

INFLUENCE OF STUDY DESIGN AND ASSOCIATED SHRINKAGE ON POWER OF THE TESTS USED FOR COVARIATE DETECTION IN POPULATION PHARMACOKINETICS

François Combes^{1,2,3}, Sylvie Retout^{2,3}, Nicolas Frey³ and France Mentré¹

1. Univ Paris Diderot, Sorbonne Paris Cité, UMR 738, F-75018 Paris, France; INSERM, UMR 738, F-75018 Paris, France
2. Institut Roche de Recherche et Médecine Translationnelle, Boulogne-Billancourt, France
3. Pharma Research and Early Development, Clinical Pharmacology, F. Hoffmann-La Roche Ltd, Basel, Switzerland

CONTEXT

- Individual parameters are usually estimated in population analysis through a Bayesian methodology as Maximum *a Posteriori*. These parameters are then used to predict individual response, to select covariates and to draw diagnostic plots
- Shrinkage occurs when few information is available for an individual (sparse design), and is characterized by a shrunk *a posteriori* distribution of estimated η towards the population mean. In a previous article [1], the authors extended from linear mixed effect methodology [2] a formula to predict shrinkage of individual parameters estimation. Through an extensive simulation study, this article showed a good prediction of observed shrinkage using the Bayesian information matrix (M_{BF}), avoiding extensive clinical trial simulation
- Savic *et al* [3] explored the influence of sparse design on random effects (η) distribution. The authors also studied the influence of shrinkage on the relationship between individual parameters and covariates. An interesting finding was that individual parameters may, in the presence of high shrinkage, indicate false relationships or hide true relationships when used for covariate screening
- To the authors' knowledge, no exploration has been performed regarding the impact of shrinkage on the power of tests used for covariate detection in population analysis, such as the Pearson Correlation Test (CT) or the Likelihood Ratio Test (LRT)

OBJECTIVE

Investigate the impact of various designs, with various levels of associated shrinkage, on the power to detect the effect of a continuous covariate of:

- The correlation test based on individual parameters
- The likelihood ratio test

MATERIALS AND METHODS

Notations

- Individual statistical model: $y = f(\theta, \xi) + \epsilon$ with $\xi = \{t_1, \dots, t_n\}$ and $f(\theta, \xi)$ describing the PK model
 - $\theta = \mu e^\eta$: individual parameters
 - Fixed effects $\mu = (\mu_1, \dots, \mu_p)$
 - $\eta \sim N(0, \Omega)$; $\Omega = \text{diag}(\omega_1^2, \dots, \omega_p^2)$
 - $\epsilon \sim N(0, \Sigma(\theta, \xi))$: residual error
 - $\Sigma(\theta, \xi) = \text{diag}((\sigma_{inter} + \sigma_{slope} f(\theta, \xi))^2)$

Prediction of shrinkage

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

- M_{BF} is approximated by First-Order linearization [5]

$$M_{BF}(\xi) = M^T F(\mu, \xi)^T \Sigma(\mu, \xi) F(\mu, \xi) M + \Omega^{-1}$$

where $M = \text{diag}(\mu_1, \dots, \mu_p)$ for exponential random effects [4] and $F(\theta, \xi) = \frac{\partial f(\theta, \xi)}{\partial \theta^T}$

Pharmacokinetic example

- From Mentré *et al* [5], a simple PK model with one compartment, oral absorption and a linear elimination was simulated. Two scenarios were considered (*cf* Table 1)

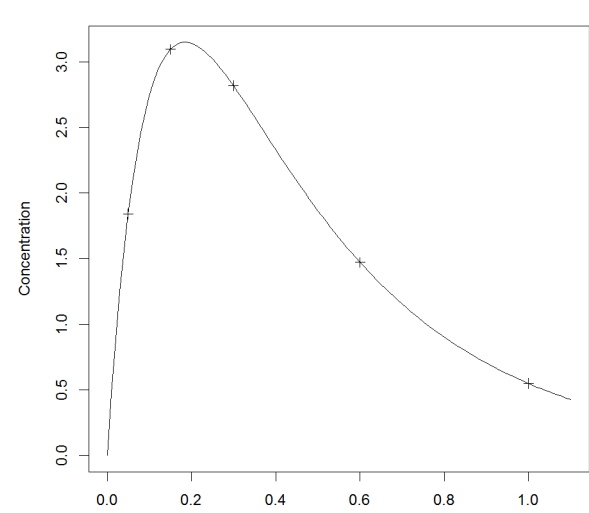


FIGURE 1: PK profile of simulated example

Covariate model

- Weight (WT) following a log-normal law with median = 70 kg and 10% CV
- Covariate effect modeled as a power function: $\theta_i = \mu \left(\frac{WT_i}{\text{med}(WT)} \right)^\beta e^{\eta_i}$

