

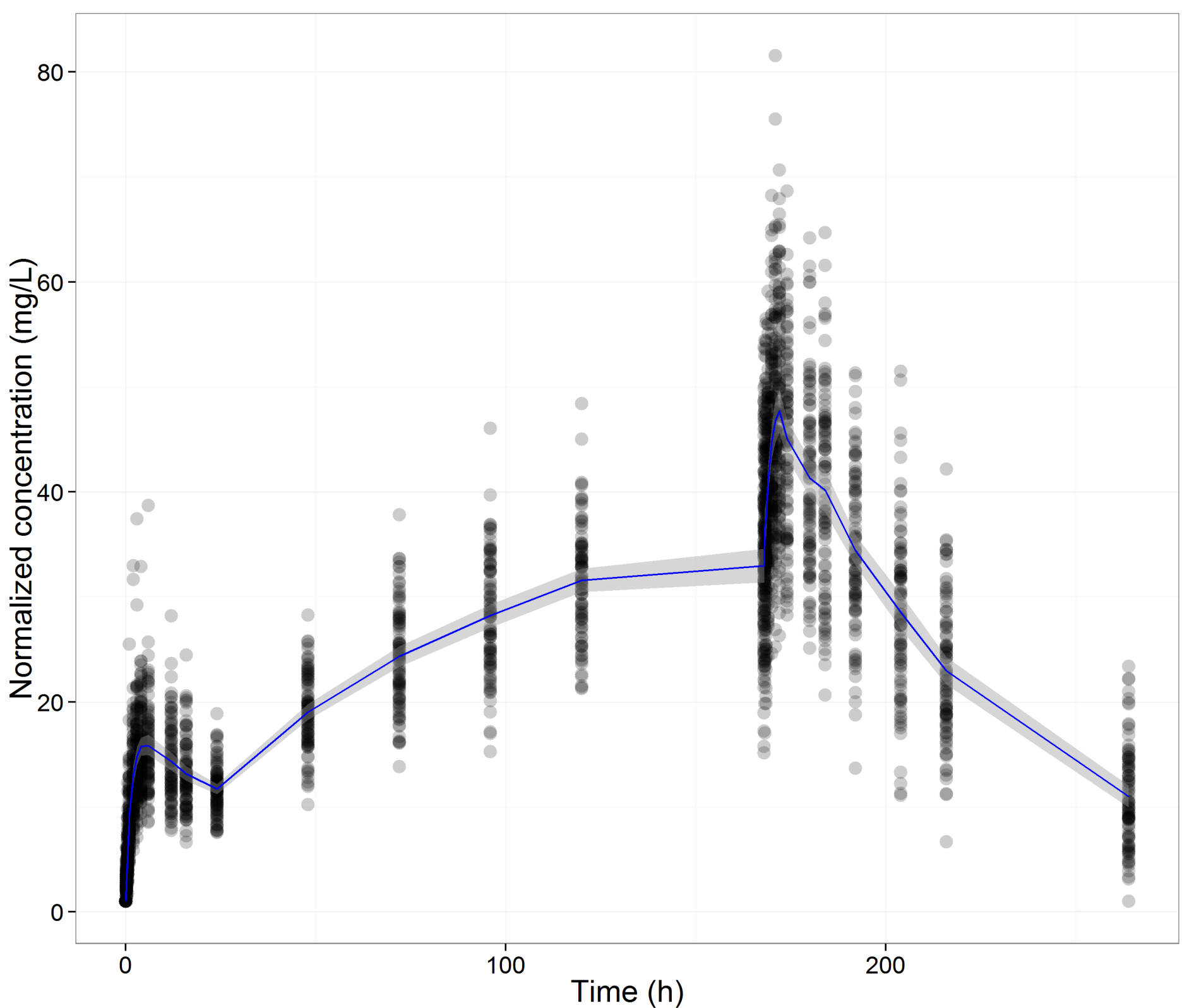
Introduction:

Stepwise covariate modeling (SCM) is a commonly used tool for covariate model selection. Traditionally, SCM as implemented in Perl Speaks NONMEM (PsN)[1] is performed using deterministic estimation methods (e.g. FOCE-I, Laplace). The recent availability of stochastic methods, such as: stochastic approximation EM (SAEM), importance sampling EM (IMPEM), and Bayesian Markov Chain Monte Carlo methods (BAYES) [2] raises the question of how the SCM process fares in the face of stochastic noise in the objective function. Prompted by a real case where SCM failed with FOCE-I and succeeded with BAYES the current simulation-estimation study aims to test the performance of FOCE-I vs. BAYES methods in a hypothetical SCM process and to challenge the model selection criterion used.

