

A computational way station for reporting network meta-analyses

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1 Network meta-analysis reporting

Pairwise analyses between treatment and control, exposed and unexposed, intervention and no intervention, are conventionally undertaken with meta-analysis in fields such as ecology, medicine, and the social sciences [1]. Network meta-analysis provides a means of comparing three or more treatments or interventions, including control or placebo [5]. The question answered by a network meta-analysis is not *if* a treatment works, but *which* treatments perform better, comparatively [4]. A particularly useful aspect of network meta-analysis is combining the results of more than one pairwise analysis and constructing indirect comparisons, where pairwise evidence is unavailable, from a network of direct comparisons. An example of direct comparisons provided by existing evidence is shown in Figure 1. Network meta-analysis

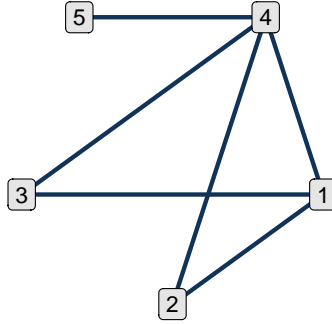


Figure 1: This network shows the direct evidence provided by pairwise comparisons in seven studies on treatments for Parkinson’s disease [11]. Each node represents a treatment, including one placebo, represented by the fourth node. Where there is an edge connecting two treatment nodes, there exists a pairwise comparison in the literature between these two treatments. Where there is no edge connecting the nodes of the network, there is no direct evidence.

17 converts the network to a complete graph, where all treatments are compared
 18 with all other treatments, that is, every node connects to every other node
 19 via direct or indirect comparison.

20 Software to implement network meta-analyses are relatively new and do
 21 not provide complete toolchains for specific protocols, such as reporting re-
 22 sults according to Cochrane’s handbook [5]. For example, the handbook
 23 recommends reporting the network of direct evidence, for which the R pack-
 24 age `multinma::` includes a tool [11], an example of which is shown in Figure
 25 1. However, the handbook also recommends reporting a **contribution ma-**
 26 **trix** of the percentage of each study’s contribution to the estimated overall

27 effect, and this is not provided as a visualisation tool with `multinma::`.

28 Furthermore, open source scientific software is shifting from all-purpose
29 packages for an entire analysis, such as `metafor::`, to smaller task-specific
30 software packages. One method of aggregation of tools is a **metapackage**,
31 such as `tidyverse::` [16], for data engineering, which comprises a number of
32 packages that each pertain to different problems, such as `ggplot2::` for data
33 visualisation, and `dplyr::` for Boolean data manipulation. Here we explore
34 another way of aggregating resources, for the specific purpose of network
35 meta-analysis reporting: a computational **way station**, a temporary resting
36 place between two points of travel, of toolchains and tool development. Since
37 protocols and tools are are still being developed, this is a way station between
38 a single person’s analysis, and a resource that is definitive for all practitioners
39 to follow.

40 1.1 A snapshot of a living resource

41 In this manuscript, we next describe the gaps in the toolchain for implement-
42 ing network meta-analysis via R according to Cochrane’s reporting standards.
43 Standards for network meta-analysis are not, however, fixed, but in devel-
44 opment, and Cochrane’s reporting standards may not be appropriate for,
45 say, ecological network meta-analyses. Thus, instead of aiming to provide
46 a complete toolchain for network meta-analysis, we instead propose a com-
47 putational way station as a meeting place for stakeholders with different
48 priorities to provide perspective and collaborate. This way station is a **liv-**

49 **ing resource**, in anticipation of future updates following stakeholder input
50 and computational development, comprising multiple points of access:

51 **website** A website with vignettes of toolchains. Currently the existing solu-
52 tions for Cochrane’s reporting standards are provided, however there is
53 scope for future vignettes for network meta-analyses according to other
54 discipline or organisational protocols.

55 **open source code repository** Source code is provided for toolchains and
56 software extensions.

57 **contributing** Detailed instructions for different stakeholders with varying
58 levels of mathematical and computational training to contribute.

59 **issues** In addition to the source code, the issues associated with the code
60 repository provide a public record for discussions.

