QRPEM, A Quasi-Random Parametric EM Method

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INTRODUCTION

Monte Carlo (MC) parametric EM algorithms such as MCPEM and SAEM are attractive alternatives to approximate likelihood FO, FOCE, and LAPLACE parametric algorithms. EM algorithms avoid likelihood approximations that compromise the statistical quality of the results. Also, in practice EM methods are usually much more reliable than approximate likelihood methods since they rely on numerically very robust sampling and numerical integration computations rather than relatively fragile numerical optimization procedures.

Recently QRPEM (quasi-random parametric EM), a new implementation of an importance sampling based EM algorithm, has been added to the Pharsight Phoenix® NLME™ software. QRPEM differs fundamentally from MCPEM algorithms in that importance sampling of the posteriors is based on quasi-random (aka 'low discrepancy') sequences rather than the more usual pseudo-random sequences used in Monte Carlo methods.

A second major innovation in QRPEM is the use of the SIR (sampling-importance-resampling) algorithm to greatly simplify and accelerate the auxiliary optimization procedure that must be used when some fixed effect and residual error parameter updates cannot be driven directly from the base EM posterior means. Such cases include, for example, fixed effects not paired with a random effect, non-linear covariate models, and mixture parameters in compound additive-proportional residual error models.

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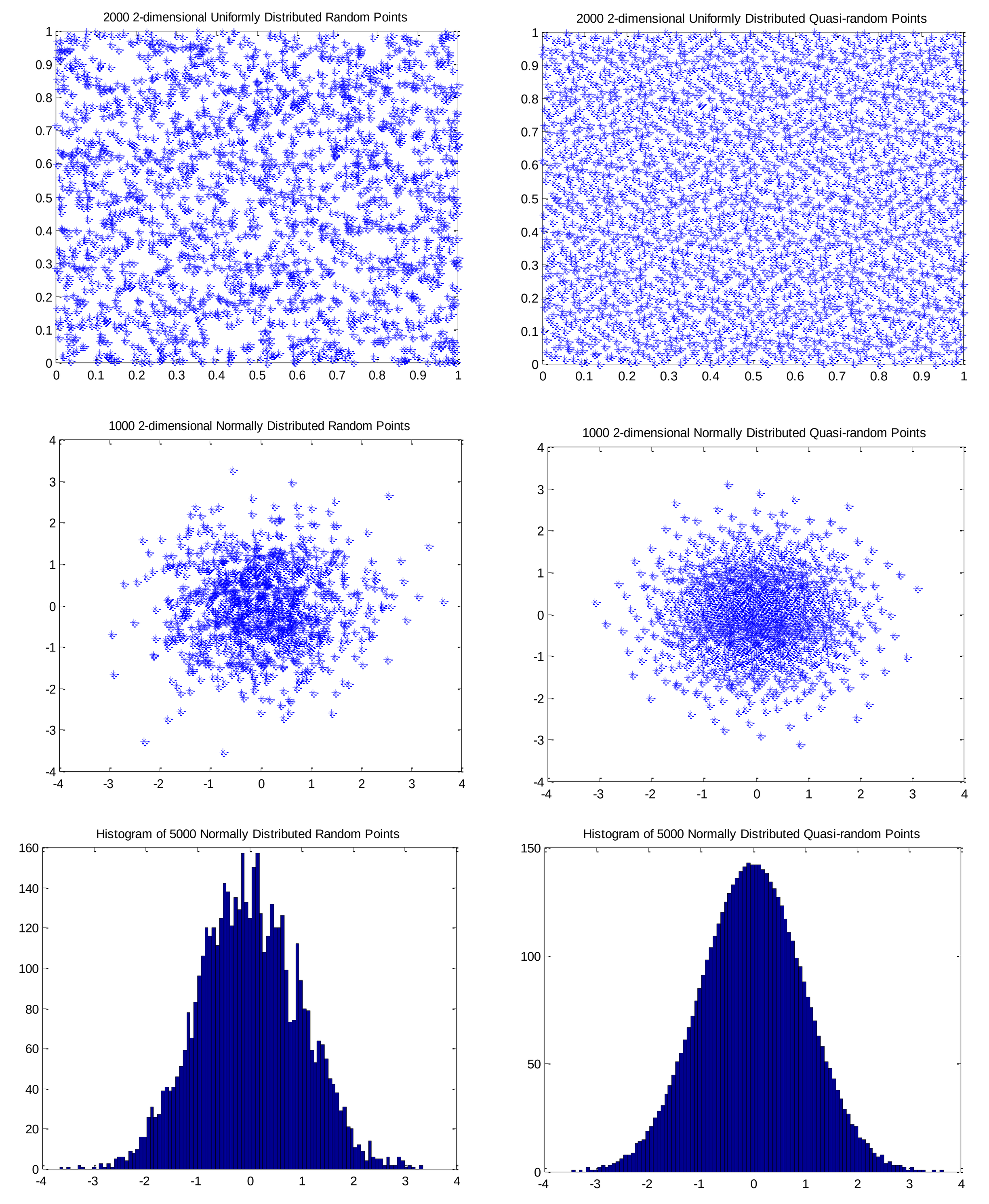
METHODS

