Comparison of Laplacian, Quasi-Random Parametric Expectation Maximization (QRPEM) and Non-parametric Methods for Population Analysis of Complex Dynamic System with Non-static BQL Data

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Objectives: To compare the capability of Laplacian and QRPEM engines in Phoenix® NLME™ (Pharsight/Certara) for population analysis of a complex dynamic system with non-static BQL data; and to use the non-parametric adaptive grid (NPAG) engine as a post-processor for parametric runs to detect any serious violation of normality assumption such as bimodality.

Methods: The example used to test the capability of these three methods is a highly nonlinear, multi-scaled and long-term HIV dynamic model [1] with clinical data [1] including treatment interruptions, total CD4+ T-cells and non-static BQL viral load. Both Laplacian and QRPEM engines started with same initial values for fixed and random effects and were implemented in the same machine with same setting. Compared to parametric methods such as Laplacian and QRPEM methods, NPAG makes no assumption on the distribution form of random effects and hence can be used as a post-processor for parametric runs.

Results: We found that QRPEM converged at iteration 110 with 12000 seconds runtime in which Laplacian estimation just finished two iterations and then stuck at iteration 4. This is not unexpected as QRPEM is based on quasi-random importance sampling approach to compute required integrals and does not use explicit numerical optimization while Laplacian engine involves explicit numerical optimization and requires evaluation of second derivatives for approximation. The Q-Q plots obtained by QRPEM for random effects show that there are discernible divergences from normal distributions for several random effects. Plots of estimated cumulative distribution functions (CDF) obtained by NPAG demonstrate that two of these random effects seem to have bimodal shape distributions (see figure shown below).

Conclusions: This example demonstrates that for population analysis of a complex dynamic system with complicated data, QRPEM is method of choice and nonparametric engine should be used as a post-processor whenever there is a doubt of the normality assumption.

References