Non-linear mixed-effects models for tests of interaction or of lack of interaction in cross-over and parallel pharmacokinetic studies: application to the test of interaction between protease inhibitors and nucleoside analogs in HIV patients

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Context (1) : tests in PK cross-over trials

Tests comparing PK parameters between the 2 treatment arms

- interaction trials $\rightarrow$ comparison test
- bioequivalence trials $\rightarrow$ equivalence test

Standard approach (FDA 1999, EMEA 1998 and 2000)

Estimate the AUC by NC approach

- comparison: paired Student or Wilcoxon test on $log(AUC)$
- equivalence (Average Bioequivalence, FDA 2000)
  - Schuirmann's two one-sided test (TOST) on $log(AUC)$
  - 1 - estimate the $CI_{90\%}$ of $\mu_{\text{AUC}}^{(T)} - \mu_{\text{AUC}}^{(R)}$

    2 - compare this $CI_{90\%}$ to [-0.2;0.2]

Drawback:

- large number of samples per subject (between 10 and 20)
- underlying PK model not taken into account

Context (2): anti-retroviral drugs of HIV infection

Anti-retrovirals prescribed in HIV infection

- combination of molecules with numerous interactions
- very high inter and intra-patient variability

Plan

1- evaluation of the type I error and power without modelling IOV

2- evaluation of the impact of modelling IOV

3- application to the Puzzle II study

4- evaluation of the randomization test on the interaction of ZDV on NFV/M8

Methods (1) - Model and notations

Subject i $(i = 1, ..., N)$, sampling times t_j $(j = 1, ..., n)$

$y_{i,j}^{(k)}$: observation of sujet i at time t_j for treatment k $(k = R, T)$

$$y_{i,j}^{(k)} = f(t_j, \phi_i^{(k)}) + \varepsilon_{i,j}^{(k)}$$

ε : measurement error, gaussian with null mean and variance:

$$\sigma_{i,j}^{(k)\,2} = \sigma^2 (a + f(t_j, \phi_i^{(k)}))^2$$

Individual parameters

$$\phi_i^{(k)} = \mu + \beta \mathbb{1}_{k=T} + \eta_i + c_i^{(k)}$$

$\eta_i \rightsquigarrow \mathcal{N}(0, \Gamma)$, $c_i^{(k)} \rightsquigarrow \mathcal{N}(0, \Psi)$

Γ and Ψ often supposed diagonal

$log(AUC)$ is a component of $\phi \rightarrow \phi_{\text{AUC}}$

Methods (2) - Comparison tests

$$H_0 : \{\mu_{\text{AUC}}^{(T)} - \mu_{\text{AUC}}^{(R)} = 0\} \Leftrightarrow \{\beta_{\text{AUC}} = 0\}$$

Standard tests (guidelines)

- separate analysis of each PK profile
- estimation of the individual NC AUC
- paired Student and Wilcoxon comparing NC $log(AUC)_i^{(k)}$

Development of 4 tests based on NLMEM

- Global tests
  - joint analysis of the two treatment groups
    1 - LRT, comparing model with $\beta_{AUC} = 0$ and model with β_{AUC} estimated
    2 - extension of the Wald test comparing β_{AUC} to 0
- EB tests
  - separate analysis of each treatment group
  - estimation of the EB $\theta_i^{(k)}$
  - Student and Wilcoxon comparing the EB $\theta_{\text{AUC},\, i}^{(k)}$

Methods (3) - Equivalence tests

$H_0 : \{\mu_{\text{AUC}}^{(T)} - \mu_{\text{AUC}}^{(R)} \leq -\delta \text{ or } \mu_{\text{AUC}}^{(T)} - \mu_{\text{AUC}}^{(R)} \geq \delta\} \Leftrightarrow \{\beta_{\text{AUC}} \leq -\delta \text{ or } \geq \delta\}$

Typically $\delta = 0.2$ ($e^{-\delta} = 0.8$ and $e^{\delta} = 1.25$)

Standard tests (guidelines)

- Student TOST on NC $log(AUC)_i^{(k)}$
- adaptation of TOST to the Wilcoxon test on NC $log(AUC)_i^{(k)}$ (Chow and Liu, 1999)

Global tests

- no simple extension of the LRT for equivalence
- Wald: same principle as for the TOST using $\text{CI}_{90\%}$ of β_{AUC} (SE of β_{AUC} is estimated by nlme)

EB tests

- adaptation of the standard tests to the $\theta_{\text{AUC},\, i}^{(k)}$

Evaluation by simulation - Theophylline

Population PK on the original dataset

- N=12 subjects, n=10 samples per subject
- one compartment, 1^{st} order absorption and elimination
- parametrization on $log(k_a)$, $log(AUC)$, $log(V)$

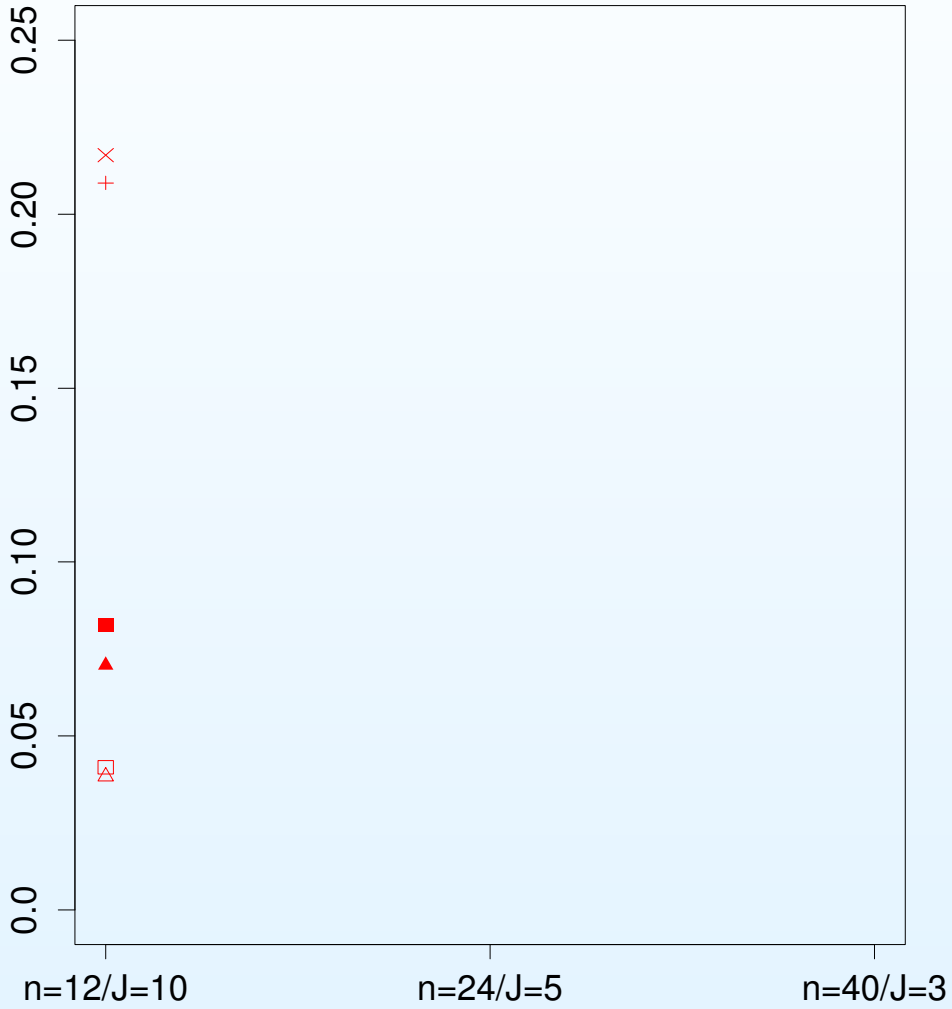
Estimated values used to simulate concentration data

- fixed effects: $\hat{\mu}_{k_a} = 0.39$, $\hat{\mu}_{AUC} = 4.61$ and $\hat{\mu}_V = -0.73$
- combined error model: a=1, σ=0.1
- SD of the random effects for $log(k_a)$, $log(AUC)$ and $log(V)$ resp.
  - IIV: 0.10, 0.20 and 0.20
  - IOV: 0.05, 0.10 and 0.10

