Modeling categorical longitudinal outcomes: GEEs and GLMMs

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What we will cover....

1. Linear Marginal Models
    - Revision of models for continuous correlated outcomes
    - Residual covariance structures
    - Choice of residual covariance structure
    - Worked example: Linear Marginal Model
2. Modelling other longitudinal outcomes
    - Example of analysis using GEEs
    - Example using GLMMs
3. Exercises LMMs and GLMMs

Linear Mixed Models

Recall (last session) that you were introduced to the **Linear Mixed Model**. This model:

- Deals with continuous correlated outcomes;
- Is conditional (subject-specific) in that the subject effect is modeled EXPLICITLY in the model
- We covered two examples of LMMs:
  - The random **Intercepts** model: Where subjects were allowed their own intercept; and
  - The random **Coefficients** model: Where subjects were allow their own (entire) regression model (i.e. Intercepts and slopes)

Now we are going to cover another approach to modelling continuous outcomes: the **Linear Marginal Model**

Differences between MIXED and MARGINAL model approach

Last session we note that in modeling continuous correlated data we just want to 'deal with' the correlated nature of the data. This is, we extend the standard general linear model:

$$y_{ij} = \beta_0 + \beta_1 X_1 + \beta_2 X_2 + \cdots + \epsilon_{ij}$$

To deal with the correlated data, the linear mixed model and linear marginal models...

$$y_{ij} = \beta_0 + \beta_1 X_1 + \beta_2 X_2 + \cdots + \text{Put something here}$$

The 'something' is quite different between the mixed model approach (which is a 'subject-specific' model), and the marginal model approach (a population averaged approach)

Differences between MIXED and MARGINAL model approach

In the mixed model approach, we EXPLICITLY state the random effects in the model (i.e. Mixed model has both FIXED and RANDOM effects → 'MIXED' (effect) model). So for example the coefficients model we covered last session:

$$Reaction_{ij} = \beta_0 + \beta_{Day} Day + Subject_{i0} + Subject_{Days,i} Days + \epsilon_{ij}$$

In other words we have a SUBJECT-SPECIFIC component of the model. We can say the value of $Reaction_{ij}$ is CONDITIONAL on the subject (in addition to the Day effect). For this reason MIXED models are often called CONDITIONAL models

In contrast, a MARGINAL model just wants to 'average-out' the effect for the entire sample

The marginal model approach

- The basic idea of a marginal model is to 'throw everything into the error'
- This allows marginal models to deal with problem of correlated data
- BUT not all data are the same, the **patterns** of variance (at each time) and covariance (correlation between observations at different times) may vary among studies
- There are several **patterns** (called **Residual (or Error) covariance structures**) available. We consider four:
  1. Independence residual covariance structure
  2. Exchangeable (Compound symmetry) residual covariance structure
  3. Autoregressive 1 (AR1) residual covariance structure
  4. Unstructured residual covariance structure

The Independent residual covariance structure

- Equal variances along main diagonal (homogeneous)
- Zero covariances for off diagonal elements (i.e. repeated values are uncorrelated) ⇒ Variances constant and residuals independent over time
- The standard General Linear Model (linear regression)
- Single parameter estimated: the pooled variance (MSE)

	2yr	3yr	5yr	9yr	13yr
2yr	σ^2	0	0	0	0
3yr	0	σ^2	0	0	0
5yr	0	0	σ^2	0	0
9yr	0	0	0	σ^2	0
13yr	0	0	0	0	σ^2

***using Autism data for example**

In matrix form:

$$R_{indep.} = \begin{bmatrix} \sigma^2 & 0 & 0 & 0 & 0 \\ 0 & \sigma^2 & 0 & 0 & 0 \\ 0 & 0 & \sigma^2 & 0 & 0 \\ 0 & 0 & 0 & \sigma^2 & 0 \\ 0 & 0 & 0 & 0 & \sigma^2 \end{bmatrix}$$

Covariance Structures: Standard cross-sectional general linear model

For longitudinal data:

- The assumption that variance between observation **for each time** is equal (after accounting for treatment differences) is often OK.
- Assumption that repeated observations on a given individual are uncorrelated is VERY unlikely to be valid.
- Therefore, the **Independent residual covariance structure** is probably not a realistic choice

