Evaluation of Recorded Time Deviations on Parameter Estimates in Nonlinear Mixed-effect Analyses

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SUMMARY

An assumption that recorded clinical data are recorded without any error is optimistically made. While some study personnel will record the actual times when there is a deviation others record the nominal time. In the current modeling and simulation work we:

I investigate an approach that includes a error correction factor on recorded time and quantitate the bias in estimated parameters;
II examining the magnitude difference between the actual and recorded time that lead to biased pharmacokinetic (PK) estimates; and
III compare the performance of first-order conditional (FOCE) and stochastic expectation-maximization (SAEM) algorithms in handling data with erroneous recorded times.

We conclude that:

- Adding a correction factor to the recorded time will lead to diluting the bias and imprecision in PK estimates compared to assuming the recorded time is absolute.
- A magnitude difference greater than 5 minutes between the actual and recorded times can lead to more than 10% bias and imprecision PK estimates.
- In comparison between estimation algorithms, SAEM estimates were more accurate than FOCE in primary PK parameters and produced similar RUV estimates on average.

Despite the limited settings, we believe this work provides general insight on the ways to handle suspected data with unrecorded time deviations.

METHODS

Two sources of error were modeled in this work: a classical error model and a combined classical and Berkson error model. The former is what the pharmacometrician/clinical pharmacologist frequently implements in NLMEM to characterize the errors in observed concentrations. The general structure for the j^{th} subject and i^{th} time point as:

$$y_{i,j} = f(\Phi, x_i, t_{i,j}) + g(\Phi, x_i, t_{i,j}, \zeta)\epsilon_{i,j} \quad (1)$$

Let us introduce the recorded time T_R for the i^{th} concentration in the j^{th} subject as a function of true time T_T and gaussian noise, κ, that is an independent and identically distributed random variable with mean 0 and standard deviation K, representing the deviation of recorded time from the true time.

$$T_{R,i,j} = T_{T,i,j} + \kappa_{i,j} \quad (2)$$

Therefore, the kappa model, M_κ, can be presented as:

$$y_{i,j} = f(\Phi, x_i, T_{T,i,j}) + g(\Phi, x_i, T_{T,i,j}, \zeta)\epsilon_{i,j} \quad (3)$$

In order to evaluate if there is a threshold of time deviation that is acceptable, we will be defining t^* in this work to represent the time used in estimation process under parts II-III, where this a mathematical case:

$$t^* = \begin{cases} T_T & |T_T - T_R| > \delta \\ T_R & \text{otherwise} \end{cases} \quad (4)$$

A 500 mg single dose study with 500 in-silico subjects were simulated under a two-compartment first-order absorption and linear elimination model, $f(.)$. Individual pharmacokinetic parameters were sampled from a multivariate log-normal distribution with a mean of the logarithmic typical values vector and diagonal variance matrix Ω. A 15% CV served as a baseline residual unexplained variability (RUV) using a proportional error model $g(.)$. Table 1 presents the true simulated PK parameters with corresponding BSV CV, and RUV magnitude.

Parameter	Estimate	BSV
CL (L/hr)	3.5	30%
V (L)	20.0	30%
Q (L/hr)	5.0	30%
Vp (L)	50.0	30%
Ka (1/hr)	0.7	30%

Table 1. Pharmacokinetic parameter values with corresponding between-subject variability reported as coefficient of variation.

Three sample collection designs were examined; (a) Intense design (I) with 8 samples: 0.5, 1, 2, 4, 8, 12, 24, 48 hours post dose, (b) sparse design (S) with 4 samples: 0.5, 2, 24, 48 hours post dose and (c) mixed design (M) with 33% of subjects having 8 samples as in I, 33% of subjects having 6 samples (0.5, 2, 4, 12, 24, 48), and 33% of subjects having 4 samples as in S.

Two models were created: the null model (Eq 1; M_0), and the kappa model, (Eq 3; M_κ), respectively. Model was built with 'PRED' subroutine to allow the implementation of M_κ since PRED has the flexibility of writing the analytical solution for the two-compartment model. Parameters were estimated using first-order conditional estimation (FOCE) with interaction between η and ϵ since a proportional error model is used.

In part two, simulations were perturbed with standard deviation of 10 minutes in time, then followed by creating a new column in the dataset presenting the time used in the estimation process as shown in equation (Eq 4; t^*). The difference, δ, was selected to be 5, 10, 15, or 30 minutes. In fitting the model to the data, t^* was used as the independent variable time with M_0.

In part 3 of this study we re-used data generated from the previous section (part II) but with different estimation methods; either with FOCE or SAEM algorithms including interaction. The AUTO=1 criteria was used to select the most suitable convergence test in SAEM, and importance sampling was used to evaluate the likelihood function.

