Component Network Meta-Analysis in a nutshell

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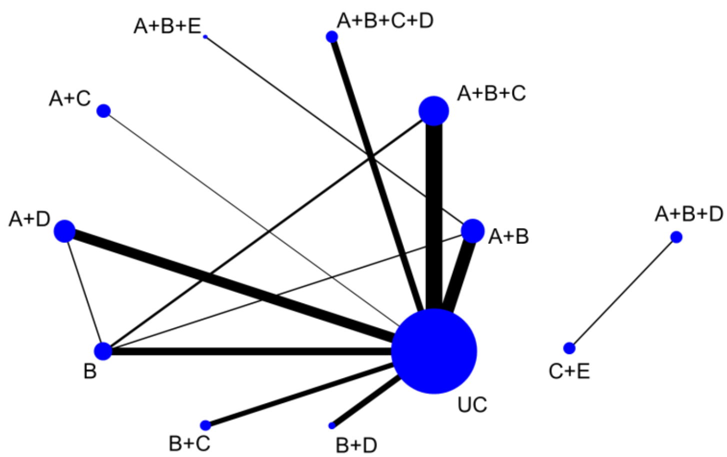
Introduction

Several organizations, such as the World Health Organization, have endorsed network meta-analysis (NMA) as a powerful tool in clinical decision-making. NMA is a statistical method which simultaneously compares multiple (three or more) interventions within a single framework, by synthesizing direct and indirect evidence from multiple studies, addressing the same scientific question. [1-4] Healthcare interventions can be complex/multicomponent in the sense that they consist of multiple, possibly interacting, components. While NMA focuses on estimating intervention effects, component network meta-analysis (CNMA) disentangles the effect of each component. Subsequently, CNMA uses these estimates to reconstruct multicomponent intervention effects. We aim to briefly introduce readers to CNMA and highlight its advantages and limitations.

(Standard) Network Meta-Analysis

Suppose we have a set of trials comparing multiple interventions (more than two) for thei safety/efficacy forming a network of evidence. An example of such a network is depicted in the network plot in Figure 1. Nodes represent interventions and edges represent direct evidence; interventions are linked with an edge, when there are studies comparing them. Intervention effects between any pair of interventions are informed both from studies directly comparing these interventions (direct evidence) and from other studies (indirect evidence), as long as there is a path one can follow from one node to the other. For example, in the network described in Figure 1, there is no line/edge (direct evidence) comparing interventions “A+B” and “A+B+C”, but one can go from “A+B” to “A+B+C” via usual care (UC) or another path. By synthesizing both direct and indirect evidence, NMA results in more precise effect estimates and allows us to estimate the relative efficacy/safety between any pair of interventions, even of those not compared directly in a study [1-3, 5]. The main assumption made is that of transitivity, suggesting that the distribution of effect modifiers should be similar across treatment comparisons. Suppose that we know severity of the condition is an effect modifier with interventions being more effective for severely ill patients. Then, when estimating an indirect effect, e.g. for “A+B” to “A+B+C” via UC, if the “A+B+C” vs UC trials include severely ill patients and the “A+B” vs UC trials include mildly ill patients, we may find a result suggesting “A+B+C” is better than “A+B”, but we cannot be sure whether this result is attributed to the intervention or it is a spurious result confounded with the severity of the illness.

Figure 1



Component network meta-analysis

As we see in Figure 1, interventions consist of certain components (A to E). Such interventions are characterized as “complex” or “multicomponent" [4, 6-8]. In NMA, we treat each node as a separate intervention but component network meta-analysis (CNMA) additionally allows us to estimate the effect of each component, answering questions such as “Which components work (or do not work)?”.[4, 7, 9] There are two main CNMA models, the additive and the interaction model.[4, 7]

CNMA: Additive and interaction models

The main idea of CNMA lies in the decomposition of multicomponent interventions to estimate the effects of their components.[4] The additive effects model firstly estimates the effect of each component and then the effect of each multicomponent intervention is estimated by summing the relative effects of the components comprising this intervention (additivity assumption).

In figure 1, we saw a network of 10 interventions, consisting of five different components (A to E) and usual care (UC). Using Usual Care (UC) as the reference intervention, NMA estimates nine different treatment effects (Table 1: $d_1, \dots, d_9$), as it considers each node as a separate intervention. For the same network, additive CNMA model firstly estimates the effects of each component versus UC (Table 1:d_A, d_B, d_C, d_D, d_E). Then, the interventions' effects are calculated by summing the respective components' effects. For example, according to CNMA the effect of intervention "A+C" = effect(A)+effect(C) or $d_{A+C} = d_A + d_C$.

The additive CNMA model assumes no interaction between components. Yet, this is a strong assumption to make as components may interact with each other. For example, we may set effect of intervention "A+C" = effect(A)+effect(C)+interaction(A,C) or $d_{A+C} = d_A + d_C + d_{AC}$. In this case, we have one more parameter to estimate (d_{AC}). If two or more components may work synergistically (have a bigger effect) we have $d_{AC} > 0$ (or $d_{A+C} < d_A + d_C$). If they work antagonistically (have a smaller effect) we have $d_{AC} < 0$ (or $d_{A+C} > d_A + d_C$). Typically, the number of interaction terms is very big and we do not have much data to inform all of them, hence, choice of interaction terms should be based on plausible reasons and they should be defined a priori in the protocol of the analysis.[4, 7-9]. Table 1 shows what effects are estimated for the network presented in Figure 1 using NMA, additive CNMA and additive CNMA with an interaction considered for components "A" and "C".