Simulated designs: combinations of N=12, 24 and 40, n=10, 5 and 3

Results (1) - Type I error

Comparison



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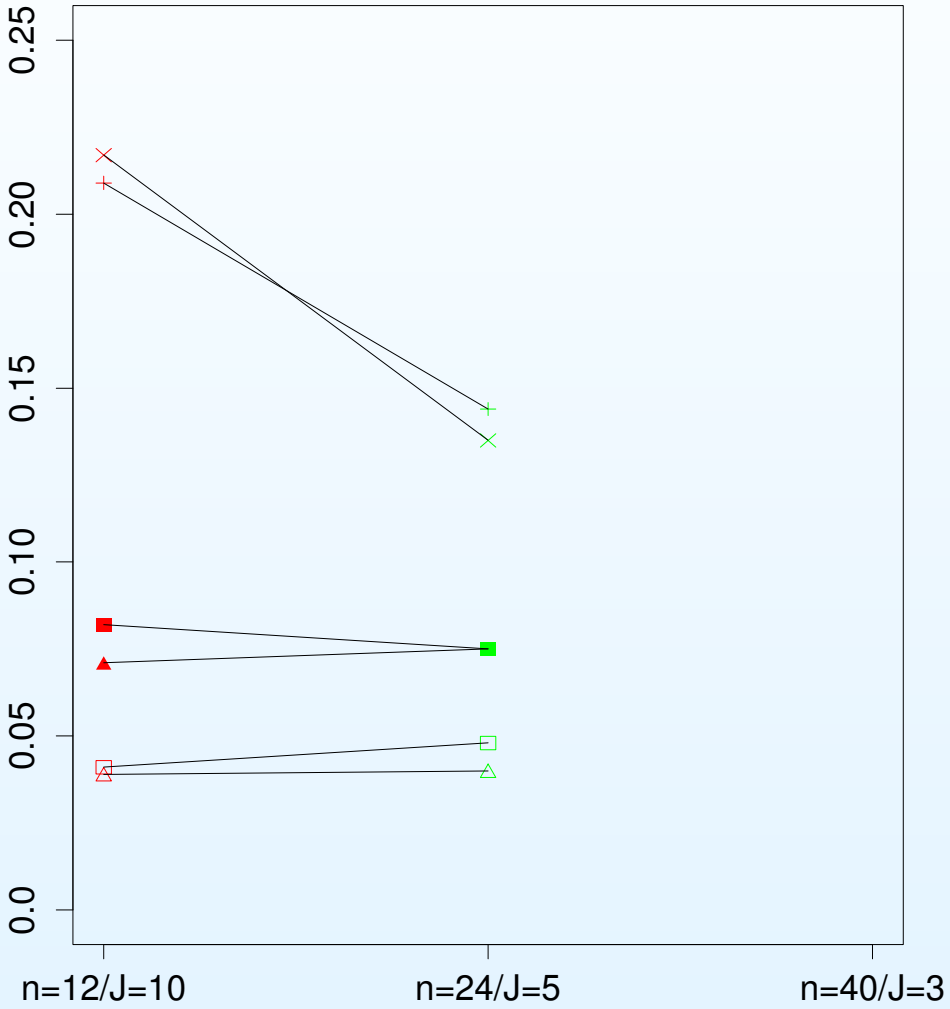

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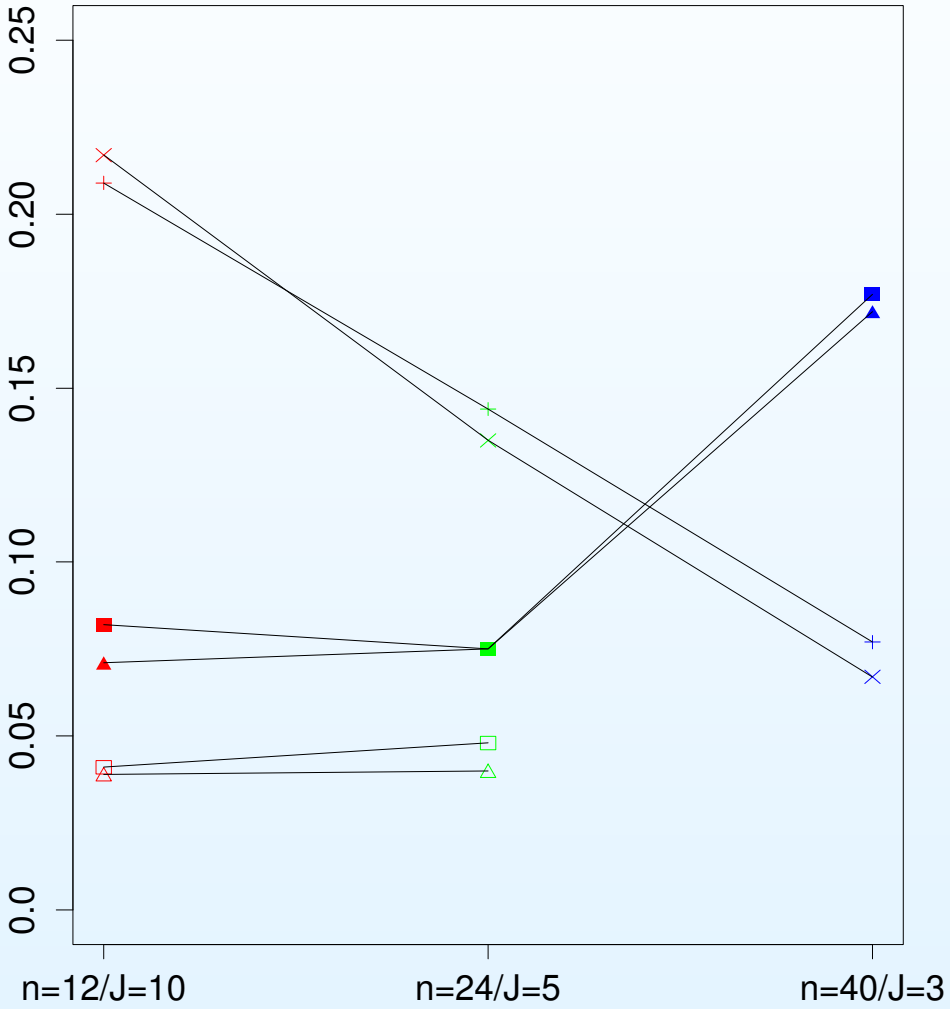

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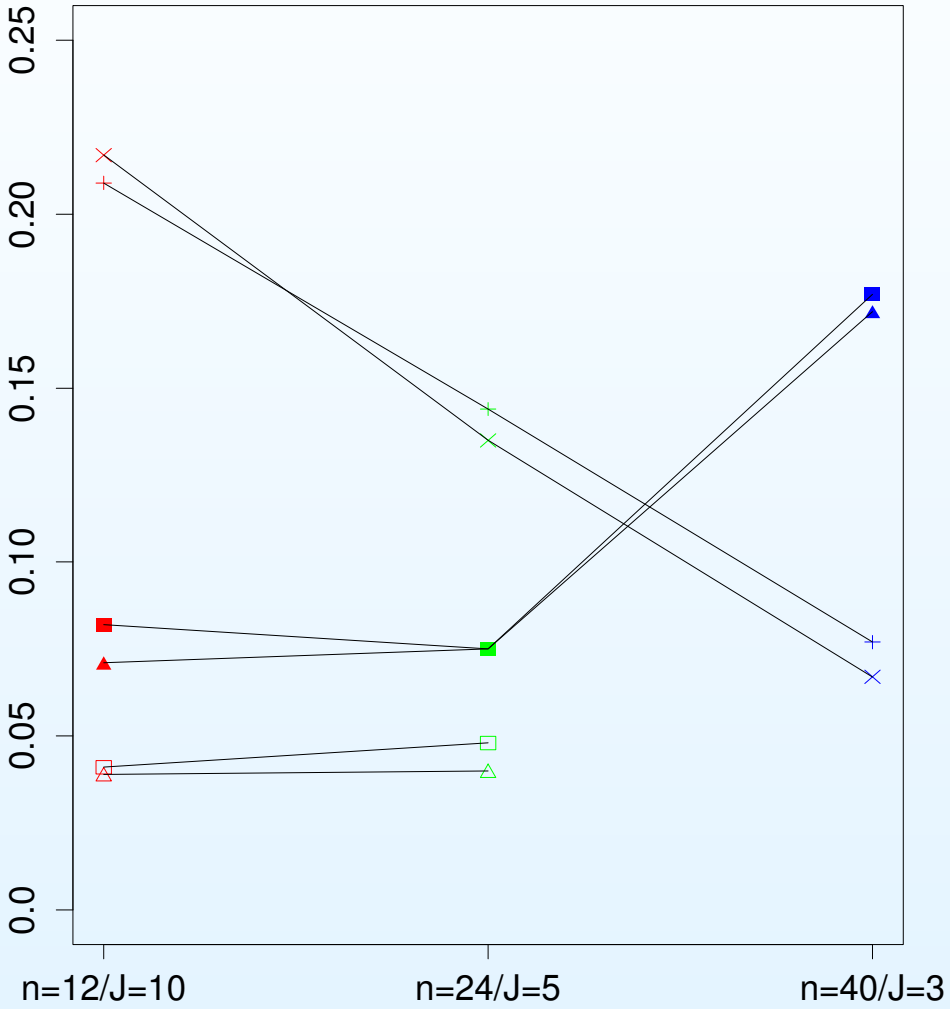
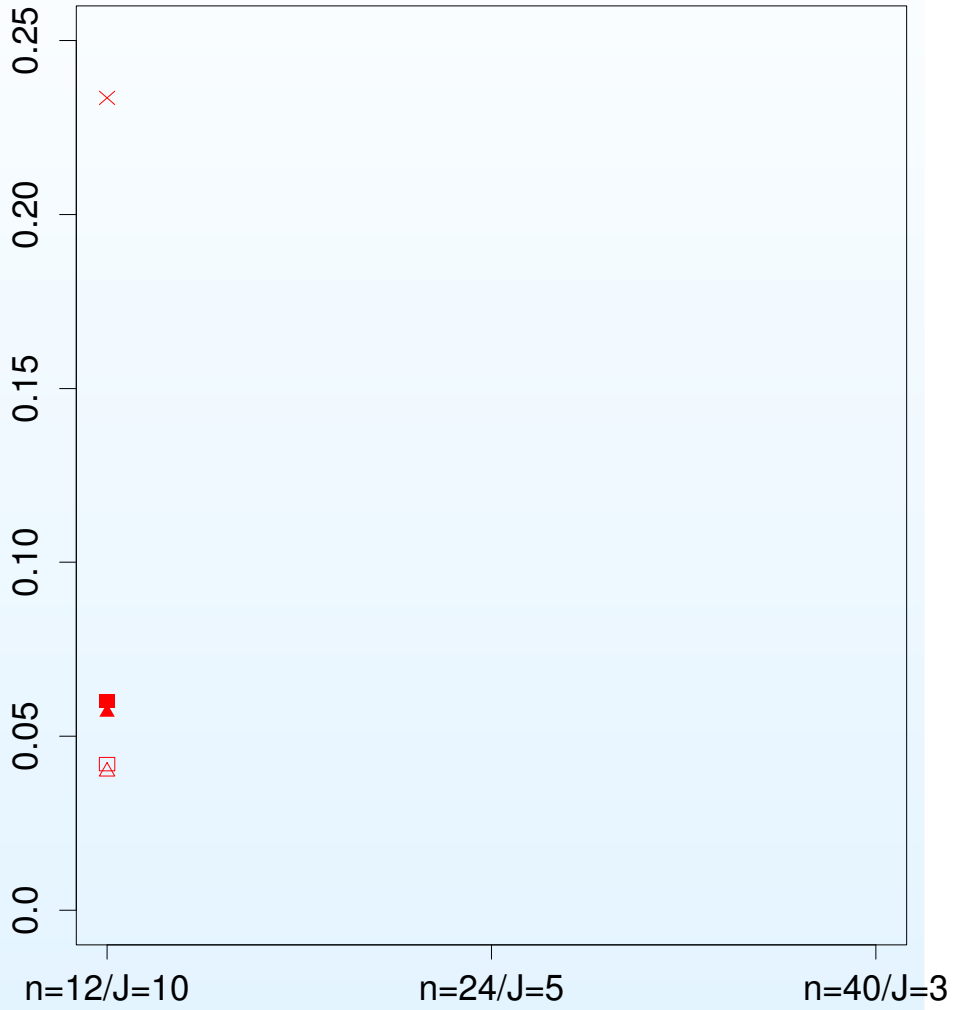


