# Two-stage optimal designs in nonlinear mixed effect models: application to pharmacokinetics in children

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**Abstract**

Nonlinear mixed effect models (NLMEM) are used in pharmacometrics to analyse longitudinal data through models. Approaches based on the Fisher information matrix ($M_F$) can be used to optimise the design of these studies. A first-order linearization of the model was proposed to evaluate MF for these models [7] and is implemented in the R function PFIM [1]. Local optimal design needs some *a priori* values of the parameters which might be difficult to guess. Adaptive designs are useful to provide some exibility and were applied in pharmacometrics [6, 9]. However, two articles in other contexts [2, 5] discussed that two-stage designs could be more efficient than fully adaptive designs. Moreover, two-stage designs are easier to implement in clinical practice. We implemented in a working version of PFIM the optimisation of the determinant of $M_F$ for two-stage designs in NLMEM. We evaluated the approach by simulation. The example concerns a drug in development for which a pharmacokinetic study in children is needed and will be analysed through NLMEM as recommended [4, 8]. For the first stage, parameters were estimated using predictions from pharmaco-chemical properties of the drug [3]. We evaluated one and two-stage designs assuming that some parameter(s) is (are) different than the initial one(s). We evaluated the impact of the size of each cohort on the precision of population parameters estimation.

## Keywords

Adaptive design, Design optimisation, Fisher information matrix, Nonlinear mixed effect models, PFIM, Population pharmacokinetics.

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