RESULTS

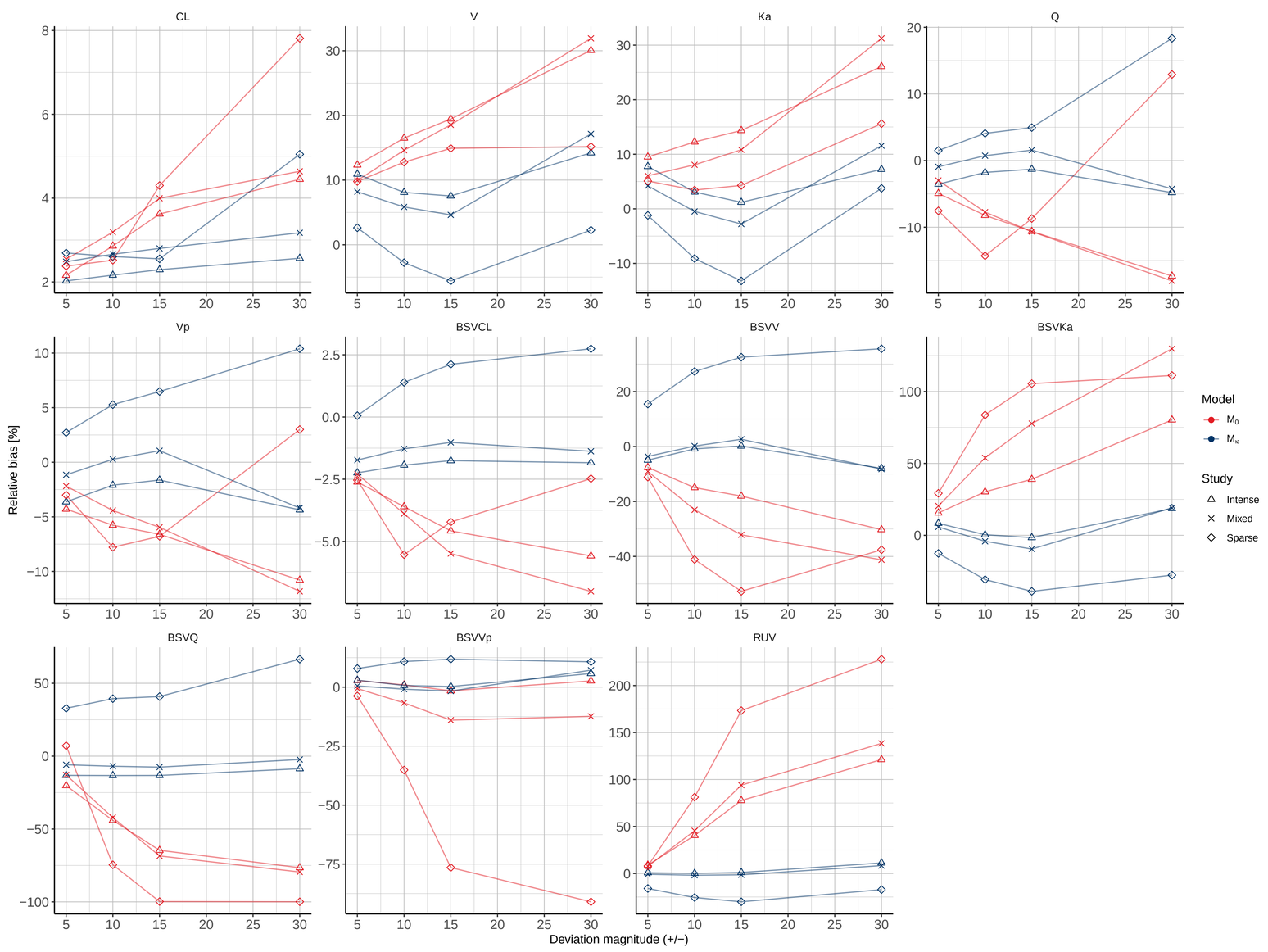

Figure 1. Comparison of the relative bias for the null model M_0 and kappa model M_K stratified on study design

