Network Meta-Interpolation; A Fast, Novel NMA Approach Accounting for Effect Modification

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ABSTRACT

❖ Effect modification (EM) causes bias in network meta-analyses (NMA) if EM varies across treatments in the network. Several methods have been developed, dealing with EM in NMAs when aggregated data (AgD) is available for at least one trial in the network. These methods typically make the shared effect modification assumption (SEMA) and disregard the available information the EM contains on the relative treatment effect (RTE) in the AgD trials. The SEMA is debatable, especially when comparing different classes of therapies. Our aim is to present a novel network meta-interpolation (NMI) that considers all available information on the impact of EMs on the RTE in the evidence network. We simulated an evidence network of seven trials: three A-B trials, three A-C trials (with both sets reported as AgD) and one A-D trial reported as individual patient data (IPD), using a binary outcome and two correlated EMs, following SEMA within but not across comparisons. The NMI technique combines the intention-to-treat RTE with typically reported subgroup RTE to predict the RTE and its uncertainty at a standardized combination of the two considered EMs for all trials. The IPD trial informed missing EM values. NMI results at standardized EM values were then compared with standard NMA, network meta-regression (NMR) and Multi-level NMR (ML-NMR) over 1000 random simulations. Our results indicate that averaging over all RTEs, NMI achieved an average mean squared error of 0.213 (non-SEM: 0.213) relative to 0.368 (0.326) by NMA, 0.272 (0.427) by NMR and 0.236 (0.321) by ML-NMR. In addition, NMI's 95% credible interval coverage was 91.1% (91.8%), compared to 62.8% (71.0%), 83.5% (68.8%) and 75.8% (92.8%), respectively. In conclusion, NMI is a novel method not relying on the SEMA, convincingly outperforming NMA and NMR and at least matching ML-NMR. This approach requires merely one IPD trial in case of multiple correlated EMs, and not one per treatment class like ML-NMR.

INTRODUCTION

❖ In clinical trials, effect modification (EM) occurs when the relative treatment effect (RTE) interacts with one or more covariates.

❖ EMs cause bias in network meta-analyses (NMA) if their distribution varies across trials in the network[1]. Lack of available IPD for all trials means IPD network meta-regression (NMR) is not feasible.

❖ Several methods have been proposed to deal with the above in health technology assessment (HTA), including aggregated data (AgD) NMR [2].

❖ Matching adjusted indirect treatment comparisons (MAIC) and simulated trial comparisons (STCs) are not considered here as they are limited to two trial comparisons.

❖ Most existing methods assume shared effect modification (SEM), i.e., the exact same interaction parameters applying to all comparisons. They also disregard available subgroup data and the information it provides on the different EMs in AgD trials.

❖ As an example, in previously treated non-small lung cancer, the hazard ratio (HR) of atezolizumab for patients with and without brain-metastasis is 0.57 and 0.77, respectively [3] whereas for Nivolumab in the same population the HRs were 0.81 and 0.66, respectively [4].

❖ Here we propose network meta-interpolation (NMI): a novel, simple technique, which

(i) Makes use of all publish subgroup data on TE estimation,

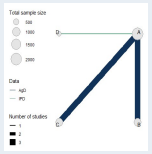
(ii) Assumes nothing about SEM, and

(iii) Is extremely fast and accurate.

METHODS AND MATERIALS

❖ **Study network**

Figure.1. NMI Study Simulated Network



METHODS AND MATERIALS

❖ **The NMI Method**

1. Use IPD to estimate the correlation between effect modifiers
2. Impute missing covariate data for reported subgroup results, using Best Linear Unbiased Prediction (BLUP)
3. Interpolate all TEs and their associated SEs at the desired covariate values
4. Perform full ITC after TE and SE adjustment, using standard NMA

❖ **Simulated Data**

- A network of 7 simulated trials (3 A-B: AgD; 3 A-C: AgD; 1 A-D: IPD), each with balanced treatment allocation, with dichotomous outcomes following a logistic model

$$\text{logit}(p_i; X_1, X_2, T) = \beta_{00i} + \beta_{01i}X_{1i} + \beta_{02i}X_{2i} + \beta_{03i}T_i + \beta_{13i}X_{1i}T_i + \beta_{23i}X_{2i}T_i + \epsilon_i,$$

where $\epsilon_i \sim N(0, 0.2^2)$, X_1 and X_2 are the effect modifiers and T is the treatment assignment, assuming the value 0 for treatment A and 1 otherwise.

