

OpenPMX software for FOCE-I estimation

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Mixed effect models are a backbone of pharmacometrics in industry and academia. The first-order-conditional estimation with interaction (FOCE-I) method with NONMEM is a standard in the field but few understand its technical details. OpenPMX is open-source software for modelling in pharmacometrics, including the FOCE-I algorithm, for inspection, auditing, and collaboration.

- Available at: <https://github.com/deleveld/OpenPMX>
- Open-source GPL-3.0 license
- Scriptable control files
- Uses C-language, uses multi-core CPUs
- Few dependencies: gcc and GNU Scientific Library
- Population estimation FOCE-I
- Free-to-use website: <http://www.openpmx.com/>

Methods

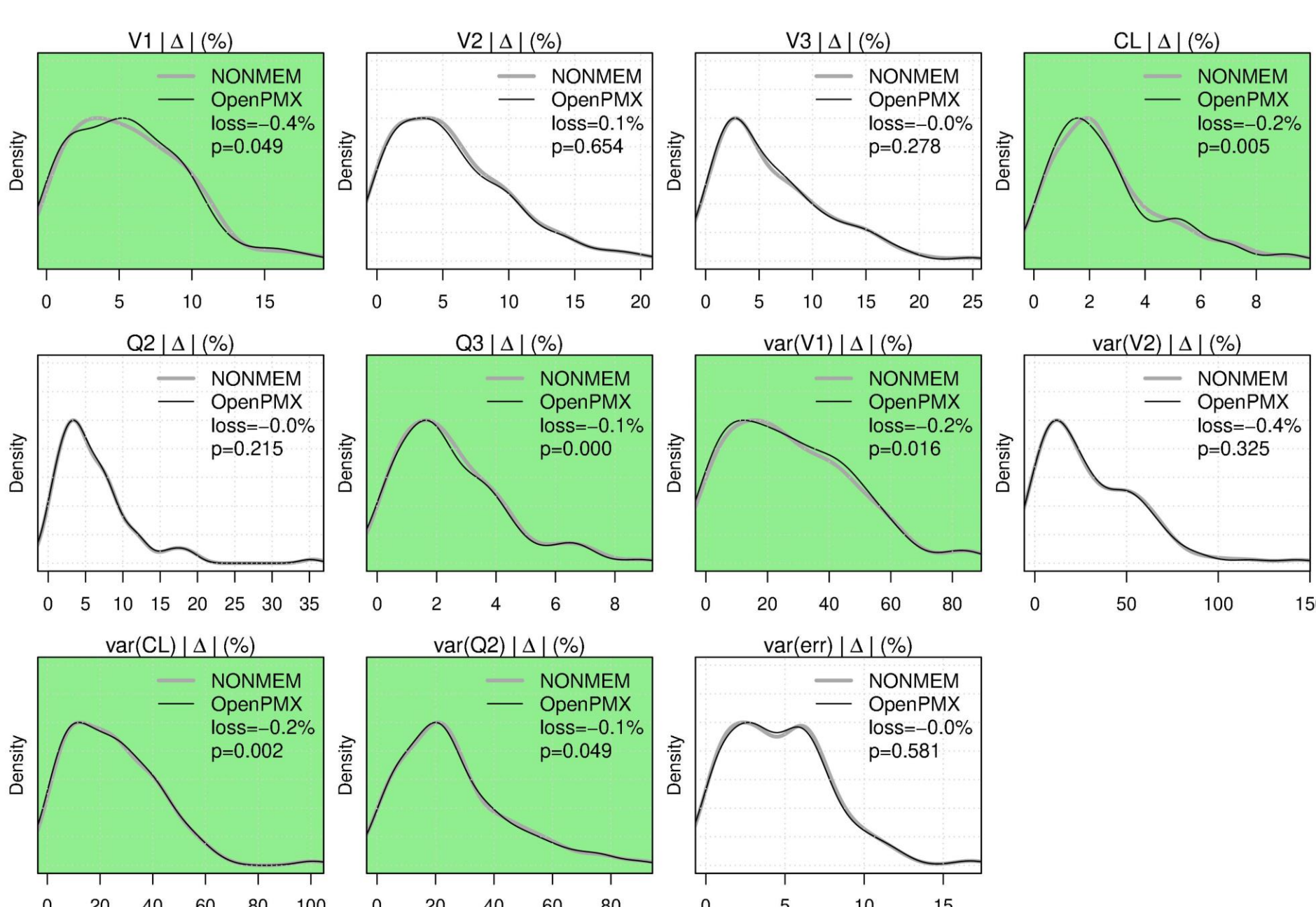
- Inner: For θ , Ω , and Σ , min $Posthoc_k$ via η_k
 - Outer: Minimize OBJFN by θ , Ω , and Σ
 - Options: OpenPMX default, NONMEM SIG=5 MAX=5000 METHOD=1 INTERACT
 - Evaluate performance on resampled dataset
- $$\Delta_i = (est_i - true)/true$$
- $$loss_i(\%) = 100 \cdot (|\Delta_{OpenPMX,i}| - |\Delta_{NONMEM,i}|)$$
- If median loss < 0 (Wilcoxon test, $p < 0.05$) then OpenPMX outperforms NONMEM 7.6.0¹