Residual covariance structure → Statistical models

Assuming patterns in residuals can be approximated using an independant error covariance structure is the same as assuming the data are cross-sectional (i.e. Independant)

Covariance Structures: Unstructured

- We can now go to the other extreme and consider a error covariance structure that allows each time to have:
  1. a different variance at each time; and
  2. every between-time correlation (1 vs 2, 1 vs 3, 1 vs 4, 2 vs 3, 2 vs 4 and 3 vs 4 etc) allowed to differ
- This is the same covariance structure used by the RM-MANOVA and is generally expensive (lots of parameters)
  - For example, if we consider 5 time points, so there are 5 (variances) and 10 covariances = 15 parameters being estimated
- However, running an unstructured residual covariance matrix gives us a **sample estimate of the ’true’ residual covariance matrix** (so can be informative regarding the best choice of covariance structure)

Covariance Structures: Unstructured ≈ RM-MANOVA model

- Difference variances on diagonal
- Difference covariances off diagonal
- Variance estimated for each time, covariance for each pair of times
- Most complex structure
- E.g. 5 times→need to estimate 15 parameters

$$R_{unstr} = \begin{bmatrix} \sigma_1^2 & \sigma_{12} & \sigma_{13} & \sigma_{14} & \sigma_{15} \\ \sigma_{21} & \sigma_2^2 & \sigma_{23} & \sigma_{24} & \sigma_{25} \\ \sigma_{31} & \sigma_{32} & \sigma_3^2 & \sigma_{34} & \sigma_{35} \\ \sigma_{41} & \sigma_{42} & \sigma_{43} & \sigma_4^2 & \sigma_{45} \\ \sigma_{51} & \sigma_{52} & \sigma_{53} & \sigma_{54} & \sigma_5^2 \end{bmatrix}$$

Covariance Structures: Compound symmetry

- Compound symmetric (aka **Exchangeable**) residual covariance structure can be thought as a compromise.
- **Like** the 'independence' covariance structure, variances are assumed to be same at different times
- **Unlike** Independent residual covariance structure, observations (over-time) allowed to be correlated.
- BUT level of between-time correlations same regardless of how many time points (amount of time) separate them
- Advantage: Only two parameters in the error covariance structure (one for variances and one for covariance)
- Compound symmetric is the error covariance structure underlies the RM-ANOVA model

Covariance Structures: Compound symmetry $\approx$ RM-ANOVA

- Equal variances-on diagonal
- Equal covariances-off diagonal (equal correlation)
- Simplest structure for repeated measures
- Used for past 50 years(RM-ANOVA)
- Requires estimation of 2 parameters

$$R_{CS} = \begin{bmatrix} \sigma_1 + \sigma^2 & \sigma_1 & \sigma_1 & \sigma_1 & \sigma_1 \\ \sigma_1 & \sigma_1 + \sigma^2 & \sigma_1 & \sigma_1 & \sigma_1 \\ \sigma_1 & \sigma_1 & \sigma_1 + \sigma^2 & \sigma_1 & \sigma_1 \\ \sigma_1 & \sigma_1 & \sigma_1 & \sigma_1 + \sigma^2 & \sigma_1 \\ \sigma_1 & \sigma_1 & \sigma_1 & \sigma_1 & \sigma_1 + \sigma^2 \end{bmatrix}$$

Covariance Structures: First order Autoregressive, AR(1)

- This is also a 2-parameter residual covariance structure
- It differs from compound symmetry in that allows between time correlations to decay as time points get further apart (which seems sensible)
- However, assumes decay rate in correlation follows a particular pattern
- This structure is sensible when time points are equally-spaced (e.g. Baseline, 1 week, 2 weeks, 3 weeks etc)

Covariance Structures: Autoregressive(1)

- Equal variances on diagonal
- Off diagonal represents sd times correlation coefficient raised to increasing powers as the observations become increasingly separated in time.
- Increasing power ⇒ decreasing correlation (as $\rho < 1$).
- Times points should be equidistant
- Estimates 2 parameters (regardless of number of time points)

$$R_{AR(1)} = \begin{bmatrix} \sigma^2 & \rho\sigma & \rho^2\sigma & \rho^3\sigma & \rho^4\sigma \\ \rho\sigma & \sigma^2 & \rho\sigma & \rho^2\sigma & \rho^3\sigma \\ \rho^2\sigma & \rho\sigma & \sigma^2 & \rho\sigma & \rho^2\sigma \\ \rho^3\sigma & \rho^2\sigma & \rho\sigma & \sigma^2 & \rho\sigma \\ \rho^4\sigma & \rho^3\sigma & \rho^2\sigma & \rho\sigma & \sigma^2 \end{bmatrix}$$

