

Beyond GLMs: Mixed-effects models

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Questions about yesterday?



A typical workflow

- 1) Collect data
- 2) Fit a model
- 3) Check assumptions
- 4) Perform inference
- 5) Write article

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Outline

- ▶ GLMs assume independence
- ▶ Mixed-effects models for clustered observations

"Technicalities"



- ▶ We can formulate the same models
- ▶ But now, effects are from a distribution
- ▶ This allows us to incorporate correlation

Recap Likelihood: independence

$$\mathcal{L}(\mathbf{y}; \Theta) = \prod_i^n f(y_i; \Theta) \quad (1)$$

We just multiply! (assumes independence)

Our new likelihood

$$\mathcal{L}(\mathbf{y}; \Sigma) = \int \prod_i^n f(y_i | \mathbf{u}) f(\mathbf{u}; \Sigma) d\mathbf{u} \quad (2)$$

- ▶ Fixed effects: what we had so far
- ▶ Random effects: new, come from a distribution
- ▶ Mixed effects: contains both

Also notice that we cannot work with the log-likelihood here
 :(

The mixed-effects model

$$g\{E(y|u)\} = \mathbf{X}\beta + \mathbf{Z}u \quad (3)$$

1. Link-function
2. Conditional mean
3. Fixed effects parameter vector
4. Random effects parameter vector

The mixed-effects model

$$g\{E(\mathbf{y}|\mathbf{u})\} = \mathbf{X}\boldsymbol{\beta} + \mathbf{Z}\mathbf{u} \quad (3)$$

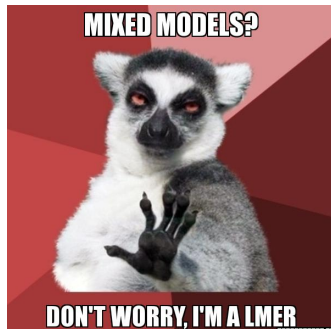
1. Link-function
2. Conditional mean
3. Fixed effects design matrix
4. Random effects design matrix

The random effects design matrix

- ▶ it's the kind of thing as the fixed effects design matrix!

A linear mixed-effects model

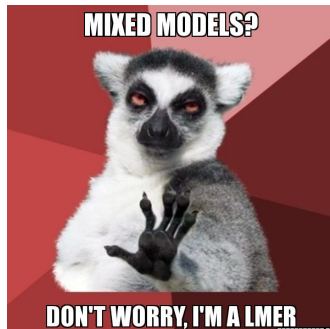
$$E(\mathbf{y}|\mathbf{u}) = \boldsymbol{\mu} \quad (4)$$



A linear mixed-effects model

$$\mathbb{E}(\mathbf{y}|\mathbf{u}) = \boldsymbol{\mu} \quad (4)$$

$$\mathbf{y} = \mathbf{X}\beta + \mathbf{Zu} + \mathbf{e} \quad (5)$$



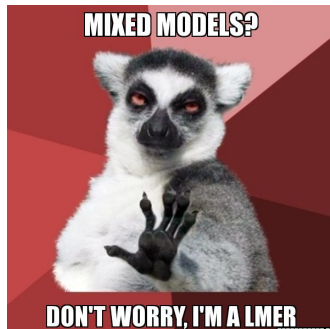
A linear mixed-effects model

$$E(\mathbf{y}|\mathbf{u}) = \boldsymbol{\mu} \quad (4)$$

$$\mathbf{y} = \mathbf{X}\boldsymbol{\beta} + \mathbf{Z}\mathbf{u} + \mathbf{e} \quad (5)$$

with $\mathbf{u} \sim \mathcal{N}(0, \boldsymbol{\Sigma})$

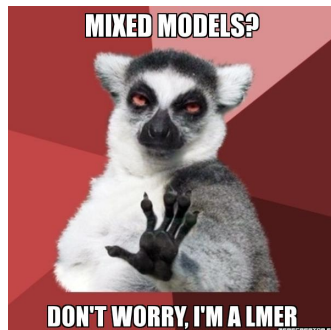
with $\mathbf{e} \sim \mathcal{N}(0, \mathbf{I}\sigma^2)$

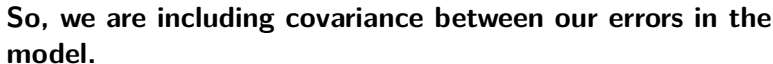


A linear mixed-effects model

We can rewrite the model in terms of the complete error term.

$$\mathbf{y} = \mathbf{X}\beta + \epsilon \quad (6)$$





The objective function

$$\mathbf{y} = \mathbf{X}\beta + \mathbf{Z}\mathbf{u} + \mathbf{e} \quad (7)$$

with $\epsilon = \mathbf{Z}\mathbf{u} + \mathbf{e}$ and $\epsilon \sim \mathcal{N}(0, \mathbf{Z}\Sigma\mathbf{Z}^\top + \mathbf{I}\sigma^2)$

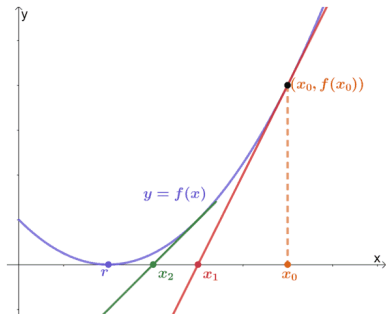
we have the marginal distribution $\mathbf{y} \sim \mathcal{N}(\mathbf{X}\beta, \mathbf{Z}\Sigma\mathbf{Z}^\top + \mathbf{I}\sigma^2)$

This is not how things are done in practice (because the covariance matrix can get quite big!)

