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

¹ INSERM U738, Université Paris 7, Paris, France

² Université Paris 5, Université Paris-Sud, Orsay, France
Nonlinear mixed model

\[ y_{ij} = f(\phi_i, t_{ij}) + g(\phi_i, t_{ij})\varepsilon_{ij} \]
\[ \varepsilon_{ij} \sim \mathcal{N}(0, \sigma^2) \]
\[ \phi_i \sim \mathcal{N}(X_i\mu, \Omega) \]

- \( y_{ij} \) observation of subject \( i \) at time \( t_{ij} \)
- \( \phi_i \) individual random parameter of subject \( i \)
- \( \varepsilon_{ij} \) measurement error at time \( t_{ij} \)
- Homoscedastic or heteroscedastic error model
- \( X_i \) covariate

- Estimation of parameters \( \mu, \Omega, \sigma^2 \) by maximum likelihood
Estimation algorithms

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
  Statistical convergence
HIV-cells dynamics
HIV-cells dynamics modeling

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

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
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)*
Methods

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

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

<table>
<thead>
<tr>
<th>Parameters</th>
<th>Bias (%)</th>
<th>before censoring</th>
<th>Naive method</th>
<th>Simple imputation</th>
<th>SAEM</th>
</tr>
</thead>
<tbody>
<tr>
<td>$\ln P_2$</td>
<td>0.1</td>
<td>2.6</td>
<td>10.7</td>
<td>0.2</td>
<td></td>
</tr>
<tr>
<td>$\ln \lambda_2$</td>
<td>0.1</td>
<td>10.5</td>
<td>22.9</td>
<td>0.6</td>
<td></td>
</tr>
<tr>
<td>$\text{Var} (\ln P_2)$</td>
<td>2.2</td>
<td>12.7</td>
<td>24.8</td>
<td>6.2</td>
<td></td>
</tr>
<tr>
<td>$\text{Var} (\ln \lambda_2)$</td>
<td>0.9</td>
<td>47.1</td>
<td>98.3</td>
<td>6.6</td>
<td></td>
</tr>
<tr>
<td>$\sigma^2$</td>
<td>0.5</td>
<td>10.3</td>
<td>440.8</td>
<td>0.6</td>
<td></td>
</tr>
</tbody>
</table>

## RMSE (%)

<table>
<thead>
<tr>
<th>Parameters</th>
<th>RMSE (%)</th>
<th>before censoring</th>
<th>Naive method</th>
<th>Simple imputation</th>
<th>SAEM</th>
</tr>
</thead>
<tbody>
<tr>
<td>$\ln P_2$</td>
<td>1.3</td>
<td>3.2</td>
<td>10.9</td>
<td>1.6</td>
<td></td>
</tr>
<tr>
<td>$\ln \lambda_2$</td>
<td>3.1</td>
<td>11.4</td>
<td>23.4</td>
<td>3.9</td>
<td></td>
</tr>
<tr>
<td>$\text{Var} (\ln P_2)$</td>
<td>26.6</td>
<td>37.1</td>
<td>58.3</td>
<td>37.7</td>
<td></td>
</tr>
<tr>
<td>$\text{Var} (\ln \lambda_2)$</td>
<td>25.7</td>
<td>56.0</td>
<td>113.5</td>
<td>36.8</td>
<td></td>
</tr>
<tr>
<td>$\sigma^2$</td>
<td>16.3</td>
<td>26.2</td>
<td>453.2</td>
<td>19.3</td>
<td></td>
</tr>
</tbody>
</table>
Analysis of Trianon-ANRS 81 trial

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)
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

Model with stochastic differential equations

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

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

Cophar 2-ANRS 111 trial

- 32 HIV-infected patients initiating anti-retroviral treatment with lopinavir protease inhibitor
- Measurements during 1 year
  - Viral load ($LOQ = 50 \text{ cp/mL}$)
  - 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*

\[
\frac{dT_Q}{dt} = \lambda + rT_{NI} - \alpha T_Q - \mu T_Q T_Q
\]

\[
\frac{dT_{NI}}{dt} = \alpha T_Q - \gamma (1 - \eta_{RTI}) T_{NI} V_I - rT_{NI} - \mu T_{NI} T_{NI}
\]

\[
\frac{dT_I}{dt} = \gamma (1 - \eta_{RTI}) T_{NI} V_I - \mu T_I T_I
\]

\[
\frac{dV_I}{dt} = (1 - \eta_{PI}) \pi T_I - \mu V V_I
\]

\[
\frac{dV_{NI}}{dt} = \eta_{PI} \pi T_I - \mu V V_{NI}
\]
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