Optimal sampling times for pharmacokinetic modelling of a cocktail of phenotyping drugs

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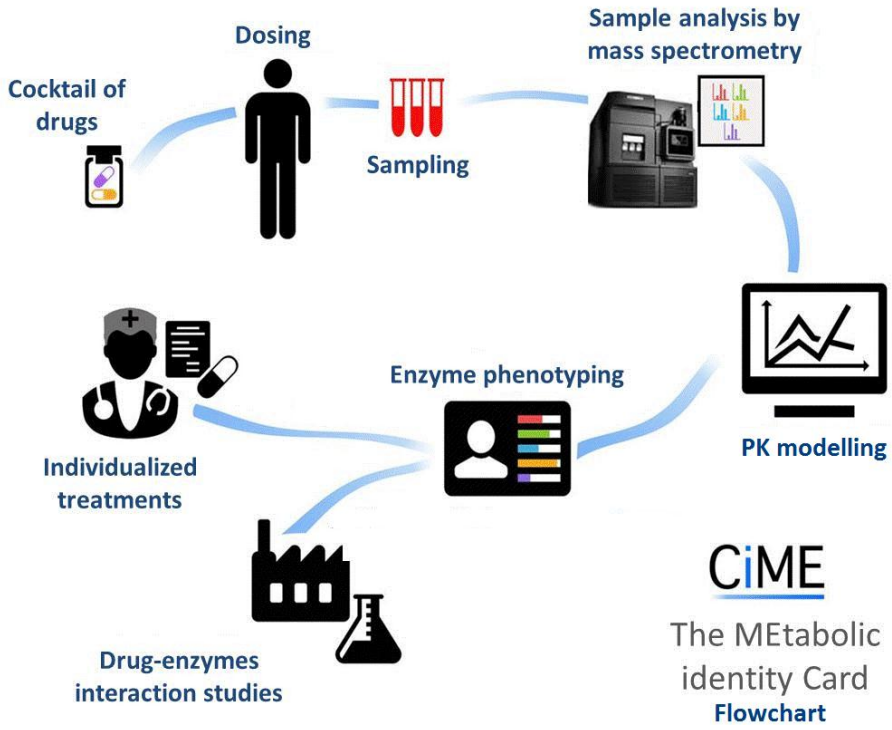
Background

Cocktails of phenotyping drugs are of high interest to determine activity of enzymes responsible for drug metabolism and pharmacokinetics (PK) [1]

- **CIME (MEtabolic Identity Card) cocktail:** developed by CEA [2]

PARENT		METABOLITE
Caffeine	CYP1A2	Paraxanthine
Tolbutamide	CYP1A2	4-OH-Tolbutamide
Omeprazole	CYP2C19	5-OH-Omeprazole
Midazolam	CYP3A4	1-OH-Midazolam
Dextromethorphan	CYP2D6	Dextrorphan
Digoxin	P-glycoprotein	

...



- **Pilot phase 1 study CIME1**: showing the safety of the cocktail [3]

[1] Fuhr et al. *Clin. Pharmacol. Ther.*, 2007.
[2] Videau et al. *Rapid Commun. Mass Spectrom.*, 2010.
[3] Lenuzza et al. *Eur. J .Drug Metab. Ph.*, in revision.

Background

Phenotyping indexes (PI) for assessment of metabolizer status

- AUC of substrates or ratio AUC substrate/AUC metabolite [1]
- derived from a few samples using nonlinear mixed effect models (NLMEM) and maximum *a posteriori* (MAP) estimation of individual parameters [2]

Importance of choice of design on precision of parameters

- Inspection of covariates
- Identification of sub-populations requiring dose adjustment
- Treatment individualisation

[1] EMA. *Guideline on the Investigation of Drug Interactions*, 2012.
[2] Smith and Vincent. *Clin. Pharmacol. Ther.*, 2010.

Background

Approach for design evaluation and optimisation:

based on the Fisher information matrix (FIM) in NLMEM

- design for estimation of population parameters -> population FIM (M_{PF}) [1], implemented in several design tools [2]
- design for MAP estimation of individual parameters -> Bayesian FIM (M_{BF}) [3], recently implemented in PFIM 4.0 [4]

[1] Mentré et al. *Biometrika,* 1997.
[2] Nyberg et al. *Br. J. Clin. Pharmacol.*, 2014.
[3] Combes et al. *Pharm. Res.,* 2012.
[4] www.pfim.biostat.fr

