Appendix

This model was built for the meta-analytical assessment of a linear increase of treatment effects with increasing doses of clonidine added to a constant dose of an intrathecal local anesthetic.

1. Preliminaries

Each study i consists in the collection of measurements. In a given study i, there can be g_i active groups, each testing a dose of clonidine. Within each study i, each dose of clonidine will always be added to the same dose of a local anesthetic. Each of these active groups consists of a sample size M_{ij}, where j denotes the j^{th} group of the study i, with $1<j<g_i$. We assume that all individuals in these g_i groups are independent, but that they share the same control group.

Control groups:

Individuals in the control groups do not receive clonidine, but they do receive a local anesthetic alone. For each individual in the control groups, the outcome Y_{ijk} is the effect measured on the k^{th} individual in the j^{th} control group of the i^{th} study. We assume that the sample size of the control groups is given by N_{ij}, and therefore, that $1<k<N_{ij}$.

The statistical model we assume is a linear model of the form:

$$Y_{\text{ijk}} = \beta_0 + \beta_1 x_i + \varepsilon_{ijk}$$

for the unknown parameters βl, $l = 0,1$ and where x_i stands for the dose of the local anesthetic that is injected (in both the individuals of the control and the active group(s) of this study *i*), and ε_{ijk} denotes the statistical error which we assume to be centered of variance σ_i^2.

We then assume that there is only one control group in each study (which is the case in most clinical studies), that is we set that:
$N_{ij}=N_i$ and reduce the model to

$$Y_{ik} = \beta_0 + \beta_1 x_i + \varepsilon_{ik} \qquad 1<k<N_i$$

Active groups:

In the active groups (of sample size M_{ij}), individuals receive clonidine as an additive to the local anesthetic. We shall denote by $x^{'}_{ij}$ the dose of clonidine that is given to an individual in the j^{th} group of the study *i*, and Z_{ijl} the effect measured on the l^{th} individual in the j^{th} active group of the study *i*.

The statistical model is linear of the form:

$$Z_{ijl} = \beta^{'}_0 + \beta_1 x_1 + \beta^{'}_2 x^{'}_{ij} + \varepsilon_{ijl} \qquad 1<l<M_{ij}$$

2. Observations

This is about meta-analysis; thus, the data consists in empirical means and empirical standard deviations within each group j of each study i, that is, for the unique control group per study,

$$D_i = \frac{1}{N_i}\sum_{k=1}^{N_i} Y_{ik} = \beta_0 + \beta_1 x_i + E_i$$

where we set $$E_i = \frac{1}{N_i}\sum_{k=1}^{N_i} \varepsilon_{ik}$$

E_i is an error term associated with the controls of group i, and is of variance

$$Var(E_i) = \frac{1}{N_i}\sigma_i^2$$

Turning to the j^{th} active group of study i, we proceed similarly to obtain

$$D'_{ij} = \frac{1}{M_{ij}}\sum_{l=1}^{M_{ij}} Z_{ijl} = \beta'_0 + \beta_1 x_i + \beta'_2 x_{ij} + E'_{ij}$$

where we set $$E'_{ij} = \frac{1}{M_{ij}}\sum_{l=1}^{M_{ij}} \varepsilon_{ijl}$$

of variance $$Var(E'_{ij}) = \frac{1}{M_{ij}}\sigma'^2_{ij}$$

Our observations thus follow the linear model with correlated errors

$$O_{ij} = D'_{ij} - D_i$$

$$= (\beta'_0 - \beta_0) + \beta'_2 x'_{ij} + \Delta_{ij} \qquad\qquad \Delta_{ij} = E'_{ij} - E_i$$

The correlation matrix between studies vanishes (since the different studies are independent of each other); inside each study, we have:

$$\mathrm{E}(\Delta_{ij}\Delta il) = \frac{\sigma_i^2}{N_i} \qquad\qquad \text{when } j \neq l,$$

and

$$\mathrm{E}(\Delta_{ij}\Delta il) = \frac{\sigma_i^2}{N_i} + \frac{\sigma_{ij}^2}{M_{ij}} \qquad\qquad \text{when } j = l.$$

Let us then denote by C the covariance matrix of the error process. C is known from the data.

The data consists thus in vector (D_i) of the means of the control groups, and in vector (D_{ij}) of the means of the various active groups of each study, and of covariance matrix C which can be obtained from the data as shown above.

Linear model:

Let B be a upper triangular matrix such that $BB^T = C$, which can be obtained using Cholewsky's decomposition.

Then our model is of the form

$$O = A\theta + BG \qquad (1)$$

where the unknown parameter θ is given by

$$\theta = \begin{pmatrix} \beta_0^{'} - \beta_0 \\ \beta_2 \end{pmatrix}$$

and the design matrix A is given as

$$A \begin{pmatrix} 1 & x_1 \\ \ldots & \ldots \\ 1 & x_l \end{pmatrix}$$

and where the Gaussian error G is composed of i.i.d. standard normal components N(mean=0, variance=1), that is with Cov(G)=Id.

The coefficient of interest is β_2, and our aim is to check if it is significantly positive.

To this purpose, we transform linearly the above model to get

$$B^{-1}O = B^{-1}A\theta + G, \qquad (2)$$

We then use a basic statistical software to check the significance of the unknown parameter β_2 which models the effect of the additive (i.e. clonidine) on the data.