- ## Measure of central tendency: Mean or Mode

Fitting

- ▶ Objective function is assumed to be quadratic (often)



- ▶ Usually navigate it with newton's method (numerical optimization)

Recall: Maximum Likelihood Estimation

At the maximum of the likelihood:

- ▶ The gradient is zero (tangent is straight)
- ▶ The hessian (of -LL) should
 - ▶ have positive diagonals
 - ▶ positive eigenvalues
 - ▶ be symmetric
 - ▶ and is thus invertible (we go up in both directions)
- ▶ Asymptotic covariance matrix is given by the inverse of the negative Hessian

These are important concepts to understand error messages and convergence in mixed-models.

There are many R-packages

- ▶ nlme
- ▶ lme4
- ▶ glmmTMB (or glmmADMB)
- ▶ sdmTMB
- ▶ MASS
- ▶ glmmML
- ▶ repeated
- ▶ glmm
- ▶ hglm
- ▶ spaMM
- ▶ gllym
- ▶ mcmcGLMM
- ▶ INLA
- ▶ inlabru
- ▶ MCMC frameworks (JAGS, STAN, NIMBLE, greta)

lme4 and glmmTMB are most commonly used.

lme4 (Bates et al. 2015)

- ▶ Correlation between random effects
- ▶ Sparse matrices
- ▶ Modern matrix algebra libraries
- ▶ Likelihood profiling

But can be fussy about convergence

glmmTMB (Brooks et al. 2017)

- ▶ Correlation between and within random effects (e.g., spatial)
- ▶ Uses state-of-the art AD software (TMB, Kristensen et al. 2015)
- ▶ More supported distribution
 - ▶ E.g. zero-inflation
 - ▶ Double hierarchical GLMs

Specification with formula syntax in R

- ▶ We can think of our model in the same way
 - ▶ Intercepts for categorical covariates
 - ▶ Slopes for continuous covariates
 - ▶ Interactions
- ▶ Now the “parameters” can be correlated
- ▶ With the R syntax we formulate:
 - ▶ The design matrix \mathbf{Z}
 - ▶ The covariance matrix Σ
- ▶ Just as before: intercepts are categorical, slopes for continuous covariates

Random effects R formula

Now some examples of how it works in R. Generally:

$y \sim (\text{continuous and/or categorical} \mid \text{categorical})$

“Nested”:

$y \sim (1 \mid a/b)$ is the same as $y \sim (1 \mid a:b + b)$

“Crossed”:

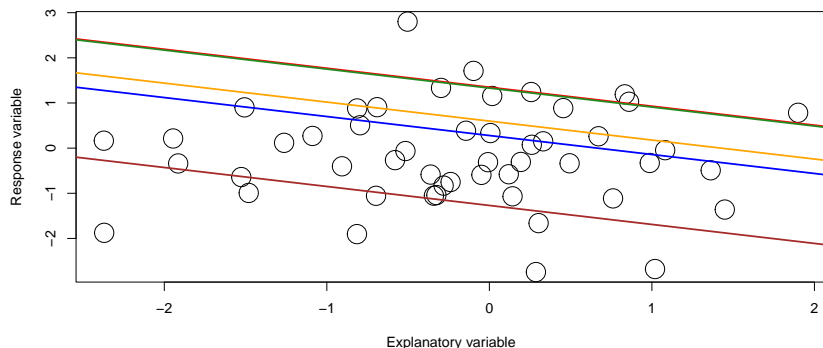
$y \sim (1 \mid a) + (1 \mid b)$

`\textcolor{A few examples next}`

Random intercepts

$$y_{ij} = \mathbf{x}_i \boldsymbol{\beta} + \alpha_j, \quad \text{with } \alpha_j \sim \mathcal{N}(0, \sigma^2)$$

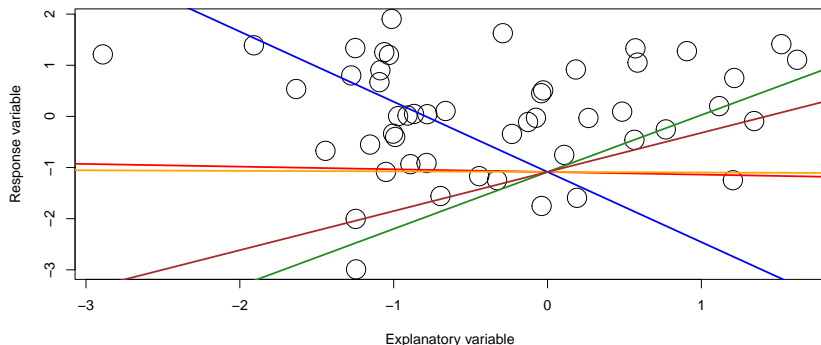
`y ~ fixed effects + (1|random intercept)`



