An Improved Framework for Shrinkage Computations in NLME Population Models

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Overview and Objectives

η shrinkage evaluation is based on comparing the variance over subjects of empirical Bayesian estimates (EBEs) η_i of a random effect to the corresponding Omega parameter estimate:

$$shrinkage = 1 - \frac{var(\eta_i)}{\widehat{\omega^2}}$$

An η shrinkage value in [0,1] arises from the fact that usually this variance ratio is also in [0,1], so larger shrinkages corresponds to smaller fractional ratios. Generally shrinkage increases with the amount of imprecision in the η_i estimates – typically sparse data leads to high shrinkage. Many diagnostics are directly or indirectly based on the EBE, and it is well known [1,2] that such diagnostics become progressively more suspect as shrinkage increases.

The most common form of EBE in current use is the MAP estimate (mode) of the empirical Bayesian posterior distribution (EBD), as MAP estimates are the central focus of common conditional methods such as FOCE(I) and LAPLACE. However, in EM-based methods such as QRPEM, IMPEM and SAEM, the mean rather than the mode of the EBD plays the central role and the mean can be used as the EBE. Here we focus on properties of the mean vs. mode based EBE and present cases strongly suggesting that the mean based version is often more robust, useful, and amenable to analytic interpretation. We also note that many EBE diagnostics are easily extended to diagnostics based on multiple random samples from the empirical Bayesian distribution, as opposed to a distinguished EBE point in that distribution. This may overcome some of the problems due to shrinkage.

Example 1 - Simple log normal random intercept model

In [1] a simple random intercept model

$$Y_{ij} = \mu + \eta_i + \varepsilon_{ij}$$

is considered to derive some theoretical properties of shrinkage in a simple case. Note that there must be at least one subject i with number of observations $Nbs_i > 1$ for this model to be identifiable (otherwise there is no information to separate inter-individual from residual error). Here the EBD is a normal distribution assuming the random and residual errors are normal, so there is no difference between mean and mode based EBEs. We make a simple log normal modification

$$Y_{ij} = \mu\, e^{\eta_i} + \varepsilon_{ij}$$

which separates mean and mode of the EBD. Results from simulations with N_{sub}=10000 and $Nobs_i$ =1 (9000 subjects) and $Nobs_i$ =2 (1000 subjects) are presented for increasing residual error. The true Ω used to simulate the data is fixed at 1, as is μ.

