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

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Introduction

- 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

$$FIM_{\text{Reduced}} = \begin{pmatrix} A & 0 \\ 0 & B \end{pmatrix} \qquad FIM_{\text{Full}} = \begin{pmatrix} A^* & C \\ C & B \end{pmatrix}$$

$$A^* = A + \frac{1}{2} tr\left(\frac{\partial V}{\partial \theta} V^{-1} \frac{\partial V}{\partial \theta} V^{-1} \right)$$

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

1. PK Example

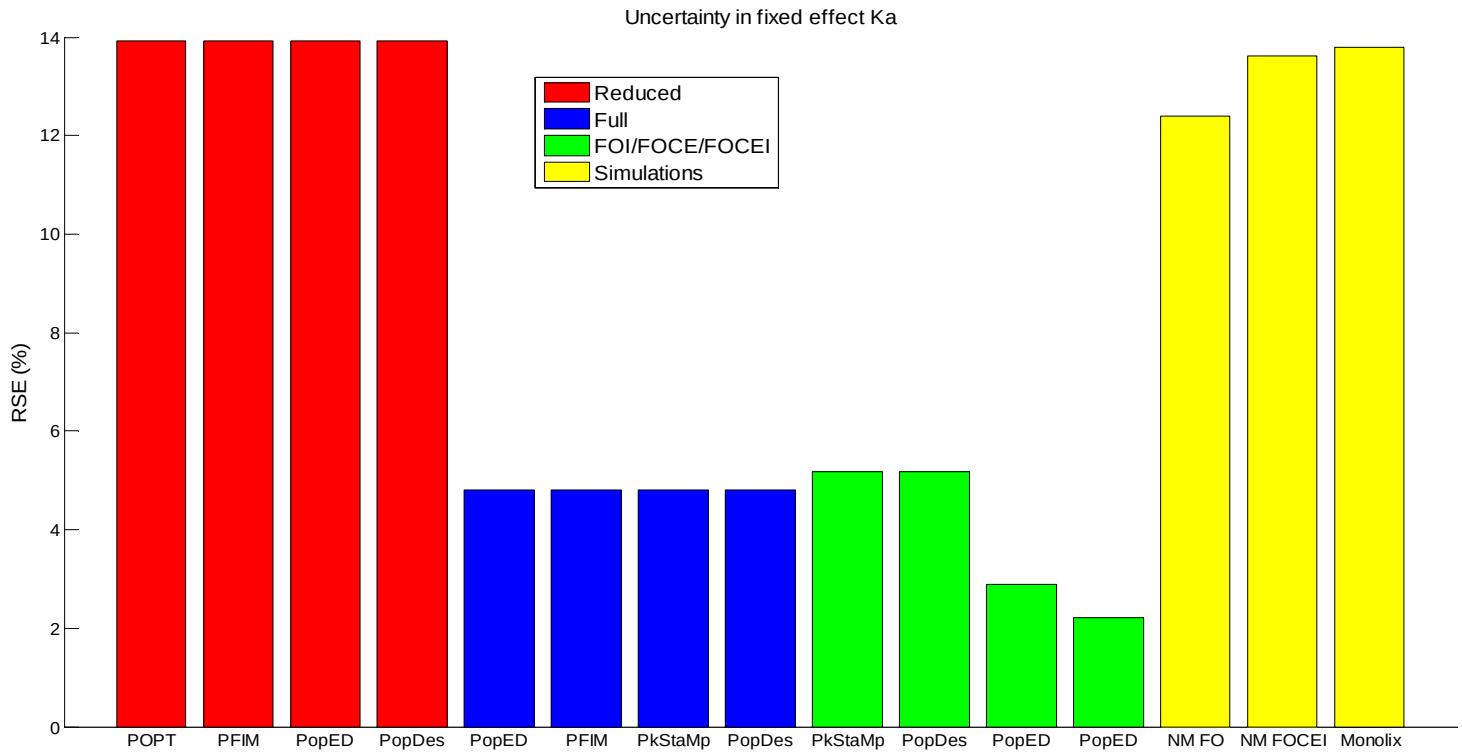
- **PK of warfarin single dose**
- 1-compartment model, 1st order absorption, single oral dose 70 mg
- Proportional error model (σ^2=0.01)
- Design: 32 subjects with 8 samples:

