Network meta-analysis with integrated nested Laplace approximations (INLA)

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Network meta-analysis (NMA)

Motivation

- A systematic review collects trials comparing not only treatment A vs. B ...
  but also A vs. C, A vs. D and D vs. B, etc.
- A network meta-analysis (NMA) aggregates the evidence combining direct and indirect comparisons instead of using pairwise direct comparisons only.

Challenges of a NMA

- Like in pairwise meta-analysis the treatment effects can show excessive between-trial variability called heterogeneity.
- Combining direct and indirect evidence may produce contradictory estimates, called network inconsistency.

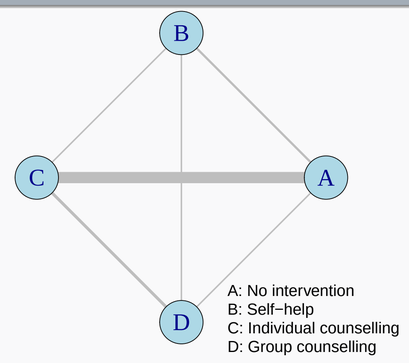
Advantages of a NMA:

- Comprehensive use of all available data (direct and indirect evidence).
- Comparison of interventions which have not been directly compared in any experiment.
- Improved precision for each comparison.

$\Longrightarrow$ **We implement established NMA models in INLA**, instead of computationally intensive MCMC sampling!

Application: a network about smoking cessation (Hasselblad, 1998)

- The binomial outcome $y_{iX} \sim \text{Bin}(n_{iX}, \pi_{iX})$ for treatment X and trial i is successful smoking cessation after 6 to 12 months.
- The network compares interventions A, B, C, D.
- There are 24 (22 two-arm and 2 three-arm) trials.
- An edge represents an observed direct treatment comparison d_{XY}.

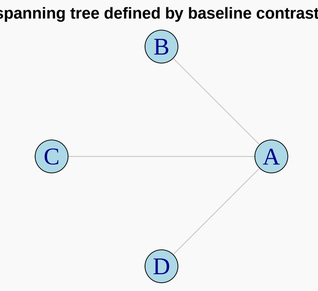


- Network consistency implies...

$$d_{BC} = d_{AC} - d_{AB}$$
$$d_{BD} = d_{AD} - d_{AB}$$
$$d_{CD} = d_{AD} - d_{AC}$$

... thus only 3 baseline contrasts $\boldsymbol{d}_b = (d_{AB}, d_{AC}, d_{AD})^\top$ are needed to describe the network.

- The remaining contrasts $\boldsymbol{d}_r$ are linear combinations of $\boldsymbol{d}_b$.



NMA model

- A logistic regression model describes the smoking cessation network

$$\text{logit}(\pi_{iX}) = a_{iX}$$
$$\text{logit}(\pi_{iY}) = a_{iX} + d_{XY} + \gamma_{iXY}.$$

- The baseline treatment effect a_{iX} is a nuisance parameter. Our interest is in d_{XY}.
- Heterogeneity is modeled by trial-specific random effects $\gamma_{iXY} \sim \text{N}(0, \tau^2)$.

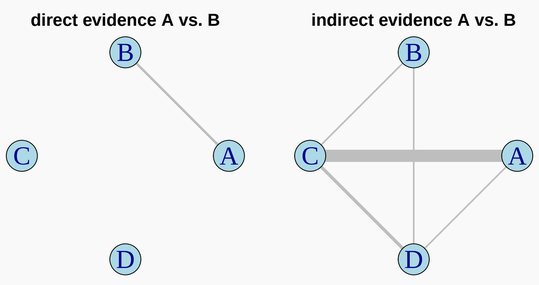
2 approaches to include inconsistency:

Random effects inconsistency

- Lu and Ades (2006) introduce inconsistency by cycle-specific random effects $\xi_{XYZ} \sim \text{N}(0, \kappa^2)$ for $\boldsymbol{d}_r$ such that e.g. $d_{YZ} = d_{XZ} - d_{XY} + \xi_{XYZ}$.
- The model for treatment π_{iY} with baseline treatment X is extended:
  $\text{logit}(\pi_{iY}) = a_{iX} + d_{XY} + \gamma_{iXY} + \xi_{XYZ}$.

Node-splitting inconsistency

- Dias et al. (2010) suggest to estimate d_{XY} based on direct $d_{XY}^{\text{dir.}}$ and based on indirect $d_{XY}^{\text{ind.}}$ evidence only. This is a node-split for X, Y.



- Inconsistency for d_{XY} is defined by the linear combination

$$i_{XY} = d_{XY}^{\text{dir.}} - d_{XY}^{\text{ind.}}.$$

Bayesian estimation with INLA

- This NMA model can be estimated with integrated nested Laplace approximations (INLA) (Rue et al., 2009).
- INLA approximates the marginal posterior distributions and is a fast and accurate alternative to MCMC sampling.

