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Efficiency Comparison of an Exact Gradient Solution in First Order Conditional methods Mixed Effect Non Linear Regression in NLME

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Background & Objectives

First Order Conditional Estimation (FOCE) is a commonly used maximum likelihood parametric method in pharmacokinetics (PK) and pharmacodynamics (PD). The FOCE method uses the slope of the objective function value (OFV) WRT the parameter values to iteratively improve the OFV. Typically, the gradient is calculated using the finite difference (FD) method, calculating the OFV at multiple values for each parameter. We propose to replace FD with automatic differentiation for parameter estimation (ADPO [1]). The advantages of ADPO may include improved computational speed as well as accuracy, as the FD method is a numerical approximation to the slope. This method is in some ways, similar to the sensitivity equations used in the FAST option in NONMEM, proposed by Almquist [2]. We do not directly compare ADPO to the FAST option in NONMEM.

Methods

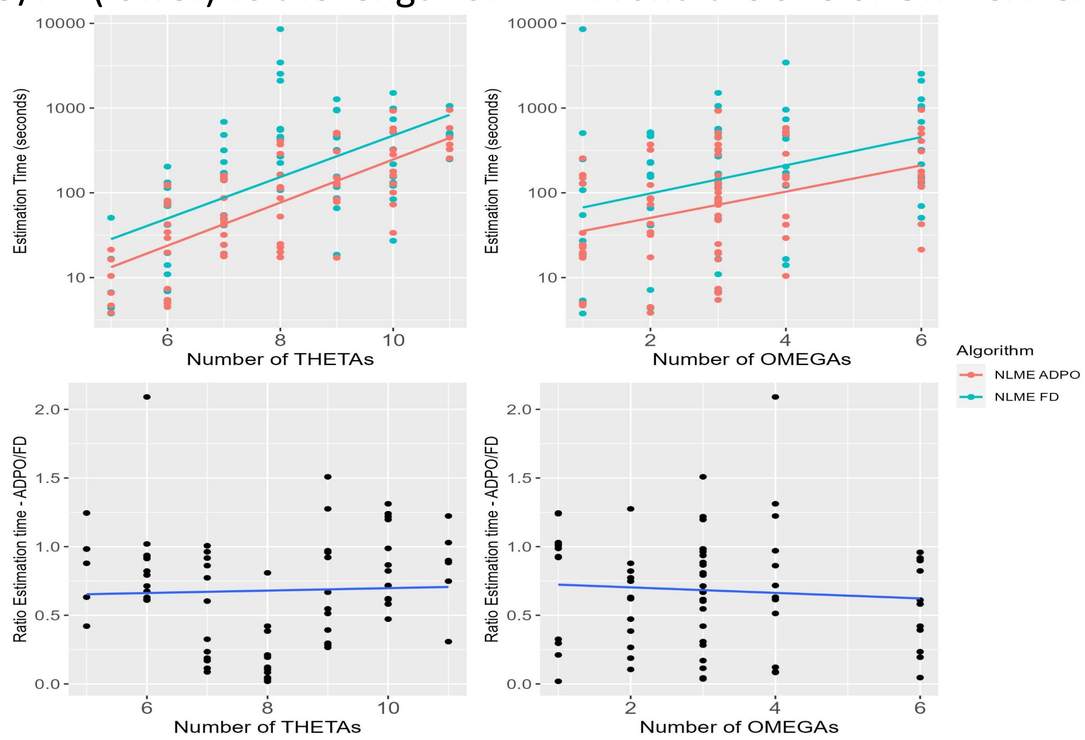
Criteria for evaluation include estimation and covariance time, and probability of successful covariance step. 72 simulated data sets were generated from 72 control files. The models were saturable elimination and ranged from well identified to poorly identified. Actual sampling times were drawn from a log-normal distribution with geometric means of 0.5, 2, 6, 12, 24, 48, 96, 120 and a cv of 0.1. Weight was simulated with a log-normal distribution with a mean of 70 and cv of 0.2. Model structure options included:

- 1, 2, or 3 compartments
- Central volume as independent of weight, or a power model function of weight with an exponent of 0.75
- A gamma term (exponent on Concentration and Km) in the Michaelis-Menten equation of 1.2 vs a default value of 1.
- A range of OMEGA structures was included.