Choice of Residual covariance structure

- Many different covariance structures available and we have only covered three viable ones (independence model is not realistic)
- In ideal situations, we can be guided by the study design. For example, are the repeated measures taken at equally spaced times (so AR(1) might be best).
- However, if it is not clear from study design, we have to resort to 'empirical' approaches to gauge the best error covariance structure
- Perhaps the best way to gauge the nature of the TRUE residual covariance structure is to look at the **unstructured** residual covariance structure, as this provides a PICTURE of the real correlation between the observations

Empirical strategies for finding suitable covariance structures

- Two aspect in selecting best covariance structure:
  1. Model fit
  2. Number of parameters (how 'expensive' is it)
- *Information criterion* (IC) statistics commonly used to assess both model fit AND complexity
- Unfortunately, AIC can't be used on models that don't use maximum likelihood (like GEEs), but we can use an alternative measure, QIC

Empirical strategies for finding suitable covariance structures

Approach I use for choosing best (Marginal) model is:

1. Run the model with the unstructured error pattern matrix to get an idea of the 'true' error covariance structure
2. Use the above to try different (other) residisidual covariance structures and gauge their fit (and parsimony) using AIC (for mixed models) or QIC (for GEEs)

The importance of the unstructured error covariance matrix

Fitting a marginal model with the **Unstructured** error covariance matrix gives a pretty good idea of the true pattern of the residual covariance

Comparing models: Unstructured covariance structure

- Won't go into any detail about Linear Mariginal Models(I avoid marginal models) and we'll see them in GEEs
- But, I would like you to better understand how unstructured cov. matrices can be used to gauge 'reality'
- Below is the unstructured covariance matrix(Autism data)

Estimated (**true**) residual covariance structure:

	2yr	3yr	5yr	9yr	13yr
2yr	1.000	0.088	0.021	-0.038	-0.012
3yr	0.088	1.000	0.222	0.135	0.030
5yr	0.021	0.222	1.000	0.643	0.143
9yr	-0.038	0.135	0.643	1.000	0.431
13yr	-0.012	0.030	0.143	0.431	1.000

Comparison of models: Independence

$$R_{Independant} = \begin{bmatrix} 1.000 & 0.000 & 0.000 & 0.000 & 0.000 \\ 0.000 & 1.000 & 0.000 & 0.000 & 0.000 \\ 0.000 & 0.000 & 1.000 & 0.000 & 0.000 \\ 0.000 & 0.000 & 0.000 & 1.000 & 0.000 \\ 0.000 & 0.000 & 0.000 & 0.000 & 1.000 \end{bmatrix}$$

- Treating the Unstructured matrix (last slide as reality).....
- Do you think the Independant error covariance structure is realistic

Comparison of models: Compound symmetry

What about the compound symmetric???

$$R_{CS} = \begin{bmatrix} 1.000 & 0.267 & 0.267 & 0.267 & 0.267 \\ 0.267 & 1.000 & 0.267 & 0.267 & 0.267 \\ 0.267 & 0.267 & 1.000 & 0.267 & 0.267 \\ 0.267 & 0.267 & 0.267 & 1.000 & 0.267 \\ 0.267 & 0.267 & 0.267 & 0.267 & 1.000 \end{bmatrix}$$

Comparison of models: Autoregressive order 1

The Autoregressive(1)

$$R_{AR(1)} = \begin{bmatrix} 1.000 & 0.429 & 0.184 & 0.079 & 0.034 \\ 0.429 & 1.000 & 0.429 & 0.184 & 0.079 \\ 0.184 & 0.429 & 1.000 & 0.429 & 0.184 \\ 0.079 & 0.184 & 0.429 & 1.000 & 0.429 \\ 0.034 & 0.079 & 0.184 & 0.429 & 1.000 \end{bmatrix}$$

Out of the four Error covariance structures which would you pick: 1. Unstructured, 2. Independnant, 3. Compound symetric, 4. AR(1)??????

