

Supplementary material to:
Extension of the SAEM algorithm for nonlinear mixed
models with two levels of random effects

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The simulation step of the SAEM-MCMC algorithm performs the simulation of the missing data ϕ through a Markov chain which has $p(\phi|\mathbf{y}; \theta)$ as unique stationary distribution. For subject i , by Bayes formula, this conditional distribution is proportional to

$$p(\phi_i|\mathbf{y}_i; \theta) \propto \prod_{k=1}^K p(\mathbf{y}_{ik}|\phi_{ik}; \theta)p(\phi_i; \theta).$$

We propose to use a Metropolis-Hastings (M-H) algorithm to simulate this Markov chain. Let us recall the principle of this algorithm. At iteration r of the M-H algorithm, given the current value $\phi_i^{(r)}$ of the Markov Chain, the M-H algorithm proceeds as follows:

1. Simulate ϕ_i^c with a proposal distribution $q(\cdot, \phi_i^{(r)})$
2. Compute the acceptance probability

$$\alpha(\phi_i^c, \phi_i^{(r)}) = \frac{\prod_{k=1}^K p(\mathbf{y}_{ik}|\phi_{ik}^c; \theta)p(\phi_i^c; \theta)}{\prod_{k=1}^K p(\mathbf{y}_{ik}|\phi_{ik}^{(r)}; \theta)p(\phi_i^{(r)}; \theta)} \frac{q(\phi_i^{(r)}, \phi_i^c)}{q(\phi_i^c, \phi_i^{(r)})}$$

3. Simulate u with a uniform distribution $\mathcal{U}[0, 1]$
4. Update the Markov chain with

$$\phi_i^{(r+1)} = \begin{cases} \phi_i^c & \text{if } u \leq \alpha(\phi_i^c, \phi_i^{(r)}) \\ \phi_i^{(r)} & \text{else} \end{cases}$$

The convergence of the M-H algorithm strongly depends on the choice of the proposal distribution q . The convergence is ensured for some proposal distributions such as independent ($q(\cdot, \phi_i^{(r)})$ independent of $\phi_i^{(r)}$) or symmetrical ($q(\cdot, \phi_i^{(r)}) = q(\phi_i^{(r)}, \cdot)$) proposals (?). These proposals are detailed below. Given the dimension of ϕ , we also consider a Metropolis-Hastings-Within-Gibbs algorithm, combining both Gibbs algorithm and M-H procedure. The advantage of the Gibbs algorithm is to reduce the multi-dimensional simulation problem to the successive simulations of one-dimension vectors. Finally, at iteration ℓ of the SAEM algorithm, given the current estimate $\widehat{\theta}_\ell$, we combine the three following proposal transitions:

1. the prior distribution of ϕ_i , that is the Gaussian distribution $\mathcal{N}(\widehat{\mu}_\ell + \widehat{\beta}_\ell, \widehat{\Gamma}_\ell)$, corresponding to an independent M-H algorithm,

2. the multidimensional random walks $\mathcal{N}(\phi_i^{(\ell-1)}, \rho \widehat{\Gamma}_\ell)$ (symmetric proposal), where ρ is a scaling value chosen to ensure a satisfactory acceptance rate, namely around 30% as proposed in ?,
3. a succession of Kp unidimensional Gaussian random walks (symmetric proposal), i.e each component of ϕ_i is successively updated, leading to a Metropolis-Hastings-Within-Gibbs algorithm,

where $\widehat{\Gamma}_\ell$ is equal to

$$\widehat{\Gamma}_\ell = \begin{pmatrix} \widehat{\Omega}_\ell + \widehat{\Psi}_\ell & \widehat{\Omega}_\ell & \dots & \widehat{\Omega}_\ell \\ \widehat{\Omega}_\ell & \widehat{\Omega}_\ell + \widehat{\Psi}_\ell & \ddots & \vdots \\ \vdots & \ddots & \ddots & \widehat{\Omega}_\ell \\ \widehat{\Omega}_\ell & \dots & \widehat{\Omega}_\ell & \widehat{\Omega}_\ell + \widehat{\Psi}_\ell \end{pmatrix}.$$

Given the proposal distributions, as previously detailed, and using the theoretical convergence results proposed in ?, this hybrid Gibbs algorithm converges and generates an uniformly ergodic chain with $p(\phi|\mathbf{y}; \theta)$ as the stationary distribution. Consequently, by applying the convergence theorem of ? and under assumptions (A1) and (A2), we prove that the estimate sequence $(\widehat{\theta}_\ell)_{\ell \geq 0}$ produced by the extended SAEM algorithm converges towards a (local) maximum of the likelihood $p(\mathbf{y}; \theta)$.

In practice, the convergence of the MCMC algorithm is difficult to verify. As in Bayesian inference, the only convergence criteria existing for MCMC procedure are graphical criteria. We have to check if the estimate sequence explores a sufficiency large domain of the Markov chain. A convergence figure is presented and commented in section ??.