MULTIVARIATE DERSIMONIAN AND LAIRD RANDOM EFFECTS META-ANALYSIS - THEORY AND APPLICATIONS

Dan Jackson, Ian R. White and Simon G. Thompson

MRC Biostatistics Unit, Cambridge, U.K.

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Univariate random effects meta-analysis

- We assume that the studies' outcomes (typically these are estimates of treatment effect) are normally distributed: $Y_i|\mu_i \sim N(\mu_i, \sigma_i^2)$, where σ_i^2 is 'known'.
- We assume between-study normality: $\mu_i \sim N(\mu, \tau^2)$.
- Hence we have marginal normality and the conventional model random effects model: $Y_i \sim N(\mu, \sigma_i^2 + \tau^2)$.
- Once τ^2 has been estimated the standard procedure for making inference about μ is straightforward.

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DerSimonian and Laird univariate meta-analysis

- This is a *very* popular approach.
- Cochran's heterogeneity statistic is: $Q = \sum_{i=1}^{n} w_i (Y_i - \bar{Y})^2$, where $w_i = \sigma_i^{-2}$, $\bar{Y} = \sum_{i=1}^{n} w_i Y_i / \sum_{i=1}^{n} w_i$ and n denotes the number of studies.
- DerSimonian and Laird (1986) evaluated $\mathrm{E}[Q] = (n-1) + \left(S_1 - \frac{S_2}{S_1}\right)\tau^2$, where $S_r = \sum_{i=1}^{n} w_i^r$, and suggested a moments estimate for τ^2.

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Why is the univariate DerSimonian and Laird procedure so popular?

- The DerSimonian and Laird procedure is non-iterative, is very easy to implement and is intuitively appealing.
- The DerSimonian and Laird procedure is not optimal but is valid even if the random effect is not normally distributed.
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Multivariate random effects meta-analysis

- In the bivariate case ($k = 2$) we have

$$\begin{pmatrix} X_i \\ Y_i \end{pmatrix} \sim N\left(\begin{pmatrix} \mu_X \\ \mu_Y \end{pmatrix}, \begin{pmatrix} \sigma_{X_i}^2 + \tau_X^2 & \rho_i \sigma_{X_i} \sigma_{Y_i} + \kappa \tau_X \tau_Y \\ \rho_i \sigma_{X_i} \sigma_{Y_i} + \kappa \tau_X \tau_Y & \sigma_{Y_i}^2 + \tau_Y^2 \end{pmatrix} \right)$$

- This variance matrix is the sum of the 'known' within-study variance matrix and the between-study variance matrix. We now have three between-study variance matrix entries to estimate however.
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Multivariate DerSimonian and Laird meta-analysis

- Despite the popularity of the univariate DerSimonian and Laird procedure, no-one has hitherto managed to extend this to the multivariate scenario, so computationally intensive and fully parametric procedures like REML and MCMC have been used in the multivariate setting instead.
- For a more detailed account of our method, including an extension to multivariate meta-regression (with potentially different covariates for each study outcome) see our paper on Statistics in Medicine early view.

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‘Cochran’s Q matrix’

- We define a Q matrix:

$$Q = \begin{bmatrix} \sum_{i=1}^{n} \frac{(X_i - \bar{X}_1)^2}{\sigma_{X_i}^2} & \sum_{i=1}^{n} \frac{(X_i - \bar{X}_2)(Y_i - \bar{Y}_2)}{\sigma_{X_i}\sigma_{Y_i}} \\ \sum_{i=1}^{n} \frac{(X_i - \bar{X}_2)(Y_i - \bar{Y}_2)}{\sigma_{X_i}\sigma_{Y_i}} & \sum_{i=1}^{n} \frac{(Y_i - \bar{Y}_1)^2}{\sigma_{Y_i}^2} \end{bmatrix}$$

where (and similar definitions are used for $\bar{Y}_1$ and $\bar{Y}_2$)

$$\bar{X}_1 = \frac{\sum_{i=1}^{n} X_i/\sigma_{X_i}^2}{\sum_{i=1}^{n} 1/\sigma_{X_i}^2}; \qquad \bar{X}_2 = \frac{\sum_{i=1}^{n} X_i/(\sigma_{X_i}\sigma_{Y_i})}{\sum_{i=1}^{n} 1/(\sigma_{X_i}\sigma_{Y_i})}.$$

'Cochran's Q matrix' (allowing for missing outcomes)

- If there are missing outcomes we use

$$Q = \begin{bmatrix} \sum_{i \in \mathbf{R}_X} \frac{(X_i - \bar{X}_1)^2}{\sigma^2_{X_i}} & \sum_{i \in \mathbf{R}_{X,Y}} \frac{(X_i - \bar{X}_2)(Y_i - \bar{Y}_2)}{\sigma_{X_i}\sigma_{Y_i}} \\ \sum_{i \in \mathbf{R}_{X,Y}} \frac{(X_i - \bar{X}_2)(Y_i - \bar{Y}_2)}{\sigma_{X_i}\sigma_{Y_i}} & \sum_{i \in \mathbf{R}_Y} \frac{(Y_i - \bar{Y}_1)^2}{\sigma^2_{Y_i}} \end{bmatrix}$$

