Supporting slides

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Section 1

NLME fitting algorithms

Notation

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- y_i: observations of subject i
- x_i: covariates of subject i

NLME Notation

- $p(y = y_i \mid \theta = \theta, \eta = \eta_i, x = x_i) = p(y_i \mid \theta, \eta_i, x_i)$: likelihood of (θ, η_i) given subject i's data (x_i, y_i). Also known as the conditional probability of y_i given θ, η_i, x_i. Or just the conditional likelihood of η_i given θ and (x_i, y_i).

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- $p(\eta = \eta_i \mid \theta = \theta) = p(\eta_i \mid \theta)$: prior probability of the random effects η_i given the population parameters θ.

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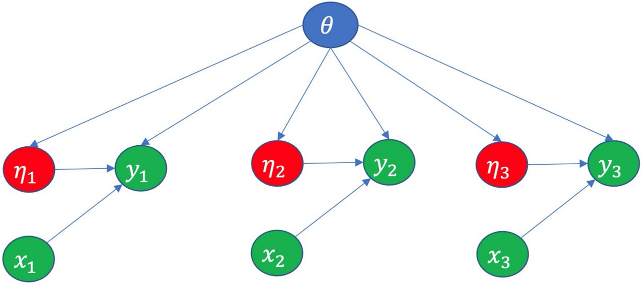
- $p(\eta = \eta_i \mid \theta = \theta) = p(\eta_i \mid \theta)$: prior probability of the random effects η_i given the population parameters θ.
- $p(y = y_i \mid \theta = \theta, x = x_i) = p(y_i \mid \theta, x_i) = \int p(y_i \mid \theta, \eta_i, x_i) \cdot p(\eta_i \mid \theta) \, d\eta_i$: marginal likelihood of θ given subject i's data y_i.

NLME Notation



NLME Notation

θ

$\eta_i \mid \theta$

x_i

$y_i \mid \theta, \eta_i, x_i$

```
@model begin
  @param begin
    θ ∈ VectorDomain(4, lower = zeros(4))
    Ω ∈ PSDDomain(2)
    Σ ∈ RealDomain(lower = 0.0)
    a ∈ RealDomain(lower = 0.0, upper = 1.0)
  end
  @random begin
    η ~ MvNormal(Ω)
  end
  @covariates sex wt etn
  @pre begin
    θ1 := θ[1]
    Ka = θ1
    CL = θ[2] * ((wt / 70)^0.75) * (θ[4]^sex) *
      exp(η[1])
    Vc = θ[3] * exp(η[2])
  end
  @dynamics begin
    Depot' = -Ka * Depot
    Central' = Ka * Depot - (CL / Vc) * Central
    Res' = Depot - Central
  end
  @derived begin
    conc = @. Central / Vc
    dv ~ @. Normal(conc, conc * Σ)
    T_max = maximum(t)
  end
  @observed begin
    obs_cmax = maximum(dv)
  end
end
```

Marginal likelihood maximization

$$\theta^* = \arg max_\theta \prod_{i=1}^{N} p(y_i \mid \theta, x_i)$$

$$= \arg max_\theta \prod_{i=1}^{N} \int p(y_i \mid \theta, \eta_i, x_i) \cdot p(\eta_i \mid \theta) \, d\eta_i$$

$$\text{EBE}_i = \eta_i^* = \arg max_{\eta_i} \Big(p(y_i \mid \theta = \theta^*, \eta_i, x_i) \cdot p(\eta_i \mid \theta = \theta^*) \Big)$$

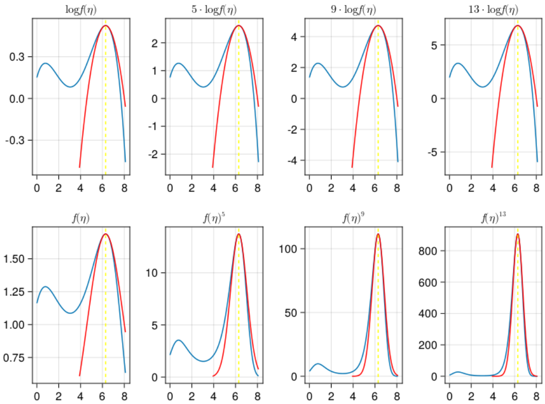
General Laplace method

$$\int f(\eta)\, d\eta \approx f(\eta^*)\sqrt{(2\pi)^m/|-H|}$$

- f: a positive scalar-valued functon of η
- η: vector of m integration variables
- η^*: global maximizer of $\log f$, $\frac{d \log f}{d\eta}(\eta^*) = 0$
- H: second derivative matrix of $\log f$ wrt η at η^*, must be negative definite at $\eta = \eta^*$
- $|-H|$: determinant of $-H$

