

mixed models: challenges and frontiers

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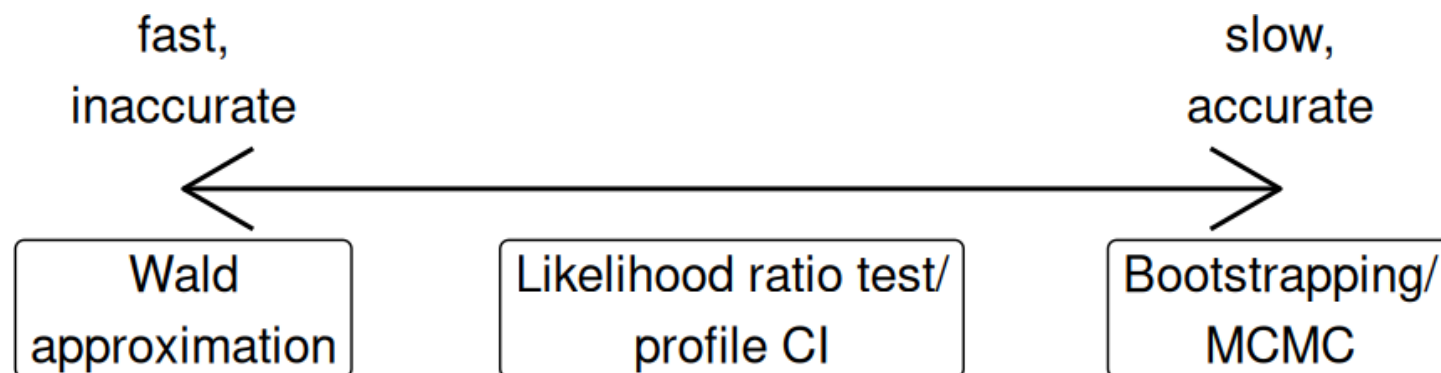
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Inference details

Confidence intervals/ p -values



- easy methods work better as number of observations *and* number of clusters grow
- easy methods better for fixed effects than for RE variances

Wald approximation: hypothesis tests

- assumes log-quadratic likelihood surface (exact for linear models)
- output of `summary()` (and `car::Anova()`, `afex::anova()`)
- contrasts/post-hoc tests: `emmeans`
- especially unreliable for random-effects (co)variances/correlations
- confidence intervals: `confint(., method = "Wald")` (fixed only)

Degrees of freedom

- account for uncertainty in variance estimation (Z vs t)
- matters when number of groups is 'small' (<50?)
- level-counting: `nlme::lme()`, `R/calcDenDF.R`
- `lmerTest/afex`; Satterthwaite:

##	Estimate	Std. Error	df	t value	Pr(> t)
## (Intercept)	251.04	8.72	12.12	28.80	1.6e-12
## Days	9.69	2.09	12.26	4.63	0.00055

- Kenward-Roger: only applicable to REML fits (LMMs?); also adjusts variances

##	Estimate	Std. Error	df	t value	Pr(> t)
## (Intercept)	251.04	8.72	11.99	28.79	2e-12
## Days	9.69	2.10	11.86	4.62	0.00061