  at 0.5, 1, 2, 6 ,24, 36, 72,120 hours

Parameters	Fixed effects	ω^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

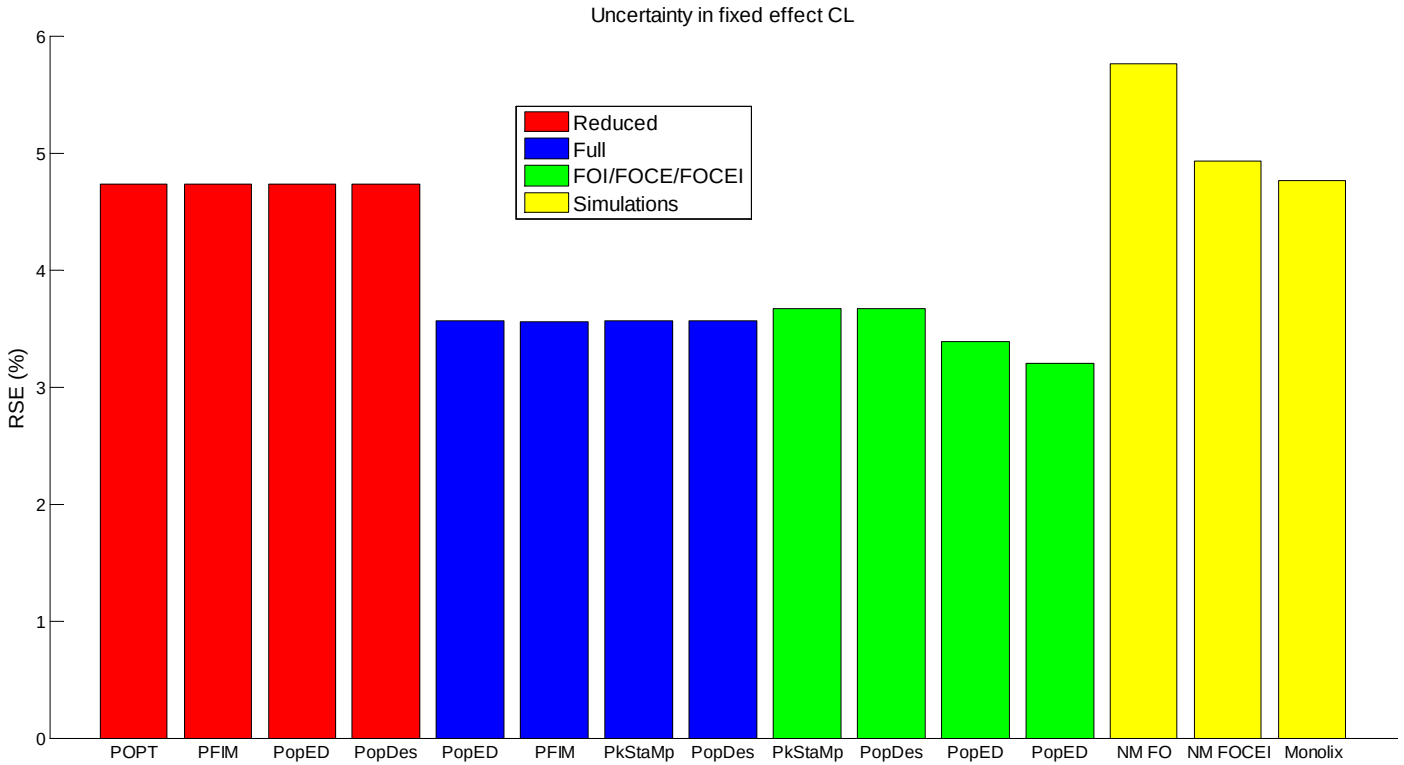
Results (1)

