Multilevel, multivariate, and network meta-analysis with the *metafor* package in R

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Purpose of Talk
- describe how multilevel and multivariate structures can arise in meta-analytic data
- illustrate how to fit multilevel, multivariate, and network meta-analyses with the *metafor* package in R

Meta-Analytic Data
- \( i = 1, \ldots, k \) studies
- have \( y_i \) and corresponding \( v_i \)
- assume:
  \[ y_i \mid \theta_i \sim N(\theta_i, v_i) \]
- and independence of the estimates (for now)
- approx. 95% CI for \( \theta_i : y_i \pm 1.96 \sqrt{v_i} \)

Example: BCG Vaccine
- effectiveness of the Bacillus Calmette-Guérin (BCG) vaccine against tuberculosis (TB)
- for each study, can compare the proportion of TB positive cases in the vaccinated versus the non-vaccinated group

Example: BCG Vaccine

<table>
<thead>
<tr>
<th>Study</th>
<th>Year</th>
<th>RR</th>
<th>( y = \ln(\text{RR}) )</th>
<th>( \nu )</th>
<th>Allocation</th>
<th>Latitude</th>
</tr>
</thead>
<tbody>
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<tr>
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<td>-0.79</td>
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<tr>
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<td>1973</td>
<td>0.20</td>
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<tr>
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</tr>
</tbody>
</table>
Example: BCG Vaccine

Standard Random-Effects Model

\[ y_i = \mu + u_i + e_i \]

- \( y_i \): average true outcome
- \( u_i \): random effect that makes the true outcome for a particular study larger/smaller by some amount (heterogeneity between studies)
- \( e_i \): sampling error

\[ e_i \sim N(0, \nu_i) \quad u_i \sim N(0, \tau^2) \]

Marginal Variance-Covariance Matrix

\[
\begin{bmatrix}
    y_1 & y_2 & \cdots & y_n \\
    y_2 & y_1 & \cdots & y_{n-1} \\
    \vdots & \vdots & \ddots & \vdots \\
    y_n & y_{n-1} & \cdots & y_1 \\
\end{bmatrix}
\]

\[ \text{Var}(y_i) = \begin{bmatrix}
    \tau^2 + \nu_1 \\
    \tau^2 + \nu_2 \\
    \vdots \\
    \tau^2 + \nu_n
\end{bmatrix} \]

Meta-Analysis with R

- **metafor**: meta-analysis package for R
- install with: `install.packages("metafor")`
- load with: `library(metafor)`
- comments start with #

Computing Observed Outcomes

- can of course use external software for data management and preparations
- to compute outcomes: `escalc()` command
- basic syntax:

```r
dat <- escalc(measure="", ..., data=dat)
```

> # load BCG vaccine data
> dat <- get(data(dat.bcg))
> # show data
> dat

<table>
<thead>
<tr>
<th>trial</th>
<th>Author</th>
<th>Year</th>
<th>TB+ tpos</th>
<th>TB+ tneg</th>
<th>TB- cpos</th>
<th>TB- cneg</th>
<th>ablat</th>
<th>alloc</th>
</tr>
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<td>128</td>
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</tr>
<tr>
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<td>Ferguson &amp; Simes</td>
<td>1949</td>
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<td>308</td>
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<td>274</td>
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<td>random</td>
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<tr>
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<td>1973</td>
<td>33</td>
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<td>1969</td>
<td>27</td>
<td>16886</td>
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<td>16886</td>
<td>29</td>
<td>17928</td>
<td>33</td>
<td>systematic</td>
</tr>
</tbody>
</table>

### load BCG vaccine data
```r
dat <- get(data(dat.bcg))
```

### show data
```r
dat
```

To specify the outcome measure (RD, RR, OR, SMD, RDM, PLO, ...) to specify the variables needed to compute the observed outcomes
### calculate log relative risks and sampling variances

```r
dat <- escalc(measure="RR", ai=tpos, bi=tneg, ci=cpos, di=cneg, data=dat)
```

