**Title?**

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# Introduction

Network meta-analysis (NMA) is often used to synthesize evidence in systematic reviews of multiple interventions. The results of such syntheses can be highly important and are increasingly being used for decision making (1,2). Treatment comparisons in a network of interventions may be associated with particular characteristics. Such characteristics may be identified either in the stage of collecting relevant evidence, although theoretically the best efforts have been made to ensure the plausibility of transitivity, or when analysing and interpreting the results. For instance, a comparison may include studies which are on average of highest risk of bias compared to the rest of the network or a comparison may show evidence of inconsistency (alternatively termed incoherence), meaning that the direct studies feeding into it differs from the indirect evidence which also drives its estimation.

A method to identify the flow of evidence in a network of interventions (3) has been developed and is used to identify the degree in which direct comparisons drive the estimation of NMA treatment effects. In particular, it has been shown that network estimates can be derived as a linear combination of pairwise meta-analysis effects. The respective projection matrix is called matrix and provides insight regarding the flow of information in a network of interventions.

Several methodological developments have been based on matrix; among them, Krahn et al. constructed a tool, the net-heat plot, to identify hot spots of inconsistency in a network (4) and Krahn et al. introduced the independent path decomposition for visualizing potentially conflicting inferences of different sources of evidence (5). Salanti et al. proposed the use of matrix to facilitate the evaluation of the quality of evidence (6). In gross terms, Salanti et al. propose to 1) consider the quality of evidence of all pieces of direct evidence 2) derive the percentage contributions of each direct to each network effect and 3) judge upon the quality of evidence of each network estimate.

It is not straightforward how to translate the projection matrix into percentage contributions of each direct comparison to each NMA treatment effect. The approach implemented by Salanti et al., and described in Appendix S1 of (6), has turned out to have some flows [*ref erratum*]. In particular, it underestimates the percentage contribution of direct evidence while does not accurately specifies the percentage contributions of the rest (indirect) comparisons. In this paper, we present a method to translate the entries of the projection matrix into percentages taking into account the properties of the matrix as a flow matrix.

# Methods

Several models have been proposed for synthesizing evidence in a NMA model (7–12). Throughout this paper we will consider the NMA as a random-effects two-stage model described in (7). In the first stage, all pairwise meta-analysis treatment effects are derived and in the second stage evidence from the separate pairwise meta-analyses is synthesized to produce the NMA treatment effects.

## Notation

Consider a set of total treatments examined in studies. The letter is set to be the reference treatment. Studies are classified according to the treatments they compare and we denote the number of comparisons with direct data as . The number of relative NMA treatment effects to be estimated is but the estimation of relative treatment effects allows the derivation of the rest as their linear combination. We collect the treatment effects of the relative treatment effects against the reference treatment in a vector of basic parameters .]

In the following, we will not take into account the correlation induced by multi-arm trials. That is because we want to end up with a matrix to infer how much each direct comparison impacts on each NMA treatment effect. The question of quantifying the influence of each design in the NMA results is of less interest for our purposes that include the investigation of the inheritance of certain comparison-specific characteristics to NMA treatment effects.

## Assumptions

We assume that the similarity of effect modifiers across comparisons is justified and thus the transitivity assumption is deemed plausible. The consistency assumption refers to the statistical manifestation of transitivity and implies that all sources of evidence are in agreement. Consistency is expressed in terms of a consistency equation

and implies that all trials, irrespective of whether they evaluate directly the ‘Y versus X’ comparison, are estimating the same ‘true’ average ‘Y versus X’ treatment effect, .

## Model

Separate pairwise meta-analysis treatment effects are derived and collected in a vector . The vector has elements. Note that if we were taking into account the correlation induced by multi-arm trials the length of would potentially be greater depending on the number of designs –set of treatments being compared- that appear in the studies.

At the second stage the network estimates are derived as

equation 1

where is calculated as

equation 2

where is the design matrix expressing the linear relationships between the available direct comparisons and the basic parameters, is a diagonal matrix containing the variances of the observed direct effects and is a design matrix that links the network estimates with the basic parameters. Thus, matrixwill be of dimensions , will be of dimensions and will be of dimensions . Note that will be identical to only when there are direct studies for all pairwise comparisons in the network. It turns out that has dimensions .

