(Generalized) Linear Mixed Models

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Generalized linear mixed model

- So far we have allowed very flexible models for the expected response and very simplistic models for its stochastic component. Let's fix that.
- ▶ A Generalized linear mixed model (GLMM) has the form

$$\mathbf{g}(\mu_i) = \mathbf{X}_i oldsymbol{eta} + \mathbf{Z}_i \mathbf{b}, \quad \mathbf{b} \sim N(\mathbf{0}, oldsymbol{\psi}_{ heta}), \quad y_i \sim \mathsf{EF}(\mu_i, \phi)$$

- **Z** is a model matrix for the *random effects* **b**.
- The parameters are β, φ and θ, the latter parameterizing b's covariance matrix, ψ_θ.
- First consider finding estimates $\hat{\beta}$ and posterior modes $\hat{\mathbf{b}}$, given ϕ and θ . $\hat{\phi}$ and $\hat{\theta}$ will be covered subsequently.

$\hat{oldsymbol{eta}}$ and $\hat{f b}$ — Bayesian

- Treat β as random variables with improper uniform priors, and then find their posterior modes (MAP estimates).
- ► $f(\beta, \mathbf{b}|\mathbf{y}) \propto f(\mathbf{y}|\beta, \mathbf{b})f(\beta, \mathbf{b}) \propto f(\mathbf{y}|\beta, \mathbf{b})f(\mathbf{b})$ where $f(\mathbf{y}|\beta, \mathbf{b})$ is determined by the EF used, and $f(\mathbf{b})$ is $N(\mathbf{0}, \psi_{\theta})$.
- Maximization of $f(\beta, \mathbf{b}|\mathbf{y})$ is achievable by Penalized IRLS.
- Initialize $\hat{\eta}_i = g(y_i)$, then iterate the following steps.
 - 1. Form pseudodata z_i and weights w_i , exactly as for a GLM, except using linear predictor $\hat{\eta} = \mathbf{X}\hat{\beta} + \mathbf{Z}\hat{\mathbf{b}}$.
 - 2. Minimize the penalized weighted sum of squares $\sum_{i} w_{i}(z_{i} - \mathbf{X}_{i}\beta - \mathbf{Z}_{i}\mathbf{b})^{2}/\phi + \mathbf{b}^{\mathsf{T}}\psi_{\theta}^{-1}\mathbf{b} \text{ w.r.t. } \beta, \mathbf{b} \text{ to obtain a}$ new $\hat{\beta}, \hat{\mathbf{b}}$, and hence new $\hat{\eta}$ and $\hat{\mu}$.
- ► In LMM case don't need to iterate, and $\hat{\mathbf{b}} = \widehat{E(\mathbf{b}|\mathbf{y})}$.

$\hat{oldsymbol{eta}}$ by MLE

Integrate out b by Laplace approximation...

$$f_{oldsymbol{eta}}(\mathbf{y}) \simeq f_{oldsymbol{eta}}(\mathbf{y}, \hat{\mathbf{b}}) rac{(2\pi)^{\mathsf{dim}(\mathbf{b})/2}}{|\mathbf{Z}^\mathsf{T}\mathbf{W}\mathbf{Z}/\phi + \psi_{ heta}|^{-1/2}}$$

- ► This is exact for a LMM, in which case $\mathbf{W} = \mathbf{I}$ and $L(\beta) = f_{\beta}(\mathbf{y})$ is maximized by the MAP estimates.
- For other GLMMs MAP and MLE differ, but are close if W varies only 'slowly' with β.
- Most users of GLMMs are Bayesians out of laziness, and use the MAP estimates. So will we ...

$\hat{\phi}$ and $\hat{\boldsymbol{\theta}}$ — Laplace approximation

- To estimate φ and θ we need to integrate β and b out of f_β(y, b), and optimize the result w.r.t. φ, θ.
- The result of the integration is known as marginal likelihood or restricted likelihood, L_r.
- ► The integral can be obtained by Laplace approximation, with the resulting expression dependent on ϕ , θ via $\hat{\beta}$, $\hat{\mathbf{b}}$ and ψ_{θ} plus direct dependence on ϕ .
- ► $I_r = \log L_r$ can be optimized numerically w.r.t. ϕ, θ , with each I_r evaluation requiring a PIRLS loop to find $\hat{\beta}, \hat{\mathbf{b}}$.
- For a LMM the Laplace approximation is exact, and the PIRLS iteration is not needed.
- A cheaper, but less reliable method is PQL...

