Facebook

Mixed effects models: Maximum Likelihood and Inference

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Program

1. Problem
2. Parameter Estimation: SAEM algorithm
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Problem

Notations

- $Z = (Z_1, \dots, Z_N) \in \mathcal{Z} \subset \mathbb{R}^d$, $Y = (Y_1, \dots, Y_N) \in \mathcal{Y} \subset \mathbb{R}^d$ Random Variables
- Measurable spaces with the associated incomplete and complete densities $p(y_i, \theta)$ and $p(y_i, z_i, \theta)$ where:
  - y_i is observed
  - z_i is the individual parameter
  - θ is the population parameter
- Continuous, non linear and mixed effects population models:

$$y_i = f(z_i) + \epsilon_i \tag{1}$$

  Where:
  - The structural model $f : \Theta \to \mathbb{R}$ is non linear and twice differentiable
  - $\epsilon_i \sim \mathcal{N}(0, \sigma^2)$ and $\sigma \in \mathbb{R}$
  - $z_i \sim \mathcal{N}(z_{pop}, \Omega)$ such that $z_i = z_{pop} + \eta_i$ with $\eta_i \sim \mathcal{N}(0, \Omega)$
  - $y_i | z_i \sim \mathcal{N}(f(z_i), \sigma^2)$
- In our case $\theta = (z_{pop}, \Omega, \sigma)$

Maximum likelihood

The goal is to compute the maximum likelihood estimate

$$\theta^{ML} = \arg\max_{\theta \in \Theta} p(y, \theta) \tag{2}$$

The EM algorithm (Dempster, Laird and Rubin) is an iterative algorithm that computes this quantity by maximizing an auxialiary quandity $Q : \Theta^2 \to \mathbb{R}$ at a given parameter estimate θ':

$$Q(\theta, \theta') = \mathbb{E}_{p(z|y,\theta')}\left[\log p(y, z, \theta)\right] \tag{3}$$

Unfortunately, in the framework of nonlinear mixed effects models, there is no explicit expression for the E-step since the relationship between observations y and individual parameters z is nonlinear so the expectation cannot be computed in closed form. Thus, we use a stochastic version of the EM.

Parameter Estimation: SAEM algorithm

SAEM

At a given θ^{k-1}:

1. $z_i^k \sim p(z_i|y_i, \theta^{k-1})$ (MCMC)
2. $Q^k(\theta) = Q^{k-1}(\theta) + \gamma_k(\log p(y_i, z_i^k, \theta) - Q^{k-1}(\theta))$
3. $\theta^k = \arg\max_{\theta \in \Theta} Q^k(\theta)$

My goal being to accelerate this algorithm, three approaches have been taken yet:

- Incremental/mini-batch strategies (see Neal & Hinton on the EM or F.Bach on the SGD)
- Faster MCMC dynamics (SG-MCMC based on an Itô diffusion, see for instance MALA based on a Langevin diffusion)
- Efficient proposal for a Metropolis Hastings algorithm based on a Laplace Approximation of the incomplete log likelihood $\log p(y, \theta)$

Inference: MCMC

Inference: MCMC

- Laplacian Method
  1. Laplace Approximation of the incomplete likelihood around the MAP ($z_{i,MAP} = \arg\max_z p(z_i|y_i,\theta)$)

$$p(y_i,\theta) = \int p(y_i, z_i, \theta) dz_i = \int e^{\log p(y_i, z_i, \theta)} dz_i \tag{4}$$

$$\approx e^{\log p(y_i, z_{i,MAP}, \theta)} \sqrt{\frac{(2\pi)^p}{|-\nabla^2 \log p(y_i, z_{i,MAP}, \theta)|}} \tag{5}$$