Random slopes

$$y_{ij} = \mathbf{x}_i \boldsymbol{\beta} + z_i u_j, \quad \text{with } u_i \sim \mathcal{N}(0, \sigma^2)$$

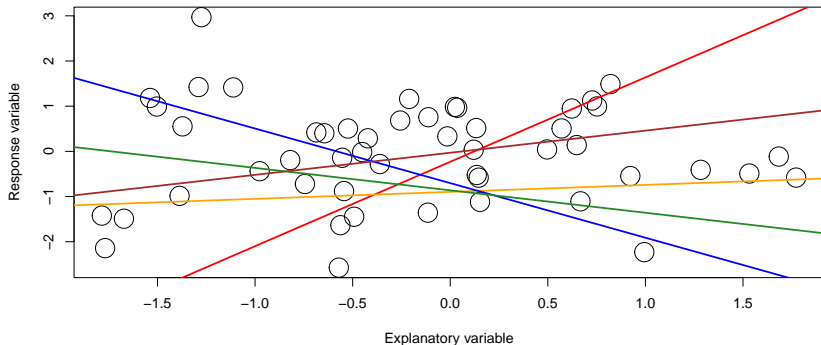
`y ~ fixed effects + (0+random slope|categories)`



Random intercepts and slopes

$$y_{ij} = \mathbf{x}_i \boldsymbol{\beta} + \alpha_j + z_i u_j, \text{ with } \begin{pmatrix} \alpha_j \\ u_j \end{pmatrix} \sim \mathcal{N} \left\{ \mathbf{0}, \begin{pmatrix} \sigma_1^2 & \mathbf{0} \\ \mathbf{0} & \sigma_2^2 \end{pmatrix} \right\}$$

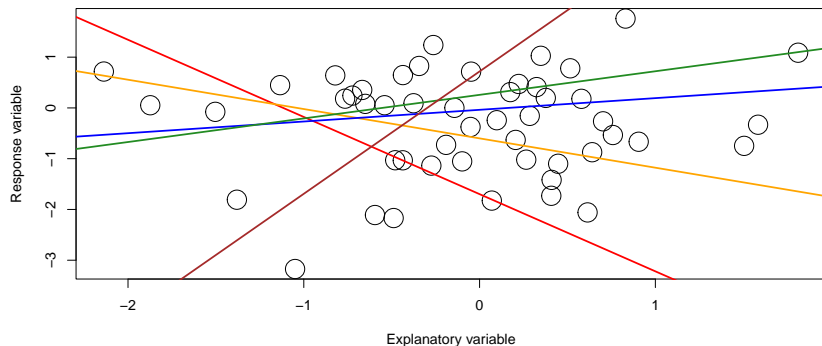
`y ~ fixed effects + (1|random intercept)+(0+random slope|categories)`



Correlated random intercepts and slopes

$$y_{ij} = \mathbf{x}_i \boldsymbol{\beta} + \alpha_j + z_i u_j, \text{ with } \begin{pmatrix} \alpha_j \\ u_j \end{pmatrix} \sim \mathcal{N} \left\{ \mathbf{0}, \begin{pmatrix} \sigma_1^2 & \sigma_{12} \\ \sigma_{21} & \sigma_2^2 \end{pmatrix} \right\}$$

$y \sim$ fixed effects + (random slope | random intercept)



Example: Owls data in glmmTMB

Originally by Roulin and Bersier (2007)

- ▶ Count of begging attempts by chicks
- ▶ Also data on treatments, nest ID, sex of the parent, and broodsize

Nest	FoodTreatment	SexParent	ArrivalTime	SiblingNegotiation
AutavauxTV	Deprived	Male	22.25	4
AutavauxTV	Satiated	Male	22.38	0
AutavauxTV	Deprived	Male	22.53	2
AutavauxTV	Deprived	Male	22.56	2
AutavauxTV	Deprived	Male	22.61	2
AutavauxTV	Deprived	Male	22.65	2
AutavauxTV	Deprived	Male	22.76	18
AutavauxTV	Satiated	Female	22.90	4
AutavauxTV	Deprived	Male	22.98	18
AutavauxTV	Satiated	Female	23.07	0

