



Nonlinear Mixed Effects Estimation Algorithms: A Performance Comparison for Continuous Pharmacodynamic Population Models

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Background

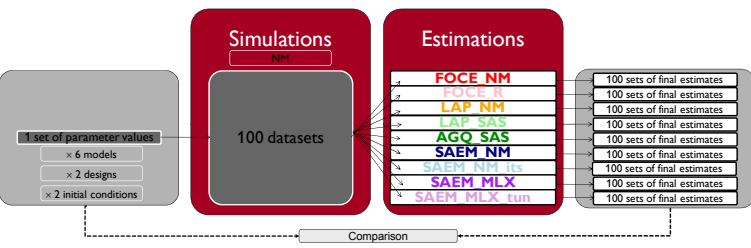
- Improvements in statistical softwares for estimation in NLMEM
- Algorithms tested with PD data for categorical and count models
- Communications^{1,2} done for continuous models

Objectives

To compare estimation performance of FOCE in NONMEM and R, LAPLACE in NONMEM and SAS, adaptive Gaussian quadrature in SAS, and SAEM in NONMEM and MONOLIX for a set of continuous population PD models

Methods

Stochastic Simulations and Estimations study



6 models (m):

All derived from a sigmoid Emax model
2 residual error ε models (Additive, Proportional) & 3 Hill factor γ values (1, 2, 3)

$$Y_{i,j} = E_{i,j} + \varepsilon \quad \text{or} \quad Y_{i,j} = E_{i,j} \cdot (1 + \varepsilon)$$

$$E_{i,j} = E_{0i} + \frac{E_{\max,i} \times \text{Dose}^\gamma}{ED50_i^\gamma + \text{Dose}^\gamma}$$

$$\theta_i = \theta \cdot e^{\eta_i}$$

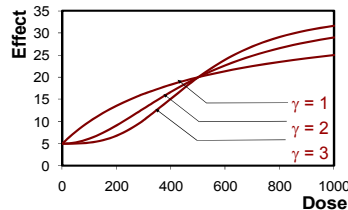
9 parameters (p) per model.

2 designs:

100 patients included in this hypothetical study
4 dose levels: 0, 100, 300 and 1000mg
Subjects allocated to all dose levels (Rich) or to 2 randomly chosen (Sparse)

2 initial conditions:

Initial estimates set to values used during simulation (True)
Or to a set of values chosen far away from the truth (False)



	Emax		ED50		Hill		E0		Var(Emax)		Cov(Emax,ED50)		Var(ED50)		Var(E0)		Var(ε)	
	True	False	True	False	True	False	True	False	True	False	True	False	True	False	True	False	True	False
Add error Hill X	30	60	500	1000	X	1	5	10	0.490	0.100	0.245	0.010	0.490	0.100	0.090	0.100	4	1
Prop error Hill X	30	60	500	1000	X	1	5	10	0.490	0.100	0.245	0.010	0.490	0.100	0.090	0.100	0.010	0.0625

X = 1, 2, 3

FOCE_R: simulated random effects as initial conditions

Settings of the 9 algorithms (a):

Algorithm	Software	Method	Settings
FOCE_NM	NONMEM 7	FOCE	Default + INTERACTION for prop error
FOCE_R	R 2.9.1	FOCE	nlme routine
LAP_NM	NONMEM 7	LAPLACE	Default + INTERACTION for prop error
LAP_SAS	SAS 9.2	LAPLACE	apoints=1 gtol=1e-8 fconv=1e-8 xtol=1e-8 tech=quanw/dbldog ebsteps=300 ebsubsteps=300 ebsfrac=0.2 ebtol=1e-6 instep=1E-1 ebopt cov itdetails
AGQ_SAS	SAS 9.2	AGQ	apoints=9 gtol=1e-8 fconv=1e-8 xtol=1e-8 tech=quanw/dbldog ebsteps=300 ebsubsteps=300 ebsfrac=0.2 ebtol=1e-6 instep=1E-1 ebopt cov itdetails
SAEM_NM	NONMEM 7	SAEM	Default (NBURN=<=2000 NITER=1000 ISAMPLE=2 SEED=14455 IACCEP=0.4) + CTYPE=3
SAEM_NM_its	NONMEM 7	SAEM	Mu-parameterized parameters + ITS INTER CTYPE=3 preceding step
SAEM_MLX	MONOLIX 3.1	SAEM	Default (NBURN=<=500 NITER=<=200 ISAMPLE=1 SEED=123456 IACCEP=0.3)
SAEM_MLX_tun	MONOLIX 3.1	SAEM	NBURN=500 ISAMPLE=5