Equivalence



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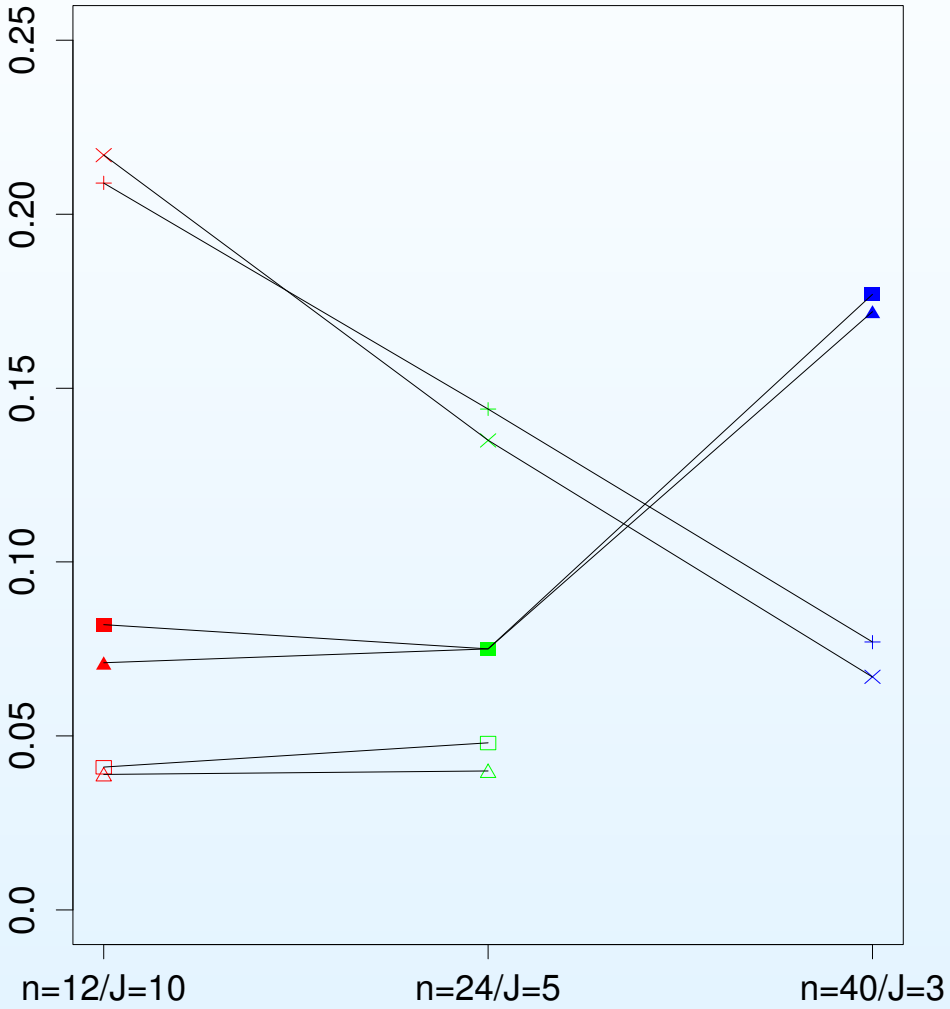

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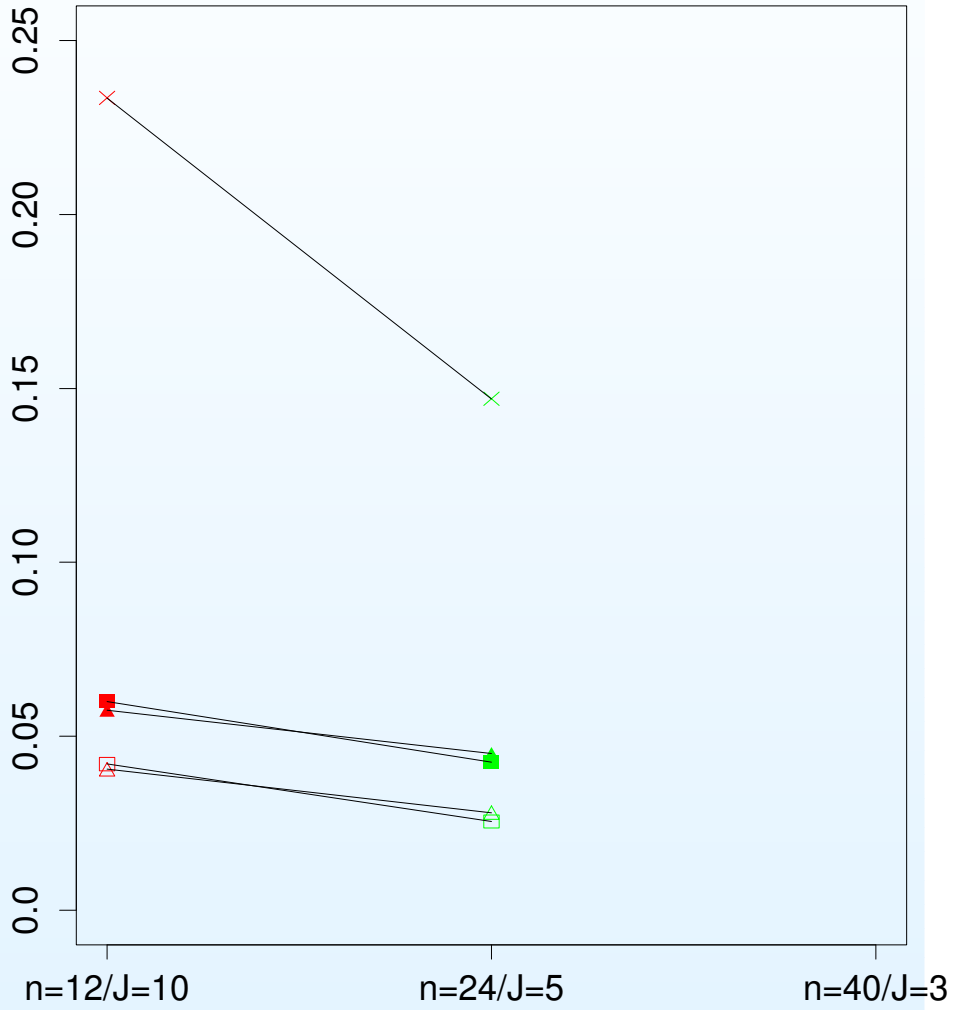

