mlxDesignEval: A novel R package for design evaluation based on MonolixSuite

Géraldine Cellière[1], Matthias Pierre[1], Monika Twarogowska[1], Jonathan Chauvin[1]
(1) Simulations Plus, Product & Technology division. **Contact**: geraldine.celliere@simulations-plus.com

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INTRODUCTION

- When clinical trial data is used to fit population PK/PD models, one may **design the trial to optimize the parameter estimation** of the model [1].
- This consists of determining sampling times, number of individuals, dose groups, etc. that enable estimating the population parameters with high confidence (i.e., **with low relative standard errors** - RSE).
- An efficient approach uses the **Fisher Information Matrix (FIM)** and a first-order approximation around the typical population parameter values [2]**.**
- The FIM approach is implemented in the R packages popED [3] and PFIM [4], but **their usage is limited** because their model definition language differs from the language used by NLME model estimation software.

OBJECTIVE: Develop an R package for design evaluation which can use Monolix or Simulx projects as input

OVERVIEW OF FEATURES

- mlxDesignEval can use a **Monolix project, Simulx project or mlxtran model as input**, which avoids error-prone model conversions and streamlines the workflow.
- It offers wide **flexibility** in the model and design definition with **clear syntax.**

Feature	mlxDesignEval	popED	PFIM
Import of Monolix/Simulx projects	✓	×	×
Library of models with analytical solutions	✓	×	✓
Custom models including ODEs	✓	✓	✓
Combination of arms with different designs	✓	✓	✓
Combination of multiple dose routes	✓	✓	✓
Combination of multiple outputs	✓	✓	✓
Continuous and categorical covariates	✓	✓	✓
Inter-occasion variability	✓	✓	✓
Fixed parameters	✓	✓	✓
Prior FIM (added on estimated FIM)	✓	✓	✓
Full omega matrix (correlations)	✓	✓	✓
Uncertainty in model parameters	✓	✓	×
Shrinkage (Bayesian FIM)	×	✓	✓
Handling of BLQ data	*(in development)*	✓	×
Design evaluation	✓	✓	✓
Design optimization	*(in development)*	✓	✓
Graphical visualization of the design	✓	✓	✓
Hypothesis testing and power calculation	✓	✓	✓

PREREQUISITES

- mlxDesignEval makes use of MonolixSuite in the background and thus requires **MonolixSuite** (2023 or 2024) and the **R package lixoftConnectors** (2023 or 2024) installed.
- mlxDesignEval requires a dedicated paid license, as well as a Monolix and Simulx license.

VALIDATION

- The mlxDesignEval implementation has been **validated** by reproducing the results of the 14 examples available on the popED documentation.
- The calculated **RSEs are identical between popED and mlxDesignEval** (less than 1% difference).

REFERENCES

[1] Mentré et al., *CPT: Pharmacometrics & Sys Pharm*, 2 (2013).
[2] Nyberg et al., *British Journal of Clinical Pharm, 79* (2015)
[3] https://andrewhooker.github.io/PopED/index.html
[4] https://iame-researchcenter.r-universe.dev/PFIM

Download the R package here!

EX1: DESIGN COMPARISON

Goal: assess the impact of early samples on parameter identifiability.

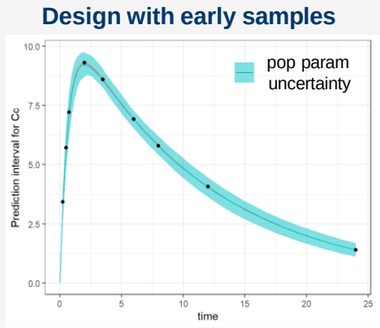
Model: one compartmental model with first-order absorption and linear elimination.

Design: single dose of 5 mg, 20 individuals, **sampling times with or without early time points** (at 0.25, 0.5, 0.75, 2, 3.5, 6, 8, 12, 24, 48 hr or only at 3.5, 6, 8, 12, 24, 48 hr).

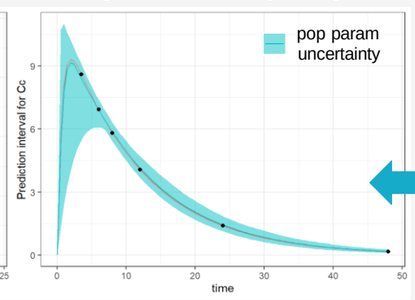
```
evaluate_design(model_file = "1cpt_firstOrder_linearElim.txt",
   pop_param      = data.frame(ka_pop=1.5,V_pop=0.45,Cl_pop=0.04,  omega_ka=0.66,
                               omega_V=0.12, omega_Cl=0.27, a=0.43, b=0.055),
   treatment      = list(data=data.frame(time=0, amount=5)),
   output         = list(output="CONC",
                         data=data.frame(time=c(3.5, 6, 8, 12, 24, 48)))
   group          = list(size=20),
   saved_project = "ex1a.mlxtran")
```