RSE(%) for fixed effect of ka



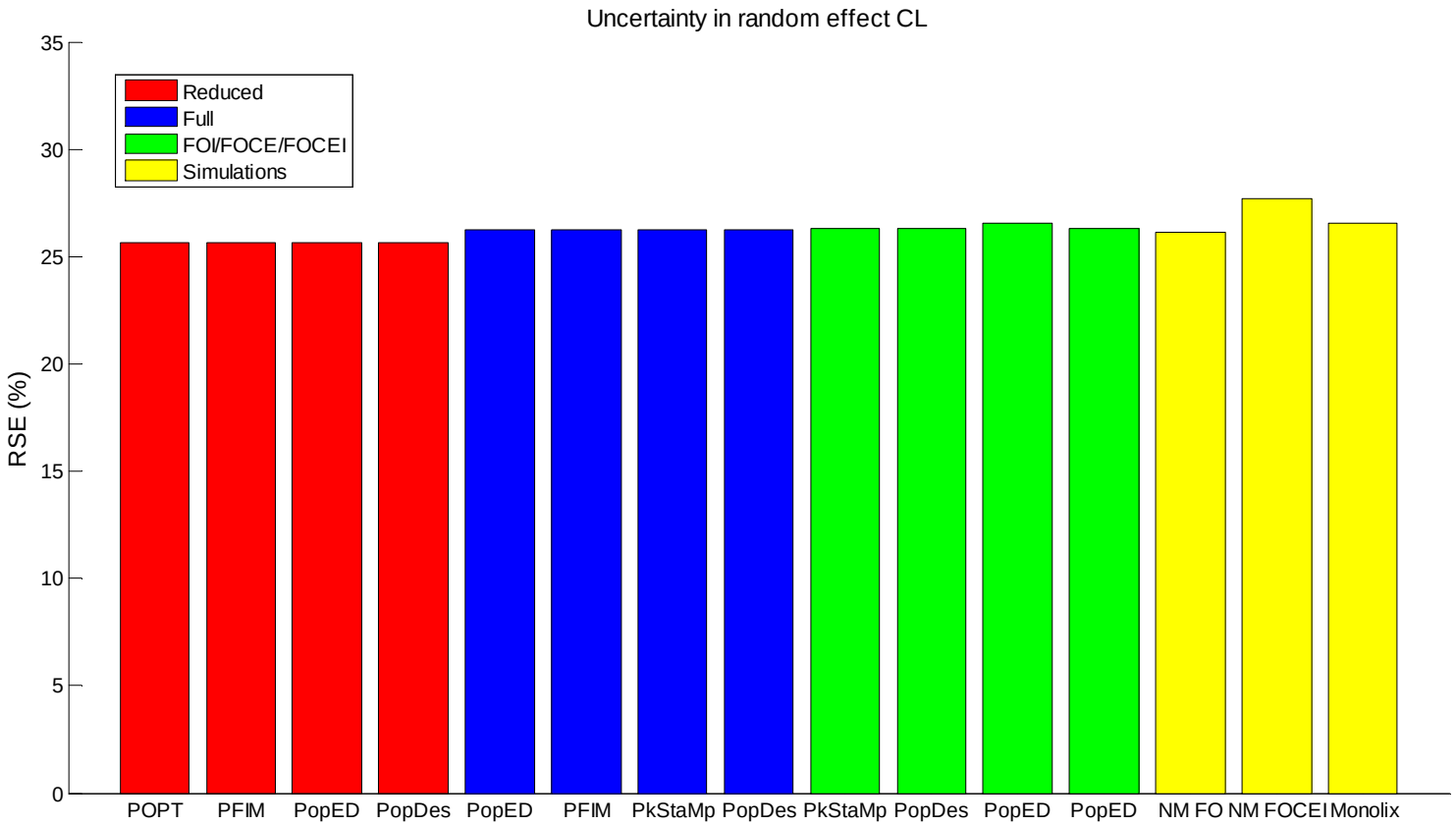
Results (2)

RSE(%) for fixed effect of CL/F



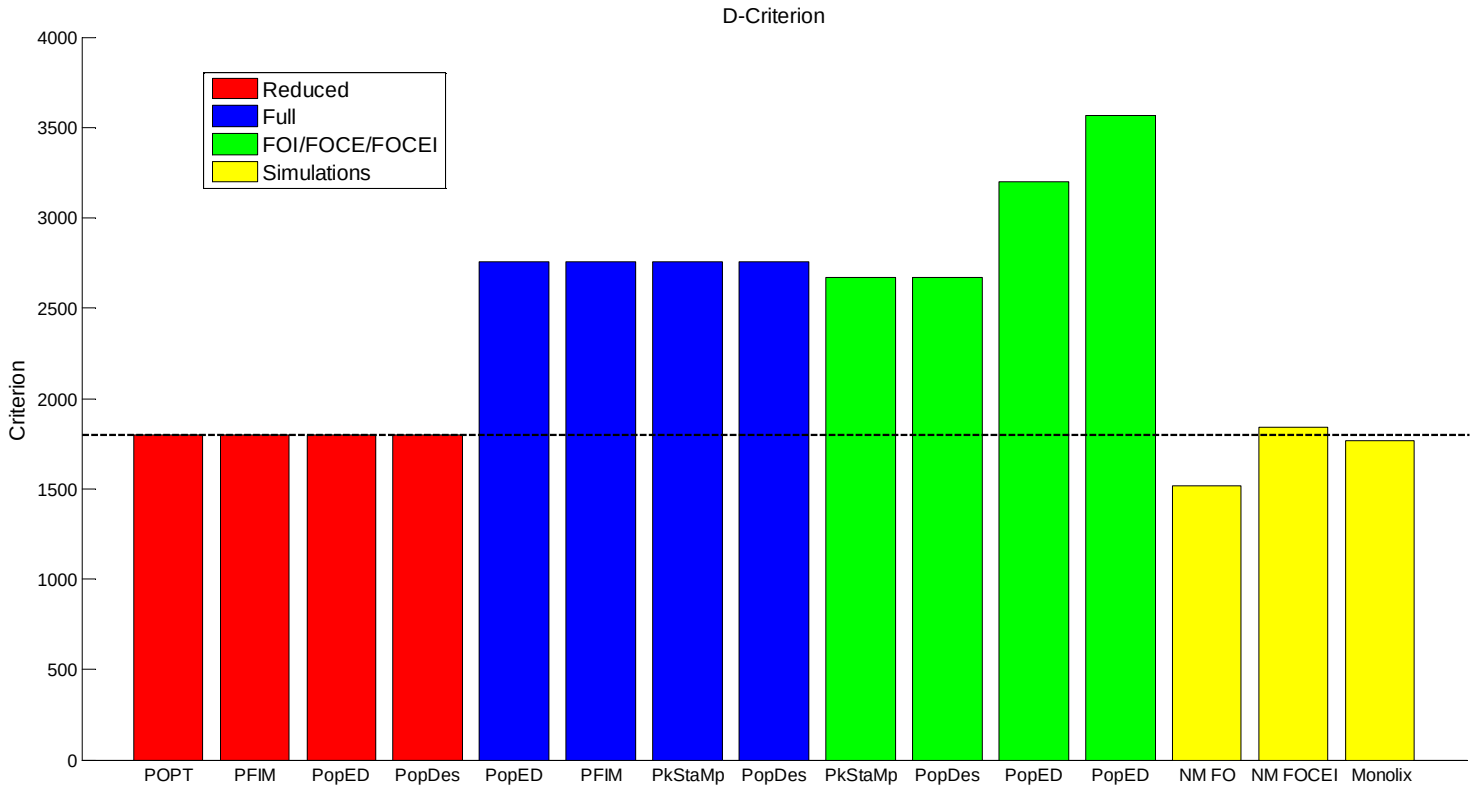
Results (3)

