Population design in nonlinear mixed effects multiple responses models: extension of PFIM and evaluation by simulation with NONMEM and MONOLIX

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ABSTRACT

Objectives: Multiple responses are increasingly used in population analyses. In this context, efficient tools for population designs evaluation and optimisation are necessary. The objectives are 1) to extend the population Fisher information matrix (MF) for nonlinear mixed effects multiple responses models and 2) to evaluate it by a simulation study using the FO and FOCE methods in NONMEM and the SAEM algorithm of MONOLIX.

Methods: We first extend the expression of MF for multiple responses model using a linearisation of the model as proposed for a single response by Mentré et al. [1]. We implement this method in an extension of PFIM [2], a R function for population designs evaluation and optimisation. Using a PKPD model example [3], we evaluate the relevance of the predicted standard errors (SE) computed by PFIM. To do that, first, we compare the SE of PFIM to those computed under asymptotic convergence assumption by MONOLIX through a simulation of 10000 subjects. MONOLIX is based on the SAEM algorithm [4], and uses two methods to compute SE: a linearization method and the Louis method [5]. Then, we also compare the predicted SE of PFIM to the distribution of the SE obtained by estimation on 1000 data sets with FO, FOCE and with the two methods of SAEM. We also compare those predicted SE to the empirical SE obtained for each method defined as the standard deviation on the 1000 estimates. Last, we compute bias and root mean square errors (RMSE) for the estimates obtained by FO, FOCE and SAEM.

Results: The SE of PFIM are equivalent to those predicted by SAEM and to the empirical ones obtained with FOCE and SAEM; they are in agreement with the distribution of the SE for FOCE and for the linearization method of SAEM. Regarding FO, the range of the SE and the empirical ones are much larger than the SE of PFIM and those obtained with FOCE or SAEM. The distribution of the SE for FOCE and the linearization method of SAEM are closed and are in accordance with the empirical SE. The Louis method of SAEM provides larger distribution of SE. Last, we show large bias and large RMSE for the estimates obtained with FO, whereas with SAEM or FOCE they are good, especially for SAEM on the fixed effects.

Conclusion: We show the relevance of the extension of PFIM for multiple responses models. Despite the linearization used to compute MF in PFIM, it adequately predicts the SE obtained by FOCE and SAEM but not those of FO which are much larger.

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