Table.1. Description of simulated model parameters per data sample and treatment arm

Trial	Model	Parameters
A-B	SEM	$\beta_{AB} = (-1.39, 0.00, 0.00, 0.69, 1.61, 1.00)$
	Non-SEM	$\beta_{AB} = (-1.39, 0.00, 0.00, 0.69, 1.00, 0.00)$
A-C	SEM	$\beta_{AC} = (-1.39, 0.00, 0.00, 1.00, 1.61, 1.00)$
	Non-SEM	$\beta_{AC} = (-1.39, 0.00, 0.00, 1.00, 1.61, -1.00)$
A-D	SEM	$\beta_{AD} = (-1.39, 0.00, 0.00, 1.50, 1.61, 1.00)$
	Non-SEM	$\beta_{AD} = (-1.39, 0.00, 0.00, 1.50, -1.20, -1.00)$

- Each simulated study consisted of 300 patients per treatment arm
- The proportion of 1's in each of X_1 and X_2 was randomly selected to be in the $[0.50, 0.85]$ and $[0.30, 0.65]$ range, respectively
- X_1 and X_2 were sampled with Pearson correlation $\rho = 0.24$

❖ **Implementation**

1. Each trial's partial treatment effect (TE) and standard error (SE) were obtained by fitting a logistic model on treatment assignment alone
2. Fixed effect NMI, NMA, and NMR models were fitted to each dataset. NMI and NMR covariate values for comparison were set to $x_1 = 0.675$ and $x_2 = 0.475$.
3. MCMC samples consisted of three chains totaling 1500 iterations with the first 500 iterations discarded.
4. The simulation used R.4.0.5 and WINBUGS1.4 and consisted of $N = 1000$ random datasets.

❖ **Outcomes**

Given true TE values $\{d^{(i)}\}_{i=1}^{6}$, with $d^{(1)} = \text{TE}_{AB}$, $d^{(2)} = \text{TE}_{AC}$, $d^{(3)} = \text{TE}_{AD}$, $d^{(4)} = \text{TE}_{BC}$, $d^{(5)} = \text{TE}_{BD}$, $d^{(6)} = \text{TE}_{CD}$ and simulation estimates $\{\hat{d}_j^{(i)}\}_{j=1}^{1000}$ $(1 \le i \le 6)$, the following key measures were calculated

Table.2. List of study outcomes of interest

$$\widehat{\text{RMSE}} = \left(\frac{1}{N}\sum_{j=1}^{N}\left|\hat{d}_j^{(i)} - d^{(i)}\right|^2\right)^{\frac{1}{2}},$$

$$\widehat{\text{Coverage}} = \frac{1}{N}\sum_{j=1}^{N} I_{\left[\hat{a}_{0.025}^{(i)}, \hat{a}_{0.975}^{(i)}\right]}(d^{(i)}).$$

SIMULATION RESULTS

❖ **SEM simulation study results**

1. Overall RMSE and Coverage

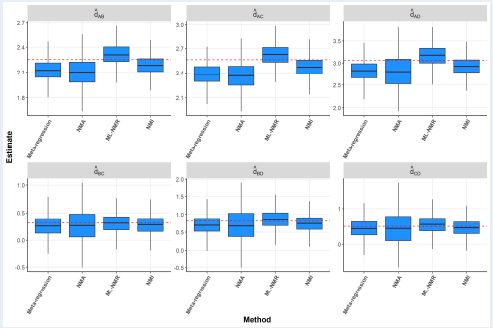
Method	RMSE	Coverage
Meta-regression	0.272	83.5%
NMA	0.368	62.8%
ML-NMR	0.236	92.8%
NMI	0.213	91.1%

2. RMSE and Coverage by parameter

RMSE					Coverage				
Parameter	Meta-regression	NMA	ML-NMR	NMI	Parameter	Meta-regression	NMA	ML-NMR	NMI
d_{AB}	0.188	0.228	0.152	0.135	d_{AB}	78.9%	61.7%	91.7%	89.5%
d_{AC}	0.227	0.261	0.157	0.154	d_{AC}	68.6%	56.1%	93.8%	87.3%
d_{AD}	0.345	0.444	0.293	0.258	d_{AD}	79.6%	58.5%	91.1%	88.2%
d_{BC}	0.221	0.302	0.183	0.170	d_{BC}	92.0%	69.9%	94.4%	96.1%
d_{BD}	0.309	0.448	0.289	0.265	d_{BD}	90.6%	66.1%	93.0%	92.7%
d_{CD}	0.304	0.452	0.288	0.255	d_{CD}	91.6%	64.3%	93.1%	92.9%

RESULTS (CONT.)

