A design-by-treatment interaction model for network meta-analysis with integrated nested Laplace approximations (INLA)

Burak Kürsad Günhan [1] Tim Friede [1] Leonhard Held [2]

[1]Department of Medical Statistics, University Medical Center Göttingen, Göttingen, Germany

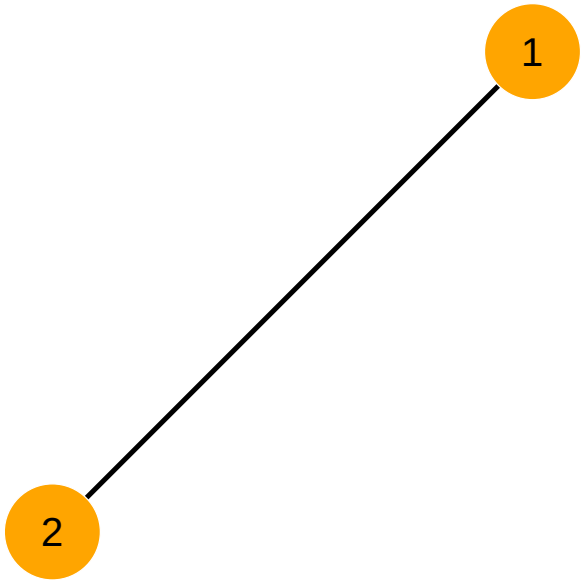
[2]Epidemiology, Biostatistics and Prevention Institute, University of Zürich, Zürich, Switzerland

InSPiRe Conference, April 28, 2017

InSPiRe Innovative methodology for small populations research

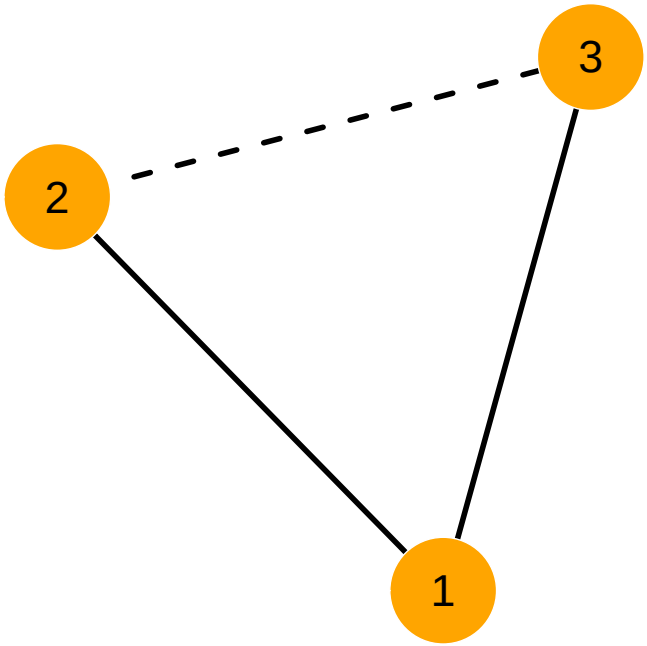
This project has received funding from the European Union's Seventh Framework Programme for research, technological development and demonstration under grant agreement number FP HEALTH 2013-602144.

Pairwise meta-analysis



- Only two treatments are compared
- Trt 1 vs Trt 2 can be **directly** estimated ($d_{1,2}$)
- **But**, increasingly, many competing treatments exist
- And multi-arm trials