<table>
<thead>
<tr>
<th>trial</th>
<th>author</th>
<th>year</th>
<th>yi</th>
<th>vi</th>
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</tr>
<tr>
<td>4</td>
<td>Hart &amp; Sutherland 1977</td>
<td></td>
<td>-1.4416</td>
<td>0.0300</td>
</tr>
<tr>
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<td>Friedl-Moller et al 1973</td>
<td></td>
<td>-0.2175</td>
<td>0.0512</td>
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<tr>
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<td>1953</td>
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<tr>
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<td>Vandiviare et al 1975</td>
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<td>-1.6399</td>
<td>0.2330</td>
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<td>1980</td>
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<td>0.0040</td>
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<td>1968</td>
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<td></td>
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<td>0.0750</td>
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<td></td>
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<td>0.0124</td>
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<tr>
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<td>0.5325</td>
</tr>
<tr>
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<td>Comstock et al 1976</td>
<td></td>
<td>-0.0573</td>
<td>0.0816</td>
</tr>
</tbody>
</table>

Random-Effects Model

- basic syntax:
  ```r
  res <- rma(yi, vi, method="REML", data=dat)
  ```

- name of variable for the observed outcomes
- name of variable for the corresponding sampling variances
- to select the $\tau^2$ estimator (DL, ML, REML, PM, EB, ...)
- name of data frame containing the variables

- to print results, type: `res`
- or use: `print(res, digits=2)`
- use `predict()` for back-transformation

Mixed-Effects Meta-Regression Model

- can include moderators/predictors/covariates in the model (to account for heterogeneity)
- mixed-effects meta-regression model:
  - $y_i = \beta_0 + \beta_1 x_{i1} + \cdots + \beta_p x_{ip} + u_i + e_i$
  - $u_i \sim N(0, \tau^2)$ (but now 'residual' heterogeneity)
  - $e_i \sim N(0, \sigma^2)$

- for multiple predictors/moderators:
  - main effects: `mods = ~ var1 + var2 + ...`
  - interactions: `mods = ~ var1 * var2 + ...`
- character/factor variables:
  - are automatically dummy-coded
  - to remove the intercept: `mods = ~ var1 - 1`
### fit mixed-effects meta-regression model
```r
res <- rma(yi, vi, mods = ~ alloc + ablat, data = dat)
```
```
> Mixed-Effects Model (k = 13; tau^2 estimator: REML)
> tau^2 (estimated amount of residual heterogeneity): 0.1446
tau (square root of estimated tau^2 value): 0.3803
I^2 (residual heterogeneity / unaccounted variability): 70.11%
H^2 (unaccounted variability / sampling variability): 3.35
R^2 (amount of heterogeneity accounted for): 53.84%

Test for Residual Heterogeneity:
Q(df = 9) = 26.2034, p-val = 0.0019
Test of Moderators (coefficient(s) 2,3,4):
QM(df = 3) = 11.0605, p-val = 0.0114
```
```
> Model Results:
```
<table>
<thead>
<tr>
<th></th>
<th>estimate</th>
<th>se</th>
<th>zval</th>
<th>pval</th>
<th>ci.lb</th>
<th>ci.ub</th>
</tr>
</thead>
<tbody>
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<td>0.4193</td>
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<td>0.3795</td>
<td>0.1540</td>
<td>0.8776</td>
<td>-0.6854</td>
<td>0.8023</td>
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<tr>
<td>ablat</td>
<td>-0.0273</td>
<td>0.0092</td>
<td>-2.9650</td>
<td>0.0030</td>
<td>-0.0453</td>
<td>-0.0092</td>
</tr>
</tbody>
</table>

> Wald-Type Tests and Contrasts
```
```r
anova(res, btt=<>)
```
```
vector of numbers indicating which coefficients to test
```
```
```r
anova(res, L=c())
```
```
comma separated vector to specify the values to use for the contrast
```
```
> omnibus test of the ‘alloc’ factor
```r
anova(res, btt=2:3)
```
```
Test of Moderators (coefficient(s) 2,3):
QM(df = 2) = 1.2850, p-val = 0.5260
```
```
> test random versus systematic allocation
```r
anova(res, L=c(0,1,-1,0))
```
```
Hypothesis:
1: allocrandom - allocsystematic = 0
```
```
> ### fit standard random-effects model
```r
res <- rma(yi, vi, data = dat)
```
```
> Random-Effects Model (k = 56; tau^2 estimator: REML)
> tau^2 (estimated amount of total heterogeneity): 0.0884
tau (square root of estimated tau^2 value): 0.2974
I^2 (total heterogeneity / total variability): 94.70%
H^2 (total variability / sampling variability): 18.89