Objectives

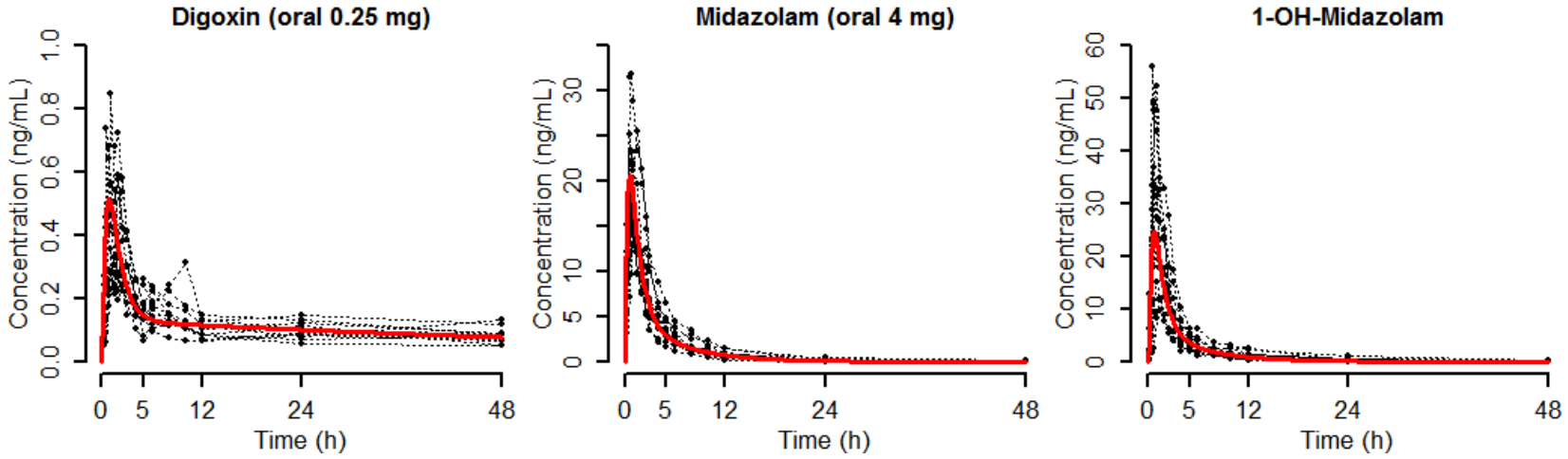
To design a phenotyping study with two molecules of the CIME cocktail

- Digoxin (probe for P-glycoprotein)
- Midazolam and its metabolite 1-OH-midazolam (probe for CYP3A activity)

1. **To propose and evaluate by simulation an optimal compound design for both molecules (based on results of CIME1 study)**
2. **To study the influence of weights on the optimal compound design**
3. **To optimise sampling windows for more flexibility in experiments**

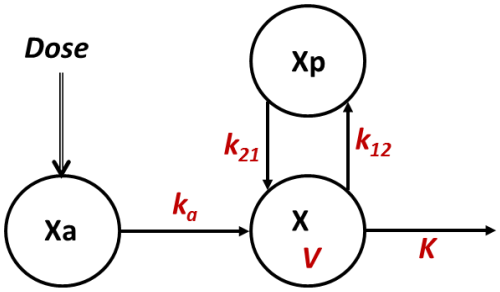
CIME1 study

Data: 10 healthy volunteers, rich PK profiles with 18 samples/subject

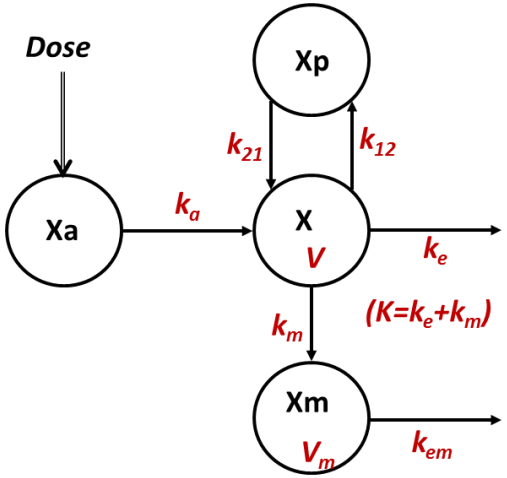


Structural models

Digoxin:



Midazolam:



Phenotyping indexes

Digoxin: AUC

Midazolam: Ratio AUC parent/metabolite

Optimal compound design - Methods

Notation

- Identical elementary design $\xi = (t_1, \ldots, t_n)$ in all subjects
- Population parameters Ψ_m of each molecule m ($m=1,\ldots,M$)

D-optimality

- D-criterion $\Phi^D = \det(\mathrm{M}_{PF}(\Psi_m, \xi))^{1/P_m}$

where P_m = length(Ψ_m)

