Optimising covariate allocation at design stage using Fisher Information Matrix for Non-Linear Mixed Effects Models in pharmacometrics

Lucie Fayette [1 2] Karl Brendel[2] France Mentré [1]

[1]Université Paris Cité and Université Sorbonne Paris Nord, Inserm, IAME, F-75018 Paris, France
[2]Pharmacometrics, Ipsen Innovation, Les Ulis, France

Pharmacometrics in France

19 septembre 2025

MOCLID iame RESEARCH CENTER ON INFECTIOUS DISEASES Inserm Université Paris Cité IPSEN

Importance of covariates in Pharmacometrics

- **Clinical phase of new drug development**

Detect individual characteristics = **covariates**, likely to **explain inter-individual variability**

1. FDA (2022) *Guidance for Industry Population Pharmacokinetics*
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- **Ratio of change** in the value of the parameter, for given values of the covariate and relative to a reference value
  - **Clinically relevant** : 90% confidence interval (CI) outside equivalence interval [2]
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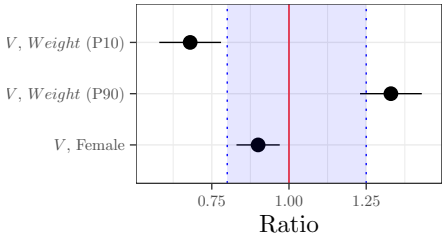

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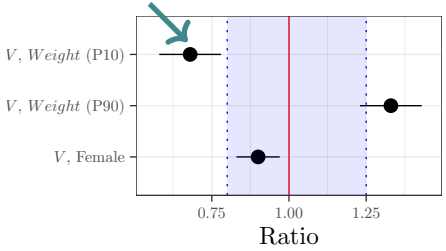

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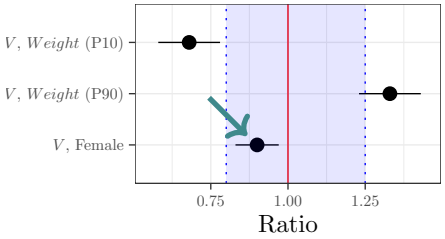

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- **Design optimisation :** Before data collection $\rightarrow$maximise informativeness of data to be collected
  - FDA [1] highlights use of Clinical Trial Simulations (CTS) and optimal design

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- **Optimal design theory in NLMEM**
  - Based on Fisher Information Matrix (FIM) [3] [4] , no analytical solution
  - For continuous responses :
    - First-order linearisation around mean of random effects $\rightarrow$Gaussian approximation with analytical FIM [5]
      $\rightarrow$Implemented in various software tools [6]

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      →Implemented in various software tools [6]

- Covariates ? →Literature lacks comprehensive treatment of the influence covariate distributions
  - Considering covariates allows quantifying impact on
    - CI of ratios • Statistical power • Number of subjects needed (NSN) for desired power
  - Tools handle only fixed covariate values →Discrete combinatorial explosion
    →impractical for continuous covariates
  - Considering covariates as random variables introduce another integral

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Previous work[7] - Design evaluation with covariates

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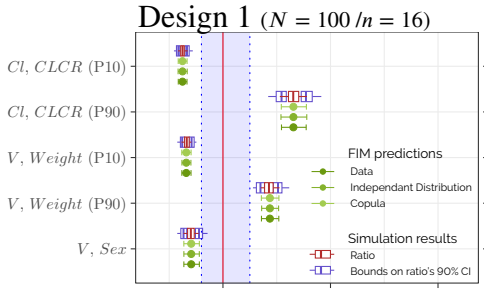

- Design evaluation accounting for covariate distribution : Discrete, continuous + correlations
- FIM with **Monte Carlo integration** over covariate distribution
- Validated via simulation study + application to Cabozantinib PK
- Predict uncertainty, power of test and NSN
- Applied to optimise sampling in missing data imputation study [8]

7. Fayette *et al.* (2025) *Journal of Pharmacokinetics and Pharmacodynamics*
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Objectives

Support pharmacometrics design of future clinical trials

- Compute optimal covariate distribution
- Define NSN to demonstrate relevance (or non-relevance) of important covariate relationships with desired power
- Develop a faster integration over covariate distribution in FIM computation

Overview

Non-Linear Mixed Effect Models

The j^{th} observation y_{ij} for the i^{th} subject :

$$y_{ij} = f(\xi_i, \theta_i) + g(\xi_i, \theta_i, \sigma)\varepsilon_{ij}$$

- f, structural non-linear model
- ξ_i, elementary design
- Individual parameters : $\theta_i = u\left(\mu, \beta, Z_i, \eta_i\right)$
  - μ, typical values
  - β, covariate effects
  - Z_i, covariate vector
  - $\eta_i \sim \mathcal{N}(0, \Omega)$ individual random effects
- Residual error
  - g, depending on ξ_i, θ_i + some parameters σ
  - random variable $\varepsilon_i \sim \mathcal{N}\left(0, I_{n_i}\right)$
- $\Psi = \{\mu, \beta, \lambda, \Omega, \sigma\}$, P-vector of population parameters

FIM definition with covariates

- Given ❍ an elementary design ξ_i ❍ a population parameter vector Ψ ❍ a covariate realisation z_i

$$M_F(\xi_i, \Psi, z_i) = \mathbb{E}\left(\frac{\partial \log l(y_i; \xi_i, \Psi, z_i)}{\partial \Psi} \frac{\partial \log l(y_i; \xi_i, \Psi, z_i)}{\partial \Psi^T}\right)$$

where $l(y_i; \xi_i, \Psi, z_i) = \int p(y_i \mid \eta_i; \Psi, z_i, \xi_i) p(\eta_i; \Psi, z_i) d\eta_i$

