An Evolutionary Nonparametric NLME Algorithm

Robert H. Leary

Pharsight ® Corporation, Cary, North Carolina 27518, USA

Introduction

Nonparametric NLME methodologies make no assumptions regarding the form of the random effects distribution and are a more general alternative to more common parametric NLME methods. Mallet showed that a maximum likelihood nonparametric distribution estimator can always be found as a discrete distribution $\{P_J, S_J\}$, j=1, 2 , , M where each S_J is a point in the D-dimensional random effects space, and the P_J's are positive probabilities that sum to 1. The total number of support points M does not exceed N, the number of subjects and often is considerably smaller.

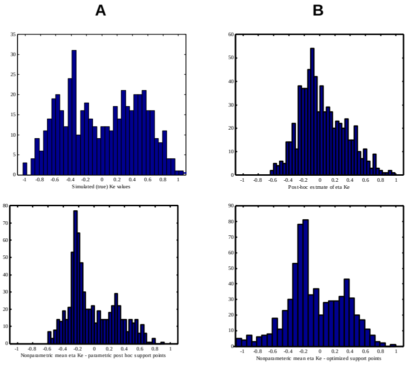
Recently NONMEM® 6 introduced a simple nonparametric methodology where support points are fixed to the post hoc estimates from a preliminary parametric (e.g. FO, FOCE, or Laplace) analysis. Optimal probabilities on these supports are then computed, which is a relatively simple convex optimization problem. Here we extend that methodology to optimize both probabilities and support point positions, a much more difficult non-convex global optimization problem.

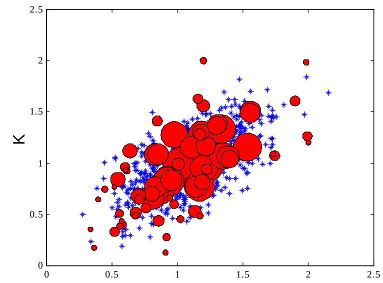
Parametric post hoc estimates are suboptimal nonparametric support points

Fig A) shows the true observed bimodal distribution for 700 subjects (ETA_Ke ~ 1/2 N(-0.41, 0.0625) + ½ N(0.41, 00625), eta_V~N(0, 0.0625), Ke = exp(eta_Ke), V=exp(eta_V), from a simulated linear one-compartment IV bolus NLME model

*DV = dose*exp(-Ke*time)/V *exp(eps) , eps= 0.1*

while B) shows the distribution of the post hoc estimates of eta_Ke after an FOCE fit using a normality assumption for the random effects . Note that the bimodality in eta_Ke has been completely masked by the shrinkage phenomenon. Fig C) shows the bimodal but still too narrow distribution of the means of the individual subject nonparametric distributions from a nonparametric fit with parametric FOCE post hoc supports, while D) shows the wider corresponding distribution of the individual means for the fully optimized nonparametric fit using the algortihm described here. The nonparametric 2LL value for D is higher than for C by 24.506. At right (bottom of central column), the nonparametric estimate of the cdf for eta_Ke is shown in comparison with the observed distribution of the true (simulated) eta_Ke values.





*An optimal (over probabilities and support point positions) discrete nonparametric estimator from simulated data for a simple linear one compartment IV-bolus PK model: the M=70 optimal support points (red circles) and probabilities (proportional to areas of circles) are superimposed on N=800 normally distributed true values (blue crosses) of the elimination rate constant K and volume of distribution V. Note here K and V represent structural parameters (e.g. , K = TV_K*exp(eta_K)). Here the true random effect distribution is normal.*

Optimization of nonparametric log likelihood over probabilities

Maximize LL(P), where

$$LL(P) = \sum_{I=1}^{N} \log\left(\sum_{J=1}^{M} L_{IJ} P_J\right)$$

$$P_J \geq 0, \sum_{J=1}^{M} P_J = 1$$

L_{IJ} are fixed conditional likelihoods determined by evaluating the residual error model at all support point S_J for subject I.

This is a convex problem with a convex dual:

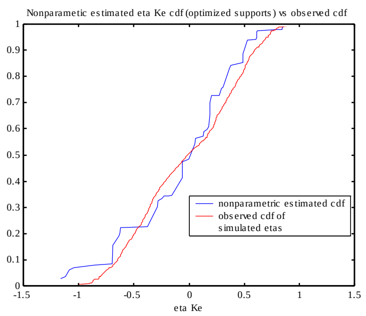
Maximize

$$G(W) = \sum_{I=1}^{N} \log(W_I)$$

$$\sum_{I=1}^{N} L_{IJ} W_I \leq 1$$

$$J = 1, 2, \ldots, M$$

A very fast primal dual algorithm due to Burke can be used that simultaneously solves the primal and dual. The dual solution weights W_I define a simple Fedorov type criterion as a linear combination of conditional likelihoods over subjects. This allows new candidate support points to be quickly screened to determine if entry into the support point set will improve the solution.



An evolutionary algorithm:

1 . Initialization

Set initial population = $\{S_J\}$, the post hoc estimates from an initial parametric estimation analysis.

Compute $\{P_J\}$ using the primal dual probability optimization algorithm. The nonzero components of P identify an optimal support subset of size M =JN.

2. Population expansion

For each S_J (regardless of membership in current optimal subset), compute a set of 'promising' candidate descendants

$\{C_{1J}, C_{2J}, \ldots, C_{KJ}\}$ using a proposal function (e.g. , random, quasi-random, or grid based search of a localized region centered at S_J, screening proposed points with the Fedorov duality criterion).

3. Population reduction

Optimize probabilities on current population of support points to find optimal next generation starting points. Keep all optimal support points as well as the best (by Fedorov duality criterion) descendant of each original S_J to maintain population diversity.

Iterate steps 2 and 3 for as many 'generations' as desired.

Results

The algorithm has been successfully run on over 40 distinct 'real world' and simulated models. Validations of selected models against the USC*PACK NPAG algorithm usually show similar results but the current algorithm is more efficient (note NPAG uses a special case of steps 2 and 3 of the algorithm presented here without the Fedorov screening)

Conclusion

An evolutionary nonparametric algorithm that optimizes both support point positions and probabilities has been developed. It can produce nonparametric distributions with much higher likelihoods than nonparametric algorithms such as that used in NONMEM 6 which use fixed support points. A novel component that significantly enhances efficiency is the use of the dual solution in the probability optimization step to screen candidates for the next generation of the population of support points.

Trademarks

Contact

Robert H. Leary, PhD

Pharsight Corporation

Ph: +1 919.852.4625

Email: bleary@pharsight.com