

Non-linear mixed effect models - part 2

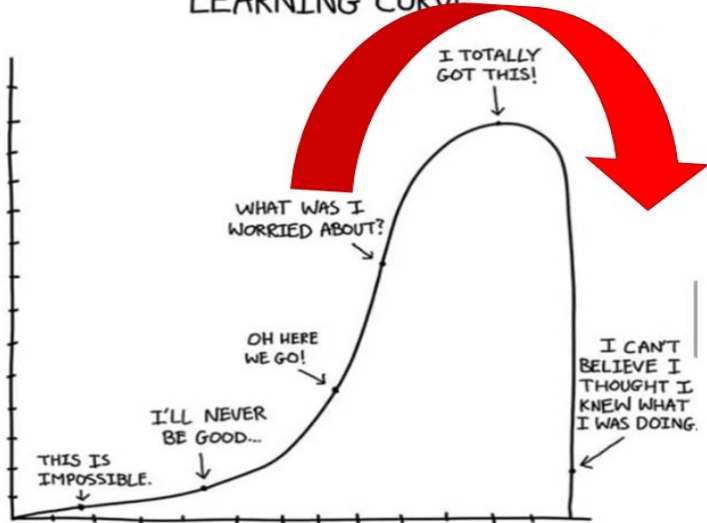
Philip Dixon

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Disclaimer

- These notes, code and recommendations reflect my understanding in late July 2020
- Mixed effect models and meta analysis are active areas of statistical research
 - and (mostly) active areas of code development
- One can use these models for many different purposes
- I can not guarantee that code here is appropriate for your purpose
- Please let me know if something here or in the code is misleading or incorrect.

LEARNING CURVE



Meta analysis and related ideas

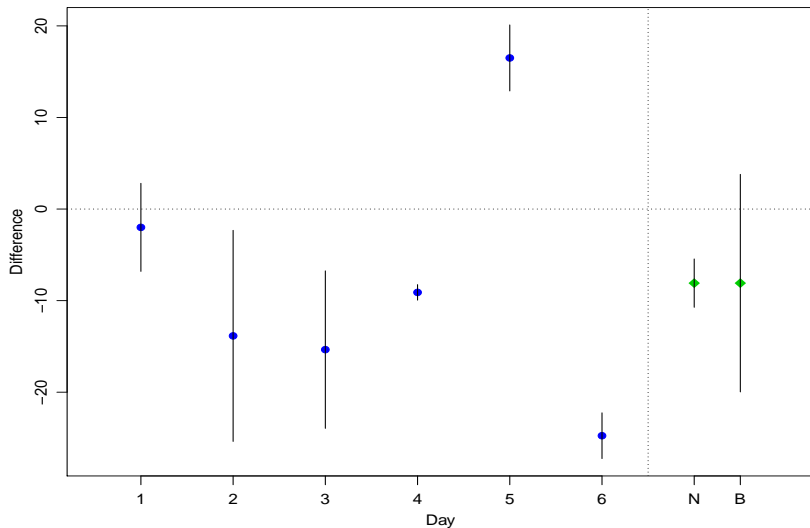
- Reminder: I described NL ME as fitting clusters of data
- Alternate view: each cluster is its own “experiment”
 - Estimate parameters from each cluster separately
 - Probably no partial pooling of estimates
 - Maybe no pooling of error variance
 - But see notes below and code
- Meta analysis, traditional view
 - Multiple studies of the same phenomenon
 - Each gives an estimate (e.g. of treatment effect) and its se
 - Study-specific information
 - What can you conclude from the entire collection of studies?

Example

- Two chemical methods to measure triglyceride concentration in meat samples
- Each day: one piece of meat divided into 4 pieces,
- randomly assigned to method, 2 reps per method
- Repeated on 6 days. 24 observations total
- Analysis for one day, i : t-test $\Rightarrow D_i, s_i$: for each day
 D_i : estimated difference, s_i : se of difference, 2 df for error
- Analysis for all days:

Source	df	
Day	5	
Method	1	
Day*Method	5	
Error	12	(2 df from each day, pooled)
c.total	23	

Example



Meta analysis models

- Fixed effects meta analysis

- Model 1: $D_i = \mu + \varepsilon_i$, $\text{sd } \varepsilon_i = s_i$
- D_i and s_i are results from study i
- s_i is within-study uncertainty, considered known
- Goal is to estimate μ = overall mean difference
- weighted average: $\hat{\mu} = \Sigma_i w_i D_i / \Sigma w_i$ $w_i = 1/s_i^2$
 - Studies with more precise results, smaller s_i , get more weight

