Comparative Performance of Bayesian Markov Chain Monte Carlo and Maximum Likelihood Population Estimation Methods when Applied to Nonlinear Pharmacokinetics of Monoclonal Antibodies

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Background

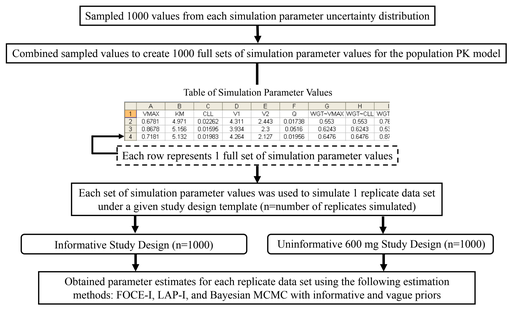
Nonlinear elimination is a common characteristic of the pharmacokinetics (PK) of therapeutic monoclonal antibodies (mAbs), and accordingly, PK models with nonlinear elimination have been used in almost half of the population PK analyses of therapeutic mAbs published in the scientific literature to date [1]. Difficulties detecting and characterizing this nonlinear PK have been reported in a number of population PK analyses of therapeutic mAbs [1]. The challenge with detecting and characterizing this nonlinear PK is not only dependent on the study design, but also on the estimation method used for the population PK analysis [2]. However, little work has been done so far evaluating population estimation methods using PK models that are representative of the typical disposition characteristics of therapeutic mAbs, as most method comparison studies used a one-compartment model with linear elimination for comparison [3, 4, 5, 6, 7, 8].

Objective

- To compare the parameter estimation performance of the first-order conditional estimation and Laplacian methods with interaction (FOCE-I and LAP-I) in NONMEM (version VI) and a Bayesian Markov Chain Monte Carlo (MCMC) method in WinBUGS (version 1.4.3) with BUGSModelLibrary [9] for population PK modeling of therapeutic mAbs with nonlinear elimination.
- To explore the impact of study design on estimation performance.
- To evaluate the sensitivity of conclusions to uncertainty in simulation model parameters.

Methods

Figure 1: *Overview of the methodology of the simulation and estimation steps*



Population PK Model

For purposes of this study it was assumed that the theoretical mAb was of the human IgG1 type that targets a cell membrane receptor primarily expressed in tissue and is indicated in the area of oncology. Published findings from population PK analyses of therapeutic mAbs and their general PK behavior were used to define the population PK model in terms of model structure and fixed and random effect parameters [1]. The structural PK model used for the simulation/estimation steps was a two-compartment model with parallel linear and nonlinear elimination from the central compartment. Between-subject variability was included in the parameters Vmax, CLL, V1, and V2, and was modeled using an exponential error. Body weight (kg) was considered to be a predictor of Vmax, CLL, V1, and V2, and was modeled using a power model (with weight normalized). Residual variability was modeled using an exponential error.

Clinical Study Designs

Replicate data sets were simulated under two different study designs typically encountered during drug development: a dose-ranging design ('informative design') and a single dose level design ('uninformative design'). The study templates were designed to be representative of phase I/II studies included in published population PK analyses of therapeutic mAbs. In the informative design there were six dose groups with six patients per group. The mAb was administered weekly for 4 weeks as a 1 hr IV infusion at doses of 50, 100, 200, 400, 800, or 1600 mg, resulting in concentration ranges below and above the Km. Peak and trough mAb concentrations were obtained at weeks 2 and 3, and on weeks 1 and 4 a full PK concentration-time profile was obtained with concentrations sampled at 1, 3, 6, 10, 24, 48, 72, 96, and 168 hours after the start of the infusion. In the uninformative design there were 36 patients and all were treated at the 600 mg dose level, resulting in concentrations generally above the Km, thereby making it more difficult to detect and characterize the nonlinear elimination of the therapeutic mAb. The dosing and sampling schedules in the uninformative design were the same as in the informative design except for the full PK concentration-time profile at week 1 which was removed.

