HIERARCHICAL MODELS
A framework for evidence synthesis

Innovative Methodology for Small Populations Research (InSPiRe), WP4 “Evidence synthesis”

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EVIDENCE SYNTHESIS

- **Pairwise meta-analysis**
  - comparing two treatments

- **Meta-regression**
  - including study-level covariates

- **Network meta-analysis**
  - comparing multiple treatments indirectly

- **RCT with historical controls**
  - integrating control group data from previous trials

- **Generalized (or cross design) synthesis**
  - combining data from different types of studies
HIERARCHICAL MODELS

Meta-analysis

Studies

Patients

Example: **Normal-normal hierarchical model (NNHM)** for random-effects meta-analysis

\[
y_i | \theta_i \sim \text{Normal}(\theta_i, s_i^2) \quad \theta_i | \Theta, \tau \sim \text{Normal}(\Theta, \tau^2)
\]
Empirical studies scraping large databases of meta-analyses (e.g. Cochrane Library) show

- Meta-analyses of (very) **few studies** common
- Extent of between-trial heterogeneity

**METHODOLOGY**

**Predicting the extent of heterogeneity in meta-analysis, using empirical data from the Cochrane Database of Systematic Reviews**

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STANDARD METHOD FAILS

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Standard method (DerSimonian-Laird, DL)

- Underestimates between-study heterogeneity
- Fails to account for uncertainty in estimation of heterogeneity

IntHout et al, 2014; Röver et al, 2015
WITH VERY FEW STUDIES: KNAPP-HARTUNG METHOD DOES NOT SOLVE THE PROBLEM

- 97.5% quantile of t-distribution with 1 df = 12.7 !!!
- Example from Friede et al (2017b)

**Crins et al. (2014) example: acute graft rejection**

<table>
<thead>
<tr>
<th>Method</th>
<th>Odds Ratio</th>
</tr>
</thead>
<tbody>
<tr>
<td>Heffron (2003)</td>
<td>0.10 [0.03, 0.32]</td>
</tr>
<tr>
<td>Spada (2006)</td>
<td>0.28 [0.08, 1.00]</td>
</tr>
<tr>
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HSJK: Hartung-Knapp-Sidik-Jonkman; mHK: modified Knapp-Hartung; normal: DL
BAYESIAN META-ANALYSIS

- **Idea**: Weakly informative prior on between-trial heterogeneity for meta-analysis with few studies (Spiegelhalter et al., 2004), with uninformative prior on treatment effect
  - Avoids zero estimates of between-trial heterogeneity
  - Accounts for uncertainty in the estimation

- **Easy to compute**
  - Application of DIRECT algorithm (Röver & Friede, 2017a) (which is faster than MCMC sampling and does not require inspection of convergence diagnostics)
  - R package bayesmeta (available from CRAN)
EXAMPLE REVISITED

Bayesian intervals appear to be a reasonable compromise (supported by simulation studies in e.g. Friede et al, 2017a,b)

Crins et al. (2014) example: acute graft rejection

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<td>half-normal(1.0)</td>
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AN EXAMPLE OF CROSS-DESIGN SYNTHESIS

Creutzfeldt-Jakob disease (CJD)
- prevalence of 1–9 cases per 1,000,000 people

Varges et al (2017) investigated doxycycline in early CJD:
- double-blinded randomized phase II trial (n=12)
- observational study (n=88) (Cox regression stratified by terciles of the propensity scores)
- survival time as primary outcome
Different quantities of interest in a random effects meta-analysis

- average effect ($\theta$) across studies
- effect ($\theta_{k+1}$) of a future study (prediction / extrapolation)
- effect ($\theta_i$) of an individual study in the light of the other studies (shrinkage estimator)
SHRINKAGE ESTIMATOR: EXAMPLE IN CJD

RCT shrinkage interval width: 66% of original CI width

- Translates into 129% gain in sample size (about 27 instead of 12 patients)

Röver & Friede (2017b) in preparation
**Idea:** Use of heavy-tailed meta-analytic predictive (MAP) prior (Schmidli et al, 2014)

- $n_1 = 25, \ n_2 = 400, \ p(\tau) = HN(0.5), \ interested \ in \ \theta_1$

Röver & Friede (2017b) in preparation
MORE COMPLEX EXAMPLE: EARLY PRO-TECT TRIAL IN ALPORT DISEASE

- Alport syndrome is a rare genetic disorder that inevitably leads to end-stage kidney disease.
- Observational data suggest that the ACE inhibitor ramipril delays renal failure and improves life-expectancy in Alport patients.
- Our work (Unkel et al, 2017) is inspired by the ongoing EARLY PRO-TECT Alport trial in paediatric Alport patients (Gross et al. 2012).

**Diagram:**

- **Open-label arm**
  - \( n_{TO} \) patients receiving treatment

- **RCT**
  - \( n_{TR} \) patients receiving treatment
  - \( n_{CR} \) patients receiving placebo

- **Registry data**
  - \( n_{CO} \) patients receiving no treatment
CONCLUSIONS AND DISCUSSION

- **Hierarchical models**
  - flexible statistical framework for evidence synthesis

- **Bayesian inference**: advantages over traditional methods in the presence of heterogeneity and only (very) few studies
  - easy to apply using R package `bayesmeta`

- **Cross-design synthesis of available evidence**
  - Promising in rare diseases
  - more practical (and regulatory) experience needed
The InSPiRe WP4 “Evidence synthesis” team includes

- University Medical Center Göttingen (UMG): Tim Friede, Steffen Unkel, Christian Röver, Burak Günhan, Katharina Kramer
- Medical University Vienna (MUW): Martin Posch
- INSERM (Paris): Sarah Zohar
- University of Warwick: Nigel Stallard
- BfArM: Norbert Benda
- Novartis: Beat Neuenschwander, Simon Wandel