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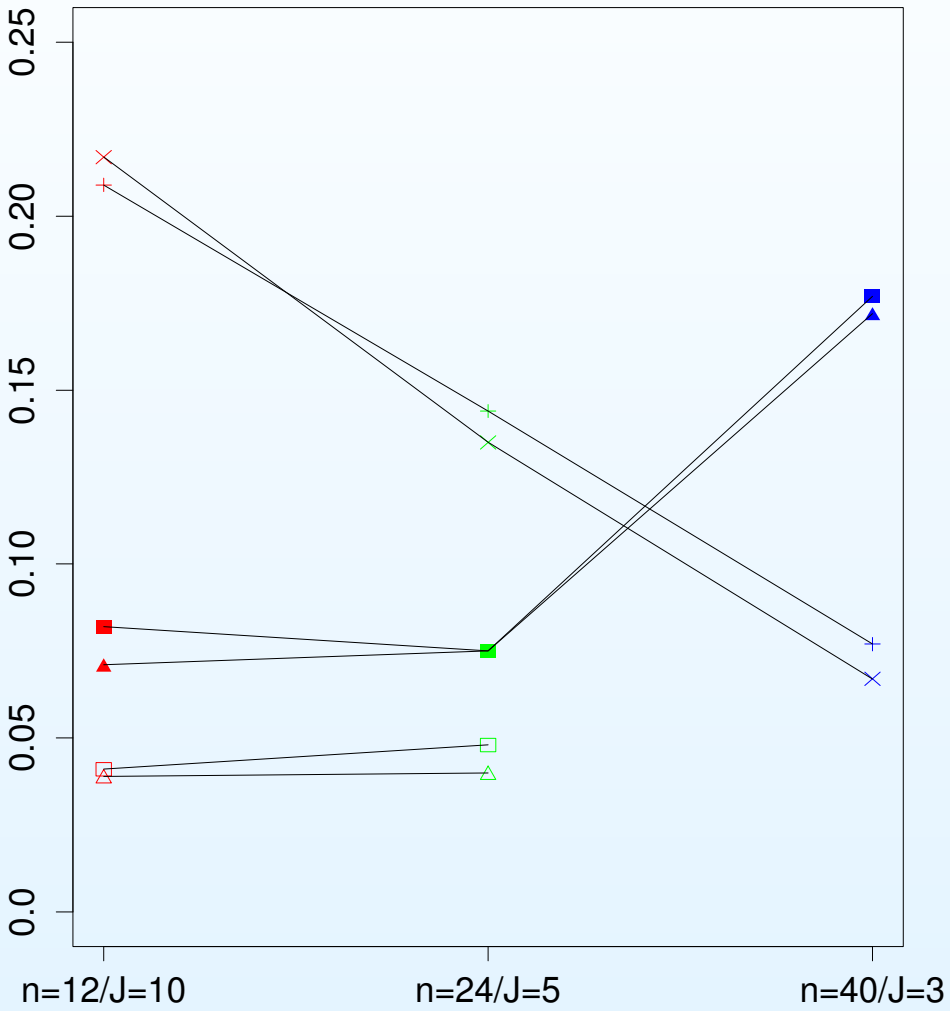

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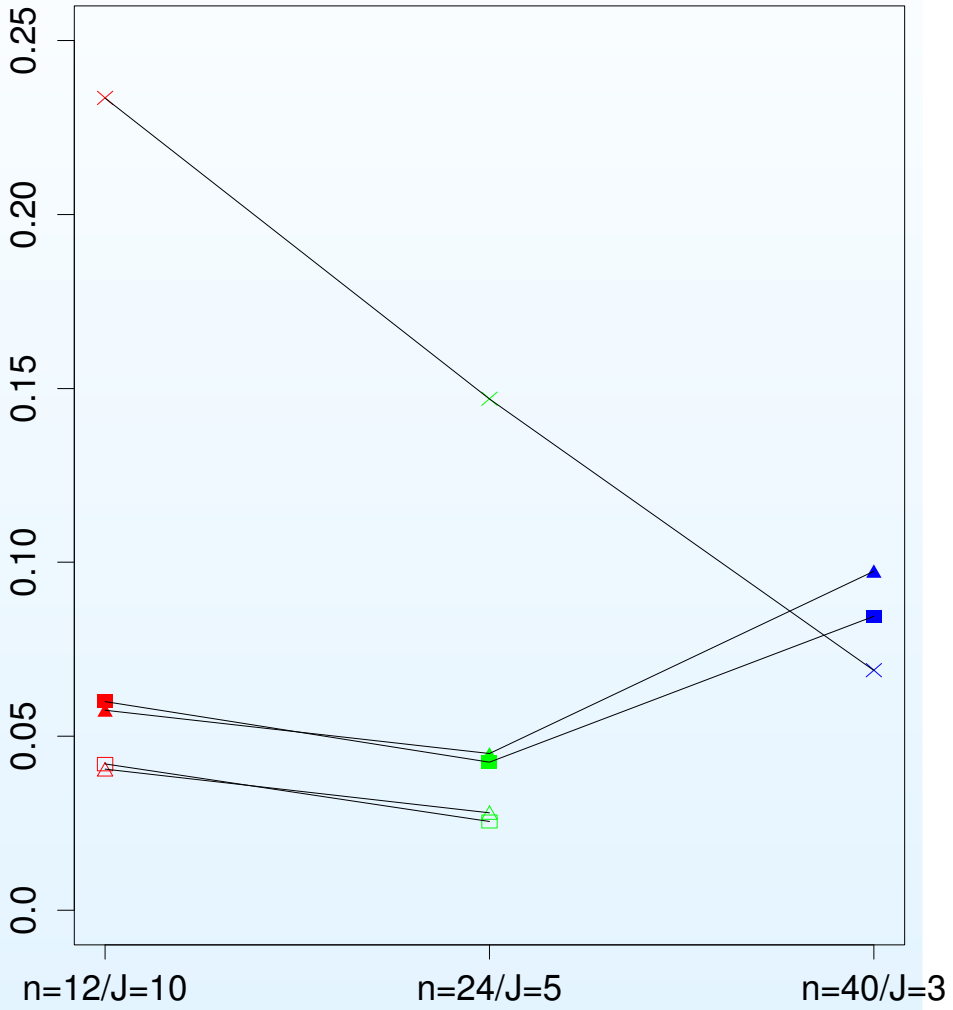

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Results (2) - Power

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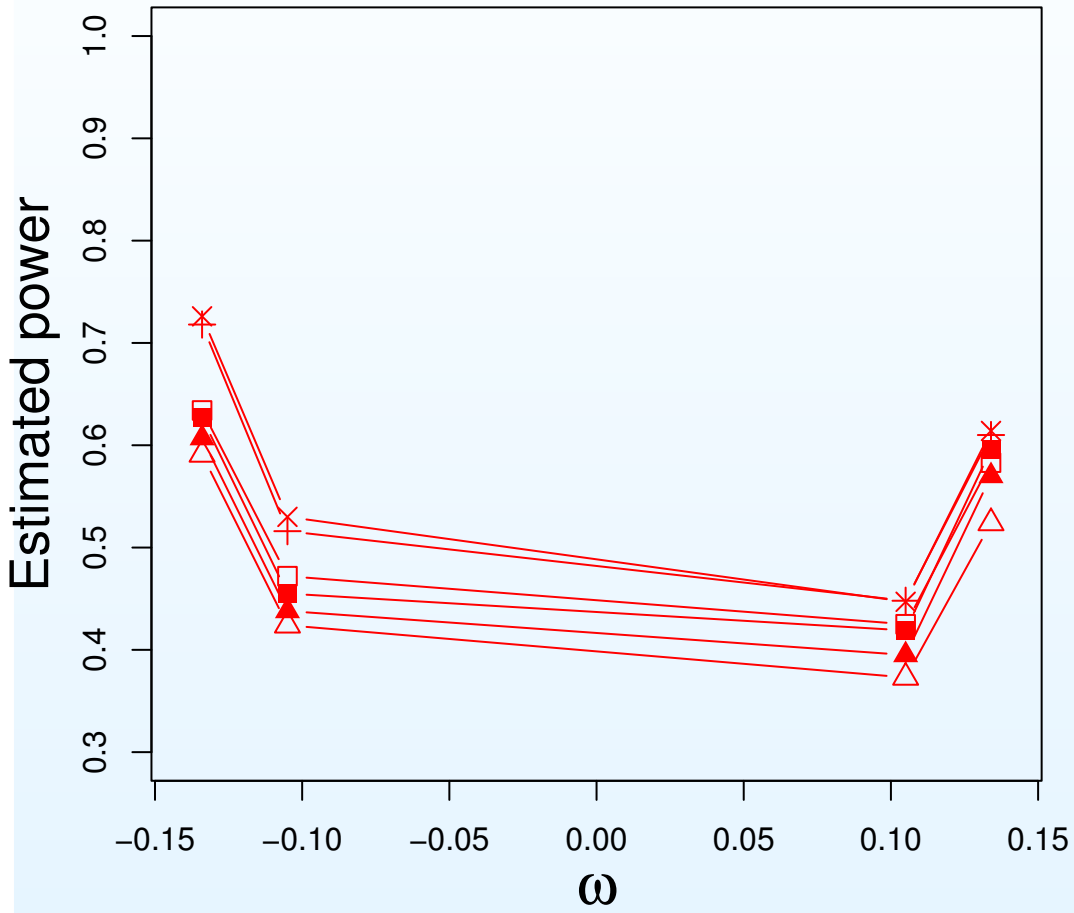