NLME Laplace method

Laplace uses a second order Taylor series approximation of $\log f$ at η^*.



NLME Laplace method

The mode is the same after multiplying $\log f$ by a scalar. The ratio of peaks is not the same. Consider the 2 local maximizers η_1 (lower peak) and η_2 (higher peak).

$$
\begin{aligned}
c &= \log f(\eta_2) - \log f(\eta_1) \\
n \cdot c &= n \cdot (\log f(\eta_2) - \log f(\eta_1)) \\
e^{n \cdot c} &= f(\eta_2)^n / f(\eta_1)^n
\end{aligned}
$$

Summary

Approximation error of $n \cdot \log f$ away from the mode η^* is not significant as n increases.

NLME Laplace method

- There are N functions $\{f_i : i = 1 \dots N\}$ to be integrated, one for each subject
- $f_i(\eta_i) = p(y_i \mid \theta, \eta_i, x_i) \cdot p(\eta_i \mid \theta)$
- Laplace method

$$\int f_i(\eta_i)\, d\eta_i = f_i(\mathsf{EBE}_i)\sqrt{(2\pi)^m / |-H_i|}$$

- H_i: second derivative matrix of $\log f_i$ wrt η_i at EBE_i, must be negative definite at $\eta_i = \mathsf{EBE}_i$

General FOCE(I)

FOCE(I) approximates the Hessian H_i for each subject i. Assume the following:

$$\begin{aligned}\log f_i(\eta_i) &= \log p(y_i \mid \theta, \eta_i, x_i) + \log p(\eta_i \mid \theta) \\ &= L_i(g_i(\eta_i)) + \log p(\eta_i \mid \theta)\end{aligned}$$

where:

- g_i returns the vector of IPREDs μ_i and the residual standard deviations σ_i (constant in the additive error model case), at all observed time points, and
- L_i is the log probability of y_i given μ_i and σ_i

General FOCE(I)

g_i is usually the most expensive component of $\log f_i$, because it often involves solving a differential equation. So let's approximate it!

First order Taylor series expansion

- FO

$$g_i(\eta_i) = g_i(0) + \frac{dg_i}{d\eta_i}(0) \cdot \eta_i$$

- FOCE(I)

$$g_i(\eta_i) = g_i(\text{EBE}_i) + \frac{dg_i}{d\eta_i}(\text{EBE}_i) \cdot (\eta_i - \text{EBE}_i)$$

General FOCE(I)

Summary

- FOCE(I) ensures that the approximation error in g_i (and $\log f_i$ by extension) is low in the proximity of EBE$_i$.
- FO does not ensure that so it only works well if:
  - EBE$_i$ is not far from 0, or
  - g_i is close to linear in the interval $[0, \text{EBE}_i]$.
- FO requires a correction term in the Laplace method because the gradient of $\log f_i$ wrt η_i at $\eta_i = 0$ is not 0.

General FOCE(I)

Chain rule for Hessians

$$(L_i \cdot g_i)''(\eta_i) = \frac{dg_i}{d\eta_i}^T \cdot \frac{\partial^2 L_i}{\partial g_i \cdot \partial g_i^T} \cdot \frac{dg_i}{d\eta_i} + \sum_{t=1}^{d} \left(\frac{\partial L_i}{\partial g_{i,t}} \cdot \underbrace{\frac{\partial^2 g_{i,t}}{\partial \eta_i \cdot \partial \eta_i^T}}_{\text{0 if linear}} \right)$$

where d is twice the number of observed time points (corresponding to μ_i and σ_i) and $g_{i,t}$ is the t^{th} component of g_i.

