

Introduction

- Model-informed precision dosing (MIPD) combines prior knowledge about patient pharmacokinetics/pharmacodynamics (PK/PD) with patient data to predict drug exposure in the patient
- Current tools rely on maximum a posteriori (MAP) Bayes estimation
- Full Bayesian approaches like Hamiltonian Monte Carlo (HMC) may be less biased and better estimate uncertainty
- Median estimates for MAP and full Bayes are often similar, but the uncertainty estimate could affect clinical decision making

Methods

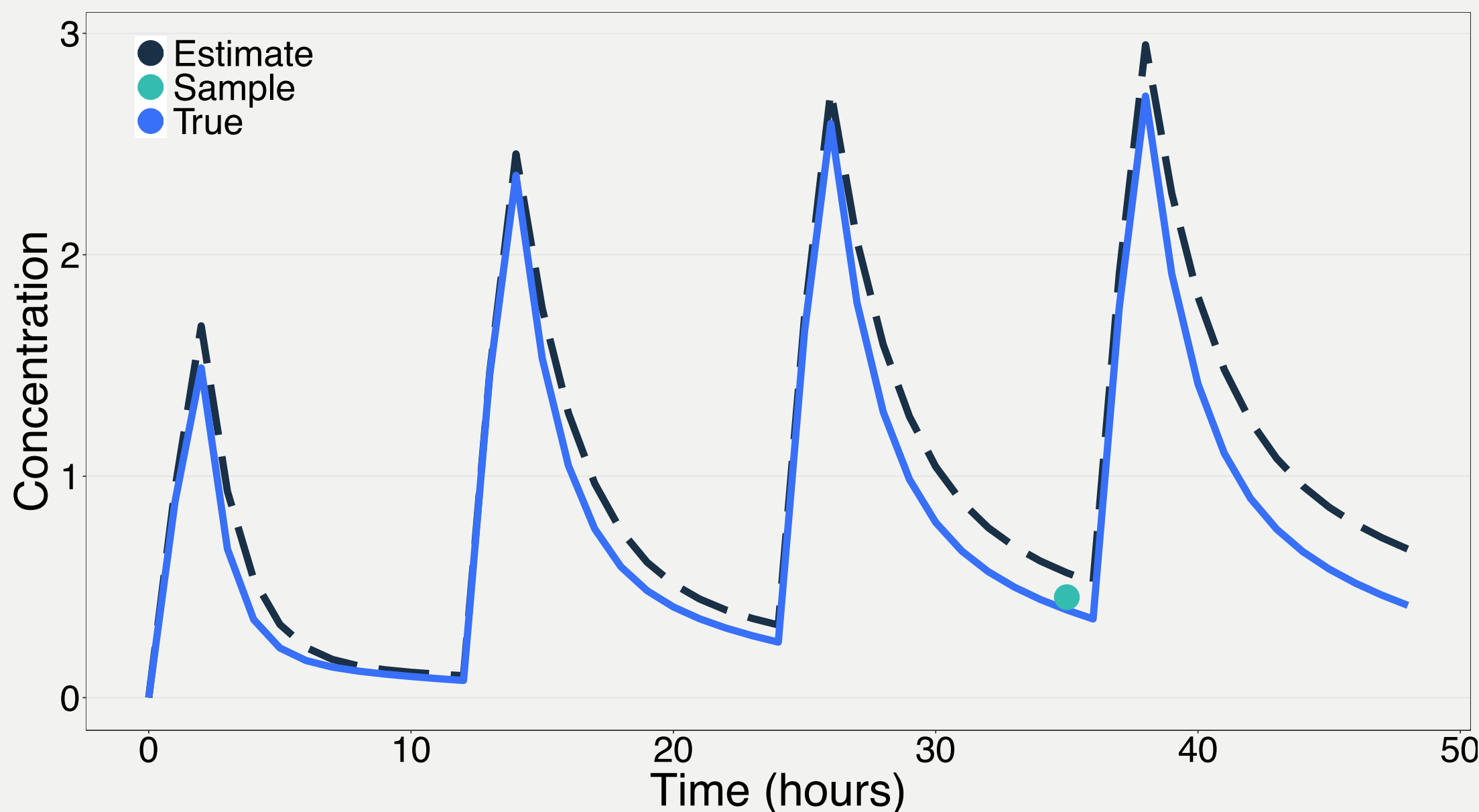
- MAP Bayesian estimation using R package stats (stats::optim)
- Full Bayesian estimation (Hamiltonian Monte Carlo) using open-source R package PKPDposterior [1]