$\hat{\phi} ~ \mathrm{and} ~ \hat{\theta} - \mathrm{PQL}$

Consider the expression minimized at each PIRLS step:

$$Q = \sum_{i} w_{i} (z_{i} - \mathbf{X}_{i} \boldsymbol{\beta} - \mathbf{Z}_{i} \mathbf{b})^{2} / \phi + \mathbf{b}^{\mathsf{T}} \psi_{\theta}^{-1} \mathbf{b}$$

- ► -Q/2 is a (rough) quadratic approximation to the log of the part of $f_{\beta}(\mathbf{y}, \mathbf{b})$ which needs to be integrated w.r.t. **b**.
- ► It is also *exactly* the log of the part of f_β(y, b) which would need to be integrated w.r.t. b for a weighted LMM.
- So, at each PIRLS step, why not estimate this weighted LMM to optimize Q w.r.t. β, b, and get estimates of φ and θ into the bargain? No reason!
- This is 'PQL'. It works surprisingly well, except for binary data.

Distributional results

- ► Distributions for $\hat{\phi}$, $\hat{\theta}$ are from large sample MLE theory applied to I_r or the PQL working model I_r .
- Distributions for (conditional on ô, ô) are from MLE theory applied to *l*(Â), if this is computed. (Conditionally exact for LMM).
- Alternatively use the large sample Bayesian result

$$\begin{bmatrix} \boldsymbol{\beta} \\ \mathbf{b} \end{bmatrix} \sim N\left(\begin{bmatrix} \hat{\boldsymbol{\beta}} \\ \hat{\mathbf{b}} \end{bmatrix}, \begin{bmatrix} \mathbf{X}^{\mathsf{T}}\mathbf{W}\mathbf{X} & \mathbf{X}^{\mathsf{T}}\mathbf{W}\mathbf{Z} \\ \mathbf{Z}^{\mathsf{T}}\mathbf{W}\mathbf{X} & \mathbf{Z}^{\mathsf{T}}\mathbf{W}\mathbf{Z} + \psi_{\theta}/\phi \end{bmatrix}^{-1} \phi \right)$$

Model Comparison

- If fixed effects are the same in the alternative models, then *l_r* can be used for GLRT testing or AIC model comparison.
- If fixed effects differ then estimation has to be performed without integrating out β: then GLRT and AIC can be used.
- When using the GLRT take care that the null model is not restricting alternative model parameters to the edge of the parameter space. If it is, the results are only a rough guide.
- PQL estimated model comparison is difficult. The working *l_r* is not really a valid basis for model comparison.

Residuals and fitted values

- ► We can produce fitted values at different *levels*, depending on which components of **b** are set to their unconditional mean 0, and which are set to their conditional mean E(b_i|**y**).
- ullet At the highest level the fitted values are: $\hat{\mu} = oldsymbol{X} \hat{oldsymbol{eta}} + oldsymbol{Z} \hat{oldsymbol{b}}$
- ► The residuals $\hat{\epsilon} = \mathbf{y} \hat{\mu}$ are examined to check assumptions about ϵ .
- $\hat{\mathbf{b}}$ is examined to check the random effects assumptions. Note that if $\mathbf{b} \sim N(\mathbf{0}, \psi_{\theta})$ then $\sqrt{\psi_{\theta}^{-1}}\mathbf{b} \sim N(\mathbf{0}, \mathbf{I})$. Standardizing $\hat{\mathbf{b}}$ in the same way is a help when model checking.