Example: random intercept in glmmTMB

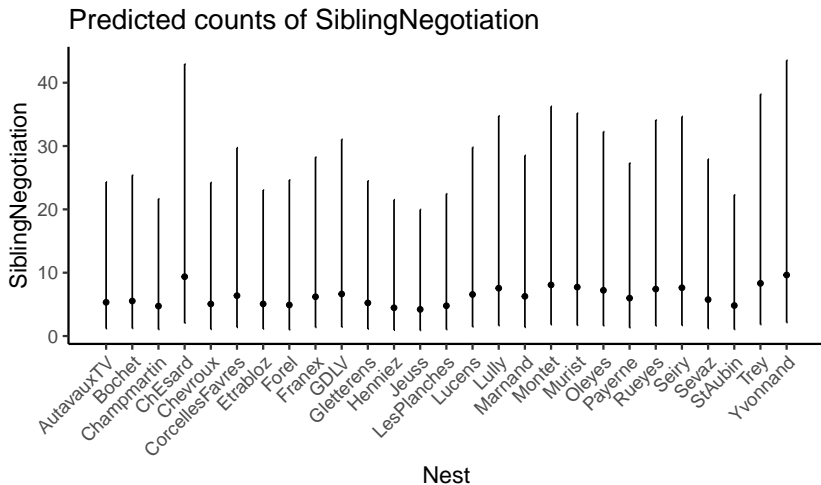
```
## Family: nbinom2 ( log )
## Formula:          SiblingNegotiation ~ (1 | Nest)
## Data: Owls
##
##           AIC           BIC    logLik deviance df.resid
##    3533.1    3546.3   -1763.5    3527.1         596
##
## Random effects:
##
## Conditional model:
##   Groups Name          Variance Std.Dev.
##   Nest   (Intercept) 0.09591   0.3097
## Number of obs: 599, groups: Nest, 27
##
## Dispersion parameter for nbinom2 family (): 0.75
##
## Conditional model:
##           Estimate Std. Error z value Pr(>|z|)
```

Example: extract random effect in glmmTMB

```
ranef(model1)
```

```
## $Nest
##                (Intercept)
## AutavauxTV        -0.154702417
## Bochet            -0.116696108
## Champmartin       -0.273447716
## ChEsard            0.410074693
## Chevroux          -0.205451776
## CorcellesFavres    0.025333070
## Etrabloz          -0.203155670
## Forel             -0.236717059
## Franex            -0.002254524
## GDLV              0.065028688
## Gletterens        -0.173183282
## Henniez           -0.331197524
## Jeuss             -0.390415694
```


Example: plot random effect in glmmTMB



Combining fixed and random effects

Having the same covariate in the fixed and random effects, is equal to having a mean effect, and variation around that

On the previous example: global intercept with nest-specific deviation

We can do this for slopes too (not covered in these examples)

Example: random slopes in glmmTMB

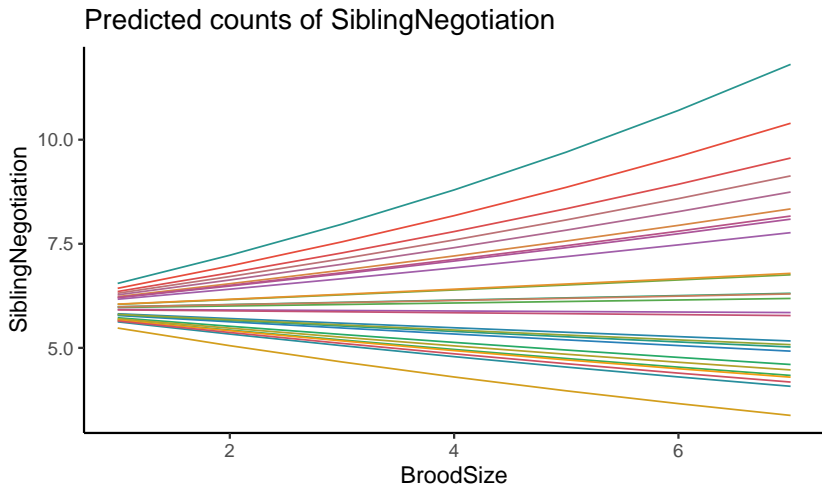
```
## Family: nbinom2 ( log )
## Formula:      SiblingNegotiation ~ (0 + BroodSize | Nest)
## Data: Owls
##
##           AIC           BIC    logLik deviance df.resid
##    3533.2    3546.4   -1763.6    3527.2        596
##
## Random effects:
##
## Conditional model:
##   Groups Name      Variance Std.Dev.
##   Nest   BroodSize 0.004544 0.06741
## Number of obs: 599, groups:  Nest, 27
##
## Dispersion parameter for nbinom2 family (): 0.746
##
## Conditional model:
##           Estimate Std. Error z value Pr(>|z|)
```

Example: extract random effect in glmmTMB

```
ranef(model2)
```

```
## $Nest
##               BroodSize
## AutavauxTV      -0.026764924
## Bochet          -0.019826801
## Champmartin     -0.053656369
## ChEsard          0.098280324
## Chevroux        -0.023913350
## CorcellesFavres  0.008748365
## Etrabloz        -0.036398867
## Forel           -0.044787068
## Franex           0.005923827
## CDLV            0.018460824
```