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- Given ❍ a population design $\Xi = \{N, (\xi_1, \ldots, \xi_N)\}$ with N subjects ❍ a distribution p_Z for covariates

$$M_F(\Xi, \Psi, p_Z) = \sum_{i=1}^{N} M_F(\xi_i, \Psi, p_Z) \quad \text{where} \quad M_F(\xi_i, \Psi, p_Z) = \int M_F(\xi_i, \Psi, z) p_Z(z) dz$$

Computing $M_F(\xi_i, \Psi, p_{Cont})$: Copula + Gauss-Legendre Quadrature

- p_Z characterisation :
  - D discrete covariates, each with $Q_\delta,\ \delta = 1, \dots, D$ categories
    $\rightarrow Z_{Dis,i} \sim$ distribution with $n^{(QD)} = \prod_{\delta=1}^{D} Q_\delta$ values : $z_{Dis,d}$ with probability $p_{Dis,d},\ d = 1, \dots, n^{(QD)}$
  - $\forall\ z_{Dis,d}$, we denote $p_{Cont|z_{Dis,d}}$ the distribution of $Z_{Cont,i}$ conditionally to $z_{Dis,d}$

$$M_F(\xi_i, \Psi, p_Z) = \sum_{d=1}^{n^{(QD)}} p_{Dis,d}\ M_F(\xi_i, \Psi, z_{Dis,d},\ p_{Cont|z_{Dis,d}})$$

- Distribution $p_{Cont|z_{Dis,d}}$ $\rightarrow$Continuous covariate modelling with **copula** [7] [9]
  - Rosenblatt transform [10] : $T_{Cont|z_{Dis,d}}(Z_{Cont}) \sim \mathcal{U}\left([0;1]^C\right)$

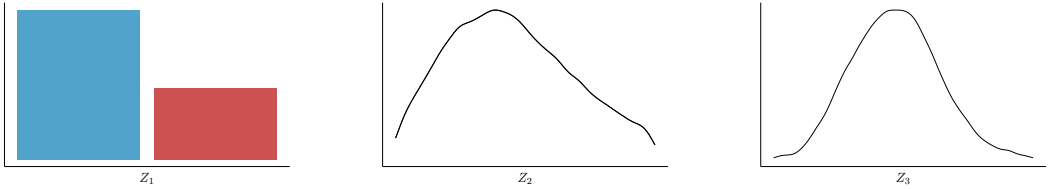
$$M_F\left(\xi_i, \Psi, z_{Dis,d}, p_{Cont|z_{Dis,d}}\right) = \int_{[0;1]^C} M_F\left(\xi_i, \Psi, z_{Dis,d},\ T^{-1}_{Cont|z_{Dis,d}}(u_1, \dots, u_C)\right) du_1 \dots du_C$$

- **Gauss–Legendre Quadrature** (GLQ) [11] with $n^{(Q)}$ nodes

$$M_F\left(\xi_i, \Psi, z_{Dis,d}, p_{Cont|z_{Dis,d}}\right) \approx \sum_{q_1=1}^{n^{(Q)}} \cdots \sum_{q_C=1}^{n^{(Q)}} w_{q_1} \dots w_{q_C} M_F\left(\xi, \Psi, z_{Dis,d},\ T^{-1}_{Cont|z_{Dis,d}}(v_{q_1}, \dots, v_{q_C})\right)$$

7. Fayette et al. (2025) *Journal of Pharmacokinetics and Pharmacodynamics*
9. Zwep et al. (2024) *Clinical Pharmacology & Therapeutics*
10. Rosenblatt (1952) *The Annals of Mathematical Statistics*
11. Golub & Welsch (1969) *Mathematics of Computation*

Covariate distribution optimisation



- Discrete covariates $\rightarrow$Optimise the proportion of each category

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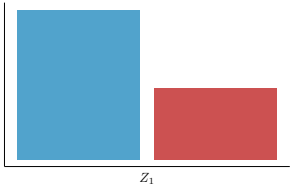
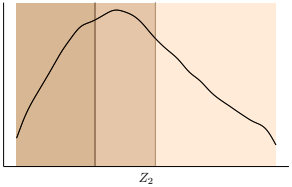
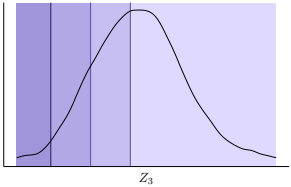
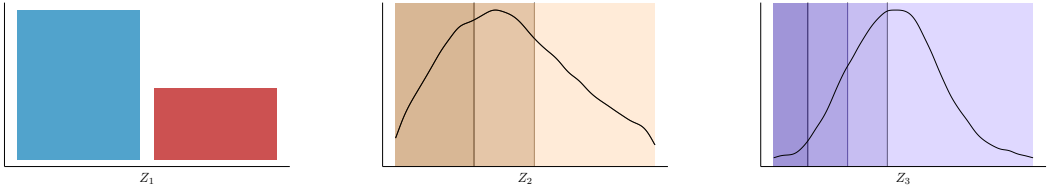