General FOCE(I)

Summary

If g_i is linear in η_i:

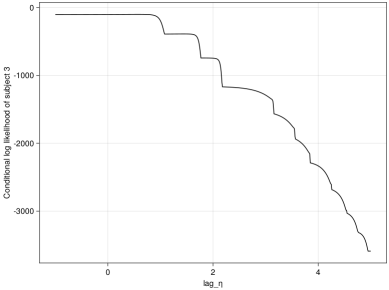
- $\frac{\partial^2 g_{i,t}}{\partial \eta_i \cdot \partial \eta_i^T} = 0$
- $J_i = \frac{\partial g_i}{\partial \eta_i}$ is constant

The Hessian simplifies to:

$$(L_i \cdot g_i)''(\eta_i) = J_i^T \cdot \frac{\partial^2 L_i}{\partial g_i \cdot \partial g_i^T} \cdot J_i$$

General FOCE(I)

- One surprising advantage of FOCE(I) is that the Hessian approximation is often negative definite even when the exact Hessian is singular or not well defined at $\eta_i = \eta_i^*$.



General FOCE(I)

- J_i can be computed for each subject using finite difference at
  - $\eta_i = 0$ for FO, or
  - $\eta_i = \text{EBE}_i$ for FOCE(I)
- For many data distributions, $\frac{\partial^2 L_i}{\partial g_i \cdot \partial g_i^T}$ is both diagonal and has a closed form. Doesn't have to be Gaussian!

General FOCE(I)

Recall

$$\begin{aligned}\log f_i(\eta_i) &= \log p(y_i \mid \theta, \eta_i, x_i) + \log p(\eta_i \mid \theta) \\ &= L_i(\underbrace{g_i(\eta_i)}_{\text{approx}}) + \log p(\eta_i \mid \theta)\end{aligned}$$

For many random effects distributions, the Hessian of $\log p(\eta_i \mid \theta)$ wrt η_i has a closed form. Doesn't have to be Gaussian!

General FOCE(I)

Summary

- In Pumas, FOCE is always “with interaction”.
- Pumas FOCE supports a number of data distributions:
  - **Continuous**: Normal, LogNormal, Gamma, Exponential, Beta
  - **Discrete**: NegativeBinomial, Bernoulli, Binomial, Poisson, Categorical

General FOCE(I)

Summary

- Pumas supports a number of random effect distributions:
  - **Unbounded**: Cauchy, Gumbel, Laplace, Logistic, Normal, NormalCanon, NormalInverseGaussian, PGeneralizedGaussian, TDist
  - **Positive**: BetaPrime, Chi, Chisq, Erlang, Exponential, Frechet, Gamma, InverseGamma, InverseGaussian, Kolmogorov, LogNormal, NoncentralChisq, Rayleigh, Weibull
  - **Between 0 and 1**: Beta, LogitNormal
  - **Other bounded**: Uniform, Arcsine, Biweight, Cosine, Epanechnikov, LogUniform, Semicircle, SymTriangularDist, Triweight

General FOCE(I)

Summary

- Use FOCE if supported, otherwise use Laplace.
- Avoid FO.

Section 2

Diagnostics

Standard error estimation

Goal

Estimate the covariance matrix of the estimator θ^*:

$$\theta^* = \arg max_\theta \prod_{i=1}^{N} p(y_i \mid \theta, x_i)$$

Sandwich estimator of standard errors

Asymptotic covariance

$$\theta^* \sim \mathcal{N}(\theta_0, V) = \mathcal{N}(\theta_0, A^{-1}BA^{-1})$$

$$A = \sum_{i=1}^{N} \frac{\partial^2 \log p(y_i \mid \theta, x_i)}{\partial\theta \cdot \partial\theta^T}(\theta_0)$$

$$B = \sum_{i=1}^{N} \frac{\partial \log p(y_i \mid \theta, x_i)}{\partial\theta}(\theta_0) \times \frac{\partial \log p(y_i \mid \theta, x_i)}{\partial\theta}(\theta_0)^T$$

where θ_0 is the set of unknown true parameters.