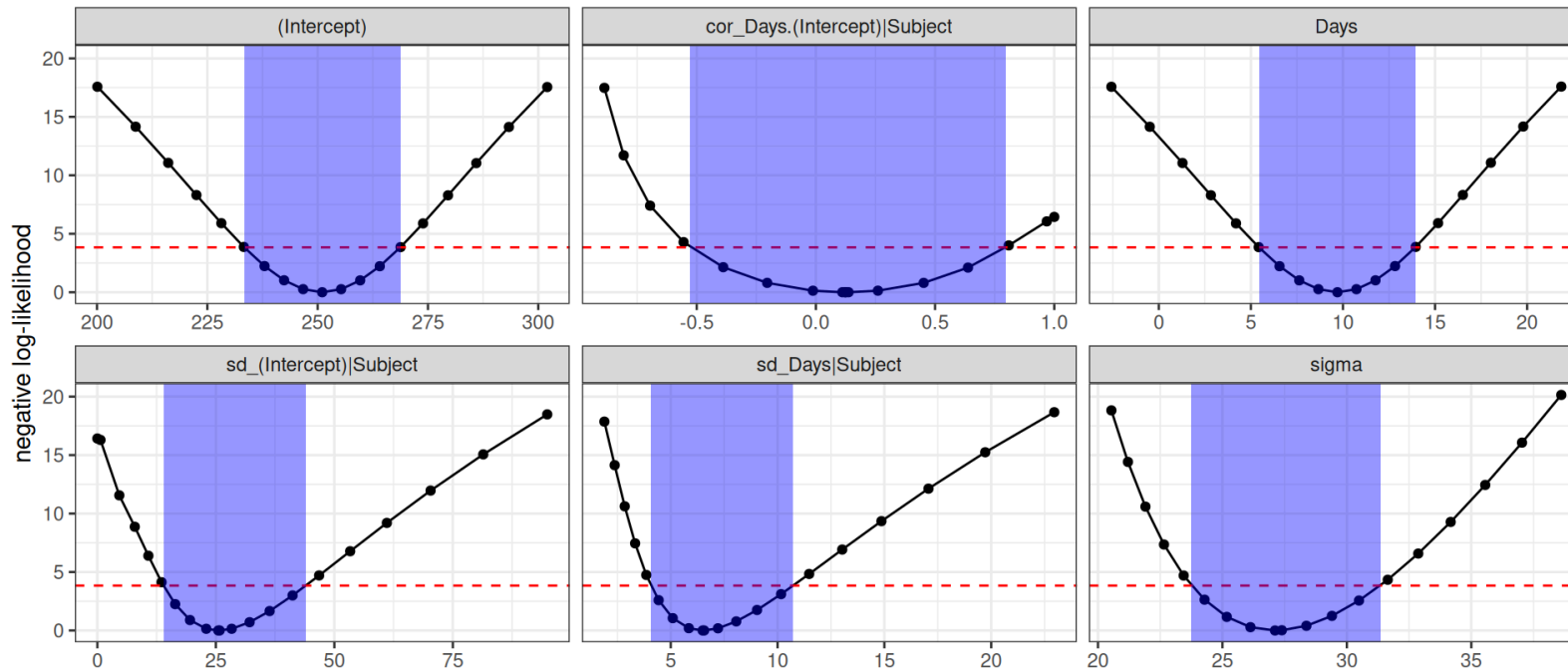
Likelihood ratio test/profile confidence intervals

- individual parameters: `profile()`, `confint()`
- fit pairwise models and use `anova()` to compare
- `drop1, afex::anova()`

##	2.5 %	97.5 %
## sd_(Intercept) Subject	13.934	43.987
## cor_Days.(Intercept) Subject	-0.528	0.796
## sd_Days Subject	4.072	10.732
## sigma	23.757	31.341
## (Intercept)	233.352	268.740
## Days	5.433	13.929

Likelihood profiles

Why did `confint()` take so long?



Likelihood ratio tests of variances are problematic

- theory of LRT fails when H_0 is “on the boundary”
- e.g. testing whether variance is 0
- simplest cases, conservative (p -vals are 2X nominal)
- do you really need to hypothesis-test random effects?
- bootstrapping ...

Bootstrap

- Thai et al. (2013)
- *nonparametric*: resampling with replacement (`lmeresampler` package)
- straightforward for nested models
- hard for crossed models: *nonparametric* bootstrapping
 - simulate from fitted model, refit, extract estimates
 - `confint(., method = "boot")`, `bootMer()`, `pbkrtest` package
- slow! (some methods are parallelized)
- estimate CIs on any quantity, e.g. ratios of variances

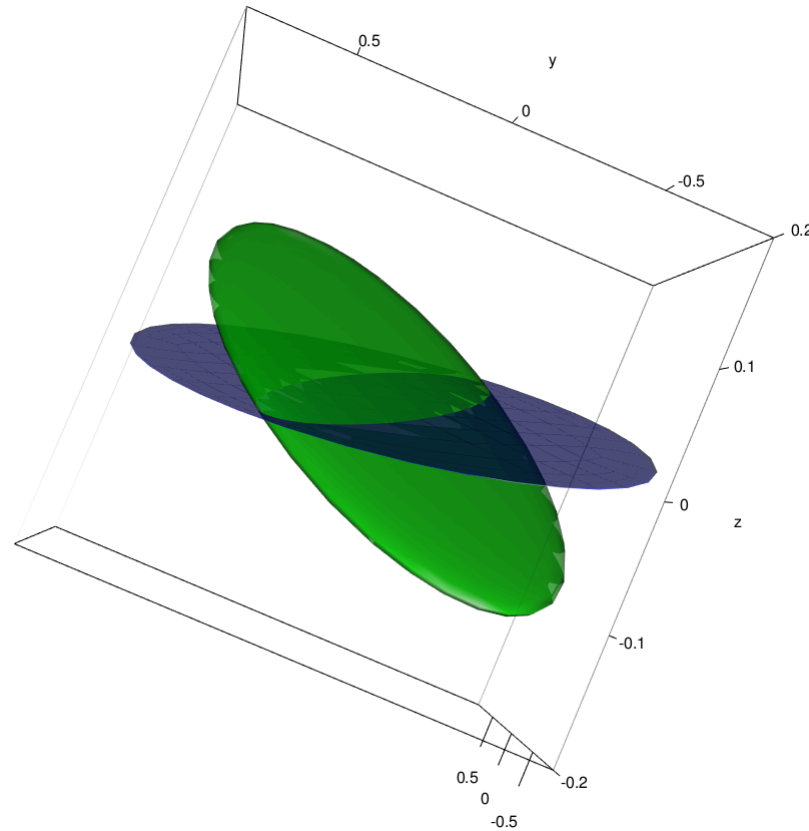
Predictive simulation

- `simulate()` new data from fitted model
- parameters fixed at best estimates (unlike nonpar bootstrap)
- can either use 'estimated' conditional modes or draw new random values
- does *not* include parameter uncertainty

Troubleshooting

What is a “singular fit”?

