Mixed effects models: modelling and inference

Ecole de printemps de la chaire
Modélisation mathématique et biodiversité

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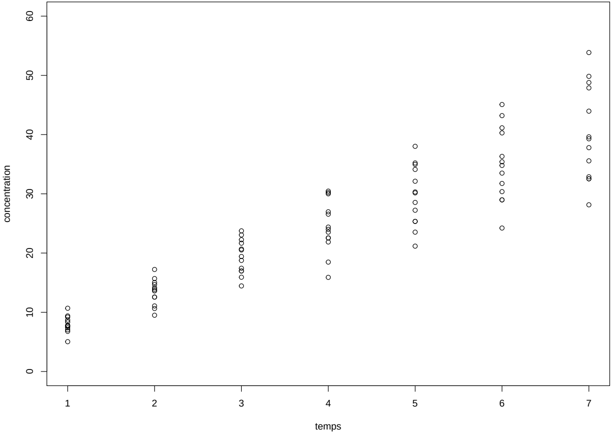
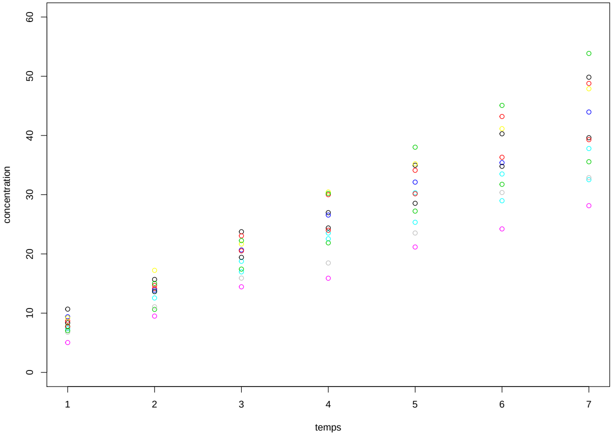
Outline

Measurements of concentration at several times



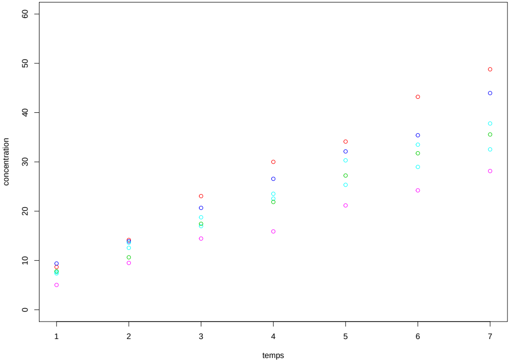
Repeated measurements of concentration at several times

$\Rightarrow$ concentrations for each individual of the population is measured at several times



Repeated measurements of concentration at several times

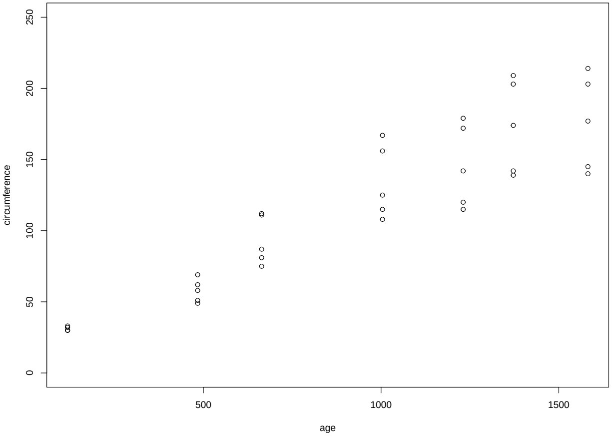
zoom on some individuals



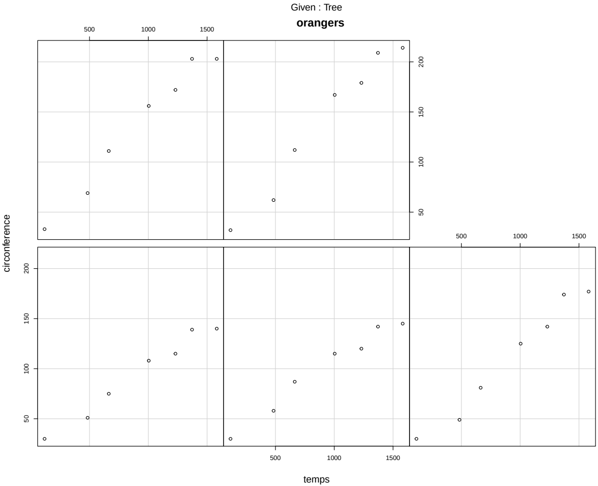
model suggestion for each individual i $y(t) = A_i + B_i t$ meaning that slope and intercept depend on individual i

Observations of growing process of orange trees

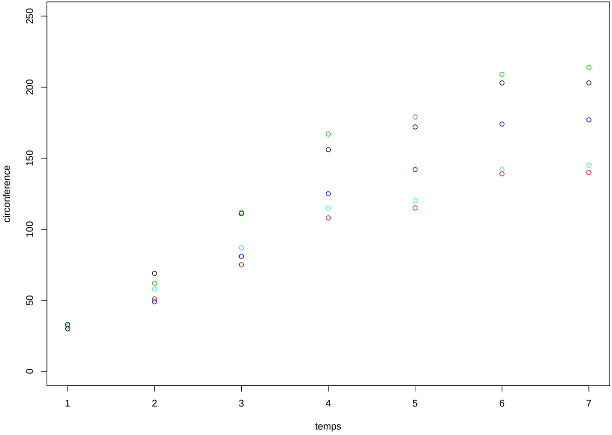
[Pinheiro and Bates (2000)]



Observations of growing process of five orange trees



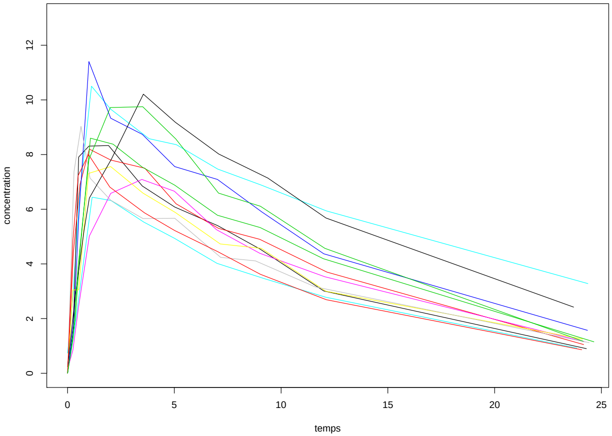
Observations of growing process of five orange trees



individual model suggestion $y(t) = \frac{\varphi_{i1}}{1+\exp\left(-\frac{t-\varphi_{i2}}{\varphi_{i3}}\right)}$

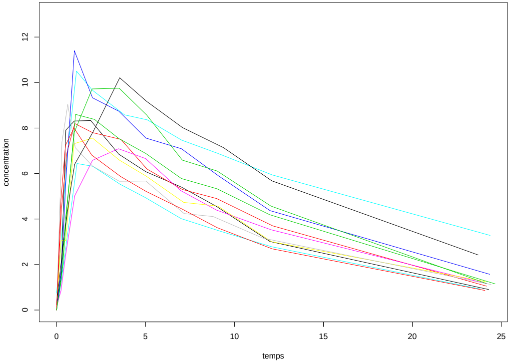
Theophylline concentration along time

[Davidian and Giltinian (1995)]



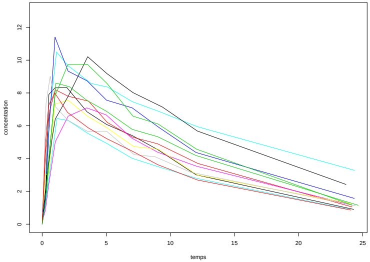
12 subjects, same oral dose (mg/kg) times in hours theophylline concentration in mg/L

Theophylline concentration along time



- Similarly-shaped concentration-time profiles across subjects
- Peak, rise, decay vary considerably
- Attributable to inter-subject variation in underlying PK processes (absorption, etc)

Some pharmacokinetic objectives



- Understanding intra-subject processes of drug absorption, distribution, and elimination governing achieved concentrations
  $\Rightarrow$ variabilities intra (within) subject and inter subject
- Understanding variations of these processes across subjects
  $\Rightarrow$ fundamental for developing dosing strategies and guidelines

Pharmacokinetic (PK) models

- One-compartment model for theophylline following oral dose d at time 0 describing the evolution of drug concentration over time.

$$y(t) = \frac{d_i ka_i}{V_i ka_i - Cl_i}\left[e^{-\frac{Cl_i}{V_i}t} - e^{-ka_i t}\right]$$

  where V_i, ka_i and Cl_i respectively denote the volume of the central compartment, the drug's absorption rate constant and the drug's clearance of individual i.
- ka_i, Cl_i and V_i summarize PK processes underlying observed concentration profiles for subject i

Some statistical objectives

- Determine mean/median values of ka_i, Cl_i and V_i and how they vary in the population of subjects
- Elucidate whether some of this variation is associated with subject characteristics (e.g. weight, age, renal function)
- Develop dosing strategies for subpopulations with certain characteristics (e.g. elderly, female)

General context

- Consider a response evolving over time (or other conditions) within individuals from a population of interest
- Inference focuses on mechanisms that underlie individual profiles of repeated measurements of the response and how these vary in the population
- A model for individual profiles with parameters that may be interpreted as representing such features or mechanisms is available

$\Rightarrow$ Common situations in agricultural, environmental, biomedical, economical applications

General setting of repeated measurements

- Measurements are repeated on each of N individuals
- Y_{ij} denotes the response at the jth measurement for individual i for $1 \leq j \leq J$
- X_i covariates of individual i