A new implementation QRPEM of EM importance sampling-based NLME estimation has been implemented in the Phoenix NLME application on the Pharsight Phoenix software platform. The method differs from stochastic MCPEM versions in that it samples the relevant integrands at positions that are based on quasi-random points rather than random points.

For a *d*-dimensional problem with *d* random effects, the initial samples are drawn from a Sobol QR sequence uniformly covering the unit hypercube $[0,1]^d$. These are transformed to QR N(0,I) Gaussians by component-wise application of a inverse cumulative normal distribution function, and then scaled and shifted to the target $N(\mu,C)$ importance sampling distribution.

GAUSSIAN RANDOM vs. QUASI-RANDOM IMPORTANCE SAMPLES

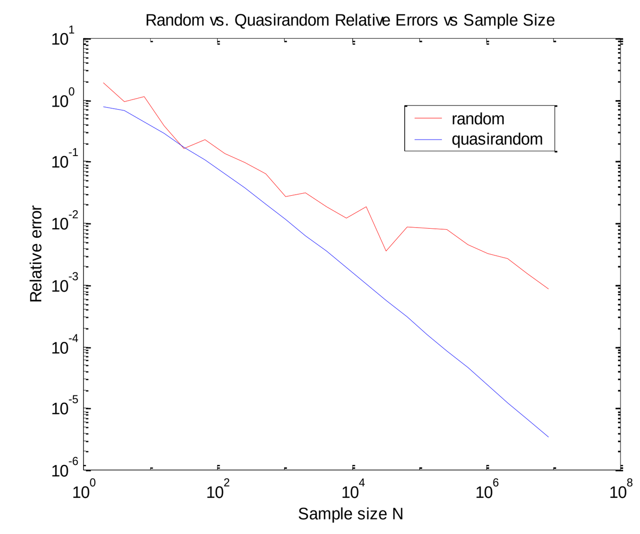


OBJECTIVE

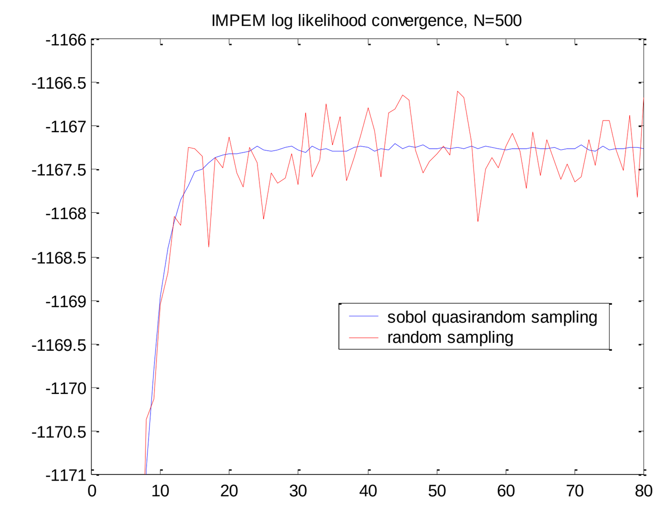
To improve the performance of the MCPEM algorithm through the use of quasi-random sampling for increased EM integral accuracy and the SIR algorithm for increased efficiency in the estimation of fixed effects and residual error parameters than cannot be estimated by the base EM algorithm.

