Generalisation of the SAEM algorithm to nonlinear mixed effects model defined by differential equations: application to HIV viral dynamic models

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Introduction

- Usual Pharmacokinetic/Pharmacodynamic (PK/PD) models, HIV dynamic models defined by a system of ordinary differential equations (ODE)
- No analytical solution in general
- Introduction of a numerical solving method of ODE in estimation algorithms
- Two software available: NONMEM and nlme-ODE (estimation by linearization of the model)
- No theoretical results of the convergence of these two estimation algorithms using numerical solving method
- Alternative estimation algorithm: the SAEM algorithm, a stochastic version of the EM algorithm, with theoretical results of convergence

Objective

- Generalization of the SAEM algorithm to model defined by ODE
- Control the error induced by the numerical evaluation of the regression function
- Application to simulated and real data sets

Method

Model

$$\begin{array}{rcll} y_{ij} & = & f(t_{ij},\phi_i)+\varepsilon_{ij}, & 1\leq j\leq n_i, \quad 1\leq i\leq N \\ \varepsilon_{ij} & \sim_{i.i.d.} & \mathcal{N}(0,\sigma^2), & \phi_i\sim\pi(\phi;\beta) \end{array}$$

- $f:\mathbb{R}\times\mathbb{R}^k\longrightarrow\mathbb{R}^d$ defined as the solution of

$$\frac{\partial f(t,\phi)}{\partial t}=F(f(t,\phi),t,\phi), \quad t\in[t_0,T],$$

$$f(t_0,\phi)=f_0, \quad \text{known initial condition,}$$
$$F:\mathbb{R}^d\times\mathbb{R}\times\mathbb{R}^k\longrightarrow\mathbb{R}^d \text{ known}$$

- Aim: estimation of $\theta=(\beta,\sigma^2)$

SAEM algorithm

- Implemented in the Monolix Matlab software
- Free on www.math.u-psud.fr/∼lavielle/monolix/logiciels.html
- Delyon, Lavielle, and Moulines, 1999 ; Kuhn, and Lavielle, 2004
- Likelihood $p(y,\phi,\theta)=\exp\{-\psi(\theta)+\langle S(y,\phi),\Phi(\theta)\rangle\}$, with S sufficient statistic of the model
- k^{th} iteration
  - S step: simulation of ϕ_k by a MCMC procedure with $p(\phi|y;\theta_k)$ as unique stationary distribution
  - SA step: update of s_{k+1} with (γ_k) a sequence of positive numbers by $s_{k+1}=s_k+\gamma_k\{S(y,\phi_k)-s_k\}$
  - M step: update of θ_k by $\theta_{k+1}=\arg\max_\theta\left(-\Psi(\theta)+\langle s_{k+1},\Phi(\theta)\rangle\right)$

MCMC algorithm

- Markov Chain with $p(\phi|y;\theta)$ as stationary distribution
- Simulation of a candidate ϕ^c using an instrumental distribution $q_\theta(\phi^c|\phi)$

1. Prior distribution $q(\phi^c|\phi)=\pi(\phi^c;\beta)$ 2. Small moving $\phi^c=\phi+\delta$

- Computation of the acceptation probability of the candidate ⇒ Evaluation of the solution of the ODE for a fixed ϕ

Classical numerical solving methods of ODE

- Euler Scheme
- Runge-Kutta algorithm of order 4, implemented in Matlab: ode45
  - Efficient for non stiff system, implicit version for stiff system
- Local Linearization Scheme (LL) of order 2; Ramos and Garcia-Lopez, , Appl. Math. Comput, 1997
  - Linearization of the ODE with respect to time t, and exact integration through exponential matrix computation
  - Efficient for stiff system

Generalization of the LL numerical solving scheme of ODE

- Donnet and Samson, Biometrika, submitted
- Modification of the LL scheme for the second instrumental distribution of the MCMC procedure
  - Evaluation of $f(\phi^c,t)$ knowing $f(\phi,t)$, and ϕ^c in a neighborhood of ϕ
  - Linearization of the ODE with respect to time t and parameter ϕ, and exact integration
  - No exponential matrix computation
- Implementation in Matlab