Example of Theophylline dataset

- Y_{ij} is drug concentration for subject i at time t_{ij}
- X_i contains subject characteristics such as weight, age, renal function, smoking status, etc for subject i

Individual-level model (Stage 1)

modelling the observations for $1 \leq i \leq N, 1 \leq j \leq J$

$$Y_{ij} = f(X_{ij}, \varphi_i) + \varepsilon_{ij}$$

- f function governing within-individual behavior
- $X_i = (X_{ij})_j$ covariates of individual i
- φ_i parameters specific to individual i
- ε_{ij} centered random error term

Example: Theophylline pharmacokinetic model

$$f(d_i, t_{ij}, \varphi_i) = \frac{d_i ka_i}{V_i ka_i - Cl_i}\left[e^{-\frac{Cl_i}{V_i} t_{ij}} - e^{-ka_i t_{ij}}\right]$$

where $\varphi_i = (ka_i, Cl_i, V_i)$ absorption rate, volume, and clearance for subject i

- $E(Y_{ij}|X_{ij}, \varphi_i) = f(X_{ij}, \varphi_i) \Rightarrow f$ represents an average profile
- f may not capture all within-individual variations

Population model (Stage 2)

Modeling the individual parameters for $1 \leq i \leq N$

$$\varphi_i = U_i \beta + V_i b_i$$

- U_i, V_i covariates of individual i
- β fixed effects of size d_f
- b_i centered random effects of individual i of size d_r

$\Rightarrow$ characterizes how elements of φ_i vary across individuals due to

- association with covariates modeled by β
- unexplained variation in the population represented by b_i

Example: Theophylline pharmacokinetic model
ka_i, Cl_i and V_i are individual random parameters such that
$\log ka_i = \log(ka) + b_{i,1},\ b_{i,1} \sim \mathcal{N}(0, \gamma_1)$
$\log Cl_i = \log(Cl) + \beta BW_i + b_{i,2},\ b_{i,2} \sim \mathcal{N}(0, \gamma_2)$
$\log V_i = \log(V) + b_{i,3},\ b_{i,3} \sim \mathcal{N}(0, \gamma_3)$
where BW_i is the body weight of individual i

Mixed effect model: art of modeling variabilities ?

- Modeling the observations for $1 \leq i \leq N, 1 \leq j \leq J$

$$Y_{ij} = f(X_{ij}, \varphi_i) + \varepsilon_{ij},$$

- Modeling the individual parameters for $1 \leq i \leq N$

$$\varphi_i = U_i \beta + V_i b_i$$

where

- X_i, U_i, V_i covariates of individual i
- β fixed effects
- b_i random effects of individual i
- φ_i parameters specific to individual i

Usual assumptions:

- $(b_i)_i$ are independent identically distributed
- $(Y_{ij} | b_i)_j$ are independent

Linear mixed effect models

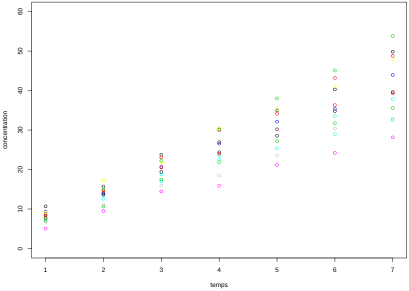
[Davidian and Giltinian (1995)]

$$Y_{ij} = X_{ij}\beta + Z_{ij}b_i + \varepsilon_{ij} \ , \ 1 \leq i \leq N, \ 1 \leq j \leq J$$

- $Y_i = (Y_{ij})_j$ is the observation vector for individual i
- X_i and Z_i are matrices of known covariates of individual i
- β is the vector of fixed effects
- $b_i \overset{iid}{\sim} \mathcal{N}(0, \Gamma)$
- ε_i is a random error vector, with $\varepsilon_i \overset{iid}{\sim} \mathcal{N}_J(0, \Sigma)$

$\Rightarrow$ Parameters of models: $\theta = (\beta, \Gamma, \Sigma)$

Example of concentrations with slope and intercept depending on the individual



$$Y_{ij} = (A + a_i) + (B + b_i)t_{ij} + \varepsilon_{ij} \ , \ 1 \leq i \leq N, \ \ 1 \leq j \leq J$$

with $a_i \overset{iid}{\sim} \mathcal{N}(0, \gamma_a^2)$ and $b_i \overset{iid}{\sim} \mathcal{N}(0, \gamma_b^2)$ and $\varepsilon_{ij} \overset{iid}{\sim} \mathcal{N}(0, \sigma^2)$

Nonlinear mixed effects model

[Davidian Giltinian (1995), PInheiro Bates (2000), Lavielle (2014)]
$\Rightarrow$ the function f is nonlinear in the individual parameter φ_i

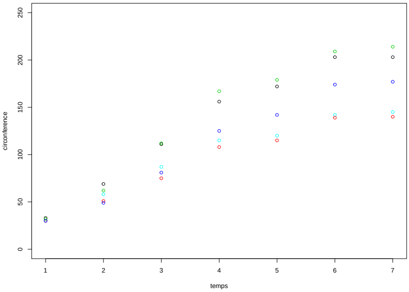
$$\begin{cases} Y_{ij} & = f(X_{ij}, \varphi_i) + \varepsilon_{ij}, \quad 1 \leq i \leq N, \ 1 \leq j \leq J \\ \varphi_i & = U_i \beta + V_i b_i, \quad 1 \leq i \leq N \end{cases}$$

where

- $Y_i = (Y_{ij})_j$ is the observation vector for individual i
- X_i and U_i, V_i are matrices of known covariates of individual i
- β is the vector of fixed effects
- b_i is a random effect of individual i, e.g. $b_i \overset{iid}{\sim} \mathcal{N}(0, \Gamma)$
- ε_i is a random error vector, e.g. $\varepsilon_i \overset{iid}{\sim} \mathcal{N}_J(0, \Sigma)$

$\Rightarrow$ Parameters of models: $\theta = (\beta, \Gamma, \Sigma)$

Example of the orange trees



$$Y_{ij} = \frac{\varphi_{i1}}{1+\exp\left(-\frac{t_j-\varphi_{i2}}{\varphi_{i3}}\right)} + \varepsilon_{ij}, \quad \text{with} \quad \varphi_i = \beta + b_i \ ,$$

where $\beta = (\beta_1, \beta_2, \beta_3) \in \mathbb{R}^3$, $b_i \overset{iid}{\sim} \mathcal{N}_3(0, \Gamma)$ and $\varepsilon_{ij} \overset{iid}{\sim} \mathcal{N}(0, \sigma^2)$.

Representation as hierarchical model

? link between mixed effects models and hierarchical models

$\Rightarrow$ differents representations of the same model [Lavielle (2014)]

$$\begin{cases} \varphi_i &= & U_i\beta + V_i b_i & \text{with} & b_i \sim q(.;\Gamma) & \text{(stage 2)} \\ Y_i &= & f(X_i,\varphi_i) + \varepsilon_i & \text{with} & \varepsilon_i \sim q(.;\Sigma) & \text{(stage 1)} \end{cases}$$

more generaly :

$$\begin{cases} b_i & \sim & q(.;\Gamma) \\ Y_i | b_i; X_I, U_i, V_i & \sim & q(.;\beta,\Sigma) \end{cases}$$

$\Rightarrow$ latent variables model structure

Summary of the day

$$\begin{cases} Y_{ij} &= f(X_{ij}, \varphi_i) + \varepsilon_{ij}, \quad 1 \le i \le N,\ 1 \le j \le J \\ \varphi_i &= U_i \beta + V_i b_i, \quad\quad 1 \le i \le N \end{cases}$$

with $b_i \overset{iid}{\sim} q(.;\Gamma)$ and $\varepsilon_{ij} \overset{iid}{\sim} q(.;\Sigma)$
wth parameters of models: $\theta = (\beta, \Gamma, \Sigma)$

- modeling observation level and individual level
- combining fixed effects and random effects
- possibly linear or nonlinear dependency of the response
- possible with heteroscedastic error model:

$$\begin{cases} Y_i &= f(X_i, \varphi_i) + g(X_i, \varphi_i)\varepsilon_i \quad \text{with} \quad \varepsilon_i \sim q(.;\Sigma) \\ \varphi_i &= U_i \beta + V_i b_i \quad \text{with} \quad b_i \sim q(.;\Gamma) \end{cases}$$

- representation as hierarchical modeling
- latent variables model structure

Context of plant breeding

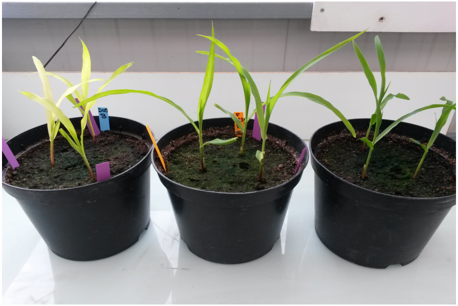


Figure: Maïs en stress froid (INRA Mons)

- genotype by environment interaction
- Challenge : find the "best" variety for a given environment
- Opportunity : adaption to climate change

Data acquisition

phenotyping platform in controled condition
$\Longrightarrow$ measurement of biomass, height, yield

Figure: Phenoarch INRA Montpellier

Data acquisition

phenotyping platform in open field

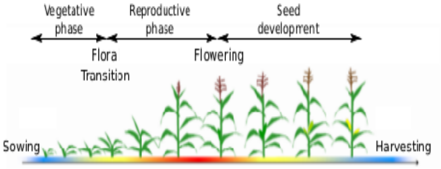
$\Longrightarrow$ under semi controlled condition

Figure: Pheno3C INRA Clermont-Ferrand

$\Longrightarrow$ Using data to calibrate crop model

$\Longrightarrow$ Compute "good" values for parameters as root emergence rate, leaf emergence rate