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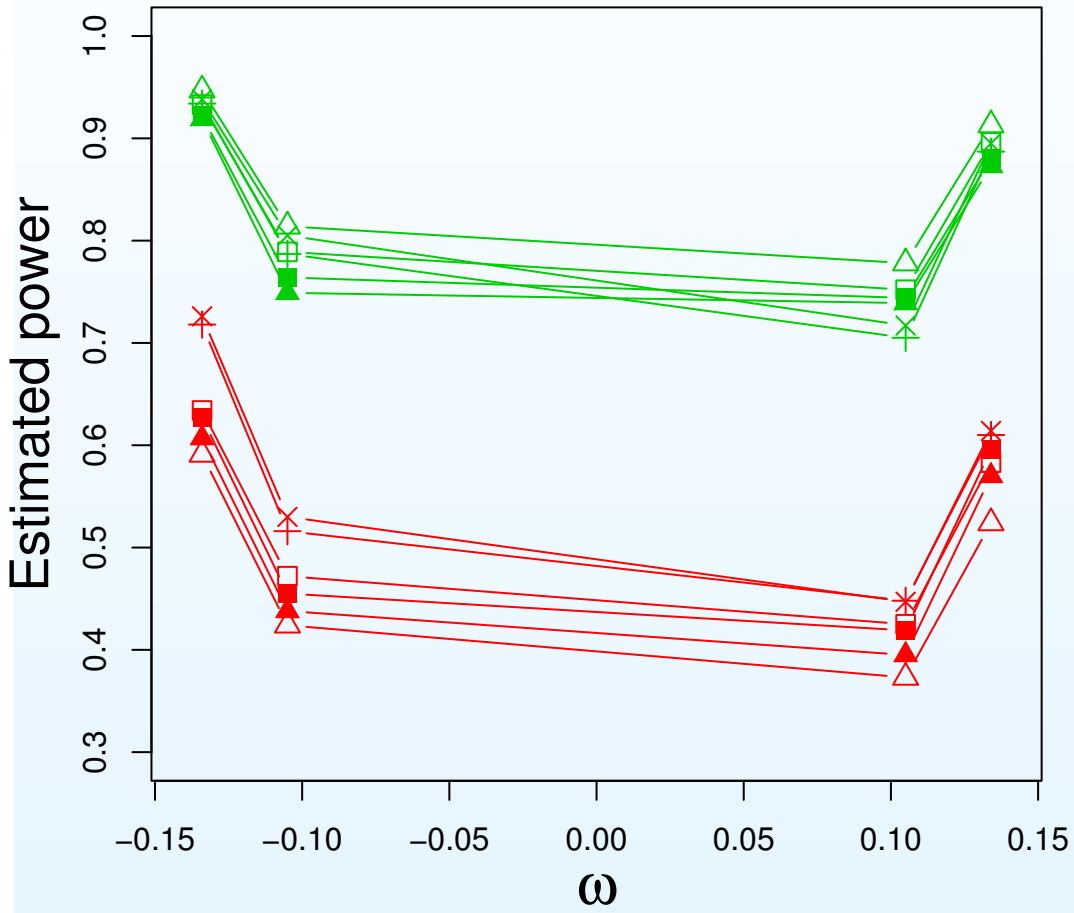

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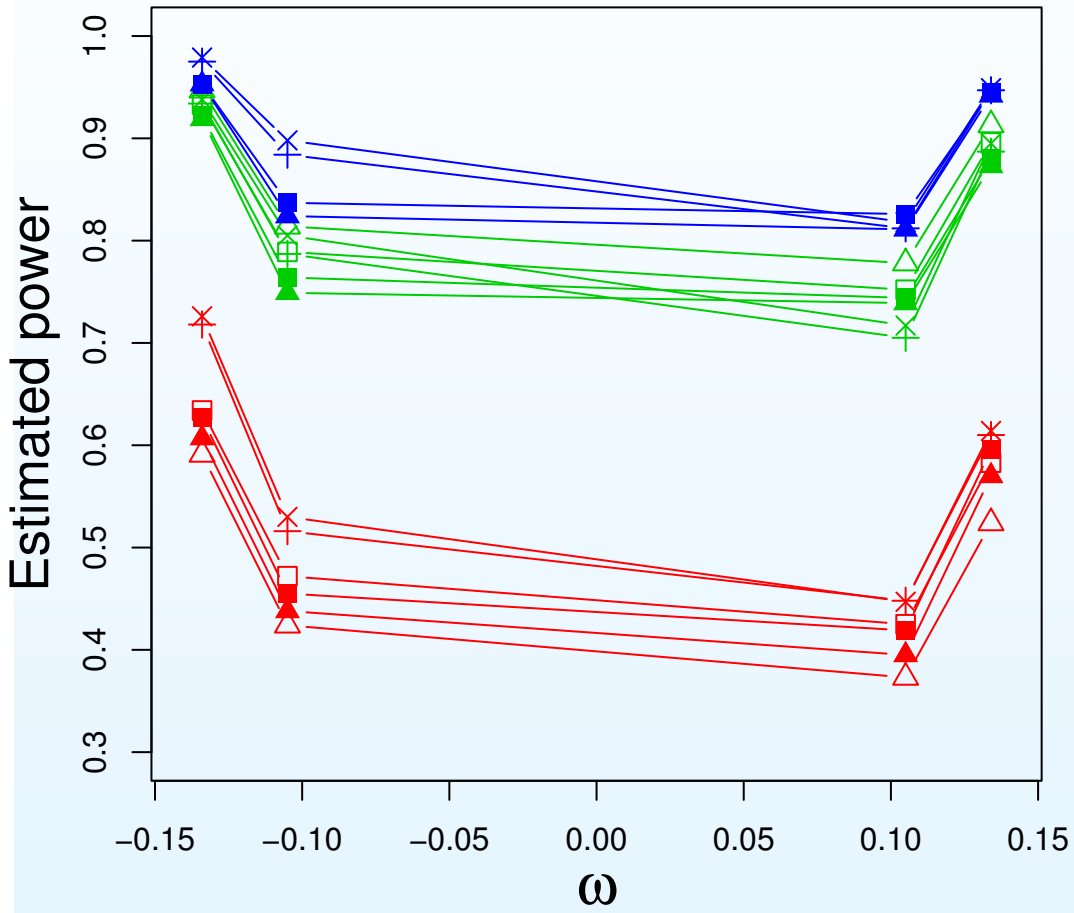

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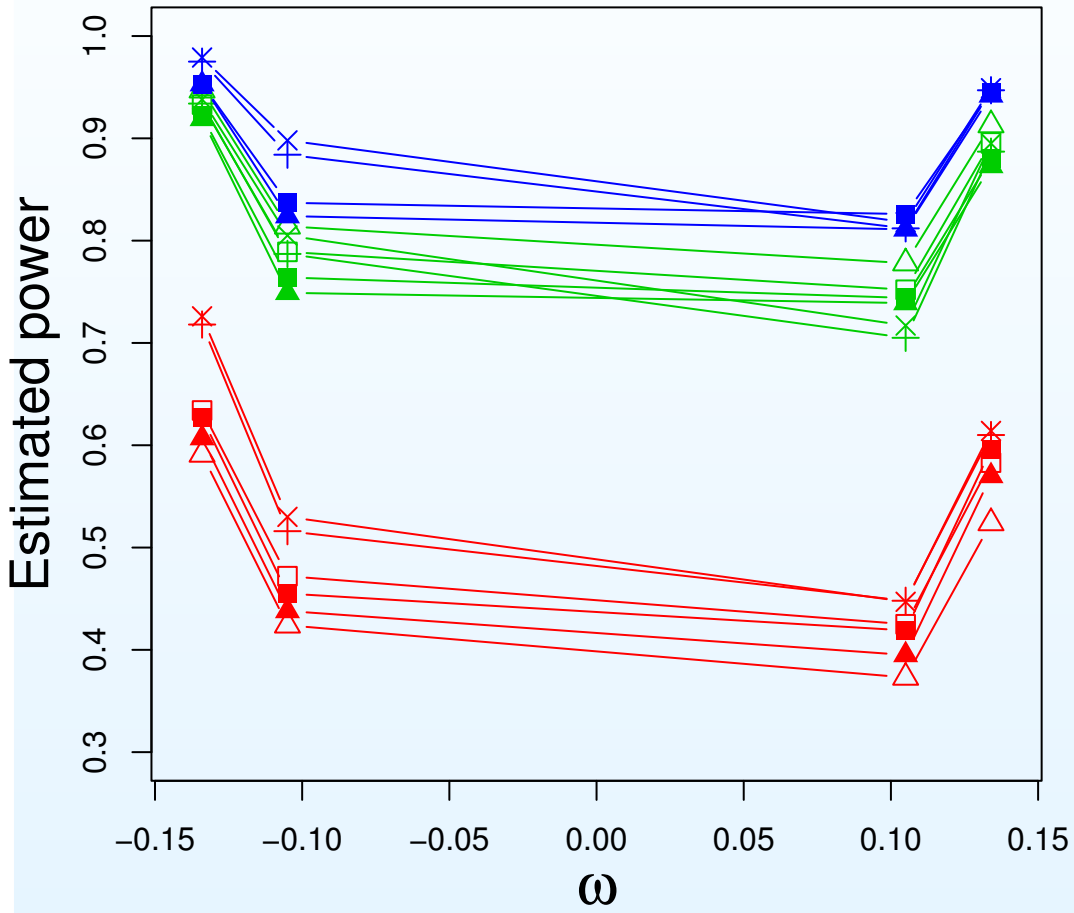