Is there anything else you would consider?????

Final step: Interpretation of model

After choosing 'best' error covariance structure, we intepret our fixed effects (as with any other model)

Table : Coefficients table from Linear marginal model(AR1)

	Estimate	Std.err	Wald	p-value
(Intercept)	-21.74	3.77	33.30	< 0.001
sicdegp	11.27	1.75	41.30	< 0.001
age	4.55	0.41	125.83	< 0.001

- Highly significant and positive association between sicdegp and VSAE (Those with ↑ expressive language at 2 years old, ended up having ↑ socialization scores)
- Age highly associated with socialization. Each successive observation ⇒ 4.55 point ↑ socialization score

Mixed vs Marginal models

- Why have I wasted so much time on linear marginal model when they aren't often used (esp for continuous longitudinal data)
- Main point: Unlike the Linear Mixed model (last session), I did not present a 'subject-specific' regression lines (recall plots from random coefficients LMM)
- **Why not?** Because **Marginal** models assume effect of correlation is same for everyone; the 'average' within-subject correlation is applied to every subject (hence the name **Population averaged** models)
- In contrast, for **Mixed** Models, within-subject correlation is conditional on (specific to) each individual patient: so aka **Conditional** or **Subject-specific** models

Where now: Other longitudinal outcomes

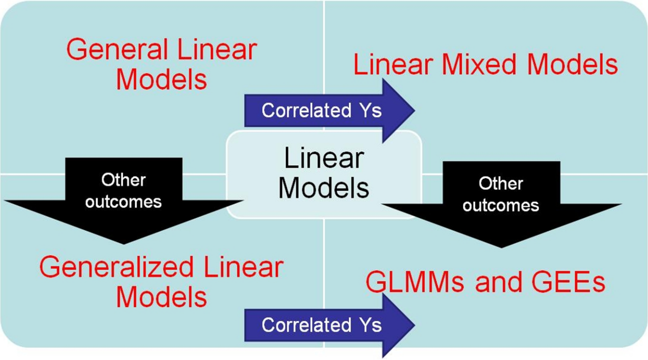
This difference between Marginal (population-averaged) and Mixed (conditional) represents the fundamental difference between the last two methods we will cover: Generalized Estimating Equations (GEEs) and Generalized Linear Mixed Models (GLMMs)

- **GEEs** can be used for categorical longitudinal outcomes (e.g. Binary, Ordinal etc) and represent a **Marginal** model approach (i.e. Population averaging)
- **GLMMs** can be used for categorical longitudinal outcomes (e.g. Binary, Ordinal etc) and represent a **Mixed** model approach (i.e. Conditional, or subject-specific)

There are other subtle differences between GEEs and GLMMs (mathematics used to estimate βs), but I won't go into too much detail about this

Life, the universe and everything

So where do GEEs and GLMMs fit into the universe of (most) biostatistical modelling



Obviously other models out there (e.g. Cox regression), but this far and away accounts for most models used in health and medical research

Coverage of GEEs and GLMMs

- As promised, I am not going too much into the mathematics of GEEs and GLMMs
- I will just present a couple of slides on each, and then we will get to running them in R, and interpreting the results
- Also, I will only focus on binary outcomes (binary logistic regression), but GEEs and GLMMs work on other categorical outcome types too (e.g. Multicatergory, Counts etc.)
- We will use the *Respiratory* RCT data presented at the beginning of last session for our example

A brief description of Generalized Estimating Equations (GEEs)

- As already mentioned, we can use GEEs to model longitudinal categorical data
- GEEs use a marginal (population-averaging) approach (i.e. Residual covariance structures) and βs are estimated using a Quasi-MLE approach
- In GEEs, the correlated nature of the data is considered a *nuisance* and we just want to remove it from the data
- Compared to other models, GEEs deal with the correlated nature of data in a rather 'informal' way.
- In practice, there are only two steps:
  1. Specify the distribution and link function (as in GLMs)
  2. Specify the residual covariance structure: Exchangeable, AR1, Unstructured, etc

GEEs in R

I will use the r library, `geepack`, to run the GEEs.