Modeling plant growth process

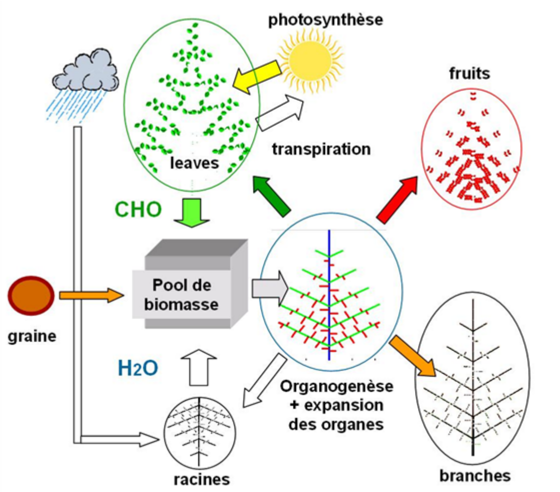


$\Longrightarrow$ Many questions:

- times of interest: floral transition, flowering time, leaf appearance, root appearance
- covariables of interest
- genotypic effect

$\Longrightarrow$ Describe the growth process by ecophysiological model

Crop growth modeling



$\Longrightarrow$ many unknown mecanistic parameters

Ecophysiological modeling: Greenlab model

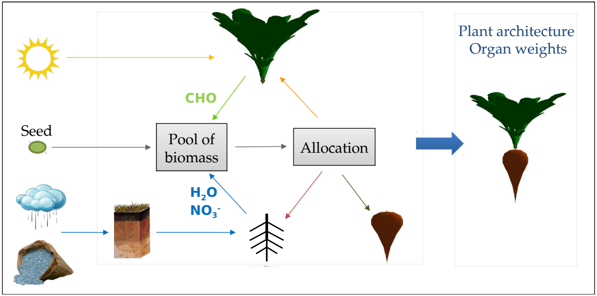


Figure: Overview of the Greenlab model

$\Longrightarrow$ estimate many unknown mechanistic parameters

$\Longrightarrow$ modeling the different levels of variability

$\Longrightarrow$ identify which parameters depend on the genotype

$\Longrightarrow$ reduce the number of parameters to estimate

Mixed effects model for crop model analysis

$\Longrightarrow$ modeling observations conditionaly to individual paramater

$$y_{ijk} = f(\varphi_i, e_j) + \varepsilon_{ijk}, \quad 1 \leq i \leq N, \quad 1 \leq j \leq J, \quad 1 \leq k \leq K$$

with y_{ijk} measurement of plant kth of genotype i in environnemental condition j
φ_i parameter of genotype i
e_j environnemental covariates
Σ population parameters vector

$\Longrightarrow$ modeling genotypic variability of crop model parameter using individual parameter meaning that for genotype i model parameter are modeled by:

$$\varphi_i = \beta + b_i \text{ with } b_i \sim \mathcal{N}(0; \Gamma), \quad 1 \leq i \leq N,$$

$\Longrightarrow$ model parameters $\theta = (\beta, \Gamma, \Sigma) \in \Theta$

Inference in mixed effects models

- Linear mixed effects models

$$Y_{ij} = X_{ij}\beta + Z_{ij}b_i + \varepsilon_{ij} \;\; 1 \leq i \leq N, \; 1 \leq j \leq J$$

- Nonlinear mixed effects models

$$\begin{cases} Y_{ij} & = & f(X_{ij}, \varphi_i) + \varepsilon_{ij} & 1 \leq i \leq N, \; 1 \leq j \leq J \\ \varphi_i & = & U_i\beta + V_i b_i, & 1 \leq i \leq N \end{cases}$$

with U_i, V_i and Z_i design matrices,
β population parameters also called fixed effects,
$b_i \overset{iid}{\sim} q(.;\Gamma)$ random effects
$\varepsilon_i \overset{iid}{\sim} q(.;\Sigma)$ noise term independent of b_i
f a nonlinear function of φ_i.

Parameters of models: $\theta = (\beta, \Gamma, \Sigma)$

Statistical issues

Consider the following mixed effects model:

$$\left\{ \begin{array}{lcll} Y_{ij} & = & f(X_{ij}, \varphi_i) + \varepsilon_{ij} & 1 \leq i \leq N,\ 1 \leq j \leq J \\ \varphi_i & = & U_i \beta + V_i b_i, & 1 \leq i \leq N \end{array} \right.$$

with $b_i \overset{iid}{\sim} q(.; \Gamma)$ random effects
and $\varepsilon_{ij} \overset{iid}{\sim} q(.; \Sigma)$ noise term independent of (b_i)

Objectives:

- estimate model parameters $\theta = (\beta, \Gamma, \Sigma) \in \Theta$
- predict individual output as $\hat{\varphi}_i$ or $\hat{Y}_i$
- test if some fixed effects β are significant
- test if some random effects (b_i) are fixed
- ...

Likelihoods in mixed effects model

Consider random variables $(Y_i, b_i)_i$ following the model given by:

$$\left\{ \begin{array}{lcll} Y_{ij} & = & f(X_{ij}, \varphi_i) + \varepsilon_{ij} & 1 \leq i \leq N,\ 1 \leq j \leq J \\ \varphi_i & = & U_i \beta + V_i b_i, & 1 \leq i \leq N \end{array} \right.$$

with $b_i \overset{iid}{\sim} q(.;\Gamma)$ and $\varepsilon_{ij} \overset{iid}{\sim} q(.;\Sigma)$ with $\theta = (\beta, \Gamma, \Sigma) \in \Theta$

Define the complete likelihood:

$$\begin{aligned} L_{comp}(\theta; Y_1^N, b_1^N) &= \prod_1^N L_{comp}(\theta; Y_i, b_i) \\ &= \prod_1^N \left(p(Y_i | b_i; \beta, \Sigma) p(b_i; \Gamma)\right) \end{aligned}$$

$\Rightarrow$ the random effects (b_i) are non observed

$\Rightarrow$ integrate over the random effects b_i

Likelihoods in mixed effects model

Define the observed (or marginal) likelihood:

$$
\begin{aligned}
L_{marg}(\theta; Y_1^N) &= \prod_1^N L_{marg}(\theta; Y_i) \\
&= \prod_1^N \int L_{comp}(\theta; Y_i, b_i) db_i \\
&= \prod_i \int p(Y_i | b_i; \beta, \Sigma) p(b_i; \Gamma) db_i
\end{aligned}
$$

Define the maximum likelihood estimate (MLE) by:

$$\hat{\theta}_N = \arg\max_{\theta \in \Theta} L_{marg}(\theta; Y_1^N)$$

- ? theoretical properties of MLE? as N goes to infinity? consistency ? asymptotic normality ?
- computational aspects

Maximum likelihood estimator: consistency

[Nie, Metrika (2006)]

$$\hat{\theta}_N = \arg\max_{\theta \in \Theta} L_{marg}(\theta; Y_1^N)$$

Under regularity and moment conditions on the model, the MLE estimator $\hat{\theta}_N$ exists almost surely and

$$\lim_{N \Rightarrow +\infty} \hat{\theta}_N = \theta_0 \ P_{\theta_0} - p.s.$$

$\Rightarrow$ Example of logistic model for orange trees satisfayes these conditions.

Maximum likelihood estimator: convergence rates

- in general regular parametric models MLE is $\sqrt{N}$ consistent
- what is the role of J in mixed effects model?

Example of balanced ANOVA model with one way:

$$Y_{ij} = \alpha + b_i + \varepsilon_{ij}\ ,\ 1 \leq i \leq N,\ 1 \leq j \leq J$$

with $b_i \overset{iid}{\sim} \mathcal{N}(0, \gamma^2)$, $\varepsilon_i \overset{iid}{\sim} \mathcal{N}_J(0, \sigma^2)$, ε_i independent of (b_i)

$\Rightarrow \hat{\alpha} - \alpha_0 = O_p(N^{-1/2})$

$\Rightarrow \hat{\gamma}^2_{MLE} - \gamma^2_0 = O_p((N)^{-1/2})$

$\Rightarrow \hat{\sigma}^2_{MLE} - \sigma^2_0 = O_p((NJ)^{-1/2})$

Maximum likelihood estimator: convergence rates

- in general regular parametric models MLE is $\sqrt{N}$ consistency
- what is the role of J in mixed effects model?

Example of with "intercept and slope":

$$Y_{ij} = \alpha + \beta X_j + b_i + \varepsilon_{ij} \; , \; 1 \leq i \leq N, \; 1 \leq j \leq J$$

with $b_i \overset{iid}{\sim} \mathcal{N}(0, \gamma^2)$, $\varepsilon_i \overset{iid}{\sim} \mathcal{N}_J(0, \sigma^2)$, ε_i independent of (b_i)

$\Rightarrow \hat{\alpha} - \alpha_0 = O_p(N^{-1/2})$

$\Rightarrow \hat{\beta} - \beta_0 = O_p((NJ)^{-1/2})$

Maximum likelihood estimator: convergence rates

[Nie, JSPI (2007)]

$$\begin{cases} Y_{ij} = f(X_{ij}, \varphi_i) + \varepsilon_{ij} & 1 \le i \le N, \ 1 \le j \le J \\ \varphi_i = U_i \beta + V_i b_i, & 1 \le i \le N \end{cases}$$

with $b_i \overset{iid}{\sim} q(.; \Gamma)$ and $\varepsilon_{ij} \overset{iid}{\sim} q(.; \Sigma)$ with parameters $\theta = (\beta, \Gamma, \Sigma)$

$$\hat{\theta}_N = \arg\max_{\theta \in \Theta} L_{marg}(\theta; Y_1^N)$$

Under regularity assumptions and moment conditions on the model

- For fixed J, $\hat{\theta}_N$ is $\sqrt{N}$ consistent when N tends to infinity.
- the MLE $\hat{\beta}_N$ for β is $\sqrt{NJ}$ consistent and
  the MLE $\hat{\Gamma}_N$ for Γ is $\sqrt{N}$ consistent when N and J tend to infinity

Moreover the asymptotic covariance matrix is equal to the inverse of the Fisher matrix information.