- Discrete covariates $\rightarrow$Optimise the proportion of each category
- Continuous covariates $\rightarrow$Segment their domains into intervals, chosen for their clinical meaning $\rightarrow$Optimise proportion of each interval in the trial population
  - Preserves the continuous nature of covariates in the FIM computation
  - Discrete segmentation $\rightarrow$Reduces dimensionality + Facilitates subject inclusion in clinical setting

Covariate distribution optimisation



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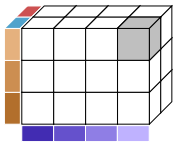

- Combining categories × intervals →L **possible distributions for covariate vector** Z

$$M_F(\xi_i, \Psi, p_Z(\boldsymbol{x})) = \sum_{l=1}^{L} x_l \; M_F\left(\xi_i, \Psi, p_{Z,l}\right)$$

where $\boldsymbol{x} = (x_l)_{l=1,\dots,L}$ the vector of proportions of subjects in the trial population associated with covariate distributions $p_{Z,l}$

Optimisation with Projected Gradient Descent Algorithm (PGD)

- D-criterion $\phi_D(\Xi, \Psi, p_Z(\boldsymbol{x})) = \left(det\left(M_F\left(\Xi, \Psi, p_Z(\boldsymbol{x})\right)\right)\right)^{1/P}$ with P the size of Ψ
- Constraints $\rightarrow \mathcal{Q}$ the constraint space
  - $\boldsymbol{x}$: vector of proportions : • $\forall l, \quad x_l \in [0;\ 1]$ • $\sum x_l = 1$
  - Bound constraints

12. Fayette *et al.* (2023) *The AAPS Journal*
13. PFIM : CRAN package version 6.1

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$$\boldsymbol{x}_{k+1} = \mathcal{P}_{\mathcal{Q}}\left(\boldsymbol{x}_k + \alpha_k \nabla \phi_D\left(\Xi, \Psi, p_Z(\boldsymbol{x}_k)\right)\right)$$

with $\alpha_k \in [0; \infty]$ gradient step-size at the k^{th} iteration, $\nabla \phi_D$ gradient of ϕ_D with respect to $\boldsymbol{x}$ [12] , $\mathcal{P}_{\mathcal{Q}}$ projection on $\mathcal{Q}$

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- Predicted SE : $SE(\Xi, \Psi, p_Z(\boldsymbol{x}))_\beta$
  - Derive the required $SE^\star$ to reach a given power in relevance/non-relevance tests
  - Deduce NSN_R and NSN_{NR} $\quad NSN(\Xi, \Psi, p_Z(\boldsymbol{x}))_\beta = N\left(\frac{SE(\Xi, \Psi, p_Z(\boldsymbol{x}))_\beta}{SE^\star}\right)^2$

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- Implementation in R using an extension of PFIM6.1. [13]

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Overview

PK model with continuous covariate defining Renal function

- 1 compartment - IV bolus - linear elimination : $f(\xi_i = (t_i, Dose_i), \theta_i) = \frac{Dose_i}{V_i} e^{-\frac{Cl_i}{V_i} t_i}$
- Combined error : $y = f + (a + bf)$
- Covariate effects : $\log \theta_i = \log \theta_{pop} + \beta_{\theta,Z} Z_i + \eta_{\theta,i}$
  - SEX and $\log\left(\frac{BMI_i}{BMI_{pop}}\right)$ on V
  - $\log\left(\frac{CLCR_i}{CLCR_{pop}}\right)$ on Cl

Table 1 – Population PK parameter values

Parameter	μ_{Cl} (L/h)	μ_V (L)	ω_{Cl}	ω_V	a (mg/L)	b	$\beta_{V,Sex}$	$\beta_{V,BMI}$	$\beta_{Cl,CLCR}$
Value	0.43	7.13	0.24	0.30	2.39	0.08	-0.35	0.50	0.27

- Design
  - 250 mg of drug at time 0
  - 3 samples : 1, 4 and 12 hours post-dose

Covariate effects

Table 2 – Continuous segmentation

Condition on covariate	Interval Name
$18.5 \leq BMI < 25\ kg/m^2$	Healthy Weight
$25 \leq BMI < 30\ kg/m^2$	Overweight
$BMI \geq 30\ kg/m^2$	Obesity
$CLCR \geq 90\ mL/min$	Normal RF
$60 \leq CLCR < 90\ mL/min$	Mild RF
$30 \leq CLCR < 60\ mL/min$	Moderate RF
$CLCR < 30\ mL/min$	Severe RF

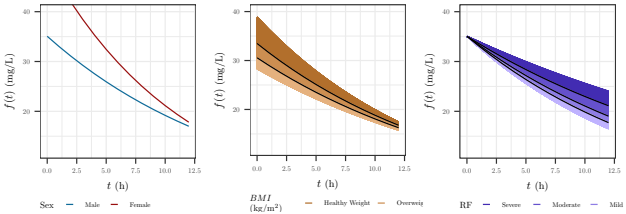

Fig. 1 – Concentration evolution according to the fixed effects and univariate covariate effects

Table 3 – Ratio values

$r_{V,\text{ Female}}$	$r_{V,\text{ Obesity}}$	$r_{Cl,\text{ Severe RF}}$
0.70	**1.14**	**0.70**

- Reference interval $[0.80;\ 1.25]$

Initial covariate distribution and optimisation

- Initial covariate distribution : NHANES [14] - 2009 to 2020 $\rightarrow$29 409 covariate vectors
  - Age between 18 and 80 years old
  - Body Mass Index (BMI) $\geq$ 18.5 kg/m^2
  - No missing data

