

# **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 Gunhan et al. (2017).

## **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:

```
install.packages("INLA", repos = "https://www.math.ntnu.no/inla/R/testing")
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.

```
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).

```
library(nmainla)
data("Smokdat", package = "nmainla")
head(Smokdat)
```

##	r1	r2	r3	n1	n2	n3	t1	t2	t3	na	des
## 1	9	23	10	140	140	138	1	3	4	3	1
## 2	11	12	29	78	85	170	2	3	4	3	2
## 3	75	363	NA	731	714	1	1	3	NA	2	3
## 4	2	9	NA	106	205	1	1	3	NA	2	3

```
## 5 58 237 NA 549 1561 1 1 3 NA 2 3
## 6 0 9 NA 33 48 1 1 3 NA 2 3
```

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:

```
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**:

```
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:

```
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:

```
print(fit.consistency)

## Time used:
## Pre-processing      Running inla Post-processing      Total
##      0.86043358      0.09777284      0.05283070      1.01103711
## Network meta-analysis using INLA
## Relative treatment effects
##      mean      sd 0.025quant 0.5quant 0.975quant
## d12 0.494 0.401      -0.285      0.488      1.308
## d13 0.842 0.238      0.391      0.834      1.337
## d14 1.101 0.437      0.268      1.090      1.998
## Heterogeneity stdev
##      mean      sd 0.025quant 0.5quant 0.975quant
##      0.838      0.183      0.546      0.814      1.268
```

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).

```
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):

```
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'`:

```
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 Atrial dataset which is originally analyzed in Batson et al. (2016) (see `?Atrialdat`). 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:

```
data("Atrialdat", package = "nmainla")
# deleting 13th study
```

```
Atrialdat.mreg <- Atrialdat[-c(13),]
# centering the covariate
Atrialdat.mreg$age <- Atrialdat.mreg$age - mean(Atrialdat.mreg$age)
# data preparation for INLA
AtrialdatINLA.mreg <- create_INLA_dat(dat = Atrialdat.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.Atrial.CON.S.MREG.INLA <- nma_inla(AtrialdatINLA.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 3.3.2 (2016-10-31)

Base packages: stats, graphics, grDevices, utils, datasets, methods, base

Other packages: INLA, Matrix, sp, knitr, nmainla, devtools, pcnetmeta, rjags, coda

Versions of other packages (respectively): 0.0.1483095018, 1.2.7.1, 1.2.4, 1.15.1, 0.1.0, 1.12.0.9000, 2.4, 4.6, 0.19.1

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## References

- BATSON, S., SUTTON, A. and ABRAMS, K. (2016). Exploratory network meta regression analysis of stroke prevention in atrial fibrillation fails to identify any interactions with treatment effect. *PLoS One* **11** e0161864.
- GUNHAN, B. K., FRIDE, T. and HELD, L. (2017). A design-by-treatment interaction model for network meta-analysis using integrated nested laplace approximations In preparation.
- R CORE TEAM (2016). *R: A Language and Environment for Statistical Computing*. R Foundation for Statistical Computing, Vienna, Austria.  
URL <https://www.R-project.org/>
- SAUTER, R. and HELD, L. (2015). Network meta-analysis with integrated nested Laplace approximations. *Biometrical Journal* **57** 1038–1050.  
URL <http://dx.doi.org/10.1002/bimj.201400163>

WICKHAM, H. and CHANG, W. (2016). *devtools: Tools to Make Developing R Packages Easier*. R package version 1.12.0.9000.  
URL <https://github.com/hadley/devtools>

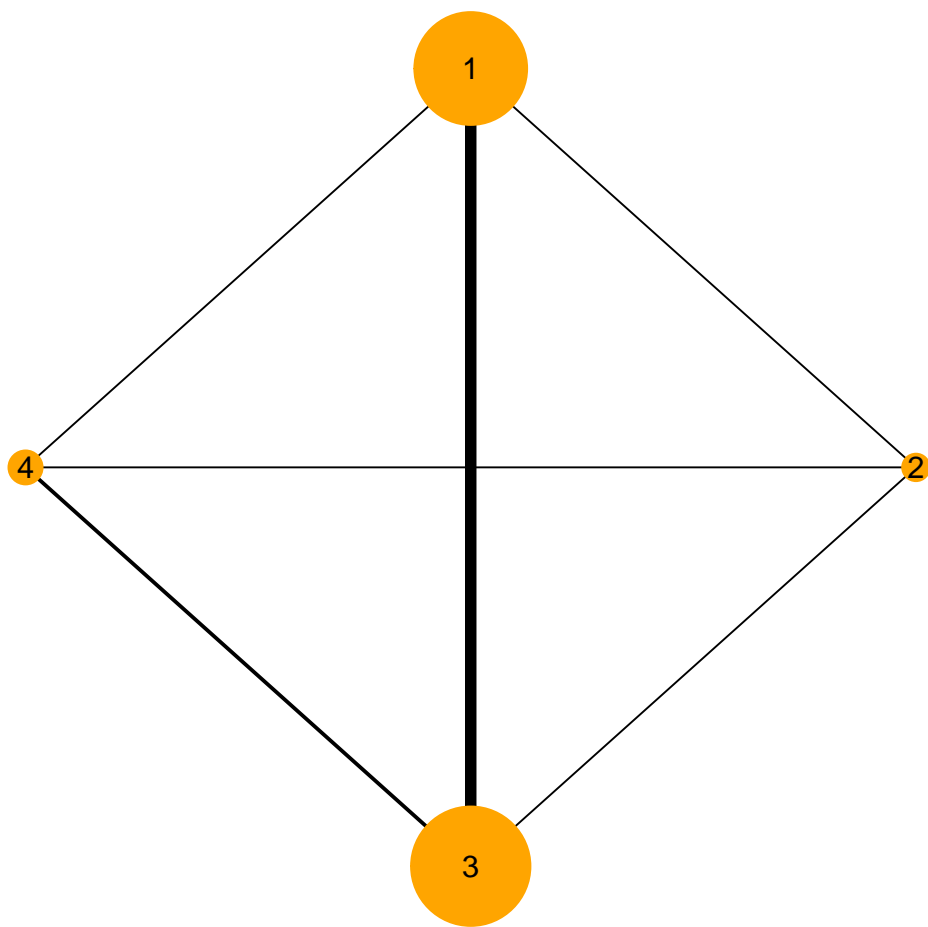


Figure 1: Network of trials of Smoking cessation.

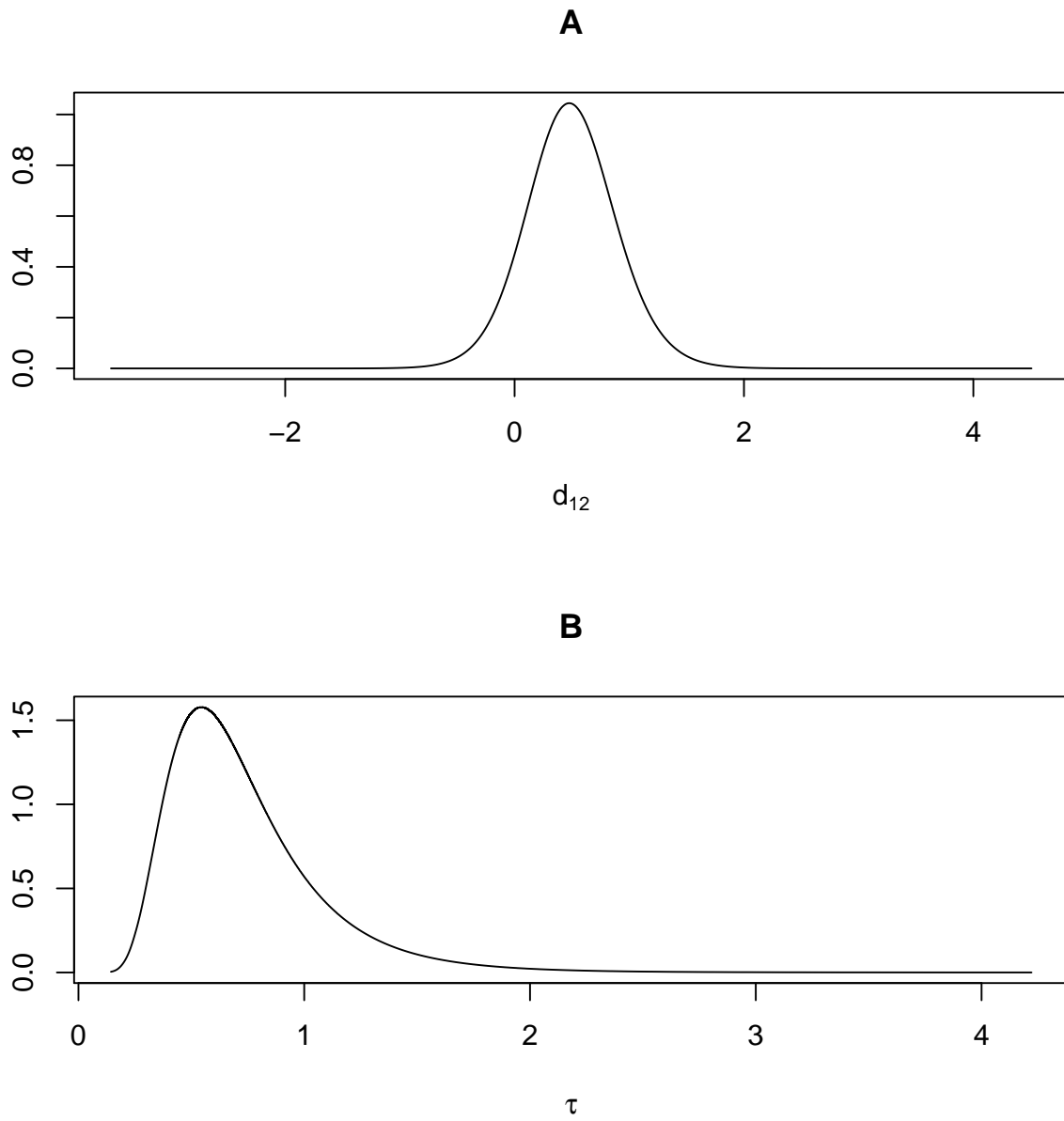


Figure 2: Plot for the marginal posterior density of  $d_{1,2}$  and  $\tau^2$ .