Example: plot it with ggeffects



Example: random slopes in glmmTMB

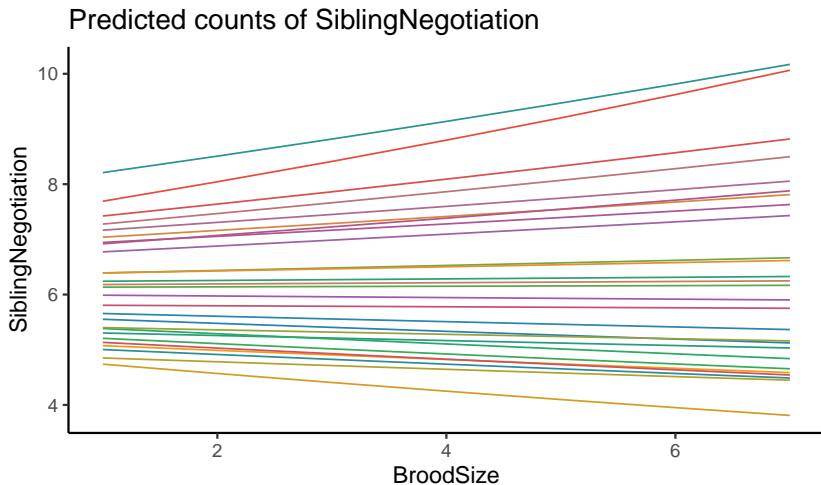
```
## Family: nbinom2 ( log )
## Formula:          SiblingNegotiation ~ (BroodSize || Nest)
## Data: Owls
##
##           AIC           BIC    logLik deviance df.resid
##    3534.8     3552.4   -1763.4    3526.8         595
##
## Random effects:
##
## Conditional model:
##   Groups Name          Variance Std.Dev. Corr
##   Nest   (Intercept)  0.055801  0.2362
##           BroodSize    0.001893  0.0435    0.00
## Number of obs: 599, groups:  Nest, 27
##
## Dispersion parameter for nbinom2 family (): 0.749
##
## Conditional model:
```

Example: extract random effect in glmmTMB

```
ranef(model3)
```

```
## $Nest
##           (Intercept)      BroodSize
## AutavauxTV    -0.078914423 -0.0133831926
## Bochet        -0.064845645 -0.0087978012
## Champmartin   -0.178163213 -0.0181289491
## ChEsard        0.263158987  0.0357035612
## Chevroux      -0.129255881 -0.0087682646
## CorcellesFavres 0.022424439  0.0022817927
## Etrabloz      -0.105057944 -0.0178169040
## Forel         -0.137744812 -0.0186882477
## Franex        0.006561821  0.0008902617
## GDLV          0.041464534  0.0070320206
## Gletterens    -0.112220377 -0.0076126359
## Henniez       -0.212817836 -0.0144368139
## Jeuss         -0.214329310 -0.0363483675
```

Example: plot it with ggeffects



Example: extract random effect in glmmTMB

```
ranef(model4)
```

## \$Nest		
##	(Intercept)	BroodSize
## AutavauxTV	0.043009382	-0.0365814235
## Bochet	-0.151705211	0.0137061099
## Champmartin	-0.576358671	0.0969512834
## ChEsard	0.502738309	-0.0454208954
## Chevroux	-0.514525480	0.0981411962
## CorcellesFavres	0.038313328	-0.0064448173
## Etrabloz	0.056787822	-0.0483006101
## Forel	-0.224348318	0.0202691963
## Franex	-0.014459691	0.0013063896
## GDI V	0.014317234	0.0121774546

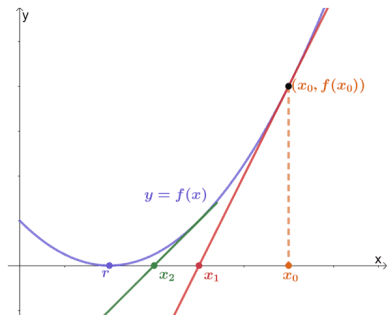
Example: plot it with ggeffects

Convergence



see Ben Bolker's GLMM FAQ, `lme4` page on performance, and the `glmmTMB` troubleshooting vignette

Assessing arrival at the MLE



Assessing arrival at the MLE

1. Stopping criteria

- ▶ Maximum iterations
- ▶ Gradient close to zero
- ▶ Relative criterion: objective function value improvement
- ▶ Absolute criterion: objective function becomes zero (say)

2. Gradient

3. Hessian

lme4 warnings: hessian

- ▶ Warning: Problem with Hessian check (infinite or missing values?)
- ▶ Warning: Hessian is numerically singular: parameters are not uniquely determined
- ▶ Warning: Model failed to converge: degenerate Hessian with 2 negative eigenvalues
- ▶ Warning: Model is nearly unidentifiable: very large eigenvalue - Rescale variables?
- ▶ Warning: Model is nearly unidentifiable: very large eigenvalue ratio - Rescale variables?