R syntax: GEEs

```
library(geepack)

 my.gee<-geeglm(my.y~my.x1+my.x2, id=id, corstr =
"exchangeable", family = binomial(), data=mydata.df)
summary(my.gee)
anova(my.gee)

# functions included to get ORs and CIs, and QIC
print.ORCIs.gee(my.gee)
QIC(my.gee)
```

Note: I have provided an R workspace (`chStuff.Rdata`) that includes all the longitudinal data and functions I use [inc. `QIC`() and `print.ORCIs.gee`()] with these lecture notes. Just load this workspace, and you will have access

Generalized Linear Mixed Models

- GLMMs are a direct generalization of Linear Mixed Models ⇒ they EXPLICITLY model individual patients
- **Like** LMMs, we can specify **Random Intercept** and **Random coefficients** models in GLMMs
- **Unlike** GEEs (and all marginal models) we aren't restricted to simple simple (singl) clustered designs
- So, Mixed Models (LMMs and GLMMs) allow hierarchical levels-**EG. Opthamology: Repeated measurement, of TWO eyes, WITHIN patient, WITHIN clinics**

Take home emssage:

Mixed Models can be used for **multi-level** analysis in a much more sophisticated way than Marginal models

GLMMs in R

I will use the R library, `lme4`, to run the GLMM

R syntax: GLMMs

```
library(lme4)

# GLMM: Random intercept
glmm.ri<-glmer(my.y~myx1+myx2 + (1|pat.id), family =
binomial(), data=mydata.df)
summary(glmm.ri)

# functions included to get ORs and CIs
print.ORCIs.glmm(glmm.ri)
```

Note: The function `print.ORCIs.glmm()` is also included in the R workspace, `chStuff.Rdata`.

Respiratory data

A multi-centre, placebo-controlled RCT to investigate the efficacy of a 'drug' on respiratory illness. A group of 111 patients (from two centres) were randomized to either the placebo or treatment arm. Respiratory illness (y/n) was observed at baseline, and then again on three subsequent visits. Variables:

- **Respiratory illness** present (y/n);
- **Visit:** 1 (baseline) and three follow-up visits (2,3 and 4);
- **Treat:** P=Placebo or A=Active
- **Patient.id:** Unique patient identifier
- **Centre.id:** Centre ID (1 or 2)

Note: **Centre.id** is a potential clustering effect (another source of correlation among observations)

Clarification of research question

In this analysis (and many RCTs conducted over time), we are not just interested in the main effect, **Treatmnent**, but also the **Treatment x Time** effect. WHY?

- If the treatment is first administered at baseline, we would expect some lag time before the treatment starts to work
- To consider the main effect, Treatment, we would combining baseline and later values in the same sample (reducing effect size)
- Also the main effect, Time (or Visit) is going to combine all subjects together (both control and treatment subjects)
- Only the **Treatment x Time** is going to give us an idea of the two groups (treatment and control) differential response over time

Approach

I will keep our analysis pretty simple here and consider a single **Within-subject** effect (VISIT), and a single **Between-subject** effect (TREATMENT)

- Unlike the previous analyses, I am going to treat visit (time) as a factor

GEE for respiratory data

```
# Make life easier, convert visit to a factor before we start
respire.df$visit.f<-factor(respire.df$visit)

# Start with a GEE with exchangeable covariance structure
gee.exc<-geeglm(outcome~treat+visit.f+treat:visit.f, id=id,
corstr = "exchangeable", family = binomial(), data=respire.df)
anova(gee.exc)
summary(gee.exc)

print.ORCIs.gee(gee.exc)

QIC(gee.exc)
```

Output 1a) ANOVA (Note I have been lazy, I should have compared the whole model with the null model)

```
> gee.exc<-geeglm(outcome~treat+visit.f+treat:visit.f, id=id, corstr =
> anova(gee.exc)
Analysis of Wald statistic Table
Model: binomial, link: logit
Response: outcome
Terms added sequentially (first to last)

              Df    X2 P(>|Chi|)
treat          1 10.02    0.0016 **
visit.f        3  3.57    0.3117
treat:visit.f  3  3.13    0.3727
---
Signif. codes:  0 *** 0.001 ** 0.01 * 0.05 . 0.1
```

