# Comparison of results of the different software for design evaluation in population pharmacokinetics and pharmacodynamics

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## Context

- Nonlinear mixed effects models (NLMEM) are increasingly used during drug development
- Design software tools are needed to evaluate/compare/optimize "population designs" based on Fisher Information Matrix (MF)
- Following early work, now several research teams working on methodological aspects and/or applications of optimal design for NLMEM
- Presently 5 software tools implement MF for PKPD population analysis:
  1. PFIM (C. Bazzoli , F. Mentré) in R
  2. PkStaMP (S. Leonov, A. Aliev) in Matlab
  3. PopDes (K. Ogungbenro) in Matlab
  4. PopED (J. Nyberg, S. Ueckert & A. Hooker) in Matlab
  5. WinPOPT/POPT (S. Duffull) in Matlab
- Each of the software uses approximations in the evaluation of MF and are coded in different languages

## Objectives

To compare the **standard errors (SE)** and **criterion** provided by the different software for population designs on two examples:

1. a simple PK model
2. a complex PKPD example

## Methods

- The same methodology was used for both examples
  - Evaluation of a single group population design
  - Prediction of SE for each parameter (fixed effects, variances) by each software tool using different options for approximations
  - Evaluation of overall information: criterion = $\det(MF)^{1/P}$
  - Comparison to empirical SE obtained by clinical trial simulation (CTS) analyzed using MONOLIX (SAEM algorithm) and NONMEM (FOCEI)
    - 1000 replications for PK example, 500 for PKPD example

- Different approximation of MF
  - FO: First Order Approximation (FO)
    - "Reduced" or "Full" matrix (A: block for fixed effects)

$$FIM_{\text{Reduced}} = \begin{pmatrix} A & 0 \\ 0 & B \end{pmatrix} \qquad FIM_{\text{Full}} = \begin{pmatrix} A^* & C \\ C & B \end{pmatrix} \qquad A^* = A + \frac{1}{2} tr\left(\frac{\partial V}{\partial \theta} V^{-1} \frac{\partial V}{\partial \theta} V^{-1}\right)$$

  - Other approximations: FOI (PkStaMP, PopDes), FOCEI / FOCE (PopED)

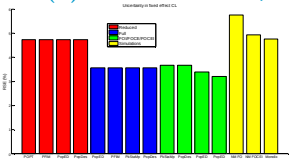
## 1. PK example

- **PK of warfarin single dose**
- 1-compartment model, 1st order absorption, oral dose 70 mg
- Proportional error model ($\sigma^2$=0.01)
- Design: 32 subjects with 8 samples at 0.5, 1, 2, 6 ,24, 36, 72,120 hours

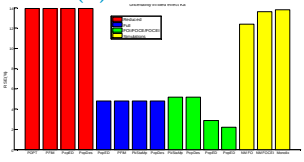
| Parameters | Fixed effects | $\omega^2$ (IIV, exp) |
|---|---|---|
| CL/F (L/h) | 0.15 | 0.07 |
| V/F (L) | 8.0 | 0.02 |
| ka (1/h) | 1.0 | 0.6 |

### RESULTS

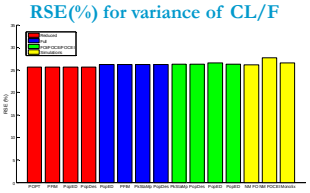
RSE(%) for fixed effect of CL/F



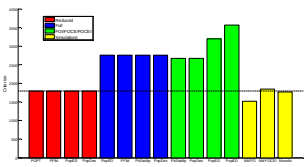
RSE(%) for fixed effect of ka



RSE(%) for variance of CL/F



Criterion



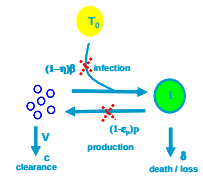
## 2. PKPD Example

- **PK of Peg-Interferon and HCV viral load decrease** (Neuman et al., Science 1998)
- ODE model: two responses C(t) and V(t) (measured in same samples)
- Dose D of 180 µg given every week as a one-day infusion
- Additive error on concentration and $\log_{10}$ viral load ($\sigma^2$=0.04)
- Some parameters are fixed:
  - p=10, s=20000 $mL^{-1}.d^{-1}$, d=0.001 $d^{-1}$, b=$10^{-7}$ $mL.d^{-1}$, η=0
- Other parameters: additive random effects on log parameters with variance of 0.25