RSE(%) for variance of CL/F



Results (4)

Criterion



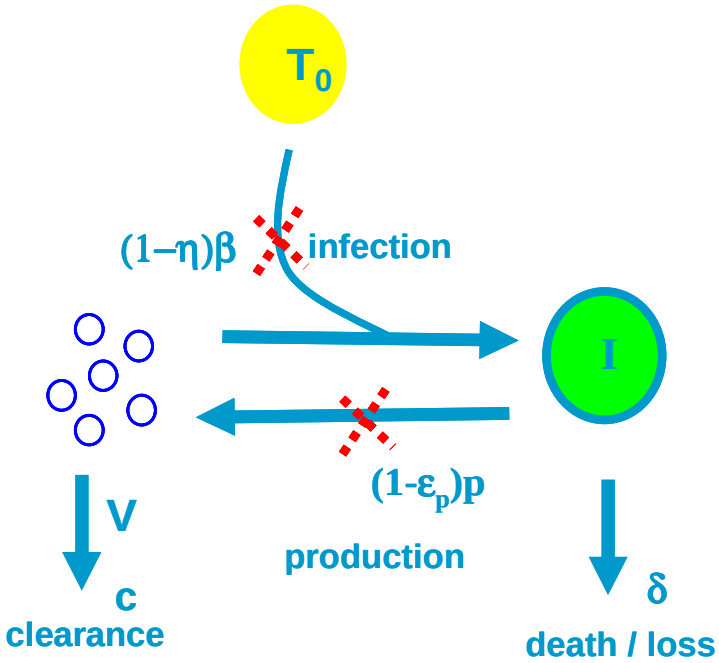
Conclusion on PK Example

- Reduced MF with FO: all software identical SE close to simulation
- Similar CTS results with MONOLIX (SAEM) and NONMEM (FOCEI)
- Different approximations for MF give different SE

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)

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



2. PKPD Example (ctd)

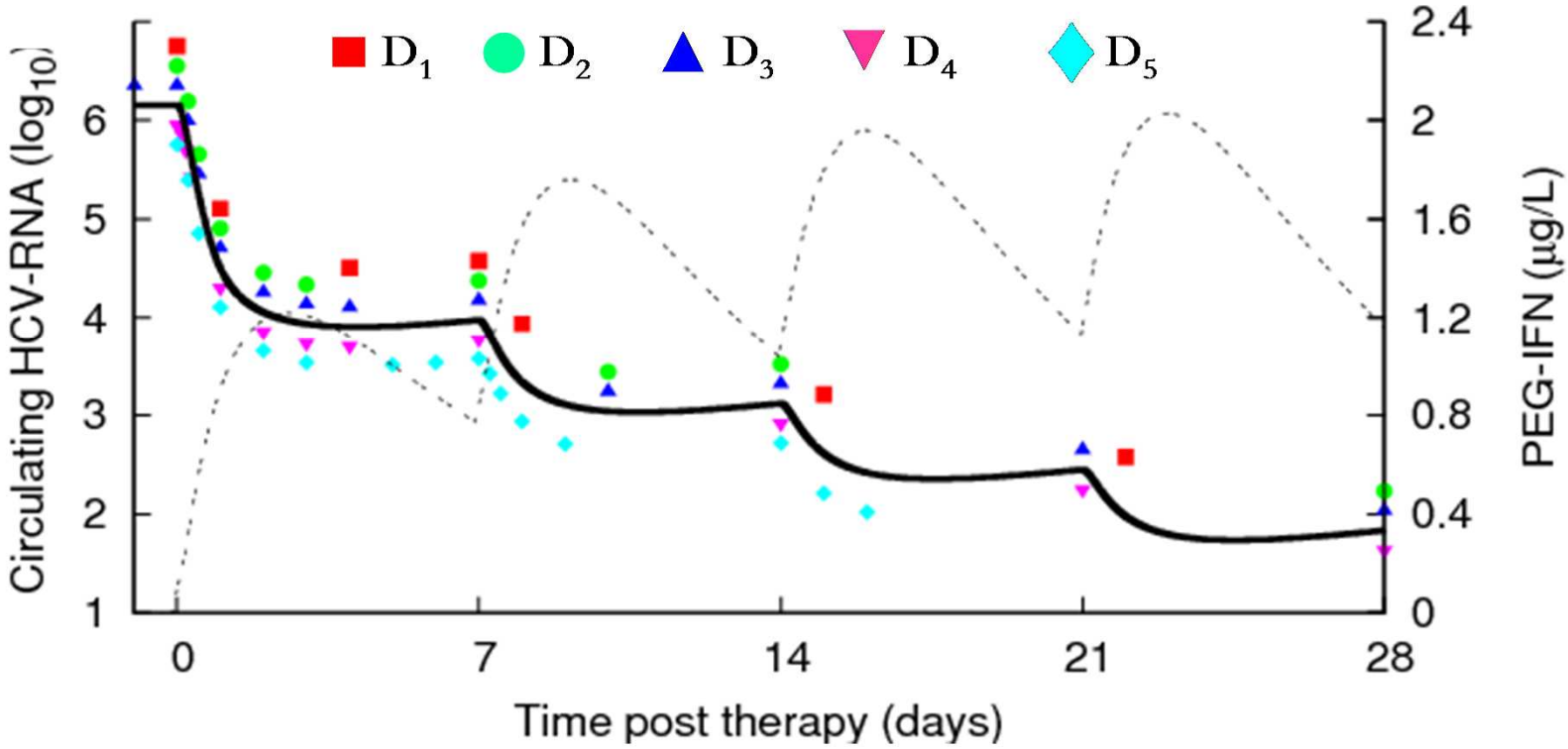
- Dose D of 180 µg given every week as a one-day infusion
- Additive error on concentration and $\log_{10}$ viral load (σ^2=0.04)
- Some parameters are fixed:
  - p=10, s=20000 $mL^{-1}.d^{-1}$, d=0.001 d^{-1}, b=10^{-7} $mL.d^{-1}$, η=0
- Other parameters: additive random effects on log parameters with variance of 0.25