Objectives:

To assess the performance of SCM with Bayesian models under different model selection criteria.

Figure 1. Example simulated dataset



Simulated, normalized concentrations for 90 subjects, with mean and standard error overlayed in blue.

Simulation model

$$C_p = \text{Dose} \frac{k_a}{V(k_a - k_e)} (e^{-k_e t} - e^{-k_a t}), \quad k_e = \frac{CL}{V} \quad \text{Structural model}$$

$$k_a = 0.75e^{\eta_{k_a}}$$

$$CL = 0.05(1 - 0.003(\text{AGE} - 52))e^{\eta_{CL}}$$

$$V = 3.0 \left(\frac{WT}{78} \right) e^{\eta_V}$$

$$sd(\eta) = 0.15$$

Simulated concentrations incorporate 15% CV error and are censored at 1 mg/L. Doses were 50, 250, and 500 mg.

Simulated parameter and covariate values for the first (of 100) simulated datasets is illustrated here.

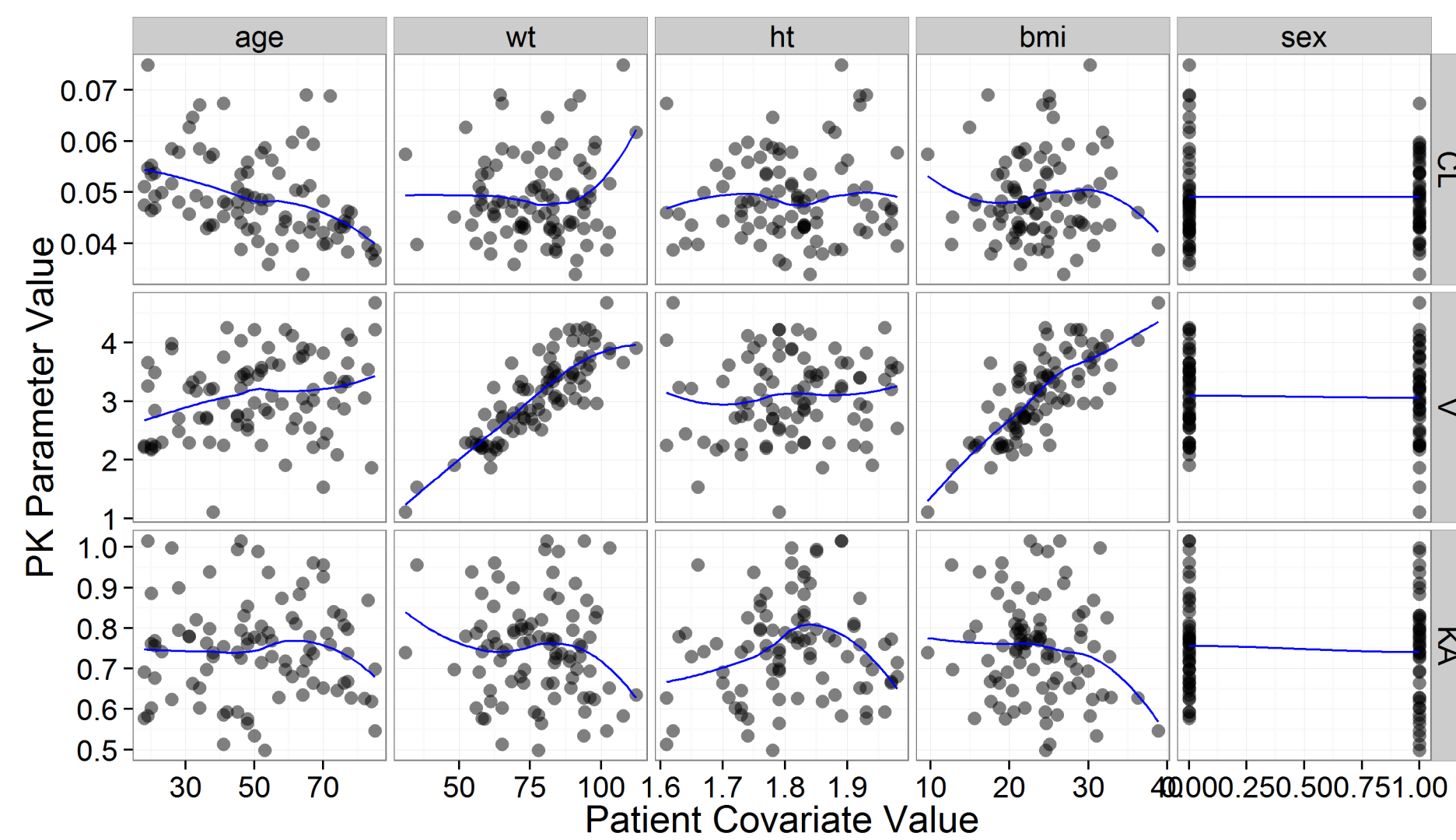
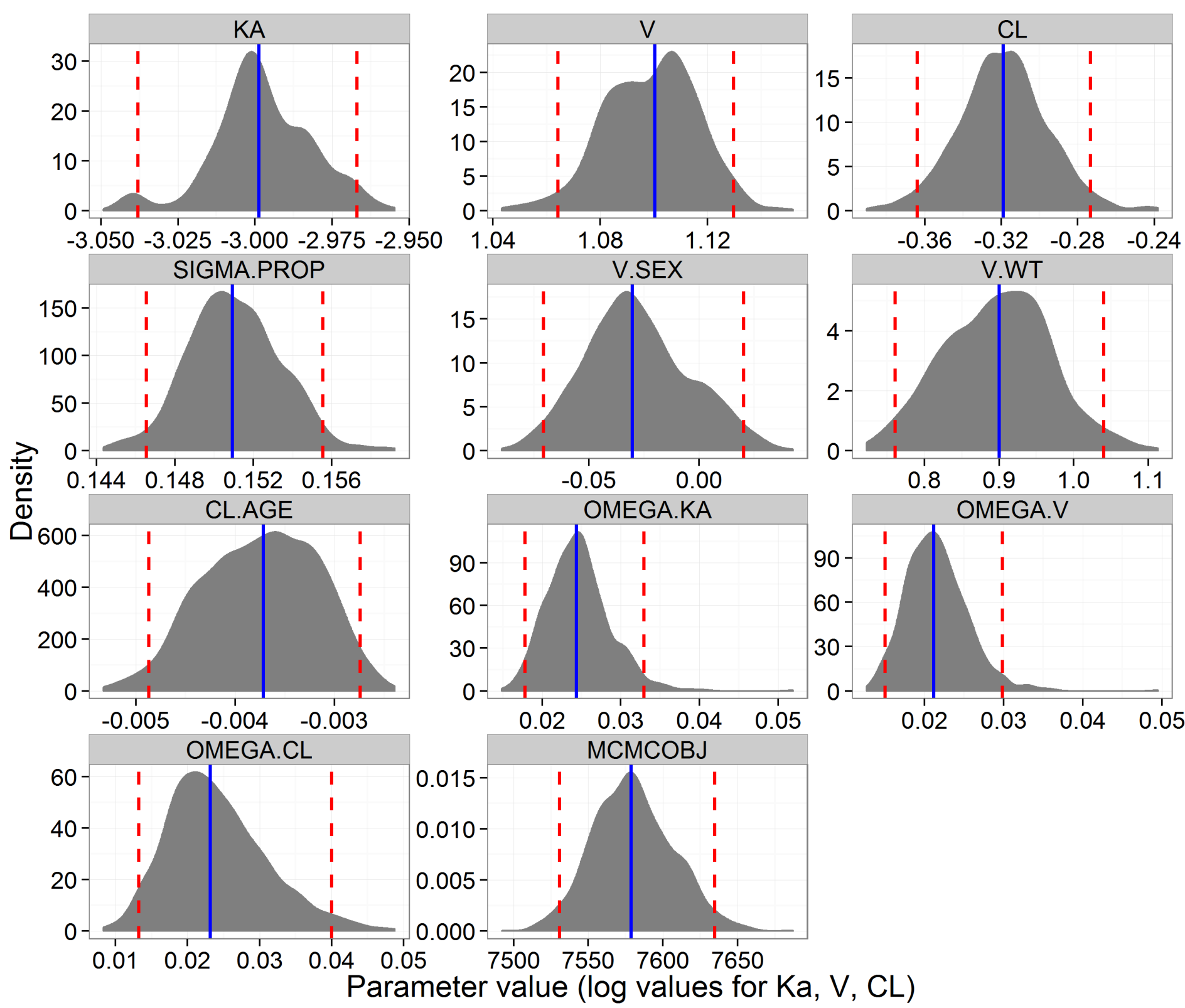