Test for Heterogeneity:
Q(df = 55) = 578.8640, p-val < .0001
```
```
> Model Results:
```
<table>
<thead>
<tr>
<th></th>
<th>estimate</th>
<th>se</th>
<th>zval</th>
<th>pval</th>
<th>ci.lb</th>
<th>ci.ub</th>
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</thead>
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<tr>
<td>intercept</td>
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<td>0.0439</td>
<td>2.9161</td>
<td>0.0035</td>
<td>0.0419</td>
<td>0.2139</td>
</tr>
</tbody>
</table>
```
```
> load data
```r
data <- get(data(dat.konstantopoulos2011))
```
```
> ### show data
```r
dat
```
```
da district school study year yi vi
1 11 11 1 1976 -0.18 0.118
2 11 11 2 1976 -0.22 0.118
3 11 11 3 1976 0.23 0.144
4 11 11 4 1976 0.30 0.144
5 12 12 1 1989 0.13 0.014
6 12 12 2 1989 0.26 0.014
7 12 12 3 1989 0.19 0.015
8 12 12 4 1989 0.32 0.024
9 18 18 1 1994 0.45 0.023
10 18 18 2 1994 0.38 0.043
11 18 18 3 1994 0.29 0.012
12 ... ... ... ... ...
56 644 4 56 1994 -0.05 0.067
```
```
> The rma() Function
```
```
- more flexible model fitting function, but must specify random effects manually
- for now, replicate previous results
```
```r
res <- rma(yi, vi, random = - 1 | study, method = "REML", data = dat)
```
```
• random = - 1 | study adds a random effect for each level of the study variable
• method = "REML" is default (other option: ML)
```r
> ## fit standard random-effects model with rma.mv()
> res <- rma.mv(yi, vi, random = ~ 1 | study, data = dat)
> res

Multivariate Meta-Analysis Model (k = 56; method: REML)

Variance Components:

<table>
<thead>
<tr>
<th>estim</th>
<th>sqrt</th>
<th>nlvls</th>
<th>fixed</th>
<th>factor</th>
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</thead>
<tbody>
<tr>
<td>sigma^2</td>
<td>0.0884</td>
<td>0.2974</td>
<td>56</td>
<td>no</td>
</tr>
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</table>

Test for Heterogeneity:
Q(df = 55) = 578.8640, p-val < .0001

Model Results:

<table>
<thead>
<tr>
<th>estimate</th>
<th>se</th>
<th>zval</th>
<th>pval</th>
<th>ci.lb</th>
<th>ci.ub</th>
</tr>
</thead>
<tbody>
<tr>
<td>0.1279</td>
<td>0.0439</td>
<td>2.9161</td>
<td>0.0035</td>
<td>0.0419</td>
<td>0.2139</td>
</tr>
</tbody>
</table>

> ### load data
> dat <- get(data(dat.konstantopoulos2011))
> dat

<table>
<thead>
<tr>
<th>district</th>
<th>school</th>
<th>study</th>
<th>year</th>
<th>yi</th>
<th>vi</th>
</tr>
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<td>-0.18</td>
<td>0.118</td>
</tr>
<tr>
<td>11</td>
<td>2</td>
<td>2</td>
<td>1976</td>
<td>-0.22</td>
<td>0.118</td>
</tr>
<tr>
<td>11</td>
<td>3</td>
<td>3</td>
<td>1976</td>
<td>0.23</td>
<td>0.144</td>
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<tr>
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<td>5</td>
<td>1989</td>
<td>0.13</td>
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<td>0.32</td>
<td>0.024</td>
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<tr>
<td>18</td>
<td>1</td>
<td>9</td>
<td>1994</td>
<td>0.45</td>
<td>0.023</td>
</tr>
<tr>
<td>18</td>
<td>2</td>
<td>10</td>
<td>1994</td>
<td>0.38</td>
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</tr>
<tr>
<td>18</td>
<td>3</td>
<td>11</td>
<td>1994</td>
<td>0.29</td>
<td>0.012</td>
</tr>
<tr>
<td>...</td>
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<td>...</td>
<td>...</td>
<td>...</td>
<td>...</td>
</tr>
<tr>
<td>644</td>
<td>4</td>
<td>56</td>
<td>1994</td>
<td>-0.05</td>
<td>0.067</td>
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</tbody>
</table>
```

Multilevel Meta-Analytic Data

- multilevel structures can arise when we have multiple estimates for some higher clustering variable (paper, lab, research group, ...)