Output 1b) Coefficients

```
> summary(gee.exc)

Call:
geeglm(formula = outcome ~ treat + visit.f + treat:visit.f, family = b
    data = respire.df, id = id, corstr = "exchangeable")

 Coefficients:
                Estimate Std.err Wald Pr(>|W|)
(Intercept)       0.7777  0.2930 7.05   0.0079 **
treatP           -0.8128  0.3950 4.23   0.0396 *
visit.f2          0.0873  0.3146 0.08   0.7814
visit.f3          0.1778  0.3074 0.33   0.5630
visit.f4         -0.3257  0.3028 1.16   0.2820
treatP:visit.f2  -0.5165  0.4104 1.58   0.2082
treatP:visit.f3  -0.3186  0.4284 0.55   0.4570
treatP:visit.f4   0.1140  0.3948 0.08   0.7729
---
Signif. codes:  0 *** 0.001 ** 0.01 * 0.05 . 0.1
```

Output 1c) ORs, Confidence intervals and QIC

```
>print.ORCIs.gee(gee.exc)
                   OR OR.L95 OR.U95
(Intercept)      2.176  1.226  3.865
treatP           0.444  0.205  0.962
visit.f2         1.091  0.589  2.022
visit.f3         1.195  0.654  2.182
visit.f4         0.722  0.399  1.307
treatP:visit.f2 0.597  0.267  1.334
treatP:visit.f3 0.727  0.314  1.684
treatP:visit.f4 1.121  0.517  2.430
> QIC(gee.exc)
      QIC Quasi Lik     Trace       px
      597      -290         8      444
```

Interpretation

- We see that in this model, only the TREATMENT effect is significant (output 1a)
- i.e. Only partial evidence that treatment works-**WHY?**
- Hint: Main effect vs interaction effect
  - The odds of better breathing for the placebo group is considerable lower [(1-0.444)x100% =55.6%] relative to the treatment group
  - We can see that the 95%CIs exclude 1
- Note for later, QIC=597

GEEs with other residual covariance structures

I won't bother running through individual GEEs with different covariance structures in R. I will just present you the results

Effect	Exchangeable	AR1	Unstructured
Treatment	10.02**	7.65**	10.11**
Visit	3.57	3.66	3.56
Treat x Visit	3.13	3.13	3.13
Overall	$p<0.05$	$p<0.05$	$p<0.05$

- The models are similar in terms of both their overall significance and fit (QIC, not included).
- The only difference we see is in the individual terms
- In this situation I would be guided by study design alone. I would choose AR1, or Unstructured (The compound symmetry assumption is unrealistic)

GLMM on the respiratory data

Now let's try running GLMMs on the data. As with LMMs, I will try both the **Random intercept** and **Random coefficients** models. REMEMBER:

- The Random INTERCEPT model allows different patients to start with different levels (in this case of respiratory status), but after accounting for treatment effect, they are expected to 'progress' in the same way
- The Random COEFFICIENTS model does not restrict us in this way

GLMMs for respiratory data: Null model

```
library(lme4)

# Start with a null model
glmm.null<-glmer(outcome∼1 +(1|id) family = binomial(),
data=respire.df)
```

Assessing the random intercept GLMM

Now to assess the random intercept model we will:

1. Use ANOVA to compare null and fit random intercept models
2. Compare the AIC of the null and fit random intercept models
3. Assess the significance of individual terms

GLMMs for respiratory data: Random intercept fit

```
# Fit our model
glmm.rint<-glmer(outcome∼ treat + visit.f +treat:visit.f
+(1|id) family = binomial(), data=respire.df)

# Is the model (overall) significant
anova(glmm.null, glmm.rint)

# Get coefficients

summary(glmm.rint)
```