Compound D-optimality

$$\xi^{CD} = Arg\max_{\xi} \sum_{m=1}^{M} \alpha_m \log(\det(\mathrm{M}_{PF}(\Psi_m, \xi))^{1/P_m}) \quad [1]$$

where α_m is the weight for each molecule m

- **Implementation in R based on PFIM 4.0** [2]
- **Application to design a phenotyping study with 2 molecules**
  - 40 subjects, sparse design of n = 6 samples/subject ≤ 48h
  - $P_{Digoxin} = 9$ & $P_{Midazolam} = 16$, $\alpha_{Digoxin} = 1/3$ & $\alpha_{Midazolam} = 2/3$

[1] Atkinson. *J. Stat. Plan. Inference*, 2008.

[2] www.pfim.biostat.fr

Optimal compound design - Methods

Evaluation by clinical trial simulation (CTS)

- **Simulation**
  - 200 datasets of 40 subjects for each molecule with the optimal compound ξ^{CD}
  - Analysis by MONOLIX 4.2.2 [1,2]

- **Comparison**

	Simulation (CTS)	Prediction (PRED)
Population parameters	$RSE_{P\text{-}CTS}$ = SD of population estimates	$RSE_{P-PRED} = \sqrt{diag(M_{PF}^{-1})}$
Individual parameters estimated by MAP	$RSE_{I\text{-}CTS}$ given by MONOLIX	$RSE_{I-PRED} = \sqrt{diag(M_{BF}^{-1})}$
Derived phenotyping indexes	RSE derived by Delta-method [3]	

[1] Kuhn and Lavielle. *Comput. Stat. Data Anal.,* 2005.
[2] www.lixoft.eu
[3] Oehlert., *Am. Stat*., 1992.

Optimal compound design - Results

Molecule	0.25	0.75	1	1.5	2	2.5	4	5	6	10	12	24	48
Digoxin	X			X	X		X			X			X
Midazolam	X	X	X			X			X		X		
Compound design	X		X			X		X			X		X

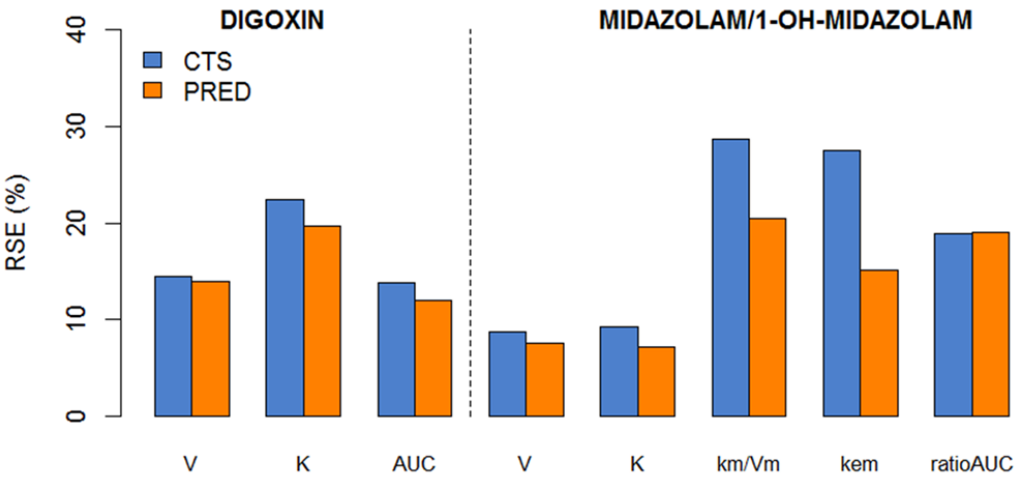
- ξ^{CD} = **(0.25, 1, 2.5, 5, 12, 48h)** instead of 11 samples if optimising separately

- Little loss of efficiency compared to the separately optimised designs: Efficiency(ξ^{CD}) = **96%** for Digoxin and **91%** for Midazolam