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

2. PKPD Example (ctd)

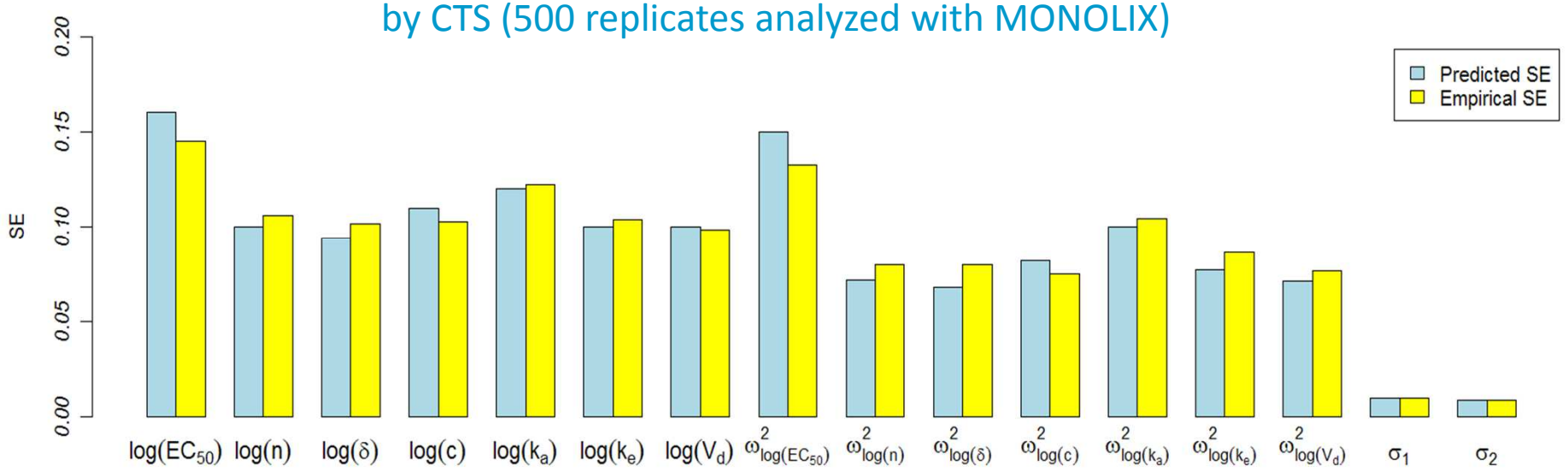
Design D3: 30 subjects with 12 samples at 0, 0.25, 0.5, 1, 2, 3, 4, 7, 10, 14, 21, 28 weeks

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



Results (1)

