A practical GLMM example: Network meta-analysis of studies of binary outcomes – occurrence of exacerbations in COPD patients

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Overview

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(1) Introduction

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Network meta-analysis investigates several treatments in several trials, but not all treatments in every trial. E.g. in patients with Chronic Obstructive Pulmonary Disease (COPD), the following comparisons have been performed:

- Salmeterol (SAL) – Placebo (PLA)
- Formoterol (FOR) – PLA
- Indacaterol (IND) – PLA
- Tiotropium (TIO) – PLA
- TIO – SAL

Specific problems:

(a) Some direct comparisons are missing, e.g. between TIO and IND, and indirect comparisons are necessary.

(b) The comparison TIO-SAL is also informed through the comparisons SAL-PLA and TIO-PLA.

(1) Introduction

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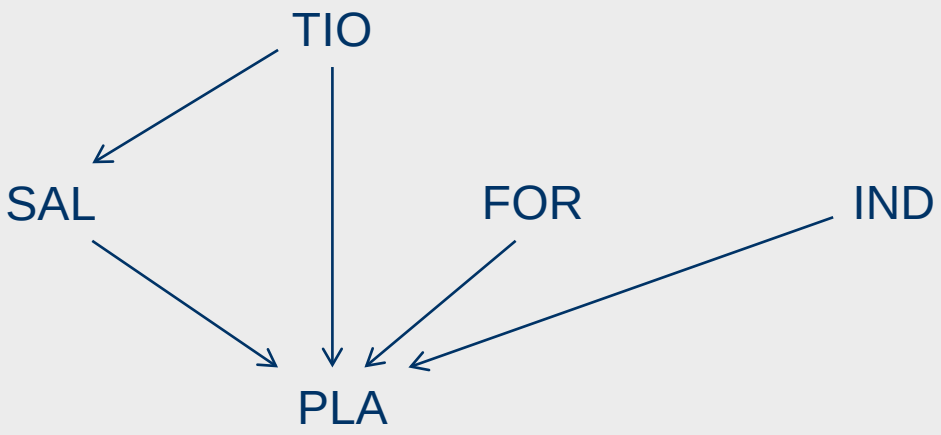
Network representation of available comparisons (instead of list):



(1) Introduction

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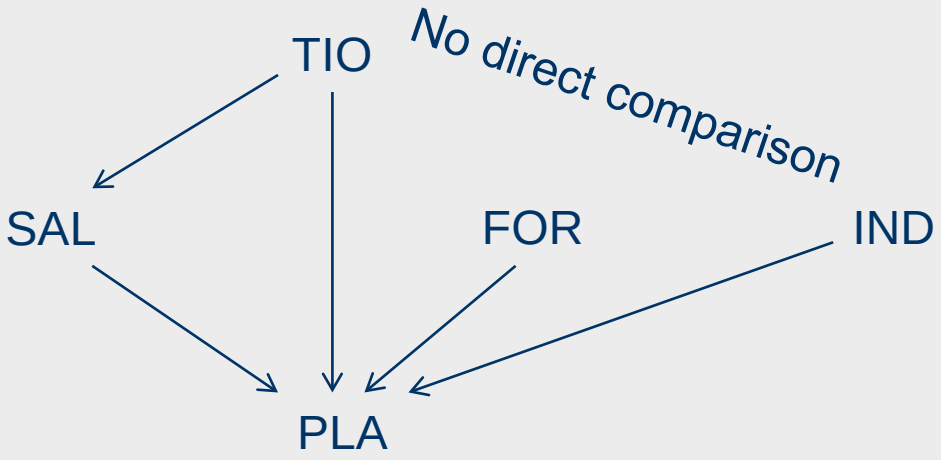
Network representation of available comparisons (instead of list):



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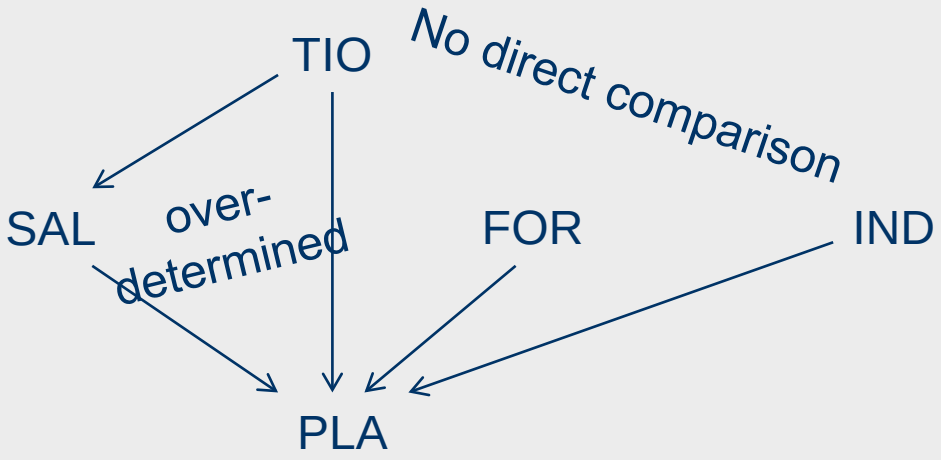

