bnma: Bayesian Network Meta-Analysis using 'JAGS'

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Bayesian Network Meta-Analysis R packages

Recently, there has been many developments of Bayesian network meta-analysis (NMA) packages in R.

- ✓ gemtc (van Valkenhoef et al., 2012)
- ✓ pcnetmeta (Lin et al., 2017)
- ✓ BUGSnet (Béliveau et al., 2019)
- ✓ bnma (Seo and Schmid, 2020)
- ✓ multinma (Phillippo et al., 2020)

The goal of this presentation is not to compare different packages, but to go over the package we developed, which we named **bnma**.

bnma package

- **bnma** implements models described in the National Institute for Health and Care Excellence (NICE) Decision Support Unit Technical Support Documents (Dias et al., 2013a)
- This document provides detailed description of the Bayesian NMA model (Lu and Ades, 2009) along with JAGS codes.
- **bnma** models normal, binomial, and multinomial outcomes.

bnma package(2)

- Required input includes: outcomes, study indicator, treatment indicator, total number of observations (for binomial and multinomial outcomes) or standard error (for normal outcomes).
- The input data should be **arm-level** so that we have observations for each treatment in each study.
- Based on the specified input, bnma creates **prior**, **JAGS code**, and **initial values** and automatically runs Bayesian NMA model.

Example dataset

- We demonstrate our model using the **smoking cessation counseling programs** dataset
- Twenty-four studies, including 2 three-arm trials, compared **4 smoking cessation counseling programs** and recorded the number of individuals with successful smoking cessation.
- Counseling programs include 1 = no intervention, 2 = self-help, 3 = individual counseling, and 4 = group counseling.

Example dataset(2)

Here is the first five studies of the smoking datasets.

```
lapply(smoking, head, n = 12)
$Outcomes
[1]  9 23 10 11 12 29 75 363 2 9 58 237
$N
[1] 140 140 138 78 85 170 731 714 106 205 549 1561
$Study
[1] 1 1 1 2 2 2 3 3 4 4 5 5
$Treat
[1] 1 3 4 2 3 4 1 3 1 3 1 3
```

Bayesian NMA

Model specification

Defining r_{ik} as the number of events, out of the total number of patients in each arm, n_{ik}, for arm k of trial i,

$$r_{ik} \sim Binomial(p_{ik}, n_{ik})$$

$$logit(p_{ik}) = \eta_i + \delta_{i,1k} I_{\{k \neq 1\}}$$

where η_i are trial-specific baselines and $\delta_{i,1k}$ are the trial-specific log odds ratios of death on the treatment group (k vs. 1). For a random effects model,

$$\delta_{i,1k} \sim N(d_{1k}, \sigma^2_{1k})$$

Bayesian NMA(2)

Model specification

Furthermore, NMA requires the consistency equations to hold

$$d_{23} = d_{13} - d_{12}$$

$$d_{24} = d_{14} - d_{12}$$

$$d_{(s-1),s} = d_{1s} - d_{1(s-1)}$$

and equal variances are assumed, i.e. $\sigma_{12}^2 = \sigma_{13}^2 = \sigma_{23}^2 = \sigma^2$

This model can be fitted using **bnma** as follows:

```
network <- with(smoking, network.data(Outcomes =
    Outcomes, Study = Study, Treat = Treat, N = N,
    response = "binomial", type = "random"))
result <- network.run(network)
```

