**nmaINLA R package: Fitting network meta-analysis models using INLA**

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**Summary**

The default choice for fitting Bayesian NMA models is Markov Chain Monte Carlo (MCMC) methods. As an alternative to MCMC, INLA which is an approximate Bayesian inference method can also be used to fit such models. INLA methodology is implemented as an R (R Core Team, 2016) package INLA. Our package nmaINLA is a purpose-built front end of the INLA. While INLA offers full Bayesian inference for the large set of latent Gaussian models using integrated nested Laplace approximations, nmaINLA extracts the features needed for many NMA models and presents them in an intuitive way. The purpose of this vignette is to demonstrate you how to use nmaINLA. For the explanations and model descriptions, we refer to Sauter and Held (2015) and Gâ€¾nhan et al.

1 **Installation**

Firstly, R-INLA package should be installed. We recommend the testing version of R-INLA. It can be downloaded from INLA website (http://www.r-inla.org/). Or it can be installed (and loaded) with following commands:

```r
install.packages("INLA", repos=c(getOption("repos"),
                                           INLA="https://inla.r-inla-download.org/R/stable"), dep=TRUE)
library(INLA)
```

The development version of nmaINLA is on GitHub (https://github.com/gunhanb/nmaINLA). One way to install nmaINLA is using devtools (Wickham and Chang, 2016) R package as follows.

```r
install.packages("devtools")
library(devtools)
install_github("gunhanb/nmaINLA")
```

2 **Fitting Consistency and Jackson models**

Here, we use the Smoking application which is a widely used NMA dataset (see ?Smokdat).

```r
library(nmaINLA)
data("Smokdat", package = "nmaINLA")
head(Smokdat)
```

<table>
<thead>
<tr>
<th>r1</th>
<th>r2</th>
<th>r3</th>
<th>n1</th>
<th>n2</th>
<th>n3</th>
<th>t1</th>
<th>t2</th>
<th>t3</th>
<th>na</th>
<th>des</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>9</td>
<td>23</td>
<td>10</td>
<td>140</td>
<td>140</td>
<td>138</td>
<td>1</td>
<td>3</td>
<td>4</td>
<td>3</td>
</tr>
<tr>
<td>2</td>
<td>11</td>
<td>12</td>
<td>29</td>
<td>78</td>
<td>85</td>
<td>170</td>
<td>2</td>
<td>3</td>
<td>4</td>
<td>3</td>
</tr>
<tr>
<td>3</td>
<td>75</td>
<td>363</td>
<td>NA</td>
<td>731</td>
<td>714</td>
<td>1</td>
<td>1</td>
<td>3</td>
<td>NA</td>
<td>2</td>
</tr>
</tbody>
</table>

1
As one can notice, the form of dataset is one-study-per-row format. This format is widely used and convenient for BUGS models. The only different covariate is des which is the vector of designs. That variable is only needed to fit Jackson model and should be added by “hand” to the dataset. Then, this dataset should be converted to one-arm-per-row format, and some indicator variables should be added as well. This can be done using create_INLA_dat function:

```r
SmokdatINLA <- create_INLA_dat(dat = Smokdat, 
   armVars = c('treatment' = 't', 'responders' = 'r', 
               'sampleSize' = 'n'), 
   nArmsVar = 'na', 
   design = 'des')
```

```
head(SmokdatINLA)
## study treatment responders sampleSize na baseline mu d12 d13 d14 g het
## 1 1 1 9 140 3 1 1 0 0 0 NA NA
## 2 1 3 23 140 3 1 1 0 1 0 1 1
## 3 1 4 10 138 3 1 1 0 0 1 2 1
## 4 2 2 11 78 3 2 2 0 0 0 NA NA
## 5 2 3 12 85 3 2 2 -1 1 0 1 2
## 6 2 4 29 170 3 2 2 -1 0 1 2 2
## inc
## 1 NA
## 2 1
## 3 1
## 4 NA
## 5 2
## 6 2
```

Figure 1 (a network plot) can be created using plot_nma:

```r
plot_nma(s.id = study, t.id = treatment, data = SmokdatINLA)
```

nma_inla is the main fitting function of this package. It is actually a wrapper for inla function from R-INLA. Since Smoking dataset has binomial endpoints, the consistency model can be fitted by specifying likelihood = "binomial" as follows:

```r
fit.consistency <- nma_inla(SmokdatINLA, likelihood = "binomial", 
   fixed.par = c(0, 1000), tau.prior = "uniform", 
   tau.par = c(0, 5), type = "consistency")
```

Note that only Normal prior is available for priors of fixed effects of the model (including baseline risks and basic parameters). A simple summary of the fitted model is given by print option:
## Network meta-analysis using INLA
## Relative treatment effects

