Using Full Random Effects Models (FREM) in different software

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Objective

- Implement FREM using Pumas, Monolix and nlmixr2 to compare their results with those obtained from NONMEM.
- Develop standardized tools for data pre-processing and post-processing of model results across software.

Background

FREM is an innovative approach for exploring covariate effects in mixed effect models [1]. It treats covariates as observations and evaluates their impact through covariances between parameters and covariates, it mitigates issues arising from high correlations among covariates and is also robust to missing covariate data [2].

FREM has been widely used in NONMEM. Due to its nature, it requires pre-processing the data for estimation and post-processing for model interpretation and diagnostics via Perl-speaks-NONMEM (PsN) and PMXFrem. However, similar tools are not available for other software.

Data and methods

Datasets

- A virtual "Phase III" study with 473 patients, including **mixed steady-state (SS) and non-SS** dosing, and **sparse sampling.**
- Covariates: weight, height, age, body mass index, creatinine clearance, race, and hepatic impairment (based on National Cancer Institute Organ Dysfunction Working Group, NCIODGW).
- A richly sampled dataset was also simulated for reference.

Models

- **One-compartment** model with **sequential zero- and first-order** absorption (Fig. 1). **CL** influenced by **NCIODGW, age, and weight; V** influenced by **weight.**
- FREM model included all available covariates, but **weight** was **log-transformed.**

Output processing

- Results were transformed into NONMEM-style output, then processed using PMXFrem [3] and PMXForest [4].
- Covariates, coefficients and datasets for full fixed effects model were generated.
- Uncertainty estimation was based on parametric re-sampling from the covariance matrix derived from the raw results of a non-parametric bootstrap with a small sample size.

Algorithms

- **SAEM** was the default estimation method.
- In Pumas, since EM algorithms don't support fixing residual errors, comparisons were done using FOCE.
- **FOCE** was also used for **nlmixr2** model runs.

Simulation structure

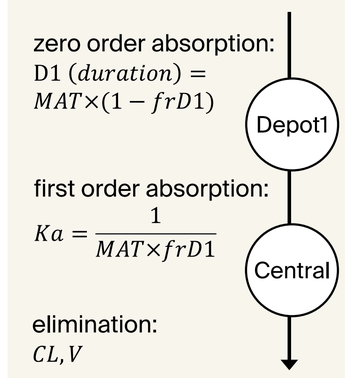

Figure 1. frD1 is the fractional duration of the first-order absorption phase. MAT (mean absorption time) is the sum of zero- and first-order absorption durations. Ka (first-order absorption rate constant) is defined by MAT and frD1. CL and V represent clearance and volume of the central compartment.

Table 1. Model setup per software.

Software (version)	Data type	Estimation method(s)
NONMEM (v7.5.0)	sparse and rich	FOCE & SAEM (sparse data); FOCE (rich data)
Pumas (v2.6)	sparse	FOCE
Monolix (v2024R1)	sparse	SAEM
nlmixr2 (v3.0.2)	rich	FOCE

Results

- FREM models were successfully estimated in NONMEM (FOCE, SAEM), Pumas (FOCE), and Monolix (SAEM), but nlmixr2 results were not considered reliable.
- Pumas and Monolix produced point estimates close to NONMEM, with absolute relative differences within 2% and 3%, respectively.
- Estimates of uncertainty varied more across software.
- Pumas and NONMEM had similar OFVs; Monolix showed higher OFVs.
- New PMXFrem functions were developed to standardize FREM inputs and outputs across software.

