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Node-Splitting Generalized Linear Mixed Models for Evaluation of Inconsistency in Network Meta-Analysis

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ABSTRACT

Background: Network meta-analysis for multiple treatment comparisons has been a major development in evidence synthesis methodology. The validity of a network meta-analysis, however, can be threatened by inconsistency in evidence within the network. One particular issue of inconsistency is how to directly evaluate the inconsistency between direct and indirect evidence with regard to the effects difference between two treatments. A Bayesian node-splitting model was first proposed and a similar frequentist side-splitting model has been put forward recently. Yet, assigning the inconsistency parameter to one or the other of the two treatments or splitting the parameter symmetrically between the two treatments can yield different results when multi-arm trials are involved in the evaluation. **Objectives:** We aimed to show that a side-splitting model can be viewed as a special case of design-by-treatment interaction model, and different parameterizations correspond to different design-by-treatment interactions. **Methods:** We demonstrated how to evaluate the side-splitting model using the arm-based generalized linear mixed model, and an example data set was used to compare results from the arm-based models with those from the contrast-based models. **Results & Conclusions:** The three parameterizations of side-splitting make slightly different assumptions: the symmetrical method assumes that both treatments in a treatment contrast contribute to inconsistency between direct and indirect evidence, whereas the other two parameterizations assume that only one of the two treatments contributes to this inconsistency. With this understanding in mind, meta-analysts can then make a choice about how to implement the side-splitting method for their analysis.

Keywords: generalized linear mixed models, inconsistency, network meta-analysis, node-splitting models.

Introduction

Network meta-analysis for comparisons of multiple treatments has been an important development in research synthesis methodology in recent years [1–8]. One of the assumptions made by network meta-analysis to integrate all available evidence into a general statistical framework is that the distributions of potential confounders and effect modifiers are similar across different pairs of comparisons within the whole network; this is known as the similarity assumption [9]. When the assumptions are violated, it suggests that the direct and indirect evidence concerning some treatment comparisons within a network meta-analysis may not be consistent, and the interpretation of network meta-analysis needs to be cautious.

The issue of inconsistency has become the focus of intensive research, and several approaches have been proposed to evaluate and detect inconsistency within a network meta-analysis [10–16]. Lu and Ades [13] first proposed to evaluate the inconsistency between direct and indirect evidence within a loop formed by three treatments, and others later proposed a full design-by-treatment interaction model by separating multi-arm trials from two-arm trials [12,17,18]. It has been shown that the loop inconsistency model can be viewed as a special case of the design-by-treatment interaction model when a treatment comparison of two-arm trials is considered not different from that of three-arm trials [12]. For instance, suppose two-arm trials comparing A to B, B to C, or A to C and three-arm trials comparing A, B, and C are included in a network meta-analysis; for the loop inconsistency model, there is only one potential inconsistency in the loop of A-B-C, because the inconsistency degree of freedom is ICDF $= T_c - T + 1 = 1$, where T is the number of treatments and T_c is the number of comparisons informed by data [13]. Nevertheless, for the design-by-treatment interaction model, the degree of freedom for inconsistency is $df_{\text{inc}} = \sum_d (T_d - 1) - (T - 1) = 3$, where T_d is the number of treatments in a design d and T is the total number of treatments in a network, because there are four study "designs" (three two-arm trial designs and one three-arm trial design) involved in the loop.

Dias et al. [14] proposed a Bayesian node-splitting model to evaluate the inconsistency between the direct and indirect evidence for each treatment contrast, which is a node in a direct acyclic graph. White recently proposed a side-splitting model, similar to the node-splitting model, and implemented it in the

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frequentist contrast-based model for network meta-analysis, in which treatment contrasts are used as the units of observation [12,19]. He noted that two parameterizations of side-splitting yielded different results when multi-arm trials were included in a network meta-analysis [19]. Consequently, White proposed a symmetrical parameterization that split the inconsistency parameter equally between the two treatments of the contrast. It is, however, not entirely clear how these different parameterizations could yield different results, and no advice has been given to meta-analysts regarding how to choose a parameterization.

The aim of this article was therefore to show that the side-splitting model can be implemented in the arm-based generalized linear mixed model framework as a special case of the full design-by-treatment interaction model. One advantage of this approach is that this model can handle any type of data that can be analyzed by a generalized linear mixed model; consequently, results could be more accurate because no data transformation is required [5,20–22]. Furthermore, in the arm-based models, it is straightforward to show that different parameterizations of the side-splitting model correspond to different design-by-treatment interaction models, thereby giving rise to different results in the evaluation of the inconsistency.

This article is organized as follows: We first briefly review the side-splitting model and its different parameterizations and explain why they correspond to different design-by-treatment interaction models. We also show how they can be implemented in generalized linear mixed models using the treatment arm as the unit of observation. We then use an example of binary outcome to demonstrate our approach and compare its results to those from the contrast-based model proposed by White [19].