Table 4 – Covariate data summary from the NHANES database

Continuous covariates

Covariate	mean (sd)	median [min ; max]
BMI (kg/m2)	29.5 (7.0)	28.2 [18.5 ; 92.3]
$CLCR$ (ml/min)	99.0 (35.6)	97.3 [4.1 ; 342.9]

Discrete covariates

Covariate	Category Name	%
SEX	Male	48.8
	Female	51.2

Continuous segmentation

Condition on covariate	Interval Name	%
$18.5 \leq BMI < 25\ kg/m^2$	Healthy Weight	27.9
$25 \leq BMI < 30\ kg/m^2$	Overweight	32.7
$BMI \geq 30\ kg/m^2$	Obesity	39.3
$CLCR \geq 90\ mL/min$	Normal RF	58.4
$60 \leq CLCR < 90\ mL/min$	Mild RF	28.3
$30 \leq CLCR < 60\ mL/min$	Moderate RF	12.0
$CLCR < 30\ mL/min$	Severe RF	**1.2**

14. https://wwwn.cdc.gov/nchs/nhanes/default.aspx

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$25 \leq BMI < 30\ kg/m^2$	Overweight	32.7
$BMI \geq 30\ kg/m^2$	Obesity	39.3
$CLCR \geq 90\ mL/min$	Normal RF	58.4
$60 \leq CLCR < 90\ mL/min$	Mild RF	28.3
$30 \leq CLCR < 60\ mL/min$	Moderate RF	12.0
$CLCR < 30\ mL/min$	Severe RF	**1.2**

- Few Severe RF →combination SEX only →$L = 20$
- **2 constraints settings :**
  - Without Constraint : proportion requirements : within [0, 1] and sum to 1
  - With constraints :
    - Each continuous interval should represent at least 5%
    - Severe RF not more than 10%

14. https://wwwn.cdc.gov/nchs/nhanes/default.aspx

Overview

Copula fit diagnostic for combinations including Severe RF

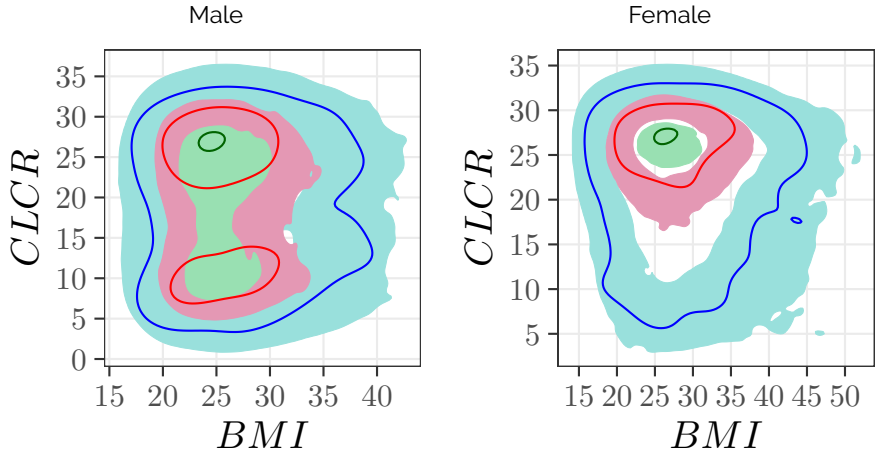

Fig. 2 – Visual predictive checks based on the contours of the bivariate density : 99% prediction intervals of percentile contours compared to the contours observed in the NHANES database.

Percentile contours : 5^{th} : , 50^{th} : , 95^{th} : ,

Optimal distributions

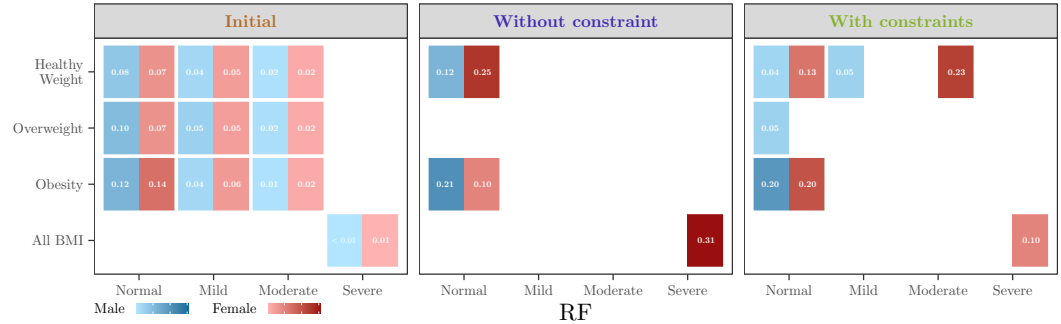

Fig. 3 – Renal case study - Optimal proportions for the covariate distributions for the D-criterion for the different sets of constraints

Optimal NSN

Table 5 – Renal case study - Number of subjects needed (NSN) to reach 80% power in relevance or non-relevance tests, with the initial and optimal covariate distributions for the D-criterion for the different sets of constraints

	Initial Distribution	Optimal Distributions Without constraint	Optimal Distributions With constraints
$NSN_R\big(V$, Female $\big)$	167	**197**	196
$NSN_{NR}\big(V$, Obesity$\big)$	143	118	107
$NSN_R\big(Cl$, Severe RF$\big)$	**602**	143	**230**