```
Cluster 1
  Y_{11}  Y_{12}   Y_{13}  ...  Y_{1k}
Cluster 2
  Y_{21}  Y_{22}   Y_{23}  ...  Y_{2k}
Cluster k
  Y_{k1}  Y_{k2}   Y_{k3}  ...  Y_{kk}
```

Marginal Variance-Covariance Matrix

```
Var Y =
|  \sigma^2_{\epsilon} + \sigma^2_{\eta} | \sigma^2_{\epsilon} + \sigma^2_{\eta} + \rho \sigma_{\epsilon} \sigma_{\eta} |
|---------------------------|-------------------------------------------------
| \sigma^2_{\epsilon} + \sigma^2_{\eta} + \rho \sigma_{\epsilon} \sigma_{\eta} | \sigma^2_{\epsilon} + \sigma^2_{\eta} + \rho \sigma_{\epsilon} \sigma_{\eta} + \rho \sigma_{\eta}^2 |
```

The rma.mv() Function

- rma.mv() allows for the addition of multiple nested random effects
- random = ~ 1 | var1/var2 adds a random effect for each level of var1 and a random effect for each level of var2 within each level of var1

Multilevel Random-Effects Model

\[ y_{ij} = \mu + \omega_i + u_{ij} + e_{ij} \]

- average true outcome
- random effect that makes the true outcomes for a particular cluster larger/smaller by some amount (heterogeneity between clusters)
- random effect that makes one of the true outcomes within a particular cluster larger/smaller by some amount (heterogeneity within clusters)
- sampling error

\[ w_i \sim N(0, \sigma^2_{\omega}) \quad u_{ij} \sim N(0, \sigma^2_{u}) \quad e_{ij} \sim N(0, \sigma^2_{e}) \]

Marginal Variance-Covariance Matrix

```
with a block-diagonal structure
```
Correlation due to Multilevel Structure
- the multilevel structure implies that the true outcomes within a cluster are correlated:
  \[ \rho = \frac{\sigma^2_x}{\sigma^2_y + \sigma^2_z} \]
- in example:
  \[ \hat{\rho} = \frac{0.0651}{0.0651 + 0.0327} = 0.67 \]
- also note: 0.0651 + 0.0327 = 0.0978

Multivariate Parameterization
- \( y_{ij} = \mu \) average true outcome
- \( + u_{ij} \) correlated random effects for the true outcomes within the same cluster
- \( + e_{ij} \) sampling error

\[
\begin{bmatrix}
  u_{1j} \\
  u_{2j} \\
  u_{3j}
\end{bmatrix} \sim MVN
\begin{bmatrix}
  0 & \tau^2 & \rho \tau^2 \\
  \tau^2 & \rho \tau^2 & \rho \tau^3 \\
  \rho \tau^2 & \rho \tau^3 & \tau^3
\end{bmatrix}
\]
\( e_{ij} \sim N(0, \sigma^2_e) \)

The rma.mv() Function
- `random = ~ var1 | var2` adds correlated random effects for each level of `var1` within each level of `var2`
- note: `var1` must be a character/factor type variable (if it is not, use `factor()` function)
Notes

- models assume independent **sampling errors** within clusters (sensible if no overlap in the data/subjects used to compute outcomes)
- examples:
  - multiple independent studies reported in paper
  - multiple papers published by the same group
  - results reported for different subgroups
- but **true outcomes** within clusters may be more similar to each other than those from different clusters (correlated true outcomes)

### Multiple (Correlated) Outcomes

- multivariate data also arise when multiple outcomes are measured within the studies

![Diagram](image)

**Study 1**

$Y_{11}$

**Study 2**

$Y_{21}$

$Y_{22}$

**Study k**

$Y_{k1}$

$Y_{k2}$

**note:** not all studies have to measure all outcomes

### Multivariate Random-Effects Model

\[
Y_{ij} = \mu_j + u_{ij} + e_{ij}
\]

- average true outcome for jth outcome
- correlated random effects corresponding to the true outcomes of the same study
- correlated sampling errors of the observed outcomes for the same study (with known var-cov matrix)

\[
\begin{align*}
\text{Var}(u_{11}, u_{12}) &= \tau_1^2 \\
\text{Var}(e_{11}, e_{12}) &= \tau_2^2 \\
\end{align*}
\]

\[
\begin{pmatrix}
\tau_1^2 & \rho \tau_1 \tau_2 \\
\rho \tau_1 \tau_2 & \tau_2^2
\end{pmatrix}
\]

\[
\begin{pmatrix}
\text{Var}(u_{ij}), \text{Cov}(u_{ij}) \\
\text{Var}(e_{ij}), \text{Cov}(e_{ij})
\end{pmatrix}
\]

### R Code