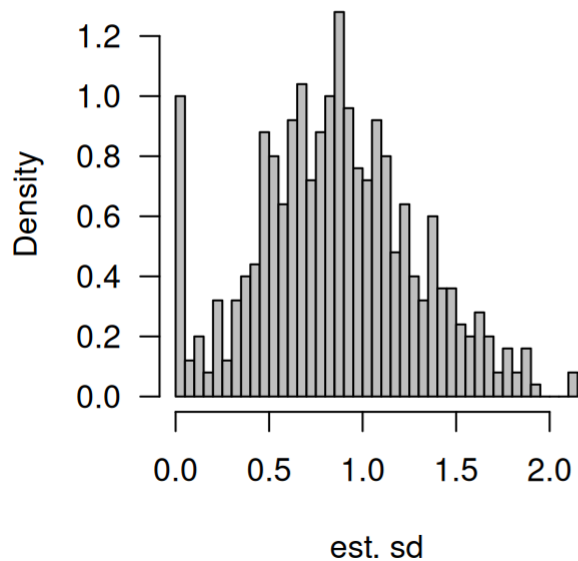
- non-positive-definite covariance matrix
- zero variance (simple case)
- ± 1 correlation (next simplest case)
- hard to recognize in the general case!
- some linear combination(s) of random-effect variables have zero variance



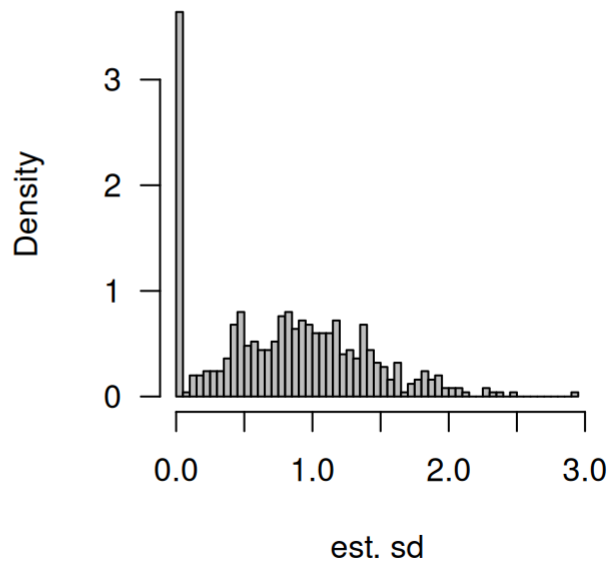
Why are fits singular?

Essentially, because the *observed* among-group variation is less than the *expected* among-group variation $\left(= \frac{\sigma_{\text{among}}^2 + \sigma_{\text{within}}^2}{n}\right)$. More generally, because *some* dimension of the variance-covariance matrix has zero extent ...

sd=1,res.sd=1,5 groups



sd=1,res.sd=1,3 groups



What to do about singular fits?

- ignore them, or drop terms
- switch from random to fixed effects
- regularize/add priors
- simplify the model
- full Bayesian treatment

Ignoring/dropping terms

- Zero variances/singular fits *are not a mistake*; they're the best fit to the data
- Dropping a (full) singular term gives the same results/predictions/etc.
 - It does narrow confidence intervals (if using profile CIs)

Switch from random to fixed effects

- especially for top-level clusters with few levels
- admit you can't estimate the variance (RE variance $\rightarrow \infty$)
 - more conservative than dropping/pooling (RE variance = 0)
- e.g. *Arabidopsis*: region (3) / population (9) / genotype (24), use `~ reg + (1 | (reg:population)/genotype)`

Regularize/add priors

- Bayesians don't care about singular fits (they look at the whole posterior distribution, not just the MLE/mode)
- quasi-Bayesian approach: *regularize*
- add a penalty (== prior) to keep estimates away from zero/boundaries
- Chung et al. (2013): add a weak prior that prevents singularity
- `blme`, `glmmTMB` + prior specification
- regularization useful in other cases (e.g. complete separation in logistic models)

Simplifying random effect terms

- drop some varying effects
 - e.g. random intercepts and slopes → random intercepts only
- set correlations among parameters to zero (diagonal covariance matrix)
- set all correlations among parameters equal (*compound symmetric* model)
- *reduced rank* models