Maximum likelihood estimation: computational aspect

Recall the definition of observed (or marginal) likelihood:

$$L_{marg}(\theta; Y_1^N) \;=\; = \prod_i \int \underbrace{p(Y_i|b_i;\beta,\Sigma)}_{stage1}\underbrace{p(b_i;\Gamma)}_{stage2} db_i$$

and of the maximum likelihood estimator (MLE):

$$\hat{\theta}_n = \arg\max_{\theta\in\Theta} L_{marg}(\theta; Y_1^N)$$

Example of gaussian linear mixed effects model:

$$Y_i = X_i\beta + Z_i b_i + \varepsilon_i \;,\; 1 \le i \le N,$$

with $b_i \overset{iid}{\sim} \mathcal{N}(0,\Gamma)$, $\varepsilon_i \overset{iid}{\sim} \mathcal{N}_J(0,\Sigma)$, ε_i independent of (b_i)
$\Rightarrow Y_i \sim \mathcal{N}(X_i\beta, Z_i'\Gamma Z_i + \Sigma)$

Maximum likelihood estimation: computational aspect

- Exact likelihood methods: Maximize likelihood "directly" using deterministic or stochastic approximation to the integrals
  - Deterministic approximation (Quadrature, Adaptive Gaussian quadrature)
  - Stochastic approximation (Importance sampling, brute-force Monte Carlo integration)

  $\Rightarrow$ computationaly expensive in particular in high-dimensional setting
- inference based on linearization of the likelihood
  $\Rightarrow$ no guarantee of convergence
- iterative procedure based on individual estimates
  $\Rightarrow$ no guarantee of convergence
- tools for maximum likelihood estimation in latent variables model

Some existing approximate methods (non exhaustive)

- Methods based on approximations of the likelihood
  - First order methods (FO, Beal and Sheiner, 1982)
  - First order conditional methods (FOCE, Lindstrom and Bates, 1990)
  - Laplace-EM (Vonesh, 1996) also called mode approximation

  No convergence property or with non realistic assumptions, default of convergence.

- Methods based on the exact likelihood
  - MCEM algorithm (Walker, 1996 ; Fort and Moulines, 2004)
  - SAEM algorithm (Delyon, Lavielle and Moulines, 1999)

  Convergence property

Estimation in latent variables model

Heuristic of approach in latent variables models

$$\begin{cases} Y_{ij} & = & f(X_{ij}, \varphi_i) + \varepsilon_{ij} & 1 \leq i \leq N, \ 1 \leq j \leq J \\ \varphi_i & = & U_i \beta + V_i b_i, & 1 \leq i \leq N \end{cases}$$

with $b_i \overset{iid}{\sim} q(.;\Gamma)$ and $\varepsilon_{ij} \overset{iid}{\sim} q(.;\Sigma)$

- Observed data (Y_i) $\Rightarrow$ observed vectors
- Random effects (b_i) $\Rightarrow$ latent variables

$\Rightarrow$ if (b_i) were observed,
then consider as objective function $\log L_{comp}(\theta; Y_1^N, b_1^N)$

$\Rightarrow$ instead consider the quantity $E[\log L_{comp}(\theta; Y_1^N, b_1^N))|Y_1^N; \theta]$.

$\Rightarrow$ iterative approach: maximize in θ the quantity
$Q(\theta|\theta_{current}) = E[\log L_{comp}(\theta; Y_1^N, b_1^N))|Y_1^N; \theta_{current}]$.

The EM algorithm [Dempster et al. (1977), Wu (1983), Vaida (2005)]

Iteration k of the algorithm:

- Expectation step :

$$Q(\theta|\theta_{k-1}) = E[\log L_{comp}(Y, b; \theta)|Y; \theta_{k-1}]$$

- Maximization step :

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

Proposition

If $Q(\theta_{k-1}|\theta_{k-1}) \leq Q(\theta_k|\theta_{k-1})$,
then $\log L_{marg}(\theta_{k-1}; Y_1^N) \leq \log L_{marg}(\theta_k; Y_1^N)$

Proposition

Under regularity condition on the model, the sequence (θ_k) *converges toward a critical point of the observed likelihood* L_{marg}.

Limits of EM algorithm

Iteration k of the algorithm:

- Expectation step :

$$Q(\theta|\theta_{k-1}) = E[\log L_{comp}(Y, b; \theta)|Y; \theta_{k-1}]$$

- Maximization step :

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

$\Rightarrow$ Limits of EM algorithm:

- theory in exponential model
- nature of the limit point
- convergence depends on the initial guess
- expression of $Q(\theta|\theta')$ often analytically intractable
  $\Rightarrow$ approximate the quantity $Q(\theta|\theta')$?

Heuristics of the stochastic approximation

Quantity of interest in the EM algorithm:

$$Q(\theta|\theta') = E(\log L_{comp}(y, b; \theta)|y; \theta')$$

$\Rightarrow$ build a sequential approximation of this quantity: at iteration k

- simulate a realization b_k of the random effects
- compute $Q_k(\theta) = Q_{k-1}(\theta) + \gamma_k \left(\log L_{comp}(y, b_k; \theta) - Q_{k-1}(\theta)\right)$ where (γ_k) is a positive decreasing step size sequence.

Then, we have:

$$\frac{Q_k(\theta) - Q_{k-1}(\theta)}{\gamma_k} = E[\log L_{comp}(y, b; \theta)|y; \theta] - Q_{k-1}(\theta)$$
$$+ \log f(y, b_k; \theta) - E[\log L_{comp}(y, b; \theta)|y; \theta]$$

$$\frac{Q_k(\theta) - Q_{k-1}(\theta)}{\gamma_k} \approx E[\log L_{comp}(y, b; \theta)|y; \theta] - Q_{k-1}(\theta) + e_k$$

If $b_k \sim p(\cdot|y, \theta)$ then $e_k \approx 0$

Stochastic Approximation of the EM algorithm

[Delyon, Lavielle, Moulines (1999) AS]

Iteration k of the algorithm:

- Simulation step : $b^k \sim \pi_{\theta_{k-1}}(.|y)$
  where π_θ is the distribution of b conditionaly to y
- Stochastic approximation :
  $Q_k(\theta) = Q_{k-1}(\theta) + \gamma_k[\log L_{comp}(y, b^k, \theta) - Q_{k-1}(\theta)]$
  where (γ_k) is a decreasing sequence of positive step-sizes.
- Maximisation step : $\theta_k = \arg\max_{\theta\in\Theta} Q_k(\theta)$

$+$ converges almost surely toward a stationary point $\widehat{\theta}$ of L_{marg}
– theory in exponential model
– nature of the limit point
– convergence depends on the initial guess

Extension of SAEM algorithm using MCMC procedure

[K. Lavielle (2004) , Allassonnière, K., Trouvé (2010)]

- Simulation step : $b^k \sim \Pi_{\theta_{k-1}}(b^{k-1}, \cdot)$
  where Π_θ is a transition probability of an ergodic Markov Chain having the posterior distribution $p(\cdot|y,\theta)$ as stationary distribution,
- Stochastic approximation :
  $Q_k(\theta) = Q_{k-1}(\theta) + \gamma_k \left(\log L_{comp}(y, b^k, \theta) - Q_{k-1}(\theta)\right)$
- Maximisation step : $\theta_k = \arg\max_{\theta\in\Theta} Q_k(\theta)$

Simulation step : one step of a Metropolis Hastings algorithm

- simulate a candidate from a proposal distribution
  $b^c \sim q_{\theta_{k-1}}(.|b^{k-1})$
- accept or reject this candidate with probability

$$\alpha(b^{k-1}, b^c) = \min\left(1, \frac{p(b^c|y,\theta)q_{\theta_{k-1}}(b^{k-1}|b^c)}{p(b^{k-1}|y,\theta)q_{\theta_{k-1}}(b^c|b^{k-1})}\right)$$

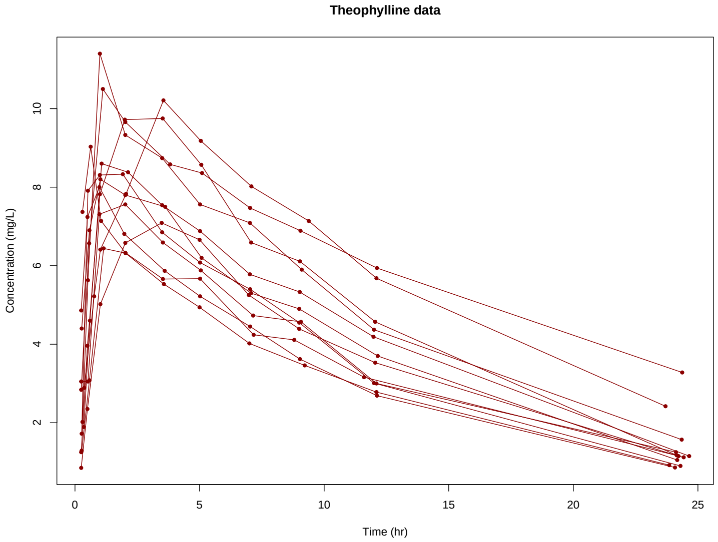
Estimation of parameters of theophylline model

⇒ use saemix R package [Comets et al (2017)]

Example of R code

```
library(saemix)
#data creation
data("theo.saemix")
theo.data <- saemixData(name.data = theo.saemix,
 header = TRUE,sep = " ", na = NA,
name.group = c("Id"),
 name.predictors = c("Dose", "Time"),
name.response = c("Concentration"),
name.covariates = c("Weight", "Sex"),
units = list(x = "hr",y = "mg/L", covariates =
c("kg", "-")),
name.X = "Time")
plot(theo.data,type = "b", col = "DarkRed", main =
"Theophylline data")
```