Detection of covariate effect

- CT: Test of correlation between η and a continuous covariate using a Pearson test
- LRT: Test of log-likelihood difference between two nested models (with or without covariate effect), using a χ^2 distribution with 1 degree of freedom

Simulation

- Simulation of 1000 datasets of 500 subjects for each design, scenario with a WT effect on V with three levels of covariate effect:
 - No effect with $\beta = 0$
 - Middle ($\beta = 0.2, 0.5$) or strong ($\beta = 0.5, 1$) effect

Evaluation of algorithm performance

- Simulations for $\beta = 0$ without any covariate
- Estimation by NONMEM 7.2 with FOCEI or SAEM (SAEM with IMP for likelihood computation following the "expert" options in [6]) with β fixed to 0
- Computation of the relative error ($RE\%$) for each population parameter estimates

Evaluation of test of covariate effect

- CT: From estimation of the model without covariate effect followed by estimation of individual parameter, CT between η_V and WT
- LRT: From estimations of the model with and without covariate effect, LRT on the difference in log-likelihood
- For both tests, computation of the percentage of significant tests

RESULTS

Algorithm performance

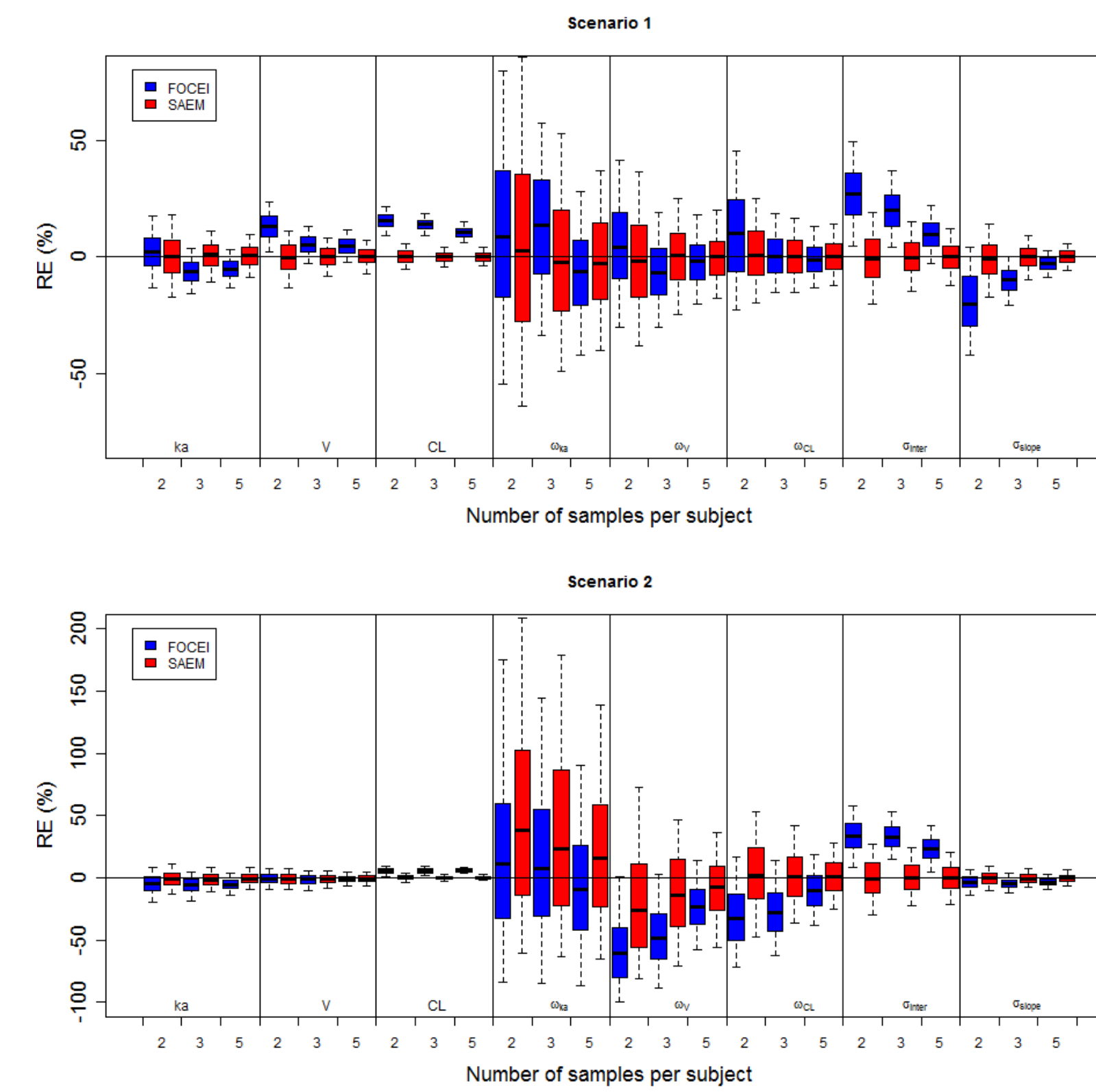


FIGURE 2: Relative error of estimation for $\beta = 0$

Influence of design on test of covariates

Table 2: Predicted shrinkage values (%)
(* : mean value on the 3 design)

	Scenario 1		Scenario 2	
Parameter	V	CL	V	CL
D2*	56	43	84	85
D3	38	22	78	69
D5	31	14	72	59

Table 3: Type one error and power of test (%) (SAEM)

Design	Test	Scenario 1			Scenario 2		
β		0	0.5	1	0	0.2	0.5
D2	LRT	3.8	29.7	84.8	4.2	14.3	59.4
	CT	3.9	29.1	84.3	4.0	14.4	60.5
D3	LRT	4.6	38.3	91.6	4.6	18.6	76.2
	CT	4.3	37.9	91.6	4.9	18.3	76.0
D5	LRT	4.8	43.5	95.4	5.0	25.0	85.7
	CT	4.7	43.6	94.9	5.0	24.2	85.8

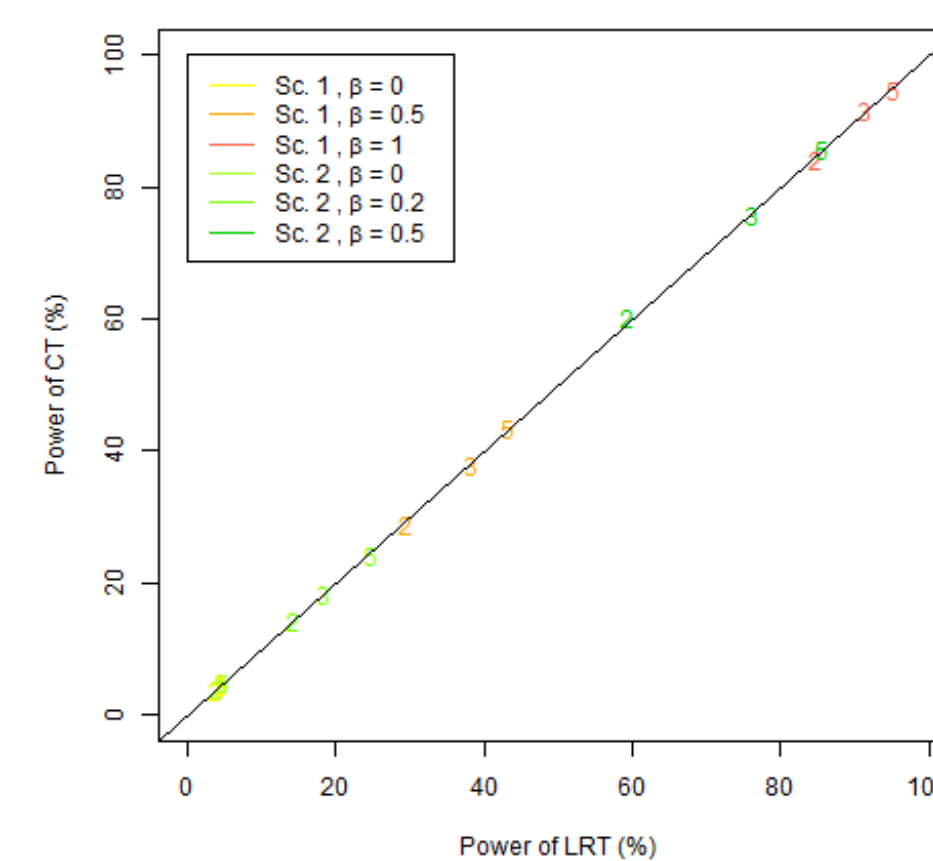


FIGURE 3: Power LRT *vs* CT for all scenarios and designs (SAEM)

Predicted shrinkage

- Scenarios 1 and 2 allow to simulate a wide range of predicted shrinkage.

