Tools on R for Dose-response curves analysis

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Keywords: R, Non linear mixed effects models, Dose response curves, Pharmacological parameters

In experimental pharmacology, studies on drug-receptor interactions commonly use dose-response curves (DRC) established under repeated measurements designs. The best approach to analyse a dose-response relationship is to use non linear mixed effects models (nlme) (Davidian and Giltinian, 1995), but specific softwares dedicated to analyse pharmacological data have not yet developped nlme procedures. The aim of this work was to provide accurate and easy-to-use tools on R to assist pharmacologists with using nlme modelling to fit DRC.

Five functions using available R packages have been built. The *Est.Pop* function, using nlme function in nlme package (Pinheiro and Bates, 2000), gives an estimation of the different parameters included in the predicted function and a qqplot of the residuals. The *IC.par* function provides a confidence interval for each parameter of the predicted function for the confidence level asked by users. The *Graph.curves* function displays a graph showing the individual fitted curves and the population fitted curve which illustrate the individual effect on physiological response. Nevertheless, nlme procedures are very susceptible to outliers points in the data sets and the convergence of the iterative calculus is not always achieved. In those situations and when the residuals seem not to be normally distributed the *Est.Boot* function is more accurate to give an estimation of the predicted function parameters by a non parametric bootstrap method using the bootstrap package (Huet et al, 2004). Depending on the bioassay and the relative asymmetry of the curves, four predictive functions (Hill equation, Richards, Gompertz, Hill modified functions) can be tested (Giraldo et al, 2002) with those tools; the *Comp.Mod* function is dedicated to compare established models and to detect the best one.

The nlme modelling analysis of a set of dose-response curves fom β- adrenoceptors-mediated blood vessels relaxation studies (Mallem et al, 2005) will be presented and discussed.

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