Estimation of parameters of theophylline model



Estimation of parameters of theophylline model

```
#model definition
model1cpt <- function(psi, id, xidep) {
dose <- xidep[, 1]
tim <- xidep[, 2]
ka <- psi[id, 1]
V <- psi[id, 2]
CL <- psi[id, 3]
k <- CL / V
ypred <- dose * ka / (V * (ka - k)) * (exp( -k * tim)
-+ exp( - ka * tim))
return(ypred)
}
```

$\Rightarrow$ correspond to model equation defined above:

$$f(d_i, \varphi_i, t) = \frac{d_i ka_i}{V_i ka_i - Cl_i}\left[e^{-\frac{Cl_i}{V_i}t} - e^{-ka_i t}\right]$$

Estimation of parameters of theophylline model

```
# model structure definition
theo.model <- saemixModel(model = model1cpt,
description = "One-compartment model with first-order
absorption",
psi0 = matrix(c(1, 20, 0.5), ncol = 3,
byrow = TRUE, dimnames = list(NULL, c("ka", "V",
"CL"))), transform.par = c(1, 1, 1),
covariate.model = matrix(c(0, 0, 1, 0, 0, 0),
ncol = 3, byrow = TRUE))
#option definition
opt <- list(save = FALSE, save.graphs = FALSE)
#fitting model with data
theo.fit <- saemix(theo.model, theo.data, opt)
```

Estimation of parameters of theophylline model: results

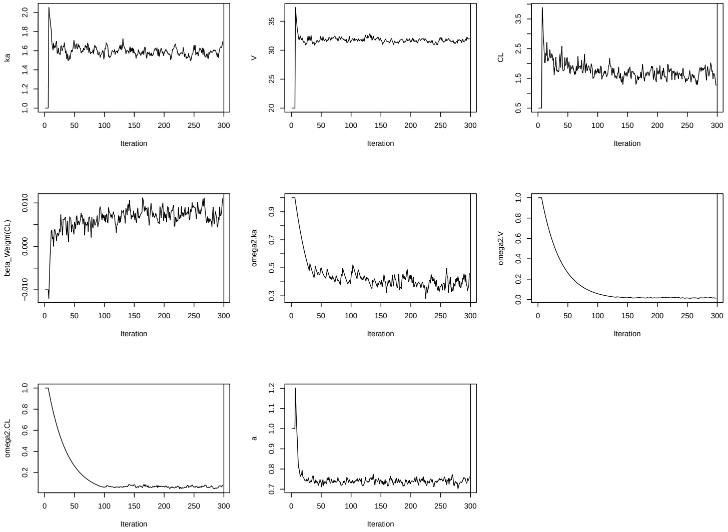
Fixed effects

Parameter	Estimate	SE	CV(%)	p-value
[1,] ka	1.5786	0.2947	18.7	-
[2,] V	31.6605	1.4322	4.5	-
[3,] CL	1.5521	0.9683	62.4	-
[4,] β_W(CL)	0.0082	0.0089	108.3	0.18
[5,] a	0.7429	0.0569	7.7	-

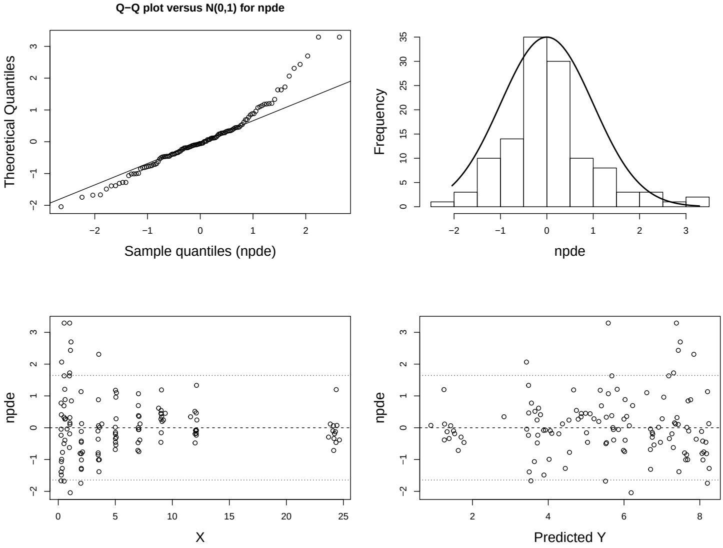
Variance of random effects

Parameter	Estimate	SE	CV(%)
ka omega2.ka	0.368	0.1668	45
V omega2.V	0.017	0.0096	57
CL omega2.CL	0.065	0.0324	50

Estimation of parameters of theophylline model



Estimation of parameters of theophylline model



Estimation of parameters of theophylline model

```
Statistical criteria
--------------------------------------------------------
Likelihood computed by linearisation
-2LL= 343.427
AIC = 359.427
BIC = 363.3063
Likelihood computed by importance sampling
-2LL= 344.8205
AIC = 360.8205
BIC = 364.6997
```

Prediction in mixed effects model

Consider a mixed effects model:

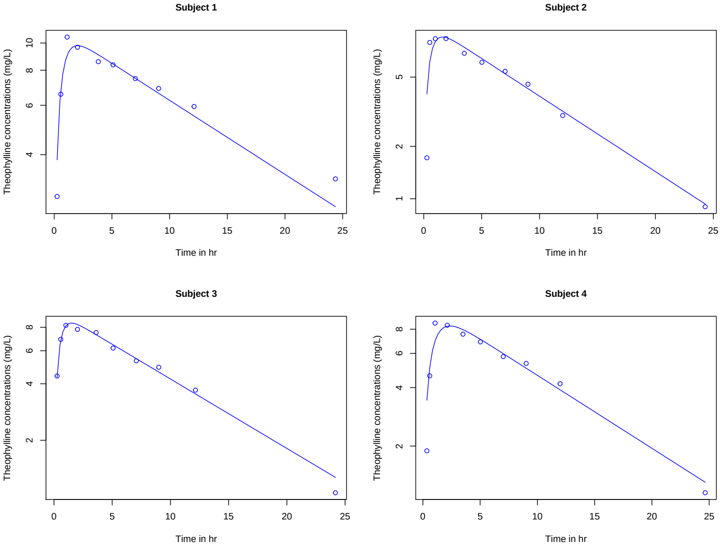
$$\begin{cases} Y_{ij} &= f(X_{ij}, \varphi_i) + \varepsilon_{ij} \quad 1 \leq i \leq N,\ 1 \leq j \leq J \\ \varphi_i &= U_i\beta + V_i b_i, \quad 1 \leq i \leq N \end{cases}$$

with $b_i \overset{iid}{\sim} q(.;\Gamma)$ and $\varepsilon_{ij} \overset{iid}{\sim} q(.;\Sigma)$

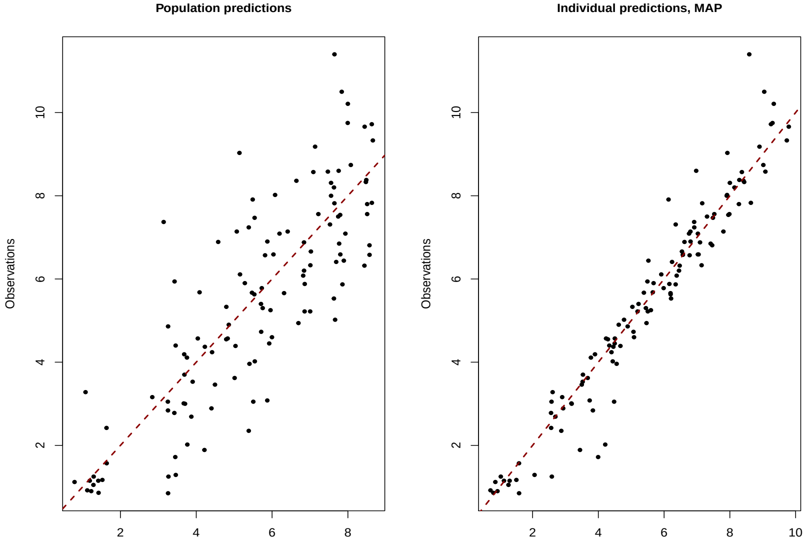
$\Rightarrow$ predicted values for random effects for $1 \leq i \leq N$:
$\hat{b}_i = E(b_i|Y_i)$ or $\hat{b}_i = \arg\max q(b_i|Y_i)$

$\Rightarrow \hat{\varphi}_i = U_i\hat{\beta} + V_i\hat{b}_i$ and $\hat{Y}_i = f(X_i, \hat{\varphi}_i)$

Prediction of individual profiles of theophylline model



Comparision between population predictions and individual predictions in theophylline model



List of toolboxs (non exhaustive)

- R package nlme [Pinheiro, J., Bates, D., DebRoy, S., Sarkar, D., and R Core Team (2019)].
- R package lme4 [Bates et al. (2019)]
- R package saemix [Comets, E., Lavenu, A., and Lavielle, M. (2017)]
- SPSS (2002). Linear mixed-effects modeling in SPSS. An introduction to the MIXED procedure.
- SAS Proc NLMIXED
- MONOLIX (2013)

Summary of the day

$$\begin{cases} Y_{ij} &= f(X_{ij}, \varphi_i) + \varepsilon_{ij}, \quad 1 \leq i \leq N,\ 1 \leq j \leq J \\ \varphi_i &= U_i \beta + V_i b_i, \quad\quad 1 \leq i \leq N \end{cases}$$

with $b_i \overset{iid}{\sim} q(.;\Gamma)$ and $\varepsilon_{ij} \overset{iid}{\sim} q(.;\Sigma)$ with $\theta = (\beta, \Gamma, \Sigma)$

