Model-based tests to detect gene effect in pharmacokinetic studies

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Pharmacogenetics

- Study of the interindividual variability in genes coding for drug transporters, drug metabolising enzymes and drug targets in relation to the drug pharmacokinetics (PK) and pharmacodymanics [1]
  - warfarine /CYP2C9 and VKORC1 [2]
  - irinotecan / UGT1A1 [3]
- Single Nucleotide Polymorphims (SNP)
  - biallelic: 1 major allele (C) and 1 minor allele (T)
  - 3 possible genotypes: common homozygote (CC), heterozygote (CT) and rare homozygote (TT)
  - Hardy-Weinberg proportions → unbalanced distribution
    - extreme for low minor allele frequency
  - variation in allelic frequencies between demes

[1] EMEA. ICH topic E15 (2008)
[2] Kim MJ et al. J Clin Pharmacol (2007)
[3] Kim TW et al. Ther Drug Monit (2007)

Pharmacogenetic data analysis

- Mainly non-compartmental approach
  - one-way analysis of variance (ANOVA) on the individual parameters of interest[4] (AUC, C_{max},...)
- More recently nonlinear mixed effect models (NLMEM)
  - screening stage
    - ANOVA on the empirical bayes estimates (EBE)
  - model building
    - likelihood ratio test (LRT)[5]
    - alternative: Wald test on the gene effect coefficients[6]

[4] Van Schaik R et al. Clin Pharmacol Ther (2009)
[5] Arab-Alameddine M et al. Clin Pharmacol Ther (2009)
[6] Yamasaki Y et al. Clin Pharmacol Ther (2008)

Objectives

- To evaluate by simulation the three model-based tests to detect a gene effect on one PK parameter
  - with different estimation algorithms
- To investigate the impact of the design on the performances of these tests
- To study the influence of CYP2D6 polymorphisms on PK of a drug under development (drug X) and its active metabolite with the appropriate test

Model and tests

- Model
  - for a gene effect on parameter θ_p of subject i

$$log(\theta_{p,i}) = log(\mu_p) + \beta_{G_i} + \eta_{p,i}$$

$$\beta_{G_i} = \begin{cases} 0 & \text{if } G_i = CC \\ \beta_1 & \text{if } G_i = CT \\ \beta_2 & \text{if } G_i = TT \end{cases}$$

$$M_{base} : \{\beta_1 = \beta_2 = 0\}$$
$$M_{full} : \{\beta_1 \neq \beta_2 \neq 0\}$$

- Tests
  - ANOVA $\sim F^2_{N-3}$
  - Wald test

$$W = \begin{pmatrix} \beta_1 \\ \beta_2 \end{pmatrix}^T V^{-1} \begin{pmatrix} \beta_1 \\ \beta_2 \end{pmatrix} \sim \chi^2_2$$

V : block for β_1 and β_2 of the estimation variance matrix

  - LRT

$$Q = -2 \times (L_{base} - L_{full}) \sim \chi^2_2$$

L_{base} and L_{full} the loglikelihoods of M_{base} and M_{full}

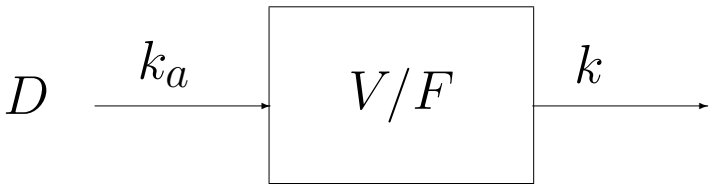
Simulation setting

- Based on the COPHAR2-ANRS 111 trial[7]
  - Objective: to assess the benefit of early therapeutic drug-monitoring
  - HIV-1 positive patients naïve of treatment by protease inhibitors
- PK substudy on indinavir two weeks after treatment onset
  - N=40 patients
  - N=4 samples at 1, 3, 6 et 12h following administration
- Indinavir substrate of P-glycoprotein (P-gP)
  - exon 26 (3534C>T) and 21 (2677G>T) of ABCB1 gene
    - exon 26: 24% CC, 48% CT, 28% TT
    - exon 21: 29% GG, 44% GT, 27% TT

