

The SAEM algorithm for nonlinear mixed models with left-censored data and differential equations

Application to the joint modeling of HIV viral load and CD4 dynamics under treatment

Adeline Samson¹, Marc Lavielle², France Mentré¹

¹INSERM U738, Université Paris 7, Paris, France

² Université Paris 5, Université Paris-Sud, Orsay, France

Nonlinear mixed model

Introduction

Objectives

Left-censored data

Differential equations

Viral dynamics estimation

Conclusion

$$\begin{aligned}y_{ij} &= f(\phi_i, t_{ij}) + g(\phi_i, t_{ij})\varepsilon_{ij} \\ \varepsilon_{ij} &\sim \mathcal{N}(0, \sigma^2) \\ \phi_i &\sim \mathcal{N}(X_i\mu, \Omega)\end{aligned}$$

- y_{ij} observation of subject i at time t_{ij}
- ϕ_i individual random parameter of subject i
- ε_{ij} measurement error at time t_{ij}
- Homoscedastic or heteroscedastic error model
- X_i covariate
- Estimation of parameters μ, Ω, σ^2 by maximum likelihood

Estimation algorithms

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Linearization algorithm (FO, FOCE)

- *Sheiner, Rosenberg, Melmon, 1972; Lindstrom and Bates, 1990*
- NONMEM, nlme in R
- Numerical limits

Gaussian quadrature

- *Pinheiro and Bates, 1995; Wolfinger, 1996*
- proc NLMIXED in SAS
- Slow convergence

Expectation-Maximisation (EM) algorithms

- MC-EM, *Leary, 2004*
- MC-PEM, *Guzy, 2006*
- SAEM, *Delyon, Lavielle, Moulines, Ann. Stat., 1999; Kuhn and Lavielle, Comput. Stat. Data An., 2005*

Statistical convergence

HIV-cells dynamics

Introduction

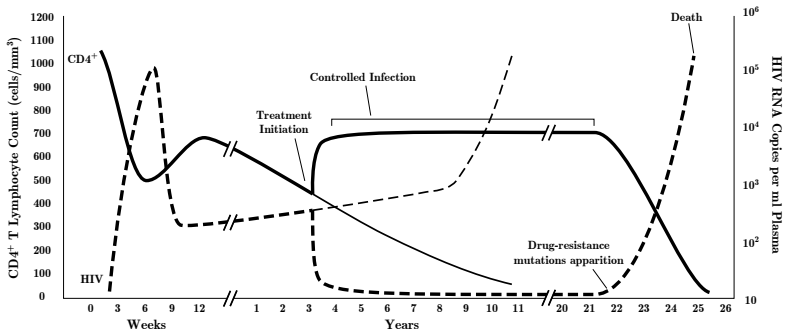
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HIV-cells dynamics modeling

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Evaluation from repeated measurements of viral load/ CD4⁺

- Nonlinear mixed effect models

Difficulties

- Limit of quantification for viral load data
- Differential system describing simultaneously viral load/CD4⁺ dynamics

Objectives

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data

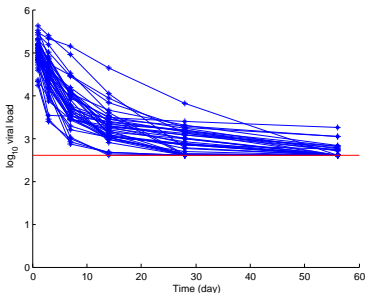
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Conclusion

- 1 Extension of SAEM for the analysis of left-censored data
- 2 Extension of SAEM for models defined by ordinary or stochastic differential equations
- 3 Modeling with SAEM the viral dynamics of the Cophar 2-ANRS 111 clinical trial

① Left-censored viral load data



Viral load not quantified below a limit of quantification (LOQ)

- Omission of all data below LOQ
- Imputation to $LOQ/2$
- Computation of likelihood conditional on censoring (*Beal, 2001*)
- Multiple imputation (*Hughes, 1999; Jacqmin-Gadda et al., 2000*)

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Extension of the SAEM algorithm

- Gibbs algorithm to perform multiple imputation of the censored data in the simulation step
- Convergence of estimates to a maximum of the likelihood proved

Evaluation on simulated datasets of left-censored viral load data

- Comparison with naive methods

Application to the Trianon-ANRS 81 trial

- Comparison of treatments

Samson, Lavielle, Mentré. Extension of the SAEM algorithm to left-censored data in non-linear mixed-effects model: application to HIV dynamics model. *Comput. Stat. Data Anal.*, to appear