Sandwich estimator of standard errors

Estimated covariance

$$\theta^* \overset{a}{\sim} \mathcal{N}(\theta_0, \hat{V}) = \mathcal{N}(\theta_0, \hat{A}^{-1}\hat{B}\hat{A}^{-1})$$

$$\hat{A} = \sum_{i=1}^{N} \frac{\partial^2 \log p(y_i \mid \theta, x_i)}{\partial\theta \cdot \partial\theta^T}(\theta^*)$$

$$\hat{B} = \sum_{i=1}^{N} \frac{\partial \log p(y_i \mid \theta, x_i)}{\partial\theta}(\theta^*) \times \frac{\partial \log p(y_i \mid \theta, x_i)}{\partial\theta}(\theta^*)^T$$

Sandwich estimator of standard errors

Standard error estiamtes

The square root of the diagonal elements of $\hat{V}$ are the standard error estimates of θ^*.

Sandwich estimator of standard errors

Computing $\hat{V}$

- $\hat{A}$ and $\hat{B}$ can be approximated with finite difference
- $\log p(y_i \mid \theta, x_i)$ itself needs to be approximated with Laplace/FOCE/FO
- $\hat{A}^{-1} \cdot \hat{B} \cdot \hat{A}^{-1}$ is computed using a generalized eigenvalue problem.

Sandwich estimator of standard errors

Computing $\hat{V}$

Consider the following generalized eigenvalue problem:

$$\hat{B} \cdot U = \hat{A} \cdot U \cdot \Lambda$$
$$I = U^T \cdot \hat{A} \cdot U$$

where U is the matrix of generalized eigenvectors and Λ is the diagonal matrix of generalized eigenvalues.

Sandwich estimator of standard errors

Computing $\hat{V}$

The inverse of the matrix of eigenvectors U is obtained from the following constraint on U:

$$(U^T \cdot \hat{A}) \cdot U = I$$
$$U^{-1} = U^T \cdot \hat{A}$$

Sandwich estimator of standard errors

Computing $\hat{V}$

The following identity is true:

$$
\begin{aligned}
\hat{B} \cdot U &= \hat{A} \cdot U \cdot \Lambda \\
\hat{A}^{-1} \cdot \hat{B} \cdot U &= U \cdot \Lambda \\
\hat{A}^{-1} \cdot \hat{B} &= U \cdot \Lambda \cdot U^{-1} \\
\hat{A}^{-1} \cdot \hat{B} &= U \cdot \Lambda \cdot U^{T} \cdot \hat{A} \\
\hat{V} = \hat{A}^{-1} \cdot \hat{B} \cdot \hat{A}^{-1} &= U \cdot \Lambda \cdot U^{T}
\end{aligned}
$$

Sandwich estimator of standard errors

Failed estimator

- If the computed $\hat{A}$ is: a) singular, b) near singular, or c) has negative eigenvalues, the sandwich estimator will fail.
- This is a sign of poor identifiability of at least 1 parameter and/or significant numerical errors.
- Even if a single (IIV) parameter is not identifiable given the data, $\hat{A}$ will be singular.

Sandwich estimator of standard errors

Failed estimator

- Numerical errors in the finite difference or Laplace/FOCE/FO can also cause the computed approximate $\hat{A}$ to be singular (or have small negative eigenvalues) even when the exact matrix $\hat{A}$ may be only *near* singular and positive definite.

Weighted residuals

Visual predictive check

Section 3

Time to event

Definitions

Quantity	Formula
Instantaneous hazard	$\lambda(t) > 0$
Cumulative hazard	$\Lambda(t) = \int_0^t \lambda(t')\,dt'$
Survival function: probability of survival up to time t	$S(t) = exp(-\Lambda(t))$
Failure function: probability of death/failure before time t	$F(t) = 1 - S(t)$
Probability density function of time of death t	$f(t) = \frac{dF}{dt} = \lambda(t) \cdot exp(-\Lambda(t))$
Expected time of death $E[t]$	$E[t] = \int_0^\infty t \cdot f(t)\,dt = \int_0^\infty S(t)\,dt$

Log likelihood

The log likelihood for censored survival data is given by the following 2 formulas:

- For censored subjects at time t (patient survived until time t)

$$\log \text{likelihood} = \log S(t) = -\Lambda(t)$$

- For subjects dead at time t

$$\log \text{likelihood} = \log f(t) = \log \lambda(t) - \Lambda(t)$$