Output 2) Model significance, AIC and βs

```
> anova(glmm.rint.null,glmm.rint)
Data: respire.df
Models:
glmm.rint.null: outcome ~ 1 + (1 | id)
glmm.rint: outcome ~ treat + visit.f + treat:visit.f + (1 | id)
               Df AIC BIC logLik Chisq Chi Df Pr(>Chisq)
glmm.rint.null  2 566 574   -281
glmm.rint       9 551 588   -267  28.7      7    0.00016 ***
---
Signif. codes:  0 *** 0.001 ** 0.01 * 0.05 . 0.1

####Coefficients
Fixed effects:
                Estimate Std. Error z value Pr(>|z|)
(Intercept)        1.060      0.378    2.80   0.0051 **
treatP            -1.156      0.469   -2.47   0.0137 *
visit.f2           0.114      0.463    0.24   0.8063
visit.f3           0.231      0.468    0.49   0.6220
visit.f4          -0.428      0.448   -0.96   0.3393
treatP:visit.f2   -0.684      0.626   -1.09   0.2750
treatP:visit.f3   -0.419      0.627   -0.67   0.5041
treatP:visit.f4    0.145      0.612    0.24   0.8122
```

Random intercept GLMM: Interpretation

- Model significance: We can see that the fit model, represents a significant improvement on the null model ($\chi^2_{LR} = 28.7$, $df = 7$, $p = 0.00016$)
- Model fit (AIC): We can see that the fit model is somewhat of an improvement over the null model ($AIC_{null} = 566$, $AIC_{rand.int} = 551$)
- Like the GEE, only the main effect of treatment was identified as significant ($\beta_{placebo} = -1.156$, $p = 0.0137$)
- I won't get the odds ratios until I decide on a final model

Random coefficients GLMM

- Our final model will be the random coefficients model
- Remember this model allows subjects to respond differently over time
- In the context of this study, we can expect patients to improve or worsen of their own accord (above the effect of the treatment), and also respond differently to treatments.
- What does this mean in a GLMM context? (Much simpler for LMMs)
  - Patients are allowed to have their own departure from the 'average' LOG odds ratios between visits

OK let's fit the model in R

Random coefficients GLMM in R

GLMMs for respiratory data: Random coefficients fit

```
# Fit our model
glmm.rcoeff<-glmer(outcome∼treat + visit.f +treat:visit.f
+(visit.f|id) family = binomial(), data=respire.df)

# Is the model (overall) significant
anova(glmm.null, glmm.rcoeff)

# Is model improvement on random intercept model
anova(glmm.rint, glmm.rcoeff)

# Get coefficients
summary(glmm.rcoeff)
```

Output 3) Model significance, AIC

```
> glmm.rcoeff<-glmer(outcome~treat+visit.f+treat:visit.f+ (visit.f|id)
> anova(glmm.rint.null, glmm.rcoeff)
Data: respire.df
Models:
glmm.rint.null: outcome ~ 1 + (1 | id)
glmm.rcoeff: outcome ~ treat + visit.f + treat:visit.f + (visit.f | id
               Df AIC BIC logLik Chisq Chi Df Pr(>Chisq)
glmm.rint.null  2 566 574   -281
glmm.rcoeff    18 569 642   -266  29.3     16      0.022 *
---
Signif. codes:  0 *** 0.001 ** 0.01 * 0.05 . 0.1

#Random intercept vs random coefficients model
> anova(glmm.rint, glmm.rcoeff)
Data: respire.df
Models:
glmm.rint: outcome ~ treat + visit.f + treat:visit.f + (1 | id)
glmm.rcoeff: outcome ~ treat + visit.f + treat:visit.f + (visit.f | id
            Df AIC BIC logLik Chisq Chi Df Pr(>Chisq)
glmm.rint    9 551 588   -267
glmm.rcoeff 18 569 642   -266   0.6      9          1
```

Random coefficients GLMM: Interpretation

Random coefficients model Vs. null model

- The first thing we should notice is that the Random coefficients model fit the data significantly better than the null model ($\chi^2_{LR} = 29.3$, $df = 16$, $p = 0.022$)
- BUT the extra model complexity (having additional sets of βs for every patient: OR_{1v2}, OR_{1v3} and OR_{1v4}) was not worth it: The null AIC was actually lower than the random coeff model AIC ($AIC_{null} = 566$, $AIC_{rand.coeff} = 569$)

Random coefficients Vs. random intercepts models

- We see that the random coefficients model neither represents a significant improvement ($\chi^2_{LR} = 0.6$, $df = 9$, $p = 1$), and the AIC actually identified the model as considerably worse ($AIC_{rand.int} = 551$, $AIC_{rand.coeff} = 569$)

So which is the best model

We have first 5 models on this data:

1. GEE with exchangeable error covariance structure
2. GEE with AR1 error covariance structure
3. GEE with unstructured error covariance structure
4. A random intercept GLMM
5. A random coefficients GLMM

Which would you pick???