RESULTS AND CONCLUSIONS

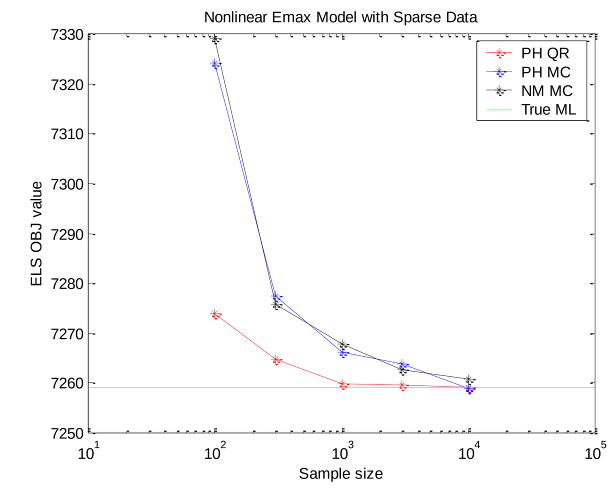
a) QRPEM EM integrals are more accurate than MCPEM, b) QRPEM converges to the true ML solution at lower sample sizes than MCPEM, c) SIR greatly improves performance when applicable



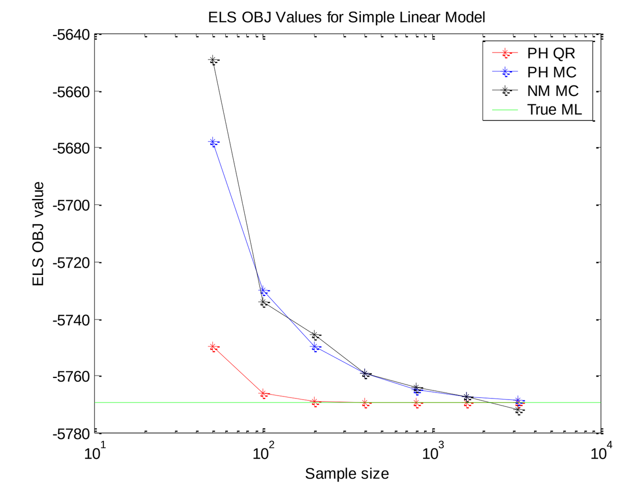
QR integral error (blue curve) decays much faster at rate $O(N^{-1})$ than MC integral error (red curve) at rate $O(N^{-1/2})$. Thus QRPEM integrals are far more accurate than MCPEM at the same sample size N.



Log likelihood (y-axis) convergence with increasing iteration count (x-axis) is much smoother, more monotonic, and more accurate with QRPEM (blue) than MCPEM (red) at same sample size.



For a difficult, nonlinear EMAX PD model with Hill coefficient=3.0, QRPEM (red curve) converges to true ML solution much faster than MCPEM (blue and black). QRPEM solution at low sample size N=100 is far superior to MCPEM at N=100. Due to use of SIR, QRPEM is 8 times faster (400 sec vs. 3200 sec) than MCPEM without SIR (black) at same sample size (1000) and iteration count (100).



For a linear model with additive residual error, FO and FOCE produce true maximum likelihood estimates (green line). QRPEM method (red curve) reaches true ML values at much smaller sample sizes (N=200) than MCPEM methods (N=4000).

d) QRPEM is less biased than FOCEI on a highly nonlinear PD test case from the literature:

QRPEM is essentially unbiased over 100 simulated data sets for a difficult, sparse, highly nonlinear PD EMAX model with Hill coefficient γ, whereas FOCEI shows significant bias (%bias) in some parameters. Model was adapted from Ref. [1]. Values shown are average FOCEI and QRPEM estimates over 100 data sets.

PARAMETER	TRUE VALUE	FOCEI	QRPEM
tvE0	5.00	5.00 (0)	5.01(+0.2)
tvEMAX	30.00	26.6(-13)	29.6(-1)
tvED50	500	521(+4)	496(-1)
γ	3.00	2.66(-10)	3.02(+1)
resid err stddev	0.1	0.128(+28)	0.103(+3)
Omega(1,1)	0.09	0.088(-2)	0.089(-1)
Omega(2,2)	0.49	0.48(-2)	0.48(-2)
Omega(3,2)	0.25	0.18(-28))	0.25(0)
Omega(3,3)	0.49	0.42(-14)	0.47(-4)

e) QRPEM is far more reliable than FOCE and f) QRPEM is much faster than NM MCPEM on a large Monolix test set:

On the MONOLIX test set described in Ref. [2] with 144 one- and two-compartment models with linear and Michaelis-Menten elimination:

NM FOCEI and Phoenix FOCE ELS both fail on approximately 40% of cases,

QRPEM successfully solves all 144 cases with good parameter estimates, and

QRPEM is 2 to 5 times faster than NM MCPEM ($EST METHOD=IMP) at the same sample sizes and iteration counts on this test set .

References

1 E. Plan et al., PAGE 19 (2010) Abstract 1880.

2. P. Jacqmin et al., Software Evaluation: Simulation of PK data sets for evaluation of the Monolix PK Library, Exprimo, 2007.