Estimating population variance matrices with a fixed pattern of zeros

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The problem

The variance of a random variable is always a positive number. The variance of a multidimensional random variable is a matrix that is also positive (in a given way). This positivity implies some constraints on the different components of the variance matrix. When the random variable has more than two dimensions, these constraints are rather difficult to write explicitly. In population PK/PD, there are situations where one can reasonably assume independence of several individual parameters. In a (Gaussian) parametric framework, this implies some "structural zeros" in the individual parameters variance matrix, that is other constraints than the one insuring positivity. Currently, in population PK/PD *no method is available* to estimate *precisely* variance matrices with a *general* pattern of zeros. We propose a *method that allows estimation of population variance matrix with prescribed zeros*

But what's a positive matrix ?

Assume that in the population, (Cl, V) is normally distributed with variance

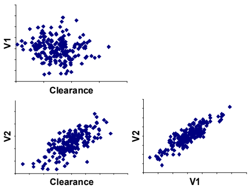
$$\begin{pmatrix} \sigma_{Cl}^2 & C \\ C & \sigma_V^2 \end{pmatrix}$$

The diagonal terms are non negative numbers.
The variance matrix is non negative when

$$C^2 \le \sigma_{Cl}^2 \sigma_V^2$$

When a non trivial pattern of zeros is desirable ?

Assume that after an IV administration of a drug (assumed to be well described by a two-comp. model) one gets the following post-hoc



that suggests the following variance structure

$$\begin{pmatrix} \sigma_{Cl}^2 & 0 & C1 \\ 0 & \sigma_{V1}^2 & C2 \\ C1 & C2 & \sigma_{V2}^2 \end{pmatrix}$$

How to proceed?

Our method [4] is a version of the Iterative Conditional Fitting (ICF) algorithm that has been recently developed for graphical models (cf [2]). It is mainly based on the Schur complement of a matrix that gives a decomposition of the variance matrix to be estimated allowing independent estimation of the variance components and preserving positivity. This decomposition can easily be mixed with the EM algorithm (cf [3]). Writing the EM contrast using these properties leads to a standard least-squares problem that has to be solved at each EM iteration. For homoscedastic models, the least-squares problem is quadratic with respect to the components of variance to be estimated. However, this nice property is lost when considering heteroscedastic models.

Our method can be used for any nonlinear mixed effects models.

The simple case : the NONMEM maximal assumption

It is not necessary to use a specific method of estimation for a matrix that contains zeros when the matrix is diagonal, or block/diagonal up to a permutation of the individual parameters (cf [1]).

These two situations are the only one possible in NONMEM

Example : This matrix does not require a specific method of estimation

$$\begin{pmatrix} X & 0 & X & 0 \\ 0 & X & 0 & X \\ X & 0 & X & 0 \\ 0 & X & 0 & X \end{pmatrix}$$

is block diagonal up to the permutation of the 2nd and 3d rows/columns

$$\left(\begin{array}{cc|cc} X & X & 0 & 0 \\ X & X & 0 & 0 \\ \hline 0 & 0 & X & X \\ 0 & 0 & X & X \end{array}\right)$$

A naïve solution to the problem : the Zero Forced Estimator

The Zero Forced Estimation is widely used in practice. It consists in estimating the matrix by ignoring the zeros and plugging the zeros into the obtained estimation. *However*, this method works only with large samples size and the obtained estimate is *not the MLE (it is imprecise) nor necessarily positive.*

Example :

The unconstrained estimate is a variance matrix

$$\begin{pmatrix} 4 & -3 & 3 \\ -3 & 4 & -3 \\ 3 & -3 & 4 \end{pmatrix}$$

But the Zero forced estimate is not positive

$$\begin{pmatrix} 4 & -3 & 0 \\ -3 & 4 & -3 \\ 0 & -3 & 4 \end{pmatrix}$$

Simulation layout

We simulated 100 datasets using the following model :

$$Y_{ij} = X_{1i} + \frac{X_{2i} d_j^{X_{3i}}}{X_{4i}^{X_{3i}} + d_j^{X_{3i}}} + \varepsilon_{ij}, 1 \le j \le 7, 1 \le i \le 30.$$

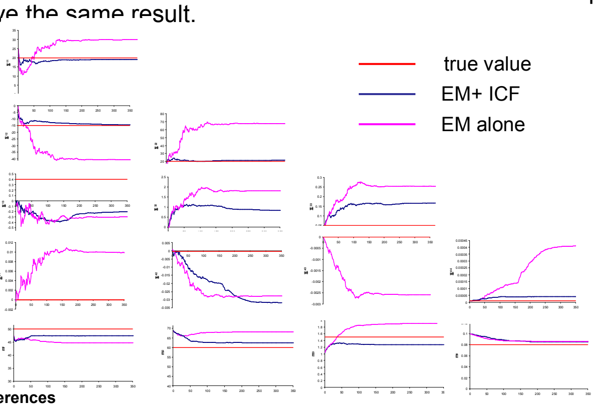
$$X_i \sim_{\text{iid}} N\left(\begin{pmatrix} 50 \\ 60 \\ 1.5 \\ 0.08 \end{pmatrix}; \begin{pmatrix} 20 & & & \\ -15 & 20 & & \\ 0.4 & -0.3 & 0.05 & \\ 0 & -5\times10^{-4} & 0 & 10^{-5} \end{pmatrix}\right)$$

$$\varepsilon_i \sim_{\text{iid}} N(0\,; 64 I_7)$$

We calculated the zero forced estimator and the MLE using the ICF algorithm.

Results

An example on a single sample of the quality of estimation : Our algorithm performed better for all but one parameter to be estimated. Estimations obtained on the 100 simulated samples gave the same result.



Conclusion

The simulations we performed suggest the following conclusions :

- Ignoring independence between individual parameters (*ie* estimating the entire variance matrix) gives imprecise parameter estimations .
- Misspecification of the variance matrix structure has an impact on the mean parameters estimation.
- The proposed algorithm gives better estimates of the variance matrix and means than other methods when zeros are well positioned.
- It is easy to implement.
- More work is necessary to propose a method that reveal the actual structure of the variance matrix.

References

[1] Pinheiro JC and Bates DM. Unconstrained Parametrizations for Variance-Covariance Matrices, Statistics and Computing, 6 (1996), 289-296.
[2] Chaudhuri S, Drton M and Richardson TS. Estimation of a covariance matrix with zeros. Biometrika, 94(2007),199-216.
[3] Dempster AP, Laird NM and Rubin DB. Maximum likelihood from incomplete data via the EM algorithm. J. Roy. Statist. Soc. Ser. B, 39(1):1–38, 1977.
[4] Chafaï D and Concordet D. Estimating Variance Matrix with Prescribed Zeros in Nonlinear Mixed Effects Models, (2007) preprint.