Figure 2. Example of Bayesian parameter estimates



MCMC derived parameter distributions in an over parameterized case – density (gray), median (blue), 95% credible interval (red)

Methods:

The true model was a one-compartment elimination, 1st-order absorption PK model with body weight proportionally increasing volume of distribution and CL decreasing with age. From this model a data set with 90 subjects with dense sampling was simulated 100 times (Figure 1). Other, non-impactful and highly correlated covariates were added to the data set.

Using the correct structural model, an SCM for three scenarios was run on all data sets and the success rate to recover the true model was retained. The three SCM scenarios and model selection methods used were:

1. FOCE-I with the final objective function value (OFV) as model selection criterion
2. MCMC BAYES with the sample mean OFV
3. MCMC BAYES and the Deviance Information Criterion[3] (DIC)

DIC has been suggested [4,5] as a robust method for model selection in Bayesian analyses. The SCM tool in PsN was modified to compute either the mode of the OFV (current SCM default) or the DIC to be used as model selection criterion.

$$DIC = OFV + \frac{1}{2} \text{var}(OFV)$$

The SCM searched AGE, HT, WT, BMI and SEX on the V and CL parameters.

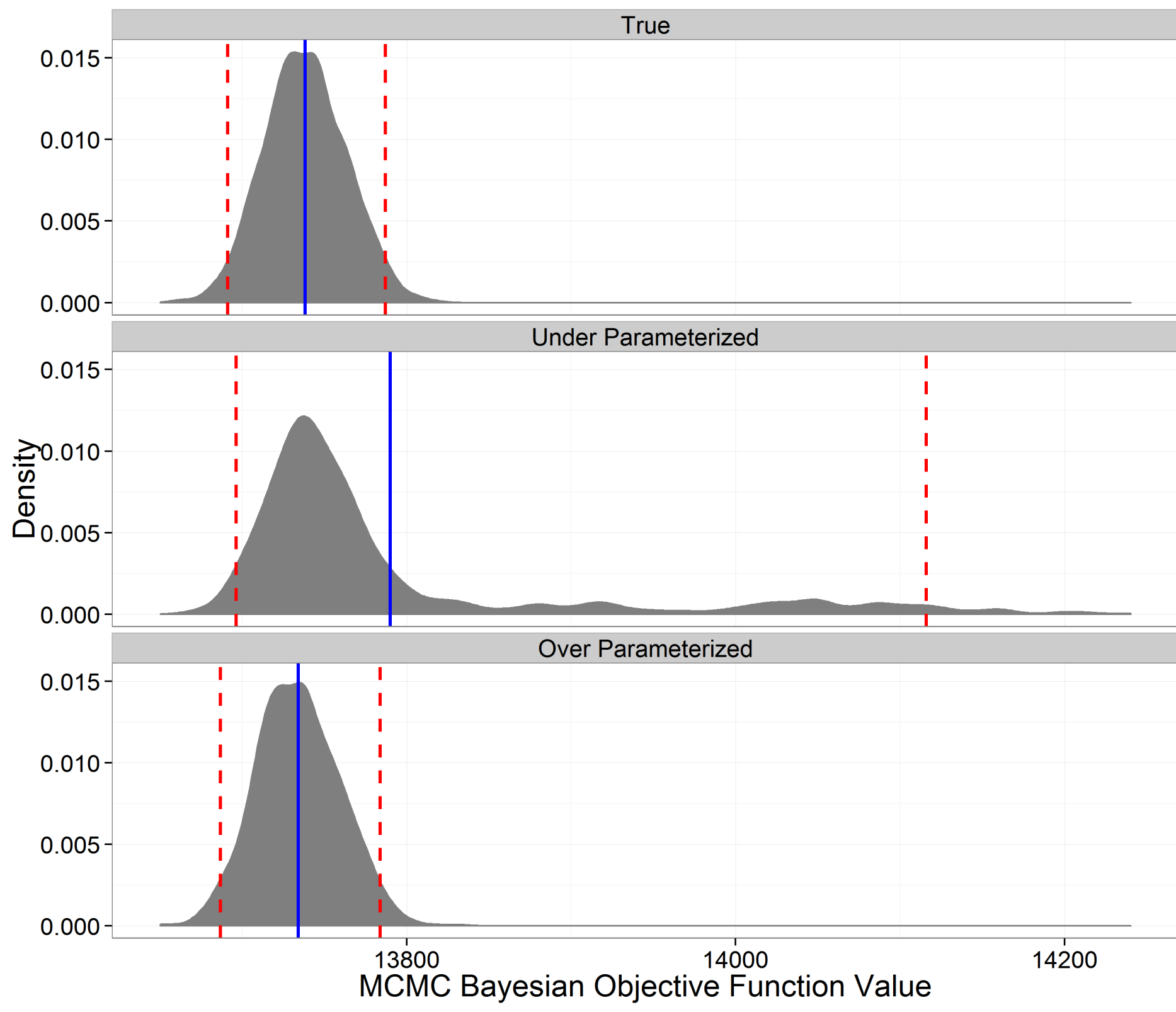
Where SCM failed to identify the true model it was determined if pruning of the selected model by removing non-significant (alpha=5%) effects would correct it to be the true model. For the FOCE-I models, pruning entailed re-running the model in backward steps, while for the MCMC models the 95% credible interval for the final model was used directly by assessing inclusion of zero.

