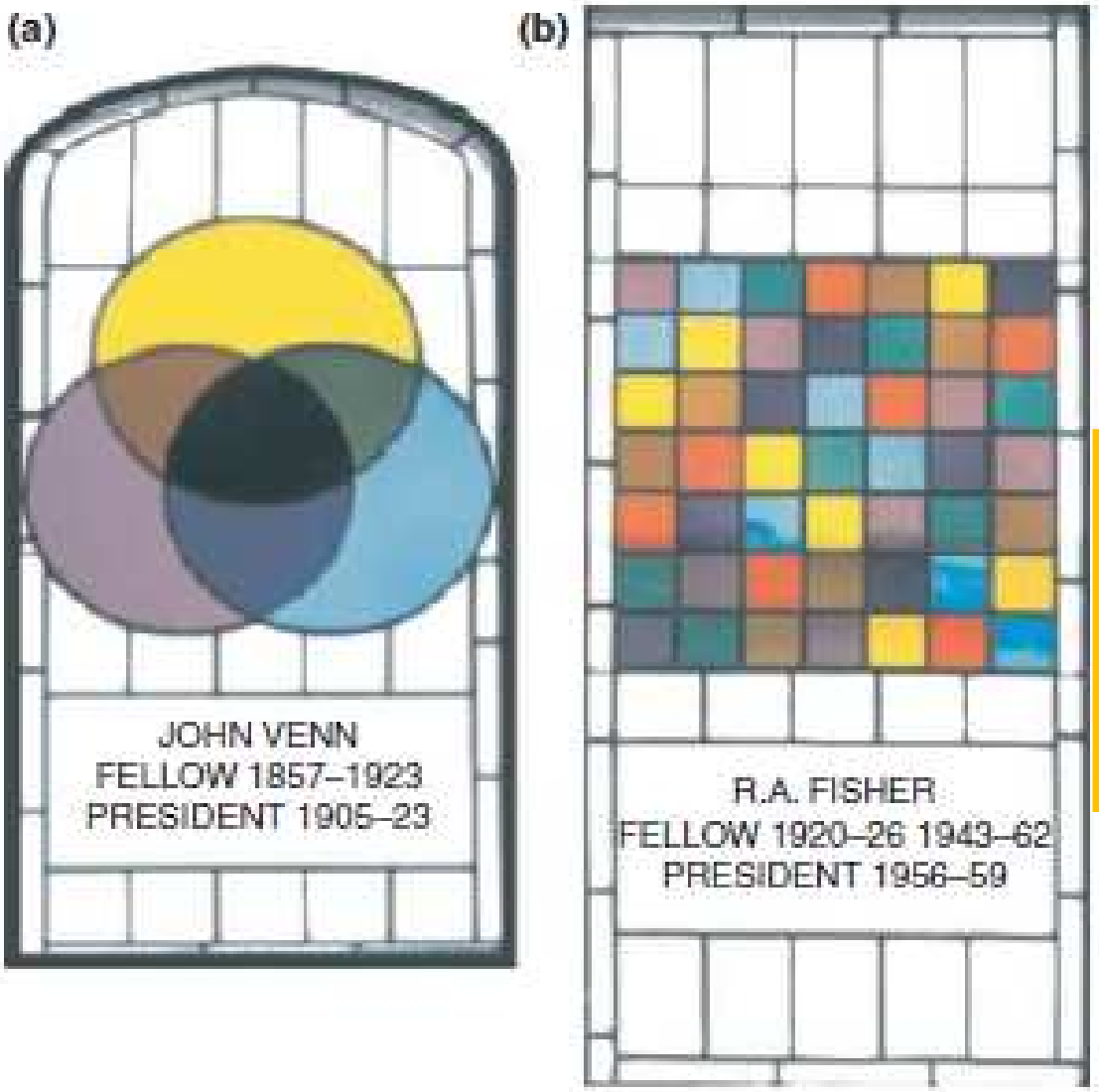


Figure 1 Stained glass windows in the Hall of Gonville and Caius College, Cambridge, commemorating (a) Venn (Fellow 1857–1923; a Venn diagram) and (b) Fisher (a Latin square).

Fisher was elected Fellow of the Royal Society in 1929, and Balfour Professor of Genetics, Cambridge, 1943–57. He was knighted in 1952 and served as President of Caius 1957–9.

To consult the statistician after an experiment is finished is often merely to ask him to conduct a post mortem examination. He can perhaps say what the experiment died of

– R.A. Fisher [1]

1 Fisher R.A. Presidential address to the first Indian Statistical Congress. *Sankhya* 1938; **4**: 14–7.

From Pandit JJ , Anesthesia 2010

2. DESIGN FOR NONLINEAR MIXED EFFECTS MODELS

Simple nonlinear model (one parameter)

Data: n observations y_1 , ... , y_n at times t_1, …. t_n

Design: $\xi = \{t_1, \ldots. t_n\}$

Model $y_j = f(t_j, \phi) + \varepsilon_j$, assume constant error variance σ^2

Estimate ϕ and σ from $y_1, y_2, \ldots, y_n$ using OLS

$$OLS = \sum (y_j - f(t_j, \phi))^2$$

Estimation of σ^2

$$\hat{\sigma}^2 = \frac{1}{n-1} \sum (y_j - f(t_j, \hat{\phi}))^2$$

Evaluation of SE(ϕ) based on **sensitivity of the model** with respect to ϕ: $\partial f(t, \phi) / \partial \phi$ function of both t and ϕ

$$\mathrm{var}(\hat{\phi}) = \frac{\hat{\sigma}^2}{\sum (\partial f(t_j, \hat{\phi}) / \partial \phi)^2}$$

1. SE decreases when information increases:
   ► influence of design on precision
2. SE increases when σ increases:
   ► influence of variability on precision

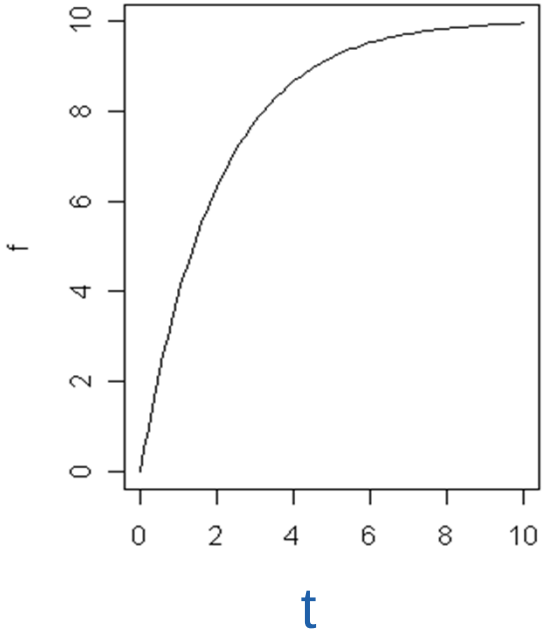
Link between sensitivity and design

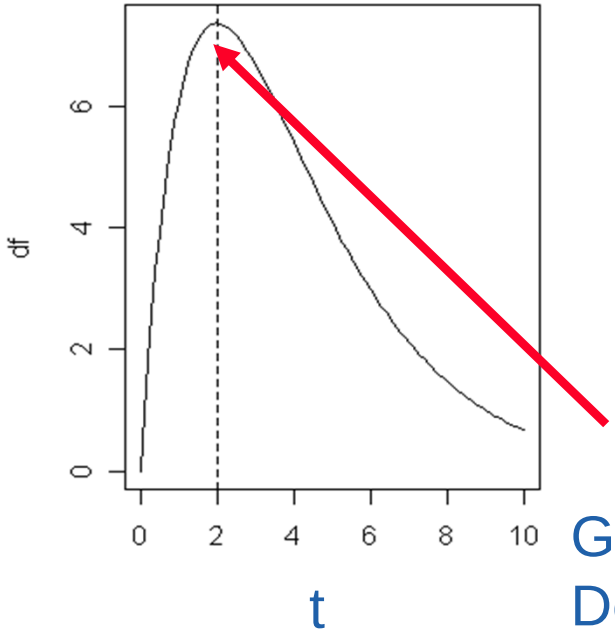
NB: Choice of t_j is important mostly for studies of limited size

"Informative t_i": sampling times where squared sensitivity of f is large

Example: $f(t,\phi) = 10(1- \exp(-\phi t))$ → $\partial f(t, \phi) / \partial \phi = 10\, t \exp(-\phi t)$

Illustration for $\phi = 0.5$





Greatest information for $t = 2 = 1/\phi$

Depends on knowledge of ϕ!

Nonlinear model with p parameters (1)

Same problem but now ϕ is a vector: OLS estimation of ϕ

Estimation of σ^2

$$\hat{\sigma}^2 = \frac{1}{n-p}\sum (y_j - f(t_j, \hat{\phi}))^2$$

Sensitivity of the model with respect to ϕ_k: $\partial f(t, \phi) / \partial \phi_k$

At each time: vector of p sensitivity functions

Jacobian matrix of the model (size n x p)

$$J(\xi, \phi) = \begin{pmatrix} \frac{\partial f(t_1, \phi)}{\partial \phi_1} & \cdots & \frac{\partial f(t_1, \phi)}{\partial \phi_p} \\ \cdots & \cdots & \cdots \\ \frac{\partial f(t_n, \phi)}{\partial \phi_1} & \cdots & \frac{f(t_n, \phi)}{\partial \phi_p} \end{pmatrix}$$

Nonlinear model with p parameters (2)

Expected Fisher Information Matrix of size p x p

$$M_F(\xi,\phi) = S(\xi,\phi)/\sigma^2 = J(\xi,\phi)^t J(\xi,\phi)/\sigma^2$$

depends on ϕ → NONLINEAR model

Observed estimation variance (lower bound)

$$\mathrm{var}(\hat{\phi}) \geq \hat{\sigma}^2 S(\xi,\hat{\phi})^{-1} = M_F(\xi,\hat{\phi})^{-1}$$

NB: for nonlinear models equality holds 'asymptotically'