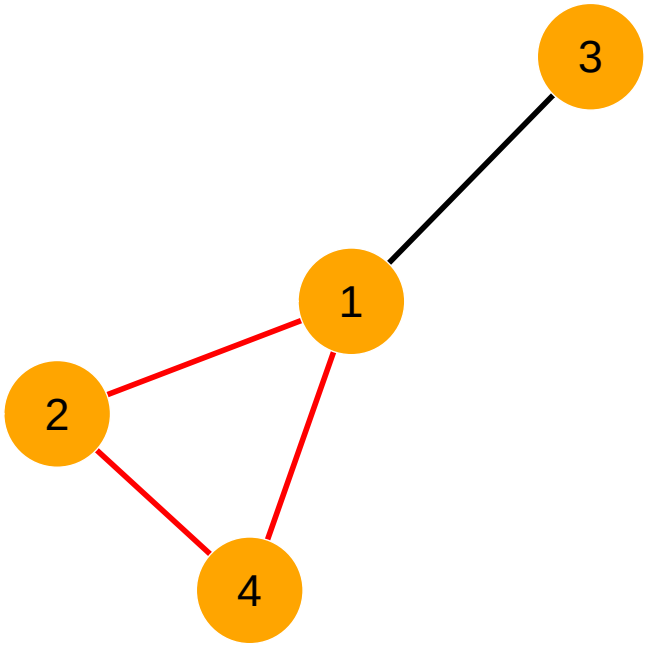
Need for a broader approach



- Network meta-analysis
- Solid lines indicate comparisons are available
- **Indirect estimate** of 2 vs 3

$$d_{2,3}^{\text{Ind}} = d_{1,2}^{\text{Dir}} - d_{1,3}^{\text{Dir}}$$

Terminology in NMA (Salanti, 2012)

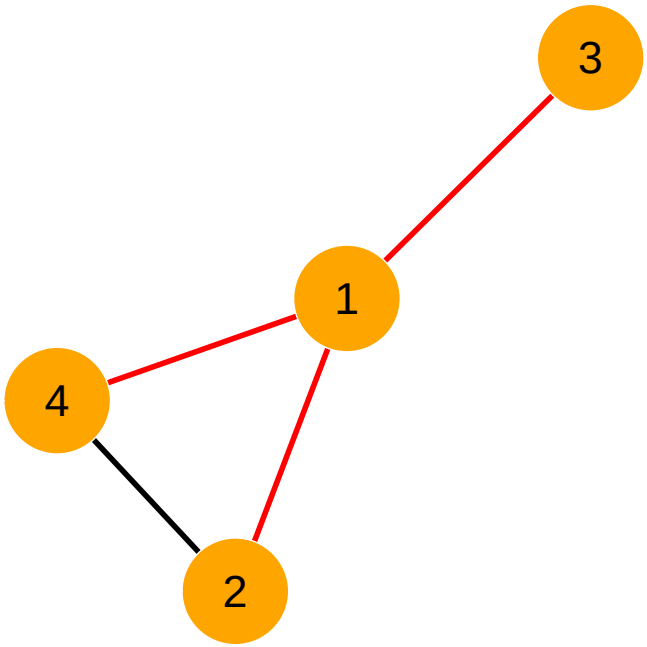


- From Graph theory: vertex, edge
- **Cycle**: Red lines
- **Design**: set of treatments included in a trial; 1-2 design, 1-2-3 design

Terminology in NMA (cont.)

- **Heterogeneity** in treatment effects between trials
  $\Rightarrow$ As in a pairwise meta-analysis
- **Consistency**: No discrepancy between indirect and direct estimates: $d_{1,2}^{\text{Dir}} = d_{1,2}^{\text{Ind}}$
- Consistency relation: $d_{1,2}^{\text{Dir}} = d_{1,3}^{\text{Dir}} - d_{2,3}^{\text{Dir}}$
- Trials of different comparisons were undertaken in different periods
- Right-hand side parameters are **basic parameters** ($\mathbf{d}_b$)
  $\Rightarrow$ Parametrization of the network
- Others are **functional parameters** ($\mathbf{d}_f$)

A simple network



- $\mathbf{d}_b = \{d_{12}, d_{13}, d_{14}\}$ (red lines)
  $\Rightarrow d_f = d_{24} = d_{12} - d_{14}$
- Consistency relation
  $\Rightarrow$ 3-cycle

Statistical models for NMA

- Hierarchical models, more specifically generalized linear mixed models (GLMMs)
- Contrast-based vs arm-based models
- Trial-arm level instead of summary-level (aggregate-level) approach
  $\Rightarrow$ Advantage: the former is one-stage approach
- Datasets with different endpoints (dichotomous, continuous, time-to-event) can be modelled
- Basic model is same, but **likelihood** and **link function** can change