Mixed models in R

- Three R packages provide the mixed modelling methods described above.
- Recommended package nlme provides function lme for Linear Mixed Modelling. It is particularly useful when the random effects have a nested structure.
- Recommended package bundle MASS provides a function glmmPQL for fitting generalized linear mixed models using PQL, based on iterative calls to lme.
- Doug Bates' package lme4 provides functions lmer (glmer) for fitting (generalized) linear mixed models. In the generalized case Laplace approximation is used.

lme

- nlme provides linear mixed model functions for R.
- ▶ The linear mixed model fitting function is lme.
- Ime is used in a similar way to lm.
 - A model formula specifies the response (on the left) and the fixed effects model structure (on the right).
 - A data argument is used to pass a data frame containing the data to be modelled.
 - A fitted model object is returned
 - But the random effects model must also be specified
 - ► A model formula, or list of model formulae, specifies the random effects model structure.

lme mixed model form

Ime assumes that your data are grouped and that you want the following model for the ith group.

$$\mathbf{y}_i = \mathbf{X}_i \boldsymbol{\beta} + \mathbf{Z}_i \mathbf{b}_i + \boldsymbol{\epsilon}_i, \quad \mathbf{b}_i \sim \mathcal{N}(\mathbf{0}, \boldsymbol{\psi}_{\theta}), \quad \boldsymbol{\epsilon}_i \sim \mathcal{N}(\mathbf{0}, \boldsymbol{\Lambda}).$$

where the \mathbf{b}_i are independent between groups.

- Note what varies with group (e.g. b_i), and what does not (i.e. θ, β and Λ).
- Λ is often Iσ², but it may have a more complicated structure, to allow residual correlation within groups.
- The model is a special case of the general model considered thus far.
- ▶ If we have just one group then the general model is recovered.

Calling lme

- Because of the assumed model structure, two parts must be supplied for the random effects specification.
 - 1. A grouping factor (or factors) indicating how the data are divided into groups.
 - 2. A model formula (or formulae) specifying the random effects model matrix for each group.
- ► For example (assuming *x* and *z* are not factors)

lme(y^x+z,dat,^z|g)

fits the model, $\mathbf{b} \sim N(\mathbf{0}, \mathbf{I}\sigma_b^2)$ and

$$y_i = \beta_0 + \beta_1 x_i + \beta_2 z_i + b_j z_i + \epsilon_i \text{ if } g_i = j.$$

Specifying random model

```
An alternative to
    lme(y<sup>x</sup>+z,dat,<sup>z</sup>|g)
is
    lme(y<sup>x</sup>+z,dat,list(g=<sup>z</sup>))
```

- In both cases the *formula*, ~z, specifies the random effect model matrix used at each level of the *grouping factor*, g.
- Nested groups are supported. e.g. ~z+x/g/f would repeat the same random effects structure at each level of g and each combination of levels of g and f.
- list(g=~z+x,f=~z+x) does the same, but also allows
 different random effects structures at each grouping level.

Simple example:Rail

- 6 Railway rails were each tested 3 times, by sending an ultrasonic pulse along the rail, and measuring the time it takes.
- Data are in data frame Rail, which contains variables Rail ID and travel time.
- A suitable model has a random effect for each rail and a fixed overall mean travel time, so that,

 $y_i = \beta + b_j + \epsilon_i$ if y_i relates to rail j. **b** ~ $N(\mathbf{0}, \mathbf{I}_6 \sigma^2)$.

In lme terms Rail is the grouping factor. Exercise: write out the model for rail i in standard lme form. The model for the i^{th} rail is simply

$$\mathbf{y}_i = \begin{bmatrix} 1\\1\\1 \end{bmatrix} \begin{bmatrix} eta \end{bmatrix} + \begin{bmatrix} 1\\1\\1 \end{bmatrix} \begin{bmatrix} b_i \end{bmatrix} + \boldsymbol{\epsilon}_i$$

where $b_i \sim N(0, \sigma_b^2)$ and the components of ϵ_i are i.i.d. $N(0, \sigma^2)$. β , σ_b^2 and σ^2 are the parameters to be estimated.