Example for an Emax model

$y_j = E0 + Emax \times d_j / (ED50 + d_j) + \varepsilon_j$

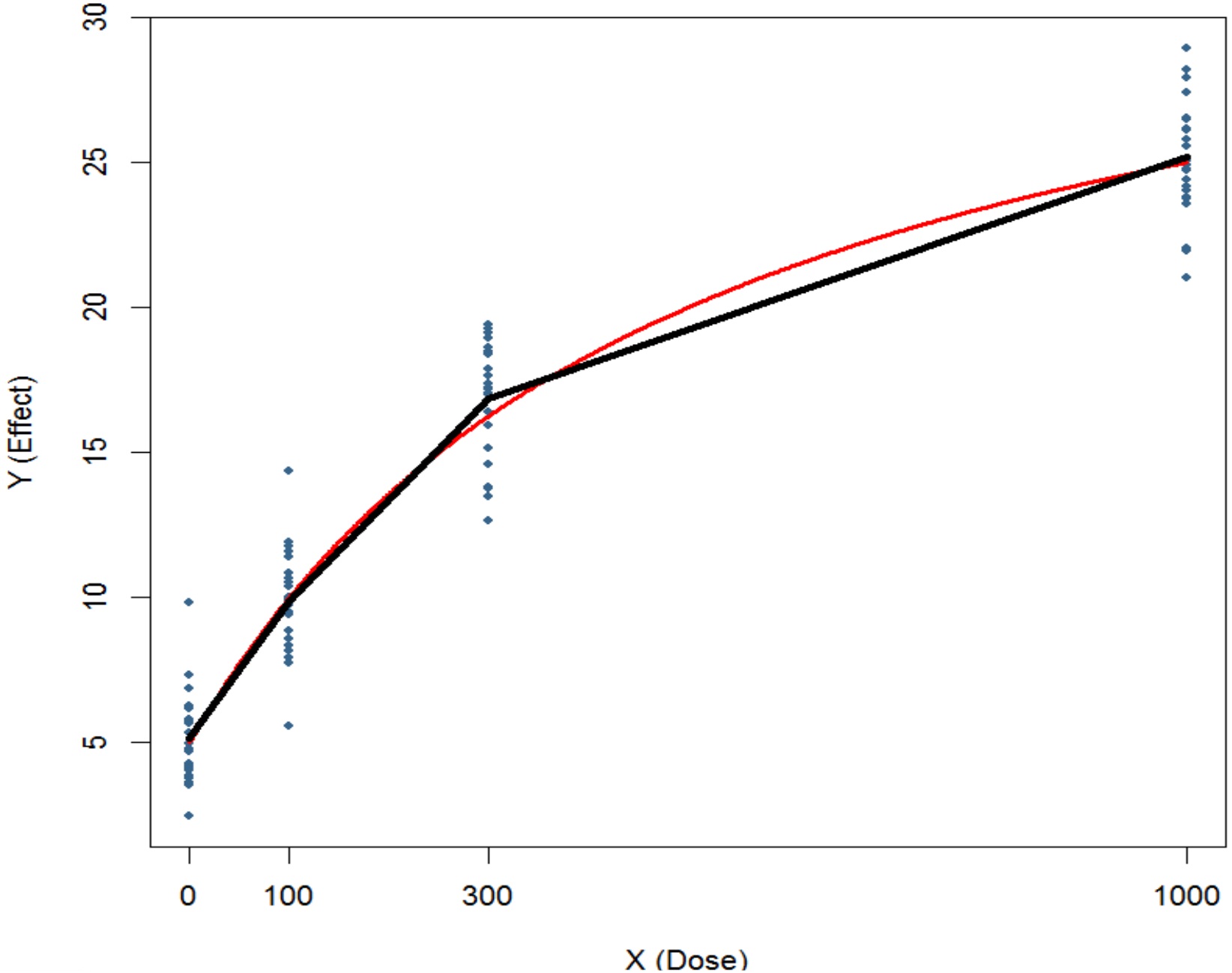
4 dose groups :
0, 100, 300, 1000

25 patient in each dose group

Total 100 patients

E0 = 5; Emax = 30; ED50=500
$\varepsilon \sim N(0, 2^2)$

One fitting



Comparison of prediction and simulation (1)

	Prediction (IFIM)	Estimation for 1 data set (nls in R)	Simulation & Estimation (for 1000 data sets)
E0	**5**	5.02	**4.99**
SE (E0)	**0.38**	0.38	**0.37**
Emax	**30**	30.9	**30.02**
SE (Emax)	**1.53**	1.65	**1.54**
ED50	**500**	527.1	**497.4**
SE (ED50)	**68.1**	73.7	**67.6**

Very close results between prediction and simulation

Influence on design on predicted SE (1)

	100 obs 25 patient/dose 4 doses 0, 100, 300, 1000	20 obs 5 patient/dose 4 doses 0, 100, 300, 1000	4 obs 1 patient/dose 4 doses 0, 100, 300, 1000
E0	5	5	5
SE (E0)	**0.38 (7.6%)**	**0.85 (17.0%)**	**1.9 (38.0%)**
Emax	30	30	30
SE (Emax)	**1.53 (5.1%)**	**3.43 (11.4%)**	**7.67 (25.6%)**
ED50	500	500	500
SE (ED50)	**68.1 (13.1%)**	**152.3 (30.4%)**	**340.6 (68.1%)**

Influence on design on predicted SE (2)

	24 obs 6 patient/dose 4 doses 0, 100, 300, 1000	24 obs 8 patient/dose 3 doses 0, 100, 1000	24 obs 8 patient/dose 3 doses 0, 100,300	24 obs 8 patient/dose 3 doses 100, 300,1000
E0	5	5	5	5
SE (E0)	**0.77 (15.5%)**	**0.71 (14.1%)**	**0.71 (14.1%)**	**2.15 (43.1%)**
Emax	30	30	30	30
SE (Emax)	**3.13 (10.4%)**	**3.50 (11.7%)**	**15.7 (52.3%)**	**2.96 (9.9%)**
ED50	500	500	500	500
SE (ED50)	**139.0 (27.8%)**	**180.3 (36.1%)**	**416.5 (83.3%)**	**238.6 (47.7%)**

Optimal design in nonlinear in regression

- Not new!!

Box GEP, Lucas HL. Design of experiments in non-linear situation. *Biometrika*. 1959;46(1-2):77-90.

Draper NR, Hunter WG. The use of prior distributions in the design of experiments for parameter estimation in non-linear situations: multiresponse case. *Biometrika*. 1967;54(3):662-5.

Atkinson AC, Hunter WG. The design of experiments for parameter estimation. *Technometrics.* 1968;10(2):271-89.

D'Argenio DZ. Optimal sampling times for pharmacokinetic experiments. *J Pharmacokinet Biopharm*. 1981;9(6):739-56.

- Problem: non robust approach
  - depends on parameter to be estimated
  - leads to replicates in the sampling times (rely on the model)

TECHNOMETRICS VOL. 10, NO. 2 MAY 1968

The Design of Experiments for Parameter Estimation[1]

ANTHONY C. ATKINSON[2]
American Cyanamid Company

WILLIAM G. HUNTER
The University of Wisconsin

This paper is concerned with the design of experiments to estimate the parameters in a model of known form, which may be nonlinear in the parameters. This problem was discussed in detail by Box and Lucas for the case where N, the number of experiments, is equal to p, the number of parameters. The present work is an extension to cases where N is greater than p. Conditions are established under which, when the number of experiments is a multiple of the number of parameters, replication of the best design for p experiments is an optimal design for N experiments. Several chemical examples are discussed; in each instance, the best design consists of simply repeating points of the original design for p experiments. An example is also mentioned where the best design does *not* consist of such replication.

then the relationship between the response η and the time ξ_1 will be of the form

$$\eta = \frac{\theta_1}{\theta_1 - \theta_2}\{\exp(-\theta_2\xi_1) - \exp(-\theta_1\xi_1)\} \qquad (1.1)$$

where θ_1 and θ_2 are the rate constants of the two steps of the reaction which could be represented schematically as

$$A \xrightarrow{\theta_1} B \xrightarrow{\theta_2} C.$$

Basic mixed-effects model (1)

- N patients i (=1,…, N)
  - n_i observations j (=1,…, n_i)
  - total number of observations: $n_{tot} = \Sigma\, n_i$

- Structural model (one continuous response)
  - $y_{ij} = f(t_{ij}, \phi_i) + \varepsilon_{ij}$
  - y_i: vector of n_i observations in patient i
  - ξ_i : vector of individual sampling times, t_{ij} j=1, …, n_i
  - ϕ_i : vector of individual parameters (size p)
  - Vector notation

$$y_i = f(\xi_i, \phi_i) + \varepsilon_i$$

Basic mixed-effects model (2)

- Error model: Residual unexplained variability (RUV)
  - ε_i: zero mean random error, N(0, Σ_i)
  - If simple homosedastic model and i.i.d. error
    - var (ε_{ij}) = σ^2 and Σ_i = diag(σ^2)
- Random-effects model
  - Between Subject Variability: BSV
  - $\phi_i = \theta + \eta_i$ or $\phi_i = \theta \exp \eta_i$
  - $\eta_i \sim N(0, \Omega)$
  - for parameter p: $\omega_p^2 = Var(\eta_{ip})$
  - when independent random effects : Ω = diag (ω_p^2)
- Population parameters: Θ (size P)
  - θ (vector of fixed effects)
  - unknowns in Ω (variance of random effects, BSV)
  - unknowns in Σ (variance of residual error, RUV)

Basic Population Design (1)

- N individuals i

- Elementary design ξ_i in individual i
  - number of samples n_i and sampling times: $t_{i1} \ldots t_{in_i}$
  - may differ between individuals
  - may be sparse ($n_i < p$)

- Population design
  - set of elementary designs $\Xi = \{\xi_1, \ldots, \xi_N\}$
  - number of observations $n_{tot} = \Sigma n_i$

Basic Population Design (2)

- If one elementary designs
  - N individuals
  - with same design ξ of n sampling times
  - $n_{tot} = N \times n$

- If Q elementary designs
  - Q groups of N_q individuals
  - Within each group same design ξ_q of n_q sampling times
  - $n_{tot} = \Sigma N_q n_q$

Evaluation of designs by simulation

- Several published studies
  - Hashimoto & Sheiner, *J Pharmacokin Biopharm*, 1991
  - Jonsson, Wade & Karlsson, *J Pharmacokin Biopharm*, 1996 …
- Evaluation of population PK 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

Fisher information matrix (1)

- Information Matrix for population design $\Xi = \{\xi_1, \ldots, \xi_N\}$

$$M F(\Xi, \Theta) = \sum_{i=1}^{N} MF(\xi_i, \Theta)$$

- Information Matrix for elementary design ξ_i

$$MF(\xi_i, \Theta) = E\left\{ \frac{\partial \log l(y; \Theta)}{\partial \Theta} \frac{\partial \log l(y; \Theta)}{\partial \Theta^t} \right\}$$

- Nonlinear structural models
  - no analytical expression for likelihood neither for MF(ξ, Θ)

Fisher information matrix (2)

- Use first order expansion of model f about random effects taken at 0 (FO/ MQL approximation)

  + assumption that variances independent of fixed effects

$$M_F(\xi,\Theta)=\begin{pmatrix} M_F(\xi,\theta) & 0 \\ 0 & M_F(\xi,\Omega,\Sigma) \end{pmatrix}$$

  - analytical expressions for $M_F(\xi,\theta)$ and $M_F(\xi,\Omega,\Sigma)$

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

- Extension to models with: multi-responses, intra-individual variability (several occasions), covariates….