Table 1

NMA		CNMA				
Intervention	**TE (Intervention vs UC)**	**Component**	**TE (Component vs UC)**	**Intervention**	**TE (Additive model-Intervention vs UC)**	**TE (Interaction model-Intervention vs UC)**
A+C	d_1	A	d_A	A+C	d_A+d_C	d_A+d_C+$\mathbf{d_{AC}}$
A+D	d_2	B	d_B	A+D	d_A+d_D	d_A+d_D
B	d_3	C	d_C	B	d_B	d_B
B+C	d_4	D	d_D	B+C	d_B+d_C	d_B+d_C
B+D	d_5	E	d_E	B+D	d_B+d_D	d_B+d_D
A+B	d_6	UC	*reference*	A+B	d_A+d_B	d_A+d_B
A+B+C	d_7			A+B+C	d_A+d_B+d_C	d_A+d_B+d_C+$\mathbf{d_{AC}}$
A+B+C+D	d_8			A+B+C+D	d_A+d_B+d_C+d_D	d_A+d_B+d_C+d_D+$\mathbf{d_{AC}}$
A+B+E	d_9			A+B+E	d_A+d_B+dE	d_A+d_B+d_E
A+B+D	-			A+B+D	d_A+d_B+d_D	d_A+d_B+d_D
C+E	-			C+E	d_C+d_E	d_C+d_E
UC	*reference*			UC	*reference*	*reference*

CNMA vs NMA

We see in Figure 1 that the relative effectiveness between UC and "C+E" cannot be estimated using standard NMA because there is no direct or indirect path that goes from UC to "C+E". The network in Figure 1 is disconnected and NMA can be applied to connected networks only. That means we can estimate the relative effectiveness between all interventions in Figure 1, except for interventions "C+E" and "A+B+D", for which we will only use evidence from the studies comparing them directly. CNMA can be used in disconnected networks as long as the subnetworks share at least one common component. Hence, in the network in Figure 1, CNMA will use information from all studies.

NMA theoretically allows the estimation of all interaction effects between components. In practice, most networks consisting of multicomponent interventions are sparse, in the sense that most studies compare an intervention to usual care and there are few head-to-head trials (just like in Figure 1). This is a constant theme that we see in most network of multicomponent interventions. In sparse networks, efficacy of interventions is confounded with study characteristics as most evidence for informing summary effects comes from those studies including the respective intervention (usually a couple of studies). For example, assume the relative effect of “A+C” vs UC in Figure 1 is informed by only one study of 50 participants that has a large effect (perhaps it was done in a population where intervention is very effective/it is of poor quality/intensity of intervention was larger, etc.) Then, this intervention may appear to be the best but we do not know if the efficacy observed is due to the intervention used or other study characteristics. This is a common problem with NMAs of sparse data where results may reflect the results of single studies.

CNMA provides more precise intervention effects, since it uses evidence from all studies that share the same components. We also observe more moderate effects because the summary CNMA estimates are not driven mainly by individual studies.

Additionally, through CNMA, the effect of all combinations of components can be estimated, regardless of whether they are observed in the included studies. This can be a problem since we do not know how these components will interact if put together or if certain components cannot be put together at all.

The reliability of any statistical method relies on the plausibility of the assumptions made. The transitivity assumption cannot be tested in a sparse network but we can infer conceptually that it is not likely to hold and results will be confounded with study characteristics. The additivity is also a strong assumption, and we expect some interaction between components. If the additivity assumption does not hold, the additive model would provide biased estimates. On the other hand, it will surely reduce the problem of confounding that we see in sparse networks. Rücker et al. have recently proposed a test to assess for the additivity assumption; yet the test applies only to connected networks.[7] Interaction model relaxes the additivity assumption, but defining the interaction terms to include in the model is challenging. It is also difficult to prespecify the interaction terms to be included in the interaction model. We cannot just add interaction terms between all components, as this will increase the number of estimated parameters and reduce precision, drastically eliminating the advantages of the additive model. In networks of multicomponent interventions, it is typical to have components such as the provider of the intervention, the intensity of the intervention, the location, the recipient, whether it is face-to-face or remote, characteristics of the intervention etc. In such interventions, the context is of paramount importance and theoretically, CNMA allows us to explore heterogeneity by looking at how efficacy variates according to these characteristics. This can also be achieved in NMA by trying to relate efficacy to components (e.g. find which components are present in the most efficacious interventions).

Conclusion

CNMA offers the chance to disengage components and explore their effectiveness separately or in various combinations, even in disconnected networks. Overall, CNMA has become appealing and easy to apply through *netmeta* package in R [10] and many CNMAs have been published recently.[11-15] We argue that both methods should be used as a sensitivity analysis and definitely the choice of method should be described in the protocol.

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