Joint modeling of longitudinal and survival data in high dimension

Application to the analysis of the effects of ostrinia attacks on the flowering date of corn

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Stat4Plant

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1. Introduction
   - Flowering date
   - Ostrinia attack proportion and mixed effect model
   - Joint modeling
2. Methodology
   - Objectives
   - High dimension
   - Expectation Maximisation algorithm
   - Stochastic Approximation EM algorithm
3. perspectives

biological context

FIGURE 1 – Ostrinia larva

FIGURE 2 – Ostrinia attack

Photo credit : Sacha Revillon

Synchronous development of ostrinia and corn

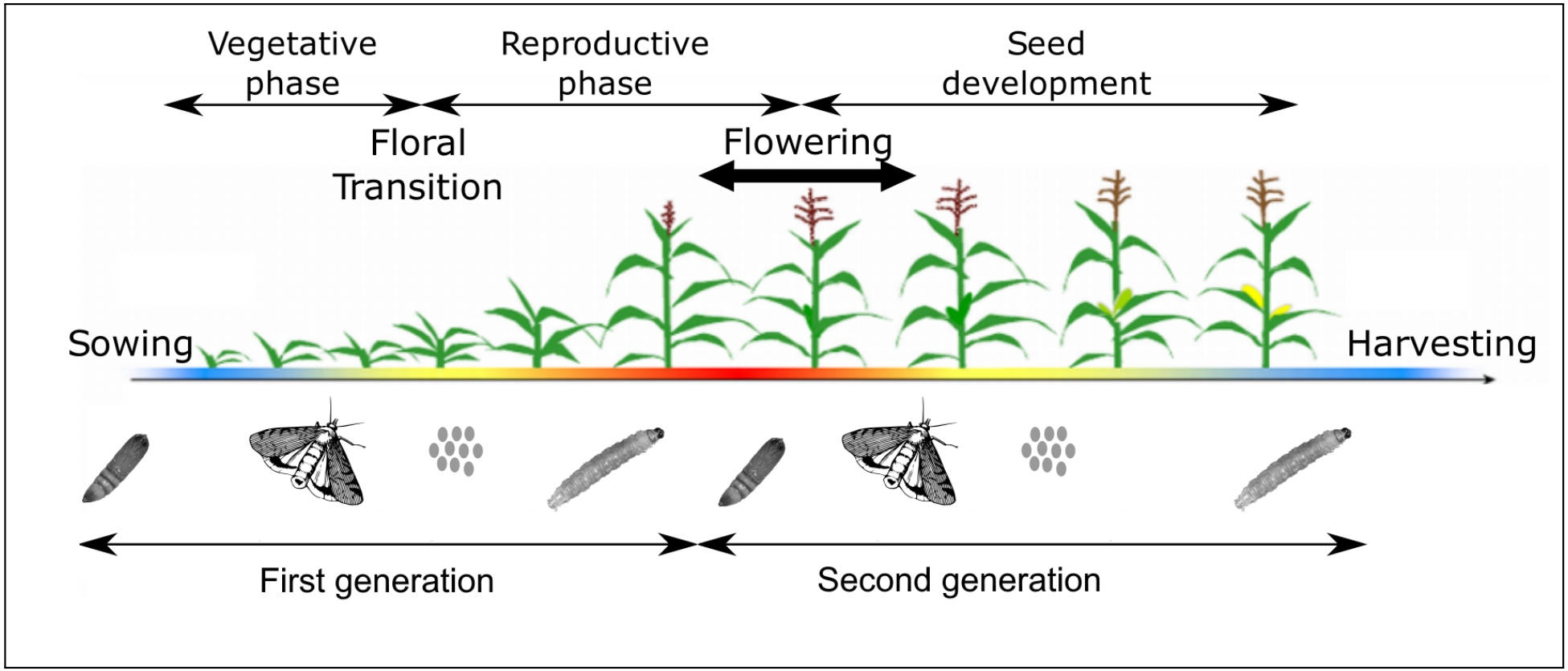


FIGURE 3 – Synchronization of the life cycles of the ostrinia and corn

Divergent selection

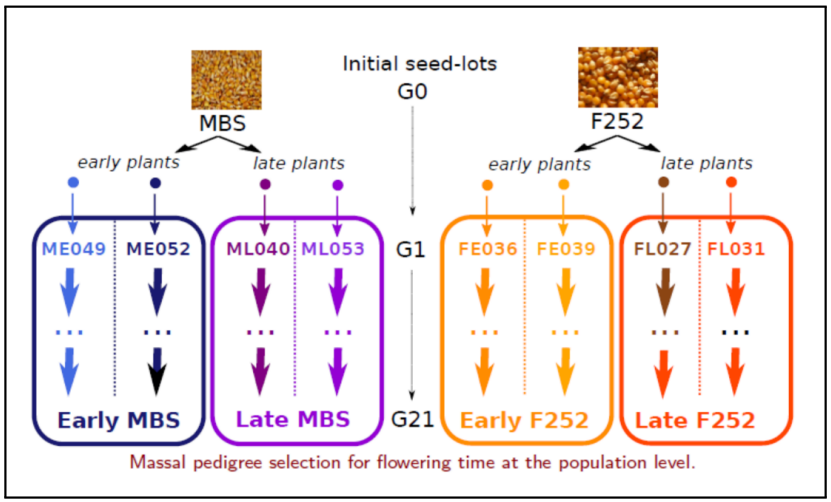