Introduction of an approximate model

- f_h, the approximation of f by a numerical solving method of order p and step size h

$$\sup_{t\in[t_0,T]}|f(t,\phi)-f_h(t,\phi)|=0(h^p).$$

- Approximate statistical model (M_h)

$$\begin{array}{rcll} y_{ij} & = & f_h(t_{ij},\phi_i)+\varepsilon_{ij} & 1\leq j\leq n_i \qquad 1\leq i\leq N \\ \varepsilon_{ij} & \sim & \mathcal{N}(0,\sigma^2) & \end{array}$$

Convergence results

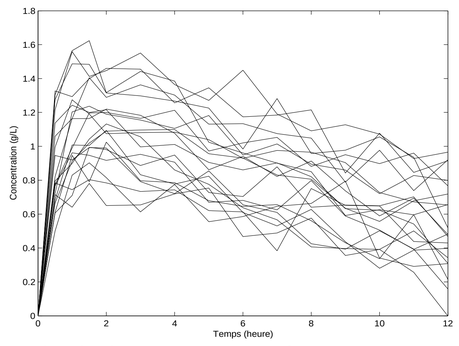
- Donnet and Samson, Biometrika, submitted
- Under regular conditions, the SAEM algorithm converges on the (M_h) model
- Distance between the likelihoods of (M) and (M_h) models controlled by $0(h^p)$

Simulation study

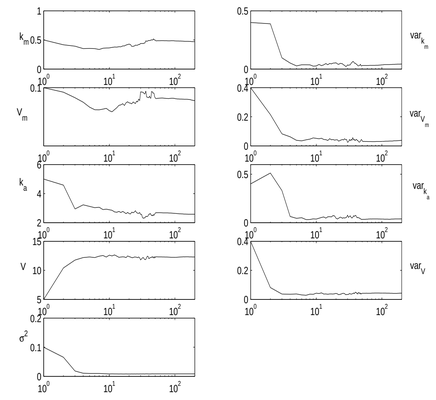
- PK model of one compartment with first order absorption and saturable elimination of Michaelis-Menten :

$$\frac{dC}{dt}(t,\phi)=\frac{k_a\cdot Dose}{V}e^{-k_at}-\frac{V_mC(t,\phi)}{k_m+C(t,\phi)}$$

- Simulated data set mimicking the kinetic of hydroxuera; Tracewell et al, Cancer Chem. Pharmacol, 1995



Individual concentrations of 20 patients



Evolution of the estimates
in function of the iteration of SAEM algorithm

- Comparison with NONMEM estimates
  - No convergence of NONMEM and convergence of SAEM

	k_m	V_m	k_a	V	var_{k_m}	var_{V_m}	var_{k_a}	var_V	σ^2
initial value	0.50	0.100	5.00	5.0	0.400	0.400	0.400	0.400	0.1000
simulation value	0.37	0.082	2.72	12.2	0.040	0.040	0.040	0.040	0.0100
SAEM	0.47	0.088	2.58	12.3	0.043	0.038	0.039	0.043	0.0084
NONMEM FOCE	0.60	0.100	2.57	12.3	10^{-8}	0.062	0.068	0.036	0.0088

Application to HIV dynamic on the COPHAR2-ANRS111 trial

The COPHAR 2-ANRS 111 trial

- Open, multi-center, prospective trial, included HIV-infected adults
- Treatment combined a protease inhibitor (PI) with two reverse transcriptase inhibitor (RTI)
- Data obtained from the lopinavir group analyzed here (initial dose of 400mg bid)
- 32 patients assessable at week 16 (15 patients taken 400 mg bid, 11 taken 266 mg bid, and 6 533mg bid)
- Viral load measured at week 0, 2, 8, 16, CD4 concentration measured at week 0, 4, 8, 16