Singular matrix

- ▶ determinant is zero
 - ▶ has zero eigenvalue(s)
- ▶ does not have inverse

$$\mathbf{HA} = \mathbf{I} \quad (8)$$

Numerical optimisation: best practices

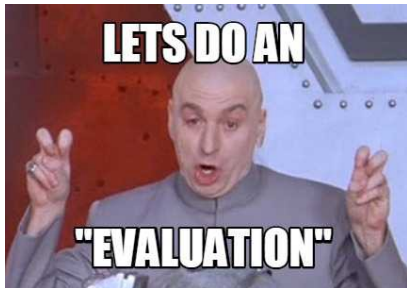
1. Standardise (center and scale) explanatory variables
2. Try different optimisation routines
3. Different starting values
4. Rethink your model

Mixed-effects model troubleshooting

see [Ben Bolker's GLMM FAQ](#)

- ▶ check data for mistakes
- ▶ check model formulation
 - ▶ correct distribution and link-function
 - ▶ few random effects levels
 - ▶ few (non-zero) observations in a category
 - ▶ overly complex: drop terms with zero variances
- ▶ double-check hessian calculation (finite differences)
- ▶ use random effect as fixed effect
- ▶ 'convergence' (and see the last line "convergence issues" for large datasets)

Assumption checking



Residuals

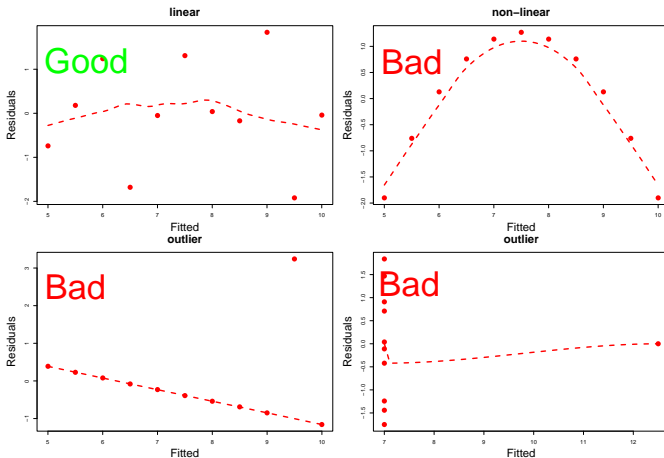
$$\mathbf{y} = \mathbf{X} + \mathbf{Zu} + \mathbf{e} \quad (9)$$

↑
 Residual



Violated residual assumptions mean that some or all of your model's results are untrustworthy.

Residual diagnostics: residuals vs. fitted



GLMM residuals

Conditional

$$g\{E(y_{ij}|x_i)\} = \hat{\alpha} + \hat{\beta}x_i + z_i\hat{u}_j \quad (10)$$

Unconditional

$$g\{E(y_{ij}|x_i)\} = \hat{\alpha} + \hat{\beta}x_i \quad (11)$$

How do we calculate the residual?

- ▶ should we condition on the predicted random effect?
- ▶ simulate from conditional distribution?

i.e. a range of options

Simulation: grouping of errors

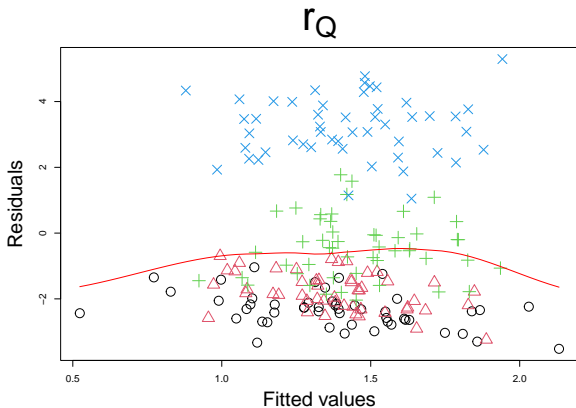
```

n <- 200
ngroups <- 4
alpha <- 0.5
beta <- -1
x <- rnorm(n, sd = 0.2)

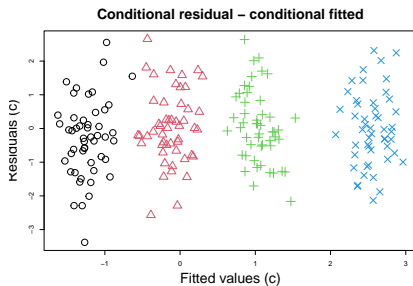
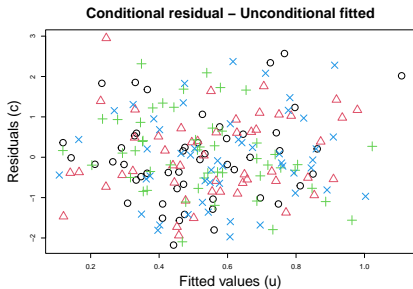
fac<-rep(1:ngroups,each=n/ngroups)
e <- seq(from=-2,to=2,length.out=ngroups)
mu <- exp(alpha + beta*x + e[fac])
y <- rpois(n = n, lambda = mu)