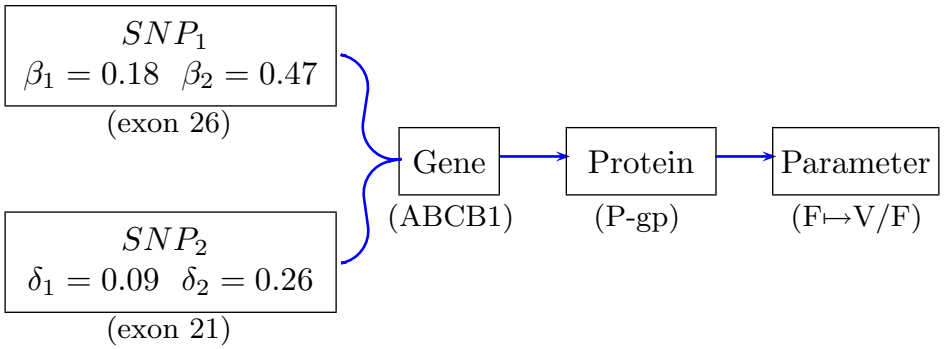
[7] Duval et al. Fundam Clin Pharmacol (2009)

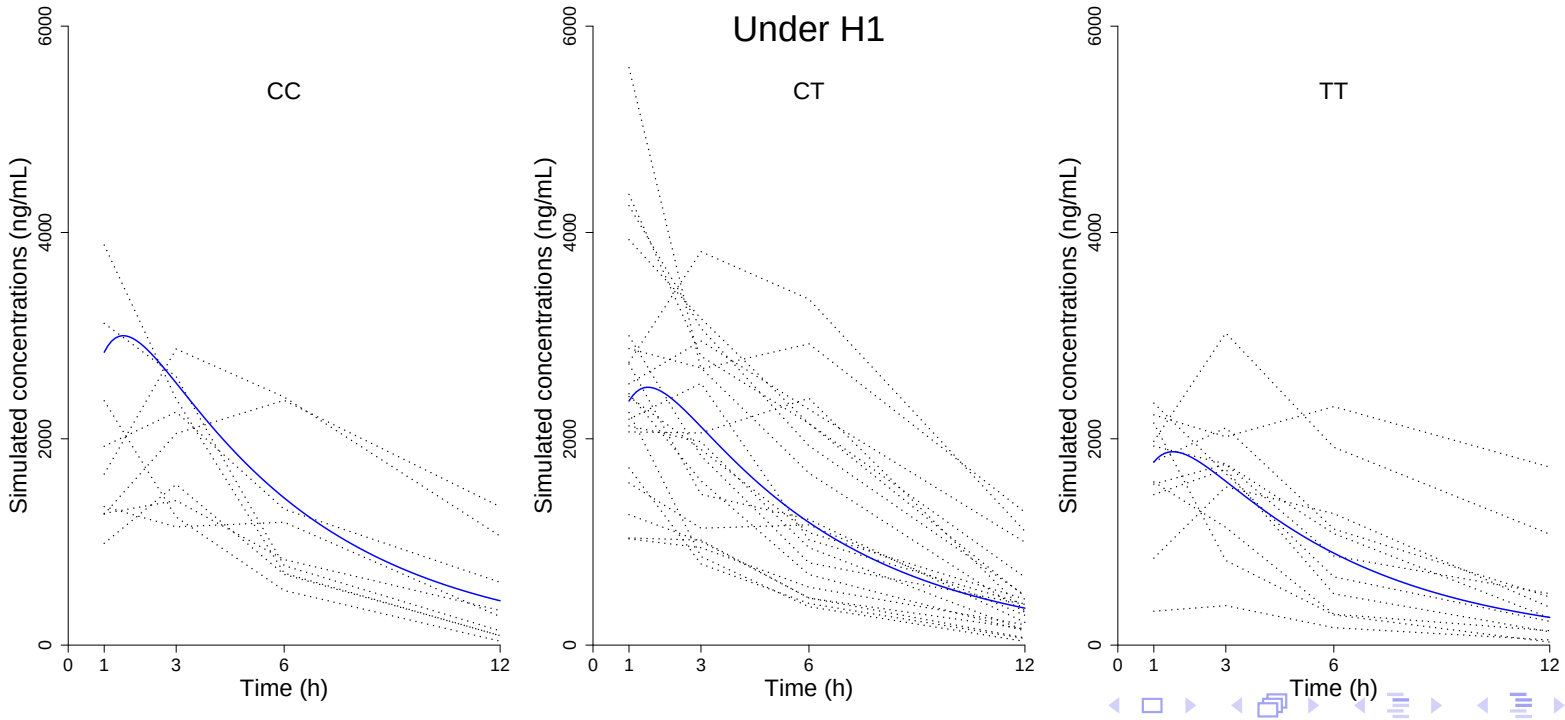
Simulated data

- Pharmacokinetic model



- Genetic model





Evaluation

Design	Total of observations	Number of groups	Patients per group /Sampling times	H_0	H_1	Estimation algorithm
N=40/n=4*	160	1	40/(1,3,6,12)	1000	1000	FOCE-I & SAEM
N=80/n=2**	160	4	30/(1,3) 10/(3,12) 30/(6,12) 10/(1,12)	1000	1000	SAEM
N=100/n=4,1	160	2	20/(1,3,6,12) 80/(12)	1000	1000	SAEM
N=200***/n=4	800	1	200/(1,3,6,12)	1000	-	FOCE-I & SAEM

*Design inspired from the COPHAR 2 study
** Design optimized using PFIM Interface 2.1 [8]
***Design with more subjects to be closer to asymptotic conditions for evaluation of type I error

[8] Retout et al. PFIM, 2007. www.pfim.biotstat.fr

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			30/(6,12)			
			10/(1,12)			
N=100/n=4,1	160	2	20/(1,3,6,12)	1000	1000	SAEM
			80/(12)			
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Tests - Evaluation[11]

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N=80/n=2**	160	4	30/(1,3) 10/(3,12) 30/(6,12) 10/(1,12)	1000	1000	SAEM