HIV dynamic model

- Joint modelisation of the decrease of the viral load and the increase of the CD4
- Perelson et al, Science, 1996; Perelson et al, Nature, 1997; Nelson et al, JAIDS, 2001

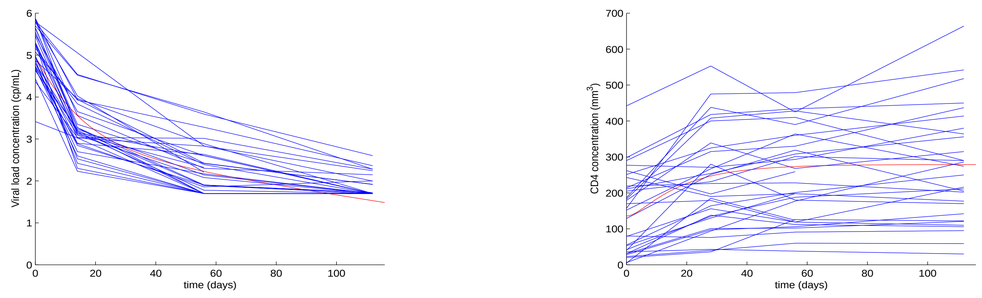
HIV dynamic model with protease inhibitor (IP) treatment Initial condition: steady-state before treatment

$$\begin{array}{rcll} \frac{dT_{NI}}{dt} & = & \Pi-(\delta_n+\beta V)T_{NI} & T_{NI}(t=0)=\frac{\delta c}{\beta p} \\ \frac{dT_I}{dt} & = & \beta VT_{NI}-\delta T_I & T_I(t=0)=\frac{c}{p}V(t=0) \\ \frac{dV_I}{dt} & = & (1-\eta_{PI})pT_I-cV_I & V_I(t=0)=\frac{\Pi p}{\delta c}-\frac{\delta_n}{\beta} \\ \frac{dV_{NI}}{dt} & = & \eta_{PI}pT_I-cV_{NI} & V_{NI}(t=0)=0 \end{array}$$

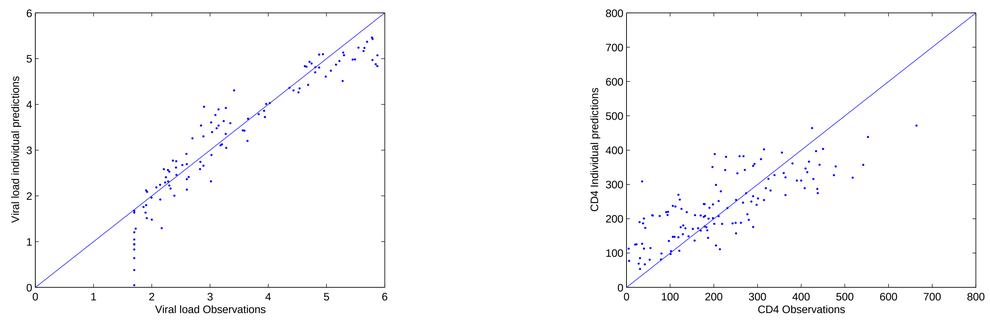
- T_{NI}, T_I, V_{NI} and V_I : concentration of non-infected, infected CD4, and non-infectious, infectious virus
- Π: thymical production of lymphocytes, p : viral production, β: cellular infection rate
- δ_n, δ, c : mortality rate of T_{NI}, T_I, and of the virus, η_{PI} : proportion of non-infectious virus product by PI

Results using the SAEM-ODE algorithm

- Mixed model with 7 fixed effects, 7 random effects and 2 residual errors



Individual concentrations (blue) and population prediction (red)



Individual predictions versus observations

Conlusion

- Efficient SAEM algorithm to estimate nonlinear mixed model defined by ordinary differential equation
- Efficient extension to stochastic differential equation