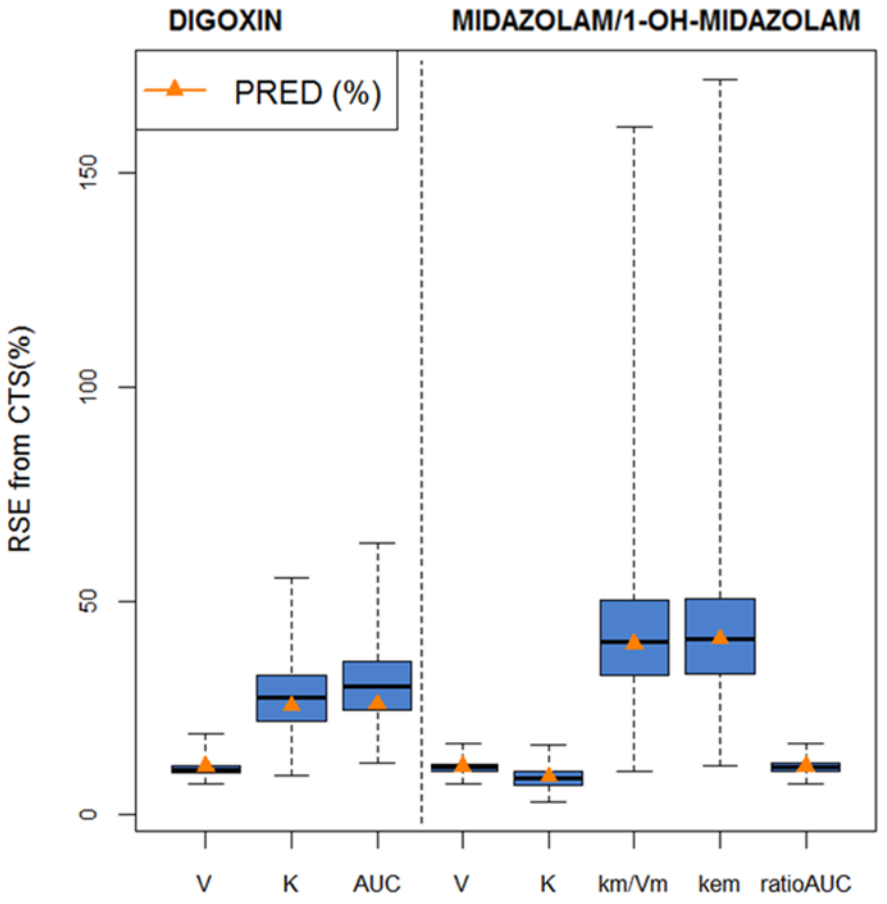
Optimal compound design - Results

- Reasonable RSE for derived phenotyping indexes: close results between CTS and FIM predictions

Population parameters



Individual parameters estimated by MAP



Evaluation of weight influence on compound design – Methods

Compound D-optimal design

$$\xi^{CD} = Arg \max_{\xi} \sum_{m=1}^{M} \alpha_m \log(\det(\mathrm{M}_{PF}(\Psi_m, \xi))^{1/P_m})$$

where P_m = length(Ψ_m)

Multi-response D-optimal design

$$\xi^{MR} = Arg \max_{\xi} \prod_{m=1}^{M} \det(\mathrm{M}_{PF}(\Psi_m, \xi))^{1/P} = Arg \max_{\xi} \sum_{m=1}^{M} \log(\det(\mathrm{M}_{PF}(\Psi_m, \xi))^{1/P})$$

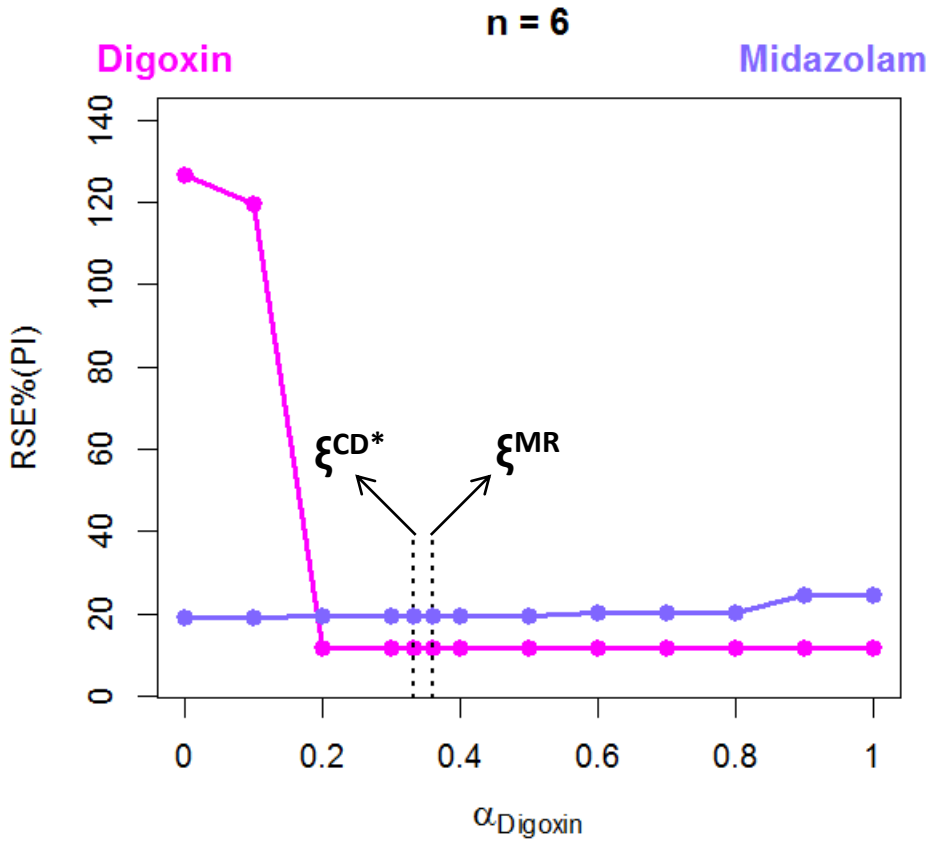
where $P = \Sigma_m$ length(Ψ_m)