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[9] Sheiner L et al. NONMEM Version 5.1, 1998
[10] Lavielle M. MONOLIX Version 2.1, 2006
[11] Bertrand et al. J Biopharm Stat (2008)

Tests - Results

Test	Algorithm	N=40					N=200	
		K	α	K	$1-\beta$	$1-\beta_{corr}$	K	α
ANOVA	FOCE-I	986	5.6	968	71.2	79.3	982	5.1
	SAEM	1000	5.3	1000	71.1	70.9	1000	5.0
Wald	FOCE-I	924	11.7	905	57.2	24.7	860	6.5
	SAEM	1000	8.9	1000	81.8	73.0	1000	5.1
LRT	FOCE-I	964	7.9	947	78.7	71.0	956	5.0
	SAEM	1000	7.6	1000	78.6	73.3	1000	5.9

K = number of data sets on which the test could be performed

α = type I error

$1-\beta$ = power

$1-\beta_{corr}$ = corrected power

Prediction interval for 5% = $[3.6; 6.4]$

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Impact of design - Evaluation[12]

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[12] Bertrand et al. J Pharmacokinet Pharmacodyn (2009)

Impact of design - Results with SAEM

	N=40			N=80			N=100			N=200
	α	1-β	1-β_{corr}	α	1-β	1-β_{corr}	α	1-β	1-β_{corr}	α
ANOVA	5.3	71.1	70.9	6.4	93.4	91.5	4.3	78.3	79.5	5.0
Wald	8.9	81.8	73.0	8.7	95.5	92.5	8.4	85.7	81.8	5.1
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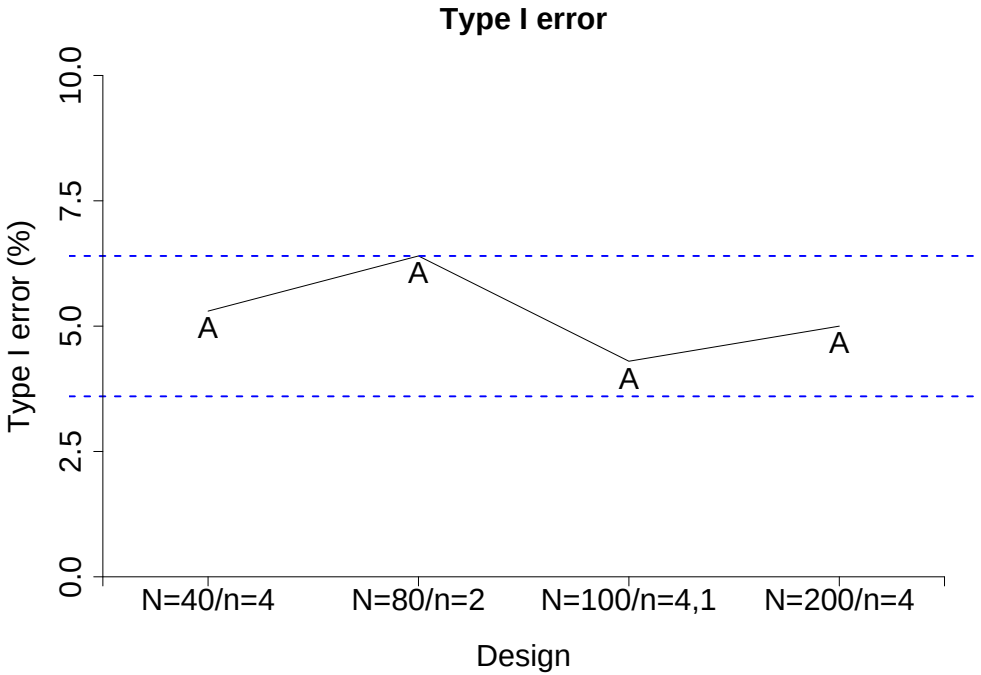