Consistency models (Dias et al., 2011)

- For convenience, consider data with binomial endpoints
- In trial i; t_k is a treatment arm
  $\Rightarrow$ when $k = 1$, t_1, is a baseline arm.
- Number of events, $y_{i,t_k} \sim \text{Bin}(\pi_{i,t_k}, n_{i,t_k})$
- Linear predictor with logit link

$$\text{logit}(\pi_{i,t_k}) = \begin{cases} \mu_i, & \text{if } k = 1 \\ \mu_i + d_{t_1 t_k} + \gamma_{i,t_1 t_k}, & \text{if } k \neq 1. \end{cases}$$

  where μ_i nuisance parameter and $d_{t_1 t_k}$ basic parameters
- Heterogeneity random effects: $\gamma_{i,t_1 t_k} \sim \mathcal{N}(0, \tau^2)$

Consistency models (cont.)

- But, for a multi-arm trial: dependency within trial!
- Example: A three-arm trial i with the design 1-2-3
  - $\boldsymbol{\gamma}_i = (\gamma_{i,12}, \gamma_{i,13})^T \sim \mathcal{N}_2(\mathbf{0}, \boldsymbol{\Sigma}_\gamma)$
  - A simple but a convenient structure is as follows (Higgins and Whitehead, 1996):

$$\boldsymbol{\Sigma}_\gamma = \begin{bmatrix} \tau^2 & \tau^2/2 \\ \tau^2/2 & \tau^2 \end{bmatrix}$$

- Models are needed to account for **inconsistency** in the network

Design-by-treatment interaction model (Higgins et al., 2012)

- **Design inconsistency**: occurs between trials involving different designs
- 1,2,3 trials can be inconsistent with 1,2 trials
- Adding design-specific inconsistency parameters to the consistency model
- Improvement of cycle-inconsistency approach (Lu and Ades, 2006)

Jackson Model (Jackson et al., 2014)

- Inconsistency parameters as random effects

$$\text{logit}(\pi_{i,t_k}) = \begin{cases} \mu_i, & \text{if } k = 1 \\ \mu_i + d_{t_1 t_k} + \gamma_{i,t_1 t_k} + \omega_{t_1 t_k}^{D(i)}, & \text{if } k \neq 1. \end{cases}$$

$\boldsymbol{\omega}^{D(i)} \sim \mathcal{N}_{T-1}(\mathbf{0}, \boldsymbol{\Sigma}_\omega)$ such that $\boldsymbol{\Sigma}_\omega$ has diagonal entries κ^2 and all others are $\kappa^2/2$

- NMA-regression: incorporating trial-specific covariates to the model in order to explain sources of heterogeneity and/or inconsistency

Fully-Bayesian inference for NMA models

Markov chain Monte Carlo (MCMC)

- A simulation-based technique and the most popular among NMA-analyzers
- Computationally intensive & convergence diagnostics

Integrated nested Laplace approximations (INLA)