Simulation Parameter Uncertainty Distributions

Simulation of the replicate data sets was performed with uncertainty included simultaneously on all parameters in the population PK model. Given that the population PK characteristics of therapeutic mAbs are quite similar [1], the published findings from over 20 population PK analyses were used to define the simulation parameter prior (uncertainty) distributions. All population PK analyses that used a two-compartment model were considered in defining the distributions regardless of the clearance model used, but the focus was on analyses where nonlinear elimination of the mAb was modeled. Either lognormal (univariate or multivariate) or uniform distributions were used for all parameters. Patient weights were simulated simultaneously with concentration data for each replicate data set, and were assumed to follow a lognormal distribution with a variance of 0.04 and a mean weight randomly sampled from a specified uncertainty distribution.

Table 1: *Simulation parameter prior (uncertainty) distributions*

Fixed Effects

$$\ln(V_{\max}) \sim N[\ln(18.0\ \text{mg/day}), 0.01]$$
$$\ln(K_m) \sim N[\ln(5.0\ \text{mg/L}), 0.01]$$
$$\ln(CL_L, V_1, V_2, Q) \sim N(\bar{\mu}, \Sigma)$$

$$\bar{\mu} = \begin{bmatrix} \ln(CL_L) \\ \ln(V_1) \\ \ln(V_2) \\ \ln(Q) \end{bmatrix} = \begin{bmatrix} \ln(0.47\ \text{L/day}) \\ \ln(4.3\ \text{L}) \\ \ln(2.7\ \text{L}) \\ \ln(0.97\ \text{L/day}) \end{bmatrix} \qquad \Sigma = \begin{bmatrix} 0.042 & 0.021 & 0.057 & 0.014 \\ 0.021 & 0.019 & 0.039 & 0.045 \\ 0.057 & 0.039 & 0.132 & 0.182 \\ 0.014 & 0.045 & 0.182 & 0.488 \end{bmatrix}$$

Weight effect on $V_{\max}$ and $CL_L \sim U(0.4, 1.0)$ Weight effect on V_1 and $V_2 \sim U(0.4, 1.0)$

Between-subject variability (defined for standard deviation)

$$V_{\max}\ \omega \sim U(0.15, 0.65) \qquad CL_L\ \omega \sim U(0.15, 0.65)$$
$$\ln(V_1\ \omega) \sim N[\ln(0.25), 0.04] \qquad \ln(V_2\ \omega) \sim N[\ln(0.25), 0.04]$$

Residual variability (defined for standard deviation)

$$\ln(\sigma) \sim N[\ln(0.15), 0.04]$$

Population mean weight

$$\ln(\text{population mean weight}) \sim N[\ln(72\ \text{kg}), 6.25\text{E}^{-4}]$$

$N(\mu, \sigma^2)$ = normal distribution with mean (μ) and variance (σ^2); $U(a, b)$ = uniform distribution with lower (a) and upper (b) limits; $\bar{\mu}$ is a vector of means and Σ is the variance-covariance matrix for a multivariate distribution

Bayesian Priors

The Bayesian MCMC method in WinBUGS was evaluated with both vague and informative priors. The rationale behind defining the informative priors were similar to that used for the simulation parameter uncertainty distributions, but they differed slightly as the informative priors were updated with additional therapeutic mAb population PK studies that were published or found in the literature from the time trial replicates were simulated. Due to prolonged run times, the number of estimation runs for evaluating WinBUGS was limited to 100 replicate data sets versus 1000 for the NONMEM estimation methods. Bayesian MCMC with vague priors was not evaluated under the uninformative design, because all of the estimation runs failed to run to completion.

Table 2: *Vague and informative Bayesian prior distributions (see Table 1 for notation definitions)*

Vague Priors

$$\ln(V_{\max}) \sim N[\ln(28.8\ \text{mg/day}), 10000]$$
$$\ln(K_m) \sim N[\ln(10.0\ \text{mg/L}), 10000]$$
$$\ln(CL_L) \sim N[\ln(0.72\ \text{L/day}), 10000]$$

$$\ln(V_1) \sim N[\ln(3.0\ \text{L}), 10000]$$
$$\ln(V_2) \sim N[\ln(2.0\ \text{L}), 10000]$$
$$\ln(Q) \sim N[\ln(1.8\ \text{L/day}), 10000]$$