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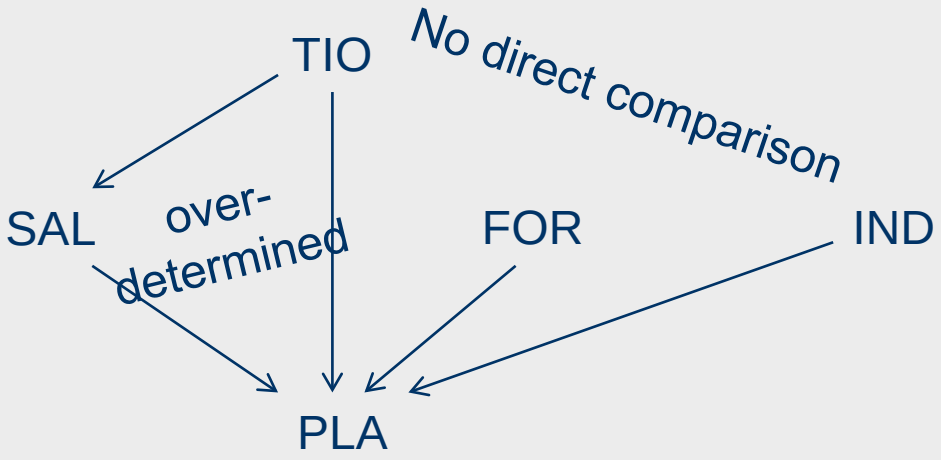

The overdetermination in the triangle TIO/SAL/PLA may lead to „inconsistency“ of the effect estimates – not to be mixed up with „heterogeneity“, which comes from multiple measurement of the same paired comparison

Krahn et al., BMC 2013; Cipriani et al., AIM 2013

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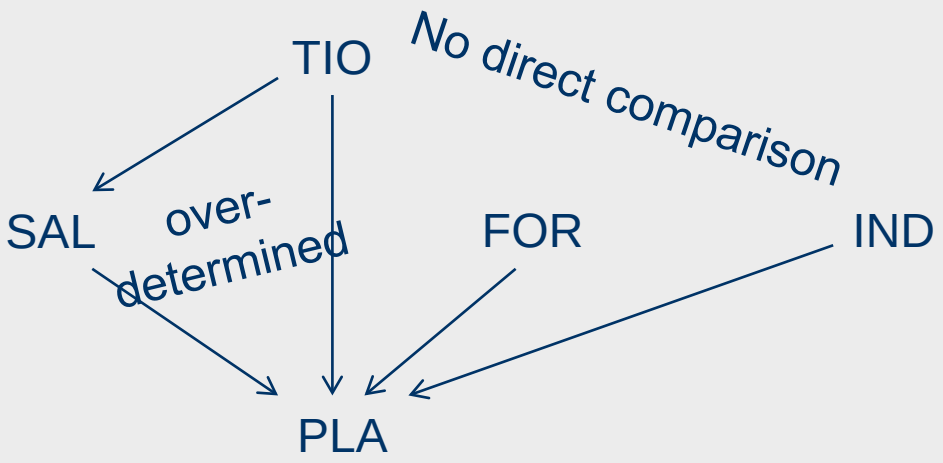
Network representation of available comparisons (instead of list):



Per trial arm (study k, treatment i), we have $r_{ik} \sim Bin(n_{ik},\pi_{ik})$.

The GLMM for the proportions of patients with event, in study k with treatment i, is:

$$\text{Logit}(\pi_{ik}) := LN(\pi_{ik}/(1-\pi_{ik})) = \tau_i + \mu_k + a_{ik}$$

with τ_i fixed for all i, μ_k fixed for all k, a_{ik} random, and $\tau_1 = 0$ (Placebo) and $\mu_1 = 0$ (Study 1).

