bnma: Bayesian Network Meta-Analysis using 'JAGS'  

Michael Seo¹, Christopher Schmid²  
January 19, 2021  

¹Institute of Social and Preventive Medicine, University of Bern, Bern, Switzerland  
²Department of Biostatistics, Brown University School of Public Health, Providence, RI, USA
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.
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).
- **bnma** models normal, binomial, and multinomial outcomes.
bnma package(2)

- Required input includes: outcomes, study indicator, treatment indicator, total number of observations (for binomial or multinomial outcomes) or standard error (for normal outcomes).
- Based on the specified input, bnma creates **JAGS code** and **initial values** and automatically runs Bayesian NMA model.
We demonstrate our package 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.
Here are the first five studies of the smoking dataset.

```r
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 $i$,

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

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

where $\eta_i$ 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,

$$\delta_{i,1k} \sim \mathcal{N}(d_{1k}, \sigma_{1k}^2)$$
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:

```r
1 network <- with(smoking, network.data(Outcomes = Outcomes, Study = Study, Treat = Treat, N = N, response = "binomial", type = "random"))
2 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:

<table>
<thead>
<tr>
<th></th>
<th>Mean</th>
<th>SD</th>
<th>Naive SE</th>
<th>Time-series SE</th>
<th>SE</th>
</tr>
</thead>
<tbody>
<tr>
<td>d[1]</td>
<td>0.0000</td>
<td>0.0000</td>
<td>0.000000</td>
<td>0.000000</td>
<td>0.000000</td>
</tr>
<tr>
<td>d[2]</td>
<td>0.4935</td>
<td>0.4015</td>
<td>0.001037</td>
<td>0.001943</td>
<td>0.001943</td>
</tr>
<tr>
<td>d[3]</td>
<td>0.8443</td>
<td>0.2388</td>
<td>0.000617</td>
<td>0.001468</td>
<td>0.001468</td>
</tr>
<tr>
<td>d[4]</td>
<td>1.1028</td>
<td>0.4396</td>
<td>0.001135</td>
<td>0.002622</td>
<td>0.002622</td>
</tr>
<tr>
<td>sd</td>
<td>0.8410</td>
<td>0.1872</td>
<td>0.000483</td>
<td>0.001847</td>
<td>0.001847</td>
</tr>
</tbody>
</table>

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.
We can use a forest plot to visualize the results.

```r
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 $\eta_i$, $d_{1k}$, $\log\sigma^2$.
– 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.

```r
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 variance i.e. \( \eta_{i1} \sim N(E, \sigma_E^2) \).
- Note that we have added 1 in the subscript in \( \eta_{i1} \). 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).
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).

```r
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)

... 

<table>
<thead>
<tr>
<th></th>
<th>Mean</th>
<th>SD</th>
<th>Naive SE</th>
<th>Time–series SE</th>
</tr>
</thead>
<tbody>
<tr>
<td>E</td>
<td>-2.4912</td>
<td>0.1280</td>
<td>0.0003304</td>
<td>0.0010630</td>
</tr>
<tr>
<td>d[1]</td>
<td>0.0000</td>
<td>0.0000</td>
<td>0.0000000</td>
<td>0.0000000</td>
</tr>
<tr>
<td>d[2]</td>
<td>0.5315</td>
<td>0.3264</td>
<td>0.0008428</td>
<td>0.0018280</td>
</tr>
<tr>
<td>d[3]</td>
<td>0.7817</td>
<td>0.1926</td>
<td>0.0004973</td>
<td>0.0011850</td>
</tr>
<tr>
<td>d[4]</td>
<td>1.0513</td>
<td>0.3367</td>
<td>0.0008695</td>
<td>0.0022016</td>
</tr>
<tr>
<td>sd</td>
<td>0.7213</td>
<td>0.1295</td>
<td>0.0003345</td>
<td>0.0008852</td>
</tr>
<tr>
<td>sdE</td>
<td>0.4624</td>
<td>0.1069</td>
<td>0.0002761</td>
<td>0.0008865</td>
</tr>
</tbody>
</table>

Common mean for the baseline risk is estimated to be -2.4912, which is equivalent to a baseline probability of quitting of 0.076.
Network Meta-regression on baseline risk

Model specification

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

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 \( \eta_{i1} \) 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

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: $\beta_{1k}$

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

```r
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)

...  

<table>
<thead>
<tr>
<th></th>
<th>Mean</th>
<th>SD</th>
<th>Naive SE</th>
<th>Time-series SE</th>
</tr>
</thead>
<tbody>
<tr>
<td>b_bl[1]</td>
<td>0.0000</td>
<td>0.0000</td>
<td>0.0000000</td>
<td>0.0000000</td>
</tr>
<tr>
<td>b_bl[2]</td>
<td>-0.4148</td>
<td>0.5315</td>
<td>0.0013723</td>
<td>0.0065083</td>
</tr>
<tr>
<td>b_bl[3]</td>
<td>-0.4148</td>
<td>0.5315</td>
<td>0.0013723</td>
<td>0.0065083</td>
</tr>
<tr>
<td>b_bl[4]</td>
<td>-0.4148</td>
<td>0.5315</td>
<td>0.0013723</td>
<td>0.0065083</td>
</tr>
<tr>
<td>d[1]</td>
<td>0.0000</td>
<td>0.0000</td>
<td>0.0000000</td>
<td>0.0000000</td>
</tr>
<tr>
<td>d[2]</td>
<td>0.6204</td>
<td>0.3511</td>
<td>0.0009066</td>
<td>0.0023820</td>
</tr>
<tr>
<td>d[3]</td>
<td>0.8988</td>
<td>0.2502</td>
<td>0.0006460</td>
<td>0.0025149</td>
</tr>
<tr>
<td>d[4]</td>
<td>1.1543</td>
<td>0.3637</td>
<td>0.0009392</td>
<td>0.0028476</td>
</tr>
<tr>
<td>sd</td>
<td>0.7524</td>
<td>0.1324</td>
<td>0.0003418</td>
<td>0.0009809</td>
</tr>
</tbody>
</table>

Odds ratio \( \exp(1.1543) = 3.17 \) is now the treatment effect of group counseling for patients with a baseline logit probability of quitting of \( \bar{\eta} = -2.745 \) (i.e. a baseline probability of quitting of 0.06)
– 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)
– The following slide is uploaded in my private website: https://mikejseo.github.io/conferences/