(Retout, Mentré, *J Biopharm Stat*, 2002; Retout, Comets, Samson, Mentré, *Stat Med*, 2007; Bazzoli, Retout, Mentré, *Stat Med*, 2009; Nguyen, Bazzoli, Mentré, *Stat Med,* 2011; Dumont, Chenel, Mentré, *J Biopharm Stat*, 2014)

Population design evaluation/ comparison

- Local planification: parameters and model given
- Population Fisher information matrix

$$M_F(\Xi, \Theta) = \Sigma\, M_F(\xi_i, \Theta)$$

- NB: If same elementary design in all patients
  - $M_F(\Xi, \Theta) = N \times M_F(\xi, \Theta)$ ► SE proportional to $N^{1/2}$
- Design comparison
  - objective: smallest SE = "smallest" M_F^{-1} or "largest" M_F
  - criteria for matrix comparison
    - D-optimality, the most usual one: det (M_F)
  - efficiency criterion = $\det(MF)^{1/P}$
  - Ratio of criteria = gain or loss of efficiency

Example 1: linear mixed effect model

$y_{ij} = \alpha_i + \beta_i d_{ij} + \varepsilon_{ij}$

N = 25 patients

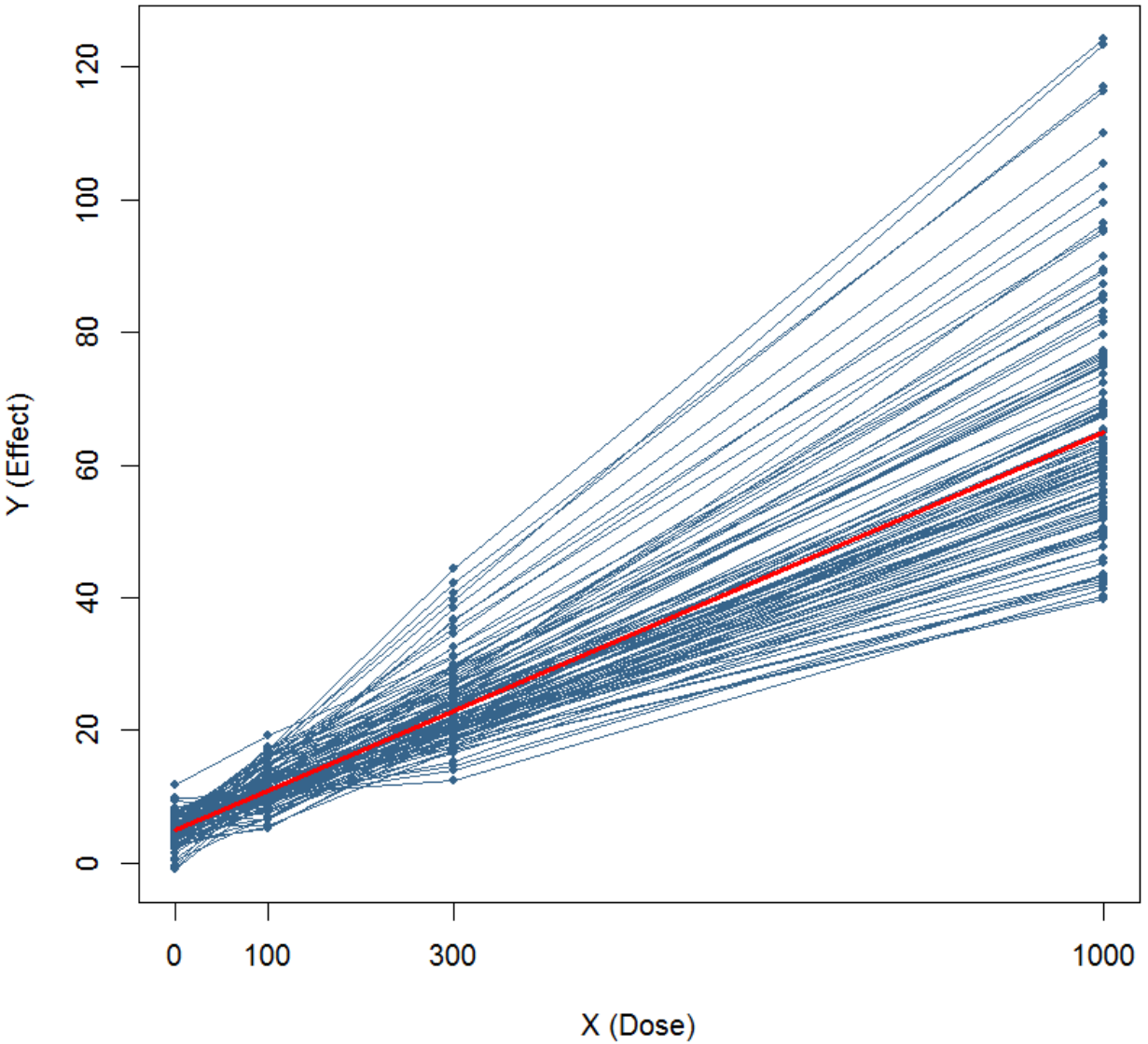
n=4 doses for each patient:
0, 100, 300, 1000

(n_{tot} = 100)

α = 5, β = 0.06

Exponential random effects: CV=30%

ε ~ N (0, 2²)



'Model predicted' curve in red

Comparison of prediction and simulation (1)

	Prediction (PFIM)	Estimation (one data set) (MONOLIX)	Simulation & Estimation (1000 data sets)
α	**5**	5.33	**5.00**
SE (α) / RSE %	**0.20 / 4.0%**	0.18 / 3.4%	**0.24 / 4.8%**
β	**0.06**	0.059	**0.060**
SE (β) / RSE %	**0.0018 / 3.0%**	0.0017 / 2.9%	**0.0018 / 3.0%**
ω_α	**0.3**	0.202	**0.296**
SE (ω_α)/ RSE %	**0.0399 / 13.3%**	0.033 / 16.3 %	**0.0394 / 13.3%**
ω_β	**0.3**	0.285	**0.298**
SE (ω_β)/ RSE %	**0.0216 / 7.2%**	0.021/ 7.4%	**0.0217 / 7.3%**

Very close results between prediction and simulation

Example 2: nonlinear mixed effect model

$y_{ij} = E0_i + Emax_i \times d_{ij} / (ED50_i + d_{ij}) + \varepsilon_{ij}$

N = 25 patients

n=4 doses each patient:
0, 100, 300, 1000

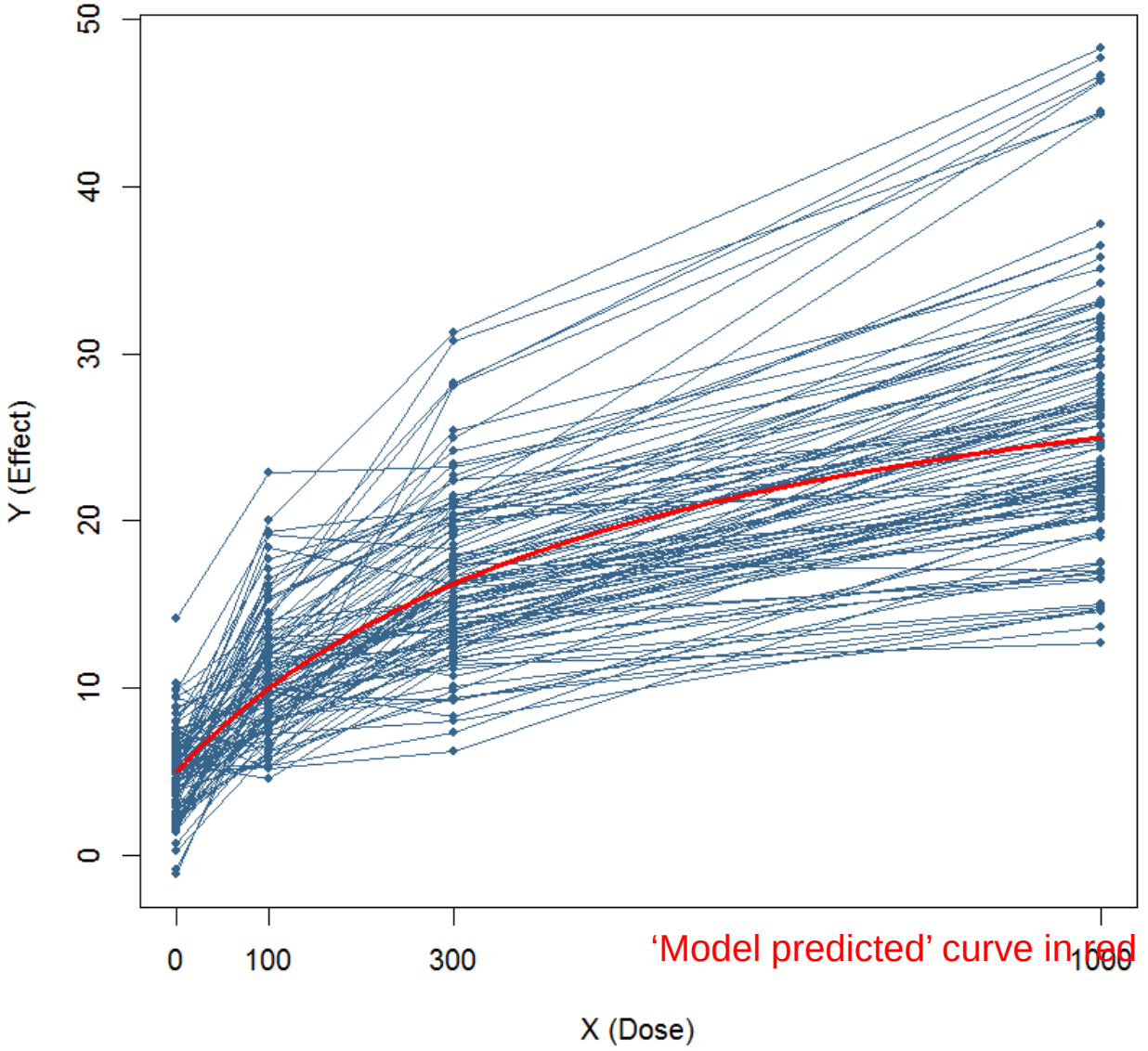
(n_{tot} = 100)

E0 = 5; Emax = 30; ED50=500

Exponential random effects:

CV=30%

$\varepsilon \sim N(0, 2^2)$



Comparison of prediction and simulation (1)

	Prediction (PFIM)	Estimation (one data set) (MONOLIX)	Simulation & Estimation (1000 data sets)
E0	**5**	5.17	**5.06**
SE (E0) / RSE %	**0.24 / 4.8%**	0.25 / 4.8%	**0.28 / 5.5%**
Emax	**30**	31.6	**31.2**
SE (Emax) / RSE%	**1.18 / 3.9%**	1.40 / 4.4%	**1.59 / 5.1%**
ED50	**500**	500	**535.6**
SE (ED50) / RSE%	**37.2/ 7.4%**	45.0 / 9.0%	**55.8 / 10.4 %**

Prediction: lower bounds of simulation results (but close!)