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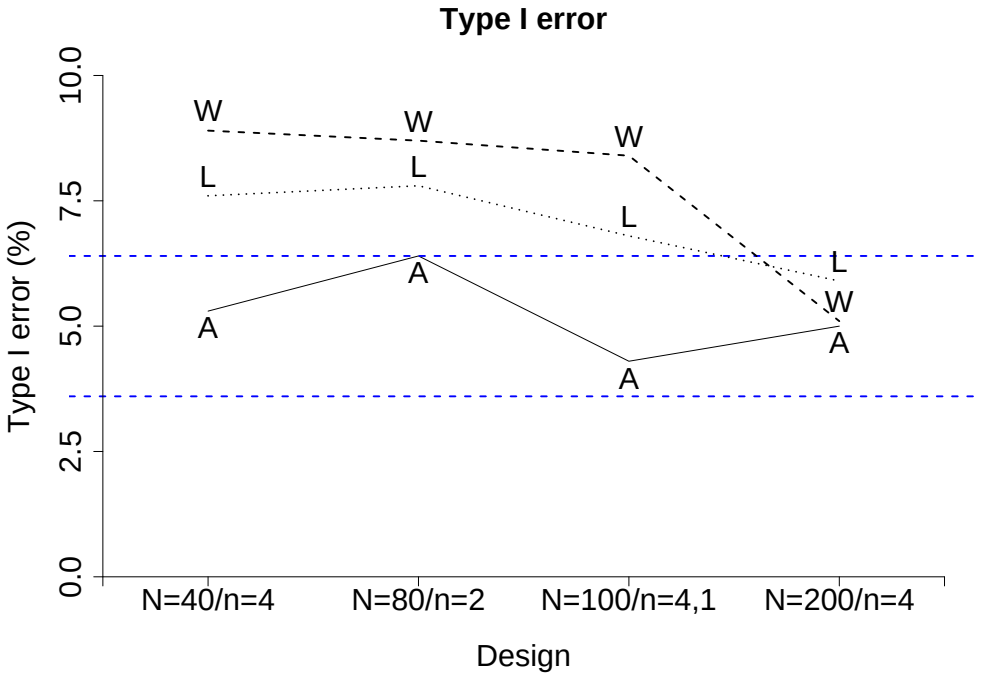