Model summary

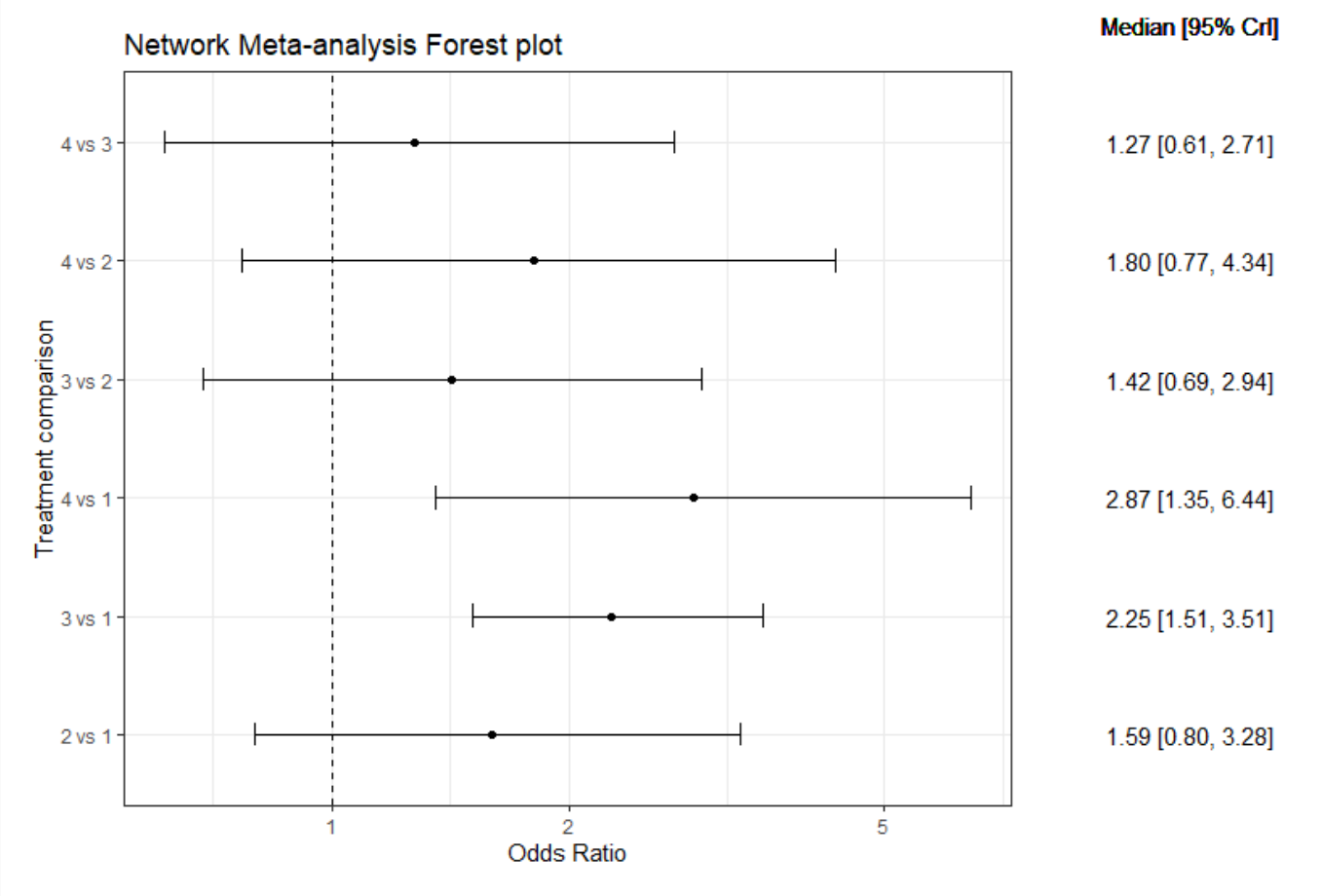
```
> summary(result)
$summary.samples
...
1. Empirical mean and standard deviation for each
    variable, plus standard error of the mean:

        Mean     SD  Naive SE Time-series SE
d[1] 0.0000 0.0000 0.0000000       0.000000
d[2] 0.4935 0.4015 0.0010368       0.001943
d[3] 0.8443 0.2388 0.0006166       0.001468
d[4] 1.1028 0.4396 0.0011351       0.002622
sd   0.8410 0.1872 0.0004833       0.001847
```

The odds ratio for Treatment 4 (group counseling) is exp(1.1028) = 3.01. The model estimated a 201% increase in the odds of quitting smoking for group counseling compared to no intervention.