Comparison of prediction and simulation (2)

	Prediction (PFIM)	Estimation (one data set) (MONOLIX)	Simulation & Estimation (1000 data sets)
ω_{E0}	**0.3**	0.20	**0.27**
SE (ω_{E0}) / RSE %	**0.048 / 15.9%**	0.061 / 32.3%	**0.056 / 20.5%**
ω_{Emax}	**0.3**	0.28	**0.30**
SE (ω_{Emax}) / RSE %	**0.028 / 9.2%**	0.028/ 9.9%	**0.034 / 11.3%**
ω_{ED50}	**0.3**	0.33	**0.43**
SE (ω_{ED50}) / RSE %	**0.09 / 28.9%**	0.11 / 33.5%	**0.13 / 28.8%**

Prediction: lower bounds of simulation results (but close!)

4. Population PK example: enoxaparin

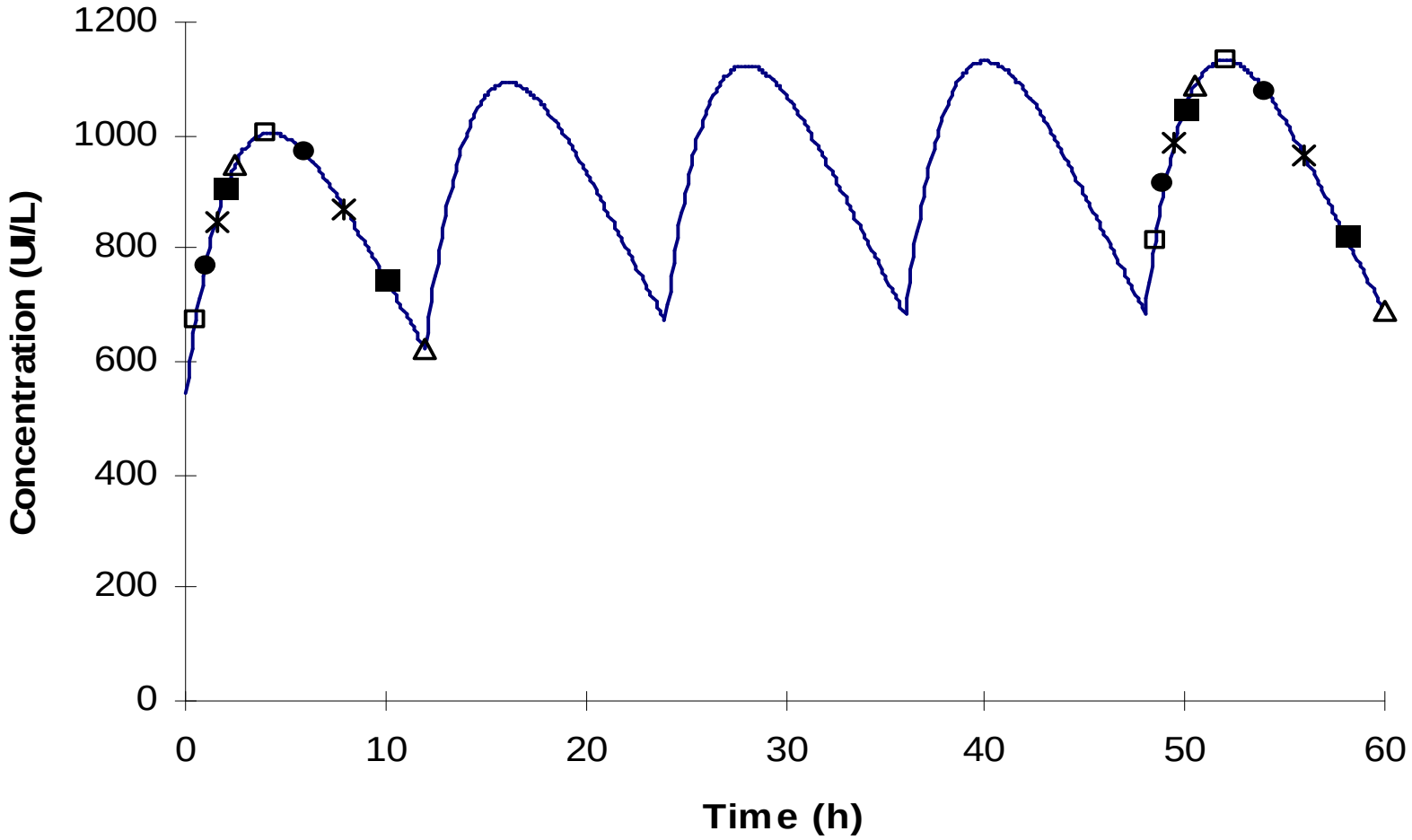
(Retout, Mentré & Bruno, *Stat Med*, 2002;
Retout & Mentré, *J Biopharm Stat*, 2003;
Retout & Mentré, *J Pharmacokin Pharmacodyn*, 2003)

Material

- Enoxaparin administration
  - 30 mg by IV bolus at t = 0
  - 1 mg/kg/12h by subcutaneous injection
- Population model (from prior popPK 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 (fixed effects)
  - ω_{CL}, ω_{V}
  - σ^2

Empirical design

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



Methods

- Constraints for design optimisation
  - 4 samples per patient: 2 at D1 (1^{rst} dose) & 2 at D3 (5th dose)
  - 10 available sampling times:
    {0.5, 1, 1.5, 2, 2.5, 4, 6, 8, 10, 12}

- Simulation (with NONMEM) of 30 sets with
  - empirical design
  - D-optimal design

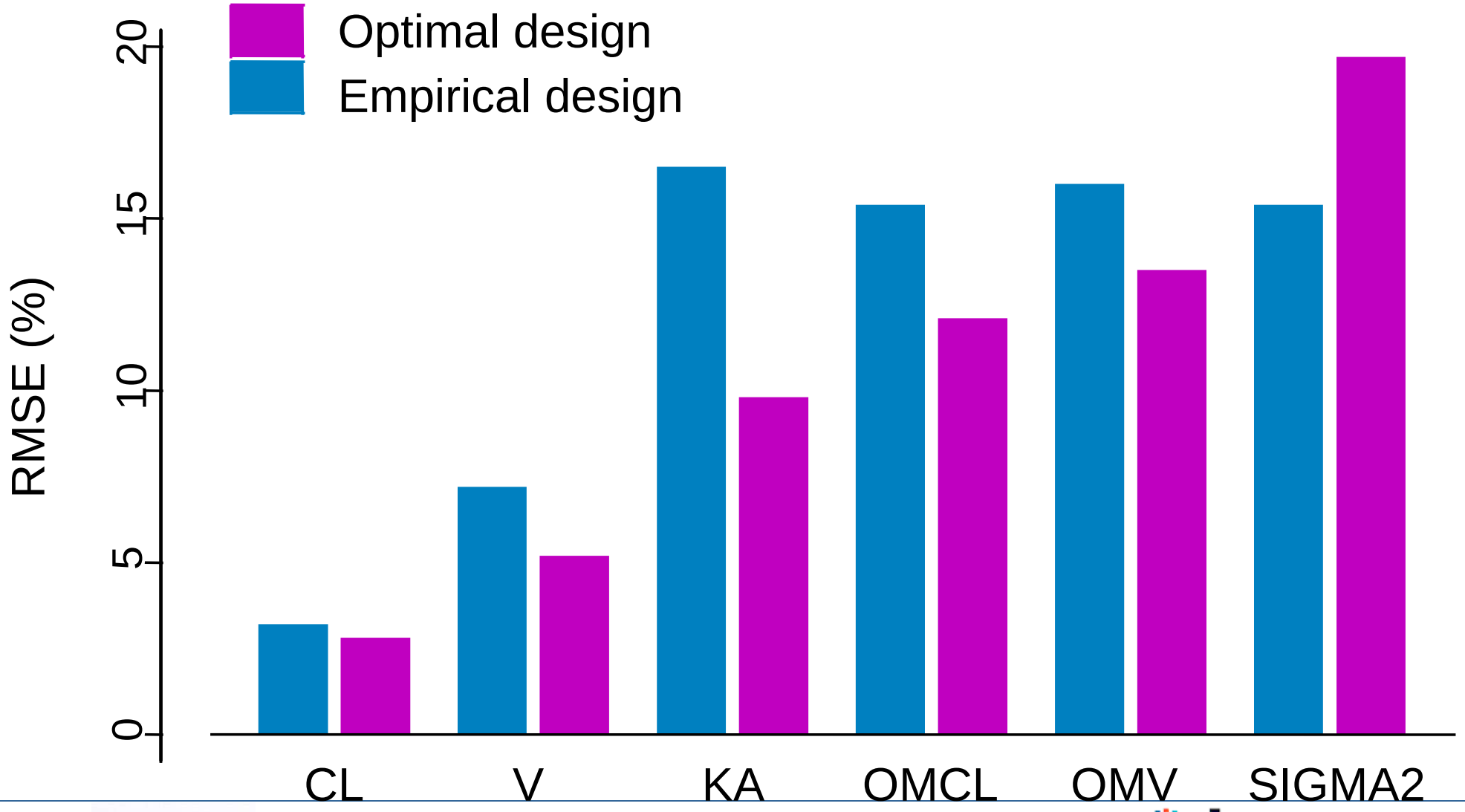
Optimal design for the basic model

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	
Optimal design	1	(0.5, 4)	(2.5, 12)	220	1742.8