61 Living resources provide a solution to the problem of overabundance of
62 systematic reviews, flooding literature to the point that decision makers are
63 unsure of where to look [3, 7, 8, 13]. Consider Covid-19, where in the first 88
64 days after naming the disease, there already existed 88 systematic reviews,
65 one for every day since the disease was named [10]. Cochrane’s COVID-NMA
66 initiative (<https://covid-nma.com/>) is a living synthesis solution to this prob-
67 lem, via network meta-analysis of regularly updated Covid-19 research [2].

68 **nmareporting::** is also a living resource, but to solve a different problem.
69 How to bring people together for open scientific collaboration when not all

70 the solutions exist. As a package it is not ready for CRAN, and may never be
71 intended for CRAN. In some ways similar to the `rethinking::` package the
72 accompanies the canonical¹ text, *Statistical Rethinking*, the intention of this
73 software is not to ship a polished piece of software to CRAN, or a publish a
74 manuscript with a definitive toolchain [6]. Rather, this manuscript provides a
75 snapshot of a living resource for open collaboration on network meta-analysis
76 reporting.

77 2 Toolchain gaps in Cochrane reporting stan- 78 dards

79 There exist several software packages for conduction network meta-analysis in
80 R; for example, `gemtc::` [15], `multinma::` [11], and `netmeta::` [14]. Different
81 tools will no doubt have unique advantages and disadvantages, however, there
82 is no one tool for all reporting standards for a Cochrane network meta-
83 analysis. Furthermore, visualisations and reporting for meta-analysis are
84 still being developed.

85 2.1 Missing tables and improved visualisations

86 Cochrane recommends reporting the percentage each study contributes to
87 the overall estimated effect via a **contribution matrix**, shown in Figure 2.

¹At the time of writing *Statistical Rethinking* has 1243 citations.

Figure 11.6.b Contribution matrix for the network on interventions for heavy menstrual bleeding presented in Figure 11.4.a. Four direct comparisons in the network are presented in the columns, and their contributions to the combined treatment effect are presented in the rows. The entries of the matrix are the percentage weights attributed to each direct comparison. The intervention labels are: A, first generation hysteroscopic techniques; B, hysterectomy; C, second generation non-hysteroscopic techniques; D, Mirena

		Direct comparisons in the network (% contribution)			
		A-B	A-C	A-D	C-D
Network meta-analysis estimates	Mixed estimates				
	A-B	100.0			
	A-C		97.8	1.1	1.1
	A-D		34.5	34.1	34.5
	C-D		14.4	14.4	71.2
	Indirect estimates				
	B-C	49.6	48.9	0.7	0.7
	B-D	38.5	28.0	15.5	28.0
Entire network		34.4	36.4	10.5	21.7
Included studies		5	11	1	3

Figure 2: A contribution matrix shows what percentage each study contributes to the overall estimated effect in a network meta-analysis. This is the example given in the Cochrane Handbook [5].

88 The `netmeta::` package has tools for contribution matrices, but if one
 89 is performing the analysis with, say, `multinma::`, it is unclear how to piece
 90 together the tools to produce a complete set of Cochrane reporting.

91 *Gav, is the contribution matrix only for frequentist analysis?*

92 Visualisations, too, are still in development. A recent improvement on
 93 standard forest plots are orchard plots which contain not only credible in-
 94 tervals, but prediction intervals, and group studies categorically, particularly
 95 useful for large meta-analyses [9].