Simplifying covariance matrices

- Suppose factor **f** (5 levels) varies within groups **g**
- $(1+f|g): (n(n+1))/2 = (5 \times 6)/2 = 15$ parameters)

$$\begin{bmatrix} \sigma_{\{g|1\}}^2 & \cdot & \cdot & \cdot & \cdot \\ \sigma_{\{g|1\},\{g|f_{21}\}} & \sigma_{\{g|f_{21}\}}^2 & \cdot & \cdot & \cdot \\ \sigma_{\{g|1\},\{g|f_{31}\}} & \sigma_{\{g|f_{21}\},\{g|f_{31}\}} & \sigma_{\{g|f_{31}\}}^2 & \cdot & \cdot \\ \sigma_{\{g|1\},\{g|f_{41}\}} & \sigma_{\{g|f_{21}\},\{g|f_{41}\}} & \sigma_{\{g|f_{31}\},\{g|f_{41}\}} & \sigma_{\{g|f_{41}\}}^2 & \cdot \\ \sigma_{\{g|1\},\{g|f_{51}\}} & \sigma_{\{g|f_{21}\},\{g|f_{51}\}} & \sigma_{\{g|f_{31}\},\{g|f_{51}\}} & \sigma_{\{g|f_{41}\},\{g|f_{51}\}} & \sigma_{\{g|f_{51}\}}^2 \end{bmatrix}$$

Sum-to-zero contrasts

- change from *treatment* to *sum-to-zero* contrasts
- coefficients are means of each level, not baseline/differences from baseline

$$\begin{bmatrix} \sigma_{\{g|f_1\}}^2 & \cdot & \cdot & \cdot & \cdot \\ \sigma_{\{g|f_1\},\{g|f_2\}} & \sigma_{\{g|f_2\}}^2 & \cdot & \cdot & \cdot \\ \sigma_{\{g|f_1\},\{g|f_3\}} & \sigma_{\{g|f_2\},\{g|f_3\}} & \sigma_{\{g|f_3\}}^2 & \cdot & \cdot \\ \sigma_{\{g|f_1\},\{g|f_4\}} & \sigma_{\{g|f_2\},\{g|f_4\}} & \sigma_{\{g|f_3\},\{g|f_4\}} & \sigma_{\{g|f_4\}}^2 & \cdot \\ \sigma_{\{g|f_1\},\{g|f_5\}} & \sigma_{\{g|f_2\},\{g|f_5\}} & \sigma_{\{g|f_3\},\{g|f_5\}} & \sigma_{\{g|f_4\},\{g|f_5\}} & \sigma_{\{g|f_5\}}^2 \end{bmatrix}$$

Complex random intercepts (Scandola et al. 2024)

- replace $(1+f|g)$ with $(1|g/f)$

$$\Sigma = \begin{bmatrix} \sigma^2 & . & . & . & . \\ \rho\sigma^2 & \sigma^2 & . & . & . \\ \rho\sigma^2 & \rho\sigma^2 & \sigma^2 & . & . \\ \rho\sigma^2 & \rho\sigma^2 & \rho\sigma^2 & \sigma^2 & . \\ \rho\sigma^2 & \rho\sigma^2 & \rho\sigma^2 & \rho\sigma^2 & \sigma^2 \end{bmatrix}$$

- where $\sigma^2 = \sigma_f^2 + \sigma_g^2$, $\rho = \frac{\sigma_g^2}{\sigma^2}$
- $\rho > 0$; all variances identical
- *compound symmetry*: `cs()` (glmmTMB), `corCompSymm` (nlme)

Diagonal covariance matrices

- `(1+x+y+z || b)` or `diag(1+x+y+z | b)`
 - or `(1 | b) + (0+x | b) + ...`
- `lme4` version **only works properly** for continuous predictors
- `afex::mixed` can do this
- contrasts/centering matters!
- n instead of $n(n + 1)/2$ parameters

Reduced-rank covariance matrices

- ‘factor analytic’ or ‘reduced rank’
- d -dimensional covariance matrix in a p -dimensional space
- $\Sigma = \Lambda D \Lambda^\top$ (Λ is the *factor loading matrix*)
- $d \cdot p - \frac{d(d-1)}{2}$ parameters (linear in p)
- available in R: `gllmmTMB`, `sommer`, `lme4breeding`: `ASReml`

Convergence failures

- convergence failures are common
- what do they really mean? how to fix them? when can they be ignored?
- **approximate** test that gradient=0 and curvature is correct
- scale and center predictors; simplify model
- use `?allFit` to see whether different optimizers give sufficiently similar answers
 - `$fixef`, etc.: are answers sufficiently similar?
 - `$llik`: how similar is goodness-of-fit?