*Example*

For instance, consider a fully connected network with three treatments, A, B and C. Matrices , and will be

where , and are the variances of the ‘B versus A’, ‘C versus A’ and ‘C versus B’ direct treatment effects.

## Interpretation of the matrix

Rows of contain the coefficients that map direct to network treatment effects (equation 1). They can be viewed as generalized weights but should not be confused with weights from pairwise meta-analysis as they do not sum up to one and cannot be standardised to do so [ref erratum]. Matrix describes the influence of each comparison with direct data (specified by the columns) to the NMA results (specified by the rows). According to equation 2, the matrix is a function of the variances of the direct effects and the network structure and therefore the exact contribution of each comparison depends on the precision of the available direct data and its connectivity to the rest of the network.

Absent of multi-arm studies, each network treatment effect i.e. ‘Y versus X’ can be written as a weighted average of the direct and the indirect estimate. We denote elements of as where is the indicated column and is the indicated row. Diagonal elements of represent the percentage contribution of the direct evidence for the particular network treatment effect. While we know that 1 minus the percentage contribution of direct evidence is the percentage contribution of indirect evidence, it is not straightforward how to derive the percentage contribution of each comparison providing indirect evidence to each network treatment effect. That is because, in the general case where indirect routes to obtain ‘Y versus X’ may not be independent between them, the indirect ‘Y versus X’ treatment effect is not a weighted average of all the separate indirect effects.

*Example*

In the example of a triangular ABC network, the matrix is

turning out to be

where .

To estimate the NMA treatment effect for the ‘B versus A’ comparison, we get

equation 3

showing that the contributions of the AB, AC and BC comparisons are , and respectively.

## Properties of the matrix

As described in (3), the composition of NMA treatment effects can be interpreted as evidence flows and be visualized in weighted acyclic directed graphs. Thus, the following conditions are met for each ‘Y versus X’ NMA treatment effect:

1. The sum of outflows out of node X is 1.
2. The sum of inflows into node Y is 1.
3. The sum of inflows equals the sum of outflows in each intermediate node.

*Example*

Figure 1 shows the flow of evidence for the ‘B versus A’ NMA treatment effect. The outflows of A and the inflows into B are . The intermediate node C has equal inflow and outflow of .

Figure 1. Illustration of the flow of evidence for the ‘B versus A’ NMA treatment effect in a hypothetical ABC network where all comparisons have been evaluated.

It turns out from properties a)-c) that the entries of the matrix can give us insight on the flow of evidence coming from direct evidence and from each indirect path. We will call *‘path evidence flows’* the flow of all evidence paths to the network estimate. In our fictional example, two independent *paths evidence flows* exist; one based on direct evidence (AB comparison) and one based on indirect evidence (BCA path).

Re-arranging equation 3 as

is the contribution of the direct evidence while is the contribution of the indirect path via C.

## Path evidence flows to percentage contributions per comparison

In order to assign percentage contributions to each direct comparison, we need to split *path evidence flows* -which represent the contribution of each path- to the involved comparisons. Unavoidably, this division will be up to an extent arbitrary, as indirect estimates are not obtained as weighted averages of the involved direct treatment effects. Each direct treatment effect involved in the calculation is necessary, and thus equally important, to obtain the indirect estimate.

To approximate percentage contributions per comparison, we suggest dividing *path evidence flows* with the length of the respective path. This will leave the direct percentage contribution equal to the diagonal of the matrix and assign to each comparison involved in an indirect route a portion of the contribution of the respective indirect route. The *path evidence flows* divided by the length of the path will be called ‘*mean path flows’*.

*Example*

In the triangular ABC network example, the percentage contribution of the direct ‘B versus A’ comparison to the ‘B versus A’ NMA treatment effect is while ‘C versus A’ and ‘C versus B’ comparisons contribute of each.

Note that in the general case it might be that a comparison is involved in more than one indirect paths to obtain a NMA treatment effect. In this case, the % contribution of that comparison will be the sum of its individual contributions (the *mean path flows*) from each indirect path.

