Practical 1: Network meta-analysis in R

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R packages

We will use the package **readxl** to import excel data and the packages **netmeta** to run network meta-analyses.

```
library(readxl)
library(netmeta)
```

Datasets

Acute mania dataset

The file AcuteMania.xls comprises data from the secondary efficacy outcome of the network meta-analysis published in Cipriani et al. (2011).

```
AcuteMania = read_excel("~/_mydrive/Teaching/Kea NMA course/Practicals/AcuteM
ania.xls")
AcuteMania = as.data.frame(AcuteMania)
str(AcuteMania)
```

This is a full network and includes 47 studies comparing the effectiveness of active drugs and placebo. The outcome is efficacy dichotomous (responders r out of randomized n).

The dataset is in *long format*; that is, each row is a study arm. The same id is used to show that different arms belong to the same study (studyid). This format is popular and we encourage researcher to use it when collecting data from studies.

The variable 'rob' contains information about the risk of bias (1 means low, 2 moderate and 3 high risk of bias).

Schizophrenia dataset

The file Leucht.xls comprises data from the primary outcome (efficacy) of the systematic review and network meta-analysis published in Leucht et al. (2013).

```
Leucht = read_excel("~/_mydrive/Teaching/Kea NMA course/Practicals/Leucht.xls
")
Leucht = as.data.frame(Leucht)
str(Leucht)
```

We present only the primary outcome (efficacy). The standardized mean difference for the change in the symptoms scale between the first treatment (treat1) and the second treatment (treat2), Negative values favor treat1.

Analysis of the network comparing antimanic drugs

Let's first get some information on the studies included in the network meta-analysis.

Which treatment is the most frequently studied?

How many studies have more than two arms?

Because our data are in long format we need first to transform them into the *contrast-based format* with a single pairwise comparison per row (this format is required by R function netmeta). This transformation can be done by using the pairwise function.

```
AcuteManiaPair = pairwise(treat = treatment, event = r, n = n,
                          data = AcuteMania, studlab = studyid, sm = "OR")
```

Now compare the two datasets by looking at the first three studies. What format have they been converted to?

```
AcuteMania[AcuteMania$studyid < 4, ]
AcuteManiaPair[as.numeric(AcuteManiaPair$studlab) < 4, 1:9]
```

What is now presented in the new variables TE and seTE?

Network plot

To plot the network you need first to create an object of class netmeta by running the command. Note: if we used pairwise to transform our data, we can use this object as the single argument to the netmeta function.

```
net1 = netmeta(AcuteManiaPair)
```

Then use the following netgraph command to produce a network plot

```
netgraph(net1)
```

Check the help file for the netgraph command to see the options you have.

Now re-create a plot by weighting the nodes and edges according to the number of studies evaluating each treatment and comparison.

```
netgraph(net1, plastic = FALSE, multiarm = FALSE, thickness = "number.of.studies",
         points = TRUE, cex.points = table(AcuteMania$treatment) / 2, col = 1
)
```

Optional: You can create 3-D plots using the **rgl** library.

```
# install.packages("rgl")
# netgraph(net1, plastic = FALSE, multiarm = FALSE, dim = "3d", col = 1)
```

Performing a network meta-analysis

The netmeta command that we run before estimates NMA treatment effects using default options. Let us define what we exactly want in terms of analysis using the arguments (see the list of arguments in the help file). Let us run only a random effects meta-analysis and use Placebo as the reference to present the results.

```
net1 = netmeta(AcuteManiaPair,  sm = "OR", ref = "PLA",
               comb.fixed = FALSE, comb.random = TRUE)
summary(net1, digits = 2)
```

What does the output matrix show?

Which drug presents the largest response rate compared to Placebo?

How much is the heterogeneity? How has it being estimated and under which assumptions?

Compare the results with those reported in Figure 3 by Cipriani et al. (2011). Note: Cipriani et al. reported placebo versus active while we calculated active versus placebo. To see the estimates for placebo versus drug simply set the argument baseline.reference=FALSE.

```
net1 = netmeta(AcuteManiaPair,  sm = "OR", ref = "PLA",
               comb.fixed = FALSE, comb.random = TRUE, baseline.reference = F
ALSE)
summary(net1, digits = 2)
```

Several elements are stored under the *net1* object.