Which model to use?

- Barr et al. (2013): “keep it maximal”; reduce until no more convergence failures
- Bates et al. (2015), Matuschek et al. (2017): more parsimony
- R. Kliegl: best non-singular
 - make singular terms diagonal
 - drop elements with small variances
 - try full (unstructured) model with only these elements
- brute-force: non-singular, best AIC (Moritz et al. 2023)
- inspect principal components of covariance matrix? (rePCA)

Structured covariances

Spatial/temporal

- AR1 (autoregressive order-1): correlations $\rho, \rho^2, \rho^3 \dots$ for lagged pairs in space/time
- irregular time/1D space: Ornstein-Uhlenbeck/CAR1 ($\rho = \phi^{-\Delta t}$)
- geostatistical (Gaussian-process) correlation models: exponential, Matérn ...
- glmmTMB, mgcv, INLA, spaMM

Smooth terms

- can use mixed-model/latent-variable frameworks to fit smooth *functional* terms
- additive models (penalized regression): add penalty $\sigma^2 \mathbf{b}^T \mathbf{S} \mathbf{b}$
- exactly equivalent to the random-effects component in a mixed model
- Wahba (1990); Wood (2017); Hefley et al. (2017); Pedersen et al. (2018)
- mgcv, gamm4, glmmTMB

'Old' and 'new' random effects (Hodges 2016)

- do random effects/latent variables represent differences among exchangeable groups ...
- ... or spatial/temporal/functional structure? (Wood 2017)
- prediction/inference: population level or the cluster level (Vaida et al. 2005) ?
- counting parameters?

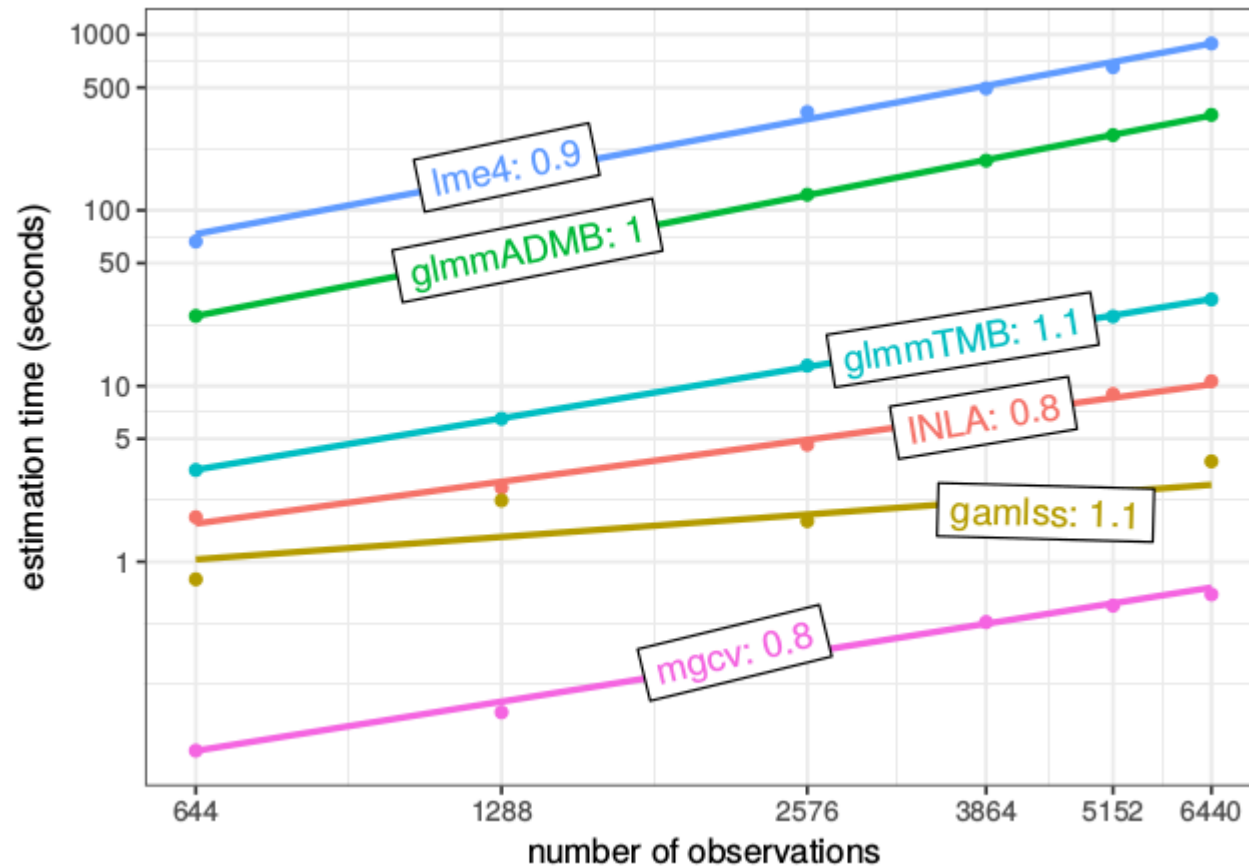
always has been

wait, it's all just quadratic
penalty matrices?