MAP and full Bayes estimation was evaluated across three simulated clinical scenarios:

1. A linear PK model for vancomycin [2]
2. A non-linear PK model for voriconazole [3]
3. A non-linear PK/PD model for predicting neutropenia during chemotherapy

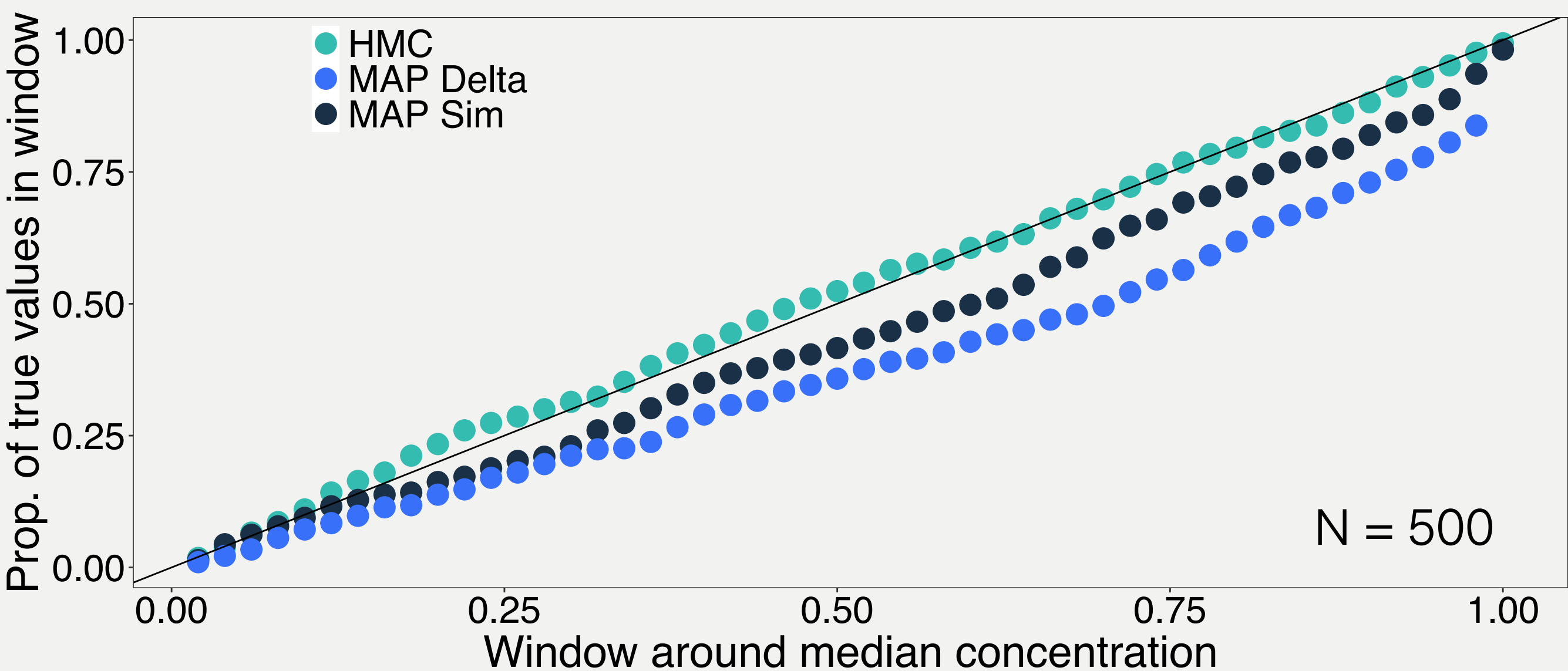
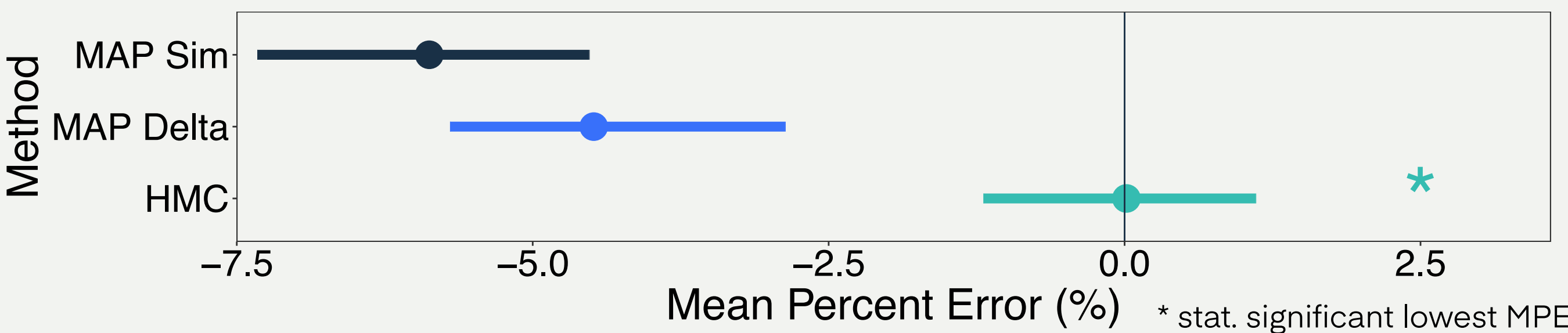
Simulation of each scenario:

1. Simulate true drug concentration curve (blue) with inter-individual variability using PKPDsim [4].

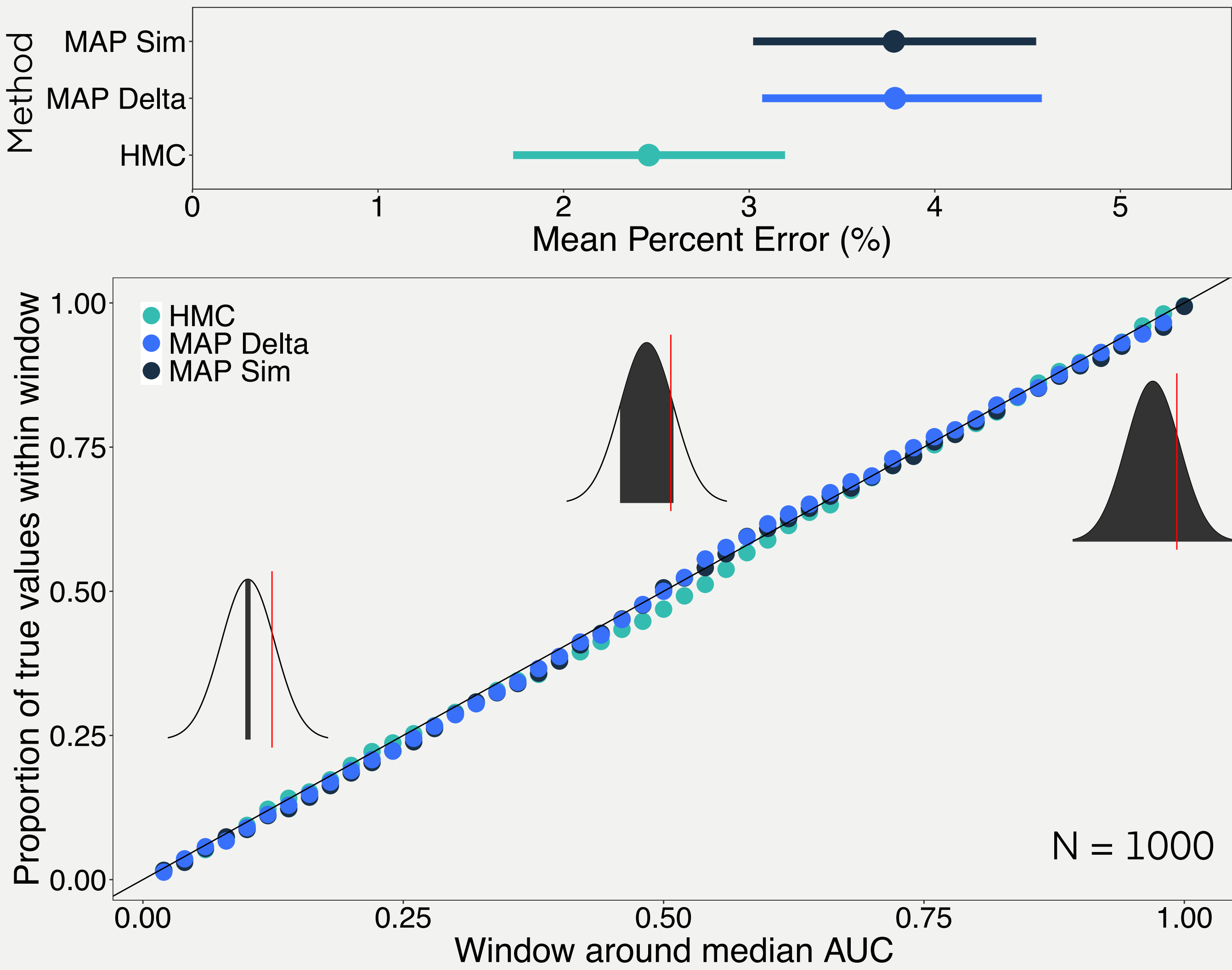


1. Simulate drug sample (teal point) including residual variability.
2. Estimate PK curve using MAP Bayes and full Bayes (navy).
3. Predict outcome: AUC, concentration, or neutropenia. Calculate mean percent error using median of distribution and true value.
4. Estimate uncertainty in outcome in 3 ways.
 - Full Bayes (HMC): sample 500 times from posterior distribution
 - MAP Bayes:
 - Delta method ("MAP Delta") [5]
 - Simulate 500 individuals using the covariance matrix ("MAP Sim")