```


Example: Poisson residuals (grouping)



Residual diagnostics: Poisson residuals (grouping)



GLMM: checking random effect assumptions

- ▶ random effect is a type of residual
- ▶ \hat{u}_j is an estimate of the mean or mode of $p(u_j|y_i)$
- ▶ we treat \hat{u}_j as a sample of the random effect distribution
- ▶ so we check assumptions (marginal normality, constant variance, independence, no outliers)!
- ▶ difficult with small number of groups
- ▶ needs to be done for every random effect

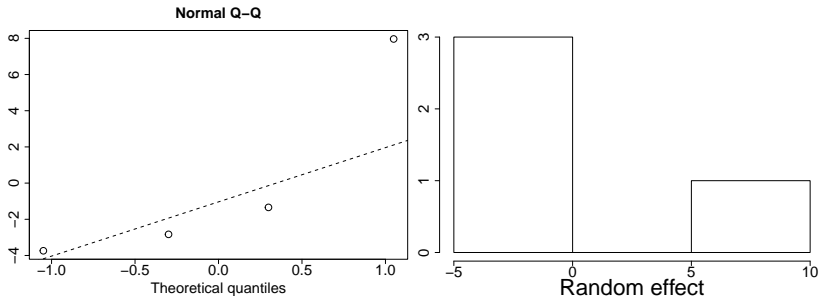
Simulation: GLMM (outlier)

```

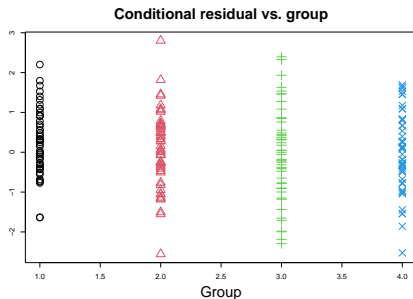
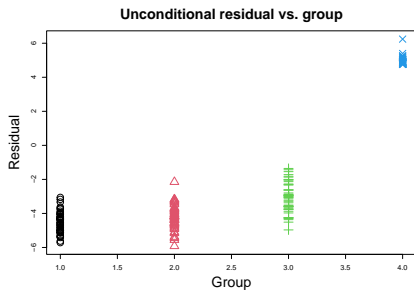
n <- 200
ngroups <- 4
alpha <- 0.5
beta <- -1
x <- rnorm(n, sd = 0.2)

fac<-rep(1:ngroups,each=n/ngroups)
e <- seq(from=-2,to=2,length.out=ngroups)
e[4] <- 10
mu <- exp(alpha + beta*x + e[fac])
y <- rpois(n = n, lambda = mu)

```



GLMM diagnostics



What if constant variance is violated

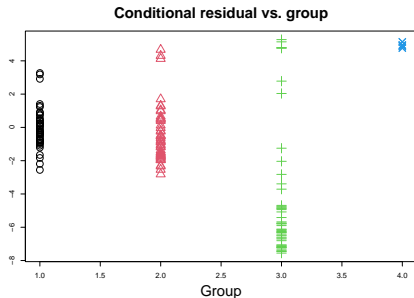
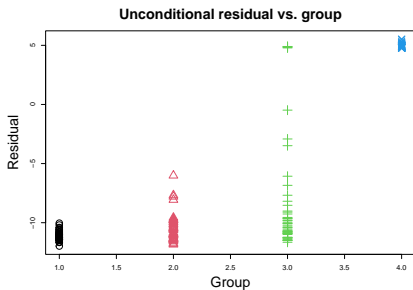
```

n <- 200
ngroups <- 4
alpha <- 0.5
beta <- -1
x <- rnorm(n, sd = 0.2)

fac<-rep(1:ngroups,each=n/ngroups)
e <- seq(from=-2,to=2,length.out=ngroups)
e[4] <- 10
e2 <- MASS::mvrnorm(1,rep(0,n), diag(rep(c(1,2,3,4),
                                         each=n/ngroups)))
mu <- exp(alpha + beta*x + e[fac] + e2)
y <- rpois(n = n, lambda = mu)

```

GLMM diagnostics



Residual checking for mixed-models

- ▶ Check assumptions
 - ▶ Use both conditional and marginal residuals
 - ▶ Have a look at the [DHARMA vignette](#)
- ▶ Correct violations

Violation of some assumptions might be OK

Inference

We have a good model!

Inference

We have a good model!