$\rightarrow NSN$ **decreased by more than 60%**

Optimal NSN as a function of covariate effect

- **Sensitivity analysis**
  - Influence of IIV : 'Normal IIV' scenario + 'High IIV' scenario, in which ω_{Cl} and ω_V were doubled
  - Influence of covariate effect : varying $\beta_{Cl,CLCR}$, resulting in $r_{Cl,\text{ Severe RF}}$ ranging from 0.40 to 0.75

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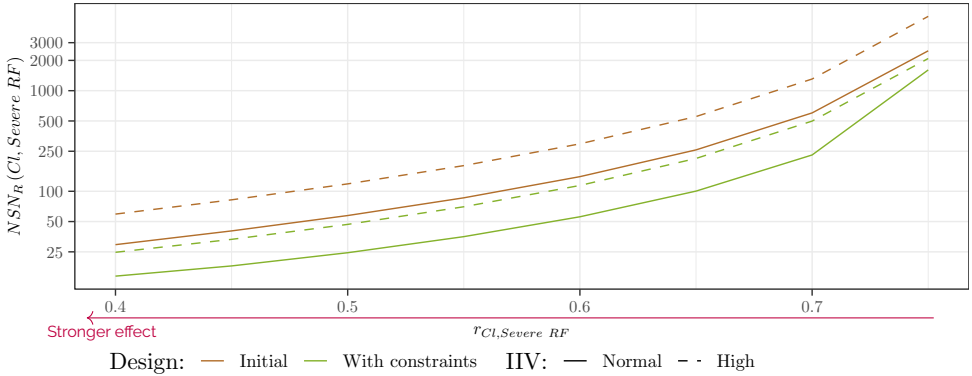

Fig. 4 – Renal case study - $NSN_R\big(Cl, CLCR\ (\text{Severe RF})\big)$ to reach 80% power in relevance test for the two IIV scenarios and as a function of $r_{Cl,\text{ Severe RF}}$ from 0.40 to 0.75

Conclusion

- New way of integrating the FIM over the covariate distribution : copula modelling + GLQ
  →Faster than Monte Carlo
- Before a study, given a model, a design and a prior covariate distribution :
  1. Compute expected power for relevance test on important covariate effects
  2. Compute NSN to reach desired confidence level
  3. Optimise covariate distribution to reduce NSN

15. Riviere *et al.* (2016) *Biostatistics*
16. Nguyen & Mentré (2014) *Computational Statistics & Data Analysis*
17. Ueckert & Mentré (2017) *Computational Statistics & Data Analysis*
18. Dodds *et al.* (2005) *Journal of Pharmacokinetics and Pharmacodynamics*
19. Foo *et al.* (2012) *Journal of Biopharmaceutical Statistics*
20. Loingeville *et al.* (2020) *Journal of Biopharmaceutical Statistics*
21. Seurat *et al.* (2020) *Statistical Methods in Medical Research*
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12. Fayette *et al.* (2023) *The AAPS Journal*
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- Joint optimisation of covariates + elementary designs

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- Full FIM computation [15] [16] [17] →Extension to non-continuous responses

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- Manuscript in revision in *Computational Statistics and Data Analysis*
  - Preprint : `https://www.medrxiv.org/content/medrxiv/early/2025/02/02/2025.01.31.25321452.full.pdf`
  - Code : `https://doi.org/10.5281/zenodo.14778034`

15. Riviere *et al.* (2016) *Biostatistics*
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Back Up

Computing FIM with covariates

- p_Z characterisation :
  - D discrete covariates, each with $Q_\delta,\ \delta = 1, \dots, D$ categories
    $\rightarrow Z_{Dis,i} \sim$ distribution with $n^{(QD)} = \prod_{\delta=1}^{D} Q_\delta$ values : $z_{Dis,d}$ with probability $p_{Dis,d},\ d = 1, \dots, n^{(QD)}$
  - $\forall\ z_{Dis,d}$, we denote $p_{Cont|z_{Dis,d}}$ the distribution of $Z_{Cont,i}$ conditionally to $z_{Dis,d}$

$$M_F(\xi_i, \Psi, p_Z) = \sum_{d=1}^{n^{(QD)}} p_{Dis,d}\, M_F(\xi_i, \Psi, z_{Dis,d},\ p_{Cont|z_{Dis,d}})$$

- Distribution $p_{Cont|z_{Dis,d}}$ $\rightarrow$Continuous covariate modelling with copula
  - Rosenblatt transform [10] : $T_{Cont|z_{Dis,d}}(Z_{Cont}) \sim \mathcal{U}\left([0;1]^C\right)$

$$M_F\left(\xi_i, \Psi, z_{Dis,d}, p_{Cont|z_{Dis,d}}\right) = \int_{[0;1]^C} M_F\left(\xi_i, \Psi, z_{Dis,d},\ T^{-1}_{Cont|z_{Dis,d}}(u_1, \dots, u_C)\right) du_1 \dots du_C$$

- Gauss–Legendre Quadrature (GLQ) [11] with $n^{(Q)}$ nodes

$$M_F\left(\xi_i, \Psi, z_{Dis,d}, p_{Cont|z_{Dis,d}}\right) \approx \sum_{q_1=1}^{n^{(Q)}} \cdots \sum_{q_C=1}^{n^{(Q)}} w_{q_1} \dots w_{q_C} M_F\left(\xi, \Psi, z_{Dis,d},\ T^{-1}_{Cont|z_{Dis,d}}(v_{q_1}, \dots, v_{q_C})\right)$$