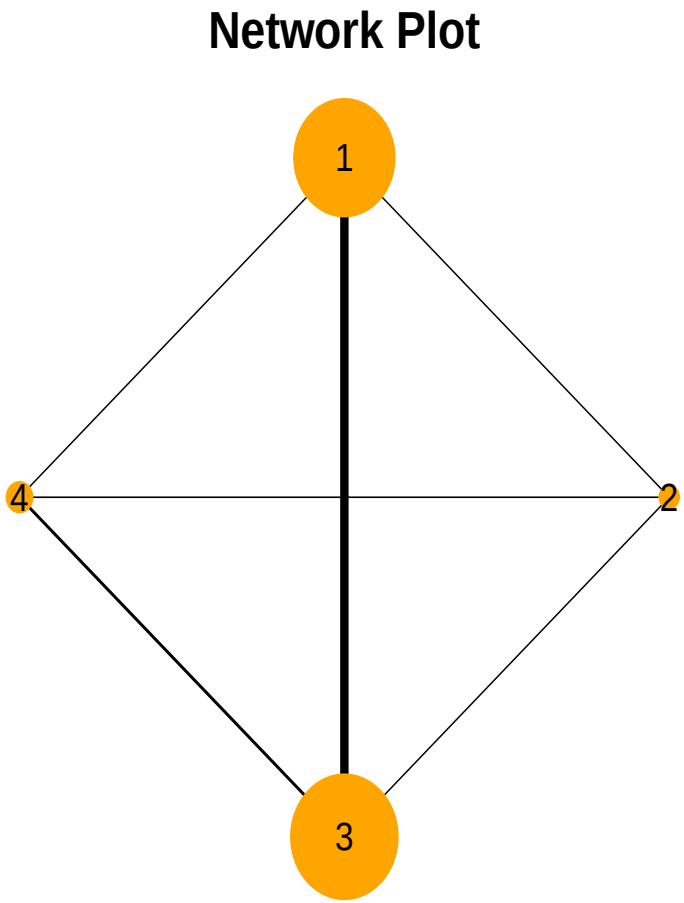
- An approximate Bayesian method (Rue et al., 2009) for latent Gaussian models (LGMs)
- Fast and accurate alternative to MCMC
- **Laplace approximations** & **numerical integration**
- Implemented in `R-INLA` (http://www.r-inla.org/)

INLA for NMA models

- How NMA models are LGMs? Three stages:
  1. Observational model: $p(\boldsymbol{y}|\boldsymbol{\alpha}, \boldsymbol{\Psi})$ where $\boldsymbol{\alpha} = (\boldsymbol{\mu}, \boldsymbol{d_b}, \beta, \boldsymbol{\gamma}, \boldsymbol{\omega})$ and $\boldsymbol{\Psi} = (\tau^2, \kappa^2)$
  2. Latent Gaussian field: $p(\boldsymbol{\alpha}|\boldsymbol{\Psi}) \sim \mathcal{N}(\mathbf{0}, \boldsymbol{\Sigma}_\Psi)$
  3. Hyperparameters: $|\boldsymbol{\Psi}| = 2$
- We extended INLA implementation (Sauter and Held, 2015) to different NMA models (Jackson model, NMA-regression) and also automation

Smoking dataset (Hasselblad, 1998)

- 24 trials investigating four interventions to aid smoking cessation
- Coding; 1: no contact, 2: self-help, 3: individual counseling and 4: group counseling
- Area of circle: participants; width of line: trials
- 8 designs, 1-3-4 and 2-3-4 three arm trials



Specifications for Jackson model

- Basic parameters: $\mathbf{d}_b = \{d_{12}, d_{13}, d_{14}\}$

- Priors:
  $\Rightarrow$ Fixed effects: $\boldsymbol{\mu}, \boldsymbol{d_b} \sim \mathcal{N}(0, 1000)$
  $\Rightarrow$ Hyperparameters: $\tau, \kappa \sim \mathcal{U}(0, 5)$.

MCMC implementation

- MCMC via JAGS program
- MCMC: 74 parameters to check convergence
- 50,000 iterations after burn-in of 30,000 iterations
- To ensure MCSE below 0.005