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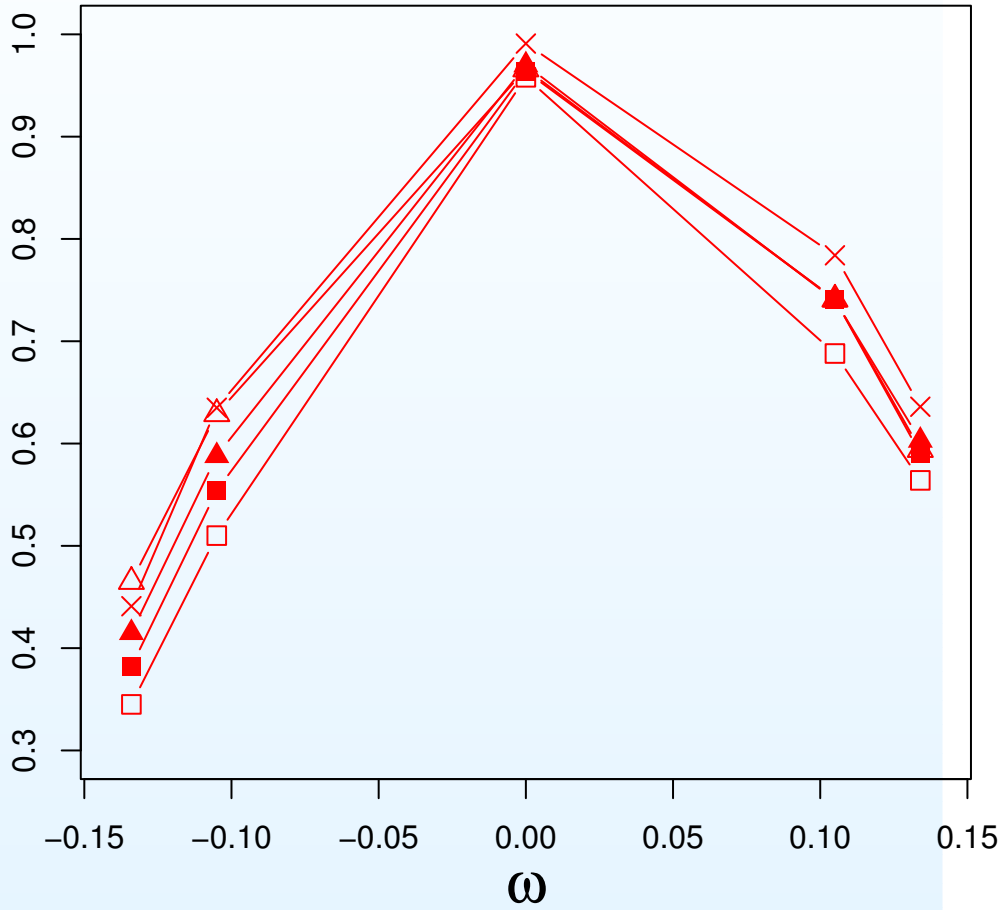

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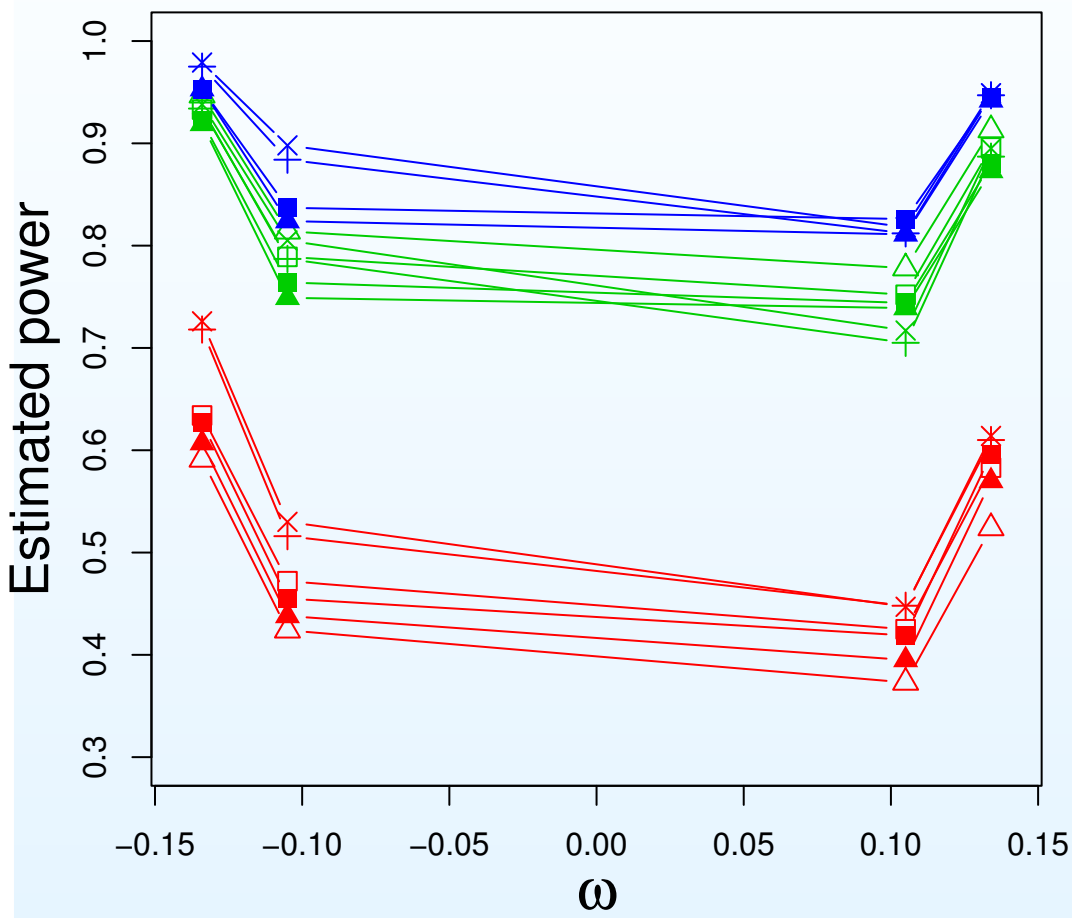

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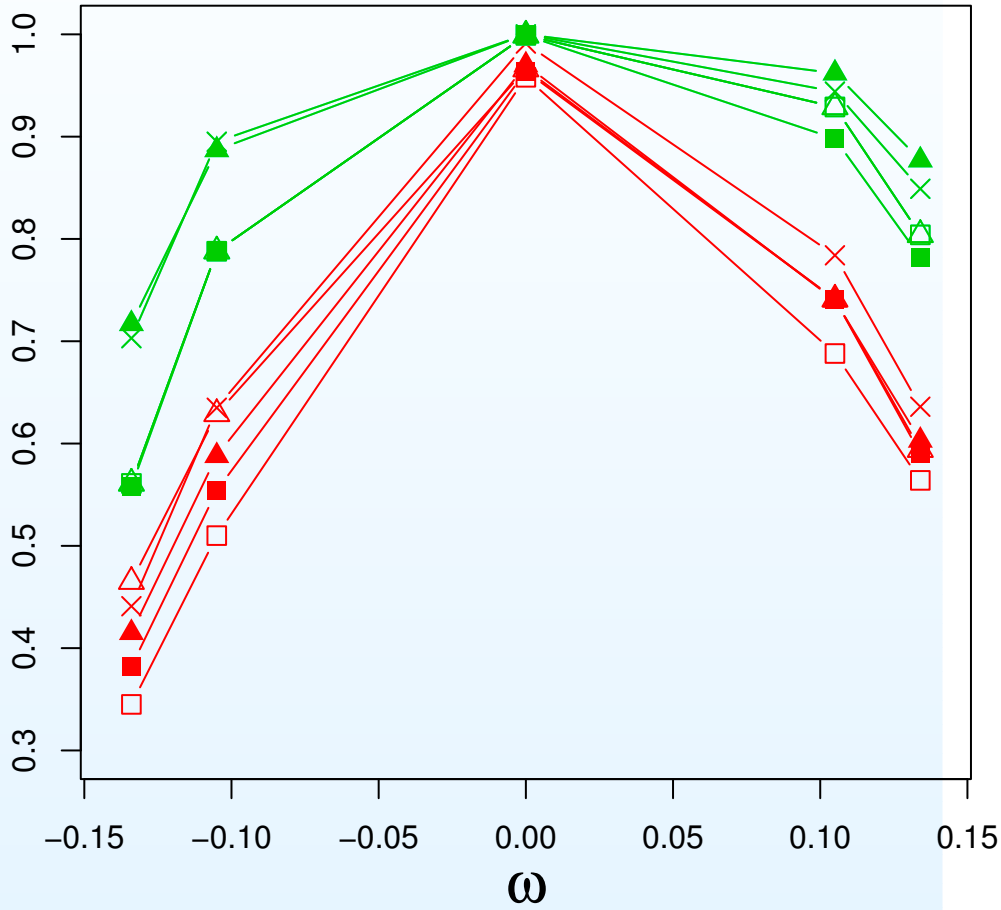