$$Posthoc_k = \sum_{i=1}^{Nobs_k} \log(V_{k,i}) + \sum_{i=1}^{Nobs_k} \frac{(Y_{k,i} - DV_{k,i})^2}{V_{k,i}} + \eta_k^T \Omega^{-1} \eta_k$$
$$OBJFN_k = Posthoc_k + \log|\Omega| + \log|B_k|$$
$$V_i = \sum_{j=1}^{N\sigma} \left(\frac{\partial Y_i}{\partial \varepsilon_j} \right)^2 \cdot \sigma_j$$
$$r_i = \frac{Y_i - DV_i}{\sqrt{V_i}}$$
$$J = \begin{bmatrix} \frac{\partial r_1}{\partial \eta_1} & \dots & \frac{\partial r_1}{\partial \eta_P} \\ \vdots & \ddots & \vdots \\ \frac{\partial r_{Nobs}}{\partial \eta_1} & \dots & \frac{\partial r_{Nobs}}{\partial \eta_P} \end{bmatrix} \quad B = \Omega^{-1} + J^T J$$

```
$ADVAN(threecomp)
$SIMODEL(V1, V2, V3, CL, Q2, Q3, SIZE)
  SIZE = WT/70.;
  V1 = THETA(1) * SIZE * exp(ETA(1));
  V2 = THETA(2) * SIZE * exp(ETA(2));
  V3 = THETA(3) * SIZE * exp(ETA(3));
  CL = THETA(4) * pow(SIZE, 0.75) * exp(ETA(4));
  Q2 = THETA(5) * pow(SIZE, 0.75) * exp(ETA(5));
  Q3 = THETA(6) * pow(SIZE, 0.75) * exp(ETA(6));
$PREDICT(IPRED)
  IPRED = A(1)/V1;
  Y = IPRED*(1 + ERR(1));
$THETA
  { 0, 6, 25, ESTIMATE},
  { 1, 20, 125, ESTIMATE},
  { 25, 200, 500, ESTIMATE},
  { 0, 2, 6, ESTIMATE},
  { 0, 1, 3, ESTIMATE},
  { 0, 1, 3, ESTIMATE},
$OMEGA(0.1, 0.1, -0, 0.1, 0.1, -0)
$SIGMA(0.1)
```