10. Rosenblatt (1952) *The Annals of Mathematical Statistics*
11. Golub & Welsch (1969) *Mathematics of Computation*

Ratios for the evaluation of covariate relationships

- Significance test : are covariate effects different from 0 ? →Expected power from FIM [24] [7]
- Relevance and non-relevance test : assess the magnitude of an effect

- Ratio of change in primary parameters when covariate values change relative to a reference value
  →Uncertainty derived from the SE on the covariate effect + power of tests[7]
  - Clinically relevant : if the 90% CI is completely outside an equivalence interval $[R_{inf}\ ; R_{sup}]$
  - Clinically non-relevant if entirely within
- For a log-normally distributed parameter with an additive covariate relationship on the log scale
  - If the covariate is binary : $r_{l,c} = e^{\beta_{l,c}}$
  - If continuous : $r_{l,c(PX)} = e^{\beta_{l,c}(PX-P50)}$ for given percentile PX, with $P50$ median of covariate distribution
- Influence of belonging to an interval subset involving several covariates
  Ratio : expected value of the ratio function, conditional on the associated covariate sub-vector following the mixture distribution corresponding to the interval subset of interest :

$$r_{\theta,\mathcal{L}^R} = \frac{1}{\sum_{l' \in \mathcal{L}^R} x_{l'}} \sum_{l \in \mathcal{L}^R} x_l \int r(\beta, z) p_{Z,l}(z) dz$$ where $\mathcal{L}^R$ the subset of covariate distributions defined over the interval subset

→Uncertainty estimated using the Delta Method + tests based on the resulting Gaussian approximation

24. Retout *et al.* (2007) *Statistics in Medicine*
7. Fayette *et al.* (2025) *Journal of Pharmacokinetics and Pharmacodynamics*

- **Copula fitting**
  - Vine copula fitted using the R package *rvinecopulib*0.6.3.1.1 [25]
  - Fit evaluation : simulation-based strategy [26] using 100 replicates + Diagnostics plots with *pmxcopula* [27]
- **Quadrature settings**
  - Number of nodes : start with $n^{(Q)} = 1$, stop if $\Delta_D(n^{(Q)}) = 100 \left(\phi_D^{(n^{(Q)})} - \phi_D^{(n^{(Q)}-1)}\right) / \phi_D^{(n^{(Q)}-1)} \leq 0.5\%$
  - Monte Carlo : target $\bar{\phi}_D$: average $\phi_D \left(n^{(MC)} = 500\right)$ across 10 repetitions - $RE\left(\phi_D\right) = 100 \left(\phi_D - \bar{\phi}_D\right) / \bar{\phi}_D$
- **Optimised distributions evaluation**
  - Initial distribution : observed proportions in the selected subset of the NHANES database
  - For each optimised distribution :
    - D-efficiency relative to the initial distribution
    - NSN to achieve 80% power in relevance/non-relevance test
- **Implementation in R** `https://doi.org/10.5281/zenodo.14778033`
  - Extension of the package *PFIM*6.1 [13] based on previous work [7]
  - Quadrature nodes computed using the function *gauss.quad()* from the package *statmod* [28]
  - Projection on the constraint spac using the function *lsei()* from the package *limSolve* [29]
  - Roots for NSN found using the R function *uniroot()* from the package *stats*[30]

25. Nagler & Vatter (2021) *R package version 0.5*
26. Guo *et al.* (2024) *Journal of Pharmacokinetics and Pharmacodynamics*
27. Guo *et al.* (2024) *PAGE*
13. PFIM : CRAN package version 6.1
7. Fayette *et al.* (2025) *Journal of Pharmacokinetics and Pharmacodynamics*
28. Giner & Smyth (2016) *R Journal*
29. R package 1.5.1
30. ISBN 3-900051-07-0

N covariate combinations

Table 6 – RF - N covariate combinations

SEX	BMI interval	Renal Status	N (%)
Male	Healthy Weight	Normal	2 290 (7.8)
		Mild	1 105 (3.8)
		Moderate	454 (1.5)
	Overweight	Normal	3 047 (10.4)
		Mild	1 616 (5.5)
		Moderate	635 (2.2)
	Obesity	Normal	3 575 (12.2)
		Mild	1099 (3.7)
		Moderate	377 (1.3)
	-	Severe	142 (0.5)
Female	Healthy Weight	Normal	2 122 (7.2)
		Mild	1 459 (5)
		Moderate	665 (2.3)
	Overweight	Normal	2 112 (7.2)
		Mild	1 389 (4.7)
		Moderate	705 (2.4)
	Obesity	Normal	4041 (13.7)
		Mild	1 659 (5.6)
		Moderate	700 (2.4)
	-	Severe	217 (0.7)

Table 7 – HF - N covariate combinations

SEX	BMI interval	HepaticStatus	N (%)
Male	Healthy Weight	Normal	3041 (10.3)
		Mild1	331 (1.1)
		Mild2	411 (1.4)
	Overweight	Normal	4218 (14.3)
		Mild1	552 (1.9)
		Mild2	477 (1.6)
	Obesity	Normal	3980 (13.5)
		Mild1	682 (2.3)
		Mild2	366 (1.2)
	-	ModerateSevere	282 (1)
Female	Healthy Weight	Normal	3804 (12.9)
		Mild1	244 (0.8)
		Mild2	217 (0.7)
	Overweight	Normal	3859 (13.1)
		Mild1	275 (0.9)
		Mild2	134 (0.5)
	Obesity	Normal	5812 (19.8)
		Mild1	513 (1.7)
		Mild2	134 (0.5)
	-	ModerateSevere	77 (0.3)