## Algorithm

The general algorithm to derive the percentage contributions to the ‘Y versus X’ NMA treatment effect is:

1. Calculate the matrix.
2. Create a percentage matrix, denoted as , of the same dimensions as .
3. Take the shortest path from X to Y (if direct data are available, this will be the direct comparison).
4. Among the columns representing the involved comparisons of the shortest path, find the smallest absolute entry in (if direct data are available, this will be )
5. Divide the smallest absolute entry in (denoted as ) to the path length to obtain the *mean path flow* .
6. Fill in the *mean path flow* to the column corresponding to the involved comparisons (if direct data are available, only to ‘Y versus X’) in the percentage matrix .
7. Treatment node X now has of outflows to be allocated.
8. Take the next shortest path. If there are two or more equally short paths, take randomly one of those.
9. From the comparisons involved in the indirect path, find the smallest absolute entry in (say ). This will be the *path evidence flow* of the particular path.
10. Divide to the path length to obtain the *mean path flow*.
11. Fill in the *mean path flow* to the columns corresponding to the involved comparisons in the percentage matrix .
12. Treatment node X has now of outflows to be allocated.
13. Continue steps g) to l) until treatment node X has not left outflows to be allocated.

We implemented the above algorithm both in R and in Stata and the code is available in [ref github repository?].

# Results

To illustrate our method, we will use a previously published network of four topical antibiotics without steroids for chronically discharging ears (no treatment (A), quilone antibiotic (B), non-quilone antibiotic (C) and antiseptic (D)) (13). The outcome is whether or not patients had persistent discharge from the ear after one week and is measured as odds ratio (OR). The network plot is shown in figure 2a and suggests that direct evidence exists for all comparisons except ‘non-quilone antibiotic versus no treatment’.

Figure 2. Network plot for the network of topical antibiotics without steroids for chronically discharging ears. (a) without information on the flow of the evidence, (b) visualising the flow of evidence for the ‘D versus B’ NMA treatment effect, (c) and (d) visualising the flow of evidence for the ‘B versus A’ NMA treatment effect.

Treatment labels: A: no treatment, B: quilone antibiotic, C: non-quilone antibiotic, D: antiseptic

## Application to the ‘D versus B’ NMA treatment effect

Let us focus on the ‘D versus B’ NMA treatment effect. We aim to find the percentage contributions of all direct comparisons to the respective network estimate. To do so, we will follow the steps of the algorithm described in Methods.

***Steps a) and b)***

Pairwise meta-analysis treatment effects are obtained using the random effects model and the matrix, which is of dimensions , is calculated using equation 2. For clarity, we have only filled in the row corresponding to the ‘D versus B’ NMA treatment effect below.

|  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- |
|  | AB | AD | BC | BD | CD |
| AB |  |  |  |  |  |
| AC |  |  |  |  |  |
| AD |  |  |  |  |  |
| BC |  |  |  |  |  |
| BD |  |  |  |  |  |
| CD |  |  |  |  |  |

We create matrix being of the same dimensions as where elements have been replaced with .

***Evidence flow***

Figure 2b shows the flow of evidence for the network estimate ‘D versus B’. The outflows of B are 0.23+0.68+0.9=100% and the inflows into D are 0.23+0.68+0.9=100%. The intermediate treatment node A has inflow of 0.9 and outflow of 0.9 while the intermediate treatment node C has inflow of 0.23 and outflow of 0.23. Three independent *paths evidence flows* exist here; one based on direct evidence (BD comparison, flow 0.68) and two based on indirect evidence (BAD path, flow 0.9 and BCD path, flow 0.23).

***Steps c) and d)***

Treatment node B has 100% of outflows to be allocated. We take the shortest path from B to D which is the direct ‘D versus B’ comparison (figure 3a) and locate the respective entry in (figure 3a).

Figure 3. Steps of the algorithm to obtain the percentage contributions of all comparison to the estimation of the ‘D versus B’ NMA treatment effect.

Treatment labels: A: no treatment, B: quilone antibiotic, C: non-quilone antibiotic, D: antiseptic

***Steps e) and f)***

We divide the absolute entry in (0.68) with the path length (1) to obtain the mean path flow (0.68/1=68%) and fill in the mean path flow to the involved comparisons in the percentage matrix.

|  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- |
|  | AB | AD | BC | BD | CD |
| BD |  |  |  |  |  |

***Steps g) and h)***

Treatment node B now has 100%-68%=32% of outflows to be allocated. We take the next shortest path; as there are two equally short paths, we take randomly BAD (figure 3b).