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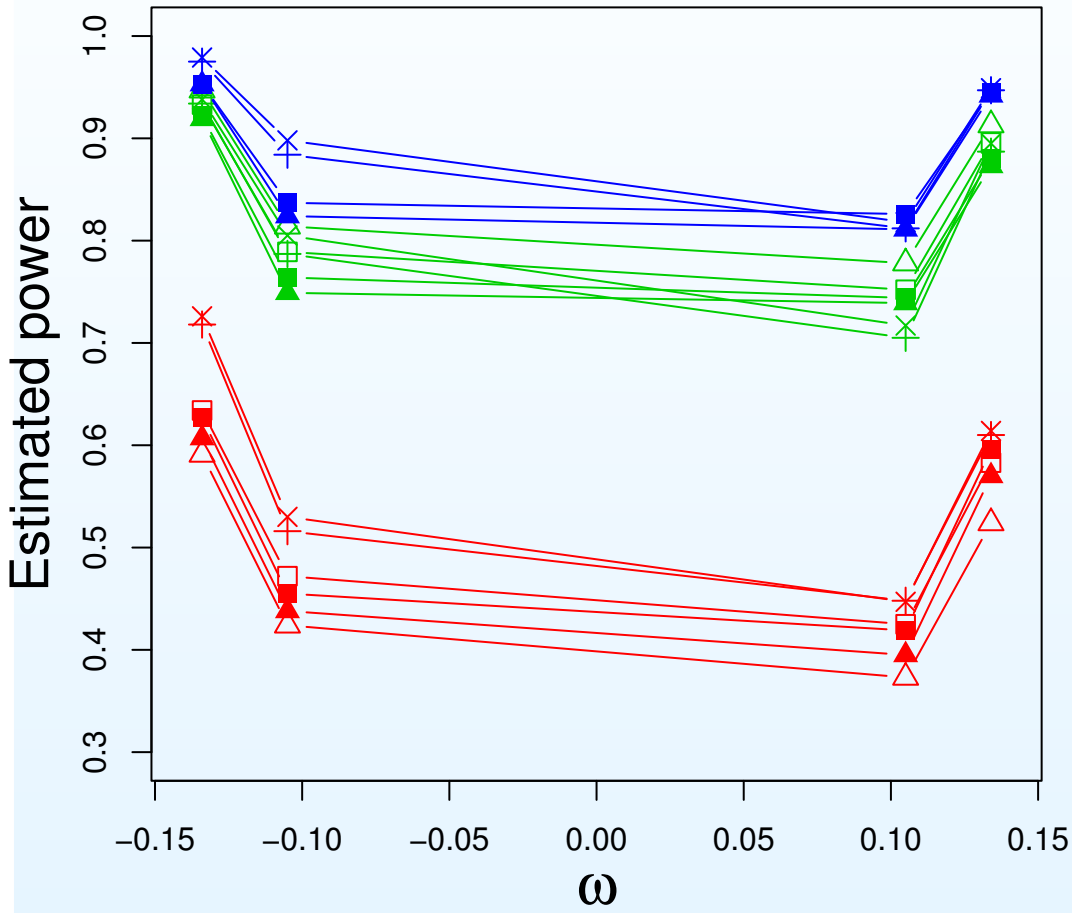

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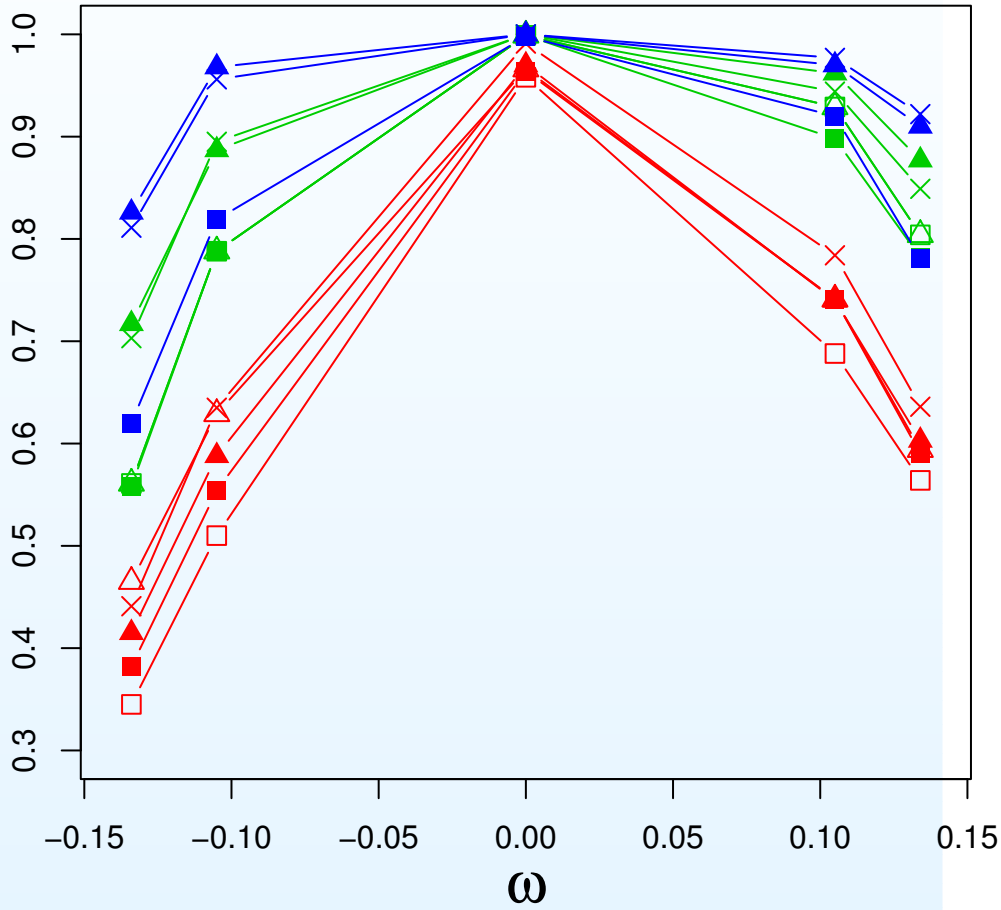

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Results (3)

- good performance of EB tests
- inflation of the type I error of global tests at finite distance
- the 2 global tests are the most powerful

→ Panhard X, Mentré F. *Evaluation by simulation of tests based on non-linear mixed-effects models in pharmacokinetic interaction and bioequivalence cross-over trials.* **Stat Med** 2005

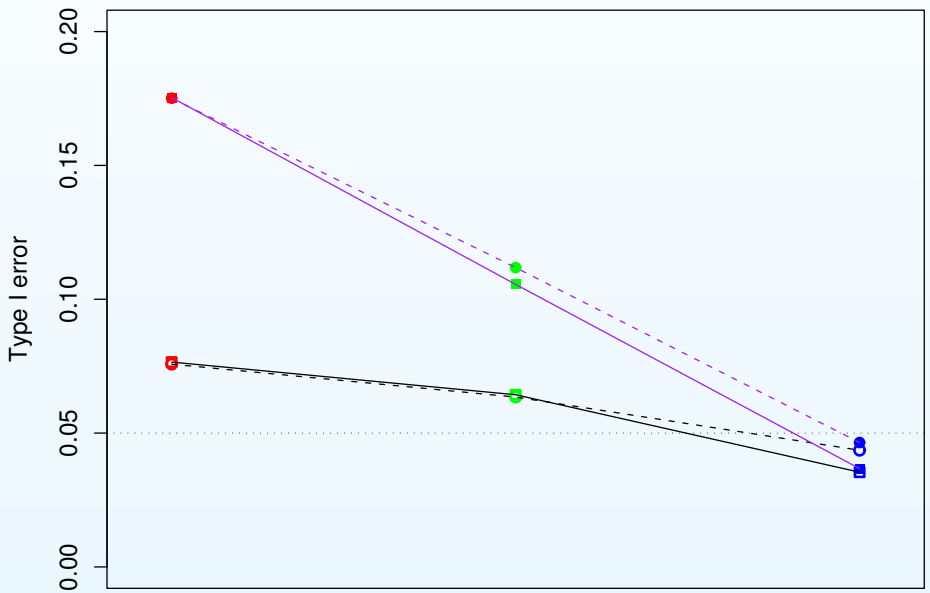
Impact of modelling IOV

- same PK model (theophylline)
- only designs with 240 samples per subject
- for each parameter, estimation of :
  - IIV
  - IOV
  - an interaction effect
- evaluation of type I error and power (only for interaction)

Results

Type I error

Comparaison



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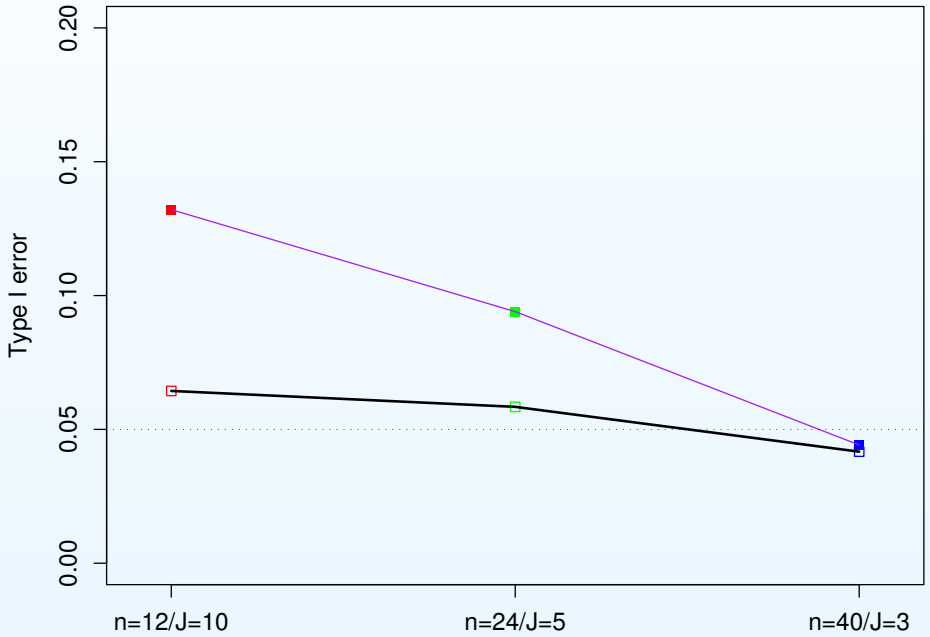