Fitting the Rail model

```
> library(nlme)
> rm <- lme(travel~1,Rail,list(Rail=~1))</pre>
> rm
Linear mixed-effects model fit by REML
  Data: Rail
  Log-restricted-likelihood: -61.0885
  Fixed: travel ~ 1
(Intercept)
       66.5
Random effects:
Formula: ~1 | Rail
        (Intercept) Residual
           24.80547 4.020779
StdDev:
Number of Observations: 18
Number of Groups: 6
```

summary(rm)

Confidence intervals: intervals

> intervals(rm) Approximate 95% confidence intervals Fixed effects: ## beta lower est. upper (Intercept) 44.33921 66.5 88.66079 Random Effects: ## sigma_b Level: Rail lower est. upper sd((Intercept)) 13.27434 24.80547 46.35341 Within-group standard error: ## sigma lower est. upper 2.695007 4.020779 5.998747

predict method for lme

predict method similar to that for lm, but

- no se argument.
- can control the level at which to predict

> predict(rm) ## default highest level: use E(b|y) for all b 54.10852 54.10852 54.10852 31.96909 31.96909 31.96909 84.50894 84,50894 84,50894 95,74388 95,74388 95,74388 50,14325 50,14325 50.14325 82.52631 82.52631 82.52631

Loblolly pine example

- Loblolly data frame contains height of a number of Loblolly pine trees at different ages.
- We expect some tree-to-tree variability from a mean growth trajectory, plus auto-correlation for within tree measurements.
- A possible model is

$$\begin{split} \texttt{height}_{ji} &= \beta_0 + \beta_1 \texttt{age}_{ji} + \beta_2 \texttt{age}_{ji}^2 + \beta_3 \texttt{age}_{ji}^3 \\ &+ b_0 + b_{j1} \texttt{age}_{ji} + b_{j2} \texttt{age}_{ji}^2 + b_{j3} \texttt{age}_{ji}^3 + \epsilon_{ji} \end{split}$$

the ϵ_{ji} are zero mean normal random variables, with within tree correlation given by $\rho(\epsilon_{j,i}, \epsilon_{j,i-1}) = \phi$. **b**_j ~ $N(0, \psi)$

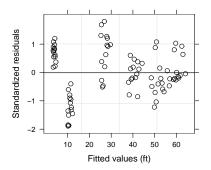
Fitting problems

The lme optimizer sometimes fails, but the situation can usually be rectified by changing some of the control parameters for optimization, via e.g.

lme(...,control=lmeControl(msMaxIter=100,niterEM=1000))

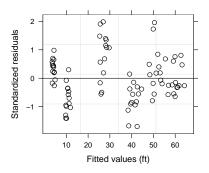
- msMaxIter controls the maximum number of Newton iterations used in MLE or REML.
- niterEM controls the number of EM algorithm steps used to find initial values for θ, before using Newton's method.
 Non-convergence can often be eliminated by increasing this, but other failures may require it to be reduced (especially errors mentioning MEEM or NaNs).
- ▶ For a full list of control constants see ?lmeControl.
- It can also help to experiment with starting values for parameters.

Fitting the Loblolly model



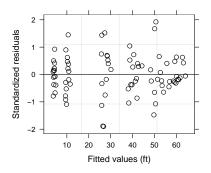
Try again...

```
m1<-lme(height ~ age + I(age^2) + I(age^3)+ I(age^4),
Loblolly,random=list(Seed=~age+I(age^2)+I(age^3)),
correlation=corAR1(-.5,form=~age|Seed),control=lmc)
plot(m1)
```



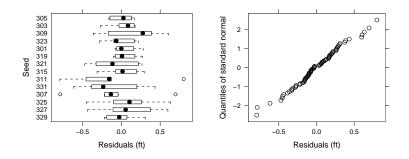
Improved Loblolly model

```
m2<-lme(height~age+I(age^2)+I(age^3)+I(age^4)+I(age^5),
Loblolly,random=list(Seed=~age+I(age^2)+I(age^3)),
correlation=corAR1(-.5,form=~age|Seed),control=lmc)
plot(m2)
```



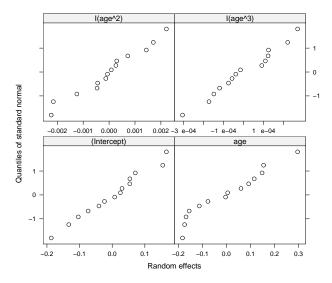
More model checking

plot(m2,Seed~resid(.))# any pattern in resid vs. tree?
qqnorm(m2,~resid(.)) # are resids normal?



qqnorm(m2, ~ranef(.))# now check random effects?