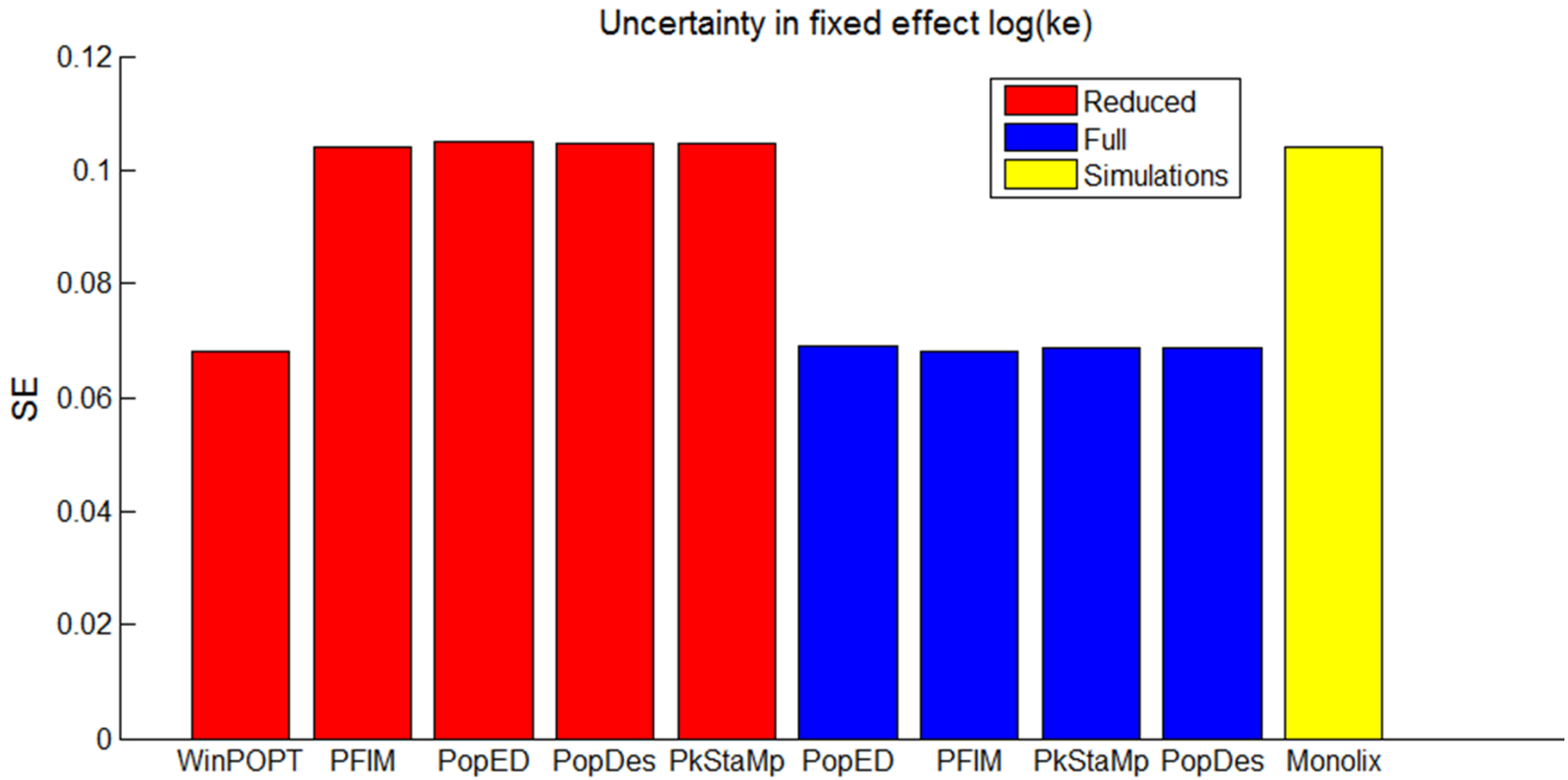
Comparison of predicted SE (PFIM block) and empirical SE
by CTS (500 replicates analyzed with MONOLIX)