FIGURE 4 – Selection

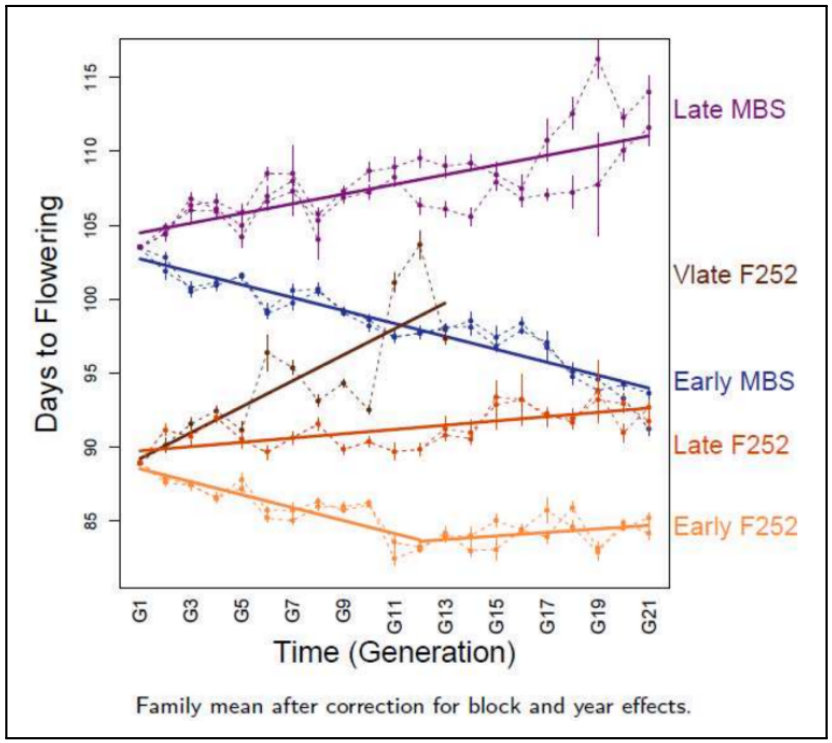


FIGURE 5 – Divergence

Flowering date

- Flowering date of each corn plant observed

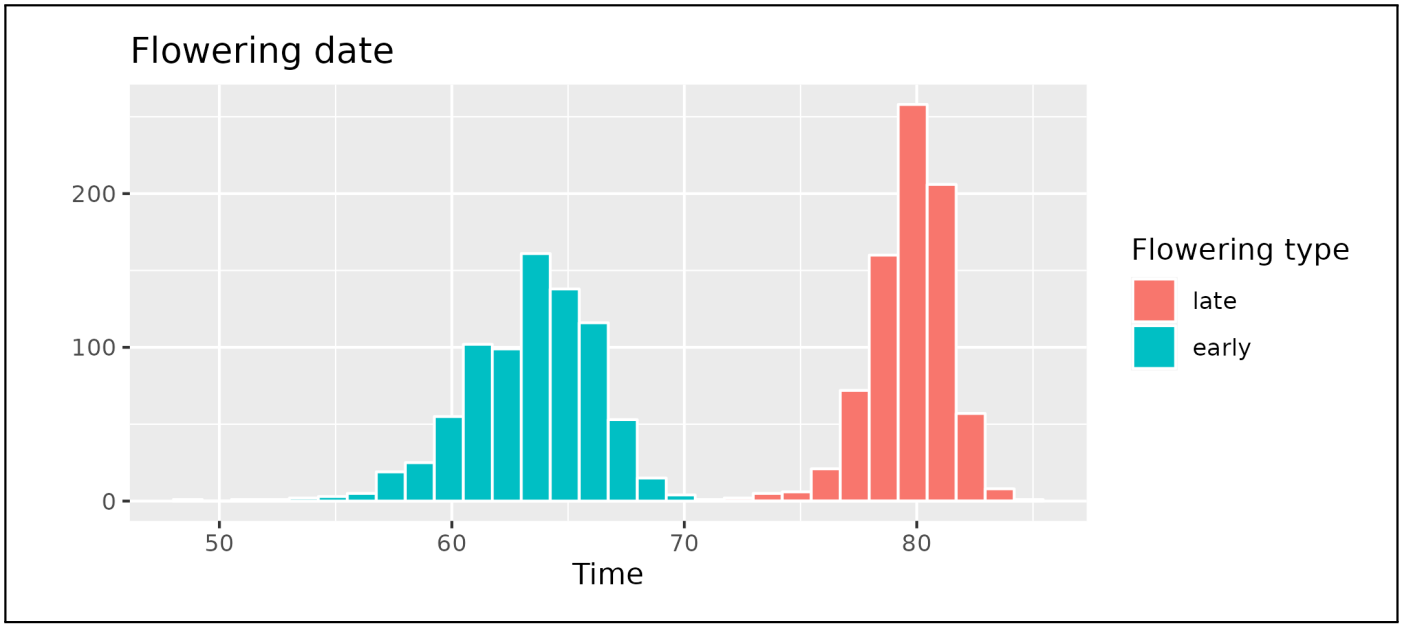


FIGURE 6 – Flowering date

- What impacts flowering :
  Genetic variability ? Insect attack ? Environmental conditions ?

Survival analysis

Focus on time to event of interest

- In medicine : Time of remission / time to death
- In our case : Date of flowering.

Definition : Survival time

The survival time $T > 0$ is the time that elapses between an initial moment (start of the study) and the appearance of an event interest.

Hazard function λ

T **is a positive random variable.** $\lambda(t)$ probability that the event occurs in a small time interval after t, knowing that it did not occur until time t :

$$\lambda(t) = \lim_{h \to 0} \frac{\mathbb{P}(t < T \leqslant t + h | T > t)}{h}$$

Cox Model

Référence : Cox 1972

Hazard function λ

$$\lambda(t) = \lim_{h \to 0} \frac{\mathbb{P}(t < T \leqslant t + h | T > t)}{h}$$

Regression model that links the survival time to explanatory variables and assume a common behavior.
The Hazard function is given by :

$$\lambda(T_i | U_i) = \lambda_0(T_i) \exp(\beta^T U_i)$$

- T_i time event
- λ_0 : baseline hazard which explain the common behavior
- U_i : covariate for individual i
- β : regression parameter

Modeling the flowering date

- For any plant $i \in \{1, ..., I\}$
  Hazard that the flowering occurs at T_i :

$$\lambda(T_i|U_i) = \lambda_0(T_i)\exp(\beta^T U_i)$$

Flowering date

Covariates

  - $T_i \in \mathbb{R}$: time event of interest (observation),
  - λ_0 baseline hazard unknown,
  - $U_i \in \mathbb{R}^p$: covariates for individual i (known),
  - $\beta \in \mathbb{R}^p$: fixed effect unknown.

