

**THE SAEM ALGORITHM IN NONLINEAR MIXED EFFECTS MODELS DEFINED BY ORDINARY  
DIFFERENTIAL EQUATIONS WITH APPLICATION IN VIRAL DYNAMICS**

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Mathematical modelling of dynamic biological processes constitutes an important application in biostatistics. In many medical trials, a number of individuals are included in the study and each is sampled only a limited number of times and the emphasis is not so much on individual profiles than on the variability within the population. Mixed effect models can be used with such situations, and are particularly useful in trials with sparse designs.

An example of application concerns the modelisation of viral dynamics. Indeed, the efficiency of antiretroviral treatments, whether in HIV or hepatitis B or C pathologies, is quantified by the decrease in viral loads and/or the increase of the number of target cells. Models have been developed to describe the time-course of these profiles through a system of ODEs, taking into account the physiology of viral replication and the mechanisms of action of the different therapeutic options. There is a large inter-patient variability in these pathologies, and the joint study of viral load decrease through mixed effect models in a set of patients provides a better understanding of differences in the response to treatment.

Several statistical issues can be studied related to nonlinear mixed effects models, such as parameter estimation, model selection (covariate model through the specification of the fixed effect structure, covariance model for the random effects), as well as design optimisation for the trial itself.

Mixed effect models are difficult to use because they require complex computations, translating in long run times, and there are few efficient algorithms implementing these methods. Amongst the possible approaches for maximum likelihood estimation in nonlinear mixed effects models, the most frequently used for the time being are parametric estimation methods relying on a linearisation of the likelihood. However over the last 15 years, major limits and drawbacks of these approaches have been amply recognised.

I will present in this talk a methodology for maximum likelihood estimation in nonlinear mixed effects models. This methodology is based on the SAEM algorithm (Stochastic Approximation version of EM algorithm) which was shown to converge under very general conditions. This algorithm is implemented in the MONOLIX software (<http://software.monolix.org>).