```r
> # load data
> dat <- get(data(dat.berkey1998))
> # show data
> dat

### construct var-cov matrix of the sampling errors

```

```
The rma.mv() Function

- name of object with the var-cov matrix of the sampling errors
- name of factor to indicate the outcome (and remove intercept)

```
res <- rma.mv(yi, V, mods = ~ outcome - 1, data = dat, 
               random = ~ outcome | study, 
               struct = "UN", data = dat)
```

Random Effects Structures

- `struct="CS"` (this is the default)
- `struct="HCS"`
- `struct="UN"`

(for two outcomes, "UN" and "HCS" are the same)

Multiple Time Points

- multivariate data also arise when an outcome is measured at multiple time points
- the sampling errors will again be correlated
- true outcomes may also be correlated
- can consider auto-regressive structures for the sampling errors and random effects (Ishak et al., 2007; Trikalinos & Olkin, 2012)

Random Effects Structures

- `struct="AR"`
- `struct="HAR"`
### Load data

dat <- get(data(dat.ishak2007))

### Create long format dataset

dat.long <- reshape(dat, direction="long", idvar="study",
                    varying=list(c(2,4,6,8), c(3,5,7,9)))

dat.long <- dat.long[order(dat.long$study, dat.long$time),]

### Remove missing measurement occasions from dat.long

is.miss  <- is.na(dat.long$yi)

dat.long <- dat.long[!is.miss,]

### Construct full (block diagonal) V matrix with AR(1) structure

rho.within <- .97
V <- lapply(split(with(dat, cbind(v1i, v2i, v3i, v4i)),
dat$study), diag)
V <- lapply(V, function(v) sqrt(v) %*%
toeplitz(ARMAacf(ar=rho.within, lag.max=3)) %*% sqrt(v))
V <- bldiag(V)
V <- V[!is.miss,!is.miss]

### Show data

dat.long

study  time     yi     vi
1        Alegret (2001)     1  -33.4   14.3
5     Barichella (2003)     1  -20.0    7.3
7     Barichella (2003)     3  -30.0    5.7
9     Barney (2002)     1  -21.1    7.1
13    Burchiel (1999)     1  -20.0    8.0
14    Burchiel (1999)     2  -20.0    8.0
15    Burchiel (1999)     3  -18.0    5.0
18    Chen (2003)     2  -32.0  125.0
92    ...                ...    ...    ...
173  Vingerhoets (2002)     1  -19.7   18.5
174  Vingerhoets (2002)     2  -22.1   18.1
175  Vingerhoets (2002)     3  -24.3   18.2
176  Vingerhoets (2002)     4  -21.0   16.7
178  Volkman (2001)     2  -37.8   20.9
179  Volkman (2001)     3  -34.0   26.4
181  Weselburger (2002)     2  -22.1   40.8

### Show var-cov matrix of sampling errors for rows 1-8

V[1:8,1:8]

[1,]  14.300
[2,]          7.300  6.069
[3,]          6.069  5.700
[4,]                               7.300
[5,]                               7.300
[6,]                               8.000  7.760  5.951
[7,]                               7.760  6.069  6.135
[8,]                                                    125.000

### Multivariate model with HAR(1) structure

res <- rma.mv(yi, V, mods = ~ factor(time) - 1, data = dat.long,
              random = ~ time | study, struct = "HAR")

Multivariate Meta-Analysis Model (k = 82; method: REML)