Model parameter : $\boxed{\theta = (\lambda_0, \beta)}$

- **Objective :** model the proportion of attack and link it into this model!

ostrinia attack proportion

- Repeated observation of the number of attacks over time

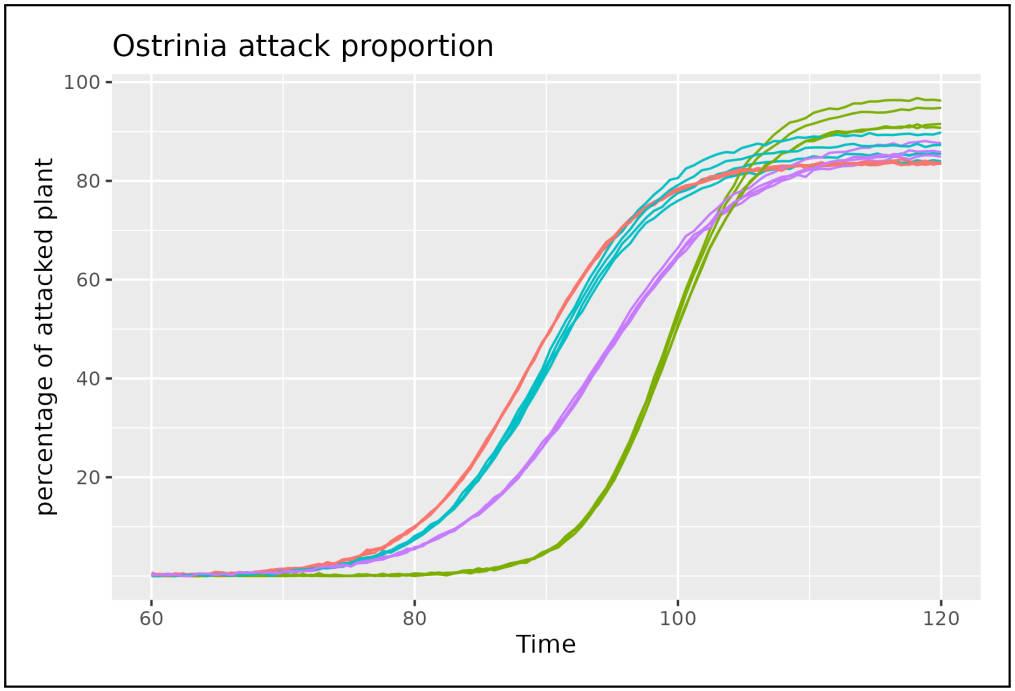


FIGURE 7 – ostrinia attack proportion

- intra (time-dependent behavior) and inter-individual variation (genetic background)

Non-linear mixed-effects model (NLME)

Référence : Davidian et Giltinan 1995

- Longitudinal data modeling :

behavior based on genetics

$$Y_{g,j} = m(t_{g,j}; \varphi_g) + \epsilon_{g,j} \ ; \ \epsilon_{g,j} \underset{i.i.d.}{\sim} \mathcal{N}(0, \sigma^2)$$

  - $Y_{g,j} \in \mathbb{R}$: j-th response of the g-th individual at time $t_{g,j}$ (observation),
  - $\varphi_g \in \mathbb{R}^3$: random group effects not observed,
  - m : a nonlinear function for φ.

- Inter-individual variation :

$$\varphi_g = \mu + \xi_g \ ; \ \xi_g \underset{i.i.d.}{\sim} \mathcal{N}(0, \Omega^2)$$

  - $\mu \in \mathbb{R}^3, \Omega^2 \in \mathcal{M}_3(\mathbb{R})$: unknown,

Model parameters : $\boxed{\theta = (\sigma^2, \mu, \Omega^2)}$

Joint Model : NLME and Survival model

Référence : Rizopoulos 2012

- Combining the two models using a link function m.

$$\begin{cases} \lambda(T_g|U_g,\gamma_g) &= \lambda_0(T_g)\exp(\beta^T U_g + \alpha m(T_g,\varphi_g)) \\ Y_{g,j} &= m(t_{g,j};\varphi_g) + \epsilon_{g,j} \end{cases}$$