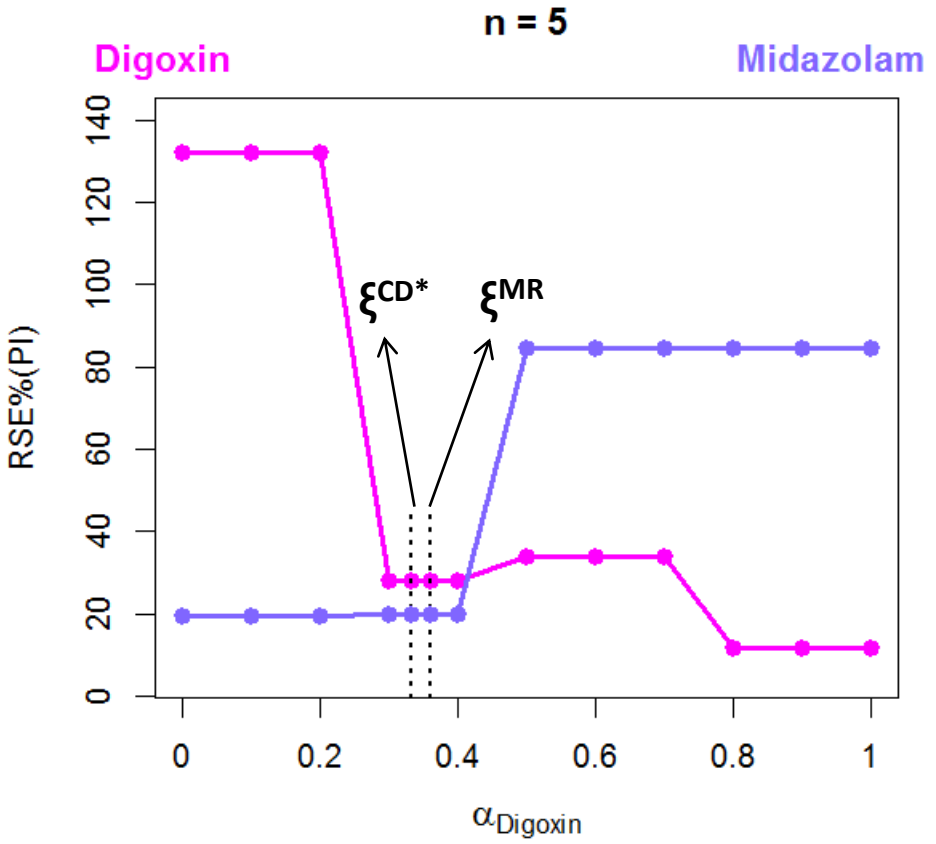
$\Rightarrow$ **$\xi^{CD} = \xi^{MR}$ for $\alpha_m = P_m/P$**

Evaluation for different values of $\alpha_{Digoxin}$ from 0 to 1

- RSE (AUC Digoxin) and RSE (ratio AUC Midazolam/metabolite)
- For 40 subjects, sparse design of n = 6 or 5 samples/subject ≤ 48h

Evaluation of weight influence on compound design – Results





ξ^{CD*}: $\alpha_{Digoxin} = 1/3 \approx 0.33$

ξ^{MR}: $\alpha_{Digoxin} = 9/25 \approx 0.36$

Sampling windows - Methods

Step 1: For each molecule, determine the windows ξ^{W1} around ξ^{CD} by recursive random sampling [1]

- Required efficiency for each design ξ^{w} composed of a window and remaining fixed samples

$$Eff(\xi^{w}) = \frac{\det(M_{PF}(\Psi, \xi^{w}))^{1/P}}{\det(M_{PF}(\Psi, \xi^{CD}))^{1/P}} \geq Eff_0 = 90\%$$

Step 2: Evaluate by Monte-Carlo simulation & adjust the joint windows ξ^{W1} [2]

- Check if 90% of the 100 randomly simulated designs have joint efficiency ≥ Eff_0; If not, reduce the length of all windows simultaneously by a certain %

$\Rightarrow$ **Final windows ξ^{W} = intersection of population window designs of 2 molecules**

[1] Foo et al. *Pharm. Stat.*, 2012.