Checking random effects, b



Is autocorrelation needed?

- AIC and hypothesis testing both strongly support retention of the autocorrelation model.
- Question: are the GLRT assumptions met for this test?

Simpler random effects structure?

```
> m4 <- lme(height ~ age + I(age^2) + I(age^3)+
+ I(age^4)+ I(age^5),Loblolly,control=lmc,
+ random=list(Seed=~age+I(age^2)),
+ correlation=corAR1(-.1,form=~age|Seed))
> anova(m4,m2)
Model df AIC BIC logLik Test L.Ratio p-value
m4 1 14 253.8 286.8 -112.9
m2 2 18 239.4 281.8 -101.7 1 vs 2 22.4004 2e-04
```

- AIC and hypothesis testing both suggest that the cubic tree specific effect is needed in the model.
- Question: are the GLRT assumptions met in this case?

Simpler random effects correlation?

We have assumed that ψ_θ can be any positive definite matrix. Let's try a simple diagonal structure, for ψ_θ...

```
> m5<-lme(height~age+I(age^2)+I(age^3)+
+ I(age^4)+I(age^5),Loblolly,random=
+ list(Seed=pdDiag(~age+I(age^2)+I(age^3))),
+ correlation=corAR1(-.5,form=~age|Seed),control=lmc)
> anova(m5,m2)
Model df AIC BIC logLik Test L.Ratio p-value
m5 1 12 293.71 321.99 -134.85
m2 2 18 239.36 281.78 -101.68 1 vs 2 66.35 <.0001</pre>
```

- AIC and GLRT both imply that the diagonal covariance matrix is insufficient.
- Question: are the GLRT assumptions met here?

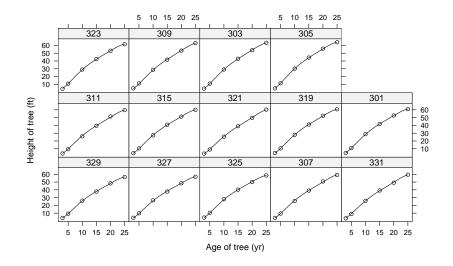
Follow up?

- We can test things about the fixed effects (conditional on \u00f8) as follows:
 - > anova(m2)

| | numDF | denDF | F-value | p-value |
|-------------|-------|-------|----------|---------|
| (Intercept) | 1 | 65 | 41.528 | <.0001 |
| age | 1 | 65 | 9957.451 | <.0001 |
| I(age^2) | 1 | 65 | 656.343 | <.0001 |
| I(age^3) | 1 | 65 | 51.842 | <.0001 |
| I(age^4) | 1 | 65 | 361.458 | <.0001 |
| I(age^5) | 1 | 65 | 69.200 | <.0001 |

intervals and a summary of the selected model, m2, would also be examined. Some quite advanced plotting facilities are available in nlme, for example: plot(augPred(m2))

Loblolly fit



lme4:lmer

▶ Use of lmer is easier than lme.

One formula specifies the model. Terms of the form (x|g) indicate random effects: g is a grouping factor; x determines the random effect model matrix for each level of g.

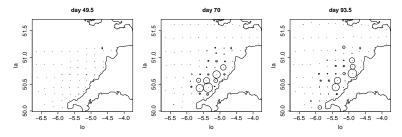
```
Here's the Rail example again
  > lmer(travel~(1|Rail).data=Rail)
  Linear mixed model fit by REML
  Formula: travel ~ (1 | Rail)
     Data: Rail
           BIC logLik deviance REMLdev
     AIC
   128.2 130.8 -61.09
                        128.6
                                122.2
  Random effects:
                    Variance Std.Dev.
   Groups
            Name
   Rail
        (Intercept) 615.311 24.8055
   Residual
                         16.167
                               4.0208
  Number of obs: 18, groups: Rail, 6
  Fixed effects:
```

```
Estimate Std. Error t value (Intercept) 66.50 10.17 6.539
```