Guedj, Bazzoli, Neumann, Mentré. *Stat Med* 2011

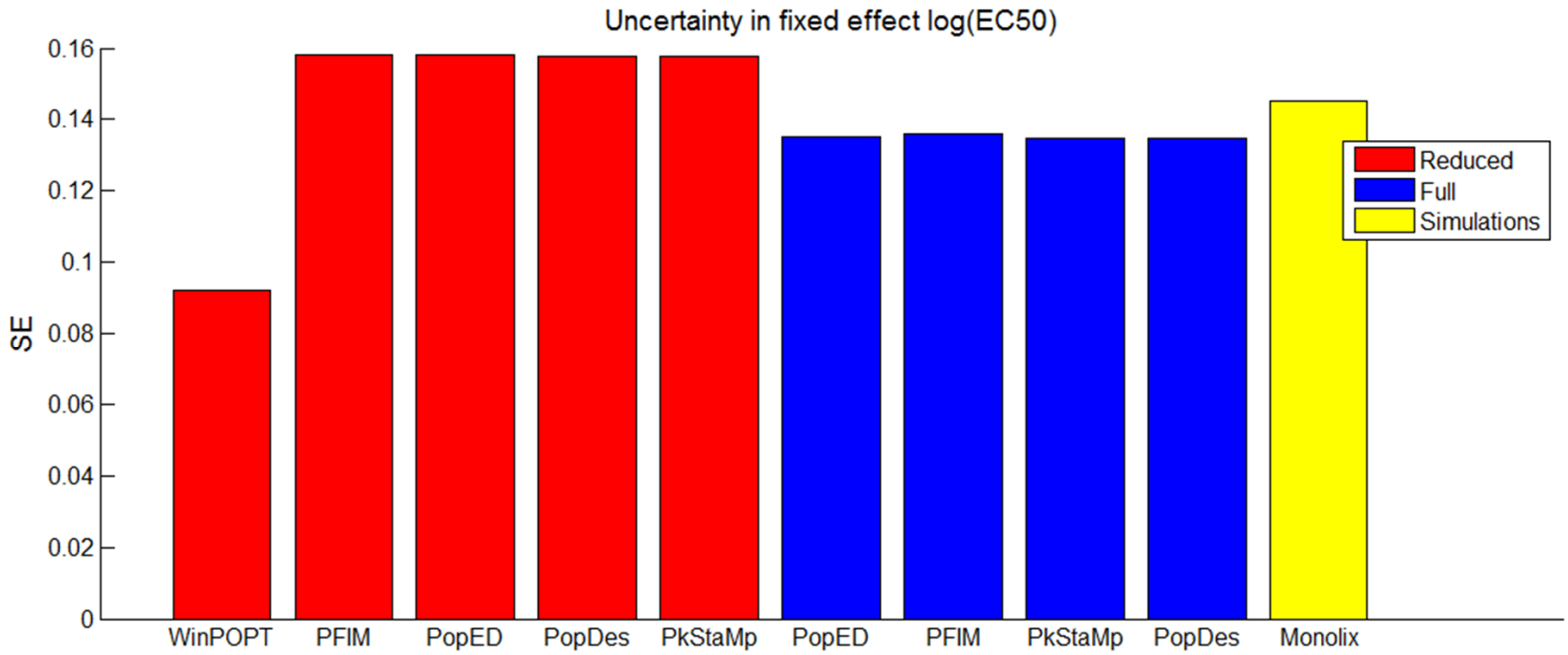
Results (2)

SE for fixed effect of log(ke)



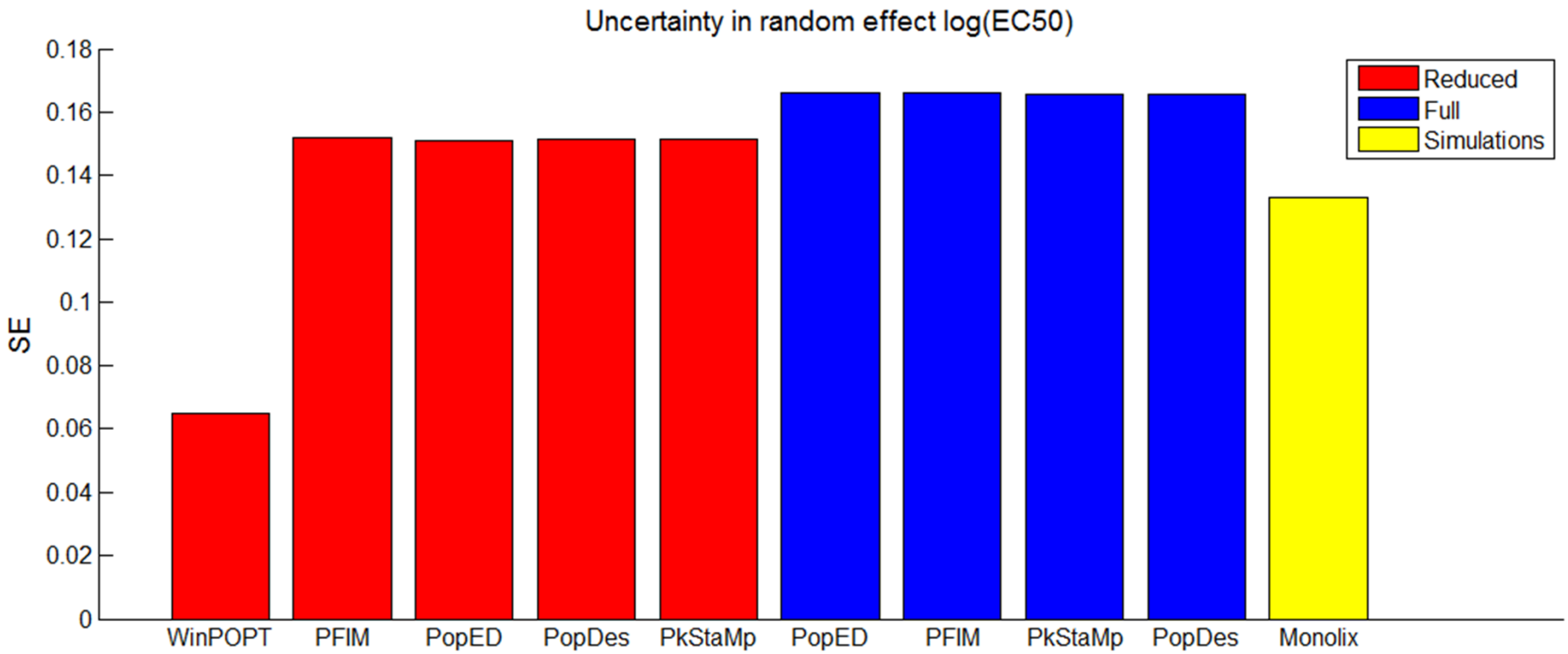
Results (3)