- Define the complete likelihood: $L_{comp}(\theta; Y_1^N, b_1^N)$
- Define the observed likelihood: $L_{marg}(\theta; Y_1^N) = \int L_{comp}(\theta; Y_1^N, b_1^N) db_1^N$
- Define the maximum likelihood estimate (MLE) by:

$$\hat{\theta}_N = \arg\max_{\theta \in \Theta} L_{marg}(\theta; Y_1^N)$$

- good properties for $\hat{\theta}_N$
- efficient convergent stochastic algorithm to evaluate $\hat{\theta}_N$
- corresponding toolbox and R packages

Extension of SAEM algorithm using MCMC procedure

[K. et al. (2004), Allassonniere et al. (2010)]

- Simulation step : $b^k \sim \Pi_{\theta_{k-1}}(b^{k-1}, \cdot)$
  where Π_θ is a transition probability of an ergodic Markov Chain having the posterior distribution $p(\cdot|y,\theta)$ as stationary distribution,
- Stochastic approximation :
  $Q_k(\theta) = Q_{k-1}(\theta) + \gamma_k \left(\log L_{comp}(y, b^k, \theta) - Q_{k-1}(\theta)\right)$
- Maximisation step : $\theta_k = \arg\max_{\theta \in \Theta} Q_k(\theta)$

Simulation step : one step of a Metropolis Hastings algorithm

- simulate a candidate from a proposal distribution
  $b^c \sim q_{\theta_{k-1}}(.|b^{k-1})$
- accept or reject this candidate with probability

$$\alpha(b^{k-1}, b^c) = \min\left(1, \frac{p(b^c|y,\theta)q_{\theta_{k-1}}(b^{k-1}|b^c)}{p(b^{k-1}|y,\theta)q_{\theta_{k-1}}(b^c|b^{k-1})}\right)$$

Additional comments and discussions on maximum likelihood estimation in mixed effects models

- tuning of the parameters in stochastic algorithms
- tuning of the MCMC procedure
- computation of the likelihood
- computation of the Fisher information matrix
- identifiability of the model

Alternative approach: bayesian inference

- consider θ as a random variable
- choose a prior distribution for θ denoted by π

$$\begin{cases} \theta & \sim & \pi \\ b_i & \overset{iid}{\sim} & q(.;\Gamma) \\ Y_i|b_i;X_i,U_i,V_i & \overset{i}{\sim} & q(.;\beta,\Sigma) \end{cases}$$

- simulate a (quasi) sample of the distribution of (θ, b) conditionaly to the observation Y

$\Rightarrow$ use intensive computational tools as MCMC, importance sampling, ABC

Testing fixed effects in mixed effects model

$$\begin{cases} Y_{ij} &= f(X_{ij}, \varphi_i) + \varepsilon_{ij}, \quad 1 \leq i \leq N,\ 1 \leq j \leq J \\ \varphi_i &= U_i \beta + V_i b_i, \quad 1 \leq i \leq N \end{cases}$$

with $b_i \overset{iid}{\sim} q(.;\Gamma)$ and $\varepsilon_{ij} \overset{iid}{\sim} q(.;\Sigma)$ with $\theta = (\beta, \Gamma, \Sigma)$

- test whether the covariate effect β is significant or not

Example: Theophylline pharmacokinetic model
ka_i, Cl_i and V_i are individual random parameters such that
$\log ka_i = \log(ka) + b_{i,1},\ b_{i,1} \sim \mathcal{N}(0, \gamma_1)$
$\log Cl_i = \log(Cl) + \beta BW_i + b_{i,2},\ b_{i,2} \sim \mathcal{N}(0, \gamma_2)$
$\log V_i = \log(V) + b_{i,3},\ b_{i,3} \sim \mathcal{N}(0, \gamma_3)$
where BW_i is the body weight of individual i

Likelihood ratio test statistic

Let $(Y_1, ..., Y_N)$ be a sample having density f_θ, $\theta \in \Theta \subset \mathbb{R}^q$

Consider the test defined by
$H_0 :$ "$\theta \in \Theta_0$" against $H_1 :$ "$\theta \in \Theta_1$"

Then the likelihood ratio test statistic equals to

$$LRT_N = -2 \log \left(\frac{\sup_{\theta \in \Theta_0} L_N(\theta)}{\sup_{\theta \in \Theta_1} L_N(\theta)} \right) = 2(\ell_N(\hat{\theta}_{H_1}) - \ell_N(\hat{\theta}_{H_0}))$$

with $L_N(\theta) = \prod_1^N f_\theta(Y_i)$

Asymptotic distribution of the LRT statistic for linear hypotheses defined by equalities when Θ is open

Consider the test defined by
H_0 : "$R\theta = 0$" against H_1 : "$R\theta \neq 0$"
where R is a full rank matrix of size $r x p$.

Then, assuming regularity conditions, under H_0:

$$LRT_N = -2\log\left(\frac{\sup_{\theta\in\Theta_0} L_N(\theta)}{\sup_{\theta\in\Theta_1} L_N(\theta)}\right) = 2(\ell_N(\hat{\theta}_{H_1}) - \ell_N(\hat{\theta}_{H_0})) \xrightarrow{\mathcal{L}} \chi^2(r)$$

Application to testing the effect of one covariate

Consider the test defined by
H_0 : "$\beta = 0$" against H_1 : "$\beta \neq 0$"

Then, assuming regularity conditions, under H_0:

$$LRT_N = -2\log\left(\frac{\sup_{\theta\in\Theta_0} L_N(\theta)}{\sup_{\theta\in\Theta_1} L_N(\theta)}\right) = 2(\ell_N(\hat{\theta}_{H_1}) - \ell_N(\hat{\theta}_{H_0})) \xrightarrow{\mathcal{L}} \chi^2(1)$$

$\Rightarrow$ require to evaluate numerically the likelihood

$\Rightarrow$ asymptotic distribution

Test for variance components in mixed effects model

Objective: test that r random effects among p have null variances.

$$\begin{cases} Y_{ij} = f(X_{ij}, \varphi_i) + \varepsilon_{ij}, & 1 \leq i \leq N,\ 1 \leq j \leq J \\ \varphi_i = U_i\beta + V_i b_i, & 1 \leq i \leq N \end{cases}$$

with $b_i \overset{iid}{\sim} \mathcal{N}_p(0; \Gamma)$ and $\varepsilon_{ij} \overset{iid}{\sim} q(.; \Sigma)$

Let $\Gamma = \left(\begin{array}{c|c} \Gamma_1 & \Gamma_{12} \\ \hline \Gamma_{12}^t & \Gamma_2 \end{array}\right)$ where $\Gamma_1 \in \mathcal{S}_{p-r}^+$ and $\Gamma_2 \in \mathcal{S}_r^+$

$\Theta_0 = \{\theta \in \mathbb{R}^q | \beta \in \mathbb{R}^p, \Gamma_1 \in \mathcal{S}_{p-r}^+, \Gamma_2 = 0, \Gamma_{12} = 0, \Sigma \in \mathcal{S}_J^+\}$

$\Theta_1 = \{\theta \in \mathbb{R}^q | \beta \in \mathbb{R}^p, \Gamma \in \mathcal{S}_p^+, \Sigma \in \mathcal{S}_J^+\}$

$\Longrightarrow$ test $H_0 : \theta \in \Theta_0$ against $H_1 : \theta \in \Theta_1$

Asymptotic distribution of the LRT statistic for testing that one variance equal zero in mixed effects model with one single random effect

[Self and Liang (1987) Annals of Statistics]

$$Y_{ij} = X_j \beta + b_i + \varepsilon_{ij} \ , \ 1 \leq i \leq N, \ 1 \leq j \leq J$$

with $b_i \overset{iid}{\sim} \mathcal{N}(0, \gamma^2)$, $\varepsilon_i \overset{iid}{\sim} \mathcal{N}_J(0, \sigma^2)$, ε_i independent of (b_i)

Consider the test defined by
H_0 : "$\gamma^2 = 0$" against H_1 : "$\gamma^2 \neq 0$"

Then, assuming regularity conditions, under H_0:

$$LRT_n = 2(\ell_n(\hat{\theta}_{H_1}) - \ell_n(\hat{\theta}_{H_0})) \xrightarrow{\mathcal{L}} \frac{1}{2}\delta_0 + \frac{1}{2}\chi^2(1)$$

Asymptotic distribution of the LRT statistic for linear hypotheses defined by inequalities when Θ is open

Consider the test defined by
H_0 : "$R\theta = 0$" against H_1 : "$R\theta \geq 0$"
where R is a full rank matrix

Denote by θ_0 the true value being in H_0
and I_0 the corresponding Fisher information matrix.

Then, assuming regularity conditions, under H_0:

$$LRT_n \xrightarrow{\mathcal{L}} \min_{R\theta=0} (Z-\theta)^t I_0 (Z-\theta) - \min_{R\theta \geq 0} (Z-\theta)^t I_0 (Z-\theta)$$

where $Z \sim \mathcal{N}(0, I_0^{-1})$
$\Longrightarrow$ reduce to test the mean of a multivariate normal distribution
$\Longrightarrow$ identify the limit distribution

Example of testing one single variance is zero

[Self & Liang, 1987]
Let $\theta = (\beta, \gamma^2, \Sigma)$ and $\Theta = \mathbb{R} \times \mathbb{R}^+ \times \mathcal{S}_J^+$.
Consider H_0 : "$\gamma^2 = 0$" against H_1 : "$\gamma^2 \geq 0$"
Let $Z \sim \mathcal{N}(0, I_0^{-1})$

$$\begin{aligned} D(Z) &= Z' I(\theta_0) Z - \inf_{\theta \geq 0} (Z - \theta)^t I_0 (Z - \theta) \\ &= \|Z\|_{I_0}^2 - \inf_{\theta \geq 0} \|Z - \theta\|_{I_0}^2 \\ &= \|\tilde{Z}\|^2 - \inf_{\theta \geq 0} \|\tilde{Z} - \theta\|^2 \\ &= \|\tilde{Z}\|^2 1_{\tilde{Z} > 0} \\ &= \frac{1}{2}\chi^2(0) + \frac{1}{2}\chi^2(1) \end{aligned}$$

where $\tilde{Z} \sim \mathcal{N}(0, 1)$

Sketch of proof

- Using Taylor series expansion

$$\begin{aligned}\ell_N(\theta) &= \ell_N(\theta_0) + \frac{1}{2}n^{-1}S_n(\theta_0)I^{-1}(\theta_0)S_n(\theta_0) \\ &- \frac{1}{2}[Z_n - n^{1/2}(\theta-\theta_0)]^t I(\theta_0)[Z_n - n^{1/2}(\theta-\theta_0)] \\ &+ O_P(1)||\theta-\theta_0||^3\end{aligned}$$

  where $Z_n = n^{-1/2}I(\theta_0)^{-1}S_n(\theta_0)$.