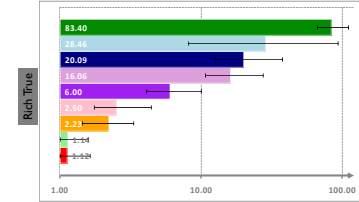
Affiliations

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Results

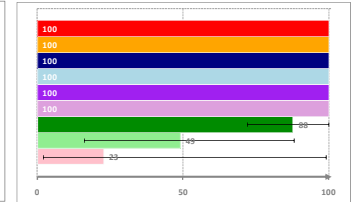
Runtimes (mean s.GHz):

Min, mean and max between models.
Corrected with computer frequencies.
Relative to the fastest for each model.



Completion rates (mean %):

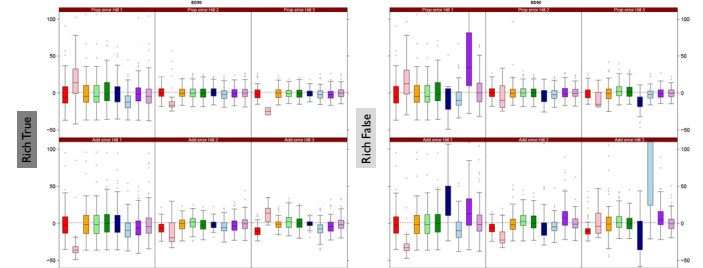
Min, mean and max between models.
Runs reaching convergence criteria.



Accuracy and Precision of the algorithms:

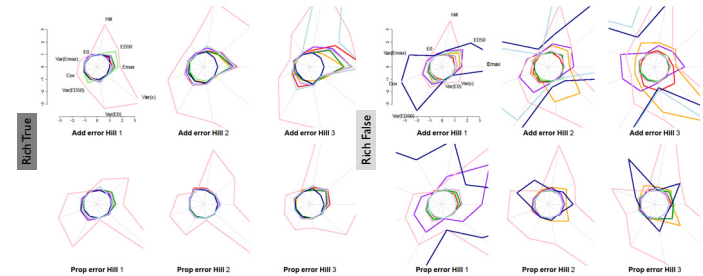
- Relative Estimation Error (RER) for each dataset - Example of ED50

$$RER_{ED50,m,a}(\%) = \left(\frac{\theta_{Est_{ED50,m,a}} - \theta_{True_{ED50,m,a}}}{\theta_{True_{ED50,m,a}}} \right) \times 100$$



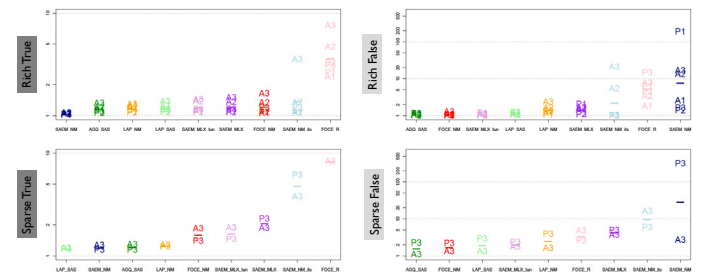
- Relative Root Mean Square Error (RRMSE) for each parameter

$$RMSE_{p,m,a} = \sqrt{\text{Mean} \left((\theta_{Est_{p,m,a}} - \theta_{True_{p,m,a}})^2 \right)} \quad RRMSE_{p,m,a} = RMSE_{p,m,a} / \min(RMSE_{p,m,a})$$



- RRMSE for each model (A = Add, P = Prop & 1, 2, 3 = Hill factor values)

$$RRMSE_{m,a} = \text{Mean}(RRMSE_{.,m,a})$$



Discussion

- FOCE_NM & LAP_SAS fastest ($\approx 8s.GHz$), AGQ_SAS slowest ($\approx 80\times$ more)
- 100% convergence, except AGQ_SAS > LAP_SAS > FOCE_R for which 2-99%
- True initial conditions: Small bias and similar RRMSE between algorithms among parameters except for FOCE_R (biased)
- False initial conditions: Similar RRMSE for AGQ_SAS, LAP_SAS, FOCE_NM, and SAEM-MLX_tun for Rich and even Sparse designs. Problems with SAEM_MLX, SAEM_NM_its, FOCE_R and SAEM_NM.

References

- (1) Girard, P. & Mentré, F. - PAGE 14 (2005)
- (2) Plan, E.L., Kjellsson, M.C. & Karlsson, M.O. - PAGE 16 (2007)