Copula fitting - RF - Combination with Severe RF

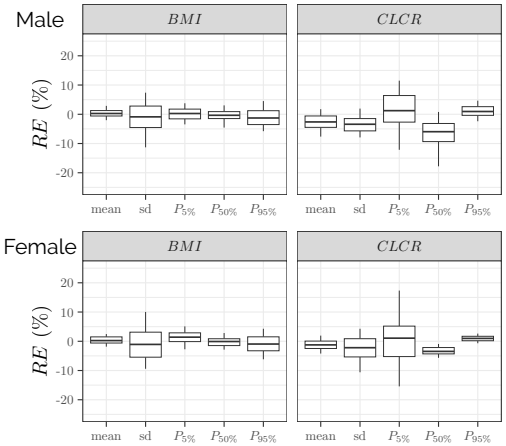

Fig. 5 – Boxplot of the relative error (RE) of marginal distributions summary statistics, compared to the NHANES database.

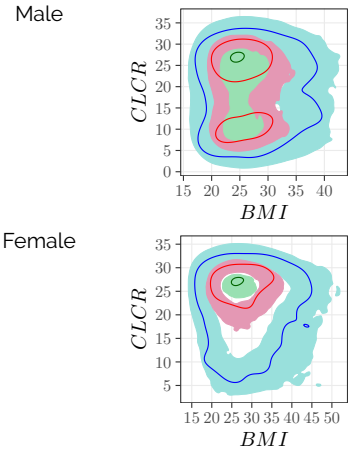

Fig. 6 – Visual predictive checks based on the contours of the bivariate density : 99% prediction intervals of percentile contours compared to the contours observed in the NHANES database.

FIM integration using GLQ vs Monte Carlo

- GLQ : start with $n^{(Q)} = 1$ and stop if $\Delta_D(n^{(Q)}) = 100\ \frac{\phi_D^{(n^{(Q)})} - \phi_D^{(n^{(Q)}-1)}}{\phi_D^{(n^{(Q)}-1)}} \leq 0.5\%$
- Monte Carlo : target $\bar{\phi}_D$: average ϕ_D $\left(n^{(MC)} = 500\right)$ across 10 repetitions - $RE\left(\phi_D\right) = 100\ \frac{\phi_D - \bar{\phi}_D}{\bar{\phi}_D}$

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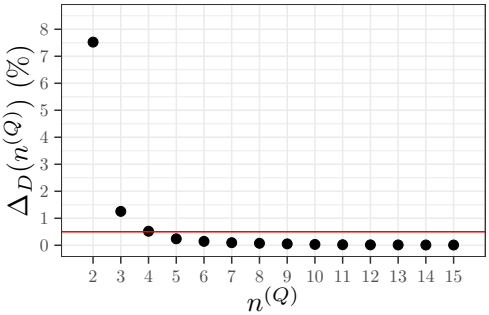


Fig. 7 – GLQ : $\Delta_D(n^{(Q)})$ function of $n^{(Q)}$
— : 0.5%

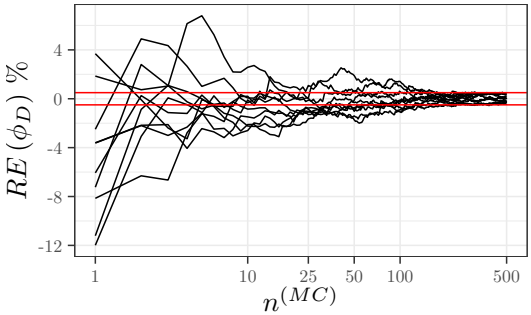


Fig. 8 – Monte Carlo : $RE\left(\phi_D\right)$ function of $n^{(MC)}$, 10 chains — : $\pm 0.5\%$

- GLQ with $n^{(Q)} = 5 \rightarrow$25 FIM evaluations vs for Monte Carlo, $RE\left(\phi_D\right)$ not controlled for $n^{(MC)} = 25$

HF example

- $\log\left(\frac{(BILI/ULN)_i}{(BILI/ULN)_{pop}}\right)$ and $\log\left(\frac{(AST/ULN)_i}{(AST/ULN)_{pop}}\right)$ on Cl
- $\beta_{Cl,BILI/ULN} = 0.05$ and $\beta_{Cl,AST/ULN} = -0.38$
- $r_{Cl,\text{ ModerateSevere HF}} = 0.97$

Continuous segmentation

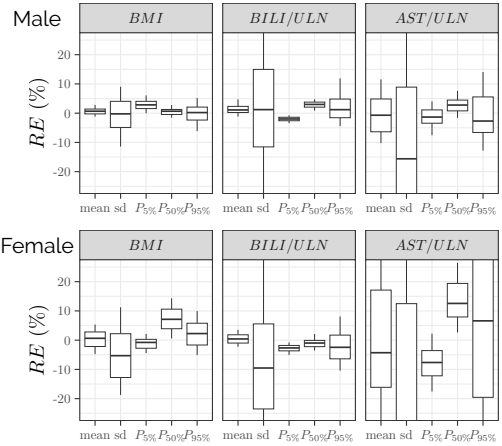
Condition on covariate	Interval Name	%
$BILI/ULN \leq 1$ and $AST/ULN \leq 1$	Normal HF	84
$BILI/ULN \leq 1$ and $AST/ULN >$	Mild1 HF	28.8
$1 < BILI/ULN \leq 1.5$	Mild2 HF	5.9
$1.5 < BILI/ULN \leq 3$	Moderate HF	1.2
$3 < BILI/ULN$	Severe HF	**0**