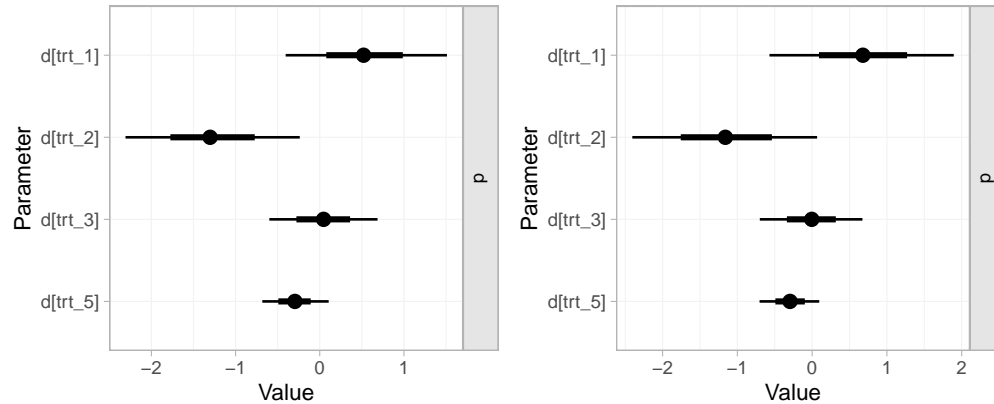


Figure 3: On the left is a forest plot of all analyses. On the right is a forest plot of the analysis with a randomly selected study omitted.

2.2 Sensitivity

Sensitivity in network meta-analysis measures how much the studies agree in results. A standard approach to measuring this is a 'leave one out analysis', shown in Figure 3, where a study is randomly selected to be omitted, and the meta-analysis is rerun to see if the results differ. We randomly² select

```
## [1] "study_1"
```

to remove from the analysis.

In this case, there is little disagreement between the studies. However, it does raise the question of what the analysis would report if another study were omitted, and, indeed, what if more than one study were omitted? In

²This manuscript is fully reproducible, with all analyses and code embedded in the document. The source for this manuscript can be found here: <https://github.com/softloud/nmareporting/blob/master/manuscript/draft/nmarep-ms.Rnw>.

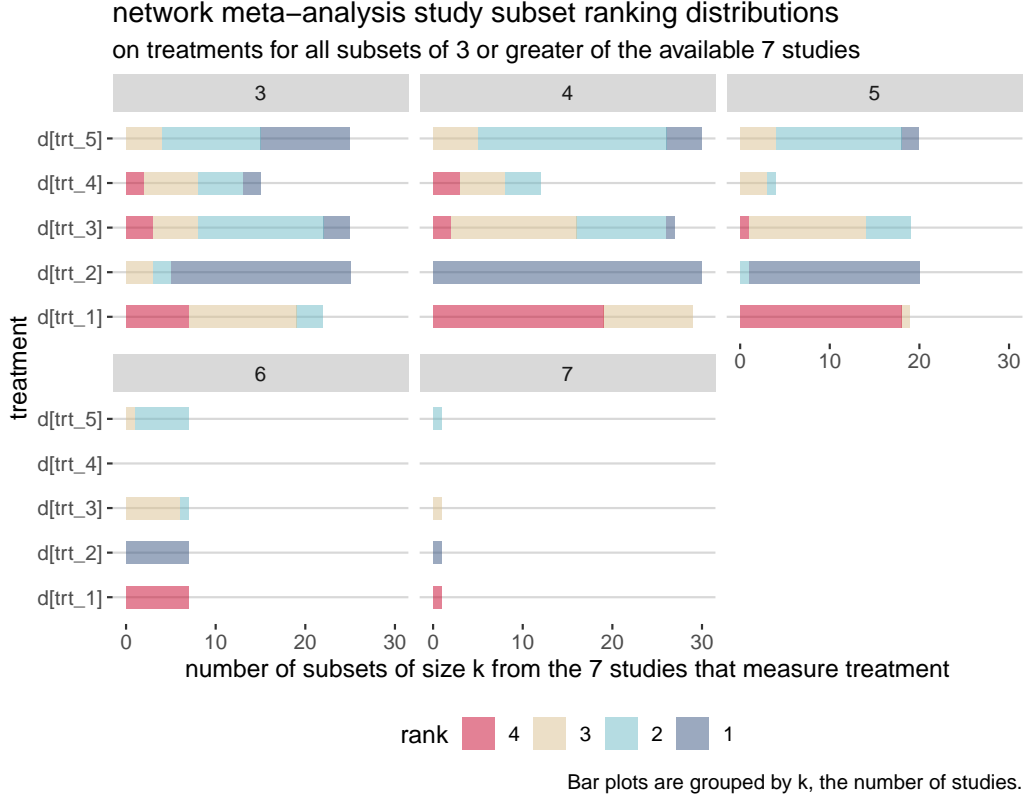


Figure 4: Rankings for leave m out analyses, where $m = 0, \dots, 4$ studies omitted from the total 7 studies available.