  2. Approximation of the posterior

$$-2\log p(y_i,\theta) = \underbrace{-p\log(2\pi) + \log(|-\nabla^2 \log p(y_i, z_{i,MAP}, \theta)|)}_{\approx +2\log p(z_{i,MAP}|y_i,\theta)} \tag{6}$$

$$-2\log p(y_i, z_{i,MAP}, \theta) \tag{7}$$

- Equivalent to linearizing the structural model f around the MAP:

$$y_i \approx z_{i,MAP} +^t (z_i - z_{i,MAP}).\nabla_{z_i} f(z_{i,MAP}) + \epsilon_i \implies z_i|y_i \sim \mathcal{N}(\mu, \Gamma) \tag{8}$$

Applications

PK-PD datasets

- 37 winter wheat experiments consisting in five to eight different nitrogen fertiliser rates, for a total of 224 nitrogen treatments. Nitrogen fertilizer was applied in two applications during the growing season. For each nitrogen treatment, grain yield (adjusted to 150 g.kg-1 grain moisture content) was measured.
- In this problem the sites are denoted by the index "i" and are the individuals in the dataset, the predictor is the dosage, the response is the grain yield and the covariate is the soil nitrogen
- We use a Quadratic Plateau model here and the structural model is:

$$f(z_i) = \begin{cases} (Y_{max})_i + B_i * (t_i - (X_{max})_i)^2, & \text{if } t \geq (X_{max})_i \\ (Y_{max})_i, & \text{otherwise} \end{cases} \tag{9}$$

Where $z_i = ((X_{max})_i, (Y_{max})_i, B_i)$.

Comparison

- New independent proposal. At a given iteration k:

$$z_i^k \sim \mathcal{N}(z_{i,MAP}, [-\nabla^2 \log p(y_i, z_{i,MAP}, \theta)]^{-1}) \tag{10}$$

With:

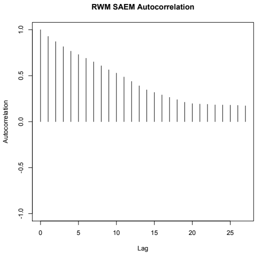
$$\nabla^2 \log p(y_i, z_{i,MAP}, \theta) = -\frac{\nabla p(y_i|z_i,\theta)^t \nabla p(y_i|z_i,\theta)}{p(y_i|z_i,\theta)^2} - \Omega^{-1} \tag{11}$$

- Comparison of the MCMC properties with:
  - Random Walk Metropolis (proposal $\mathcal{N}(z_i^k, \Omega)$)
  - Metropolis Adjusted Langevin Algorithm (proposal based on the Langevin dynamics $\mathcal{N}(z_i^k - \gamma_k \nabla \log \pi(z_i^k), \sqrt{2\gamma_k})$)

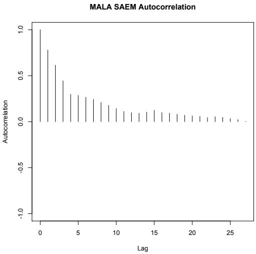
	RWM	MALA	Laplace
MJSD	0.02237	0.04297	0.14297

Comparison

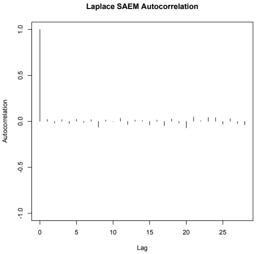
- Autocorrelation plots



RWM



MALA



Laplace

SAEM Parameter estimates

Estimates of the population parameters and the random effects using RWM SAEM vs Laplace SAEM

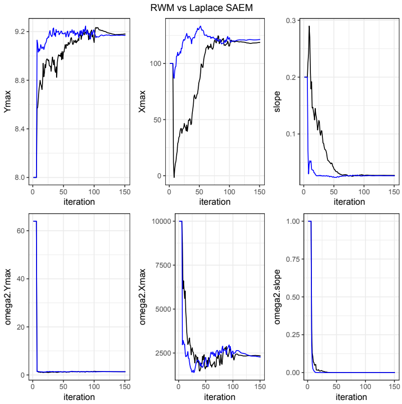


Figure: Estimates for 100 replicates

Thank you