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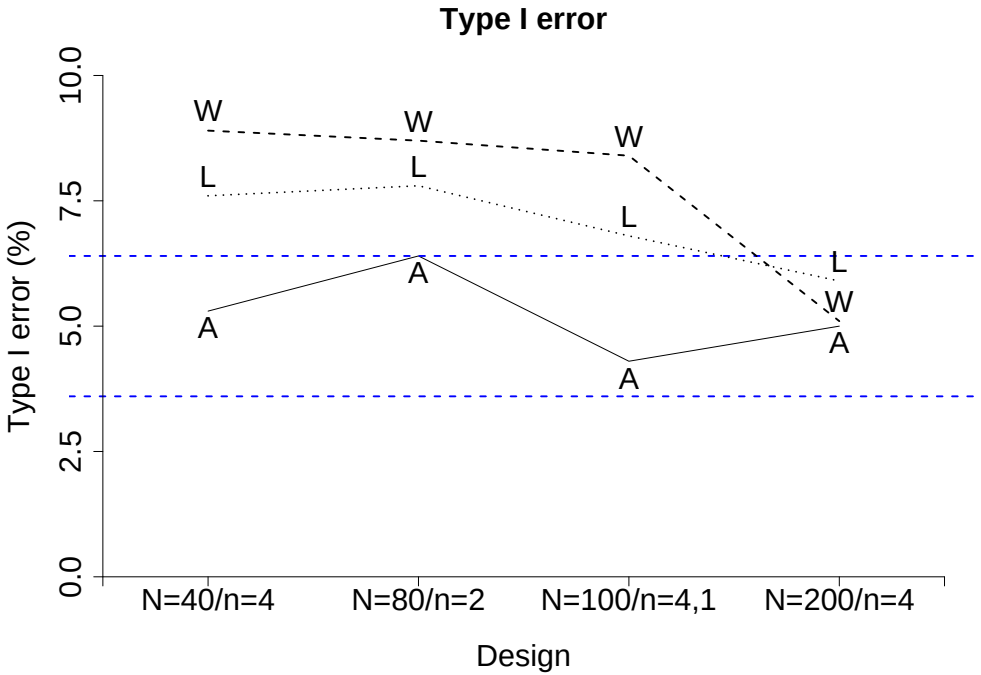
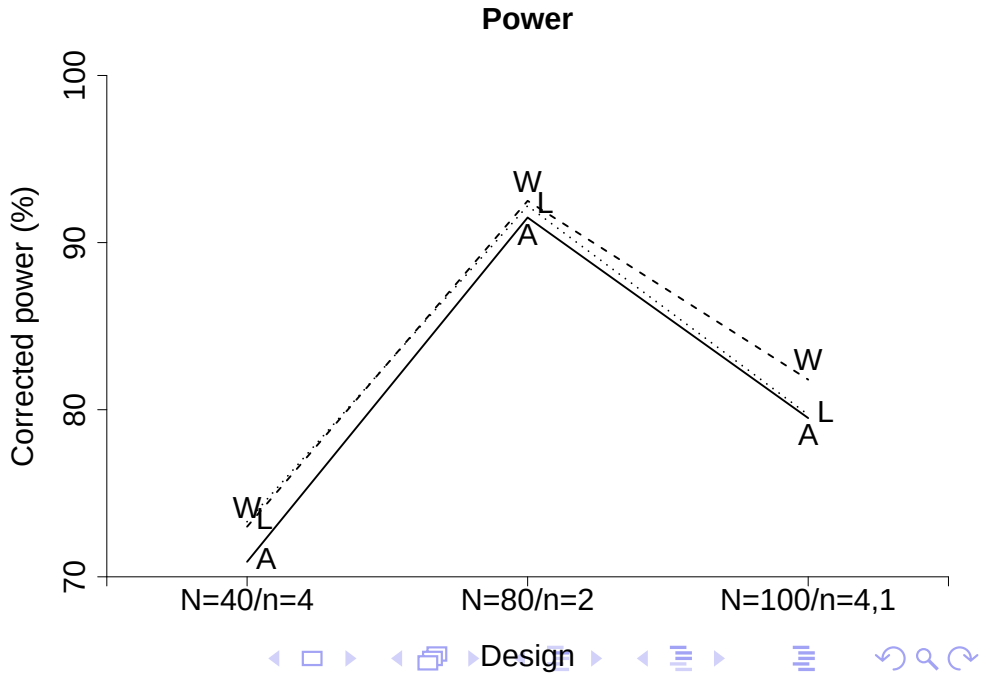




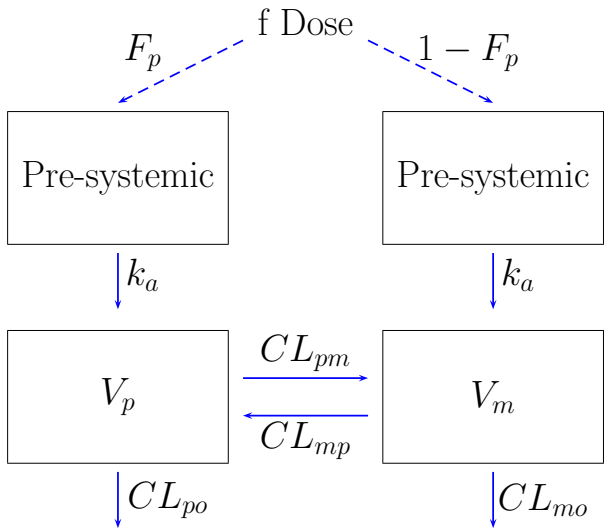
Application to drug X and its active metabolite

