Medication Adherence & dosing regimen implementation: from monthly percentages to longitudinal analysis of daily dosing regimen

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Objectives

• Understand:
  – Multilevel data
  – The impact of aggregating data
  – Random vs. fixed effects
  – ICC
  – Correlation structure
Definition: multilevel data

• Data can be non-independent for various reasons:
  – Clustered in groups (patients in wards, in hospitals)
  – Several measures from same individual (measures in patient)
Graphically: 2 levels

Figure 1: A. patients (P) nested within unit; B. patients measured at multiple time points
Graphically: 3 levels
4 levels...
Other examples from your research

• Ambulatory patients
• Insurance claims
• ...


What do the data look like?

<table>
<thead>
<tr>
<th>Patient</th>
<th>Day 1</th>
<th>Day 2</th>
<th>Day 3</th>
<th>Day 4</th>
<th>Day 5</th>
<th>Day 6</th>
<th>Day 7</th>
<th>Day 8</th>
<th>Day 9</th>
<th>Day 10</th>
<th>Day 11</th>
<th>Day 12</th>
<th>Day 13</th>
<th>Day 14</th>
<th>Day 15</th>
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<tbody>
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</tbody>
</table>

Patients stopped the treatment
What if we aggregate data?

• For each patient, take the sum of all days with correct medication over 30 days
  – What about missing data?
  – What about covariates changing within the 30 days?

• For each patient, classify him/her as compliant if he/she took, say at least 75%, of the doses
  – Same problems
Multilevel models

• Also called mixed effects ANOVA
• Also called mixed linear models
• Also called hierarchical models
• Also called random effects ANOVA
Intra-class correlations

• Degree of dependence between measures issuing from the same cluster/hospital/person

• How to model this dependence?

\[ ICC_{level\,2} = \frac{s_{level\,2}^2}{s_{level\,2}^2 + s^2} \]

• Usually, software provide the \( s_{level\,2} \)
Random intercept

• \( Y_{ij} = (b_0 + u_{0j}) + b_1 X_{ij} + \varepsilon_{ij} \)

• Where the \( u \) depend on each subject
• And we assume \( u_{0j} \) to follow a \( N(0, s^2_{level2}) \)
Graphically
Random intercept and slope

• $Y_{ij} = (b_0 + u_{0j}) + (b_1 + u_{1j})X_{ij} + \varepsilon_{ij}$

• Where the $u$ depend on each subject
Graphically
Random intercept and random slope
An example: autism and quality of life

• Treatment (PAMS vs. noPams)
• ABC: 5 dimensions (continuous variables) measuring symptoms of autism: irritability, lethargy, stereotypic behavior, hyperactivity, inappropriate speech
• Quality of life (continuous variable, from 100 to 160, with 160 being the highest QoL)
Method and hypotheses

• N=19 (bl) and 16 in 2008 in PAMS and 9 in noPAMS

• Treatment is supposed to be fully active and there should be no trend in QoL over time → time can be seen as a random factor

• Mediation hypothesis:
  • Treatment → challenging behavior (ABC) → QoL
Visually
Random intercept

...

Random intercept and Random slope

...
From multilevel models to generalized multilevel model

• For a given day, adherence is binary
• The multilevel models seen before were for continuous outcomes
• Multilevel models can be extended to binary outcomes through a link function (e.g., logit link)
• We suppose that \( u_1 \sim N \left( 0, \sigma_\varepsilon^2 I_{80} \right) \), so that
\[
\text{var} \left[ y \right] = \sigma_\varepsilon^2 I_{80} + \sigma_\delta^2 Z_1 Z'_1 = \sigma_\varepsilon^2 I_{80} + \sigma_\delta^2 \left( I_{16} \otimes 1_5 \right) \left( I_{16} \otimes 1_5 \right)' = \sigma_\varepsilon^2 I_{80} + \sigma_\delta^2 I_{16} \otimes J_5 = I_{16} \otimes \left( \sigma_\varepsilon^2 I_5 + \sigma_\delta^2 J_5 \right),
\]
with \( J_\alpha \) a \( \alpha \times \alpha \) matrix of ones.