Now we want to do inference

- ▶ Hypothesis tests (t-test, LRT)/ P-values
- ▶ Model-selection (e.g., with AIC; Akaike 1973)
- ▶ Et cetera (R^2).



me cleaning
the data

me building
a model

Next crisis

1. Estimate
2. Truth

$$t = \frac{\hat{\beta} - \beta}{\sqrt{\sigma^2}}$$

(12)

Next crisis

1. Estimate $\sim \mathcal{N}(\beta, (\mathbf{X}^\top \mathbf{X})^{-1} \sigma^2)$

2. Truth

$$t = \frac{\boxed{\hat{\beta}} - \boxed{\beta}}{\sqrt{\sigma^2}} \sim \mathcal{N}(0, \mathbf{X}^\top \mathbf{X})^{-1} \sigma^2 \quad (12)$$

Next crisis

1. Estimate $\sim \mathcal{N}(\beta, (\mathbf{X}^\top \mathbf{X})^{-1} \sigma^2)$

2. Truth

$$t = \frac{\hat{\beta} - \beta}{\sqrt{\hat{\sigma}^2}} \sim \mathcal{N}(0, \mathbf{X}^\top \mathbf{X})^{-1} \sigma^2 \quad (12)$$

Next crisis

1. Estimate $\sim \mathcal{N}(\beta, (\mathbf{X}^\top \mathbf{X})^{-1} \sigma^2)$
2. Truth

$$t = \frac{\boxed{\hat{\beta}} - \boxed{\beta} \sim \mathcal{N}(0, \mathbf{X}^\top \mathbf{X})^{-1} \sigma^2}{\sqrt{\hat{\sigma}^2} \sim \sigma^2 \chi_{n-r}^2} \quad (12)$$

Next crisis

1. Estimate $\sim \mathcal{N}(\beta, (\mathbf{X}^\top \mathbf{X})^{-1} \sigma^2)$

2. Truth

$$t = \frac{\hat{\beta} - \beta \sim \mathcal{N}(0, (\mathbf{X}^\top \mathbf{X})^{-1} \sigma^2)}{\sqrt{\hat{\sigma}^2 \sim \sigma^2 \chi_{n-r}^2}} \sim t_{n-r} \quad (12)$$

Next crisis

1. Estimate $\sim \mathcal{N}(\beta, (\mathbf{X}^\top \mathbf{X})^{-1} \sigma^2)$

2. Truth

$$t = \frac{\hat{\beta} - \beta}{\sqrt{\hat{\sigma}^2 \sim \sigma^2 \chi_{n-r}^2}} \sim t_{n-r} \quad (12)$$

- P-value (probability for the absolute value of the statistic to take on this, or a more extreme, value)

Next crisis

1. Estimate $\sim \mathcal{N}(\beta, (\mathbf{X}^\top \mathbf{X})^{-1} \sigma^2)$

2. Truth

$$t = \frac{\hat{\beta} - \beta}{\sqrt{\hat{\sigma}^2 \sim \sigma^2 \chi_{n-r}^2}} \sim t_{n-r} \quad (12)$$

- ▶ P-value (probability for the absolute value of the statistic to take on this, or a more extreme, value)
- ▶ Degrees of freedom concept in (G)LMMs is unclear and subject to ongoing debate
- ▶ Unless in the simplest (balanced and uncorrelated) case

DF approximation

- ▶ as implemented in e.g., the `lmerTest` R-package

$$\hat{\sigma}^2 = \frac{\boldsymbol{\epsilon}^\top \boldsymbol{\epsilon}}{n - r} \quad (13)$$

- ▶ i.i.f. $\boldsymbol{\epsilon} \sim \mathcal{N}(0, \sigma^2 \mathbf{I})$, $RSS/\sigma \sim \chi_{n-r}^2$
 - ▶ $F = \frac{\boldsymbol{\epsilon}^\top \boldsymbol{\epsilon}/n_1}{\boldsymbol{\epsilon}_2^\top \boldsymbol{\epsilon}_2/n_2} \sim F_{n_1, n_2}$
- ▶ Otherwise approximate df
 - ▶ Satterthwaite (1941)
 - ▶ Kenward-Roger (1997)
 - ▶ REML only
- ▶ Performance is questionable
- ▶ Can always resort to asymptotics (Wald tests)

$$\sqrt{z} = \frac{\hat{\beta} - \beta}{\sigma} \sim \mathcal{N}(0, 1)$$

Information criteria

- ▶ Not clear which measure of AIC works best (it depends)
- ▶ As usual beware model selection bias (Freedman's paradox)
- ▶ Generally proceed with caution

Take away tips

No free lunch in statistics

Take away tips

No free lunch in statistics

- ▶ Scale your predictors
- ▶ Carefully consider the model structure
- ▶ Keep your model as simple as possible, but not simpler
- ▶ Different packages have different benefits
 - ▶ glmmTMB vs. lme4
- ▶ Try not to -blindly- assume approximations perform well
- ▶ Always check (residual) assumptions
- ▶ Be pragmatic
- ▶ Consult a statistician

Write article?

- ▶ Be pragmatic (but not too much)
- ▶ Do not rely on P-values (they're mostly useless anyway)
- ▶ Report a single (full) model (if possible, see convergence)
 - ▶ Alternatively, describe your modeling procedure
 - ▶ Use information criteria e.g., to compare two competing (non-nested) hypotheses
- ▶ Nakagawa R^2 for mixed models (also approximation)

Focus on estimates (effect sizes) and statistical uncertainty

End



That's all Folks!