Multi-arm trials

- If a trial i compares more than 2 treatments then $\boldsymbol{\gamma}_i$ is not assumed to be independent.
- (Lu and Ades, 2006) assume a homogeneous correlation structure

$$\boldsymbol{\gamma}_i \sim \text{N}(\mathbf{0}, \boldsymbol{T})$$

- The variances on the diagonal of $\boldsymbol{T}$ are all equal to τ^2.
- Correlations in $\boldsymbol{T}$ are under consistency equal to $\rho = 1/2$.
- In INLA $\boldsymbol{T}$ can be written as Kronecker product

$$\boldsymbol{T} = \mathbf{C} \otimes \tau^2$$

where $\mathbf{C} = (1-\rho)\mathbf{I} + \rho\mathbf{J}$, $\mathbf{I}$ is the identity matrix and $\mathbf{J}$ is a matrix of ones.

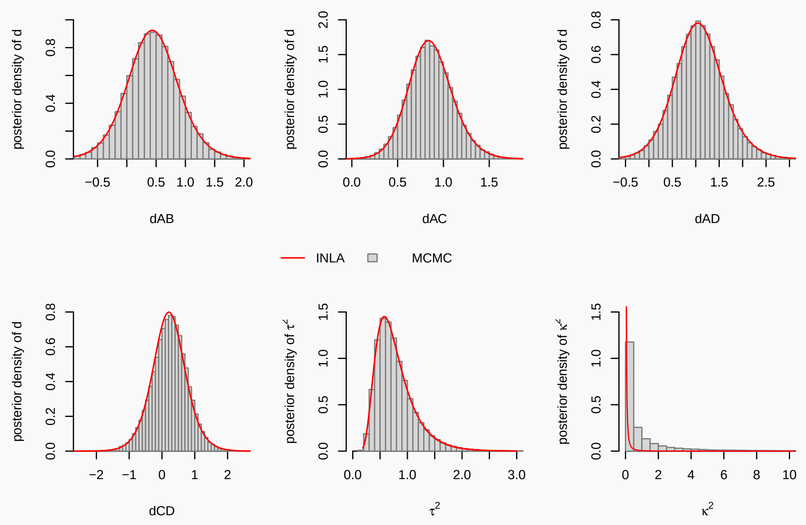
- This correlation structure is implemented in INLA with the `group` statement (see Riebler et al., 2012).

Node-splitting

- Node-splitting is implemented in INLA by using two likelihoods. One for $d_{XY}^{\text{dir.}}$ and one for $d_{XY}^{\text{ind.}}$ (see Martino et al., 2011).
- The heterogeneity hyperparameter τ^2 is the same for both likelihoods and estimated based on all data.

Application

Compare MCMC and INLA for smoking cessation NMA with random effects inconsistency



Marginal posterior distributions for $\boldsymbol{d}_b$ and one linear combination (d_{CD}) by INLA (red line) and MCMC (histogram) for the NMA model with random effects for heterogeneity τ^2 and incoherence κ^2.

Compare MCMC and INLA for smoking cessation NMA with node-splitting inconsistency

	MCMC			INLA		
	Mean	Stdev.	p-value	Mean	Stdev.	p-value
i_{AB}	-0.36	0.84	0.66	-0.42	0.77	0.58
i_{AC}	-0.24	0.80	0.77	0.22	0.69	0.74
i_{AD}	0.35	1.01	0.74	0.23	0.96	0.82
i_{BC}	-0.69	0.91	0.43	-0.65	0.83	0.42
i_{BD}	0.09	1.04	0.92	-0.03	0.96	0.97
i_{CD}	-1.85	1.10	0.08	-1.89	0.94	0.03

Inconsistency estimates i_{XY} based on the linear combination of the marginal posteriors $d_{XY}^{\text{dir.}}$ and $d_{XY}^{\text{ind.}}$.

Compare computation time for node-splitting by MCMC and INLA

Computation time for 6 node-splits in the smoking cessation network with a laptop (2.7GHz 4 core processor):

- **0.17 min.** with INLA.
- **16.73 min.** with MCMC using 150'000 iterations, done with `JAGS` through `R`-package `gemtc` (van Valkenhoef and Kuiper, 2014).

Summary

- INLA is much faster than MCMC sampling which is an advantage if node-splitting for a large network is needed.
- The approximations by INLA are deterministic and convergence checks are not needed.
- Also other NMA models can be implemented in INLA such as summary-level data models (Lumley, 2002).
- More details can be found in Sauter and Held (2015).

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