Variance Components:

estim   sqrt  k.lvl  fixed  level
tau^2.1    22.724  4.767     24     no      1
tau^2.2    33.755  5.810     22     no      2
tau^2.3    26.167  5.115     25     no      3
tau^2.4    31.207  5.586     11     no      4
rho         0.883                   no

Test for Residual Heterogeneity:
Q(df = 78) = 856.164, p-val < .001

Model Results:

estimate     se     zval   pval    ci.lb    ci.ub
factor(time)1  -25.905  1.012  -25.605  <.001  -27.888  -23.922
factor(time)2  -27.461  1.141  -24.072  <.001  -29.697  -25.225
factor(time)4  -26.494  1.382  -19.172  <.001  -29.202  -23.785
### comparison of effects between pairs of time points

```r
anova(res, L=rbind(c(1,-1,0,0), c(1,0,-1,0), c(1,0,0,-1),
                  c(0,1,-1,0), c(0,1,0,-1),
                  c(0,0,1,-1)))
```

**Hypotheses:**

1: factor(time)1 - factor(time)2 = 0
2: factor(time)1 - factor(time)3 = 0
3: factor(time)1 - factor(time)4 = 0
4: factor(time)2 - factor(time)3 = 0
5: factor(time)2 - factor(time)4 = 0
6: factor(time)3 - factor(time)4 = 0

**Results:**

<table>
<thead>
<tr>
<th>estimate</th>
<th>se</th>
<th>zval</th>
<th>pval</th>
</tr>
</thead>
<tbody>
<tr>
<td>1: 1.556</td>
<td>0.755</td>
<td>2.061</td>
<td>0.039</td>
</tr>
<tr>
<td>2: 2.751</td>
<td>0.859</td>
<td>3.204</td>
<td>0.001</td>
</tr>
<tr>
<td>3: 0.589</td>
<td>1.273</td>
<td>0.462</td>
<td>0.644</td>
</tr>
<tr>
<td>4: 1.195</td>
<td>0.761</td>
<td>1.569</td>
<td>0.117</td>
</tr>
<tr>
<td>5: -0.967</td>
<td>1.217</td>
<td>-0.795</td>
<td>0.427</td>
</tr>
<tr>
<td>6: -2.163</td>
<td>0.968</td>
<td>-2.235</td>
<td>0.025</td>
</tr>
</tbody>
</table>

### Network Meta-Analysis

- often there are multiple treatments available for the same condition/disease
- studies comparing the effectiveness of these treatments form a network of comparisons
- some of the goals:
  - synthesize evidence provided by all studies and comparisons in one parsimonious model
  - obtain indirect evidence about comparisons that have not been examined head-to-head
  - determine a hierarchy of treatment effectiveness

---

**Star-Shaped Networks**

Second-generation antiepileptic drugs in partial epilepsy

- a: levetiracetam
- b: gabapentin
- c: lamotrigine
- d: eslicarbazepine
- e: tiagabine
- f: topiramate
- g: zonisamide
- h: placebo

---

**Complex Networks**

Chemotherapy regimens for ovarian cancer

- a: platinum monotherapy
- b: platinum-based combination
- c: taxane monotherapy
- d: platinum + taxane-based combination
- e: nonplatinum/non-taxane monotherapy
- f: platinum-based combination (ip)
- g: nonplatinum/non-taxane combination
- h: taxane-based combination
- i: platinum/taxane-based combination (ip)

---

**Network Meta-Analysis**

- can analyze such data with appropriate multilevel/multivariate models
- two general approaches: arm- vs. contrast-based model (e.g., Salanti et al., 2008)
- errors are correlated in contrast-based model for studies with more than two groups
- equations for the correlation between the sampling errors can be found in Gleser and Olkin (2009) and several other papers

---

**Arm-Based Network Meta-Analysis**

\[ y_{ij} = \beta_0 + \beta_T T_{ij} + \ldots + \beta_p T_{ip} + w_i + u_{ij} + e_{ij} \]