- PK study
  - N=99/n=4 at 1, 3, 6 and 24h for both the parent drug and the metabolite
  - two occasions
    - 4 and 8 weeks after treatment onset (W4 and W8)
  - three oral doses investigated
- CYP2D6
  - involved in elimination of the active metabolite
  - known SNPs: *3 (2549delA), *4 (1846G>A), *6 (1707delT), *7 (2935A>C) and *8 (1758G>T)
  - two rare alleles carriers: poor metabolizers

	Number of patients (%)
CYP2D6 (EM/PM)	87 (86)/12 (12)

Structural model

- Modelling with MONOLIX Version 2.4
- First-pass and interconversion mechanisms



- Parameters identifiability
  - $V_p = V_m$, similar molecular mass and physicochemical properties

Population PK parameters

Parameter (unit)	Estimate	Relative standard error (%)
f	1	-
$\beta_{f,dose}$*	-0.029	19
F_p	0.84	2
K_a/h	6.16	31
VL	18.7	4
$Cl_{po}L/h$	1.32	12
$Cl_{pm}L/h$	2.15	7
$Cl_{mo}L/h$	0.41	9
$Cl_{mp}L/h$	0.14	11
$\omega f(\%)$	22	22
$\omega F_p(\%)$	0	-
$\omega K_a(\%)$	94	48
$\omega V(\%)$	20	24
$\omega Cl_{po}(\%)$	46	33
$\omega Cl_{pm}(\%)$	0	-
$\omega Cl_{mo}(\%)$	58	13
$\omega Cl_{mp}(\%)$	45	72
$\gamma f(\%)$	15	34
$\gamma F_p(\%)$	0	-
$\gamma K_a(\%)$	131	24
$\gamma V(\%)$	15	34
$\gamma Cl_{po}(\%)$	36	47
$\gamma Cl_{pm}(\%)$	0	-
$\gamma Cl_{mo}(\%)$	29	35
$\gamma Cl_{mp}(\%)$	31	166
$\sigma S33(\%)$	28	4
$\sigma S35(\%)$	9	3

*$f_i = f \times e^{\beta_{f,dose} \times (DOSE-10)} e^{\eta_{f,i}}$

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$Cl_{mp}L/h$	0.14	11
$\omega f(\%)$	22	22
$\omega F_p(\%)$	0	-
$\omega K_a(\%)$	94	48
$\omega V(\%)$	20	24
$\omega Cl_{po}(\%)$	46	33
$\omega Cl_{pm}(\%)$	0	-
$\omega Cl_{mo}(\%)$	58	13
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$\sigma S33(\%)$	28	4
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K_a/h	6.16	31
VL	18.7	4
$Cl_{po}L/h$	1.32	12
$Cl_{pm}L/h$	2.15	7
$Cl_{mo}L/h$	0.41	9
$Cl_{mp}L/h$	0.14	11
$\omega f(\%)$	22	22
$\omega F_p(\%)$	0	-
$\omega K_a(\%)$	94	48
$\omega V(\%)$	20	24
$\omega Cl_{po}(\%)$	46	33
$\omega Cl_{pm}(\%)$	0	-
$\omega Cl_{mo}(\%)$	58	13
$\omega Cl_{mp}(\%)$	45	72
$\gamma f(\%)$	15	34
$\gamma F_p(\%)$	0	-
$\gamma K_a(\%)$	131	24
$\gamma V(\%)$	15	34
$\gamma Cl_{po}(\%)$	36	47
$\gamma Cl_{pm}(\%)$	0	-
$\gamma Cl_{mo}(\%)$	29	35
$\gamma Cl_{mp}(\%)$	31	166
$\sigma S33(\%)$	28	4
$\sigma S35(\%)$	9	3