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The expectation of the Q matrix

- The expectations of the diagonal entries of the Q matrix are linear functions of the between-study variances.
- $e_{(2,1)} = e_{(1,2)} = a + b\kappa\tau_X\tau_Y$ where

$$a = \sum_{i \in \mathbf{R}_{X,Y}} \rho_i - \frac{\sum_{i \in \mathbf{R}_{X,Y}} \frac{\rho_i}{\sigma_{X_i}\sigma_{Y_i}}}{\sum_{i \in \mathbf{R}_{X,Y}} \frac{1}{\sigma_{X_i}\sigma_{Y_i}}}$$

and

$$b = \sum_{i \in \mathbf{R}_{X,Y}} \frac{1}{\sigma_{X_i}\sigma_{Y_i}} - \frac{\sum_{i \in \mathbf{R}_{X,Y}} \frac{1}{\sigma^2_{X_i}\sigma^2_{Y_i}}}{\sum_{i \in \mathbf{R}_{X,Y}} \frac{1}{\sigma_{X_i}\sigma_{Y_i}}}.$$

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Now match moments and solve linear equations

- We can very quickly and easily evaluate the necessary quadratic forms and solve the resulting linear equations to produce estimates of all entries of the between-study variance matrix.
- We call this estimated between-study variance matrix Σ_{DL}. This need not be positive semi-definite however!

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‘Truncating’ the matrix Σ_{DL}

- The Spectral Decomposition Theorem gives us $\Sigma_{DL} = \sum_{i=1}^{k} \lambda_i e_i e_i^T$, where the λ_i are the eigenvalues of Σ_{DL} and the e_i are the corresponding normalised eigenvectors.
- Our estimate of the between-study variance matrix is $\Sigma_{DL+} = \sum_{i=1}^{k} \max(0, \lambda_i) e_i e_i^T$.

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Simulation studies

- The proposed procedure performs similarly in almost all ways to the more established iterative REML approach but is much less computationally intensive.
- For full details of the simulation study, please see the afore mentioned paper on Statistics in Medicine early view.
- For 'fun', 100 studies, with complete data on 15 outcomes, were simulated. REML, implemented using the new Stata command mvmeta, took 12 hours to converge on a UNIX system; by comparison the proposed approach took around 2 seconds on a laptop.

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Application 1

- This application is a systematic review concerning the sensitivity and specificity of tumour markers used for diagnosing primary bladder cancer. One of these markers (telomerase, a ribonucleoprotein enzyme) was evaluated in 10 studies. The data comprised logit sensitivity and specificity, and their standard errors.

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- Estimating the between-study variance matrix using REML provides

$$\Sigma_{REML} = \begin{pmatrix} 0.202 & -0.723 \\ -0.723 & 2.584 \end{pmatrix},$$

  with estimated overall means of 1.166 and 2.058, with standard errors of 0.186 and 0.561, respectively .

- Using the proposed multivariate DerSimonian and Laird procedure gives

$$\Sigma_{DL+} = \begin{pmatrix} 0.200 & -0.668 \\ -0.668 & 2.233 \end{pmatrix},$$

  with estimated means of 1.166 and 2.030, and with standard errors of 0.186 and 0.520, respectively.

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Application 2

- The Fibrinogen Studies Collaboration is a meta-analysis of individual data on 154012 adults from 31 prospective studies. This random effects model involves four correlated parameters, which are log hazard ratios, of the second to fifth groups relative to the first.
- Estimating the between-study variance matrix using REML provides

$$\Sigma_{REML} = \begin{pmatrix} 0.052 & 0.064 & 0.068 & 0.053 \\ 0.064 & 0.082 & 0.088 & 0.075 \\ 0.068 & 0.088 & 0.095 & 0.086 \\ 0.053 & 0.075 & 0.086 & 0.107 \end{pmatrix},$$

with estimated log hazard ratios of 0.162, 0.393, 0.562 and 0.897, and with standard errors of 0.080, 0.088, 0.091 and 0.094, respectively.

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Application 2

- The multivariate DerSimonian and Laird procedure gives the somewhat different estimated between-study variance matrix of

$$\Sigma_{DL^+} = \begin{pmatrix} 0.030 & 0.043 & 0.050 & 0.038 \\ 0.043 & 0.063 & 0.073 & 0.068 \\ 0.050 & 0.073 & 0.085 & 0.077 \\ 0.038 & 0.068 & 0.077 & 0.126 \end{pmatrix},$$

with estimated log hazard ratios of 0.176, 0.405, 0.565 and 0.907, and with standard errors of 0.067, 0.077, 0.084 and 0.094, respectively. These inferences are in reasonable agreement with REML.

References

- Cochran WG. The combination of estimates from different experiments. Biometrics, 1954; 10: 101-129.
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