The heterogeneity standard deviation is estimated as

```
round(net1$tau, 3)
```

Presenting the results from a network meta-analysis

League table

To obtain a league table using the NMA object *net1* use the netleague function.

```
leaguetable = netleague(net1, digits = 2)
leaguetable
```

This command produces a list with several object. You can obtain the league table in an exportable format (a database) and export it in a .csv file

```
write.csv(leaguetable$random, "leaguetable-random.csv", row.names = FALSE)
```

This file can be opened, for example, with Excel or LibreOffice.

Optional: You can also directly export a league table to an Excel file.

```
# install.packages("WriteXLS")
# library(WriteXLS)
```

```
# WriteXLS(leaguetable$random, ExcelFileName = "leaguetable-random.xls",
#          SheetNames = "Leaguetable (random)", col.names = FALSE)
```

Forest plots

The function forest.netmeta will, as expected, produce forest plots of NMA estimated effect sizes against the reference. The reference can be re-specified using the 'ref' argument.

```
forest(net1)
forest(net1, ref = "HAL")
```

Which are the three most effective interventions compared to placebo?

Are there any differences between active interventions?

It is always useful to see the effect sizes in a consistent order, e.g. increasing

```
forest(net1, sortvar = TE)
```

The variable 'k' stored in *net1* contains the number of direct comparisons. We can plot them in the forest plot.

```
forest(net1, sortvar = TE,
       leftcols = c("studlab", "k"), leftlabs = c("Drug", "Direct\nstudies",
       xlab = "Response to treatment", smlab = "NMA random effects"))
```

Ranking treatments

The function netrank uses a transformation of the p-value to derive P-scores which are equivalent to SUCRA values.

```
netrank(net1, small = "bad")
```

Which intervention has the highest probability of "beating" all other treatments?

You can even add the P-scores (equivalent to SUCRA values) in the forest plot and sort the summary ORs accordingly:

```
forest(net1,
       rightcols = c("effect", "ci", "Pscore"),
       rightlabs = "P-Score", sortvar = -Pscore, small = "bad",
       xlab = "Response to treatment", smlab = "Active drug vs placebo")
```

Sensitivity analysis

When we created AcuteManiaPair we lost the information about risk of bias (this feature will be available in a future version of package **netmeta**). We can use the following two commands to copy the risk of bias column from the AcuteMania dataset (long format) to AcuteManiaPair (contrast-based format).

```
data.rob = AcuteMania[!duplicated(AcuteMania$studyid), c("studyid", "rob")]
AcuteManiaPair = merge(AcuteManiaPair, data.rob, by.x = "studlab", by.y = "st
udyid")
```

The first command expects that the AcuteMania dataset is ordered by the study number (studyid) which is the case.

As you see there are studies only at low or moderate risk of bias.

```
table(AcuteManiaPair$rob)
```

Cipriani et al. (2011) have excluded any studies at high risk of bias from the systematic review.

Let us perform a network meta-analysis using studies only at low risk of bias. Note: for this command we have to explicitly state the first five arguments instead of using AcuteManiaPair (this will also be changed in a future version of package **netmeta**).

```
net2 = netmeta(TE, seTE, treat1, treat2, studlab, data = AcuteManiaPair, subs
et=c(rob.x==1),
               sm = "OR", ref = "PLA", comb.fixed = FALSE, comb.random = TRUE
)

summary(net2, digits = 2)
```

Is there evidence that the network that includes only low risk of bias studies is more homogeneous?

Analysis of the network comparing antispychotic drugs

The schizophrenia dataset Leucht is available in the contrast-based format. Accordingly, we do not have to use pairwise to transform the dataset.

Note: Some of the SMDs (variable 'effect') or their standard errors (variable 'se') have been approximated from other data presented in the paper (such as p-values) and hence, they might not appear to be internally consistent in the multi-arm trials. Hence, you shall use the argument tol.multiarm=0.075 to have netmeta running.

```
net3 = netmeta(effect, se, treat1, treat2, study, data = Leucht,
               sm = "SMD", ref = "PBO", comb.fixed = FALSE, comb.random = TRU
E,
               tol.multiarm = 0.075)
```

Then, present and interpret the results.

```
summary(net3)
forest(net3)
netrank(net3)
```

References

- Cipriani A et al. (2011): Comparative efficacy and acceptability of antimanic drugs in acute mania: a multiple-treatments meta-analysis. *The Lancet*, **378**(9799), 1306-15.

- Leucht S et al. (2013): Comparative efficacy and tolerability of 15 antipsychotic drugs in schizophrenia: a multiple-treatments meta-analysis. *The Lancet*, **382**(9896), 951-62.