Power

- evaluated for e^{δ}=0.8, 0.9, 1.1 and 1.25
- good power for the 2 tests
- 1 to 2% inferior to that obtained without modelling IOV

Application: ANRS 107 - Puzzle II

Prospective, open, multicenter trial in HIV+ patients:

- under stable treatment for at least 1 month
- with a viral load > 10 000 copies/mL

PK substudy: 2 period cross-over in 10 patients

- from inclusion to W2 : atazanavir (ATZ)
- from W3 to W26 : ATZ + tenofovir (TFV)

Objective: evaluate the interaction of TFV on ATZ PK
Samples taken at W2 and W6: 1, 2, 3, 5, 8, and 24 h after drug intake

Population PK of atazanavir (1)

Objectives

- build the PK model, taking the 2 periods into account
- estimate IIV and IOV
- test the interaction effect of TFV on the PK parameters

PK model

- one compartment model with zero order absorption and 1^{st} order elimination
- parametrized in $log(T_a)$, $log(Cl/F)$ and $log(V/F)$
- homoscedastic variance

$$f(\theta,t) = \frac{FD}{T_a Cl}\left((1-e^{-\frac{Cl}{V}t})\mathbb{1}_{t<T_a} + \frac{e^{-\frac{Cl}{V}\tau\mathbb{1}_{t<T_a}}(1-e^{-\frac{Cl}{V}T_a})e^{-\frac{Cl}{V}(t-T_a)}}{(1-e^{-\frac{Cl}{V}\tau})}\right)$$

Resultats - population PK

	Mean	SE	IIV (%)	IOV(%)
$log(T_a)$	1.32	0.10	21.7	0
β_{T_a}	0.306	0.10	–	–
$log(AUC)$	10.7	0.17	49.2	0
β_{AUC}	-0.380	0.090	–	–
$log(V/F)$	4.01	0.20	0	53.5
$\beta_{V/F}$	0.159	0.003	–	–

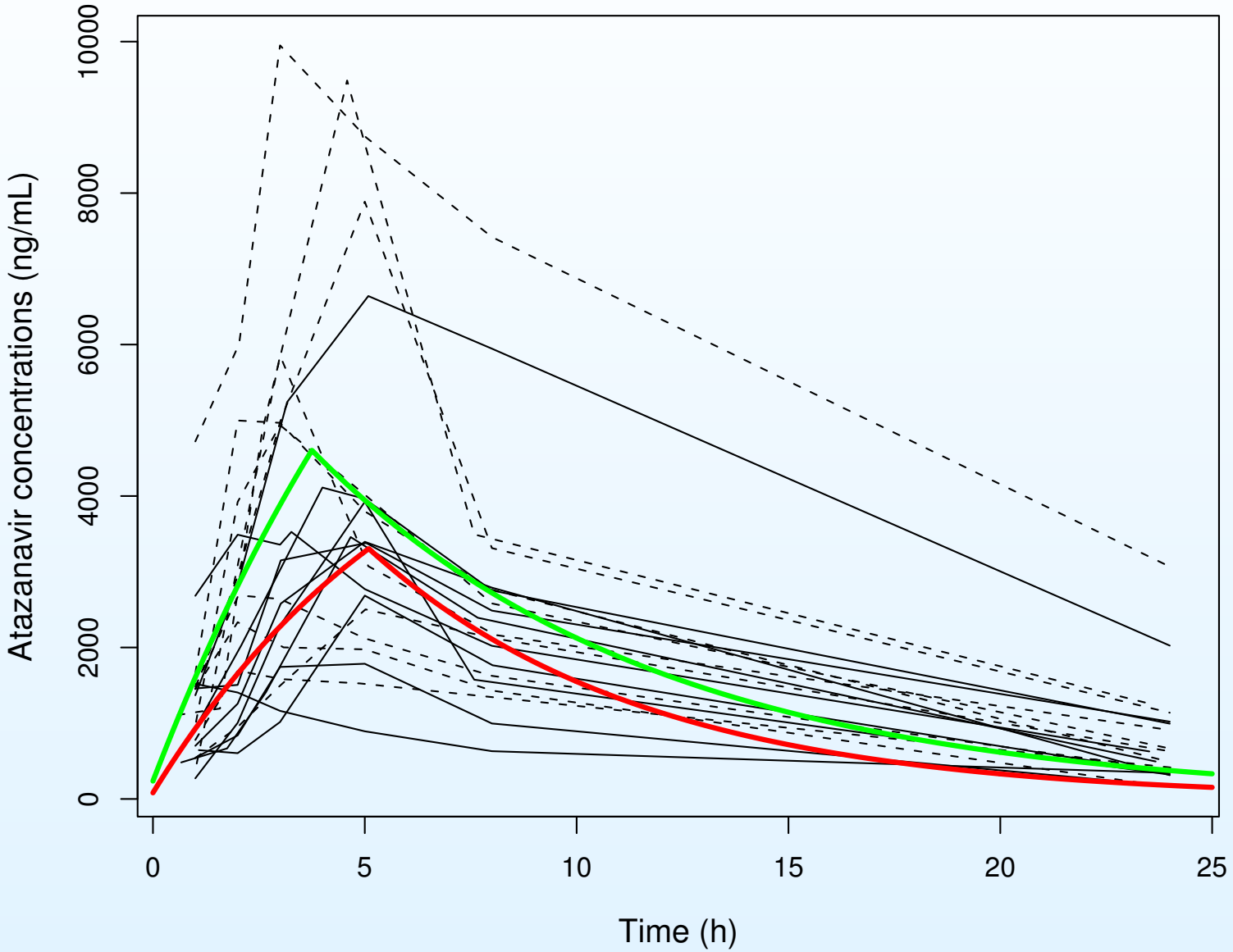
Significant interaction effect (Wald test) of TVF on:

- $log(AUC)$: p$<10^{-4}$
- $log(T_a)$: p=0.0019

Equivalence between the 2 treatment groups for:

- $log(V/F)$: 90% CI for $\beta_{V/F}$= [-0.335 ; 0.652]

Concentrations and predicted curves



Test of interaction in usual population PK analyses

Inflation of the type I error of the test of binary covariates

- already showed by several authors for comparison tests

  $\longrightarrow$ no reevaluation by simulation
- among correction methods: randomization tests
- possible extension to absence of interaction

Interaction of ZDV on the PK of NFV/M8 (1)

- Cophar I - ANRS 102 study: prospective, open, multicenter trial in HIV+ patients
  - under stable treatment for at least 4 months
  - with a viral load <200 copies/mL for at least 4 months
- Nelfinavir (NFV) and M8 concentrations obtained in 46 patients
  - first visit: before and 0.5, 1, 3 and 6h after drug intake
  - second visit: before and 3h after drug intake

→ Panhard X et al. *Population pharmacokinetic analysis for nelfinavir and its metabolite M8 in virologically controlled HIV-infected patients on HAART .* **Brit J Clin Pharmacol** in press

Simultaneous population PK of NFV/M8

- NFV: one compartment, 1st order absorption and elimination
- M8: one compartment, 1st order metabolization rate constant k_m
- identifiable parameters:
  - NFV: V/F, Cl/F and k_a
  - M8: V_m/Fk_m and Cl_m/Fk_m
- selection of random effects based on AIC:
  - IIV estimated on V/F, Cl/F and Cl_m/Fk_m
  - IOV estimated on Cl/F
- combined error model

Use of the randomization test

Significant interaction effect in the final model (LRT):

- Cl/F increased by 1.2 fold ($p_{LRT}<10^{-4}$, $p_{Wald}=0.135$)
- Cl_m/Fk_m decreased by 1.8 fold ($p_{LRT}=0.020$, $p_{Wald}=0.011$)

in the 27 patients receiving ZDV

Randomization test

- 1000 random permutations of comedication with ZDV
- pop PK analysis of the corresponding data sets
- evaluation of the significance of the interaction effect

Resulting corrected p-values

- Cl/F: $p_{LRT}=0.030$, $p_{Wald}=0.170$
- Cl_m/Fk_m: $p_{LRT}=0.052$, $p_{Wald}=0.016$

Conclusion

- tests based on NLMEM allow
  - to test PK interaction or lack of interaction
  - to greatly decrease the number of samples per patient

    $\longrightarrow$ great interest for trials performed
    - in patients, as HIV patients illustrated here
    - special populations (children, older patients)
- necessity of a correction method the type I error?
  - need of further evaluation
  - depends on the estimation method or algorithm
- next step: planification of PK interaction studies
  - estimation of the expected SE taking IOV into account using PFIM
  - estimation of the corresponding power or sample size