SE for fixed effect of log(EC50)



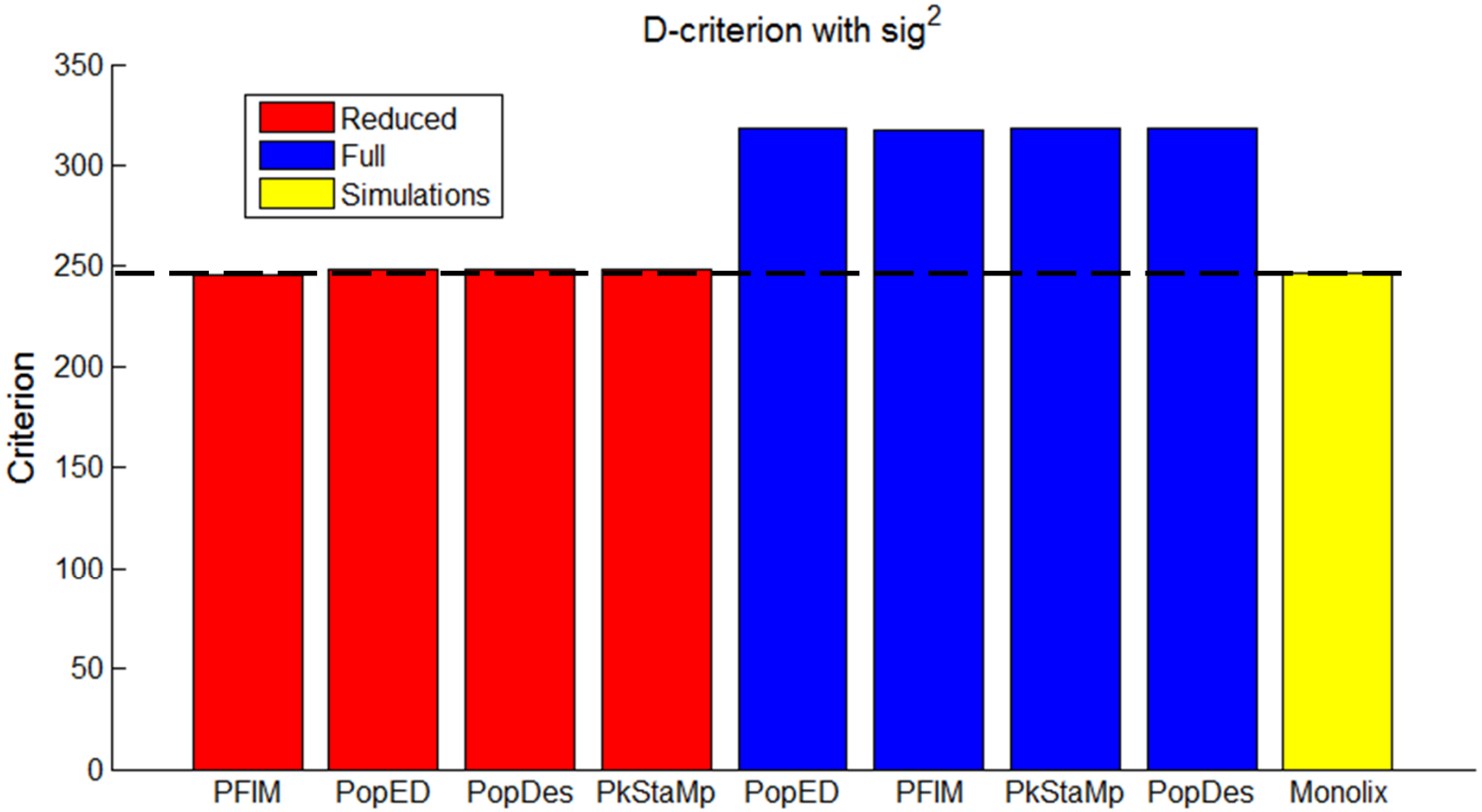
Results (4)

SE for variance of log(EC50)



Results (5)

Criterion



Conclusion on PKPD Example

- Influence of the ODE solver on model prediction and MF
- Work to understand (previous) differences
- Good prediction of SE of all PKPD parameters even with FO
- Computing time
  - CTS = 5 days
  - design evaluation with software = 5 min

General Conclusion

- 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

- *Next step: optimal designs comparison?*