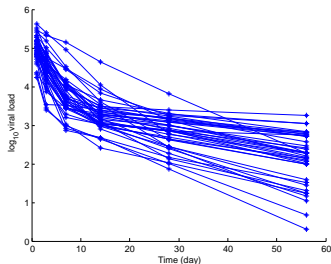
Evaluation on simulated data

Ding and Wu, 2001

Biexponential model of HIV viral load decrease

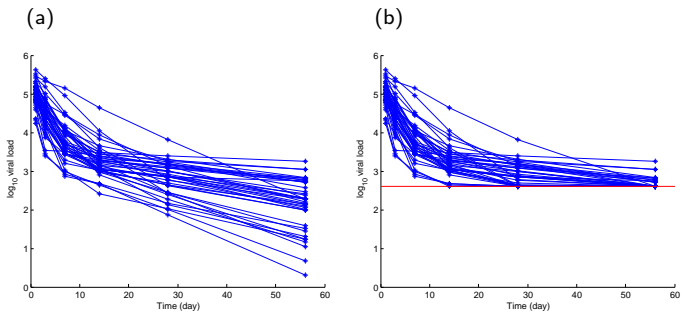
$$f(\phi, t) = \log_{10}(P_1 e^{-\lambda_1 t} + P_2 e^{-\lambda_2 t})$$

- $\phi = (\ln P_1, \ln \lambda_1, \ln P_2, \ln \lambda_2)$
- 6 measurements: 1, 3, 7, 14, 28 and 56 days
- $N = 40$ subjects



- Simulation of 1000 datasets

Analysis of left-censored data



(a) Before censoring: analysis with SAEM

(b) Censoring of data below $LOQ = 400$ cp/mL

Statistical methods to compare

- Naive method: omission of data below LOQ
- Simple imputation: first data below LOQ imputed to $LOQ/2$, omission of the followings
- Extension of SAEM with the left-censored dataset

Results

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- Left-censored data
- Differential equations
- Viral dynamics estimation
- Conclusion

Parameters	Bias (%)			
	before censoring	Naive method	Simple imputation	SAEM
$\ln P_2$	0.1	2.6	10.7	0.2
$\ln \lambda_2$	0.1	10.5	22.9	0.6
Var ($\ln P_2$)	2.2	12.7	24.8	6.2
Var ($\ln \lambda_2$)	0.9	47.1	98.3	6.6
σ^2	0.5	10.3	440.8	0.6
RMSE (%)				
$\ln P_2$	1.3	3.2	10.9	1.6
$\ln \lambda_2$	3.1	11.4	23.4	3.9
Var ($\ln P_2$)	26.6	37.1	58.3	37.7
Var ($\ln \lambda_2$)	25.7	56.0	113.5	36.8
σ^2	16.3	26.2	453.2	19.3

Analysis of Trianon-ANRS 81 trial

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Trianon trial

- 144 patients infected by HIV-1 followed during 72 weeks
- Randomized treatments
 - 3TC: lamivudine + stavudine + indinavir
 - NVP: nevirapine + stavudine + indinavir
- *LOQ*: 20 cp/mL

Initial statistical analysis

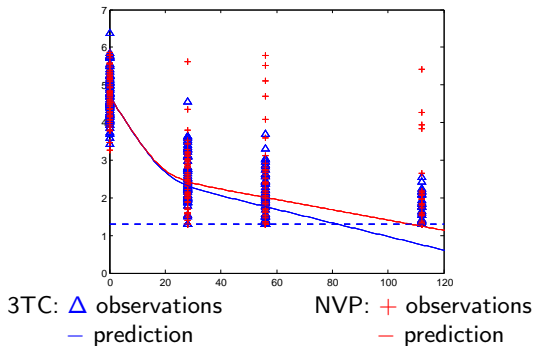
Launay et al., 2002

- Percentage of patients under *LOQ*
- Treatment 3TC more efficient than treatment NVP

Objective

- Analysis of the viral load decrease with SAEM

Results



- Naive methods: no significant treatment effect
- SAEM: significant treatment effect on the second slope of the decrease ($p < 0.01$ for Wald and likelihood ratio tests)

② Model with ordinary differential equations

Ordinary differential equations (ODE) describing dynamics of viral load decrease and CD4⁺ increase

Extension of the SAEM algorithm for ODE

- Numerical approximation of ODE
 - Runge-Kutta
 - Local linearisation schemes
 - Adapted to stiff differential equations
 - Save computational time when included in MCMC algorithm
- Convergence of estimates to a maximum of the likelihood proved
- Boundary of the error induced by the numerical approximation