[The boundary condition „$a_{1k} = 0$“ in the abstract is wrong]

Jones et al., Pharm.Stat. 2011; Senn et al., S.M.M.R. 2013

(2) Estimation methods for the parameters in the GLMM
(a) frequentist (likelihood-based)

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Investigate the likelihood (or better: its LN) around its estimated maximum:

As a function of the parameters, the inverse of the expected value of the matrix of the 2nd derivatives of LN(likelihood) is asymptotically (with the number of groups↑ or the denominators in each group↑) multi-normally distributed. That means, it can be interpreted as a „standard error“ for the parameters.

As an approximation, calculate the inverse of the matrix of the 2nd derivatives, evaluated at the estimated maximum.

Random effects are treated as nuisance parameters. We investigate the marginal likelihood of the fixed-effect parameters, and the behaviour at its maximum, through deterministic integration over a grid of values of the random parameters.

Now not shown: details of further variants of the likelihood (pseudo-L., penalized quasi-L., profile L.)

McCullagh/Nelder 1989 p. 469-473+114-117; Jones et al., Pharm.Stat. 2011; Kulinskaya et al., Int.Stat.Rev. 2014

(2) Estimation methods for the parameters in the GLMM
(b) MCMC

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The Markov chain Monte Carlo (MCMC) method scans the posterior distribution of all parameters together in a step-by-step manner. The multivariate empirical distribution of the sampled parameter values converges point-wise to the correct distribution of the parameters.

The results of a converged, sufficiently long MCMC run are therefore, with probability 1 and with vanishing simulation error, the reference with which the results of all other methods can be compared.

Geman/Geman, IEEE Trans. Pattern Analysis 1984; Gelfand/Smith, J.A.S.A. 1990; Higgins et al., J.R.S.S.A 2009; Lunn et al. 2013

(2) Estimation methods for the parameters in the GLMM
(c) INLA

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Also the integrated nested Laplace approximation (INLA) investigates the posterior distribution of the parameters. The GLMM shown above falls in its range of definition, as follows.

Rue et al., J.R.S.S.B 2009

www.imbei.uni-mainz.de/bayes/programm/2009-Rue-Lecture1.pdf

http://www.math.ntnu.no/~hrue/r-inla.org/doc/Intro/Intro.pdf

(2) Estimation methods for the parameters in the GLMM
(c) INLA

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Per trial arm (study k, treatment i), we have $r_{ik} \sim \text{Bin}(n_{ik},\pi_{ik})$ with the already known dependencies between the π_{ik}:

$\eta_{ik} := \text{logit}(\pi_{ik}) = \tau_i + \mu_k + a_{ik}$

fixed, i.i.d.random $N(0,\sigma^2)$

$\tau_1 = 0, \mu_1 = 0$

With normal prior distributions for $\tau_2, \ldots, \tau_I$ and $\mu_2, \ldots, \mu_K$, the composite variable $x := (\tau_2, \ldots, \tau_I, \mu_2, \ldots, \mu_K, \eta)$ is multivariate-normal. Re-write this in a hierarchical manner, and let the parameter vector of the normal distribution be $\theta := (\tau_2, \ldots, \tau_I, \mu_2, \ldots, \mu_K)$ with variance σ^2:

$r \mid x \sim \text{Product}_{i,k}\, p(r_{ik} \mid \eta_{ik}, \theta)$

$x \mid \theta \sim p(x|\theta) = N(0, \Sigma(\theta))$

$\theta \sim p(\theta)$ prior distribution.

This model class is called a „latent Gaussian model“. Note that η and x have large dimension while θ has low dimension.

See also Higgins et al., J.R.S.S.A 2009, p.144; Roos/Held, Bay.An. 2011, p. 264

(2) Estimation methods for the parameters in the GLMM
(c) INLA

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If now most components of x are conditionally independent, i.e.

x_i indep. from x_j | all other x's (Markov property) ,

the precision matrix (not the variance-covariance matrix) of x will be sparse, and we have a „Gaussian Markov Random Field“ (GMRF).

Note that this re-parameterisation could be done in any case. It is the estimation method where the differences between the 3 methods come in.

INLA integrates over x through Laplace integration, which sets up a 2nd-order truncated Taylor series for LN(posterior) and then integrates the posterior through application of the chain rule. This is exact for normally-distributed parameters. The variance σ^2 is integrated deterministically over a grid.