*$f_i = f \times e^{\beta_{f,dose} \times (DOSE-10)} e^{\eta_{f,i}}$

Population PK parameters

Parameter (unit)	Estimate	Relative standard error (%)
f	1	-
$\beta_{f,dose}$*	-0.029	19
F_p	0.84	2
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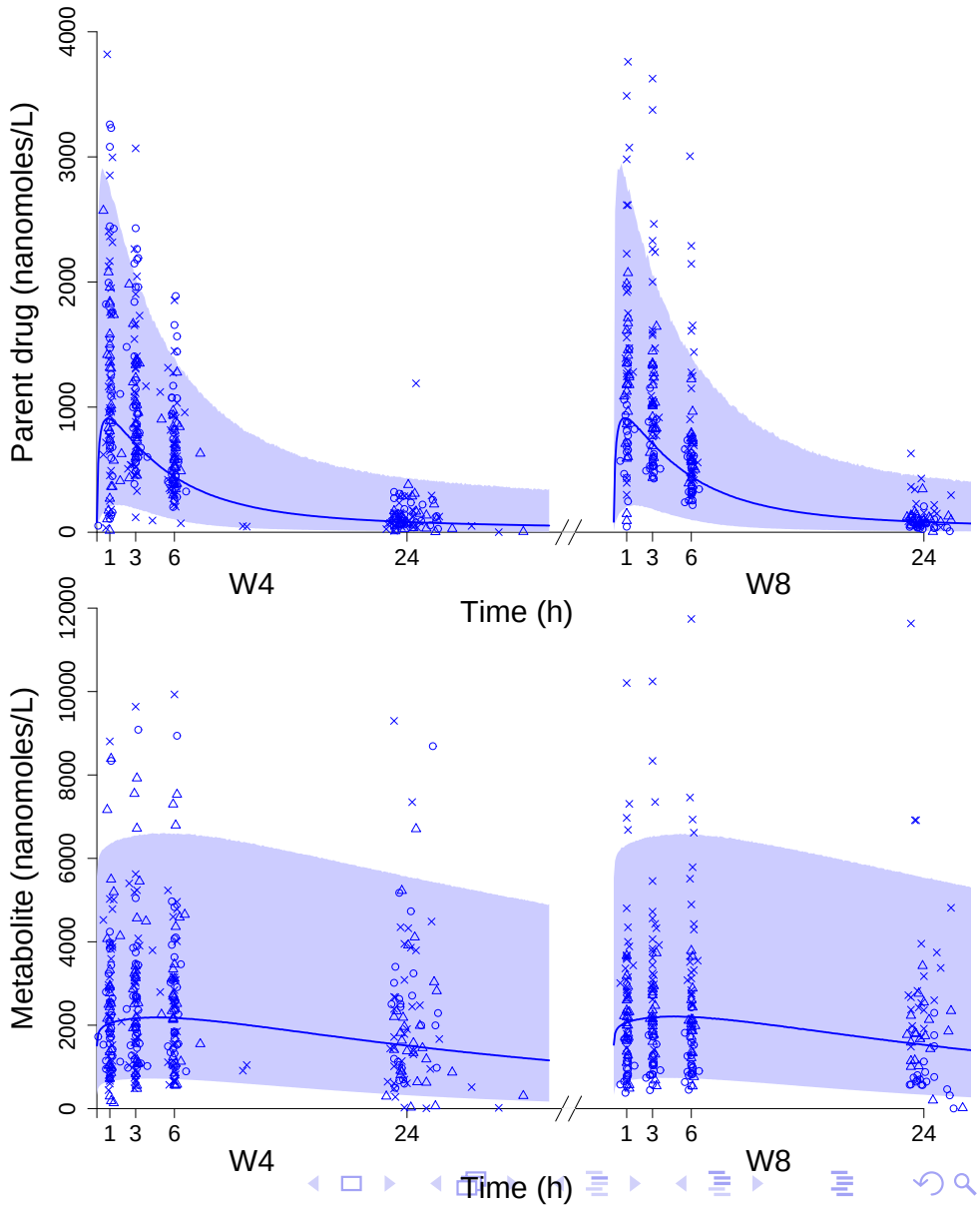


Genetic covariate model

- Genetic component of variability[13]