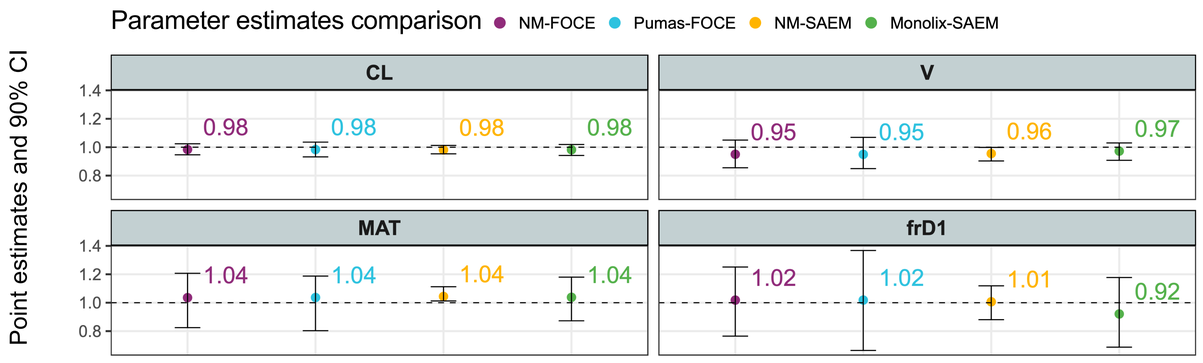

Figure 2. The dot plot illustrates the point estimates (the colored numbers, from single run) and 90% confidence intervals (the whiskers, from bootstrap uncertainty) for CL, V, MAT and frD1 across different software and algorithms.

