Mixture models in NONMEM

How to find the individual probability of belonging to a specific mixture, and why this can be useful information.

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Background:

Mixture models are used to describe populations with bi- or multimodal distributions. NONMEM (GloboMax/ICON, Ellicott City, MD) will, in the POSTHOC step, assign the individual patients to the mixture (subpopulation) with the highest probability. The assigned mixture (MIXEST) is given in the output, but not the individual probability of belonging to that mixture (IP_{mix}). This probability can be calculated from the individual objective function value (IOFV) [1] and the total probability in the population of belonging to the mixture. Our objective was to explore the possible use of IP_{mix} instead of MIXEST in further analysis with the mixture model.

Method:

The IOFVs can be obtained from NONMEM by using a script that is called by $CONTR in NONMEM. In cases where the likelihood option is used in $ESTIMATION, $CONTR can not be used, and the IOFVs have to be obtained by rerunning the model with final parameter estimates and MAXEVAL=0 for each patient. The probability of belonging to a specific mixture is calculated as follows:

$$OFV = -2\ln(L) \Rightarrow IL_{mix1} = e^{(IOFV_{mix1}/2)}$$

$$IP_{mix1} = \frac{(IL_{mix1} \cdot P_{pop,mix1})}{(IL_{mix1} \cdot P_{pop,mix1}) + (IL_{mix2} \cdot P_{pop,mix2})}$$

IL_{mix1} is the individual likelihood for mixture 1

IP_{mix1} is the individual probability of belonging to mixture 1.

The sum of IP for all mixtures is 1.

$P_{pop,mix1}$ is the population probability for belonging to mixture 1, estimated in NONMEM.

A six-category proportional odds model for clomethiazole sedation in stroke patients (n=1545) described previously [2] was used as a test model. The model has a mixture describing two subpopulations of patients, those without (mixture 1: 20%) or with (mixture 2: 80 %) stroke induced sedation. Since $CONTR could not be used for this model, IP_{mix} was calculated as described above and compared with the MIXEST.

To investigate the influence of the richness of the data on MIXEST, the calculation of MIXEST was repeated with reduced data sets where only observations up to a specific time were included. The IOFVs were also collected for each reduced data set, and IP_{mix} was calculated. All runs and calculations were done automatically by using Perl scripts.

MIXEST and IP_{mix} were plotted against the available covariates and analyzed visually to investigate the possible use of IP_{mix} in covariate analysis. For this model, the use of IP_{mix} in these plots did not seem to provide additional information (results not shown).

Results:

The wide range of IP_{mix} (Figure 1) indicate that the mixture assignment in NONMEM (MIXEST) for this model and data is associated with considerable uncertainty. When calculating MIXEST for the reduced datasets, a trend can be seen, showing that after 10-12 hours of observations, the fraction of patients assigned to mixture 1 is close to the fraction in the full data set (Figure 2). IP_{mix} was calculated for reduced data sets for individual patients. Figure 3 show the plots for some of the patients. For some patients, there were large fluctuations in IP_{mix1} when increasing numbers of observations were included.

NONMEM VI β was used for the calculations, but similar results were obtained by NONMEM V.

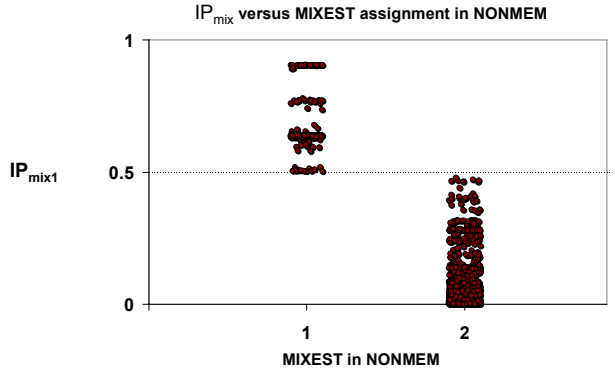

Figure 1. The patients assigned to a mixture by NONMEM (MIXEST) had a wide range of probabilities for belonging to that mixture (IP_{mix1}). IP_{mix} provided additional information about the certainity of the MIXEST-estimate.

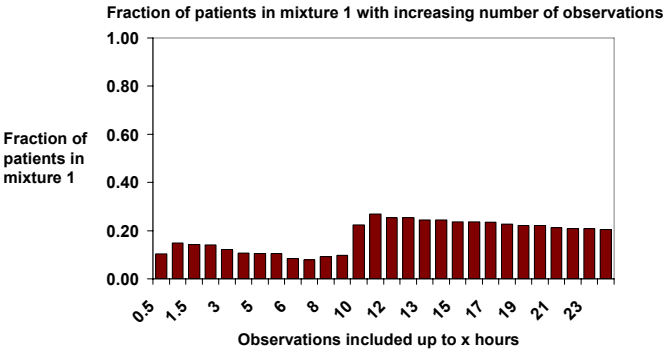

Figure 2. The MIXEST estimates appear to change when observations collected after 10-12 hours are included. After this, the fraction of patients in mixture 1 is close to the fraction in the full data set.

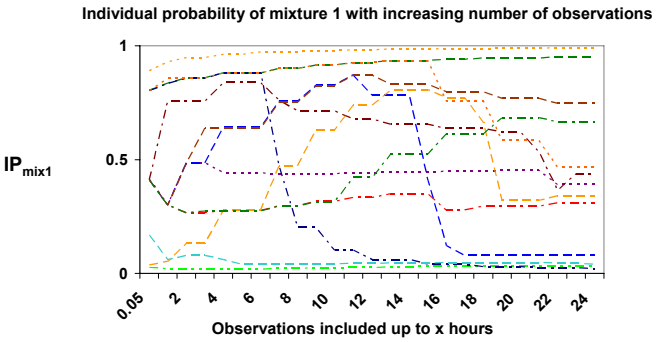

Figure 3. Examples of the change of the individual probability of belonging to mixture 1 (IP_{mix1}) when including more and more observations.

Conclusion:

The individual probability of belonging to a specific mixture can be calculated from individual objective function values in NONMEM. If calculated in real-time, IP_{mix1} for a patient will change as more data comes in. Therapeutic decisions could then be more informatively based on IP_{mix1}, rather than the dichotomous assignment of MIXEST. IP_{mix1} shows, in contrast to the MIXEST estimates, no shrinkage to the larger mixture when data are sparse. IP_{mix1} can be of use if the assigned mixture is to be used further, e.g. in diagnostics, simulations and in individualized therapy.

References:

[1] S. Sadray et al. *Likelihood-based diagnostics for influential individuals in nonlinear mixed effects model selection.* Pharmaceutical Research (1999),**9**,8, 1260 - 1265.

[2] P.- H.Zingmark et al. *Clomethiazole pharmacokinetics and sedation in stroke patients.* Br J Clin Pharmacol (2003),**56**,173 -183.