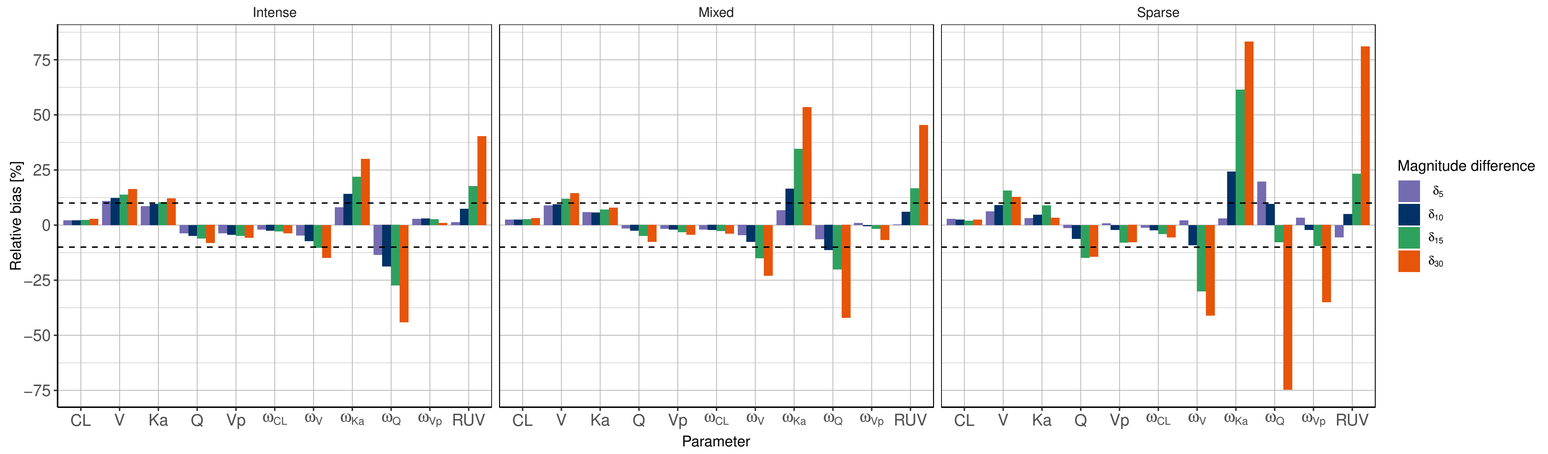

Figure 2. The magnitude difference δ between the true time and recorded time.

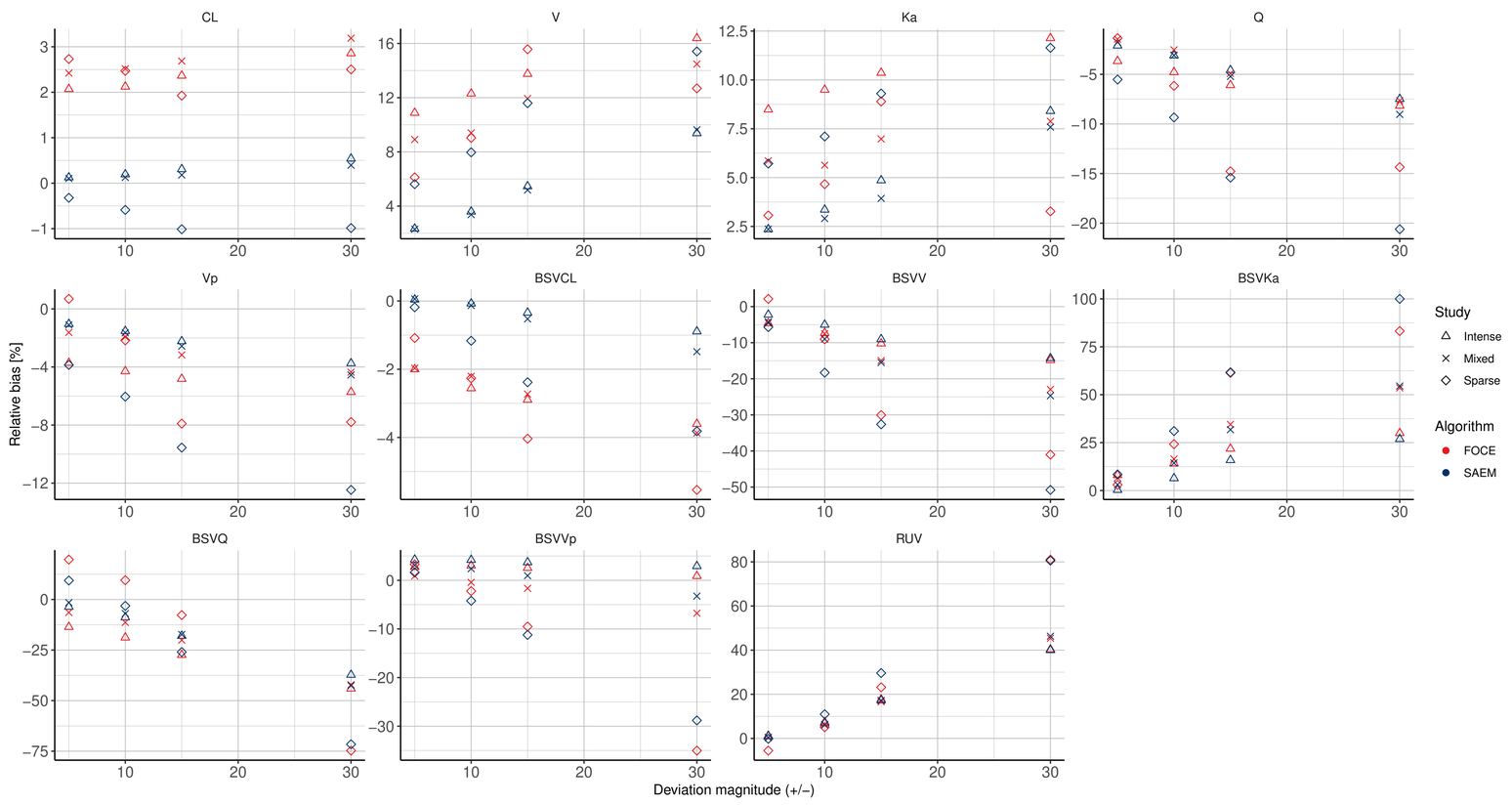

Figure 3. Comparison between FOCE and SAEM in handling erroneous times stratified on sample collection design. First-order conditional estimation (red) and stochastic approximation expectation-maximization (blue).