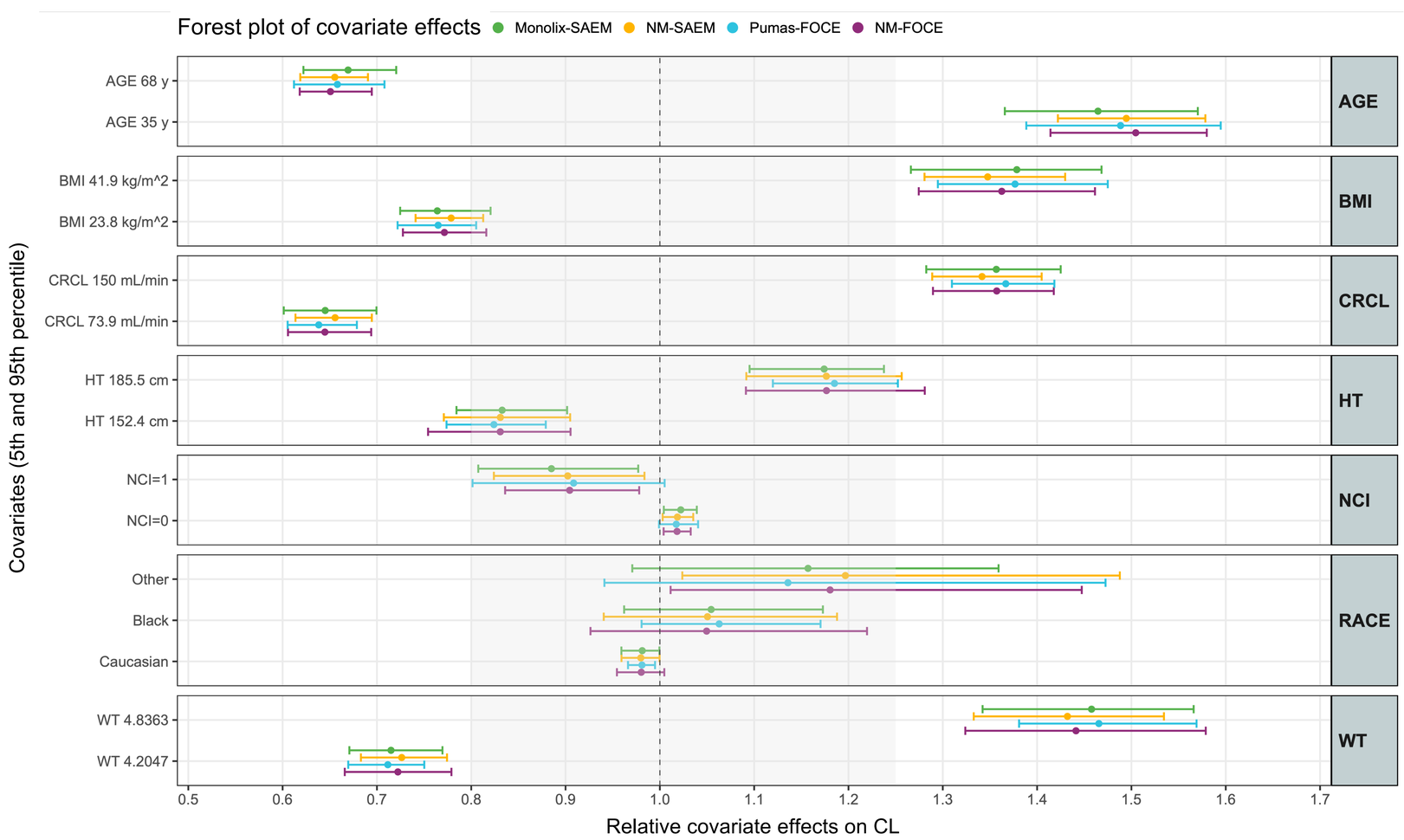

Figure 3. This figure presents the relative covariate effects (point estimates and 90% confidence intervals) for clearance (CL) across different software and algorithms.

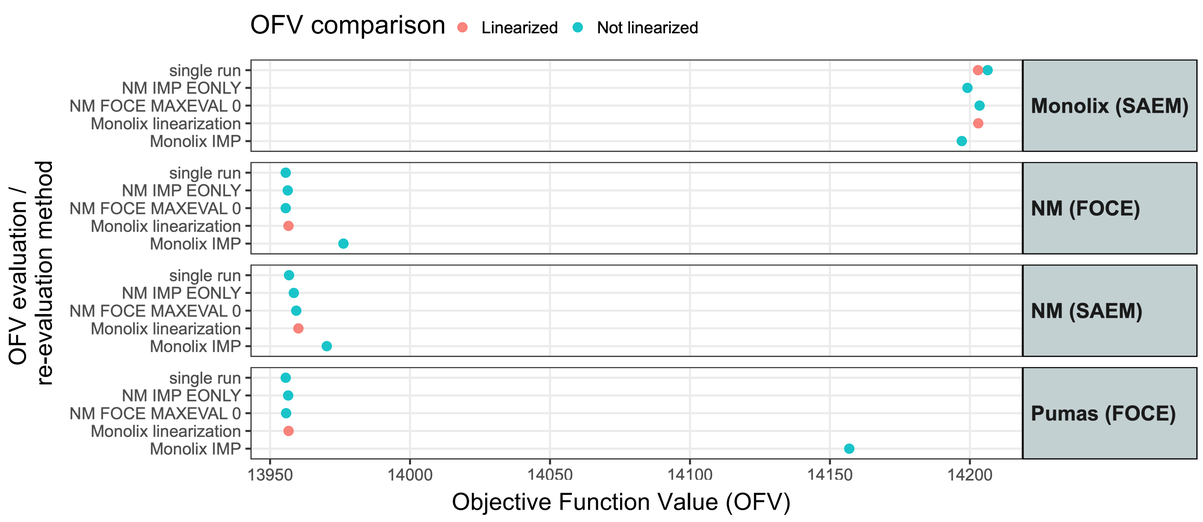

Figure 4. The dot plot compares the objective function values (OFV) across different software and algorithms.

References

1. Jonsson EN, Nyberg J. Full random effects models (FREM): A practical usage guide. CPT Pharmacometrics Syst Pharmacol.2024 Aug;13(8):1297–308.
2. Nyberg J, Jonsson EN, Karlsson MO, Häggström J. Properties of the full random-effect modeling approach with missing covariate data. Statistics in Medicine.2023 Dec 21;43(5):935–52.
3. https://github.com/pharmetheus/PMXFrem
4. https://github.com/pharmetheus/PMXForest

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