1. Objective

Meta-analysis of preclinical animal studies is vital in evaluating the internal and external validity. This informs the design and conduct of future preclinical studies and translation to a clinical setting. Investigating causes of heterogeneity between studies and choosing appropriate methods for estimation and modeling is crucial to perform a meta-analysis. Assuming aggregate level data for a continuous primary outcome variable, we focus on two topics:

- Estimation of heterogeneity using three methods: method of moments (DerSimonian-Laird, DL), maximum likelihood (REML) and Bayesian approach (FB).
- Univariable versus multivariable meta regression for adjusting heterogeneity and exploring relative impact of multiple covariates on study level treatment effects.

2. Methodology

In random effects meta-analysis model, the treatment difference in studies is a random sample of independent observations.

\[ \theta_i = \beta + b_i + \epsilon_i \]  

where \( b_i \sim N(0, \tau^2) \) and \( \epsilon_i \sim N(0, \sigma^2) \) implying \( \theta_i \sim N(\theta, \sigma^2 + \tau^2) \).

**Classical Estimation of Between Study Heterogeneity:**

1. REML estimator: A maximum likelihood-based method, where estimates of \( \tau^2 \) and \( \theta \) are obtained through an iterative procedure.
2. DL estimator: A method of moments-based estimate, where \( \tau^2 \) can be derived by using the observed value of Q statistics and its expectation.

**Frequentist Approach to Meta Regression:**

Heterogeneity between studies can be explored based on study design and characteristics by meta regression with \( \alpha_i = \beta x_{2i} \) where \( x_{2i} \) is a covariate, \( b_i \sim N(0, \tau^2) \) and \( \epsilon_i \sim N(0, \sigma^2) \).

\[ \theta_i = \beta_1 + \alpha_1 + b_i + \epsilon_i \]

**Bayesian Approach to Meta-Analysis and Heterogeneity Estimation:**

\( \theta_i \) are the estimates for effect size \( N(\theta, \sigma^2) \), where prior for \( \theta_i \) is \( N(\theta, \tau^2) \) with hyperpriors \( \theta \sim N(\theta, \sigma^2) \), \( \tau^2 \sim IG(\alpha, \lambda) \).

**Bayesian Meta Regression:**

Prior for \( \theta_i \) is \( N(\mu_1, \tau^2) \), where \( \mu_1 = \beta + \beta_2 x_{2i} \).

3. Motivating Dataset

- **To exemplify the suggested methodology for meta-analysis,** we reassess the study quality and design characteristics of systematic review data relating to the efficacy of Interleukin-1 Receptor Antagonist (IL-1RA) in animals exposed to focal cerebral ischaemia (modeling human with stroke).
- **The difference in the effects of IL-1RA compared to a control group exposed to vehicle or to no treatment in animal studies of focal cerebral ischaemia is the outcome of interest.** The primary endpoint was infarct volume.

4. Results

Table 1: (a) Summary of the selected univariate meta regression results using each study characteristic variables as a moderator to explain the extra heterogeneity present in infarct volume data, (b) Parameter estimates from multivariable meta regression model, where * represents significant effect of a moderator. (FB noninformative priors: \( \eta \sim N(0, 10^4) \), \( \tau^2 \sim 0.1 \), \( \sigma^2 \sim 0.01 \)) ran for 1000 iterations with 1000 burn-in periods.

5. Conclusions

- DL gives higher \( \tau^2 \) than REML and FB; it is negatively biased when there is high heterogeneity due to false assumption that within study variances are known akin to DL and REML.
- REML reduces bias by excluding the summary effect parameter in \( \tau^2 \) estimation but due to its iterative process, convergence is not guaranteed.
- Bayesian approach accounts for uncertainty in estimation and does not assume that within study variances are known akin to DL and REML.
- Multivariable meta-regression explains more heterogeneity between studies and leads to more generalisable results than simple random effects meta-analysis or univariate meta-regression.

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