Weight Effect on $V_{\max} \sim U(0, 5.0)$
Weight Effect on $CL_L \sim U(0, 5.0)$
Weight Effect on $V_1 \sim U(0, 5.0)$
Weight Effect on $V_2 \sim U(0, 5.0)$
$V_{\max}\ \omega \sim U(1.0\text{E}^{-4}, 1.0\text{E}^{4})$
$CL_L\ \omega \sim U(1.0\text{E}^{-4}, 1.0\text{E}^{4})$
$V_1\ \omega \sim U(1.0\text{E}^{-4}, 1.0\text{E}^{4})$
$V_2\ \omega \sim U(1.0\text{E}^{-4}, 1.0\text{E}^{4})$
$\sigma \sim U(1.0\text{E}^{-4}, 1.0\text{E}^{4})$

Informative Priors

$$\ln(CL_{\text{int}}) \sim N[\ln(2.4\ \text{L/day}), 0.25]$$
$$\ln(K_m) \sim N[\ln(10.0\ \text{mg/L}), 1.38]\{V_{\max} = CL_{\text{int}} * K_m\}$$
$$\ln(CL_L, V_1, V_2, Q) \sim N(\bar{\mu}, \Sigma)$$

$$\bar{\mu} = \begin{bmatrix} \ln(CL_L) \\ \ln(V_1) \\ \ln(V_2) \\ \ln(Q) \end{bmatrix} = \begin{bmatrix} \ln(0.25\ \text{L/day}) \\ \ln(3.6\ \text{L}) \\ \ln(2.6\ \text{L}) \\ \ln(0.80\ \text{L/day}) \end{bmatrix} \quad \Sigma = \begin{bmatrix} 0.855 & 0.266 & 0.305 & 0.234 \\ 0.266 & 0.090 & 0.125 & 0.089 \\ 0.305 & 0.125 & 0.349 & 0.140 \\ 0.234 & 0.089 & 0.140 & 0.317 \end{bmatrix}$$

Weight Effect on $V_{\max} \sim U(0.25, 1.25)$
Weight Effect on $CL_L \sim U(0.25, 1.25)$
Weight Effect on $V_1 \sim U(0.25, 1.25)$
Weight Effect on $V_2 \sim U(0.25, 1.25)$
$\ln(V_{\max}\ \omega) \sim N[\ln(0.35), 0.16]$
$\ln(CL_L\ \omega) \sim N[\ln(0.35), 0.16]$
$\ln(V_1\ \omega) \sim N[\ln(0.25), 0.16]$
$\ln(V_2\ \omega) \sim N[\ln(0.25), 0.16]$
$\ln(\sigma) \sim N[\ln(0.20), 0.16]$

Results

Figure 2: *Box plots of percent estimation errors for the population PK model parameters under the informative and uninformative 600 mg dose study designs. Outliers are not shown for visualization purposes and made up < 10% of the data for each box plot. B-IP and B-VP = Bayesian MCMC with informative and vague priors, respectively; BSV = between-subject variance; WGT = weight.*

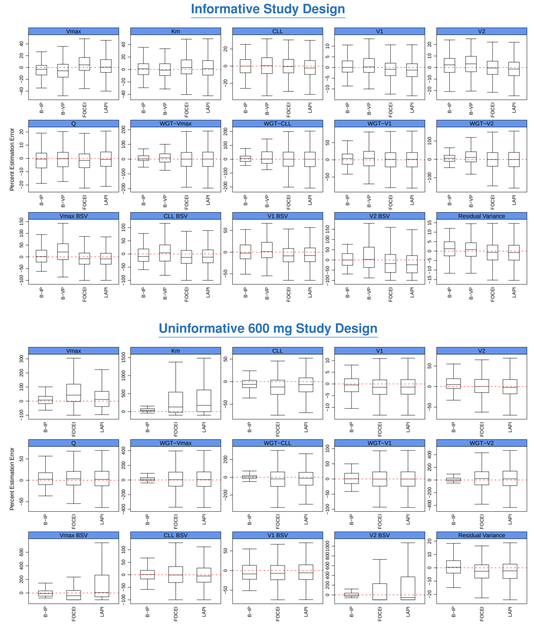
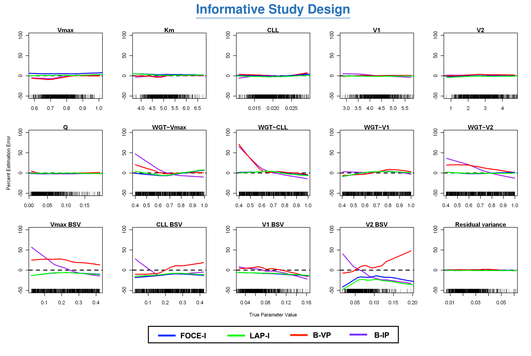
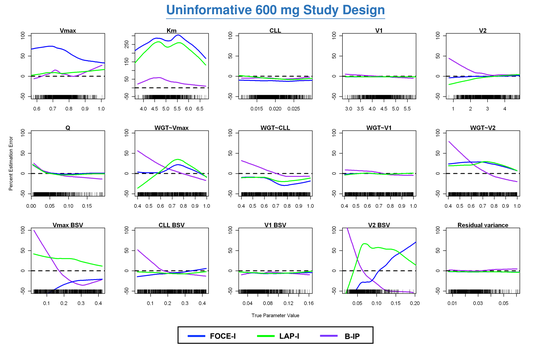