nmaINLA R package

- Publicly available from Github repository

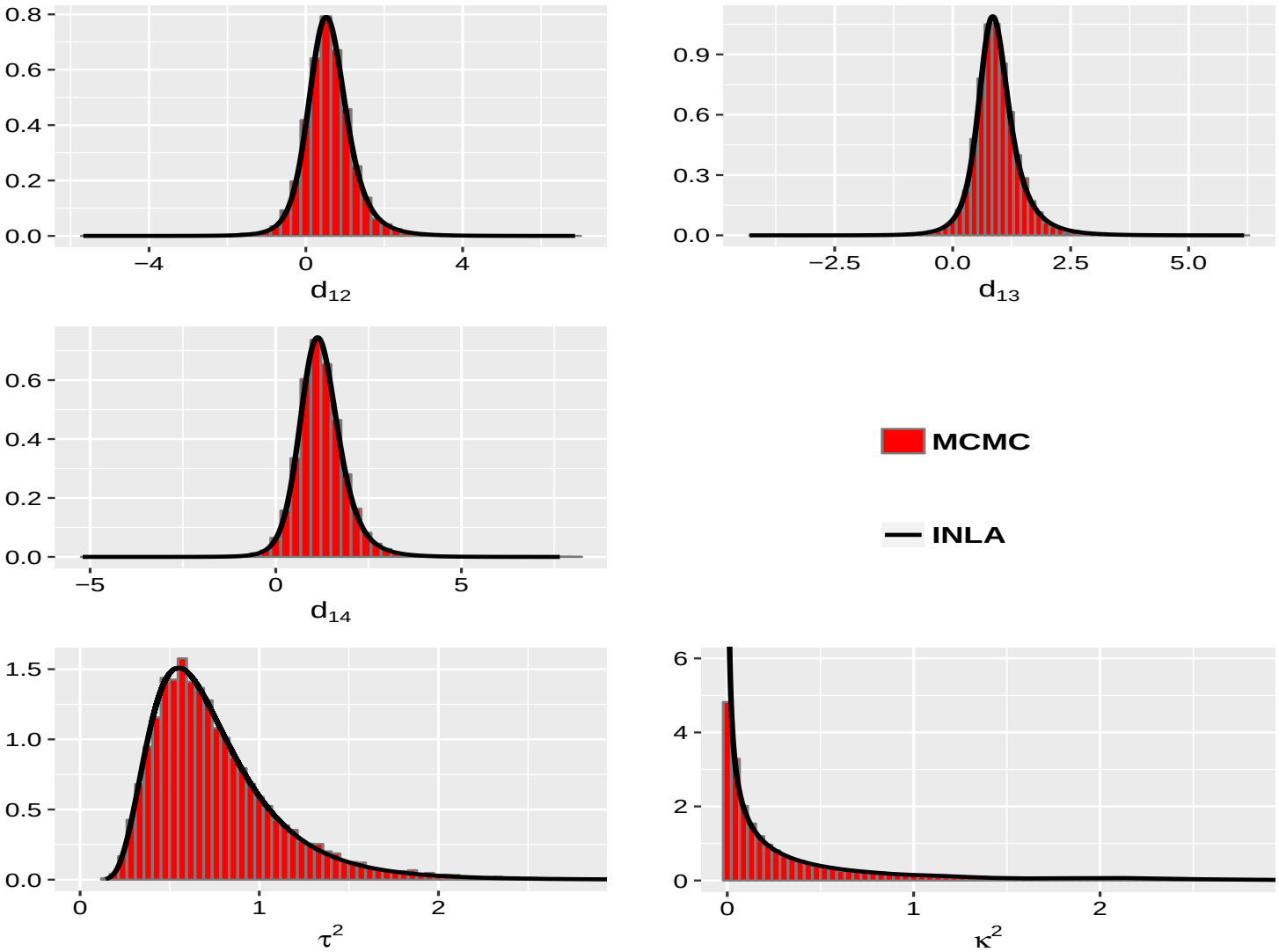
```
library(devtools)
install_github("gunhanb/nmaINLA")
```

- Data preparation step
- Fitting a Jackson model

```
nma_inla(SmokdatINLA, likelihood = 'binomial', type = 'jackson',
         fixed.par = c(0, 1000), tau.prior = 'uniform', tau.par = c(0, 5),
         kappa.prior = 'uniform', kappa.par = c(0, 5))
```

- MCMC run took 36.3, INLA took 6 seconds.

Marginal posterior density estimates



Conclusions

- Common framework for contrast-based NMA models to analyze dataset with different endpoints
- INLA's advantages over MCMC
  $\Rightarrow$ Faster, no need to check convergence diagnostics
- `nmaINLA` extracts features needed for NMA
- Arm-based models are also possible, but not implemented yet.