• One can then split the \( y \) in independent blocs \( y_i = (Y_{i1}, \ldots, Y_{i5})' \)
and the model becomes
\[
y_i = x_i / \beta + z_1 u_{i1} + e_i
\]
with \( x_i = \begin{bmatrix} 1_5 & x_{i(2)} \end{bmatrix}, z_1 = 1_5 \) and \( u_{i1} = s_i \).
GLMM vs. GEE

- Breslow and Clayton (1993)
- Random effects model
- Extends linear mixed models to generalized linear mixed models
- Uses maximum likelihood (ML)

- Liang and Zeger (1986)
- Modify the estimation methods for independent data to take into account the correlation in the data
- Uses the moment methods to estimate the covariance between measures
Advantages (GLMM vs. GEE)

- Estimation procedure is well established with good theoretical properties
- Can estimate random effects (Subject specific)
- Better for missing data
- Conditions of application are less strict (robust standard errors)
- Estimate effects at the group level (population average = at the patient level)
Disadvantages (GLMM vs. GEE)

• Long computation time
• Random effects have to be interpreted
• GEE does not accommodate really complex data structures (crossed dependence)
Subject specific vs population average

• The coefficients estimated by GLMM are subject-specific (SS):
  – Generally more extreme than the coefficients estimated by population average (PA) models
  – More extreme as the variance of the random effects increase
  – They correspond to the difference in coefficient for a given day if the predictor increase by 1 (e.g., eating breakfast on a given day compared to that same day with no breakfast increases adherence)

• Coefficients obtained by GEE models are population average and represent the difference in coefficient for the average measures if the predictor increase by 1 (e.g., adherence on an average day with compared to without breakfast)
More about SS vs. PA


Example: adherence over time

```r
# GLMM model
library(lme4)
adhRI.glmm <- glmer(adh~I(drel/30) + (1|id),
data=adherence, family="binomial")

Fixed effects:

|                | Estimate | Std. Error | z value | Pr(>|z|) |
|----------------|----------|------------|---------|----------|
| (Intercept)    | 4.1663   | 0.1470     | 28.34   | < 2e-16  *** |
| I(drel/30)     | -0.2726  | 0.0549     | -4.96   | 6.9e-07  *** |

Random effects:  

<table>
<thead>
<tr>
<th>Groups</th>
<th>Name</th>
<th>Variance</th>
<th>Std.Dev</th>
</tr>
</thead>
<tbody>
<tr>
<td>id</td>
<td>(Intercept)</td>
<td>5.83</td>
<td>2.41</td>
</tr>
</tbody>
</table>

ICC = 5.83/(5.83+\pi^2/3) = 0.64
Example: adherence over time

```r
# GEE model
library(geepack)
adh.gee <- geeglm(adh ~ I(drel/30), id=id, data=adherence, family=binomial("logit"), corstr="exc")

Coefficients:

|                | Estimate | Std.err | Wald  | Pr(>|W|) |
|----------------|----------|---------|-------|----------|
| (Intercept)    | 2.4999   | 0.1503  | 276.73| <2e-16   *** |
| I(drel/30)     | -0.1477  | 0.0648  | 5.19  | 0.023    * |

Compared to simple GLM:

|                | Estimate | Std.err | Wald  | Pr(>|W|) |
|----------------|----------|---------|-------|----------|
| I(drel/30)     | -0.1477  | 0.0402  | -3.68 | 0.00024  *** |
```
Example: adherence by intervention

# GLMM model
library(lme4)
adhRI.glmm <- glmer(adh~intervention + (1|id), data=adherence, family="binomial")

Fixed effects:

|                  | Estimate | Std. Error | z value | Pr(>|z|) |
|------------------|----------|------------|---------|----------|
| (Intercept)      | 4.373    | 0.193      | 22.66   | < 2e-16  *** |
| intnameStandard  | -0.969   | 0.266      | -3.65   | 0.00027 *** |

# GEE model
library(geepack)
adh.gee <- geeglm(adh ~ intervention, id=id, data=adherence, family=binomial("logit"),corstr="exc")

Coefficients:

|                  | Estimate | Std.err | Wald | Pr(>|W|) |
|------------------|----------|---------|------|----------|
| (Intercept)      | 2.902    | 0.153   | 358.6| < 2e-16  *** |
| intnameStandard  | -0.921   | 0.225   | 16.7 | 4.4e-05 *** |
Take home messages

• Examining adherence at the day level can be relevant if:
  – Time-varying covariates are of interest (e.g. eating breakfast)
• The non-independence of the data have to be taken into account
• There are two main models for these data:
  – GEE (similar to logistic regression with robust SE)
  – GLMM also called multilevel logistic regression