***Step i)***

Among the involved comparisons, we find the smallest absolute entry in the matrix (figure 3b). This is the *path evidence flow* of BAD.

***Step j) and k)***

We divide the found entry (0.9) to the path length (2) to obtain the mean path flow (0.9/2=4.5%) and fill in the mean path flow to the involved comparisons in the percentage matrix.

|  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- |
|  | AB | AD | BC | BD | CD |
| BD |  |  |  |  |  |

***Steps l) and m)***

Treatment node B has now 32%-9%=23% of outflows to be allocated. We follow similar steps for the BCD path (figure 3c) and fill in the percentage matrix as

|  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- |
|  | AB | AD | BC | BD | CD |
| BD |  |  |  |  |  |

Then, treatment node B has no left outflows to be allocated. The percentage contributions for the network estimate ‘D versus B’ have been obtained and can be inspected in figure 4a.

Figure 4. Percentage contributions of each direct comparison to the estimation of the network estimates ‘D versus B’ (figure 4a) and ‘B versus A’ (figure 4b).

## Application to the ‘B versus A’ NMA treatment effect

In the illustrative example of the ‘D versus B’ NMA treatment effect, each comparison is involved in only one *path evidence flow*. We focus here on the ‘B versus A’ NMA treatment effect to illustrate the algorithm of obtaining comparison percentage contributions when a comparison may be part of more than one *paths evidence flows.*

***Steps a) and b)***

The row of the matrix corresponding to the ‘B versus A’ NMA treatment effect turns out to be

|  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- |
|  | AB | AD | BC | BD | CD |
| AB |  |  |  |  |  |
| AC |  |  |  |  |  |
| AD |  |  |  |  |  |
| BC |  |  |  |  |  |
| BD |  |  |  |  |  |
| CD |  |  |  |  |  |

***Evidence flow***

Figure 2c shows the flow of evidence for the network estimate ‘B versus A’. Here 0.24 is the flow based on direct evidence and there are two dependent indirect paths sharing the AD comparison. Node D has 0.76 inflows that split into 0.57 and 0.19 outflows to the BD and CD comparisons respectively. The flow of indirect evidence can be more conveniently illustrated ‘decomposing’ the AD comparison (figure 2d) to show that the ADB *path evidence flow* is 0.57 and the ADCB *path evidence flow* is 0.19.

***Steps c) and d)***

Treatment node A has 100% of outflows to be allocated. We take the shortest path from A to B, which is the direct ‘B versus A’ comparison (figure 5a) and locate the respective entry in (figure 5a).

Figure 5. Steps of the algorithm to obtain the percentage contributions of all comparison to the estimation of the ‘B versus A’ NMA treatment effect.

Treatment labels: A: no treatment, B: quilone antibiotic, C: non-quilone antibiotic, D: antiseptic

***Steps e) and f)***

We divide the absolute entry in (0.24) with the path length (1) to obtain the mean path flow (0.24/1=24%) and fill in the mean path flow to the involved comparisons in the percentage matrix.

|  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- |
|  | AB | AD | BC | BD | CD |
| AB |  |  |  |  |  |

***Steps g) and h)***

Treatment node A now has 100%-24%=76% of outflows to be allocated. We take the next shortest path which is ADB (figure 5b).

***Step i)***

Among the involved comparisons (AD and DB), we find the smallest absolute entry in the matrix which is the entry corresponding to the BD comparison (figure 5b). This is the *path evidence flow* of ADB.

***Step j) and k)***

We divide the found entry (0.57) to the path length (2) to obtain the mean path flow (0.57/2=28.5%) and fill in the mean path flow to the involved comparisons in the percentage matrix.

|  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- |
|  | AB | AD | BC | BD | CD |
| AB |  |  |  |  |  |

***Steps l) and m)***

Treatment node A has now 76%-57%=19% of outflows to be allocated. We take the next shortest path, which is ADCB and find the smallest absolute value among the involved comparisons in the matrix (figure 5c). This value corresponds to 0.19 and is the *path evidence flow* of ADCB. We divide it to the path length to obtain the mean path flow (0.19/3=6.3%) and fill in the percentage matrix as

|  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- |
|  | AB | AD | BC | BD | CD |
| AB |  | 34.8% |  |  |  |

Then, treatment node A has no left outflows to be allocated. The percentage contributions for the network estimate ‘B versus A’ have been obtained and can be inspected in figure 4b.