Efficiency = 1.35

Optimal design for the basic model

Relative errors from the 30 simulated data sets



Rich population model

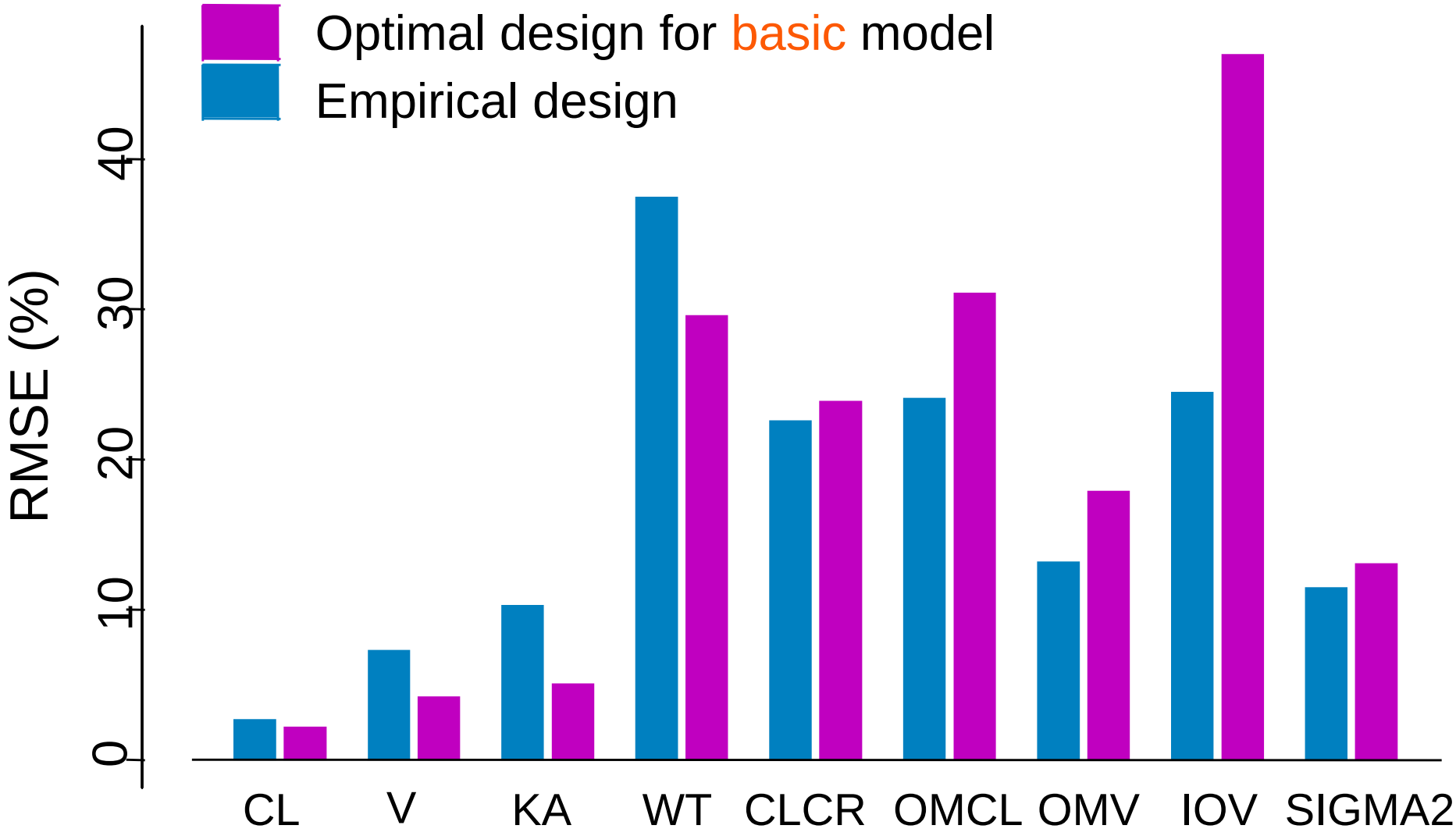
- Rich population PK model
  - two additional fixed effects for covariates
    - β_{CLCR} : creatinine clearance
    - β_{WT} : weight
  - inter-occasion variability on CL

$$Cl_{ik} = (CL + \beta_{WT}(WT_i - 82) + \beta_{CLCR}(CLCR_i - 87.91)) \exp(b_i + \kappa_{ik})$$

1. Simulation of 30 sets with rich model
2. Design optimisation with rich model

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

5. COVARIATE AND POWER

Models with discrete covariates

- Example: binary covariate C_i
  - $C_i = 0$ in reference class, $C_i = 1$ otherwise

- Exponential random effect
  - $\theta_i = \mu \exp(\beta C_i + b_i) = \mu \exp(\beta)^{Ci} \exp(b_i)$
  - $\log(\theta_i) = \log(\mu) + \beta C_i + b_i$
  - $\exp(\beta)$: relative increase (or decrease)

- Additional fixed-effects to be estimated: β

Prediction of power and NSN

- Evaluation of MF from
  - the expected distribution of covariates in the population
  - the effect size β
- For a given design and given values of β
  - SE and RSE for each β of each class of each covariates
  - ➢ Evaluate influence of design on SE (β)
- Power of test
  - Test for H_0: β = 0 (no covariate effect)
  - Wald test: t = | β | / SE (β)
  - Compute power given type I error (e.g. 5%) and β
  - Number of subject needed (NSN)
    - Given power (e.g. 80%), type I error and β

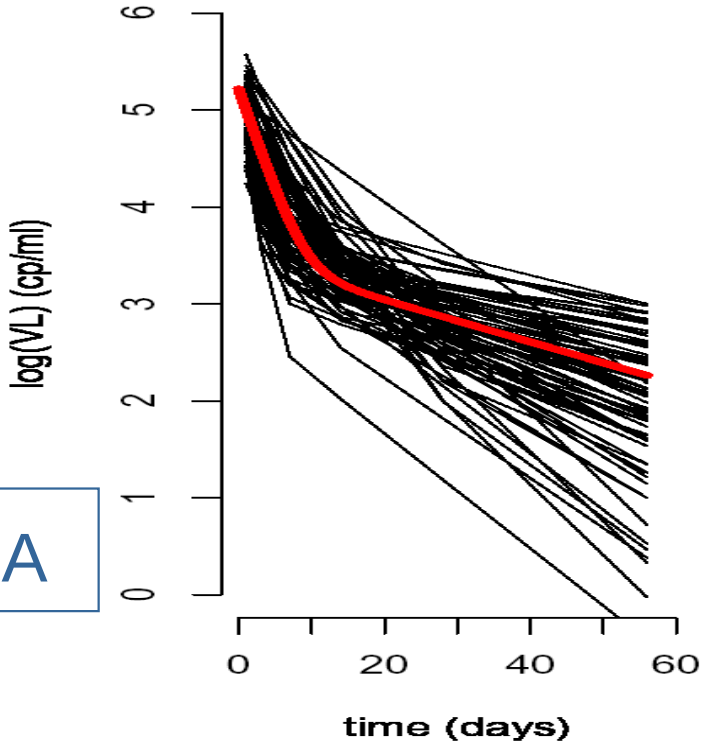
Example:
Prediction of power with application to viral load dynamics

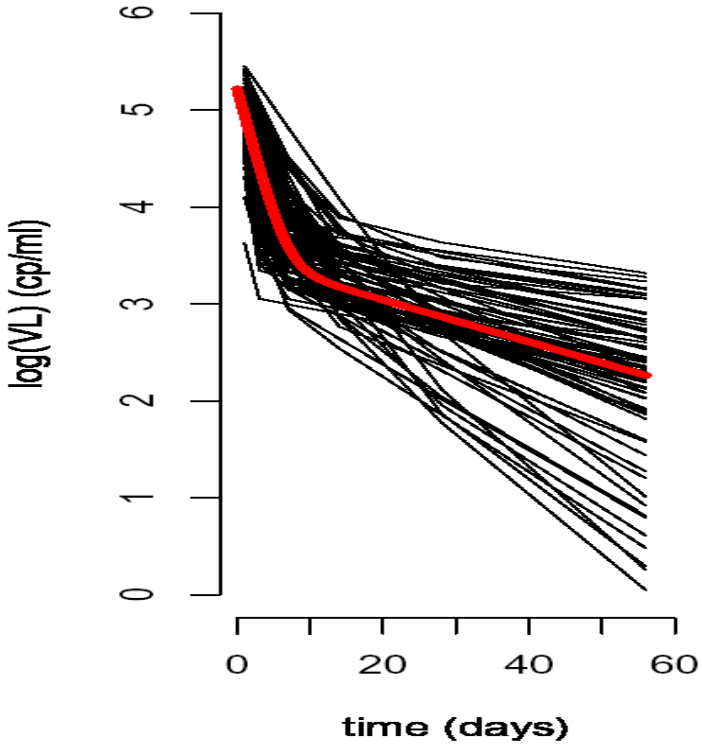
(Retout, Comets, Samson & Mentré, *Stat Med,* 2007*)*

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

(example from Kang, Schwartz &Verotta, *J Pharmacokin Pharmacodyn*, 2005)

- MF to predict SE of β
- Predict power
- Design $\xi = \{1, 3, 7, 14, 28, 56\}$ in all patients

	H_1: $\beta = 0.262$ 30% increase	H_1: $\beta = 0.405$ 50% increase
N = 40 per group	55%	90%
N = 100 per group	92%	99%