Side-Splitting Model as a Special Case of the Design-by-Treatment Interaction Model

Contrast-Based Side-Splitting Model

A treatment contrast, such as A versus B, is a side in a network map or plot [23]. To split the side, different parameters are used for the contrast of A versus B in studies containing both A and B and in other studies [19]. The two parameters are estimated jointly within the same model to evaluate whether their difference is significantly different from 0. Suppose a network meta-analysis includes three designs of studies, designs ABC, BC, and AB, where the "design" of a study is the set of treatments compared within the study [12]. When the side A versus B is split, we use A as the reference treatment, and the difference in treatment effects between A and B (e.g., the log odds ratio) in the studies that contain both A and B (denoted as δ^{AB}_{Dir}) is ω^{AB} units higher than the difference in treatment effects between A and B in the remaining network after the separation of the AB studies (denoted as δ^{AB}_{Ind}), that is, $\delta^{AB}_{Dir}-\delta^{AB}_{Ind}=\omega^{AB}$. Therefore, ω^{AB} is the inconsistency parameter for splitting side A versus side B. Because A is the reference treatment, its effect is assumed to be the same in direct and indirect evidence. This is equivalent to assuming that the effect of B (e.g., the log odds ratio for treatment B) in studies that contain both A and B is ω^{AB} units higher than the effect of B in studies that contain only B [19]. It may be expected that when the side B versus A is split, that is, when B is used as the reference treatment, $\delta^{BA}_{Dir}-\delta^{BA}_{Ind}=\omega^{BA}=-\omega^{AB}$. Contrary to our intuition, ω^{AB} can be estimated in this hypothetical network meta-analysis, whereas ω^{BA} is not identifiable. We shall later give a full explanation on how this contradiction can happen.

The general side-splitting model for A versus J that compares a total number of k treatments can be written as follows [19]:

$$\mu^{AJ}_{di}=\delta^{AJ}+\beta^{AJ}_{di}+\omega^{AJ}, \text{ if } d \text{ contains both A and J;}$$
$$\text{otherwise, } \mu^{AJ}_{di}=\delta^{AJ}+\beta^{AJ}_{di}, \quad (1)$$

where μ^{AJ}_{di} is the estimated difference in outcome between treatments A and J, such as difference in means for continuous data or log odds ratio for binary data, in study i within design d; δ^{AJ} is the fixed effect of treatment J relative to A; β^{AJ}_{di} is a study-by-treatment interaction term to estimate the standard heterogeneity, that is, the variations in the treatment effects for comparison of AJ within studies in design d; and ω^{AJ} is the inconsistency parameter between direct and indirect evidence. In Equation 1, β^{AJ}_{di} is treated as a random effect, and a multivariate distribution is assumed when multi-arm trials are involved in the comparisons:

$$(\beta^{AB}_{di},\beta^{AC}_{di},\ldots,\beta^{AK}_{di})^{T}\sim N(0,\Sigma)$$

The $(k-1)\times(k-1)$ covariance matrix Σ is usually structured by assuming that all treatment contrasts have the same degree of heterogeneity, τ^2, and the correlation between random effects is set at 0.5 [13,24,25]. The inconsistency parameter ω^{AJ} is modeled as a fixed effect, whereas it can also be modeled as a random effect [26]. Nevertheless, $\omega^{AJ}\neq-\omega^{JA}$, when multi-arm studies that contain both A and J are involved. White therefore proposed to allow ω to be shared between A and J [19]:

$$\delta^{AJ}_{Dir}=\left(t^{J}+\frac{1}{2}\omega^{AJ}_{*}\right)-\left(t^{A}-\frac{1}{2}\omega^{AJ}_{*}\right)$$

and

$$\delta^{AJ}_{Ind}=t^{J}-t^{A},$$

where δ^{AJ}_{Dir} and δ^{AJ}_{Ind} are the differences in treatment effects between A and J in studies that do or do not contain both A and J, respectively, and t^{A} and t^{J} are treatment effects of A and J, respectively, in studies that do not contain both A and J. It is, however, noted that $\omega^{AJ}=-\omega^{JA}=\omega^{AJ}_{*}$ holds only when no multi-arm studies, such as design ABJ, are involved in the network meta-analysis.

Arm-Based Side-Splitting Model

We previously proposed an arm-based generalized linear mixed model to implement the Lu and Ades model for network meta-analysis [20,21]. In a network with studies 1, 2, …, to p, and treatments A, B, …, and K, the generalized linear mixed models with treatment arms as the units of observation can be written as follows:

$$g\left(\hat{y}_{ij}\right)=\sum_{j=1}^{p}b_j\text{study}_j+\sum_{k=B}^{K}d_{Ak}t_k+\sum_{k=A}^{K}\gamma_{kj}t_k, \quad (2)$$

where $g(\cdot)$ is the link function in the model, $\hat{y}_{ij}$ is the estimated outcome for each arm i in study j, and b_1 to b_p are regression coefficients for dummy variables study_1 to study_p, respectively. Variables t_k, k = A to K, are dummy variables where treatment k is coded 1 and the other treatments are coded 0. When treatment A is used as the reference group for the whole network, t_A is excluded from Equation 2; consequently, d_{Ak}, the regression coefficient for t_k, is the estimated average difference between treatment A and k. γ_{Aj} to γ_{Kj} are random effects for treatments A to K, respectively, and those random effects follow a multivariate normal distribution:

$$\begin{pmatrix}\gamma_{Aj}\\ \gamma_{Bj}\\ \vdots\\ \gamma_{Kj}\end{pmatrix}\sim\left(0,\begin{pmatrix}\sigma^2 & 0 & \ldots & 0\\ 0 & \sigma^2 & \ldots & 0\\ \vdots & \vdots & \ddots & \vdots\\ 0 & 0 & \ldots & \sigma^2\end{pmatrix}\right).$$