glmmPQL

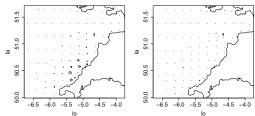
- PQL estimation of GLMMs is available in the glmmPQL routine in the MASS library.
- Use of glmmPQL is very similar to use of lme, except that a family argument is now needed.
- glmmPQL operates by iteratively calling lme, and returns the final fitted model object returned by lme, at convergence.
- The PQL iterations are not guaranteed to converge, and the routine may fail.

Bristol Channel Sole Eggs





day 140.5



Sole Egg Model

- Observe egg densities, y_{ij} in 4 distinct age classes at each of several sampling stations at 5 times of year.
- Want to know rate of spawning, and total number of eggs spawned.
- > y_{ij} is observed density for stage j at sampling station i, then

$$\mathbb{E}(y_{ij}|b_i) = \Delta_{ij}R(\mathrm{lo}_i, \mathrm{la}_i, t_i)e^{-\delta(t_i)a_{ij}}b_i.$$

R is spawning rate at (lo_i, la_i, t_i); δ is mortality rate; Δ_{ij} is the jth age class duration, while a_{ij} is the mid-point age of the class. The log(b_i) are i.i.d. N(0, σ²_b) random effects for sampling station.

Linearized Sole Egg Model

• The model is linearized by a log link.

 $\log\{\mathbb{E}(y_{ij}|b_i)\} = \log(\Delta_{ij}) + r(\mathrm{lo}_i, \mathrm{la}_i, t_i) - \delta(t_i)a_{ij} + \log(b_i)$

where $r = \log R$.

- r can modelled using a cubic in lo_i, la_i and t_i, and -δ modelled using a quadratic in time.
- Assume $\operatorname{var}(y_{ij}|b_i) \propto \mathbb{E}(y_{ij}|b_i)$
- Then the model has the structure of a GLMM, and can be estimated by glmmPQL.

Sole data preparation

The data are available in data frame sole, in the gamair package. Some manipulation is needed first:

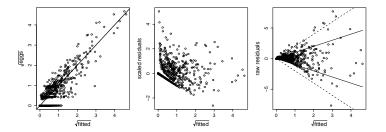
Sole model fitting

Here is the command to fit the model, in full horrible detail

Now we need residual plots...

Sole residuals

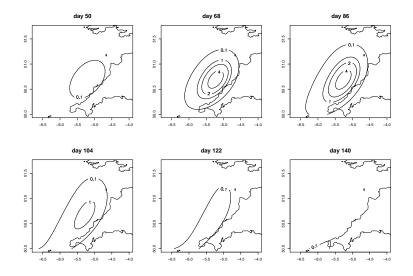
```
fv <- exp(fitted(b4)+solr$off) # note need to add offset
resid <- solr$egg-fv  # raw residuals
plot(fv^.5,solr$eggs^.5);abline(0,1,lwd=2)
plot(fv^.5,resid/fv^.5)
plot(fv^.5,resid)
fl<-sort(fv^.5)
## add 1 s.d. and 2 s.d. reference lines
lines(fl,fl);lines(fl,-fl);lines(fl,2*fl,lty=2);lines(fl,-2*fl,lty=2)</pre>
```



Model selection

- We can base model selection on backward selection using summary(b).
- Can also use anova(b,type="marginal"), which is more useful if the model has factor variables, as it gives p-values for whole term removal.
- Actually only 4 terms get dropped from b in this way.
- Can also look at CI for σ_b^2

Spawning rate predictions



lme4: glmer

- glmer fits GLMMs by Laplace approximation.
- It is just like lmer, except that the exponential family and link function are supplied by a glm style family argument.
- The fit of the sole model would look like this

... but it is not clear that quasi really works with Laplace approximate fitting!

Moving on

- Notice how cumbersome the specification of the Sole egg model was.
- Time for GAMs!