

Population designs evaluation and optimisation in R: the PFIM function and its new features

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ABSTRACT

Context: Efforts have been devoted since a decade to the development of a methodology for population designs evaluation and optimisation based on the expression of the Fisher information matrix for nonlinear mixed effects models [1, 2]. In this context, we have proposed PFIM [3], a R function for population designs evaluation and optimisation. Recently we extended PFIM for multiple responses models.

Objectives: To describe the new features of PFIM and to present the new extension for multiple responses models.

Method and Results: We first give a review of the evolution of the releases of PFIM. The last release of PFIM includes the ability to deal with models defined by differential equations, the availability of Fedorov-Wynn algorithm for optimisation of design structure and a library of PK models. This library supports three types of administration (per os, infusion, bolus) with one or two compartment models after either single dose, multiple doses or steady state. We also describe the PFIM Interface 2.0 version which allows an easier use of PFIM through a graphical user interface. Then, we show the new extension of PFIM for the case of multiple responses models. Extension for those models covers the same features as for single models. First, it can handle either analytical models or differential equations systems. Regarding optimisation, it can be performed in continuous intervals of times with the Simplex algorithm or among a fix set of allowed sampling times with the Fedorov-Wynn algorithm. Last, for the multiple responses case, users can choose to optimise identical sampling times for all type of responses or different sampling times across responses. We illustrate the new extension of PFIM and compare the different options using a real example which is the design for simultaneous population modelling of the time course of warfarin concentration and its effect on the prothrombin complex activity after single dose administration.

PFIM, including its graphical user interface, is a freely available software [4].

[1] Mentré, F., Mallet, A., Baccar, D. (1997). Optimal design in random-effects regression models. *Biometrika*. 84(2): 429-442

[2] Retout, S., Mentré, F., Bruno, R. (2002). Fisher information matrix for non-linear mixed-effects models: evaluation and application for optimal design of enoxaparin population pharmacokinetics. *Statistics in Medicine*. 21(18): 2623-39

[3] Retout, S., Mentré, F. (2003). Optimisation of individual and population designs using Splus. *Journal of Pharmacokinetics and Pharmacodynamics*. 30(6): 417-443

[4] <http://www.bichat.inserm.fr:80/equipes/Emi0357/download.html>