

New algorithms and tools for population model building and evaluation

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Building and validating a mixed effects model are generally difficult and laborious tasks for the modeler. Indeed, it requires to find the "best" covariate model, i.e. to identify which covariates significantly explain the variability of some individual parameters, to identify the "best" correlation model for the random effects, and to find the "best" residual error model for continuous data.

I will present an extension of the EM algorithm that allows to build a linear mixed effects model by optimizing a penalized likelihood criterion (AIC, BIC) in an iterative way. I will also present the SAMBA (Stochastic Approximation for Model Building Algorithm) algorithm, an extension of this method for non-linear mixed effects models.

Once the model is built, it must be validated, i.e. each of the hypotheses made on the model must be tested (covariate model, correlation structure of the random effects, distribution of the random effects, distribution of residual errors, etc.). I will show that it is possible to construct unbiased hypothesis tests using test statistics based on observations and random effects sampled from their conditional distributions.

These methods for building and validating mixed effects models are implemented in the Rsmx package (<http://rsmx.webpopix.org>).

I will illustrate them with applications in population pharmacokinetics.