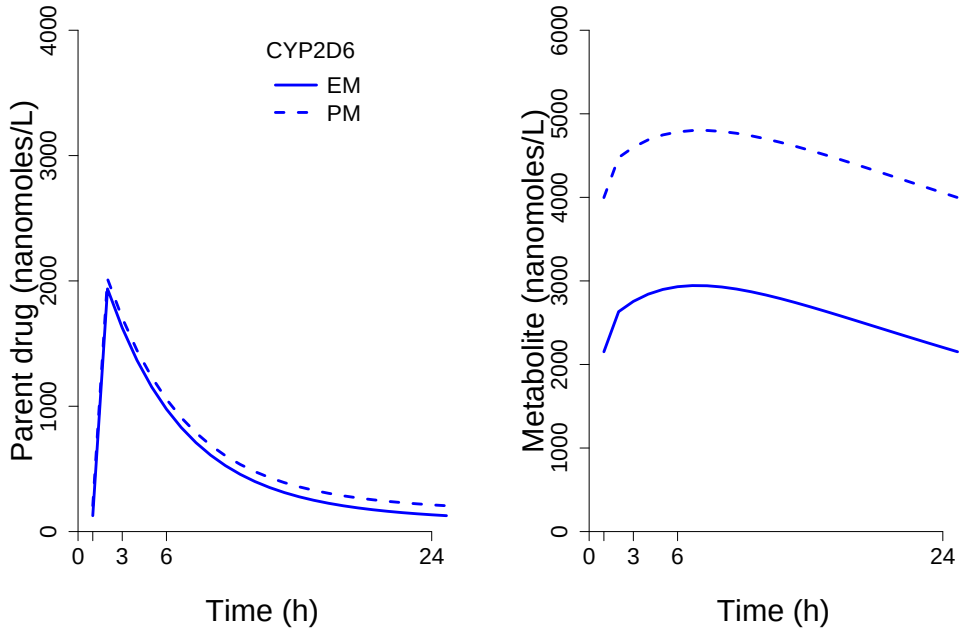
$$r_{GC,\theta} = 1 - \frac{\gamma_\theta^2}{\omega_\theta^2}$$

$$\gamma_\theta^2 = WSV$$

$$\omega_\theta^2 = BSV$$

	f	k_a	V	Cl_{po}	Cl_{mo}	Cl_{mp}
r_{GC} (%)	47	0	45	38	74	52

- Similar results with the 3 model-based tests
- 47% decrease in Cl_{mo} in PM (P-value=0.005)



[13] Özdemir et al. Pharmacogenetics (2000)

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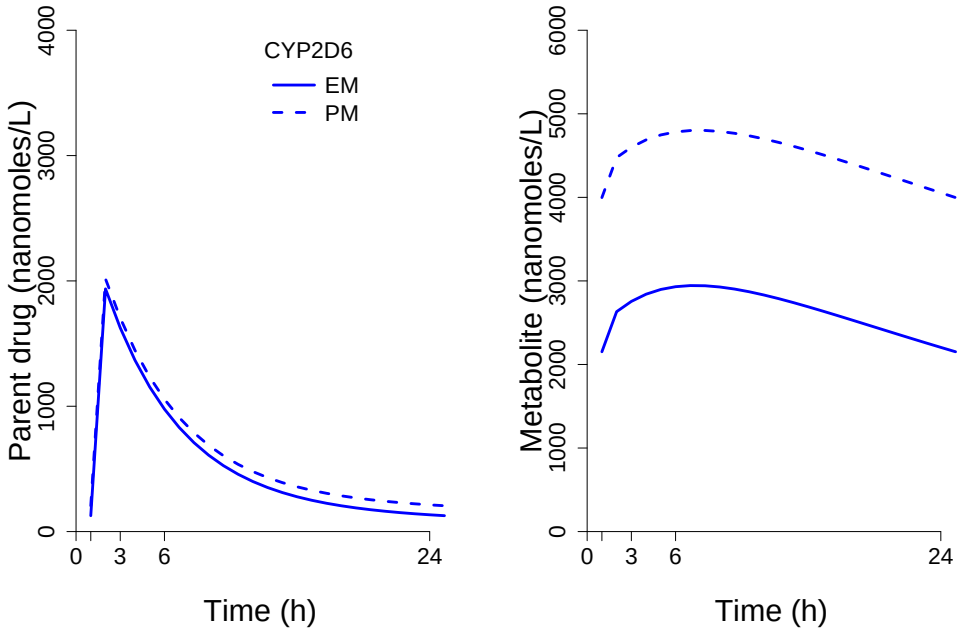

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Conclusion

"The investigation of the effect of PG on the PK of a drug substance may be performed using a population PK approach in genotyped subjects and patients, or in a conventional PK study. In both cases the study should include a satisfactory number of patients of each geno- or phenotype in order to obtain valid correlation data."

EMEA (2007)

- NLMEM are a powerful tool in the analysis of pharmacogenetic studies
  - ↪ more flexible designs
  - ↪ complex models
- Asymptotic tests require correction for type-I error inflation on designs with small N due to the imbalance in genotypes
  - ↪ simulation-based approaches or permutation tests