

# 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

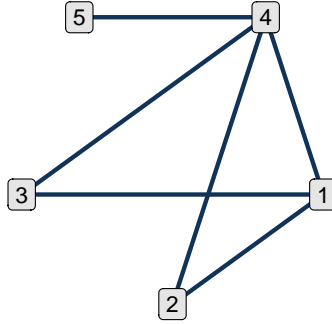


Figure 1: This network shows the direct evidence provided by pairwise comparisons in seven studies on treatments for Parkinson’s disease [11]. Each node represents a treatment, including one placebo, represented by the fourth node. Where there is an edge connecting two treatment nodes, there exists a 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 canonical<sup>1</sup> 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.

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<sup>1</sup>At 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]. `nmareporting::` is a place where imple-  
 96 mentation of orchard plots for network meta-analysis can be developed.

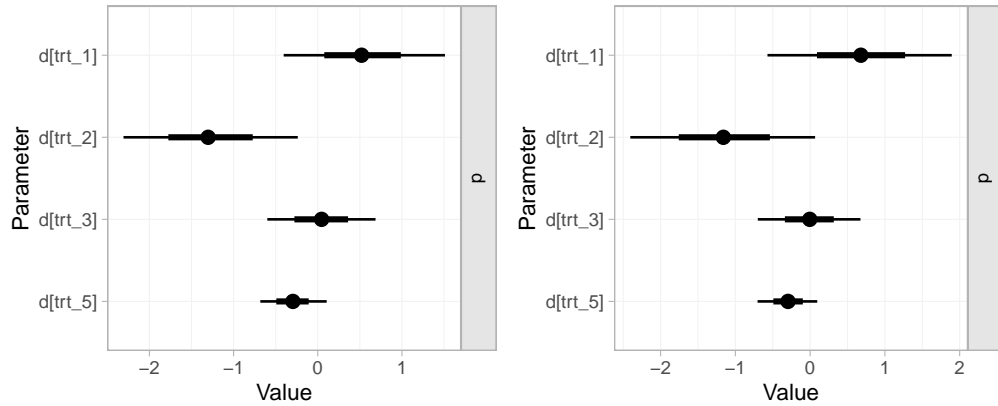


Figure 3: On the left is a forest plot of all analyses. On the right is a forest plot of the analysis with a randomly selected study omitted.

## 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’ [1], 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 randomly<sup>2</sup> 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

<sup>2</sup>This 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>.

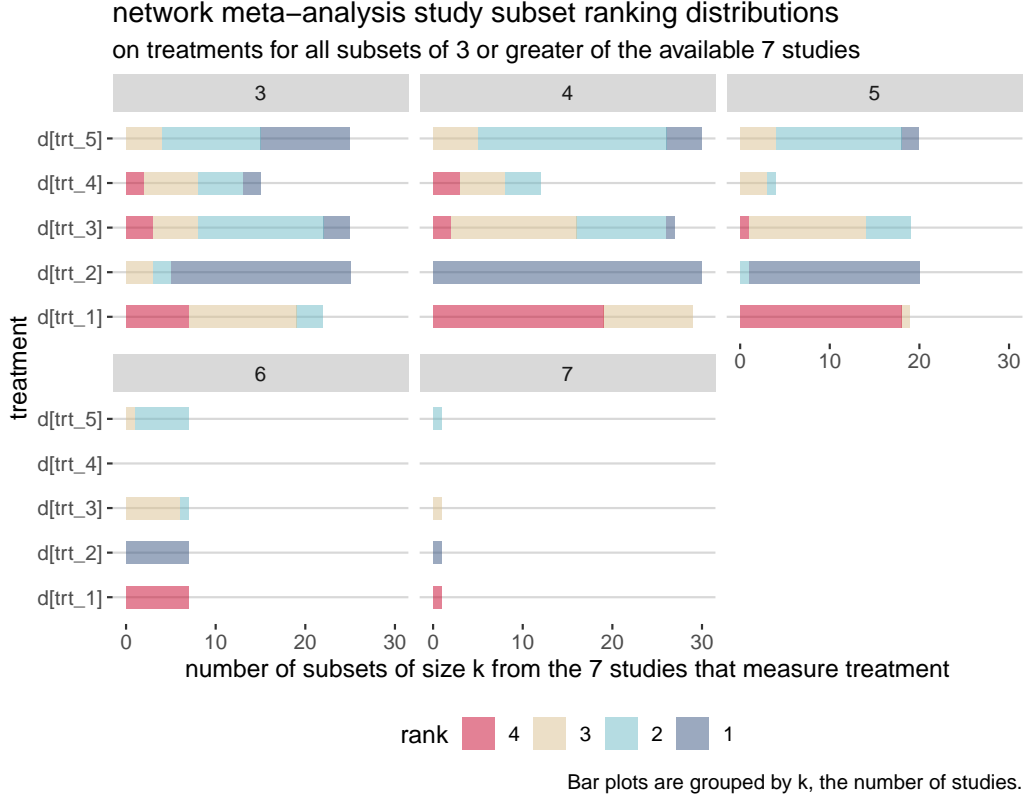


Figure 4: Rankings for leave  $m$  out analyses, where  $m = 0, \dots, 4$  studies omitted from the total 7 studies available.

106 were omitted, and, indeed, what if more than one study were omitted? In  
 107 Figure 4, we provide aggregation of rankings of network meta-analyses run  
 108 on all subsets, of size three or greater, of the studies.

109 Unsurprisingly, the ranking are in agreement when including all seven  
 110 studies, with treatment 2 predicted to have the greatest reduction in the  
 111 measure of interest, the mean off-time reduction in patients given dopamine  
 112 agonists as adjunct therapy in Parkinson’s disease [11]. And as treatment  
 113 2 dominates in all subgroups, we surmise that there is confidence in the



114 meta-analytic recommendation of treatment 2.

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

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

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

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

### 128   **3 Computational way station for open and** 129   **inclusive scientific method development**

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

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

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

### 140 **3.1 Domain-specific principal investigator**

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

### 149 **3.2 Lead statistician**

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

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

### 3.3 Computational collaborators

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

The R package `usethis::` includes a workflow for contributing to someone else's package<sup>3</sup> [17].

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

## 4 Conclusion

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

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<sup>3</sup>Workflow 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.

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

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