Non-linear PK Model



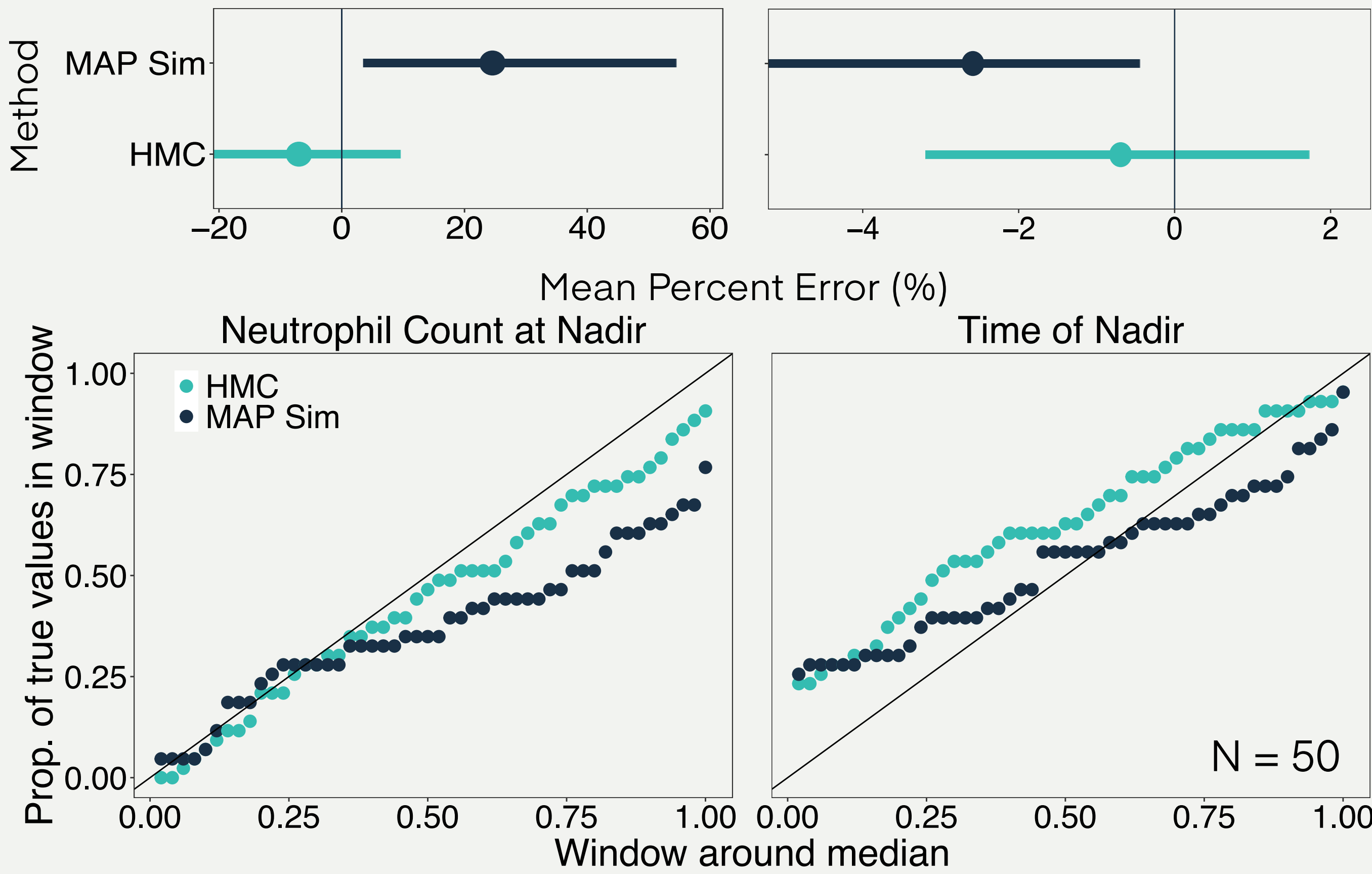
Linear PK Model



Uncertainty metrics are compared using the idea that for every percentile away from the median in the estimated distribution, a corresponding percentile of individuals should have their true value within that window.

Neutropenia PK/PD Model

- IV chemotherapeutic, 1250 mg on day 1, 2 and 3
- Concentration samples drawn at 2.5, 11.5 hours
- Neutrophil counts taken at 3, 6, 9, 12 days



Conclusions

- Point estimates for MAP and full Bayes predict similar AUC exposures in a linear PK model
- Inference using the Delta method underestimates uncertainty in posterior estimates relative to full Bayes in complex, non-linear PK or PK/PD models
- The choice of inference method can change the uncertainty in posterior estimates, which could change the clinical decision made using MIPD

References

- [1] Hughes JH et al. PAGE 2022
- [2] Thomson AH et al., J Antimicrob Chemother 2009
- [3] Friberg LE et al., Antimicrob Agents Chemother 2012
- [4] Keizer RJ. PKPDsim, 2022.
- [5] Wicha et al., PAGE 2015