Figure 4, we provide aggregation of rankings of network meta-analyses run on all subsets, of size three or greater, of the studies.

Unsurprisingly, the ranking are in agreement when including all seven studies, with treatment 2 predicted to have the greatest reduction in the measure of interest, the mean off-time reduction in patients given dopamine agonists as adjunct therapy in Parkinson’s disease [11]. And as treatment 2 dominates in all subgroups, we surmise that there is confidence in the meta-analytic recommendation of treatment 2.

113 However, other possible inferences do exist in these rankings, supposing
114 we did not have all seven studies, and it is easy to see how a different conclu-
115 sion might be drawn. Furthermore, another drawback is that whilst leave m
116 studies (for $m \leq k$ studies) works for seven studies, this analysis is not prac-
117 tical for meta-analyses that aggregate a larger number of studies. Indeed,
118 the number of network meta-analyses performed in this analysis is

```
## [1] 99
```

119 from seven studies. Clearly this type of analysis would become computa-
120 tionally intractable for larger meta-analyses.

121 A more robust approach would be threshold analysis, where an **invariant**
122 **interval** is provided for each study, showing the interval in which the study's
123 results will not change the ranking [12]. However, this solution is challenging,
124 involving mathematics and **stan** syntax, so providing toolchains, guides, and
125 support for practitioners will surely be helpful.

126 3 Computational way station for open and 127 inclusive scientific method development

128 Stakeholders engage with meta-analyses in multiple ways. A lead researcher
129 may not be interested in interacting with code repositories, but may well have
130 thoughts about how to improve reporting for inference. A computational

131 collaborator may wish to contribute tools for related analyses, even if not
132 directly involved in the project.

133 In this section, we consider developing a toolchain for reporting a Cochrane
134 network meta-analysis, considering how different researchers may wish to
135 provide feedback on the implemented protocol. With increasing levels of
136 computational complexity, we step through how researchers in various roles
137 might contribute.

138 **3.1 Domain-specific principal investigator**

139 Consider a study where the principal investigator (PI) is a psychologist who
140 delegates statistical analysis to other members of the team: a lead statis-
141 tician, and a postdoctoral scholar under their supervision. The PI will in-
142 terpret the meta-analytic findings, but will not wish to interact with code
143 repositories. In this case, an email address of the primary maintainer (the
144 postdoctoral scholar) of the living resource is provided for comments that can
145 then be converted to issues by the maintainer on the repository for discussion
146 amongst the community.

147 **3.2 Lead statistician**

148 The lead statistician will be comfortable with code, but will be time poor in
149 comparison to the maintainer of the living resource, the postdoctoral scholar
150 under their supervision. Whilst they may not have time to contribute they

151 will likely have comments for the maintainer. They will likely have a GitHub
152 account, and thus can contribute to the discussion via issues, where not
153 only the maintainer, but any interested party can consider and add to the
154 suggestions.

155 **3.3 Computational collaborators**

156 Now consider a computational ecologist, interested in developing tools and
157 protocols for their own network meta-analyses. In this case, they may wish
158 to contribute new vignettes to the website, with new toolchains, as well as
159 develop new tools to fill the toolchain gaps.

160 The R package `usethis::` includes a workflow for contributing to some-
161 one else's package³ [17].

162 In Figure 5 is a sketch of the workflow for contributing to `nmareporting::`,
163 the underlying code base of the site and development. Let us suppose
164 the ecologist is contributing an ecology-specific vignette for network meta-
165 analysis.

166 **4 Conclusion**

167 In the era of big data and rapid-fire advances in statistical software, research
168 is still adapting to what, in fact, constitutes a useful research artifact. Math-
169 ematical algorithms are conventionally implemented via software. Computa-

³Workflow documentation available here: <https://usethis.r-lib.org/articles/articles/pr-functions.html>

```

library(usethis)
# create a fork and clone
create_from_github("softcloud/nmareporting")
# create a branch for the specific contribution
pr_init("ecovignette")
#
# ecologist then writes vignette
#
# contribute the vignette to the code repository
pr_push()
#
# waits for maintainer to merge
#
# once the maintainer has merged
pr_finish()

```

Figure 5: A workflow for contributing to the `nmareporting::` computational way station.