Outlook

- INLA especially useful when refitting model is needed
  - Extensive simulations
  - Sensitivity analysis (for different priors)
  - Node-splitting method (a NMA technique)
  - Cross-validation (for model selection)

References I

Acknowledgements

- Dr. Rafael Sauter

Dias, S., Welton, N. J., Sutton, A. J., and Ades, A. (2011). NICE DSU Technical Support Document 2: A Generalised Linear Modelling Framework for Pairwise and Network Meta-analysis of Randomised Controlled Trials. last updated September 2016.

Hasselblad, V. (1998). Meta-analysis of multitreatment studies. *Medical Decision Making*, 18(1):37–43.

Higgins, J. P. T., Jackson, D., Barrett, J. K., Lu, G., Ades, A. E., and White, I. R. (2012). Consistency and inconsistency in network meta-analysis: concepts and models for multi-arm studies. *Research Synthesis Methods*, 3(2):98–110.

References II

Higgins, J. P. T. and Whitehead, A. (1996). BORROWING STRENGTH FROM EXTERNAL TRIALS IN A META-ANALYSIS. *Statistics in Medicine*, 15(24):2733–2749.

Jackson, D., Barrett, J. K., Rice, S., White, I. R., and Higgins, J. P. (2014). A design-by-treatment interaction model for network meta-analysis with random inconsistency effects. *Statistics in Medicine*, 33(21):3639–3654.

Lu, G. and Ades, A. E. (2006). Assessing Evidence Inconsistency in Mixed Treatment Comparisons. *Journal of the American Statistical Association*, 101(474):447–459.

Rue, H., Martino, S., and Chopin, N. (2009). Approximate Bayesian inference for latent Gaussian models by using integrated nested Laplace approximations. *Journal of the Royal Statistical Society: Series B (Statistical Methodology)*, 71(2):319–392.

Salanti, G. (2012). Indirect and mixed-treatment comparison, network, or multiple-treatments meta-analysis: many names, many benefits, many concerns for the next generation evidence synthesis tool. *Research Synthesis Methods*, 3(2):80–97.

References III

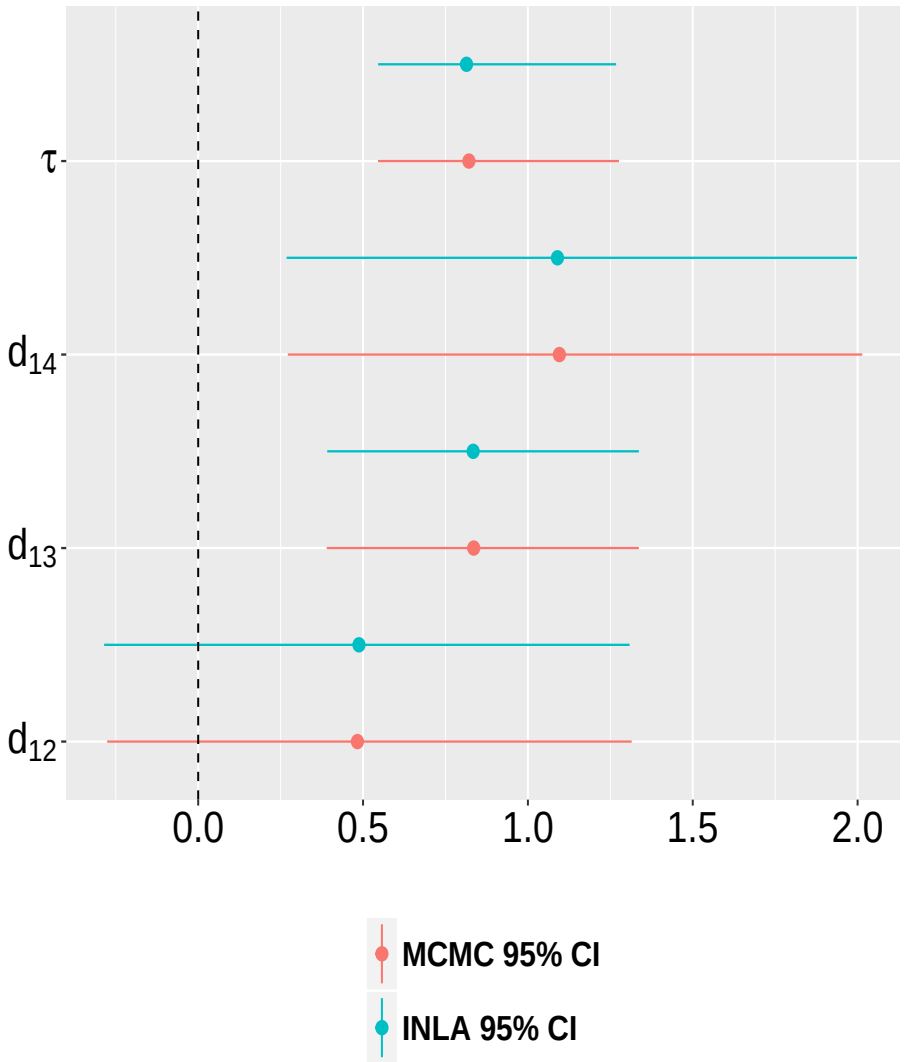
Sauter, R. and Held, L. (2015). Network meta-analysis with integrated nested Laplace approximations. *Biometrical Journal*, 57(6):1038–1050.