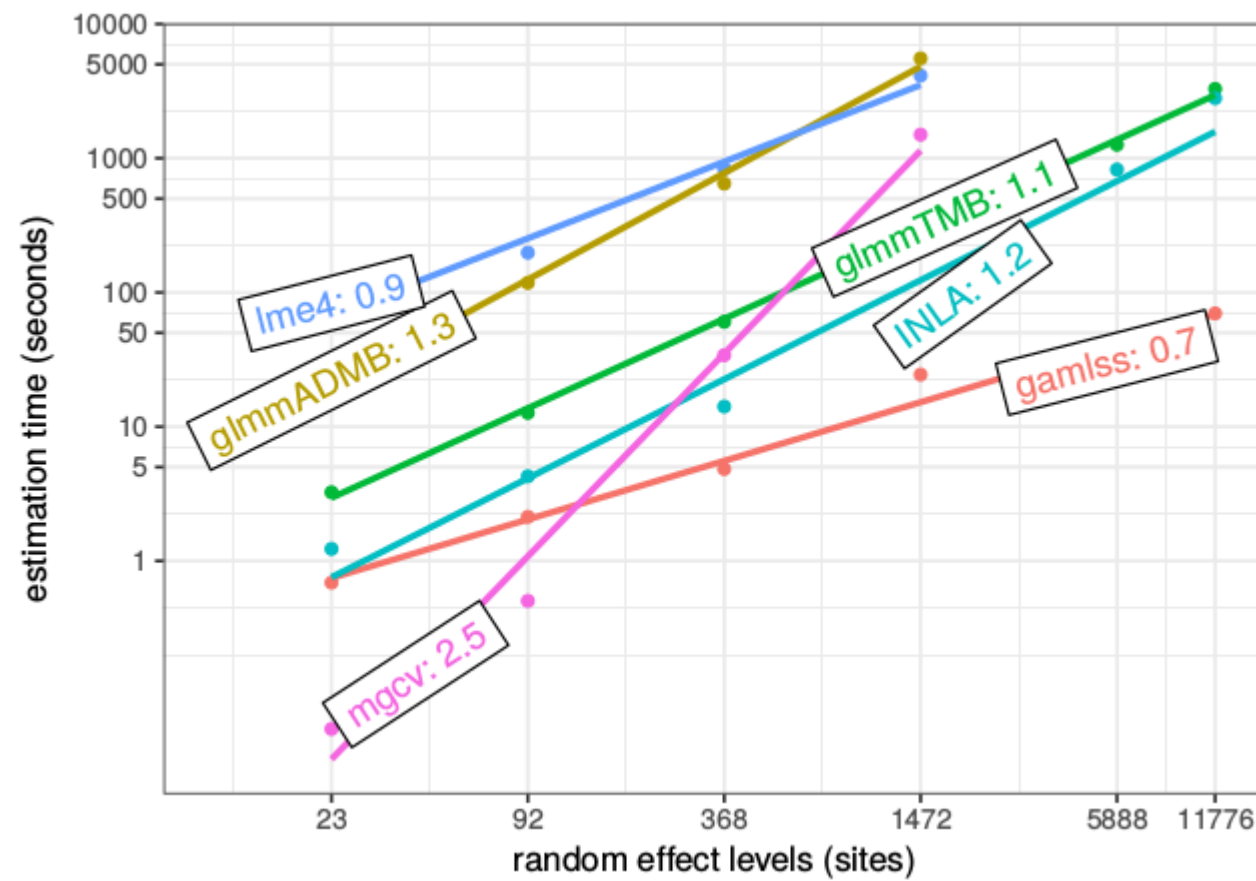
Big data?

The need for speed

Brooks et al. (2017) (negative binomial model)