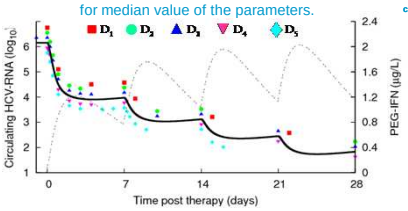
$$\frac{dX}{dt} = D - k_a X$$
$$\frac{dA}{dt} = k_a X - k_e A$$
$$C(t) = \frac{A(t)}{V_d}$$
$$\frac{dT}{dt} = s - \beta(1-\eta)VT - dT$$
$$\frac{dI}{dt} = \beta(1-\eta)VT - \delta I$$
$$\frac{dV}{dt} = p\left(1 - \frac{C(t)^*}{C(t)^* + EC_{50}^*}\right) I - cV$$

| $EC_{50}$(µg. $L^{-1}$) | n | δ ($d^{-1}$) | c($d^{-1}$) | $k_a$ ($d^{-1}$) | $k_e$ ($d^{-1}$) | $V_d$ (L) |
|---|---|---|---|---|---|---|
| 0.12 | 2 | 0.2 | 7 | 0.8 | 0.15 | 100 |

- Design D3: 30 subjects with 12 samples at 0, 0.25, 0.5, 1, 2, 3, 4, 7, 10, 14, 21, 28 weeks

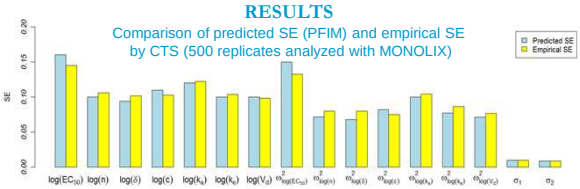



Viral dynamics (plain) and concentration profile (dashed) for median value of the parameters.

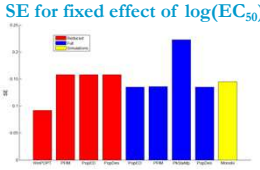



### RESULTS

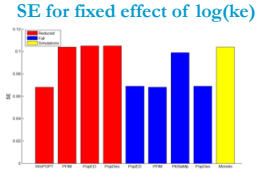
Comparison of predicted SE (PFIM) and empirical SE by CTS (500 replicates analyzed with MONOLIX)



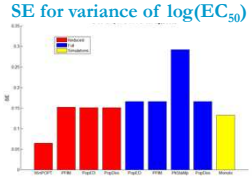

SE for fixed effect of log($EC_{50}$)



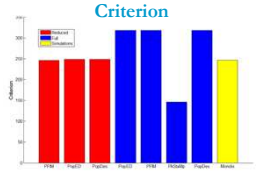
SE for fixed effect of log(ke)



SE for variance of log($EC_{50}$)



Criterion



## Conclusion

- PK model:
  - reduced MF with FO: all software identical SE close to simulation
  - similar CTS results with MONOLIX and NONMEM
  - different approximations for MF give different SE
- Complex PKPD model:
  - influence of the ODE solver on model prediction and MF
  - work ongoing to understand differences
  - good prediction of SE of all PKPD parameters even with FO
  - CTS = 5 days, design evaluation with software = 5 min
- Statistical work ongoing to improve MF for highly nonlinear models
- For most PKPD models, using one of these various available software tools will provide meaningful results avoiding cumbersome simulation and allowing design optimization