Donnet, Samson. Estimation of parameters in incomplete data models defined by dynamical systems. J. Stat. Plan. Infer., to appear

Model with stochastic differential equations

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Stochastic differential equations (SDE) taking into account for

- Correlated residual errors due to model misspecification
- Random physiological fluctuations

Extension of the SAEM algorithm for SDE

- Approximation of the diffusion process by Euler-Maruyama
- Gibbs algorithm to simulate the diffusion process
- Convergence of estimates to a maximum of the likelihood proved
- Boundary of the error induced by the Euler-Maruyama approximation

Donnet, Samson. Parametric inference for diffusion processes from discrete-time and noisy observations. Proceedings of the 38th 'Journées de Statistiques', Société française de Statistiques, 2006

③ Simultaneous modeling of viral load-CD4⁺ dynamics

Modeling of viral load

- Bi-exponential model under assumption of constant CD4⁺
 - Unsatisfactory long-term assumption
- Large number of censored viral load data after 3 months
 - Difficulty to compare efficacy of treatments

Joint modeling of virus-CD4 dynamics

- Use of differential equations
- Improve the long-term prediction
- Better understanding of
 - Infection dynamics
 - Action of treatments

Difficulties

- Stiff differential equations
- Failure of FOCE (nlme) and Gaussian quadrature

Data and methods

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Cophar 2-ANRS 111 trial

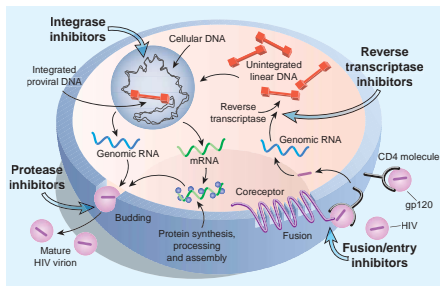
- 32 HIV-infected patients initiating anti-retroviral treatment with lopinavir protease inhibitor
- Measurements during 1 year
 - Viral load ($LOQ = 50$ cp/mL)
 - $CD4^+$

Methods

- Differential system describing virus- $CD4^+$ dynamics
- Analysis of viral load- $CD4^+$ dynamics by combining the 2 extensions of the SAEM algorithm

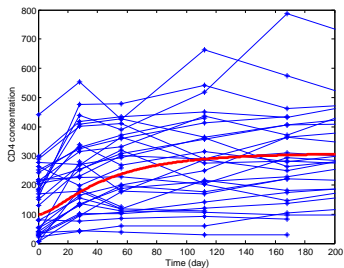
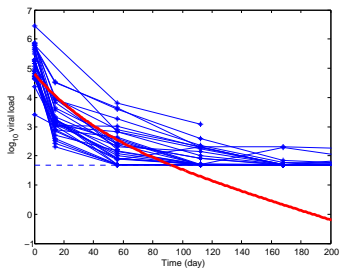
Differential system

Perelson et al., 1996; Di Mascio et al., 2004



$$\begin{aligned} \frac{dT_Q}{dt} &= \lambda + rT_{NI} - \alpha T_Q - \mu_{TQ} T_Q \\ \frac{dT_{NI}}{dt} &= \alpha T_Q - \gamma(1 - \eta_{RTI}) T_{NI} V_I - rT_{NI} - \mu_{TNI} T_{NI} \\ \frac{dT_I}{dt} &= \gamma(1 - \eta_{RTI}) T_{NI} V_I - \mu_{TI} T_I \\ \frac{dV_I}{dt} &= (1 - \eta_{PI}) \pi T_I - \mu_V V_I \\ \frac{dV_{NI}}{dt} &= \eta_{PI} \pi T_I - \mu_V V_{NI} \end{aligned}$$

Results



Conclusion

- First joint modeling of viral load/CD4⁺ dynamics
- Estimation of all parameters with SAEM

Conclusion

- Extension of the SAEM algorithm
 - Left-censored data
 - Ordinary and stochastic differential equations
 - Inter-occasion variability (*Panhard and Samson's poster: III-15*)
 - ⇒ Extension of convergence results
- Application to HIV viral dynamics modeling
 - Trianon: bi-exponential model and treatment comparison
 - Cophar-2: dynamics parameter estimation
 - ⇒ Good numerical properties of SAEM, even with complex models
- Monolix software
 - Available on web site
(www.math.u-psud.fr/~lavielle/monolix/)
 - *Lavielle et al.* software demonstration