- Define $u = n^{1/2}(\theta-\theta_0)$ and rewrite the likelihood ratio test statistics as:

$$\begin{aligned}LRT_n &= -2[\sup_{\theta\in\Theta_0}\ell_n(\theta) - \sup_{\theta\in\Theta_1}\ell_n(\theta)] \\ &= \inf_{Ru=0}||Z_n-u||_{I(\theta_0)} - \inf_{Ru\geq 0}||Z_n-u||_{I(\theta_0)}.\end{aligned}$$

$\Longrightarrow$ establish the limit distribution

Asymptotic distribution of the LRT statistic for general hypotheses when Θ is open

[Self and Liang (1987) Annals of statistics]

Consider the test defined by
H_0 : "$\theta \in \Theta_0$" against H_1 : "$\theta \in \Theta_1$"
Then, assuming regularity conditions, under H_0:

$$LRT_n = 2(\ell_n(\hat{\theta}_{H_1}) - \ell_n(\hat{\theta}_{H_0})) \xrightarrow{\mathcal{L}} D_T(Z),$$

where $Z \sim \mathcal{N}(0, I_0^{-1})$ and

$$D_T(z) = \|z - T(\Theta_0, \theta_0)\|_{I_0}^2 - \|z - T(\Theta_1, \theta_0)\|_{I_0}^2.$$

where $T(\Theta, \theta)$ is the tangent cone of Θ at θ

$\Longrightarrow$ using tangent cones to approximate Θ_0 and Θ_1

Limits of the existing results

Example of testing one variance equals to zero considering two correlated random effects:

Let $\theta = (\beta, \Gamma, \Sigma)$ with $\Gamma = \begin{pmatrix} \gamma_1^2 & \gamma_{12} \\ \gamma_{12} & \gamma_2^2 \end{pmatrix}$ and $\Theta = \mathbb{R}^2 \times \mathcal{S}_2^+ \times \mathcal{S}_J^+$.

Consider $H_0 : \theta \in \Theta_0$ against $H_1 : \theta \in \Theta_1$ with

$$\Theta_0 = \{\theta, \beta \in \mathbb{R}^2, \gamma_1^2 = \gamma_{12} = 0, \gamma_2^2 \geq 0, \Sigma \in \mathcal{S}_J^+\}$$
$$\Theta_1 = \{\theta, \beta \in \mathbb{R}^2, \gamma_1^2 \geq 0, \gamma_1^2\gamma_2^2 - \gamma_{12}^2 \geq 0, \gamma_2^2 \geq 0, \Sigma \in \mathcal{S}_J^+\}$$

$\Longrightarrow$ Θ is not open

$\Longrightarrow$ approxmation with cones for Θ_1 and Θ_0

$\Longrightarrow$ identify the limit distribution

Identifying the asymptotic distribution of the LRT statistics for testing variance components in nonlinear mixed effects model

[Baey, Cournède, K. (2019) CSDA]

Consider the test defined by
$H_0 : \theta \in \Theta_0$ against $H_1 : \theta \in \Theta_1$ where
$\Theta_0 = \{\theta \in \mathbb{R}^q | \beta \in \mathbb{R}^p, \Gamma_1 \in \mathcal{S}^+_{p-r}, \Gamma_2 = 0, \Gamma_{12} = 0, \Sigma \in \mathcal{S}^+_J\}$
$\Theta_1 = \{\theta \in \mathbb{R}^q | \beta \in \mathbb{R}^p, \Gamma \in \mathcal{S}^+_p, \Sigma \in \mathcal{S}^+_J\}$
Then, assuming regularity assumptions, under H_0:

$$LRT_n \xrightarrow{\mathcal{L}} \bar{\chi}^2(I_0^{-1}, T(\Theta_0, \theta_0)^{\perp} \cap T(\Theta_1, \theta_0)),$$

where $T(\Theta, \theta)$ is the tangent cone of Θ at θ and $\bar{\chi}^2(V, \mathcal{C})$ has a χ-bar square distribution (mixture of chi square distributions) with $\mathcal{C}$ a closed convex cone and V a positive definite matrix

The Chi-bar Square distribution

Let $\mathcal{C}$ be a closed convex cone of $\mathbb{R}^q$ and
V a positive definite matrix of size qxq.
Let $Z \sim \mathcal{N}(0, V)$
Then $\bar{\chi}^2(V, \mathcal{C}) = Z'V^{-1}Z - \inf_{\theta \in \mathcal{C}}(Z - \theta)'V^{-1}(Z - \theta)$
has a χ-bar square distribution and

$$\forall t \geq 0 \; P(\bar{\chi}^2(V, \mathcal{C}) \leq t) = \sum_{i=0}^{q} w_i(p, V, \mathcal{C}) P(\chi_i^2 \leq t)$$

where the weights $w_i(q, V, \mathcal{C})$ are some non-negative numbers summing up to one

Example of testing one variance equals to zero considering two independent random effects

Let $\theta = (\beta, \Gamma, \Sigma)$ with $\Gamma = \begin{pmatrix} \gamma_1^2 & 0 \\ 0 & \gamma_2^2 \end{pmatrix}$ and
$\Theta = \mathbb{R}^2 \times \mathbb{R}^+ \times \mathbb{R}^{+*} \times \mathcal{S}_J^+$.
Consider $H_0 : \gamma_1^2 = 0$ against $H_1 : \gamma_1^2 \geq 0$
Let $Z \sim \mathcal{N}(0, I_0^{-1})$

$$\begin{aligned} D(Z) &= \inf_{\theta_1 = 0} (Z - \theta)' I_0 (Z - \theta) - \inf_{\theta_1 \geq 0} (Z - \theta)^t I_0 (Z - \theta) \\ &= \tilde{Z}_1{}^2 - \inf_{\theta_1 \geq 0} (\tilde{Z}_1 - \theta_1)^2 \\ &= \tilde{Z}_1{}^2 1_{\tilde{Z}_1 > 0} \\ &= \frac{1}{2}\chi^2(0) + \frac{1}{2}\chi^2(1) \end{aligned}$$

where $\tilde{Z} \sim \mathcal{N}(0, 1)$

Evaluation of the empirical level of the test for one effect when two effects are non correlated in the linear model

$$Y_{ij} = \varphi_{1i} + \varphi_{2i} t_{ij} + \varepsilon_{ij} \ ,$$

Let $\Gamma = \begin{pmatrix} \gamma_1^2 & 0 \\ 0 & \gamma_2^2 \end{pmatrix}$

Consider $H_0 : \gamma_1 = 0$ against $H_1 : \gamma_1 \geq 0$

Table: Percentages of rejection for the LRT procedure for $n = 500$ for the nominal level of the test α on 300 repetitions.

α	$\hat{\alpha}_{0.5\chi_0^2+0.5\chi_1^2}$
0.01	0.010
0.05	0.046
0.10	0.093

Example of testing one variance equals to zero considering two correlated random effects

Let $\theta = (\beta, \Gamma, \Sigma)$ with $\Gamma = \begin{pmatrix} \gamma_1^2 & \gamma_{12} \\ \gamma_{12} & \gamma_2^2 \end{pmatrix}$ and $\Theta = \mathbb{R}^2 \times \mathcal{S}_p^+ \times \mathcal{S}_J^+$.
Consider $H_0 : \theta \in \Theta_0$ against $H_1 : \theta \in \Theta_1$

$\Theta_0 = \{\theta, \beta \in \mathbb{R}^2, \gamma_1^2 = \gamma_{12} = 0, \gamma_2^2 \geq 0, \Sigma \in \mathcal{S}_J^+\}$
$\Theta_1 = \{\theta, \beta \in \mathbb{R}^2, \gamma_1^2 \geq 0, \gamma_1^2\gamma_2^2 - \gamma_{12}^2 \geq 0, \gamma_2^2 \geq 0, \Sigma \in \mathcal{S}_J^+\}$

$$LRT_n \xrightarrow{d} \quad \frac{1}{2}\chi^2(1) + \frac{1}{2}\chi^2(2)$$

Evaluation of the empirical level of the test for one effect when two effects are correlated in the linear model

$$Y_{ij} = \varphi_{1i} + \varphi_{2i} t_{ij} + \varepsilon_{ij} \ ,$$

Let $\Gamma = \begin{pmatrix} \gamma_1^2 & \gamma_{12} \\ \gamma_{12} & \gamma_2^2 \end{pmatrix}$
Consider $H_0 : \theta \in \Theta_0$ against $H_1 : \theta \in \Theta_1$

Table: Percentages of rejection for the LRT procedure for $n = 500$ for the nominal level of the test α on 300 repetitions.