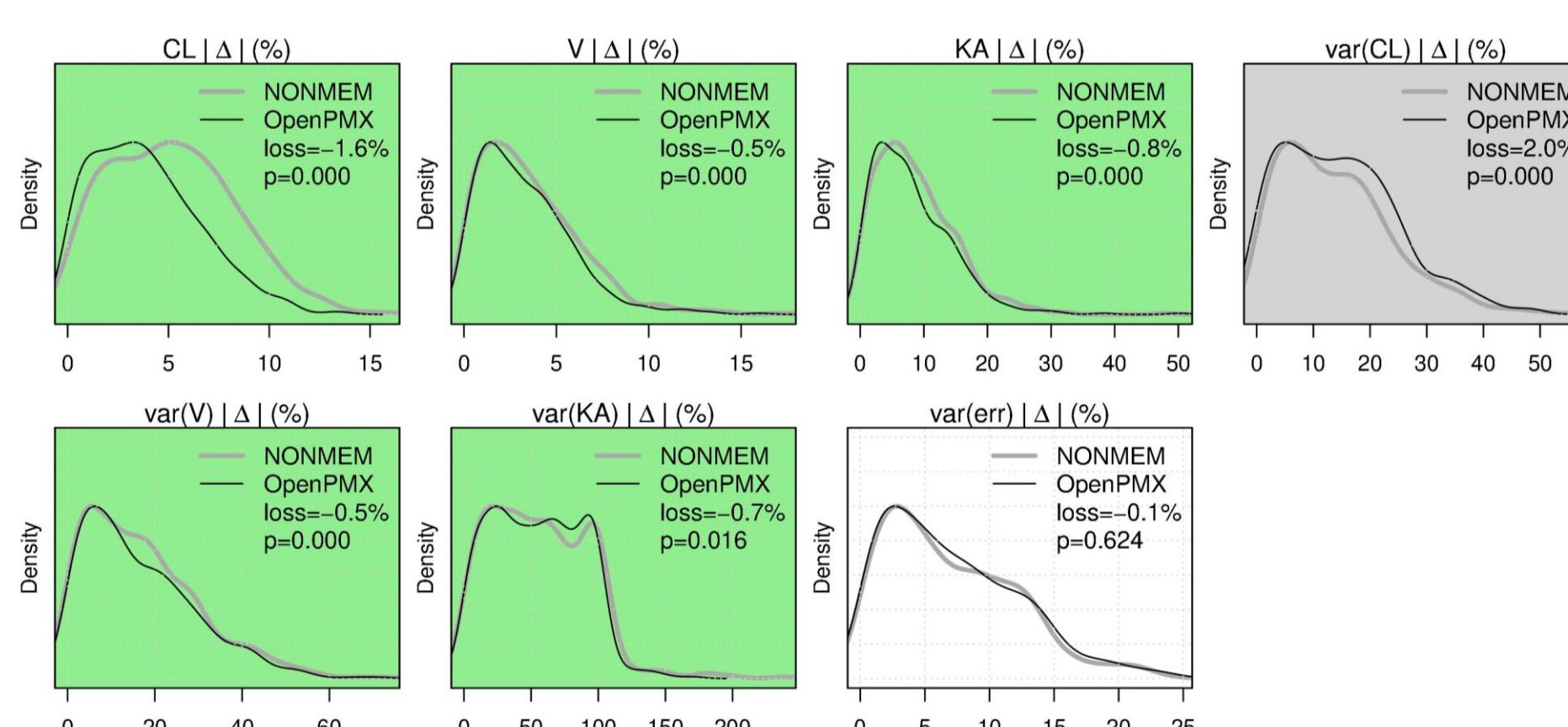
Rich-data²

- Derived from Schnider propofol data, 100 resamples
- Three-compartment allometric model, V1=5.85 l, V2=26 l, V3=313 l, CL=1.92 l/min, Q2=1.34 l/min, Q3=0.863 l/min
- Diagonal Ω , proportional residual error