3. Goodness of estimation box plots



❖ **Non-SEM simulation study results**

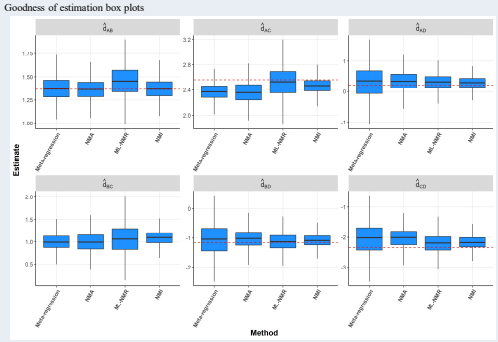
1. Overall RMSE and Coverage

Method	RMSE	Coverage
Meta-regression	0.427	68.8%
NMA	0.326	71.0%
ML-NMR	0.321	75.8%
NMI	0.213	91.8%

2. RMSE and Coverage by parameter

RMSE					Coverage				
Parameter	Meta-regression	NMA	ML-NMR	NMI	Parameter	Meta-regression	NMA	ML-NMR	NMI
d_{AB}	0.142	0.119	0.209	0.112	d_{AB}	92.5%	92.2%	73.3%	95.3%
d_{AC}	0.240	0.269	0.267	0.159	d_{AC}	64.1%	54.0%	67.8%	85.8%
d_{AD}	0.517	0.341	0.294	0.222	d_{AD}	58.1%	71.8%	85.7%	94.2%
d_{BC}	0.294	0.313	0.414	0.199	d_{BC}	77.1%	68.2%	60.8%	91.2%
d_{BD}	0.555	0.349	0.320	0.246	d_{BD}	62.9%	78.4%	86.7%	94.6%
d_{CD}	0.598	0.463	0.381	0.292	d_{CD}	57.9%	61.3%	80.4%	89.8%

3. Goodness of estimation box plots



EXAMPLE

❖ Suppose that the TE estimate and its associated SE are reported for a study in which the proportion of males is $X_1 = 79.7\%$ and the proportion of participants aged 60 and over is $X_2 = 63.5\%$

❖ In addition, males only ($X_1 = 1$), females only ($X_1 = 0$), older adults only ($X_2 = 1$) and under 60 only ($X_2 = 0$) subgroup results are reported (leftmost table)

❖ An additional IPD trial allows us to estimate the Pearson correlation between X_1 and X_2 and impute the initial table (step 1), using Best Linear Unbiased Prediction (BLUP)

❖ Once the missing covariate values have been imputed, we may obtain estimates of the treatment effect and its associated standard error at to $X_1 = 0.675$ and $X_2 = 0.475$ (step 2), solving –

1. An overdetermined linear system for the treatment effect, using simple least squares, and
2. An underdetermined linear system for the standard error, using the Moore-Penrose pseudo-inverse

X1	X2	TE	SE
0.797	0.635	1.548	0.180
1		1.840	0.205
0		0.423	0.396
	1	1.541	0.226
	0	1.551	0.296

① →

X1	X2	TE	SE
0.797	0.635	1.548	0.180
1	0.680	1.840	0.205
0	0.460	0.423	0.396
0.853	1	1.541	0.226
0.699	0	1.551	0.296

② →

X1	X2	TE	SE
0.675	0.475	1.425	0.245

NOTES AND OBSERVATIONS

❖ NMI estimated all treatment effects more accurately than NMA, NMR and ML-NMR under both SEM and non-SEM scenarios

❖ NMI also had the best overall interval coverage under non-SEM, and was comparable to ML-NMR under the SME scenario

❖ NMI's pre-processing run time is negligible: the method is effectively as fast as a standard NMA

CONCLUSIONS

❖ NMI has demonstrated more accurate TE estimation and better coverage compared to NMR and NMA

❖ This superior performance appears to be consistent under SEM and non-SEM assumptions.

❖ Maximum utilization of the available clinical data for TE estimation

❖ Unlike ML-NMR, one IPD trial overall – and not one per treatment class – is required for accurate estimation and inference

- In the case of a single EM, AgD alone suffices

❖ The method requires the availability of subgroup analyses

❖ It is only applicable if all covariates of interest are binary

- Otherwise, they could be discretized

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