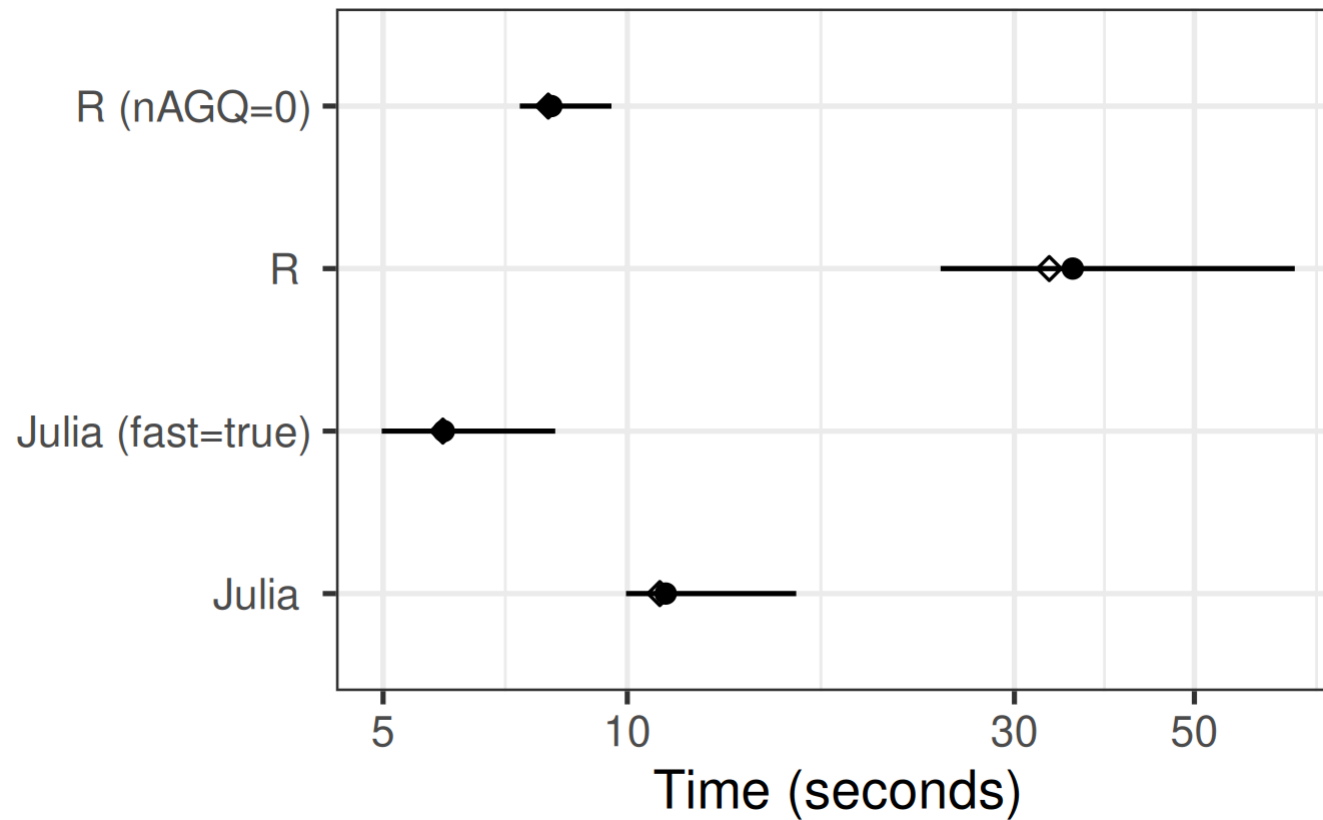


more speed



Julia/R benchmark

- Poisson model, 98K rows/151 groups (Markwick 2022)



Scalable mixed models

- Gao et al. (2020); Ghosh et al. (2022); Bellio et al. (2025)
- $\mathcal{O}(N)$ methods (`lme4` etc. are $\mathcal{O}(N^{3/2})$)
- StitchFix data: 5M observations, 6.3K items, 762K clients

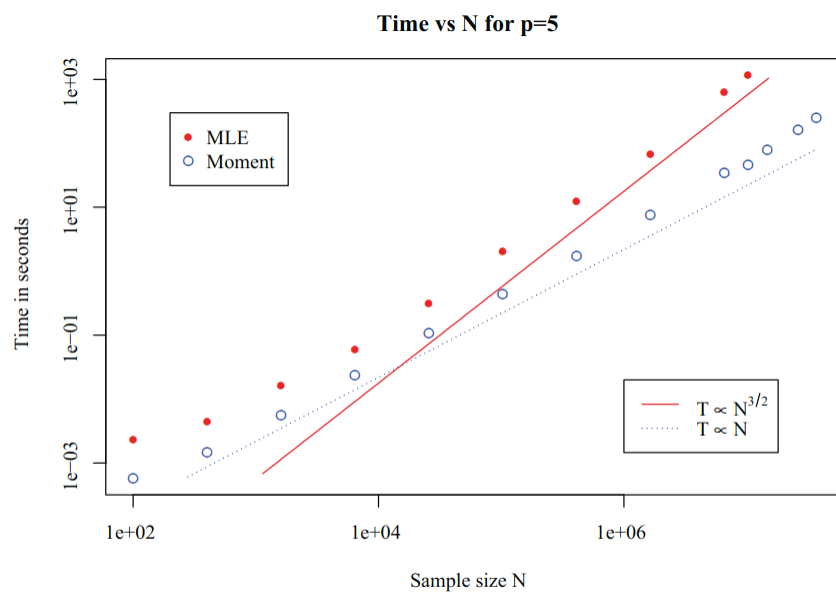


Figure 3. Computational cost for MLE and moments versus sample size N . There are reference lines parallel to $N^{3/2}$ and N^1 .