## Using percentage contributions to quantify the impact of a characteristic

Translating the matrix into percentage contributions of each direct comparison is particularly useful to quantify the influence that a characteristic pertaining to the direct comparisons has in the estimation of the NMA treatment effects. For instance, having risk of bias judgements per direct comparisons we can obtain the percentage of each NMA treatment effect that is coming from pairwise comparisons with ‘high’, ‘moderate’ or ‘low’ risk of bias. Salanti et al. proposed the visualisation of this information using a bar plot where direct comparisons of the same risk of bias have been grouped together (6). Figure 6 shows such a bar plot using the algorithm describe in Methods to obtain the percentage contributions of each direct comparison. Inspecting figure 6 can help derive judgements for the study limitations of the NMA treatment effects; i.e. direct comparisons with high risk of bias contribute more than 40% in the estimation of the ‘D versus C’ comparison, potentially impacting on the confidence that we can place on the particular NMA treatment effect.

Figure 6. Bar plot showing the percentage contributions of direct comparisons with low (green), moderate (yellow) and high (red) risk of bias. Risk of bias per direct comparison has been assumed to be the majority of per trial risk of bias. The bar plot has been produced in CINeMA (Confidence In Network Meta-Analysis) software. Studies are synthesized using the random effects model. Na thymithoume na allaxoume tous arithmous se grammata kai na valoume legends.

# Discussion

In this paper, we demonstrated an approach to derive percentage contributions of the direct comparisons to the NMA treatment effects. For obtaining the percentage contributions, we made use of the fact that the composition of network treatment effects can be interpreted as evidence flows. An assumption that underlies our algorithm is the equal split of the flow of each evidence path to the involved comparisons. Although indirect effects are not weighted averages, we find this approximation to be a pragmatic approach that reasonably reflects the amount that each comparison contributes to network effects.

Alternative methods to derive the relative contribution of all sources of evidence have been developed (3,14–16). Side splitting (also called node splitting and back calculation method) is a method to evaluate the assumption of consistency in NMA separating direct from indirect evidence (14,17). As in the absence of multi-arm trials, the network estimate can be written as a weighted average of the direct and the indirect estimate, this method implies ‘back-calculating’ the indirect estimate of a particular comparison as function of the direct and the NMA treatment effects and their variances. Equivalently, the indirect estimate is obtained excluding trials that compare the particular comparison and deriving the NMA –which will be indirect in this case- treatment effect. The idea underlying side splitting could be used to measure the change in the variance of the NMA treatment effect when excluding each comparison in the network. Such a procedure would lead to a matrix giving the impact of each direct comparison on the variances of the NMA estimates. While related to the percentage contribution matrix, the particular matrix would answer a different question, which is “to which proportion does the variance of the NMA estimate of the comparison in the row decrease due to the existence of the direct bridge in the column”. An alternative approach has been proposed to derive percentage study weights in a variety of meta-analysis models including meta-regression, network meta-analysis and individual patient data meta-analysis (15). This approach is based on the decomposition of Fisher’s information matrix and thus the derived weights are not influenced by the network structure. In (3) König et al. introduce the mean path length as a measure of indirectness; the mean path length grows as the indirect paths informing network effects are getting larger. Although the derivation of the particular measure has some similarities with the derivation of *mean path flows* in this paper, the interpretation of the two measures is entirely different.

CINeMA (Confidence In Network Meta-Analysis) is a web application that aims to simplify the evaluation of confidence in the findings from NMA. While it largely follows the framework previously developed by Salanti et al. (6), the refinement of several methodological aspects is currently under development. Core aspects of the approach includes considerations of the relative contributions of the each direct comparison to each NMA treatment effect. To this end, CINeMA uses the percentage contribution matrix as described in this paper. The command *netweight* in Stata has also been updated to use the described approach; Chaimani et al [ref erratum] illustrates the problems related to the approach that was described in Salanti et al. and previously implemented in the *netgraphs* package in Stata.

We believe that the method described in this paper is a useful addition to the various applications of the matrix. The derivation of the percentage contributions of direct to network treatment effects can be particularly important when examining the impact of a particular characteristic to the findings of a NMA.

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