[2] Ogungbenro and Aarons. *J. Biopharm. Stat.*, 2009.

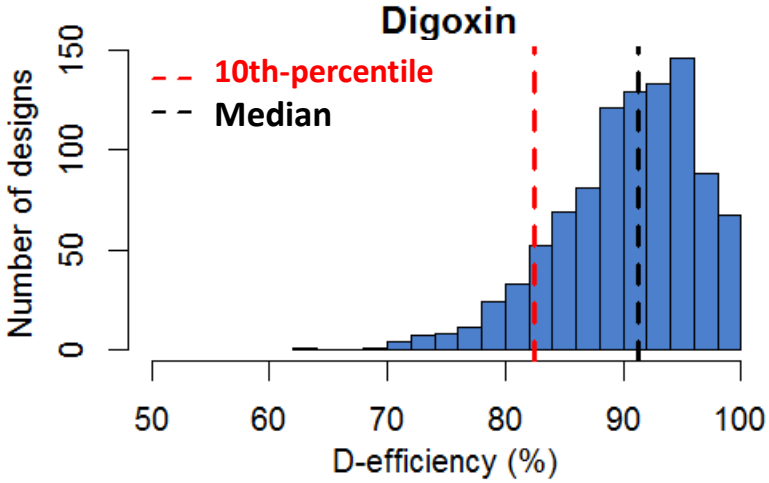
Sampling windows - Methods

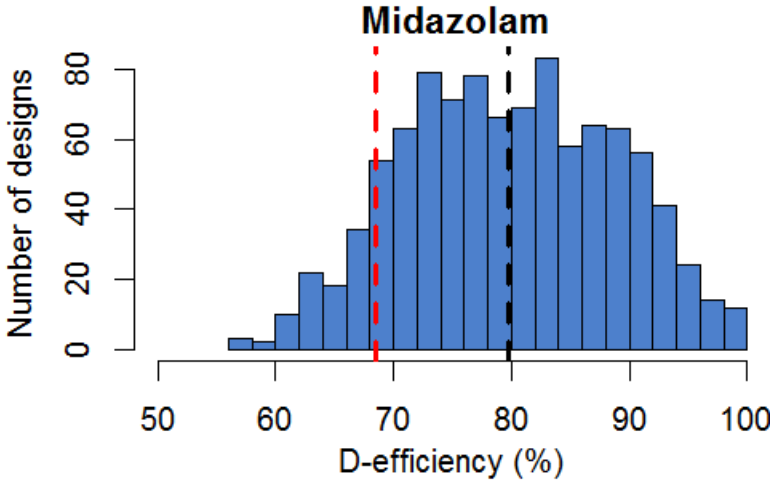
Evaluation of the performance of ξ^W for MAP estimation

- Simulation of 1000 individual designs within ξ^W and 1000 respective datasets for each molecule
- Comparison of individual RSE by CTS vs predictions by FIM