Parameter	RSE (%)	
	dense	sparse
ka_pop	15.3	**99.7**
V_pop	3.3	4.9
Cl_pop	6.4	8.9
omega_ka	16.7	**302.8**
omega_V	23.8	32.1
omega_Cl	17.8	19.5
a	14.4	15.1
b	24.1	31.5

Design with early samples



Design without early samples



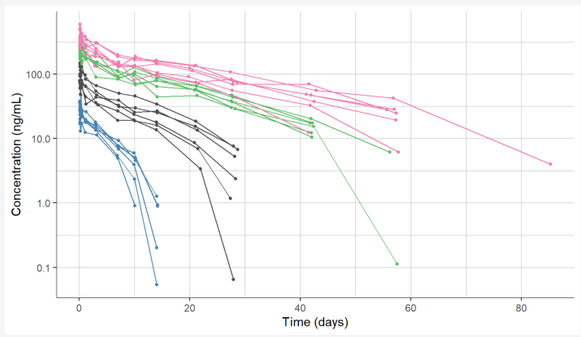

```
plot_prediction(
   saved_project = "ex1a.mlxtran",
   plot = c("PopPred",
            "PopPred_Uncertainty"),
   nrep = 100)
```

Conclusion: without the early time points at 0.25, 0.5, 0.75 and 2 hr, the ka_pop and omega_ka (IIV) parameters will have a very large uncertainty.

EX2: PARAMETER IDENTIFIABILITY

Goal: assess the identifiability of the population parameters before launching a Monolix run, for an existing dataset and several candidate models.

Dataset: PK data for a monoclonal antibody, IV injection to healthy volunteers, 4 single dose groups with 6 individuals each.




```
evaluate_design(project_file = "TMDD_MM.mlxtran")
```

using TMDD_MM.mlxtran Monolix project containing:

- PK dataset
- Candidate model
- Initial values:
  - Fixed effects selected via "auto-init"
  - IIV set to 30%
  - Error model set to 15%

Michaelis-Menten (MM) model

Parameter	RSE (%)	Parameter	RSE (%)
V_pop	6.16	omega_V	14.8
Vm_pop	11.3	omega_Vm	23.2
Km_pop	30.1	omega_Km	**121**
Cl_pop	12.6	omega_Cl	26.6
Q_pop	11.3	omega_Q	47.5
V2_pop	10.2	omega_V2	28.9
		b	4.81

Quasi-equilibrium (QE) model

Parameter	RSE (%)	Parameter	RSE (%)
V_pop	7.52	omega_V	14.8
kint_pop	**4164**	omega_kint	**17414**
KD_pop	**4222**	omega_KD	**17791**
ksyn_pop	13.3	omega_ksyn	25.8
R0_pop	**219**	omega_R0	**970**
Cl_pop	12.1	omega_Cl	24.8
Q_pop	13.7	omega_Q	53.5
V2_pop	11.2	omega_V2	29.1
		b	4.82

Conclusion: the dataset is rich enough to estimate the parameters of the MM model (except the IIV on Km), but many parameters of the QE model are unidentifiable.

EX3: COMPLEX DESIGN

Goal: show an example with several outputs (PK and PD), several administration routes (IV and PO), single and multiple doses, and subject-specific covariates

```
# different output times and output variables
out1    <- list(output="CONC",    data=data.frame(time=c(0.25, 0.5, 0.75, 2, 3, 6, 8, 12, 24)))
out2_PK <- list(output="CONC",    data=data.frame(time=c(12, 24)))
out2_PD <- list(output="Effect", data=data.frame(time=c(12, 24)))
out2    <- list(out2_PK, out2_PD)
# treatment dosing regimens and administration routes
trt1_IV <- list(data=data.frame(time=0, amount=75), admID=1)
trt1_PO <- list(data=data.frame(time=seq(from=24,to=120,by=24), amount=50), admID=2)
trt1    <- list(trt1_IV,trt1_PO)
trt2    <-  list(data=data.frame(time=seq(from=0  ,to=120,by=24),  amount=50),  admID=2)
# different covariates
cov1   <- data.frame(id=1:10,  wt=rnorm(10,  70,  10),  sex=0)
cov2    <- data.frame(id=1:10, wt=rnorm(30, 80, 10), sex=1)
# definition of groups with group-specific elements
g1 <- list(size=10,  output=out1,  treatment=trt1,  covariate=cov1)
g2 <- list(size=30, output=out2, treatment=trt2, covariate=cov2)

evaluate_design(project_file="PKPD_withCov.smlx",  group=list(g1,  g2))
```

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