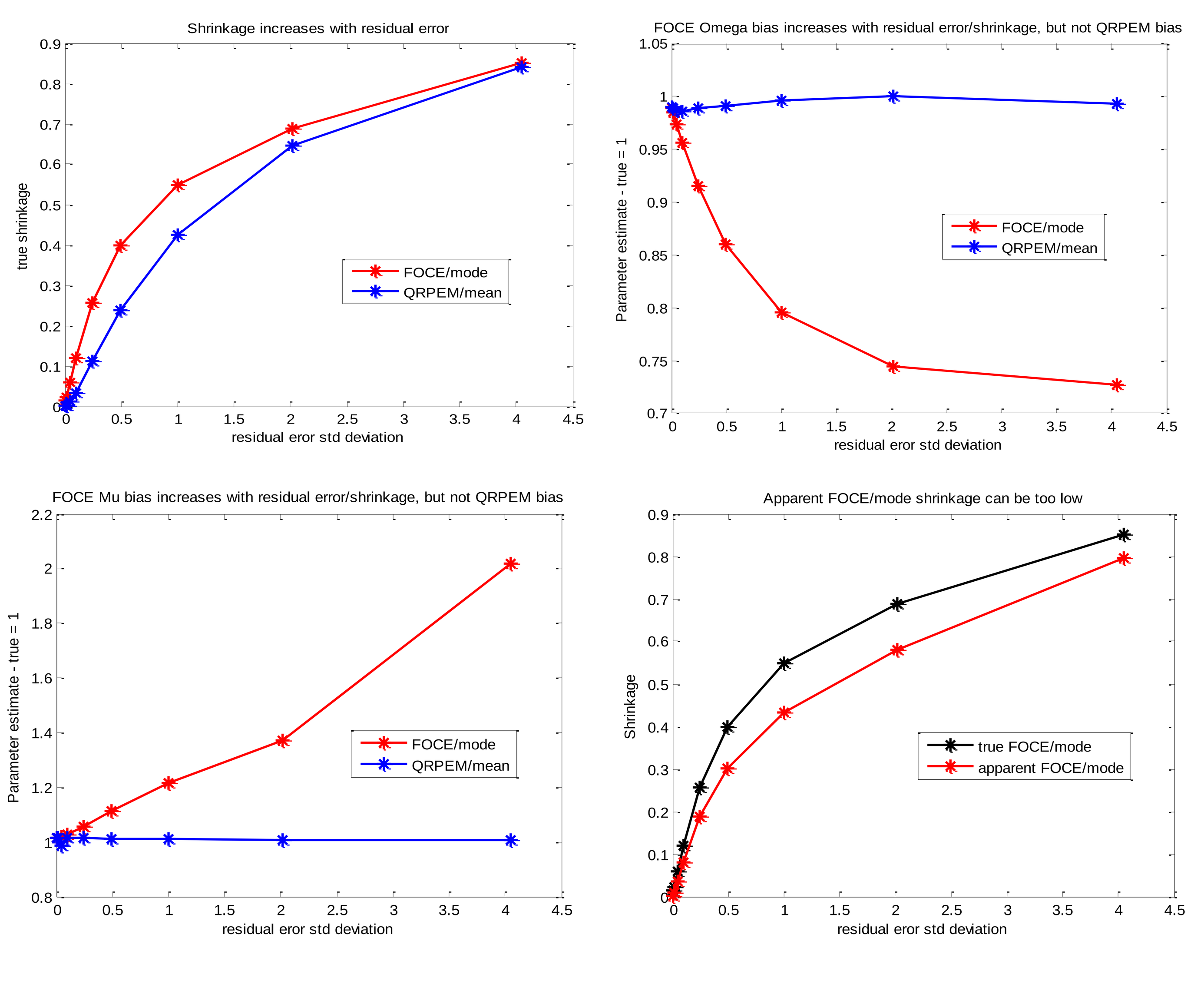


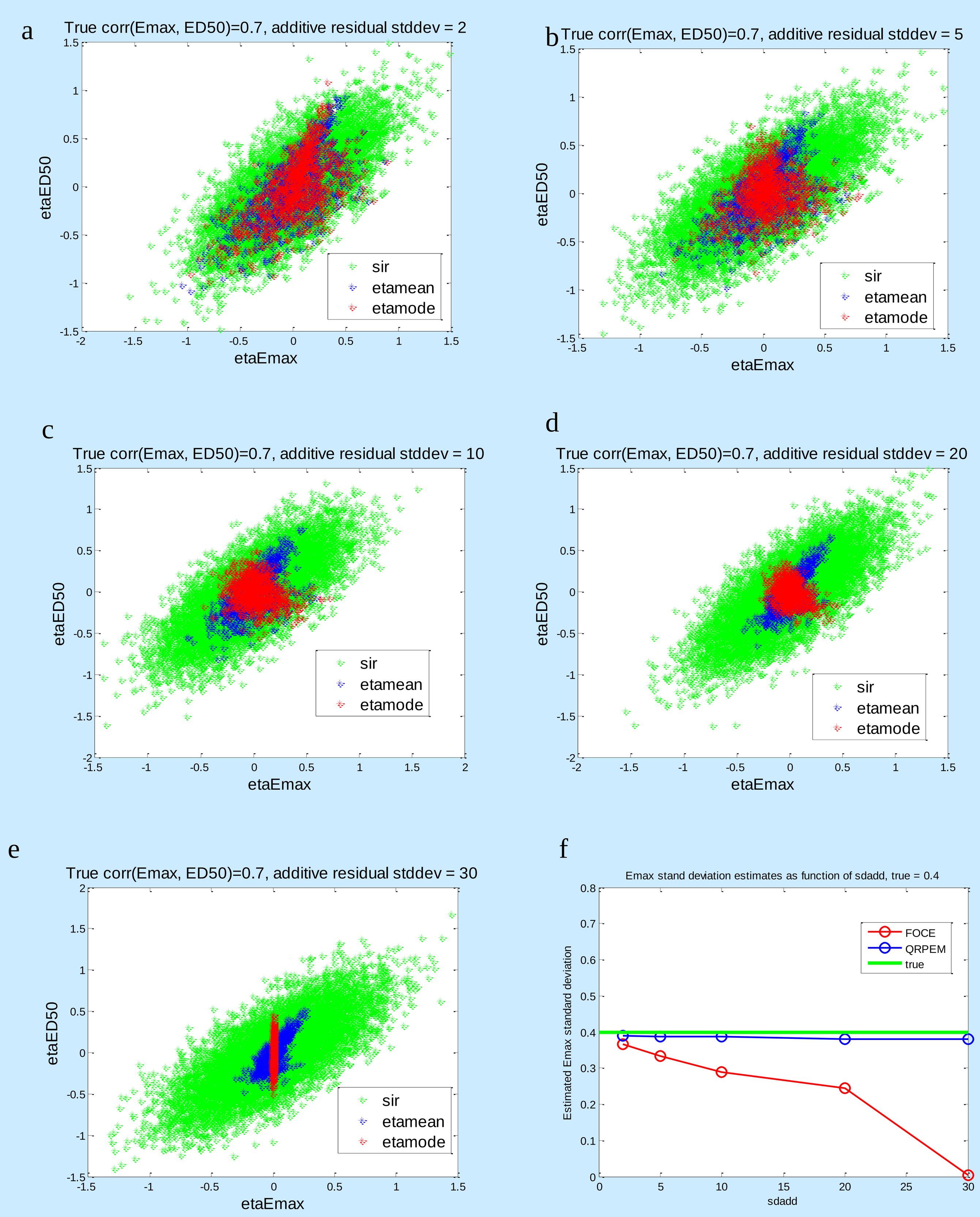
Fig 1- FOCE estimation performance deteriorates rapidly as shrinkage/residual error increases, while QRPEM is much more robust. Moreover, FOCE mode based shrinkage estimates can be misleadingly low (see also Figure 2e, where a very poor FOCE estimate has an associated mild apparent (0.19) but very high real shrinkage level (0.99) due to bias in the corresponding Omega estimate.