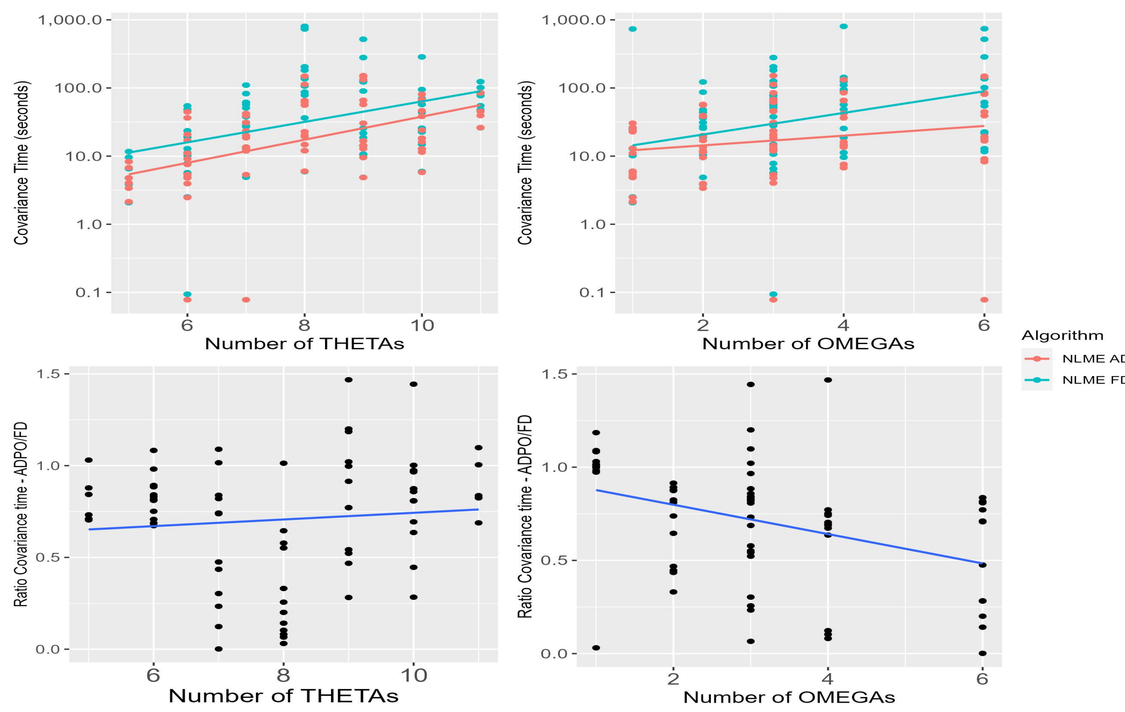
The parameters for the model were chosen such that some models would be poorly identified, with Cmax less than Km/2. All models were run with a development version of NLME using RsNLME.

Results

The figure below shows the estimation time (upper) for FD and ADPO and the ratio ADPO/FD (lower) vs the length of THETA and the size of OMEGA elements



The figure below shows the covariance time (upper) for FD and ADPO and the ratio ADPO/FD (lower) vs the size of THETA and OMEGA



The table below shows the ratio (ADPO/FD) of estimation and covariance time by the length of THETA

N THETA	N	Estimation (median (95%CI))	Covariance (median (95%CI))
5	6	0.93 (0.473,1.18)	0.788 (0.706,0.992)
6	12	0.808 (0.613,1.501)	0.823 (0.681,1.027)
7	12	0.464 (0.102,0.982)	0.607 (0.068,1.049)
8	12	0.113 (0.029,0.596)	0.228 (0.05,0.811)
9	12	0.607 (0.275,1.38)	0.843 (0.384,1.321)
10	12	0.845 (0.532,1.272)	0.834 (0.373,1.201)
11	6	0.891 (0.418,1.175)	0.831 (0.722,1.075)

The ADPO and FD methods both converged for 100% of the models, and the FD method had a successful covariance step 98.6% of the time, compared to 97.2% for ADPO.

Conclusions

ADPO consistently improves the speed of estimation and covariance in ODE PK models across a range of model complexity and identifiability compared to FD. ADPO was comparably robust to FD, with 100% convergence and > 97% successful covariance step.

[1] Neidinger, Richard D. (2010). "Introduction to Automatic Differentiation and MATLAB Object-Oriented Programming" (PDF). SIAM Review. 52 (3): 545–563. CiteSeerX 10.1.1.362.6580. doi:10.1137/080743627. S2CID 17134969.
[2] Almquist J, Leander J, Jirstrand M. Using sensitivity equations for computing gradients of the FOCE and FOCEI approximations to the population likelihood. J Pharmacokinet Pharmacodyn. 2015 Jun;42(3):191-209. doi: 10.1007/s10928-015-9409-1. Epub 2015 Mar 24. PMID: 25801663; PMCID: PMC4432110.