Table 8 – Hepatic case study - D-criterion, D-Efficiency and Number of subjects needed (NSN) to reach 80% power in relevance or non-relevance tests, with the initial and optimal covariate distributions for the D-criterion for the different sets of constraints

	Initial Distribution	Optimal Distributions Without constraint	Optimal Distributions With constraints
D-criterion	240.1	304.0	294.4
D-Efficiency	1.00	1.27	1.23
$NSN_R\,(V, SEX)$	167	**217**	**216**
$NSN_{NR}\,(V,$ Obesity)	140	105	108
$NSN_{NR}\,(Cl,$ ModerateSevere HF)	**400**	148	141

in bold : the higher NSN across the three covariate relationships, for respectively the significance tests and the (non-)relevance tests, for each design.

Copula fitting - HF - Combination with ModerateSevere HF



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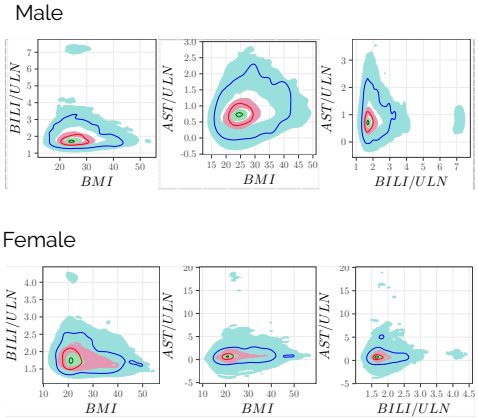

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GLQ vs Monte Carlo - HF

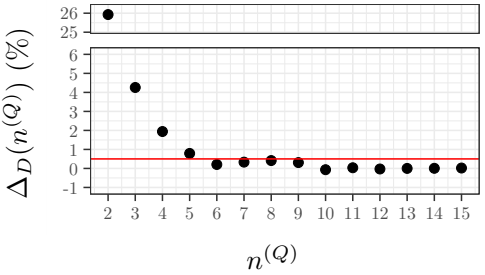

Fig. 11 – $\Delta_D(n^{(Q)})$ function of $n^{(Q)}$ — : 0.5%

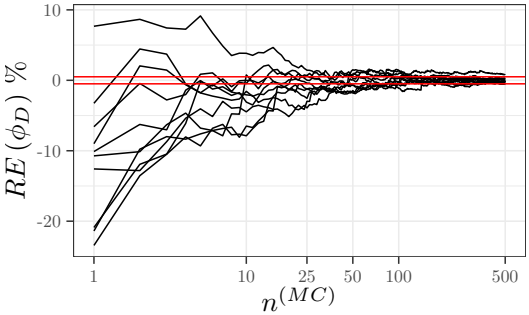

Fig. 12 – $RE(\phi_D)$ function of $n^{(MC)}$, 10 chains — : $\pm 0.5\%$

- GLQ with $n^{(Q)} = 6 \rightarrow$216 FIM evaluations vs $RE(\phi_D)$ not controlled for $n^{(MC)} = 216$

Optimal distributions - HF

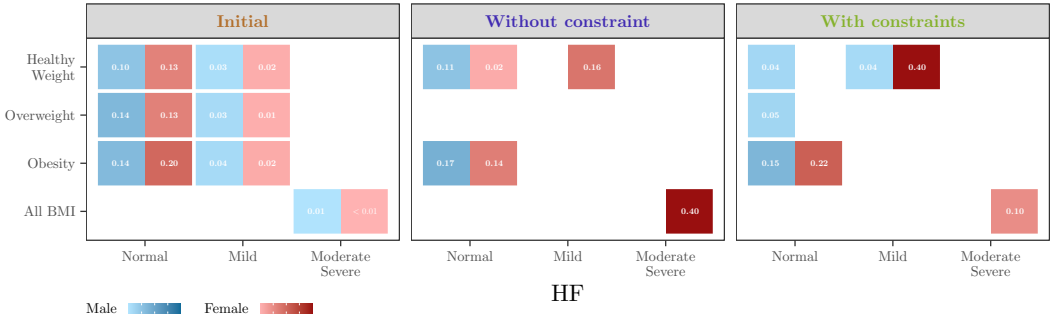

Fig. 13 – Hepatic case study - Optimal proportions for the covariate distributions for the D-criterion for the different sets of constraints

Optimal NSN - HF

Table 9 – Hepatic case study - D-criterion, D-Efficiency and Number of subjects needed (NSN) to reach 80% power in relevance or non-relevance tests, with the initial and optimal covariate distributions for the D-criterion for the different sets of constraints

	Initial Distribution	Optimal Distributions	
		Without constraint	With constraints
D-criterion	240.1	304.0	294.4
D-Efficiency	1.00	1.27	1.23
$NSN_R\,(V, SEX)$	167	**217**	**216**
$NSN_{NR}\,(V,$ Obesity)	140	105	108
$NSN_{NR}\,(Cl,$ ModerateSevere HF)	**400**	148	141

in bold : the higher NSN across the three covariate relationships, for respectively the significance tests and the (non-)relevance tests, for each design.