170 tional way stations provide a meeting point, between a scholar's inception of
 171 an analysis technique, and it's formalisation in scientific protocol.

172 References

- 173 [1] Michael Borenstein, Larry V. Hedges, Julian P. T. Higgins, and Han-
 174 nah R. Rothstein. *Introduction to Meta-Analysis*. John Wiley & Sons.
 175 Google-Books-ID: JQg9jdrq26wC.
- 176 [2] Isabelle Boutron, Anna Chaimani, Joerg J. Meerpohl, Asbjørn
 177 Hróbjartsson, Declan Devane, Gabriel Rada, David Tovey, Giacomo

- 178 Grasselli, and Philippe Ravaud. The COVID-NMA project: Building an
179 evidence ecosystem for the COVID-19 pandemic. 173(12):1015–1017.
- 180 [3] S. Gopalakrishnan and P. Ganeshkumar. Systematic reviews and
181 meta-analysis: Understanding the best evidence in primary healthcare.
182 2(1):9–14.
- 183 [4] Mathias Harrer, Prof Dr Pim Cuijpers², Prof Dr Toshi A. Furukawa³,
184 and Assoc Prof Dr David D. Ebert². *Doing Meta-Analysis in R*.
- 185 [5] Julian PT Higgins, James Thomas, Jacqueline Chandler, Miranda
186 Cumpston, Tianjing Li, Matthew J Page, and Vivian A Welch. *Cochrane
187 handbook for systematic reviews of interventions*. John Wiley & Sons.
- 188 [6] Richard McElreath. *Statistical rethinking: A bayesian course with ex-
189 amples in R and stan*. CRC Press.
- 190 [7] David Moher. The problem of duplicate systematic reviews. 347:f5040.
191 Publisher: British Medical Journal Publishing Group Section: Editorial.
- 192 [8] Morten Hylander Møller, John P. A. Ioannidis, and Michael Darmon.
193 Are systematic reviews and meta-analyses still useful research? we are
194 not sure. 44(4):518–520.
- 195 [9] Shinichi Nakagawa, Malgorzata Lagisz, Rose E. O’Dea, Joanna
196 Rutkowska, Yefeng Yang, Daniel W. A. Noble, and Alistair M.
197 Senior. The orchard plot: Cultivating a forest plot for

- 198 use in ecology, evolution, and beyond. 12(1):4–12. _eprint:
199 <https://onlinelibrary.wiley.com/doi/pdf/10.1002/jrsm.1424>.
- 200 [10] David Naumann. Too many systematic reviews for a disease that has
201 existed for a few months.
- 202 [11] David M. Phillippo. multinma: Network meta-analysis of individual and
203 aggregate data in stan.
- 204 [12] David M. Phillippo, Sofia Dias, A. E. Ades, Vanessa Didelez,
205 and Nicky J. Welton. Sensitivity of treatment recommenda-
206 tions to bias in network meta-analysis. 181(3):843–867. _eprint:
207 <https://rss.onlinelibrary.wiley.com/doi/pdf/10.1111/rssa.12341>.
- 208 [13] Derek Richards. Too many reviews too few trials. 19(1):2–2. Number:
209 1 Publisher: Nature Publishing Group.
- 210 [14] Gerta Rücker, Ulrike Krahn, Jochem König, Orestis Efthimiou, and
211 Guido Schwarzer. netmeta: Network meta-analysis using frequentist
212 methods.
- 213 [15] Gert van Valkenhoef and Joel Kuiper. gemtc: Network meta-analysis
214 using bayesian methods.
- 215 [16] Hadley Wickham. tidyverse: Easily install and load the 'tidyverse'.
- 216 [17] Hadley Wickham and Jennifer Bryan. usethis: Automate package and
217 project setup.