Model summary(2)

We can use a forest plot to visualize the results.




```
1 network.forest.plot(result)
```

Checking convergence

- Disperse initial values are generated i.e. treatment effect estimated through simple regression of log odds ratio against treatments assigned.
- We use Gelman-Rubin diagnostics to test convergence of parameters η_i, d_{1k}, $log\sigma^2$.
- We check convergence every **setsize** iterations. Once the samples converged, it keeps the last half of the converged sequence. User specifies the final sample size through parameter **n.run**; more samples are drawn if needed.

```
result <- network.run(network, n.run = 100000,
    setsize = 10000)
```

Contrast-based model with random study intercept

- Assume that the baseline risk across trials is drawn from a normal distribution with common mean and between-study $\eta_{i1} \sim N(E, \sigma_E^2)$.
- Note that we have added 1 in the subscript in η_{i1}. Baseline risk (i.e. study intercepts) now all refer to treatment 1, even if treatment 1 is not included in a trial.
- Although treatment in arm 1 will not always be treatment 1 (the reference treatment), the fundamental assumption on exchangeability means that treatment arms can be assumed to be missing at random without loss to efficacy (Achana et al., 2013).

Contrast-based model with random study intercept(2)

- The extra assumption of random intercepts should lead to greater precision. However, this comes at the price of using **between-study information**, meaning that the treatment effect estimated across the network is informed not only by the usual differences within studies but also by differences between studies (White et al., 2019).

```
network <- with(smoking, network.data(Outcomes =
    Outcomes, Study = Study, Treat = Treat, N = N,
    response = "binomial", type = "random", baseline.
    risk = "exchangeable"))
```

Contrast-based model with random study intercept(3)

```
> summary(result)
...
          Mean      SD  Naive SE Time-series SE
E      -2.4912  0.1280 0.0003304      0.0010630
d[1]    0.0000  0.0000 0.0000000      0.0000000
d[2]    0.5315  0.3264 0.0008428      0.0018280
d[3]    0.7817  0.1926 0.0004973      0.0011850
d[4]    1.0513  0.3367 0.0008695      0.0022016
sd      0.7213  0.1295 0.0003345      0.0008852
sdE     0.4624  0.1069 0.0002761      0.0008865
```

Common mean for the baseline risk is estimated to be - 2.4912, which can be converted to a baseline probability of quitting of 0.076.

Network Meta-regression on baseline risk

Model specification

$$\delta_{i,1k} \sim N(d_{1k} + \beta_{1k}(\eta_{i1} - \bar{\eta}), \sigma^2_{1k})$$

where we centered the baseline risk on $\bar{\eta}$, the observed mean log odds in the non-active control group (Treatment 1), to improve convergence.

- Using the 'true' but unobserved non-active control log odds η_{i1} in trial i as a measure of the baseline risk, we can extend the NMA to include a covariate for the baseline risk as a possible source of heterogeneity (Dias et al., 2013b).

Network Meta-regression on baseline risk(2)

Can specify three different assumptions on the regression terms

1. Common: $\beta_{1k} = \beta$
2. Exchangeable: $\beta_{1k} \sim N(B, \sigma_B^2)$
3. Independent: β_{1k}

For instance to assume **common** effect treatment x covariate interactions, we use the following code:

```
network <- with(smoking, network.data(Outcomes =
    Outcomes, Study = Study, Treat = Treat, N = N,
    response = "binomial", type = "random", baseline.
    risk = "exchangeable", baseline = "common"))
```

Network Meta-regression on baseline risk(3)

```
> summary(result)
...
                Mean      SD  Naive SE Time-series SE
b_bl[1]   0.0000 0.0000 0.0000000      0.0000000
b_bl[2]  -0.4148 0.5315 0.0013723      0.0065083
b_bl[3]  -0.4148 0.5315 0.0013723      0.0065083
b_bl[4]  -0.4148 0.5315 0.0013723      0.0065083
d[1]      0.0000 0.0000 0.0000000      0.0000000
d[2]      0.6204 0.3511 0.0009066      0.0023820
d[3]      0.8988 0.2502 0.0006460      0.0025149
d[4]      1.1543 0.3637 0.0009392      0.0028476
sd        0.7524 0.1324 0.0003418      0.0009809
```

Odds ratio exp(1.1543)=3.17 is now the treatment effect for patients with a baseline logit probability of quitting of -2.745 which can be converted to a baseline probability of quitting of 0.06.

Summary

- We showed how to fit a simple Bayesian NMA using smoking dataset with **bnma**
- We demonstrated how to incorporate baseline risk (i.e. via a exchangeable assumption or as a meta-regression) using **bnma**
- The following slide is uploaded in my private website: https://mikejseo.github.io/conferences/

References i

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