- \( w_i \sim N(0, \sigma_w^2) \)
- \( u_{ij} \sim N(0, \sigma_u^2) \)
- \( e_{ij} \sim N(0, \nu_j) \)
```r
### load data
dat <- get(data(dat.hasselblad1998))

### calculate log odds for each study arm
dat <- escalc(measure="PLO", xi=xi, ni=ni, data=dat)

### show data
dat

   id study   trt  xi  ni yi      vi
1   1      1  no_contact   75  731 -2.169  0.015
2   2      1 ind_counseling 363  714  0.034  0.006
3   3      2  no_contact    9  140 -2.678  0.119
4   4      2 ind_counseling 23  138 -1.627  0.052
5   5      2 grp_counseling 10  138 -2.549  0.108
6   6      3  no_contact    2  106 -2.951  0.510
7   7      3 ind_counseling  9  205 -3.081  0.116
8 ...    ...             ...  ...   ...     ...    ...
9 49     24  no_contact   69 1177 -2.776  0.015
10 50     24 ind_counseling 54  888 -2.737  0.020

log odds and corresponding
sampling variances

Individual
Counseling
Group
Counseling
Self-Help
No Contact

### convert trt variable to factor with desired ordering of levels
dat$trt <- factor(dat$trt, levels=c("no_contact", "self_help",
                           "ind_counseling", "grp_counseling"))

### network meta-analysis using a multilevel model
res <- rma.mv(yi, vi, mods = ~ trt, data = dat,
              random = ~ 1 | study/trt)
res

Multivariate Meta-Analysis Model (k = 50; method: REML)
Variance Components:

  estim  sqrt nlvls fixed    factor
sigma^2.1  0.195  0.441     24     no      study
sigma^2.2  0.249  0.499     50     no  study/trt

Test of Moderators (coefficient(s) 2,3,4):
  QM(df = 3) = 19.441, p-val < .001

Model Results:

  estimate     se     zval   pval   ci.lb   ci.ub
intrcpt               -2.456  0.174  -14.129  <.001  -2.796  -2.115
trt self_help          0.501  0.302    1.657  0.098  -0.092   1.093
trt ind_counseling     0.777  0.196    3.969  <.001   0.393   1.161
trt grp_counseling     1.056  0.324    3.259  0.001   0.421   1.691

### pairwise odds ratios of interventions versus no contact
predict(res, newmods=diag(3),
        intercept=FALSE, transf=exp, digits=2)

   pred  ci.lb  ci.ub
1 1.65  0.91  2.98
2 2.18  1.48  3.19
3 2.88  1.52  5.43

### pairwise odds ratios comparing interventions
predict(res, newmods=rbind(c(-1,1,0), c(-1,0,1), c(0,-1,1)),
        intercept=FALSE, transf=exp, digits=2)

   pred  ci.lb  ci.ub
1 1.32  0.73  2.39
2 1.74  0.84  3.62
3 1.32  0.72  2.43
```

---

### Network/Loop Inconsistency

<table>
<thead>
<tr>
<th>Intervention</th>
<th>OR [95% CI]</th>
<th>Odds Ratio for Intervention vs. No Contact</th>
</tr>
</thead>
<tbody>
<tr>
<td>No Contact</td>
<td>1.00 [1.00, 1.00]</td>
<td></td>
</tr>
<tr>
<td>Self-Help</td>
<td>1.65 [0.91, 2.98]</td>
<td></td>
</tr>
<tr>
<td>Individual Counseling</td>
<td>2.18 [1.48, 3.19]</td>
<td></td>
</tr>
<tr>
<td>Group Counseling</td>
<td>2.88 [1.52, 5.43]</td>
<td></td>
</tr>
</tbody>
</table>

---

### Network/Loop Inconsistency Diagram

```
A ⟷ B
```

(indirect evidence)
Network/Loop Inconsistency

![Diagram showing loop inconsistency with nodes A, B, and C, and edges with values +1.0, 0.0, and -0.5.]

Dealing with Inconsistency

- restrict analysis to a subset of studies providing consistent evidence
- try to account for it based on moderators
- model it (various proposals)

Final Notes

- `rma.mv()` allows for an arbitrary number of random effects of the form \( \sim 1 | \text{factor} \)
  (allows for 3/4/…-level models and crossed random effects)
- up to 2 terms of the form \( \sim \text{inner} | \text{outer} \)
- can also specify a known correlation matrix corresponding to a \( \sim 1 | \text{factor} \) term (e.g., for phylogenetic meta-analyses)
- website: [http://www.metafor-project.org](http://www.metafor-project.org)


Thank You!

Questions? Comments?