Monte Carlo expectation-maximization in Pumas: Leveraging sufficient statistics for flexible pharmacometric analysis

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INTRODUCTION

Expectation-maximization (EM) algorithms are a well-established alternative to likelihood-approximation-based methods such as FOCE and the Laplace method for parameter estimation in nonlinear mixed-effect (NLME) models in pharmacometric analysis.

NONMEM's implementation of Monte Carlo parametric expectation-maximization (MC-PEM) [1,2] uses MAP-centered importance sampling and a numerical optimization M-step [3].

However, inter-individual variability is restricted to normal distributions and transformations of normal distributions such as log-normal and logit-normal distributions, limiting the ability to capture non-standard variability patterns.

Pumas introduces a new experimental MCEM implementation that exploits the exponential family structure of random effect distributions, enabling native support for non-Gaussian random effects including beta, gamma, and inverse-gamma distributions.

E-step

Generate weighted samples of random effects
For each subject $\mathrm{i} = 1, \ldots, \mathrm{N}$

$$\left\{\left(\eta_i^{(s)}, w_i^{(s)}\right)\right\}_{s=1,\ldots,M} \approx p\left(\eta \middle| y = y_i, \theta = \hat{\theta}_k\right)$$

Compute summary statistics T_η **and** T_y **with**

$$Q_\eta\left(\theta; T_\eta\right) \coloneqq \sum_{i=1}^{N} \sum_{s=1}^{M} w_i^{(s)} \log p\left(\eta = \eta_i^{(s)} \middle| \theta\right)$$

$$Q_y\left(\theta; T_y\right) \coloneqq \sum_{i=1}^{N} \sum_{s=1}^{M} w_i^{(s)} \log p\left(y = y_i \middle| \eta = \eta_i^{(s)}, \theta\right)$$

M-step

Maximize the Monte Carlo estimate of the complete data log-likelihood

$$\hat{\theta}_{k+1} \leftarrow \operatorname{argmax}_\theta Q_\eta\left(\theta; T_\eta\right) + Q_y\left(\theta;\ T_y\right)$$

Figure 1: Structure of the MCEM algorithm for NLME models in Pumas.

OBJECTIVES

- Study the bias and variability of Pumas MCEM estimates on a model with log-normally distributed random effects and compare it to estimation with FOCE and the Laplace method
- Demonstrate the ability of Pumas MCEM to fit models with non-Gaussian random effect distributions by estimating a model with gamma-distributed inter-individual variability

METHODS

Two simulation scenarios were designed:

- **Scenario 1 (Log-Normal):** One-compartment IV bolus model
  $$\mathrm{conc}(t) \coloneqq 100\, e^{-k_{10} t}/Vc$$
  with log-normal random effects on volume Vc and elimination rate k_{10} ($\theta Vc \coloneqq 70$, $\theta k_{10} \coloneqq 0.2$, $\Omega \coloneqq \begin{bmatrix} 0.3 & -0.4 \\ -0.4 & 0.7 \end{bmatrix}$) and a proportional Gaussian error model ($\sigma \coloneqq 0.2$) (cf. Example 1 in [2]).
- **Scenario 2 (Gamma):** Same one-compartment IV bolus model with a gamma-distributed random effect on elimination rate k_{10} (mean $\theta k_{10} \coloneqq 0.3$, SD $\omega k_{10} \coloneqq 0.3$) and a log-normal random effect on volume Vc ($\theta Vc \coloneqq 70$, $\omega Vc \coloneqq 0.5$).

For both scenarios, 500 datasets of sparsely sampled observations ($t \in \{0.1, 3, 15\}$) of $N = 1000$ subjects were simulated.

For each simulated dataset, parameter estimation was performed using MCEM, FOCE, and the Laplace method in Pumas. MCEM was run with 50 iterations and $M_1 = 100$ initial Monte Carlo samples, increasing polynomially per [4] ($M_k \coloneqq M_1 + (k-1)^2$).

Simulations were evaluated based on the mean and standard deviation, empirical CV (%) and relative bias (%) of the parameter estimates.