van Valkenhoef, G., Tervonen, T., de Brock, B., and Hillege, H. (2012). Algorithmic parameterization of mixed treatment comparisons. *Statistics and Computing*, 22(5):1099–1111.

Lu-Ades Model (Lu and Ades, 2006)

- Uses cycle-inconsistency approach
- Assumption: inconsistency **only** occurs from 3-cycles
- Basic parameters should form a spanning tree
- Cycle-specific inconsistency random effects: $\omega_{jkl} \sim \mathcal{N}(0, \kappa^2)$
- Multi-arm trials are inherently consistent
- Number of inconsistency random effects: ICDF $= \#\mathbf{d}_f - S$ where S is the number of cycles only formed by a multi-arm trial
- Algorithm for ICDF (van Valkenhoef et al., 2012), but not efficient
- In the presence of multi-arm trials, **results depend on treatment ordering!**

Consistency model (MCMC vs INLA)



MCMC settings

Consistency model

- Burn-in: 30.000 iterations
- After burn-in: 20.000 iterations
- 3 chains, 5 thinning parameter
- MCMC run took 29.1, INLA took 2.2 seconds.

Jackson model

- Burn-in: 30.000 iterations
- After burn-in: 50.000 iterations
- 3 chains, 5 thinning parameter
- To ensure Monte-Carlo standard error is below 0.005 for all parameters

Approximation error of INLA

- No analytical expression for approximation error of INLA
- But, in (quasi)-complete separation situation (binomial endpoints), INLA shows some inaccuracy
- One way to overcome is by using **weakly informative priors**

Multi-arm trials

- Convenient and simple variance-covariance matrix of heterogeneity, since we assume
- The homogeneity of between-study variations for every treatment comparison
- Also, for inconsistency, the homogeneity of inconsistency for every treatment comparison

Inconsistency parameters

Design	Parameter	MCMC		INLA	
		Mean	Stdev.	Mean	Stdev.
1	ω^1_{13}	0.02	0.56	0.02	0.53
	ω^1_{14}	-0.29	0.67	-0.28	0.64
2	ω^2_{23}	-0.07	0.57	-0.07	0.55
	ω^2_{24}	-0.10	0.58	-0.10	0.55
3	ω^3_{13}	-0.10	0.52	-0.10	0.50
4	ω^4_{12}	-0.13	0.58	-0.13	0.55
5	ω^5_{14}	0.42	0.81	0.39	0.76
6	ω^6_{23}	-0.11	0.57	-0.11	0.55
7	ω^7_{24}	0.09	0.57	0.09	0.55
8	ω^8_{34}	-0.04	0.53	-0.03	0.50