➔ number of subjects needed for a given power

NB: if same elementary designs, SE proportional to $N^{1/2}$

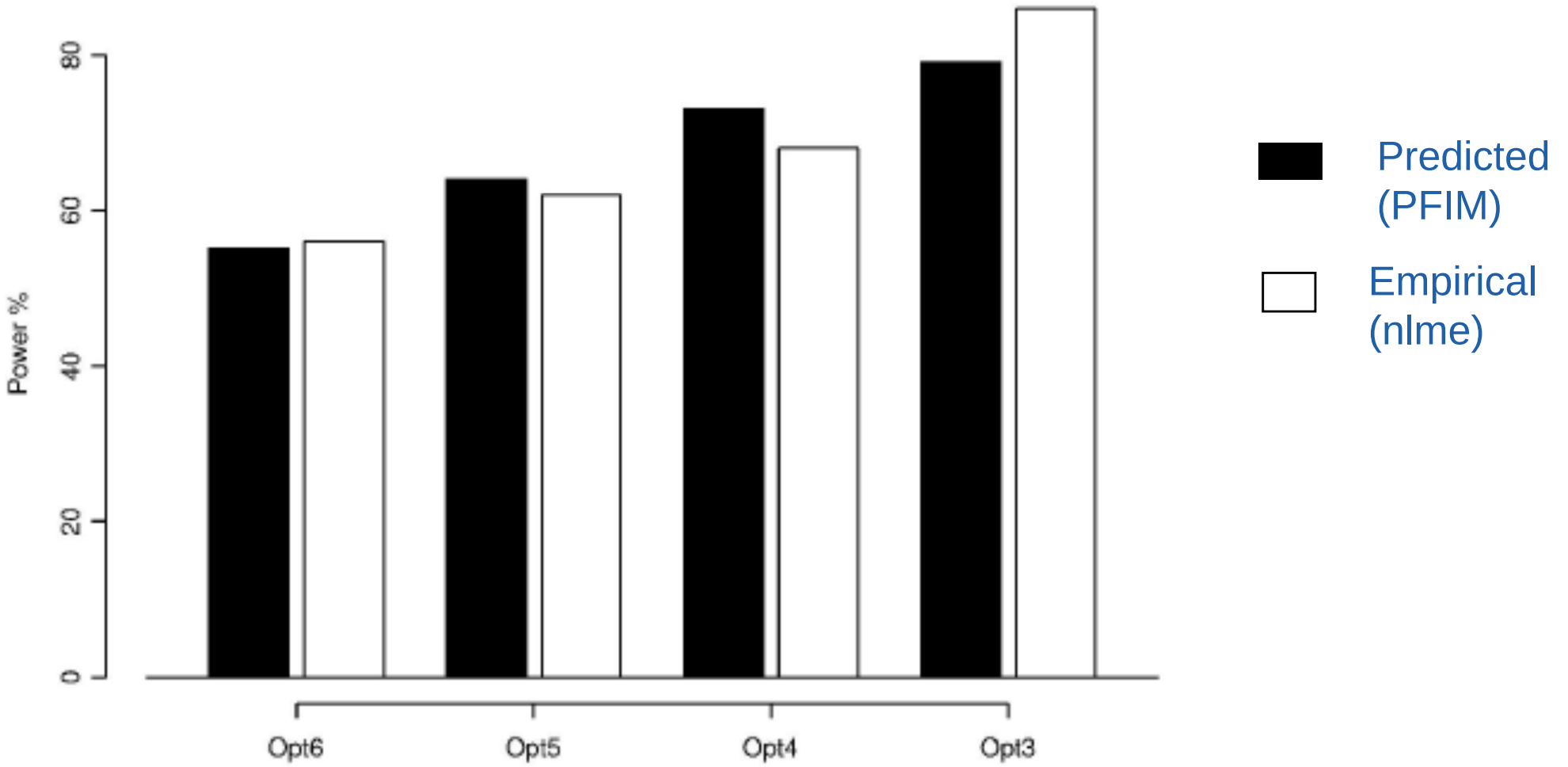
Design optimisation with FW algorithm

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%
Opt_6	40	6	0, 1, 7, 14, 21, 56	471	**0.124**	55%
Opt_5	48	5	0, 7, 14, 21, 56	523	**0.113**	64%
Opt_4[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%
Opt_3[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 design

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



Power for POC using disease progression models

Comparisons of Analysis Methods for Proof-of-Concept Trials

KE Karlsson[1], C Vong[1], M Bergstrand[1], EN Jonsson[1,2] and MO Karlsson[1]

Citation: CPT: Pharmacometrics & Systems Pharmacology (2013) 2, e23; doi:10.1038/psp.2012.24

www.nature.com/psp

Comparison of Model-based analysis to standard t-test on final end points

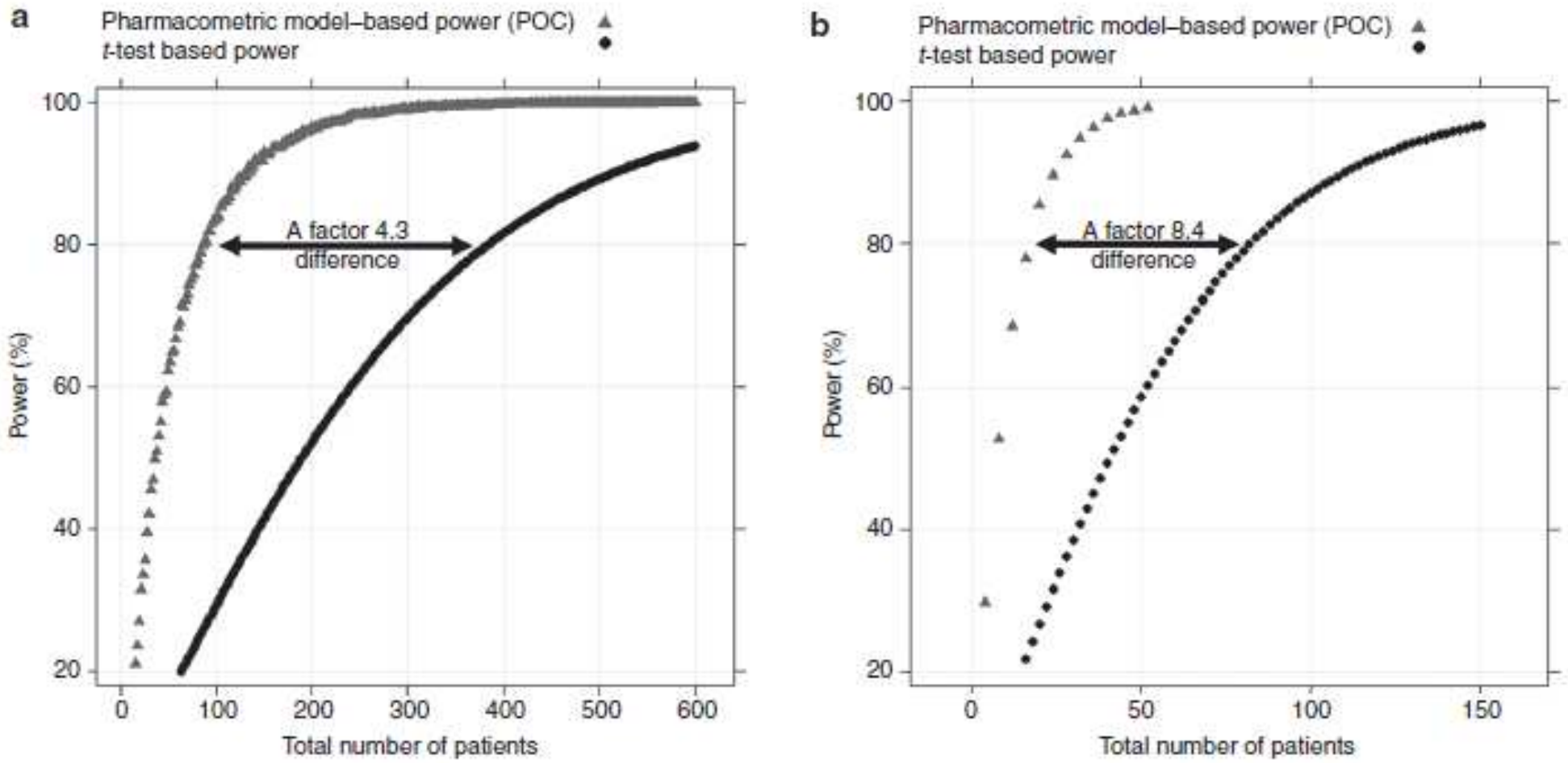


Figure 3 Power curve comparison between the pharmacometric model–based power (gray triangles) and the *t*-test based power (black diamonds), for the proof-of-concept scenario. (**a**) The power curves for the stroke example in which the difference in study size is a factor of 4.3 (90 vs. 388 total number of patients) is displayed. (**b**) In the diabetes example, the difference in study size was 8.4-fold (10 vs. 84 total number of patients) in favor of the pharmacometric approach.

5. DESIGNS FOR BAYESIAN ESTIMATION AND SHRINKAGE PREDICTION

Prediction of SE of Maximum A Posteriori estimates

- n observations in one individual with design ξ
  - Population parameters and model given
  - Bayesian estimation of individual parameters ϕ (EBE)

➢ Bayesian information matrix M_{BF}

- Computed using FO

- For exponential random effect

$$M_{BF}(\xi,\phi) = \Phi^t J(\xi,\phi)^t \Sigma^{-1} J(\xi,\phi)\Phi + \Omega^{-1}$$

with Φ = diag (ϕ)

Merlé, Mentré. *J Pharmacokin Biopharm*, 2005

Prediction of shrinkage of EBE

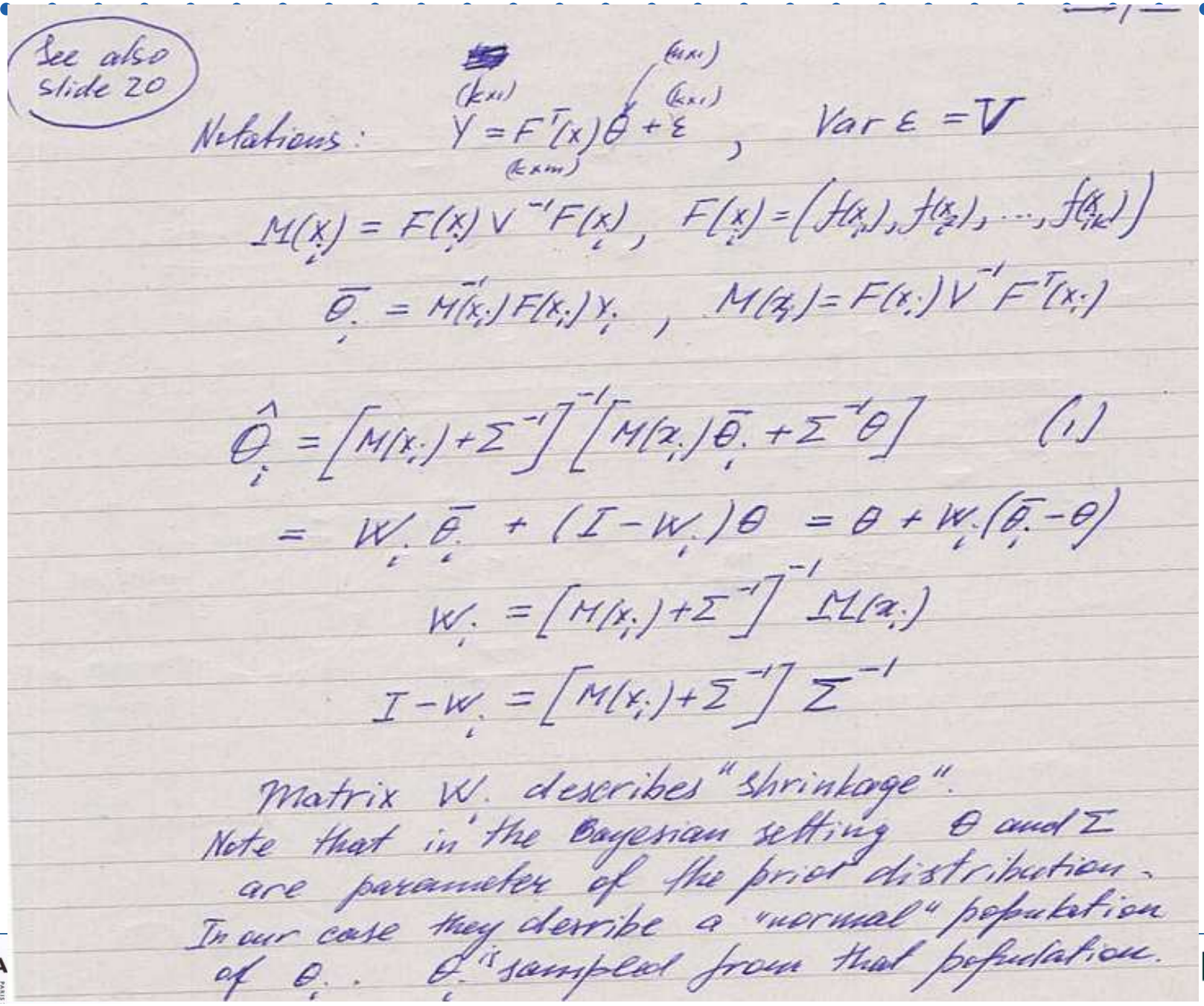
- Shrinkage computed as ratio of variances
- Using formula for linear mixed effect models