So which is the best model

- I would almost always pick a GLMM over a GEE (and always a mixed model over a marginal model in general)
- I personally have problems with the (population) averaging approach (throwing everything into the error)
- Also GEEs are limited to rather simple situations (e.g. Single level clusters)
- That Mixed models allow individual subjects to vary, (and explicitly modelling this, appeals to me)
- BUT an argument against the mixed model approach is they are expensive (often requiring a large number of model parameters)
- I will choose the **Random intercept GLMM** in this case

One last thing to do!!!!

Now that I chosen my model, I want the ORs and their 95%CIs

Obtaining GLMM ORs and 95%CIs: Random intercept model

```
# Get ORs and their 95%CIs
print.ORCIs.glmm.wald(glmm.rint)
```

Output 4) ORs and 95%CI from best model

```
> print.ORCIs.glmm.wald(glmm.rint)
      OR   L95   U95
 (Intercept)      2.879 1.352 6.130
 treatP           0.315 0.123 0.811
 visit.f2         1.120 0.446 2.811
 visit.f3         1.258 0.497 3.185
 visit.f4         0.652 0.266 1.599
 treatP:visit.f2 0.506 0.144 1.771
 treatP:visit.f3 0.659 0.188 2.305
 treatP:visit.f4 1.156 0.338 3.953
```

As with GEEs, the 95%CIs excludes 1. The odds of better respiratory status in the placebo group is (1-0.315)x100%=68.5% less than the treatment group.

BUT, we could not show the Treatment x Time interaction was significant (the main objective of studies of this type)

GLMMs and GEEs: Side-by-side

There are advantages and disadvantages to both GLMMs and GEEs

Generalized Linear mixed models

- Make fewer simplifying assumptions
- More computationally intense (and often don't converge)
- Estimates LOTS of parameters from the data
- Allow more complex designs (e.g. Multilevel)

Genralized Estimating Equations

- SImplistic (assume beyond covariates, population all the same)
- Less computationally intense (converges more often)
- Estimates fewer parameters from the data
- Only allows simple design (Only two-level⇒Single 'clustering' effect)

THANK-YOU

Questions???

Exercises for LMMs and GLMMs

The datasets we will use are all in `chStuff.RData`, and includes the datasets outlined at the beginning of the LMM lecture (repeated below).

Regardless of what type of model you are fitting (LMM, GLMM, or even GEE) you should **start with the simplest model** and then sequentially add complexity. Specifically:

1. A null model: *Interecpt only* model that contains the random effects (no fixed effects should be included)
2. Main effects models (no interactions terms)
3. Interaction terms

My suggestion is to run these for (1) The random intercept model, and then (2) the random coeffcients model

1. The model has 'significantly' improved (χ_{LRT} test)
2. Is the extra complexity worth it (e.g. AIC)

Continuous outcome: Autism data

This study (Oti et al, 2006) investigates the effect of the level of communication development (as classified at age 2) on social development in Autistic children. Cohort participants are initially measured at 2 years old and then followed up until age of 13:

- **VSAE:** parent-reported Vineland Socialization Age Equivalent
- **Age:** Age in years (2, 3, 5, 9, 13)
- **Sicdegp:** Expressive language score at 2yo:Low, Med, High
- **Childid:** Unique child identifier

We are interested in the effect of **Expressive language** and **Age** on **Socialization**.

Binary outcome: Respiratory data

A multi-centre, placebo-controlled RCT to investigate the efficacy of a 'drug' on respiratory illness. A group of 111 patients (from two centres) were randomized to the treatment arms. Respiratory illness (y/n) was observed at baseline, and then again on three subsequent visits. Variables:

- **Respiratory illness** present (y/n);
- **Visit:** 1 (baseline) and three follow-up visits (2,3 and 4);
- **Treat:** P=Placebo or A=Active
- **Patient.id:** Unique patient identifier
- **Centre.id:** Centre ID (1 or 2)

Our analysis (in the lecture) was incomplete. Let's rerun the analysis, but this time, account for the age and gender confounders. Suggestion: **Only run GLMMs** (don't bother about the GEE) plus **Remember your cheat-sheet**