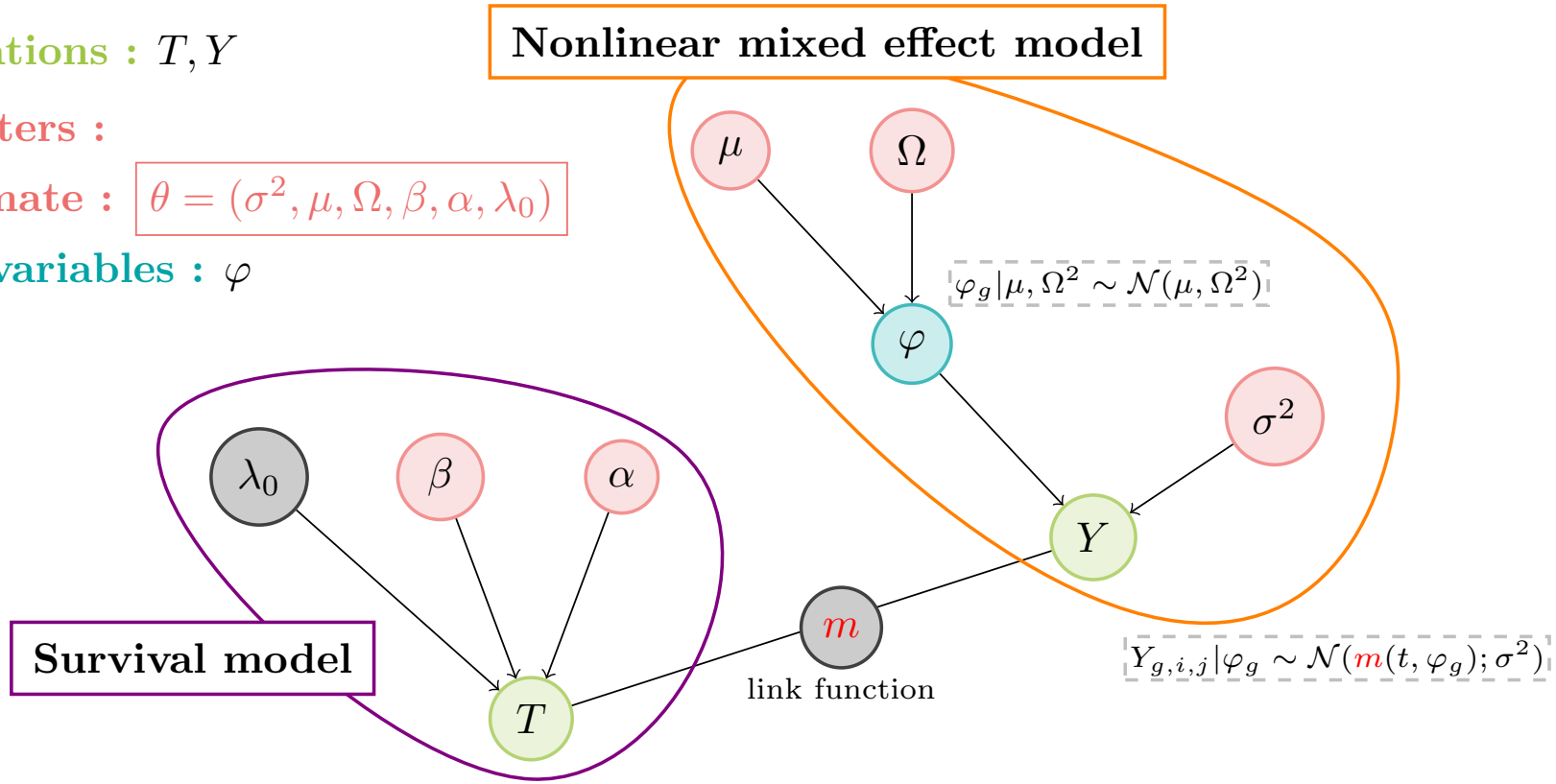
where α quantifies the association between the flowering and the attack proportion.

Model parameters : $\theta = (\sigma^2, \mu, \Omega^2, \beta, \alpha)$

Hierachical model

- **Observations :** T, Y
- **Parameters :**

  To estimate : $\theta = (\sigma^2, \mu, \Omega, \beta, \alpha, \lambda_0)$
- **Latent variables :** φ



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Objectives of the interships

$$\begin{cases} \lambda(T_g|U_g,\gamma_g) &= \lambda_0(T_g)\exp(\beta^T U_g + \alpha m(T_g,\varphi_g)) \\ Y_{g,j} &= m(t_{g,j};\varphi_g) + \epsilon_{g,j} \end{cases}$$

With : $\theta = (\sigma^2, \mu, \Omega^2, \beta, \alpha)$

- Which covariate do we want to add : NIRS (infrared spectrum of plant tissue)? genetic marker?
- Curse of high dimension : **not enough observation!**
- **Computational Complexity** too hard, etc

Likelihood

We can write the likelihood with complete-likelihood :

$$\mathcal{L}(\theta; Y) = \int \mathcal{L}_{comp}(\theta; \varphi, Y) d\varphi$$

Recall : φ is not observed

Handle the high dimension of covariate

$$\hat{\theta}_k = \arg\max_{\theta} \mathcal{L}(\theta) + pen(\theta)$$

Wich penalization will be efficient ?