Type one error

- Type one error values close to 5 %

Power

- As expected, power directly linked with the level of covariate effect
- For a given β power decrease with the informativeness of the design

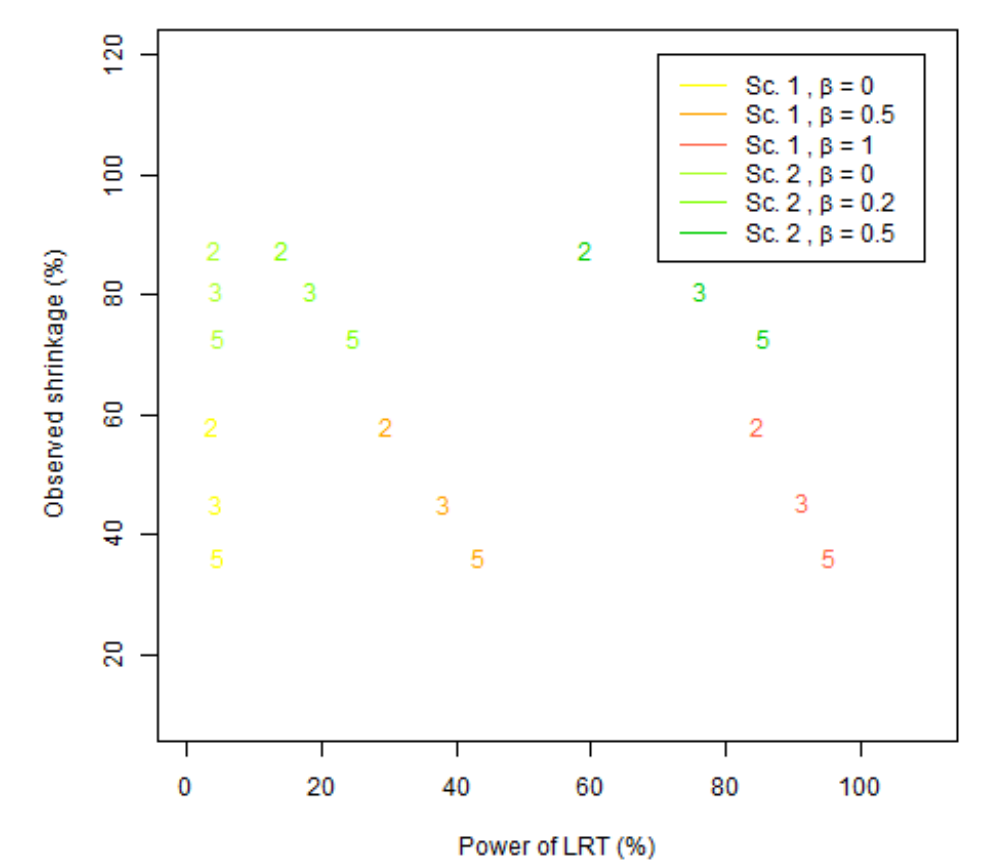


FIGURE 4: Power LRT *vs* observed shrinkage for all scenarios and designs (SAEM)

Fig. 3 & 4: Number stands for the design and color for the covariate influence level

LRT vs CT and LRT vs observed shrinkage

- As already noticed, influence of design, and therefore of shrinkage, on power of test is moderate compared to the influence of effect size
- Whatever the design and the extend of the covariate influence, same power and type one error between LRT and CT
- LRT needs twice as much (H_0 and H_1) simulations - estimations processes than CT

DISCUSSION

- The work presented here shows the importance of an accurate selection of NONMEM 7.2 algorithm and options, FOCEI being less accurate and less precise than SAEM, even for rich designs
- This study also shows on a simple PK example the moderate influence of design (number of samples) and its associated shrinkage on the power of tests to detect covariate effect. However, we showed the great influence the level of covariate effect (β) has on power
- LRT test did not shows higher power than a simple correlation test for individual estimates. Performing CT to detect covariate effect should be privileged as this test is less time and resource-consuming
- Nevertheless, this results should be confirmed in more challenging conditions, with fewer number of subjects or using a more complex pharmacokinetic model (*eg*: Target mediated drug disposition model [7])
- Finally, influence of design on covariate selection by CT or LRT between several covariate effect should be explored

¹ Combes, Retout, Frey, Mentré. *Pharm. Res.* (Epub. 2013).

² Fedorov. Presented at Design and analysis of experiments (2011).

³ Savic, Karlsson. *The AAPS. J.* (2009).

⁴ Combes, Retout, Frey, Mentré. Presented at PAGE meeting (2012).

⁵ Mentré, Burtin, Merlé, van Bree, Mallet, Steimer. *Drug Info. J.* (1995).

⁶ Gibianski, Gibianski, Bauer. *J. Pharmacokinet. Pharmacodyn.* (2012).

⁷ Frey, Grange, Woodworth. *J. Clin. Pharmacol.* (2010).