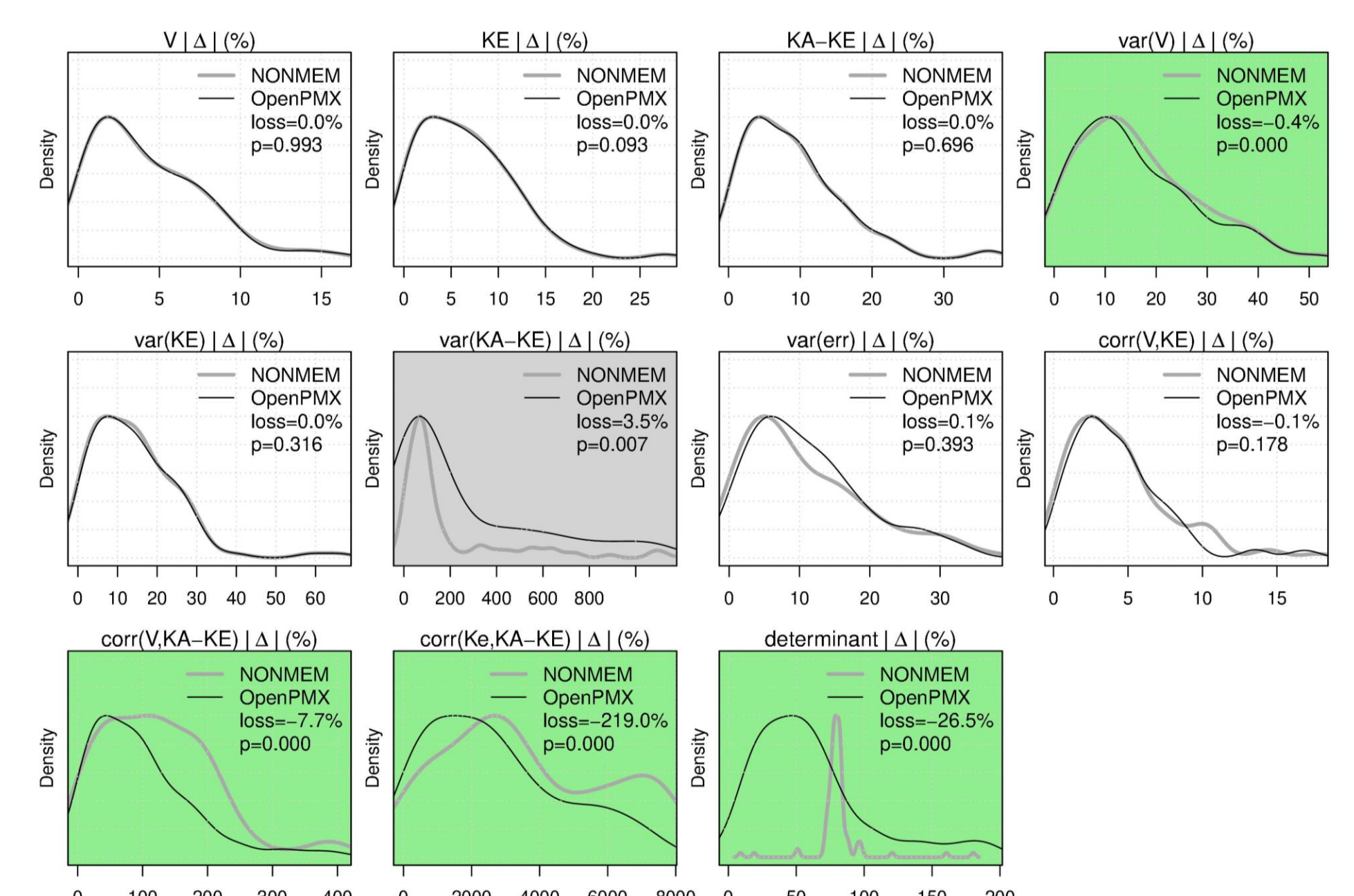
Sparse-data³

- One-compartment model, CL=4 l/hour, V=70 l, KA=1 l/hr, 500 resamples
- Diagonal Ω variance 0.09, proportional residual error 0.04.
- Single-dose 120 individuals, groups 10, 30, 60, 120 mg



DATASIM-data⁴

- Previously performed blind analysis
- One-compartment model, V, KA and KA-KE. 100 resamples, previously generated
- Block Ω with large and small variances, high correlations. Log-normal residual error



Conclusions

- OpenPMX FOCE-I estimation performance is comparable to industry standard NONMEM 7.6.0
- All technical details open for inspection, auditing, and collaboration
- Future work: 1) Error handling 2) Parameter uncertainty 3) BLQ and categorical observations 4) VPC and NPDE

1. Icon Development Solutions, Ellicott City, Maryland, USA

2. Schnider TW, Minto CF, Gambus PL, et al. The influence of method of administration and covariates on the pharmacokinetics of propofol in adult volunteers. *Anesthesiology* 1998; **88**: 1170–182

3. Schoemaker R, Fidler M, Laveille C, et. Al. Performance of the SAEM and FOCEI algorithms in the open-source, nonlinear mixed effect modeling tool nlmixr. CPT: Pharmacometrics & Systems Pharmacology. 2019 Dec;8(12):923-30.

4. PAGE 14 (2005) Abstr 834 [www.page-meeting.org/?abstract=834] oral presentation