<table>
<thead>
<tr>
<th></th>
<th>mean</th>
<th>sd</th>
<th>0.025quant</th>
<th>0.5quant</th>
<th>0.975quant</th>
</tr>
</thead>
<tbody>
<tr>
<td>d12</td>
<td>0.493</td>
<td>0.399</td>
<td>-0.282</td>
<td>0.487</td>
<td>1.302</td>
</tr>
<tr>
<td>d13</td>
<td>0.841</td>
<td>0.237</td>
<td>0.392</td>
<td>0.833</td>
<td>1.332</td>
</tr>
<tr>
<td>d14</td>
<td>1.099</td>
<td>0.434</td>
<td>0.269</td>
<td>1.088</td>
<td>1.991</td>
</tr>
</tbody>
</table>

## Heterogeneity stdev

<table>
<thead>
<tr>
<th></th>
<th>mean</th>
<th>sd</th>
<th>0.025quant</th>
<th>0.5quant</th>
<th>0.975quant</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>0.838</td>
<td>0.184</td>
<td>0.546</td>
<td>0.814</td>
<td>1.268</td>
</tr>
</tbody>
</table>

For post-processing, **R-INLA** functions can be used. A plot for the marginal posterior density of basic parameter \((d_{1,2})\) can be plotted using **inla.smarginal** **R-INLA** function (see Figure 2A).

```r
d12.inla <- inla.smarginal(marginal = fit.consistency$marginals.fixed$d12)
plot(d12.inla, type = "l", xlab = expression(paste(d[12])), ylab = "")
```

**R-INLA** internally uses precisions (on logarithmic scale) for the posterior marginals of hyperparameters (corresponds to \(\tau\) for a Consistency model). To obtain variances instead of logarithm of precisions of heterogeneity, transformation of the hyperparameter is needed. Transformation and plotting can be done as follows (see Figure 2B):  

```r
log.prec.het <- fit.consistency$internal.marginals.hyperpar$`Log precision for het`
tau2.inla <- inla.tmarginal(function(x) 1/exp(x), log.prec.het, n = 20000)
plot(tau2.inla, type = "l", xlab = expression(paste(tau)), ylab = "")
```

Finally, the Jackson model can be fitted by specifying **type** = 'jackson':  

```r
fit.jackson <- nma_inla(SmokdatINLA, likelihood = "binomial",
fixed.par = c(0, 1000), tau.prior = "uniform",
tau.par = c(0, 5), kappa.prior = "uniform",
kappa.par = c(0, 5), type = "jackson")
```

### 3 Fitting NMA-regression models

Here we use the Stroke dataset which is originally analyzed in **Batson et al.** (2016) (see ?Strokedat). There are four different covariates available. We only use **age** covariate to fit a NMA-regression model. Firstly, we delete the study in which **age** covariate information is not available. Then, centered covariate information can be given by **covariate** = 'age' as follows:

```r
data("Strokedat", package = "nmaINLA")
# deleting 13th study
Strokedat.mreg <- Strokedat[-c(13),]
# centering the covariate
Strokedat.mreg$age <- Strokedat.mreg$age - mean(Strokedat.mreg$age)
# data preparation for INLA
StrokedatINLA.mreg <- create_INLA_dat(dat = Strokedat.mreg,
```
armVars = c('treatment' = 't', 'responders' = 'r', 'sampleSize' = 'n'),
nArmsVar = 'na',
design = 'des',
covariate = 'age')

Then, a Consistency NMA-regression model can be fitted by specifying mreg = TRUE:

fit.Stroke.CONS.MREG.INLA <- nma_inla(StrokedatINLA.mreg, likelihood = "binomial",
fixed.par = c(0, 1000), tau.prior = "uniform",
tau.par = c(0, 2), type = 'consistency',
mreg = TRUE)

Feedback and comments on nmaINLA are always welcome.
Bug reports can be sent to https://github.com/gunhanb/nmaINLA/issues.

4 R version and packages used to generate this document

R version: R version 3.5.1 (2018-07-02)
Base packages: stats, graphics, grDevices, utils, datasets, methods, base
Other packages: nmaINLA, INLA, sp, Matrix, knitr
Versions of other packages (respectively): 0.1.2, 18.7.12, 1.3.1, 1.2.14, 1.20
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References


GÃ¼NHAN, B. K., FRIEDE, T. and HELD, L. (????). A design-by-treatment interaction model for network meta-analysis and meta-regression with integrated nested laplace approximations. *Research Synthesis Methods* n/a–n/aJrsm.1285.
URL http://dx.doi.org/10.1002/jrsm.1285

URL https://www.R-project.org/

URL http://dx.doi.org/10.1002/bimj.201400163

URL https://github.com/hadley/devtools
Figure 1: Network of trials of Smoking cessation.
Figure 2: Plot for the marginal posterior density of $d_{12}$ and $\tau^2$. 