➢ Shrinkage ‘matrix’

$$I - W(\xi) = M_{BF}(\xi, \phi)^{-1}\Omega^{-1}$$

Diagonal elements: predicted shrinkage for each parameter

« Notes for France » (V. Fedorov, 2011)



See also slide 20

Notations: $Y = F^T(x)\theta + \varepsilon$, $Var\,\varepsilon = V$

($k \times 1$), ($m \times 1$), ($k \times 1$), ($k \times m$)

$M(x_i) = F(x_i) V^{-1} F(x_i)$, $F(x_i) = (f(x_{i1}), f(x_{i2}), \dots, f(x_{ik}))$

$\bar{\theta}_i = M^{-1}(x_i) F(x_i) Y_i$, $M(x_i) = F(x_i) V^{-1} F^T(x_i)$

$$\hat{\theta}_i = [M(x_i) + \Sigma^{-1}]^{-1} [M(x_i)\bar{\theta}_i + \Sigma^{-1}\theta] \qquad (1)$$

$$= W_i \bar{\theta}_i + (I - W_i)\theta = \theta + W_i(\bar{\theta}_i - \theta)$$

$$W_i = [M(x_i) + \Sigma^{-1}]^{-1} M(x_i)$$

$$I - W_i = [M(x_i) + \Sigma^{-1}]^{-1} \Sigma^{-1}$$

Matrix W_i describes "shrinkage".
Note that in the Bayesian setting θ and Σ are parameter of the prior distribution. In our case they describe a "normal" population of θ_i. θ_i is sampled from that population.

Pharm Res (2013) 30:2355–2367
DOI 10.1007/s11095-013-1079-3

RESEARCH PAPER

Prediction of Shrinkage of Individual Parameters Using the Bayesian Information Matrix in Non-Linear Mixed Effect Models with Evaluation in Pharmacokinetics

François Pierre Combes • Sylvie Retout • Nicolas Frey • France Mentré

Citation: CPT Pharmacometrics Syst. Pharmacol. (2014) 3, e109; doi:10.1038/psp.2014.5

www.nature.com/psp

ORIGINAL ARTICLE

Powers of the Likelihood Ratio Test and the Correlation Test Using Empirical Bayes Estimates for Various Shrinkages in Population Pharmacokinetics

FP Combes[1,2,3,4], S Retout[3,4], N Frey[4] and F Mentré[1,2]

Comparison of observed and predicted shrinkage

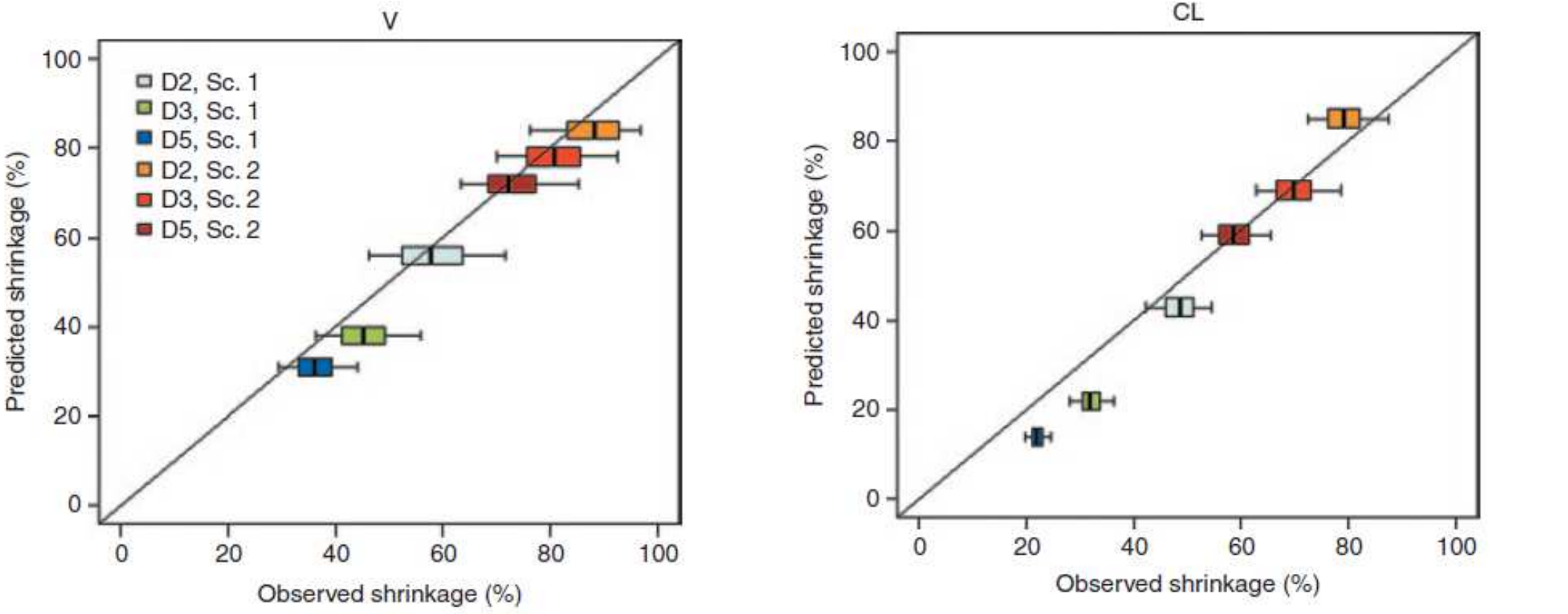
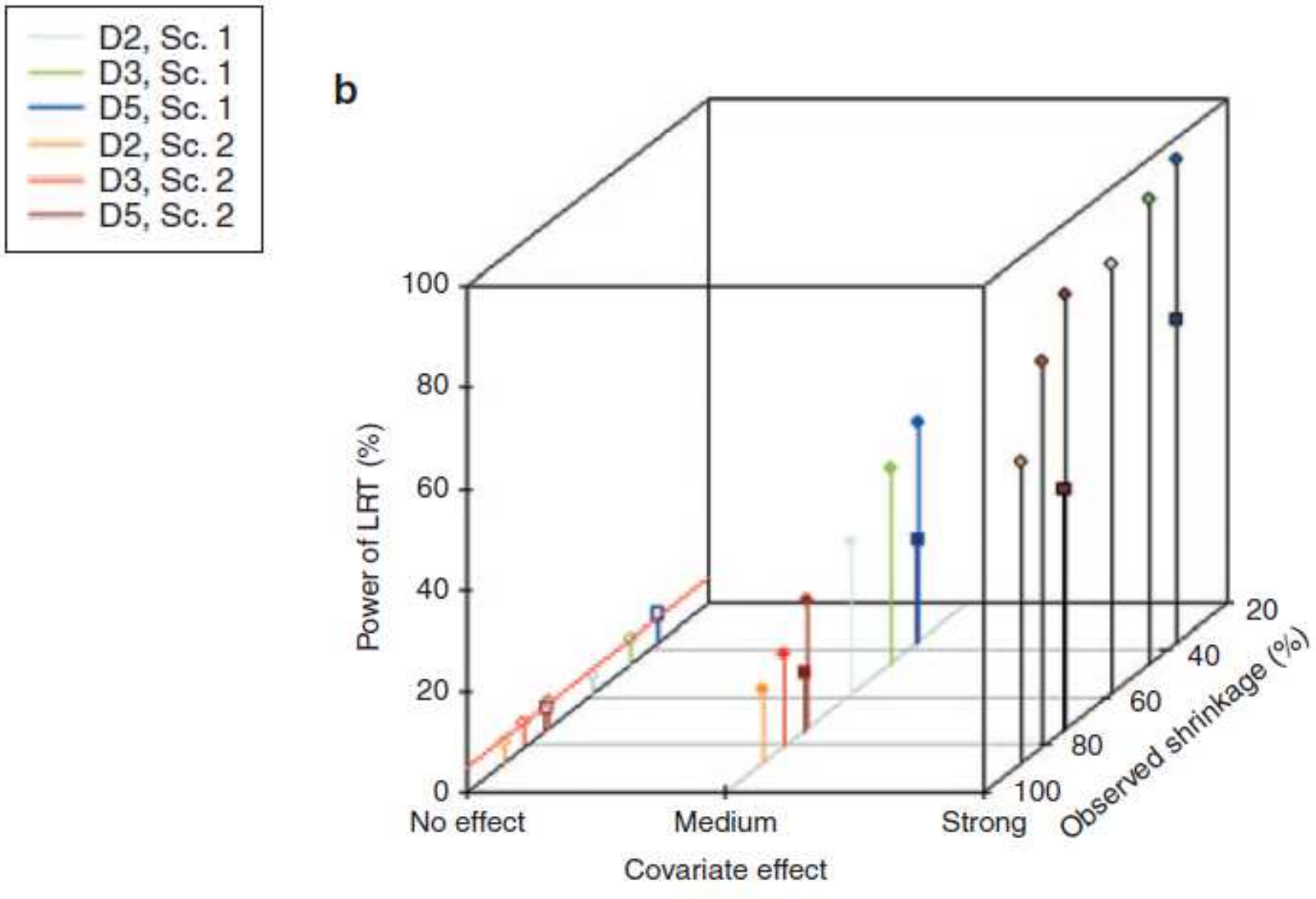
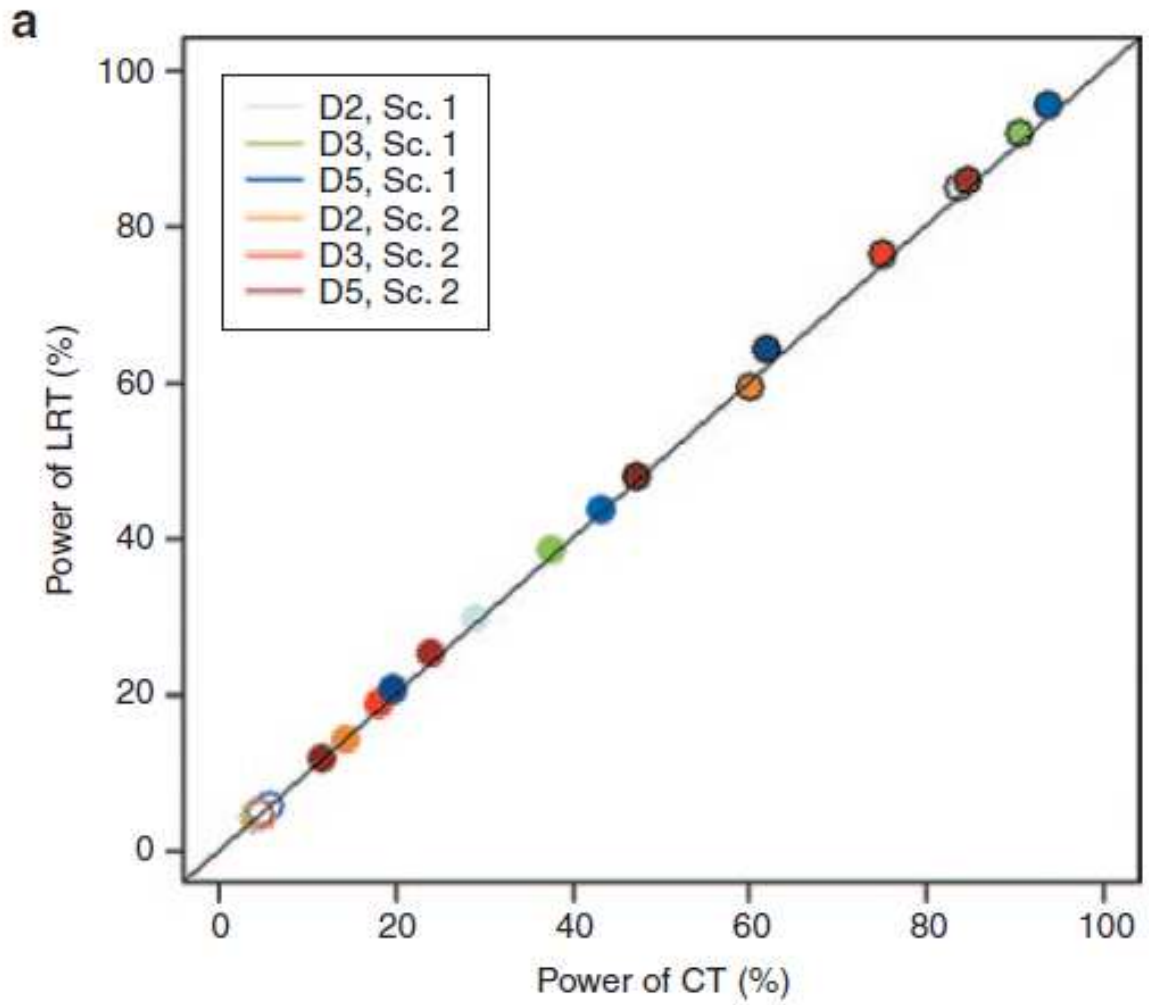