- Random effects meta analysis

- Model 2: $D_i = \mu + \tau_i + \varepsilon_i$, $\text{sd } \varepsilon_i = s_i$
 - τ_i is among-study heterogeneity
 - $\text{Var } \tau_i = \sigma_{\text{study}}^2$
 - $w_i = 1/(\sigma_{\text{study}}^2 + s_i^2)$
- MA assumes do not have raw data, just D_i and s_i

Meta analysis models

- MA models look like weighted linear or mixed models
- important practical difference
 - random effect MA model: $D_i = \mu + \tau_i + \varepsilon_i$, $\text{Var } \varepsilon_i = s_i^2$
 - weighted linear mixed model: $D_i = \mu + \tau_i + \varepsilon_i$, $\text{Var } \varepsilon_i = w_i \sigma^2$
 - MA model says the error Var **is** s_i^2
 - wt LMM says the error Var is **proportional** to w_i
also estimate σ^2 .
- SAS can fix value of $\sigma = 1$ so proc mixed / glimmix do MA
- As far as I can know (and I've tried multiple times),
R lme and lmer, can't fix σ
- Need to use a MA-specific package, e.g. metafor

Repeated experiments

- When do have raw data, can fit a linear mixed model to all the data

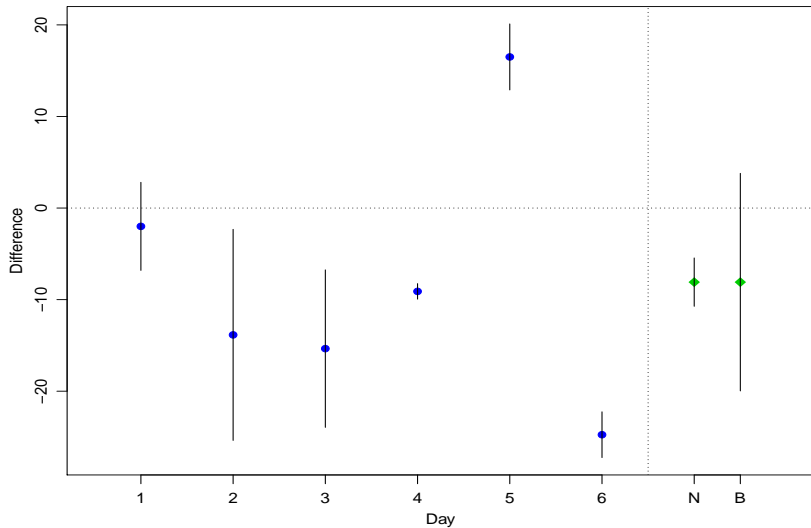
Source	df	
Day	5	Doesn't matter
Method	1	Fixed
Day*Method	5	Fixed or Random
Error	12	
c.total	23	

- Method is fixed because want to estimate the difference
- Inferences about method same for fixed Day or random Day (when balanced)
- Choice for interaction really matters

Narrow and Broad sense inference

- Narrow sense inference:
 - Day*Method: Fixed
 - inference about average method on these 6 days
 - Does not include heterogeneity among days
 - N result on the plot (next slide)
 - Analogous to Fixed effect MA
- Broad sense inference:
 - Day*Method: Random
 - inference about average method on 6 new randomly chosen days
 - Includes heterogeneity among days (treatment*day interaction)
 - B result on the plot
 - Analogous to Random effect MA

Example



Example

- One detail: How method average is computed
 - ANOVA/lme: **equally weighted** average of day estimates
 - Good reasons to do this, but many different opinions
- MA: weighted average based on s_i
 - can compute equally wt. average, est. matches ANOVA results
- Comparison of results

Inference	Difference		s.e.		Notes about MA
	lme	MA	lme	MA	
Narrow	-8.09	-8.09	1.32	1.32	fixed eff.
Broad: lme	-8.09	-8.09	5.94	5.95	separate s_i^2
Broad: lmer	-8.09	-8.09	5.79	5.79	pooled s^2

- Similarity of MA and LME not surprising, but not always the case:
 - Lin & Zheng (2010) *Biometrika* 97:321-332
 - Chen et al. (2020) *Biometrics* online

Why do broad sense results differ?