Challenges and open questions

On beyond lme4

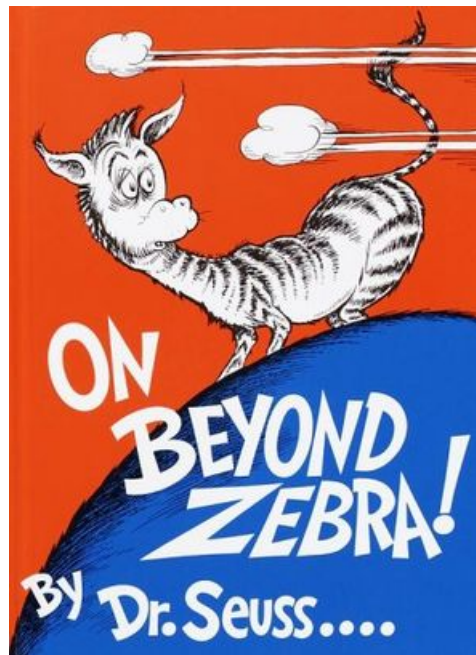
- glmmTMB: zero-inflation, weird conditional distributions
- MCMCglmm, brms, rstanarm: Bayesian
- gllvm: multivariate ecological/phylogenetic data
- INLA: great for spatial and temporal structures
- [rethinking package](#)

Toolboxes

- JAGS (R: `rjags`, `r2jags`)
- TensorFlow (R: `greta`)
- NIMBLE (R: `nimble` package)
- Stan (R: `rstan`)
- TMB (R: `TMB`, `RTMB`)

On beyond R

- Julia: `MixedModels.jl`
- SAS: PROC MIXED, NLMIXED
- AS-Reml
- Stata (GLLAMM, xtmelogit)
- HLM, MLWiN
- Python? (`pymr4`, `statsmodels`)



Package comparison

Capability	lme4	GLMMadaptive	glmmTMB	mgcv	nlme	glmmrBase
Linear mixed models	✓	✗	✓	✓	✓	✓
GLMMs	✓	✓	✓	⚠	✗	✓
Laplace approximation	✓	✗	✓	✓ (PQL)	✓	✓
Gauss-Hermite quadrature	✓ (limited)	✓	✗	✗	✗	✗
Structured covariance (CS/AR1/etc.)	⚠	✗	✓	✓	✓	✓
Space/time covariance	✗	✗	✓	⚠	✓	✓
Heteroscedasticity	✗	⚠	✓	⚠	✓	✓

Challenges

- Small clusters: need AGQ/MCMC
- Small numbers of clusters: need finite-size corrections
- Small data sets: singular fits, model selection
- Ever-expanding (desired) feature matrix; downstream ecosystems
- Big data: speed!

references

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extras

R^2

- goodness-of-fit measures for LMMs, and for GLMMs, are hard
- meanings of R^2 (variance explained; $\text{corr}(\text{obs}, \text{predicted})^2$; etc. don't coincide
- *pseudo- R^2* for GLMs (MacFadden, Nagelkerke, etc.)
- various [Jaeger et al. (2017)]
- Nakagawa/Schielzeth/Johnson most popular (Nakagawa et al. 2013; Johnson 2014; Nakagawa et al. 2017)
- (?but what about zero-inflation, new distributions, etc. etc. etc.)

Overdispersion

- “too much” variability (relative to theoretical expectation)
- very serious for fixed-dispersion families (Poisson, binomial)
- conjugate-family distributions (negative binomial, Beta-binomial)
- observation-level random effects (Elston et al. 2001; Harrison 2014; Harrison 2015)
- unidentifiable for binary data (unless groupable), Gaussian data
- little concern for families with estimated scale/dispersion (but see Hilbe (2011))

Zero-inflation

- “many zeros does not mean zero-inflation” (Warton 2005)
- can’t use Vuong test (Wilson 2015; He et al. 2019)
- `glmmTMB` or use expectation-maximization (see [here](#))
- `DHARMa` can test by simulation

Causal inference

- I don't go there very much
- Solve many issues by adding *group mean* as a covariate (Byrnes et al. 2025)
- Awareness of *general* causal issues: DAGs, mediation/confounding, etc..
(McElreath 2015; Franks et al. 2025)

Heteroscedasticity

- can be an issue (especially among groups)
- log transformation (for continuous positive data) often resolves both linearity and heteroscedasticity
- `glmmTMB`, `nlme`
- build into observation-level REs