Figure 3: *Global sensitivity analysis results from the informative and uninformative 600 mg study designs. Plots are shown as the percent estimation error plotted relative to the specific value of the simulation model parameter for each replicate. Only the LOESS smoothing curves of the data are shown for each estimation method. The parameter values used to simulate each replicate data set (i.e., those simulated from the simulation parameter uncertainty distributions) are shown as a rug plot on the x-axis.*





Simulations were performed to assess the sensitivity of model-based predictions to the observed parameter biases (median percent estimation error, see Figure 2). For the simulations, a set of true and a set of biased population PK model parameter values were specified. The true parameter values were assigned to the means and midpoints of the simulation parameter prior (uncertainty) distributions. The biased parameter values were determined by biasing the true values based on observed parameter biases under a given estimation method/study design scenario. Monte Carlo simulations were performed at different dose levels using the same dosing schedule as defined for the study designs, and 6000 patients were simulated per dose level. The simulations were carried out using both the true and biased sets of parameter values. The median and 90% prediction interval of the simulated concentrations during the week 4 full concentration-time profile served as the metrics by which the true and analysis-derived biased predictions were compared.

Figure 4: *Results of the simulations based on parameter biases observed for FOCE-I under the informative study design. Similar results were observed for LAP-I and Bayesian MCMC with both sets of priors. The true and analysis-derived biased predictions are indicated by the solid black lines and dashed red lines, respectively. The three lines represent the 5th, 50th, and 95th percentiles determined from 6000 patient concentration-time profiles simulated at each dose level.*

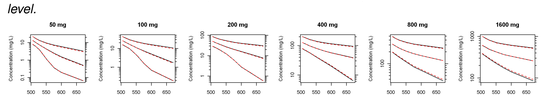
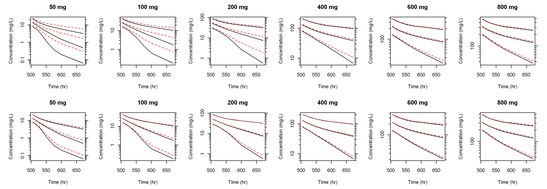


Figure 5: *Results of the simulations based on parameter biases observed for LAP-I (top panel) and Bayesian MCMC with informative priors (bottom panel) under the uninformative 600 mg study design. Similar results were observed for LAP-I and FOCE-I.*



Conclusions

- The performance of all the evaluated methods under the informative design was adequate and comparable, as the bias and precision (median absolute percent estimation error) for all parameters was less than 25% and 52%, respectively. When sufficient concentration-time data are available to characterize the nonlinear elimination of the therapeutic mAb, then any one of the evaluated methods would likely be suitable for the population PK analysis.
- Under the uninformative design, the estimation performance of FOCE-I and LAP-I decreased as bias and precision for many model parameters, in particular those related to nonlinear elimination, significantly increased to ±40–173% and 53–173%, respectively, while Bayesian MCMC with informative priors produced results that were comparable to those under the informative design. In situations where insufficient data are available to characterize the nonlinear elimination of the mAb, and relevant prior information is readily available, the use of a Bayesian MCMC method with informative priors should be considered.

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