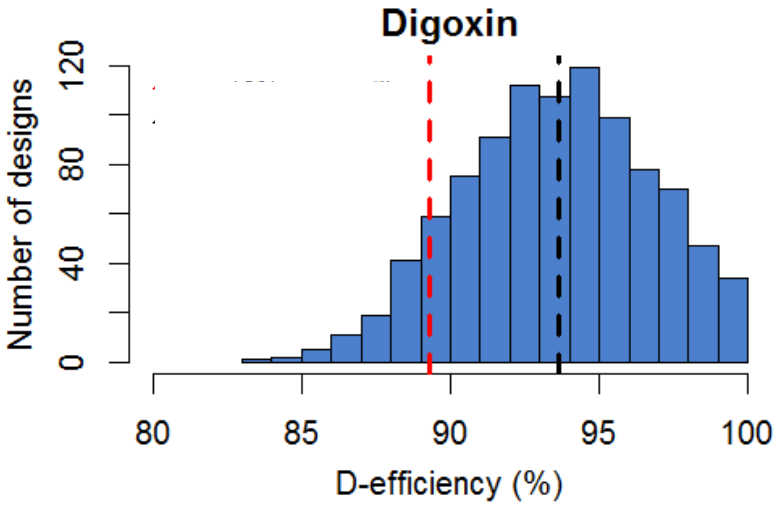
Sampling windows - Results

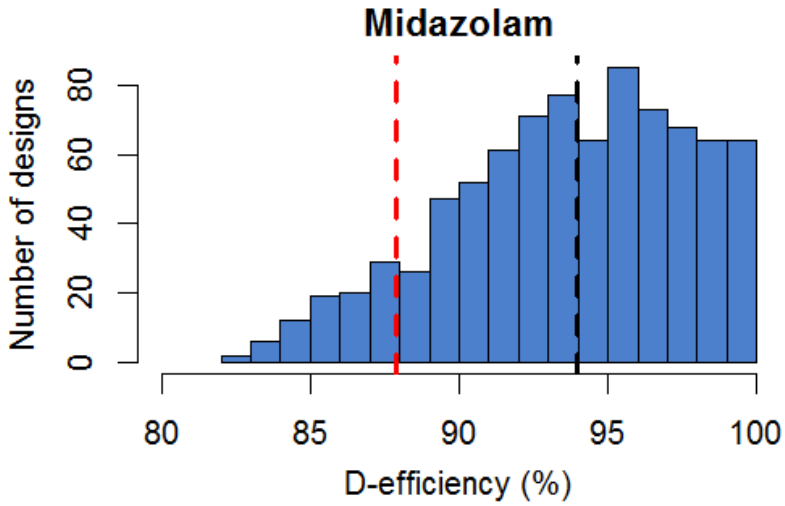
After Step 1: ξ^{W1} = {[0.17,0.47],[0.87,2.01],[2.24,4.38],[4.25,10.43],[9.02,39.54],[39.71,48]}





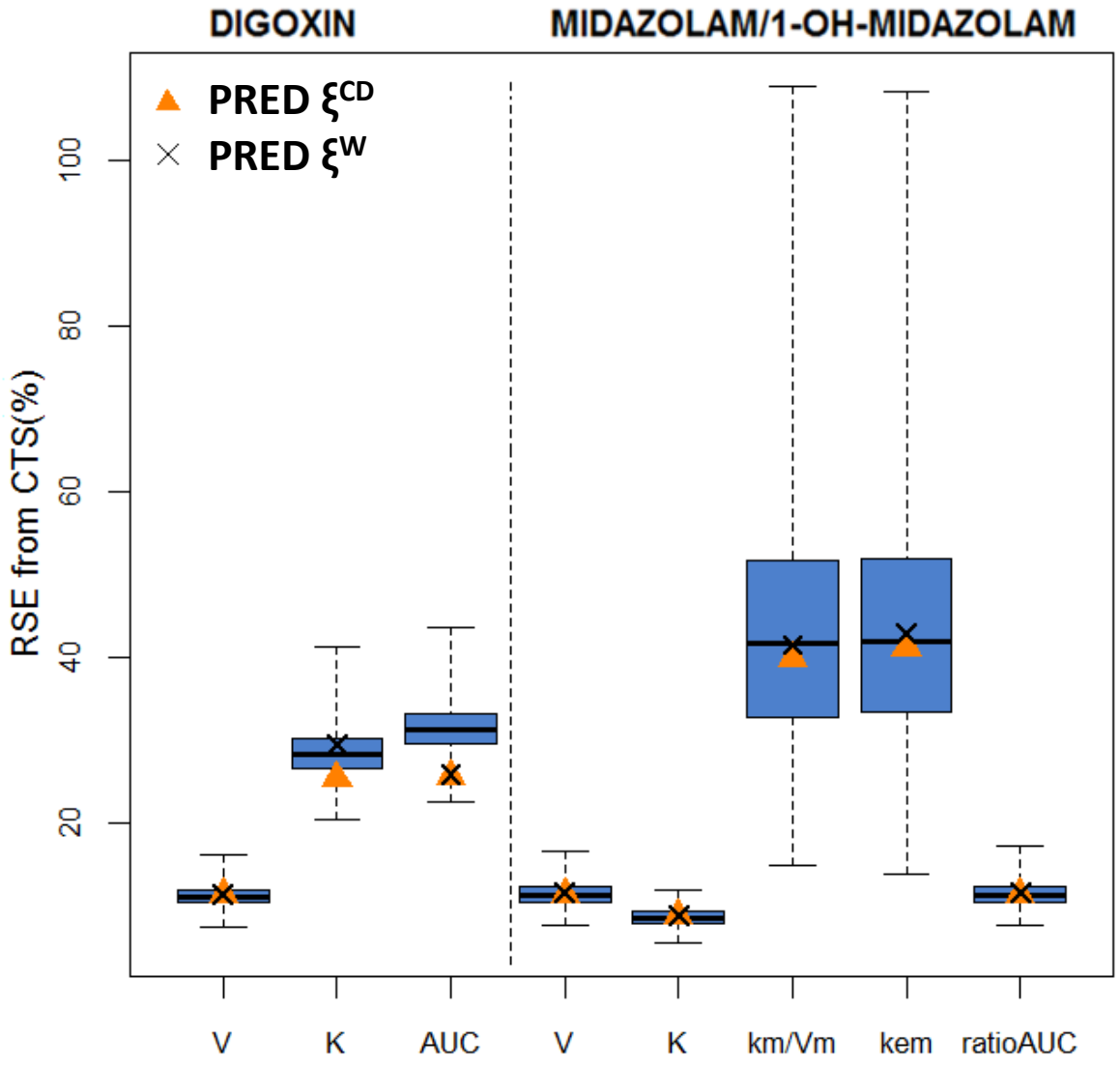
After Step 2: ξ^{W} = {[0.19,0.40],[0.92,1.48],[2.38,3.38],[4.51,7.94],[9.93,27.04],[43.21,48]}