Figure 3 Predicted shrinkage (%) value vs. boxplot of observed shrinkage (%) with the stochastic approximation expectation maximization algorithm for the 1,000 replicates without covariate effect, for parameters volume (*V*) and clearance (CL), each design, and scenarios 1 or 2. Colors stand for the design and the scenario. Sc., scenario.

Power of LRT for various effect of covariate



Power of LRT vs corelation test on EBE



Conclusion on design for EBE

- As expected: shrinkage influenced by number of samples and variabilities
- Prediction of M_{BF} by FO adequate, further studies needed when more variability
- New formula to predict shrinkage from M_{BF} (lower bound)
- Shrinkage ‘per se’ do not lead to loss of power of the correlation test vs LRT

7. Software tools in population design

PFIM and PFIM interface

- R package for design evaluation and optimisation for NLMEM
- Developed initially by Sylvie Retout & France Mentré
  - INSERM & University Paris Diderot
  - PFIM group (pfim@inserm.fr): Caroline Bazzoli, Emmanuelle Comets, Cyrielle Dumont, Anne Dubois, Hervé Le Nagard, Giulia Lestini, France Mentré, Thu-Thuy Nguyen
- Use R (free): www.pfim.biostat.fr
- Releases of PFIM
  - 2001: First release of PFIM 1.1
  - January 2010: PFIM 3.2
  - February 2011: PFIM interface 3.1
  - April 2014: PFIM 4.0

Software in population design

	PFIM	PFIM Int.	PkStaMP	PopDes	PopED	POPT
Authors	**Mentré** et al (Paris)	**Mentré** et al (Paris)	**Leonov** (US)	**Ogungbenro** (Manchester)	**Hooker** /Nyberg/Ueckert (Uppsala)	**Duffull** (Otago, NZ)
Language	**R**	**R**	**Matlab CR**	**Matlab**	**Matlab and R**	**Matlab**
Available on website	**Yes**	**Yes**	**No**	**Yes**	**Yes**	**Yes**
GUI	**No**	**Yes**	**Yes**	**Yes**	**Yes**	**No**
Library of models	**Yes**	**Yes**	**Yes**	**Yes**	**Yes**	**Yes**
User defined models	**Yes**	**Yes**	**Yes**	**Yes**	**Yes**	**Yes**

Population Optimum Design of Experiments (PODE)

- Creation of a multidisciplinary group: PODE
  - initiated by Barbara Bogacka & France Mentré
  - discuss theory of optimum experimental design in NLMEM and their application in drug development

  www.maths.qmul.ac.uk/~bb/PODE/PODE2014.html
- One day workshop
  - May 2006: London, University of London (B. Bogacka)
  - May 2007: Sandwich, Pfizer (P. Johnson)
  - June 2008: Paris, University Paris Diderot (F. Mentré)
  - June 2009: St Petersburg, GSK (S. Leonov)
  - June 2010: Berlin, Bayer (T. Schmelter & R. Schwabe)
  - August 2011: Cambridge, IN Institute (B. Bogacka, S. Leonov)
  - March 2012: Paris, University Paris Diderot (F. Mentré)
  - June 2013: London, Eli Lilly (B. Bogacka & I. Gueorguieva)
  - ➢ Sept 11, 2014: Basel, Roche (S. Retout)

Following PODE07 Meeting (1)

- Distribution list: PopDesign organised by S. Duffull
  - to register: http://lists.otago.ac.nz/listinfo/popdesign
  - to send an email: popdesign@lists.otago.ac.nz
  - any questions/comments on design in NLMEM and software
  - answers by all members of PoDe

Following PODE07 Meeting (2)

- Comparison of software

  - Overall summary of software at PODE 07, PAGE 2007
    - updated at PODE 11

  - Comparison of approximations
    - discussed at PODE 09 & 10
    - presented at PAGE 2011 and PODE12 for a complex PKPD HCV model

    ➢ Nyberg, Bazzoli, **Ogungbenro**, Aliev, **Leonov**, **Duffull**, **Hooker, Mentré**, *Br J Clin Pharmacol*, 2014 Feb 18. doi: 10.1111/bcp.12352.

survey on use of design software tools

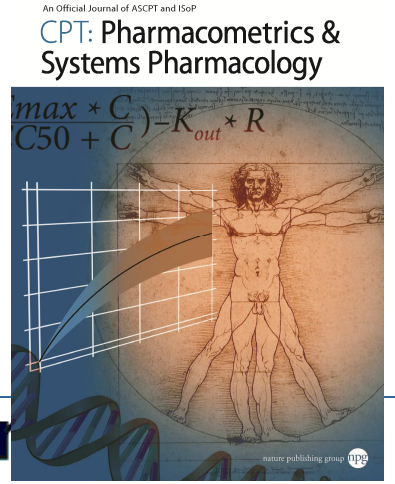
Citation: CPT: Pharmacometrics & Systems Pharmacology (2013) 2, e46; doi:10.1038/psp.2013.19

www.nature.com/psp

PERSPECTIVE

Current Use and Developments Needed for Optimal Design in Pharmacometrics: A Study Performed Among DDMoRe's European Federation of Pharmaceutical Industries and Associations Members

F Mentré[1], M Chenel[2], E Comets[1], J Grevel[3], A Hooker[4], MO Karlsson[4], M Lavielle[5] and I Gueorguieva[6]



8. CONCLUSION

Conclusion (1)

- Results of population PK/PD analyses increasingly used
  - in preclinical and clinical pharmacology
  - 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

COMPLEX MODELS = DIFFICULT TO 'GUESS' GOOD DESIGNS

Conclusion (2)

- Several recent statistical extensions for population design
  - complex multi-responses models (with ODE)
    - different optimal sampling times across responses
  - expected power of Wald test and number of subjects needed
  - within subject variability, cross-over trials…
- Several software tools available: no excuses!
  - define good population designs (ethical/financial reasons)
  - anticipate ‘fatal’ population designs
  - Careful: lower bound (nonlinearity, small sample size)
    - Clinical trial simulation for important designs
- Local planification: relies on a priori information
  - perform sensitivity analysis of parameters and models
    - optimal designs depend on statistical assumptions!
  - define compromise design, sampling windows…
  - use robust approach, adaptive design….

Limitations / Ongoing work

- Better Approximation of the FIM
- FIM for Discrete models
- Prediction of power: Wald vs LRT
- Model averaging in design
- Model based Adaptive designs
- …

➢ NEXT PODE

during workshop: "Design and analysis of experiments in healthcare"

Barbara Bogacka, Holger Dette, Ralf-Dieter Hilgers, Rosemary Bailey

Cambridge, 6-10 July 2015

Remember some simple maths…

- If ‘very rich’ design:
  - Estimation of population parameters can be seen as estimation of mean and variances of individual parameters
  - Standard errors of mean and variance of normal distribution can be seen as lower bound to population SE with sparser design
- For additive random effects

$$SE(\theta_k) = \frac{\omega_k}{\sqrt{N}} \qquad SE(\omega_k^2) = \frac{\sqrt{2}}{\sqrt{N}}\omega_k^2$$

- For exponential random effects

$$SE(\theta_k) = \frac{\omega_k}{\sqrt{N}}\theta_k \qquad \boxed{RSE(\theta_k) = \frac{\omega_k}{\sqrt{N}}} \qquad SE(\omega_k^2) = \frac{\sqrt{2}}{\sqrt{N}}\omega_k^2 \qquad \boxed{RSE(\omega_k^2) = \frac{\sqrt{2}}{\sqrt{N}}}$$

e.g.: ω = 60% and N = 36, RSE(θ) = 10 % , RSE(ω) = 24%

(from Dumont et al., *J Biopharm Stat*, 2014)