- My sense (but I'm not 100% certain about everything):
- To simplify things, only consider random interaction and error
Model: $Y_{ij} = \mu + day_i + method_j + md_{ij} [random] + \epsilon_{ij}$
- Fitting slightly different versions of the model
 - lmer: interaction variance affects both treatments
 - lme: interaction variance only affects trt 2 (fixed = 0 for trt 1)
 - Possible that adding a correlation fixes this
 - To me, lme doesn't make sense;
 - does make sense when model is a regression
- I haven't done the checking to verify every interpretation
 - e.g. could fit a heterogeneous variance lme model
 - or different versions of the MA model

Implementing partial pooling to feed MA

- Fit each cluster separately
(no pooling of estimates or error variance)
 - Use a for loop or `apply()` to extract each cluster, estimate separately
- Pool error variance, cluster-specific parameters
 - Use `lmList()`. It pools the error variance.
 - MA se = `lmer se`
- Pool error variance, pool some parameters
 - Fit a model with main effect for pooled parameters
 - and `cluster:parameter` interaction for separate parameters
 - omit parameter main effect so interaction estimates are cluster-specific estimates
 - not differences from reference level

Diagnosis: what model was fit?

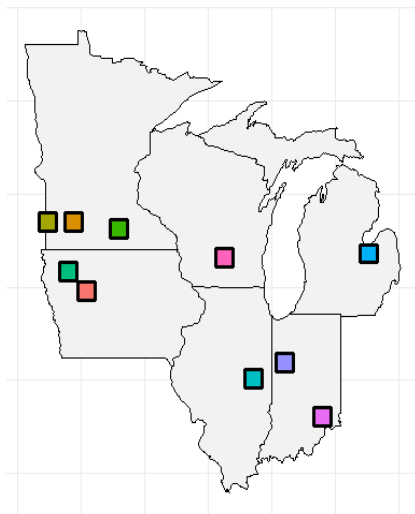
- Look at the coefficients
- if there is a random effect for that parameter, cluster ests. differ
- Compare (3) $Y_{ij} = \mu + \text{day}_i + \text{method}_j + \varepsilon_{ij}$ (random day)
and (4) $Y_{ij} = \mu + \text{day}_i + \text{method}_j + \text{md}_{ij} + \varepsilon_{ij}$ (random day, int)

	Model 3, no int		Model 4, random int	
Day	(Intercept)	method2	(Intercept)	method2
1	148.12	-8.09	145.83	-2.81
2	139.53	-8.09	142.03	-15.10
3	148.72	-8.09	151.40	-14.05
4	150.58	-8.09	150.85	-8.24
5	160.51	-8.09	150.78	16.11
6	139.29	-8.09	145.87	-24.46

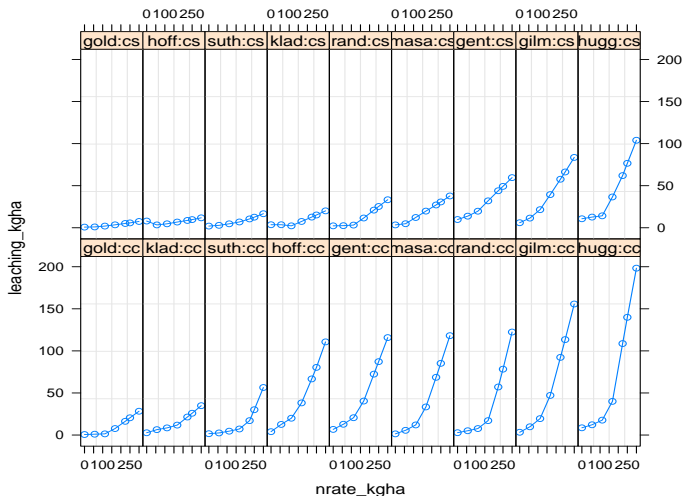
What's next?

- Continue the lfmc example (one site, one species, 3 plots)
 - Goal is to estimate the mean of each NL parameter
 - Last meeting, we looked at lme results
 - lmer results are similar, code in file, will not discuss
 - Look at MA results
 - Look at Bayesian results
- More complicated example, from Gina:
- N leaching (kg/ha) as a function of N fertilizer applied (kg/ha)
 - 9 sites, 20 years, 2 crop rotations at each site/year
 - 7 N rates, same N for all site years.
 - leaching derived from a crop model
- Code in gina.r
 - lfmc example code in nlme.r
 - broad/narrow sense code in test lme.r

Examples: N leaching sites



Examples: N leaching, 2010 data



Examples: N leaching, from Gina

- Goals / questions
 - Choose a non-linear model
 - Estimate difference between cropping systems for each parameter
 - Correlation among parameters?
 - Variation between sites? between years?
 - Which sites have highest year-year variation in leaching?