Sampling windows - Results

Evaluation by CTS for MAP estimation of individual parameters



Discussion

Summary

- By combining NLMEM, compound design and sampling windows based on FIM, we were able to determine sparse samples allowing correct estimation of parameters for both molecules
- This approach will be extended to efficiently design studies with full CIME cocktail including more drugs [1,2]
  - Requiring a priori knowledge of models & parameters => sensitivity analyses

Prospects

- Development of an optimality criterion combining population and Bayesian FIM
- Robust design for MAP estimation of individual parameters

[1] Lenuzza et al. *Eur. J .Drug Metab. Ph.*, in revision.
[2] Videau et al. *Rapid Commun. Mass Spectrom.*, 2010.

Thank you for your attention !

BACK-UP Sampling windows

Methods

- **Input**
  - The compound optimal design
  - Required efficacy of the windows compared to the discrete optimal times

$$Eff(\xi^{\omega}) = \frac{\det(M_{PF}(\Psi, \xi^{\omega}))^{1/P}}{\det(M_{PF}(\Psi, \xi^{D}))^{1/P}} \geq Eff_0 = 90\%$$

- **Step 1: Determine windows around each optimal time by recursive random sampling** [1]
  - Number of iterations K=100
  - Initialisation $(t^{(0)}{}_1, \ldots, t^{(0)}{}_n) = (t^{D}{}_1, \ldots, t^{D}{}_n)$
  - For each iteration from 1 to K, for each sampling *j* from 1 to *n*: determine $a_j^{(iter)}$ and $b_j^{(iter)}$ around $t_j^{(iter-1)}$ such as for all times T in $[a_j^{(iter)}, b_j^{(iter)}]$, the required efficacy is satisfied for $\xi^{(iter)} = (t^{(iter)}{}_1, \ldots, t^{(iter)}{}_{j-1}, T, t^{(iter-1)}{}_{j+1}, \ldots, t^{(iter-1)}{}_n)$
  - Randomly generate $t_j^{(iter)}$ from *Unif*$[a_j^{(iter)}, b_j^{(iter)}]$

⇒ **Sampling windows ξ^{W1} obtained from the mean of the K lower & upper bounds**

[9] Foo et al. *Pharm. Stat.*, 2012.

BACK-UP Sampling windows

- **Step 2: Evaluate/adjust the joint windows ξ^{W1}**
  - Simulation of H=100 individual designs ξ_h within ξ^{W1}
  - Joint efficacy $Eff(\xi^W) = \frac{\det(M_{PF}(\Psi, \xi^W))^{1/P}}{\det(M_{PF}(\Psi, \xi^D))^{1/P}}$ where $FIM(\xi^W) = \frac{1}{H}\sum_{h=1}^{H} M_{PF}(\Psi, \xi_h)$
  - Check if 90% of the simulated designs have efficacy $>Eff_0$;

    If not, we reduce the length of all windows simultaneously by a certain % until the required efficacy level is obtained [1]

$\Rightarrow$ **Final sampling windows ξ^W = intersection of population window designs of two molecules**

- **Evaluation of the performance of ξ^W for MAP estimation**
  - Simulation of 1000 individual designs within ξ^W and 1000 respective datasets for each molecule
  - Comparison of individual RSE and shrinkage by CTS vs predictions by FIM

[1] Ogungbenro and Aarons. *J. Biopharm. Stat.*, 2009.