Results:

MCMC with DIC selection criteria performed very poorly, while MCMC with OFV performed on par with FOCE-I, or even better when SCM final models were corrected.

Model Identification			
Parameter	Successful	Corrected	Incorrect
FOCE-I	65%	3%	32%
Bayes-OFV	60%	13%	27%
Bayes-DIC	14%	8%	78%

Figure 3. Comparison of Bayesian OFV distributions



Density (gray), mean (blue), and 95% credible interval (red) for representative cases of true, under parameterized, and over parameterized models.

Discussion:

- SCM selected over parameterized model in many of the MCMC cases (both DIC and OFV). Often these models included the true effects and addition effects and it was readily to ascertain the true effects from the parameter distributions. See Figure 2 for an over parameterized SCM result where it can be seen that the SEX effect on V can probably be ignored - which recovers the true model.
- The poor performance of DIC as a model selection metric was surprising as our interpretation of the literature suggested that DIC would be a better criteria for MCMC models. Figure 3 shows three representative MCMC runs. Clearly the under-parameterized case will have a worse DIC, but the true and over-parameterized cases are quite similar. It may be that outliers in the sample space add considerable noise to the OFV variance, causing DIC to be overestimated at smaller posterior sample sizes.

Conclusions

- SCM can be performed using MCMC Bayesian or FOCE-I estimation interchangeably using the OFV as model selection criterion. The DIC criterion was found to be unsuitable for the stepwise covariate search when using Bayesian estimation.

Key References

- [1] Lindbom, L.; Pihlgren, P. & Jonsson, N. PsN-Toolkit -- A collection of computer intensive statistical methods for non-linear mixed effect modeling using NONMEM. *Computer Methods and Programs in Biomedicine*, **2005**
- [2] Bauer, R. NONMEM Users Guide: Introduction to NONMEM 7.3.0. ICON Development Solutions; 2014
- [3] Spiegelhalter, D. J.; Best, N. G.; Carlin, B. P. & Van Der Linde, A. Bayesian measures of model complexity and fit. *Journal of the Royal Statistical Society: Series B (Statistical Methodology)*, Blackwell Publishers, **2002**
- [4] Lunn, D. J.; Best, N.; Thomas, A.; Wakefield, J. & Spiegelhalter, D. Bayesian Analysis of Population PK/PD Models: General Concepts and Software. *Journal of Pharmacokinetics and Pharmacodynamics, Journal of Pharmacokinetics and Pharmacodynamics*, Kluwer Academic Publishers-Plenum Publishers, **2002**
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