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RESULTS

Scenario 1 (Log-Normal)

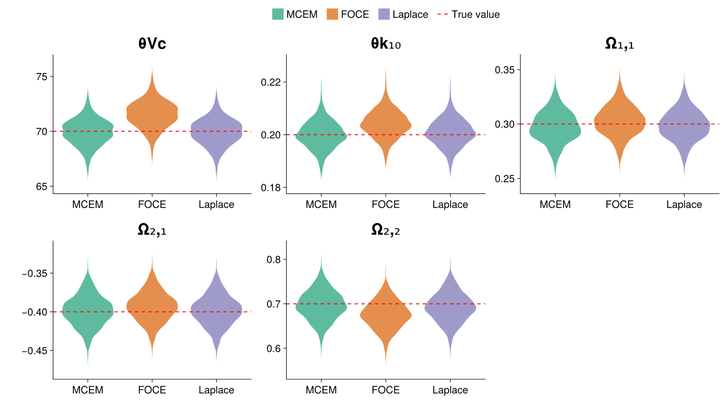

Figure 2: Distributions of parameter estimates.

	Mean			SD			CV (%)			Relative bias (%)		
Parameter	MCEM	FOCE	Laplace	MCEM	FOCE	Laplace	MCEM	FOCE	Laplace	MCEM	FOCE	Laplace
θVc	69.93	71.53	69.94	1.18	1.21	1.18	1.68	1.69	1.69	-0.10	2.18	-0.09
θk_{10}	0.20	0.20	0.20	0.01	0.01	0.01	2.56	2.50	2.55	-0.01	2.04	0.40
$\Omega_{1,1}$	0.30	0.30	0.30	0.01	0.01	0.01	4.69	4.49	4.52	-0.80	0.97	-0.39
$\Omega_{2,1}$	-0.40	-0.39	-0.40	0.02	0.02	0.02	-4.85	-4.77	-4.82	-0.29	-1.59	-0.38
$\Omega_{2,2}$	0.70	0.68	0.69	0.03	0.03	0.03	4.61	4.55	4.64	-0.50	-3.48	-1.19

Table 1: Mean, standard deviation, coefficient of variation and relative bias of parameter estimates.

Scenario 2 (Gamma)

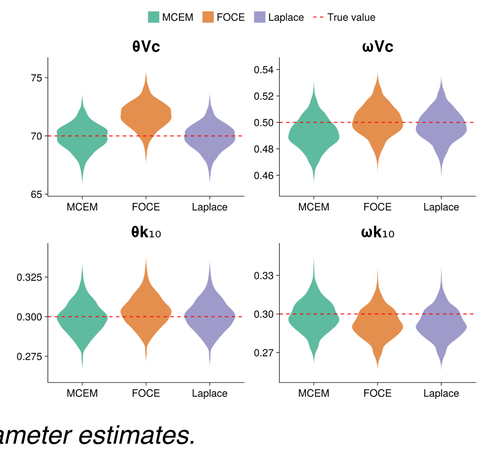

Figure 3: Distributions of parameter estimates.

	Mean			SD			CV (%)			Relative bias (%)		
Parameter	MCEM	FOCE	Laplace	MCEM	FOCE	Laplace	MCEM	FOCE	Laplace	MCEM	FOCE	Laplace
θVc	69.88	71.74	69.90	1.09	1.11	1.08	1.56	1.55	1.55	-0.17	2.49	-0.15
ωVc	0.49	0.50	0.50	0.01	0.01	0.01	2.31	2.26	2.28	-1.65	0.26	-0.44
θk_{10}	0.30	0.30	0.30	0.01	0.01	0.01	3.16	3.11	3.14	-0.27	1.07	0.18
ωk_{10}	0.30	0.29	0.29	0.01	0.01	0.01	3.92	3.87	3.87	-0.61	-2.50	-2.52

Table 2: Mean, standard deviation, coefficient of variation and relative bias of parameter estimates.

Summary: Maximum relative bias

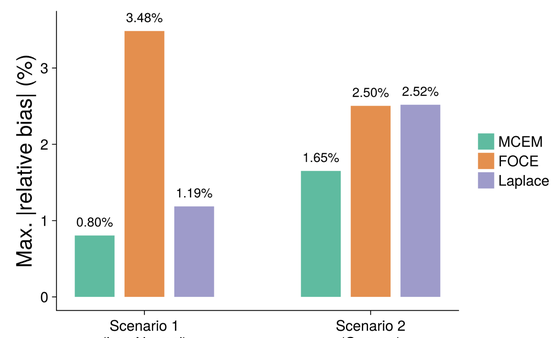

Figure 4: MCEM exhibits the smallest maximum relative bias in both scenarios.

CONCLUSIONS

- MCEM can be an alternative to FOCE and the Laplace approximation for maximum-likelihood estimation of NLME models, with low bias and native support for non-Gaussian random effects
- Improvements to proposal distributions, convergence diagnostics, and post-estimation inference are planned for upcoming releases

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