Modélisation jointe de données longitudinales et de survie en grande dimension

Application à l'analyse des effets des attaques de pyrale sur la date de floraison du maïs

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1. Introduction
   - Flowering date
2. Methodology
3. Simulation study

biological context

Figure 1 – ostrinia larva

Figure 2 – ostrinia attack

Photo credit : Sacha Revillon

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Flowering date

- flowering date of each corn plant observed,

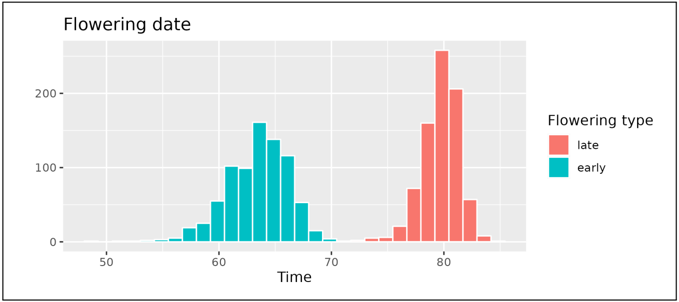


FIGURE 3 – Flowering date

- What impacts flowering : Genetic variability ? Insect attack ?

Survival analysis

We focus on the analysis of **time event of interest.**

- In medicine : Time of remission or 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.
T **is a random variable positive.**

Hazard function λ

$\lambda(t)$ probability that the event occurs in a small time interval after t, knowing that it did not occur until time t :

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

Survival analysis : Cox Model

Definition : Cox model

The Cox model is a regression model that links the survival time of an individual to explanatory variables. And it allows to assume a common behavior to all individuals.
The Hazard function is given by :

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

- λ_0 : baseline hazard which explain the common behvior
- U_i : covariate for individual i
- β regression parameter

Modeling the flowering date

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

Flowering date

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

Genetic covariates

  - $T_i \in \mathbb{R}$: time event of interest (observation) ,
  - λ_0 base line hazard unknown ,
  - $U_i \in \mathbb{R}^p$: covariate for individual i (known) ,
  - $\beta \in \mathbb{R}^p$: fixed effect not observed .

Current population parameters : $\boxed{\theta = \beta}$

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

Modeling of the attack proportion

- Mixed-effects models : number of plants attacked in a field line over time collected repeatedly,

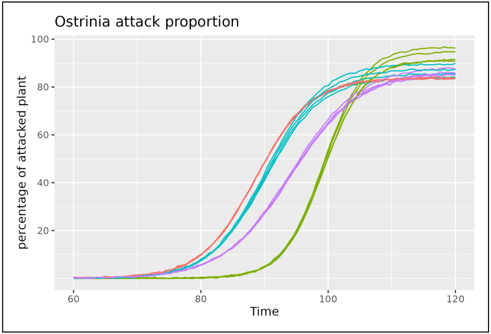


FIGURE 4 – Ostrina attack proportion

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

Non-linear mixed-effects model (NLME)

- Longitudinal data modeling :

behavior based on genetics

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

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

- Inter-individual variation :

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

  - $\mu \in \mathbb{R}^3$: intercept(c'est ça ?) **unknown** ,

Current population parameters : $\boxed{\theta = (\sigma^2, \mu, \Omega^2, \beta}$

Joint Model : NLME and Survival model

- Joining the two models using a link function m.
  We assume that the proportion of attack at the time of flowering is explanatory of it.
- The joint model is :

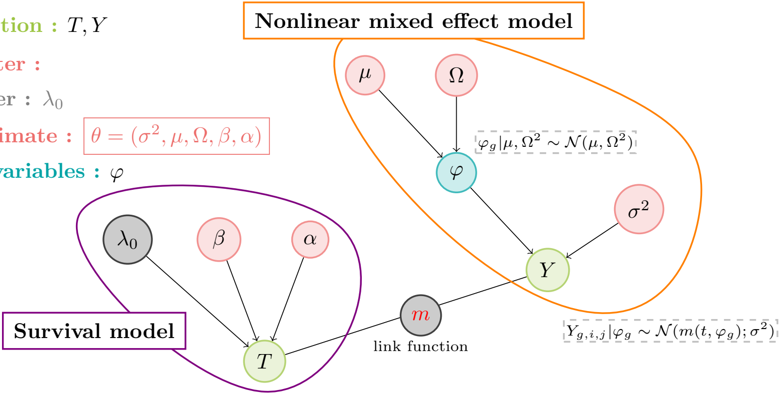
$$\begin{cases} \lambda(T_{g,i}|U_{g,i},\gamma_g) & = \lambda_0(T_{g,i})\exp(\beta^T U_{g,i} + \alpha m(T_{g,i},\varphi_g,\eta_{g,i}) + \gamma_g) \\ Y_{g,i,j} & = m(t_j;\varphi_g,\eta_{g,i}) + \epsilon_{g,i,j} \\ \dots & \end{cases}$$

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

population parameters : $\boxed{\theta = (\sigma^2, \mu, \Omega^2, \beta, \alpha}$

Hierachical model

- **Obseravtion :** T, Y
- **Parameter :**
  - **To infer :** λ_0
  - **To estimate :** $\boxed{\theta = (\sigma^2, \mu, \Omega, \beta, \alpha)}$
- **Latent variables :** φ



Handle the high dimension of covariate

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

Expectation-Maximisation algorithm

- **Require :** Starting point $\theta_0 \in \mathbb{R}^{100000}$ and a subset Θ of $\mathbb{R}^{10000}$
- At the iteration $k \geqslant 0$:
  1. **E-Step (Expectation)**, evaluate the quantity :

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

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

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

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

Problem : $Q(\theta|\theta_k)$ is not easy to compute due to the lack of observation of φ

Stochastic Approximation -EM algorithm

- **Require :** Starting point $\theta_0 \in \mathbb{R}^{100000}$ and a subset Θ of $\mathbb{R}^{10000}$
- At the iteration $k \geqslant 0$:
  1. **S-Step (Simulation)**, simulate $\varphi^{(k)}$ according to $f(\varphi|Y)$
  2. **A-Step (stochastic Approximation)**, approximate the quantity :

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

  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 $(u_k)_{k\in\mathbb{N}}$ is a sequence of positive step size such that $\sum_{k=1}^{\infty} u_k = \infty$ and $\sum_{k=1}^{\infty} u_k^2 < \infty$

Logistic growth model

Thank you for your attention !

Appendix 1 : full model

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