$L_1 - norm$ or Ridge and Elastic-Net ?

Likelihood

We can write the likelihood with complete-likelihood :

$$\mathcal{L}(\theta; Y) = \int \mathcal{L}_{comp}(\theta; \varphi, Y) d\varphi$$

Recall : φ is not observed

Due to the non-linear function, this probability is not calculable !

Expectation Maximisation algorithm

Référence : Dempster, Laird et Rubin 1977

- **Require :** Starting point θ_0
- At the iteration $k \geqslant 0$:
  1. **E-Step (Expectation)**, evaluate the quantity :

$$Q(\theta|\theta_k) = \mathbb{E}_{\varphi|(Y,\theta_k)}\left[\log(\mathcal{L}_{comp}(\theta; \varphi, Y))\middle| Y, \theta_k\right]$$

  2. **M-Step (Maximisation)**, compute :

$$\theta_{k+1} = \arg\max_{\theta} Q(\theta|\theta_k))$$

- **Return :** $\hat{\theta} = \theta_K$ with K large enough

Problem : $Q(\theta|\theta_k)$ is not easy to compute

Stochastic Approximation EM algorithm

Référence : Delyon, Lavielle et Moulines 1999

- **Require :** Starting point θ_0
- At the iteration $k \geqslant 0$:
  1. **S-Step (Simulation)**, simulate $\varphi^{(k)}$ according to $\mathcal{L}(\varphi|Y, \theta_k)$
  2. **A-Step (stochastic Approximation)**, evaluate :

$$Q_{k+1}(\theta) = (1 - u_k)Q_k(\theta) + u_k \log \mathcal{L}_{comp}(\theta; \varphi^{(k)}, Y)$$

  3. **M-Step (Maximisation)**, compute :

$$\theta_{k+1} = \arg\max_{\theta \in \Theta} Q_{k+1}(\theta)$$

- **Return :** $\hat{\theta} = \theta_K$ with K large enough

where $(u_k)_{k \in \mathbb{N}}$ such that $\sum_{k=1}^{\infty} u_k = \infty$ and $\sum_{k=1}^{\infty} u_k^2 < \infty$

On going work and perspectives

- Finish coding the SAEM in the common model
- Achab 2017 : Use of proximal algorithm in survival analysis,
- Fort, Ollier et Samson 2017 : Use of proximal algorithm in Mixed model
- Perform an analysis of the real data.

Thank you for your attention !

Bibliographie

Achab, Massil (2017). « Learning from Sequences with Point Processes ». Thèse de doct.

Cox, D. R. (1972). « Regression Models and Life-Tables ». In :

Davidian, M. et D.M. Giltinan (1995). « Nonlinear Models for Repeated Measurement Data ». In :

Delyon, Bernard, Marc Lavielle et Eric Moulines (1999). « Convergence of a Stochastic Approximation Version of the EM Algorithm ». In :

Dempster, A. P., N. M. Laird et D. B. Rubin (1977). « Maximum Likelihood from Incomplete Data via the EM Algorithm ». In : *Journal of the Royal Statistical Society. Series B (Methodological).*

Fort, Gersende, Edouard Ollier et Adeline Samson (2017). *Stochastic Proximal Gradient Algorithms for Penalized Mixed Models*.

Rizopoulos, Dimitris (2012). « Joint models for longitudinal and time-to-event data : With applications in R ». In :

Appendix 1 : full model

- **Observations :** T, Y
- **Parameters :**
  - **Fixed hyperparameters :** $\omega_{\mathbf{a}}^2, \omega_{\mathbf{b}}^2$
  - **To estimate :** $\theta = (\sigma^2, \mu, \Omega, \omega_\eta^2, \omega_\gamma^2, \beta, \alpha)$
- **Latent variables :** $Z = (\varphi, \eta, \gamma, a, b)$