Example 2: Sigmoidal Emax Model – False EBE(mode) negative correlation of Emax-ED50 is ameliorated with EBE(mean)

$$E = E0 + Emax * \frac{Dose^3}{Dose^3 + ED50^3}$$

Parameters E0, Emax, ED50 are all log normal (tvParam*exp(η_Param), with additive residual error, sparse 2 samples per subject. True correlation Emax-ED50=0.7.

Figure 2a – 2e show actual EBE correlation for mean (QRPEM) and mode (FOCE) based EBEs, as well as properly correlated SIR (Sampling Importance Resampling) samples from the QRPEM computed posterior. Figure 2f shows large and increasing (with residual error) EMAX Omega element bias for FOCE/mode case, but no bias for QRPEM/mean case. Note the collapse of the mode-based Emax η's in figure 2e is not accompanied by a high apparent shrinkage (0.19) , since the corresponding Omega element is severely underestimated. True shrinkage using actual Omega is 0.99.



Other advantages of EBE (QRPEM/mean) relative to EBE (FOCE/mode)

1. From the convergence condition for EM algorithms, the Omega estimate decomposes as

$$\hat{\Omega} = cov(EBEs) + \overline{cov(EBD)}$$
$$= \Omega_1 + \Omega_2$$

where shrinkage is captured by the relative sizes of Ω_1 and Ω_2 – this can be easily extended to individual level shrinkage. The 1-1 relation between shrinkage and estimation error conjectured in [1] follows immediately. Also, directions of minimal and maximal shrinkage can be computed as solutions to the generalized eigensystem.

$$\Omega_1 \eta = \lambda\, \Omega_2 \eta$$

2. Mean-based shrinkage can easily and naturally be extended to nonparametric NLME methods. Mode-base EBEs do not make sense in that context .
3. The mean over subjects of mean-based EBEs is necessarily zero at QRPEM convergence– no p-test on the mean is required or even meaningful and there is no necessity for anything like a separate 'FOCE with centering' algorithm.
4. The linear regression used in EM models to update linear covariate models is based on responses defined by EBE means. Thus we expect investigation of prospective covariate models via the same linear regression to be more informative than regressions based on mode-based EBEs. It can be shown that the mean based methodology is equivalent to regression over a large number of SIR samples directly from the EBD posteriors.

References:

[1] X.S. Xu, M. Yuan, M.O. Karlsson, A. Dunne, P. Nandy, and A. Vermeulen, Shrinkage in NLME Population Models: Quantification, Influencing Factors, and Impact, *AAPS J.*, 2012.

[2] R. M. Savic and M. O. Karlsson, Importance of Shrinkage in Empirical Bayes Estimates for Diagnostics: Problems and Solutions, *AAPS J.*, 2009.

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