α	$\hat{\alpha}_{0.5\chi_1^2+0.5\chi_2^2}$	$\hat{\alpha}_{0.5\chi_0^2+0.5\chi_1^2}$
0.01	0.016	0.049
0.05	0.055	0.174
0.10	0.103	0.311

Perspectives

- need for efficient numerical evaluation of likelihood
- need for efficient numerical evaluation of Fisher information matrix
- limits of non asymptotic test procedure ...
  $\Rightarrow$ Likelihood ratio tests in linear mixed models with one variance component, Crainiceanu and Ruppert, JRSS B (2004)

Comments on the distribution of random effect

- centered distribution
- usual choice Gaussian distribution
- possible to choose other ones: Student, mixture ...
- test for the adequation of Gaussian distribution for random effects
  $\Rightarrow$ Diagnosing misspecification of the random-effects distribution in mixed models Drikvandi et al. Biometrics (2016)
- Nonparametric estimation of random effects densities in linear mixed-effects model. Comte F, Samson A, Journal of Nonparametric Statistics, (2012)

Summary of the day

$$\begin{cases} Y_{ij} & = & f(X_{ij}, \varphi_i) + \varepsilon_{ij}, & 1 \leq i \leq N,\ 1 \leq j \leq J \\ \varphi_i & = & U_i \beta + V_i b_i, & 1 \leq i \leq N \end{cases}$$

with $b_i \overset{iid}{\sim} q(.;\Gamma)$ and $\varepsilon_{ij} \overset{iid}{\sim} q(.;\Sigma)$ with $\theta = (\beta, \Gamma, \Sigma)$

- Testing procedure for fixed effects β via LRT
- Testing procedure for variance components Γ via LRT
- alternatives: Wald test, score test

Model choice criteria

Consider the mixed effects model

$$\begin{cases} Y_{ij} &= f(X_i, \varphi_i) + \varepsilon_{ij}, \quad 1 \leq i \leq N,\ 1 \leq j \leq J \\ \varphi_i &= U_i \beta + b_i, \quad\quad 1 \leq i \leq N \end{cases}$$

with $b_i \overset{iid}{\sim} \mathcal{N}(0, \Gamma)$ and $\varepsilon_{ij} \overset{iid}{\sim} q$ and $\theta = (\beta, \Gamma)$

Recall the
Bayesian information criterion defined as:

$$BIC = -2 \log L_{marg}(\widehat{\theta}; Y_1^N) + dim(\theta) \log(n_{obs})$$

$\Rightarrow$ what is the "real" sample size in mixed effects model? NJ? N?
From a practical point of view, the $\log(NJ)$ penalty is implemented in the R package nlme and in the SPSS procedure MIXED while the $\log(N)$ penalty is used in Monolix, saemix or in the SASproc NLMIXED.

Model choice criteria

[A note on BIC in mixed-effects models, Delattre, Lavielle, Poursat, EJS 2014]

Consider the following mixed effects model:

$$\left\{ \begin{array}{ccc} \varphi_i & \sim & q(.|U_i, \theta) \\ Y_i|\varphi_i; X_i & \sim & q(.|\varphi_i; X_i) \end{array} \right.$$

where $\varphi_i = U_i \beta + b_i$ with U_i block diagonal, $b_i \sim \mathcal{N}(0, \Gamma)$ and Γ is potentially degenerated.

$$\Gamma = \left(\begin{array}{cc} 0 & 0 \\ 0 & \Gamma_R \end{array} \right)$$

Denote the parameter $\theta = (\theta_F, \theta_R)$ where $\theta_F = \beta_F$ and $\theta_R = (\beta_R, \Gamma_R)$.

Consider the hybrid Bayesian information criterion defined as:

$$BIC_{hyb} = -2 \log L_{marg}(\widehat{\theta}; Y_1^N) + \dim(\theta_R) \log(N) + \dim(\theta_F) \log(NJ)$$

$\Rightarrow$ intensive simulation study to highlight the good statistical properties of this criterion

Model choice criteria

[A note on BIC in mixed-effects models, Delattre, Lavielle, Poursat, EJS 2014]
Consider the hybrid Bayesian information criterion defined as:

$$BIC_{hyb} = -2 \log L_{marg}(\widehat{\theta}; Y_1^N) + \dim(\theta_R) \log(N) + \dim(\theta_F) \log(NJ)$$

- In a pure fixed-effects model,
  $\Rightarrow \theta = \theta_F$
  $\Rightarrow$ penalty $\dim(\theta) \log(NJ)$
- if all the individual parameters are random,
  $\Rightarrow \theta = \theta_R$
  $\Rightarrow$ penalty $\dim(\theta) \log(N)$
- the criterion proposed appears to be an hybrid BIC version that automatically adapts to the random-effects structure of a mixed model

Variable selection in linear mixed effects model

Consider the linear mixed effect model:

$$Y_i = X_i\beta + Z_i b_i + \varepsilon_i \ , \ 1 \leq i \leq N,$$

- Y_i is the observation vector for individual i of size J
- X_i and Z_i are matrices of known covariates of individual i
- β is the vector of fixed effects of size p
- $b_i \overset{iid}{\sim} \mathcal{N}_q(0, \Gamma)$
- ε_i is a random error vector, with $\varepsilon_i \overset{iid}{\sim} \mathcal{N}_J(0, \Sigma)$

$\Rightarrow$ In case where $NJ << p$ not possible to use classical maximum likelihood approach

$\Rightarrow$ penalize the estimation criterion

Variable selection in linear mixed effects model

Consider the linear mixed effect model:

$$Y_i = X_i\beta + Z_i b_i + \varepsilon_i \ , \ 1 \leq i \leq N,$$

- Y_i is the observation vector for individual i of size J
- X_i and Z_i are matrices of known covariates of individual i
- β is the vector of fixed effects of size p
- $b_i \overset{iid}{\sim} \mathcal{N}_q(0, \Gamma(\gamma))$
- $\varepsilon_i \overset{iid}{\sim} \mathcal{N}_J(0, \sigma^2 I)$

$\Rightarrow Y_i \sim \mathcal{N}(X_i\beta, Z_i'\Gamma(\gamma)Z_i + \sigma^2 I)$

Variable selection in linear mixed effects model

[Estimation for High-Dimensional Linear Mixed-Effects Models Using L_1 Penalization, Schelldorfer et al., SJS (2011)]

Consider the linear mixed effect model:

$$Y_i = X_i\beta + Z_i b_i + \varepsilon_i \ , \ 1 \leq i \leq N,$$

where β is of size p, $b_i \overset{iid}{\sim} \mathcal{N}_q(0, \Gamma(\gamma))$ and $\varepsilon_i \overset{iid}{\sim} \mathcal{N}_J(0, \sigma^2 I)$

$\Rightarrow Y_i \sim \mathcal{N}(X_i\beta, Z_i'\Gamma(\gamma)Z_i + \sigma^2 I)$

Consider the setting where $NJ << p$, $dim(\gamma) << p$,
q might as high as p

Consider the following objective function

$$C(\beta, \gamma, \sigma^2) = \frac{1}{2}\log|V| + \frac{1}{2}(Y - X\beta)'V^{-1}(Y - X\beta) + \lambda\sum_{k=1}^{p}|\beta_k|$$

with $V = diag(V_1, \ldots, V_N)$ and $V_i = Z_i\Gamma(\gamma)Z_i + \sigma^2 I$
and define the penalized estimator $(\hat{\beta}, \hat{\gamma}, \hat{\sigma^2}) = \arg\max Q(\beta, \gamma, \sigma^2)$

Variable selection in linear mixed effects model

$$Y_i = X_i\beta + Z_i b_i + \varepsilon_i \ , \ 1 \leq i \leq N,$$

where β is of size p, $b_i \overset{iid}{\sim} \mathcal{N}_q(0, \Gamma(\gamma))$ and $\varepsilon_i \overset{iid}{\sim} \mathcal{N}_J(0, \sigma^2 I)$

$$C(\beta, \gamma, \sigma^2) = \frac{1}{2}\log|V| + \frac{1}{2}(Y - X\beta)' V^{-1}(Y - X\beta) + \lambda \sum_{k=1}^{p} |\beta_k|$$

$(\hat{\beta}, \hat{\gamma}, \hat{\sigma}^2) = \arg\max Q(\beta, \gamma, \sigma^2)$

- theoretical properties of consistency for the penalized estimates and for the support of β
- implemented in R package lmmlasso and glmmlasso

$\Rightarrow$ other approach [An iterative algorithm for joint covariate and random effect selection in nonlinear mixed effects models, Delattre et al. (2019)]

$\Rightarrow$ further work needed for variable selection in nonlinear mixed effects models

Short global summary

- fixed and random effects
- maximum likelihood estimator with good properties
- convergent stochastic algorithm to evaluate its value
- testing procedures for fixed effects and variance components
- model choice criteria
- variable selection in linear mixed effects model

Somes extensions of mixed models

- Modeling the observation level through a function defined by an Ordinary Differential Equation [Donnet S., Samson A., JSPI (2007)]
- Parametric inference for mixed models defined by stochastic differential equations, [Donnet S., Samson A. (2008) ESAIM PS (2008)]
- Parametric estimation of complex mixed models based on meta-model approach, [Barbillon P, Barthelemy C, Samson A, Statistics and Computing, (2017)]
- ...

Others models with random effects

- Maximum likelihood estimation in frailty models [K., El Nouty Stat Compu (2013)]
- Maximum likelihood estimation for stochastic differential equations with random effects [Delattre M., Genon-Catalot V., Samson A., SJS (2013)]
  $\Rightarrow$ Mixedsde: a R package to fit mixed stochastic differential equations [Dion C., Hermann S., Samson A. (2018)]
- ...

Books bibliography

- Mixed effects models in S and S-PLUS, J.C. Pinheiro D.M. Bates (2000)
- Linear mixed models for longitudinal data, G. Verbeke and G. Molenberghs (2000)
- Mixed effects models for the population approach, M. Lavielle (2014)
- Nonlinear Models for Repeated Measurement Data, M. Davidian and D.M. Giltinian (1995)