(3) The COPD/exacerbation example

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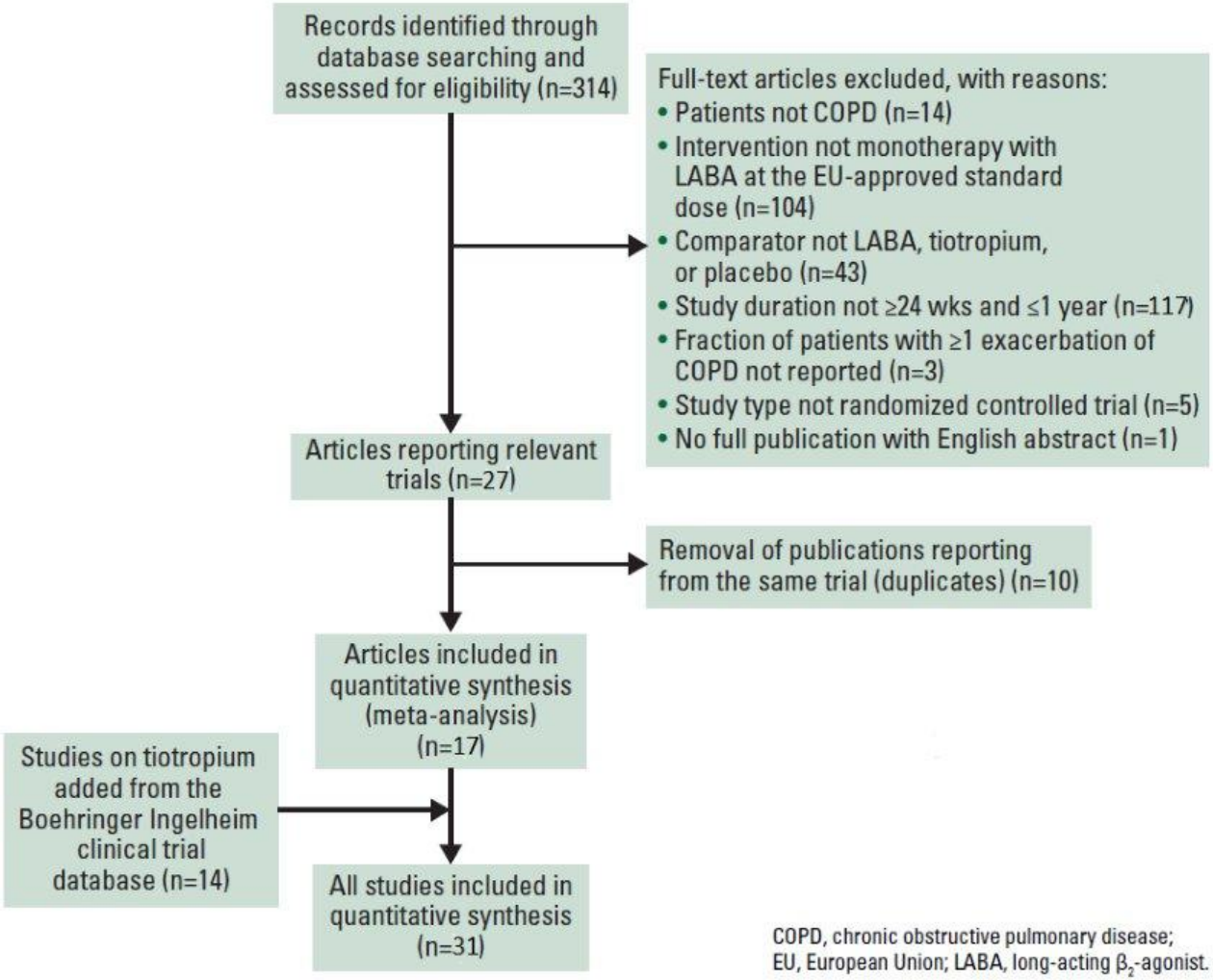
Studies were selected that were comparable in length ($\geq 6, \leq 12$ months), in the patient characteristics, and in the treatments (double-blind inhalations) and doses.

The endpoint was in all cases binary (patient had exacerbation no/yes), and the definition was uniform across studies. Note that all patients who dropped out with no observed event were counted as „no“.

See the warning example of Thorlund et al. (2013): In a survey of 13 NMAs in rheumatoid arthritis, unclear and often too broad pooling was detected.

Thorlund et al., Ann.Rheum.Dis. 2013

(3) The COPD/exacerbation example



COPD, chronic obstructive pulmonary disease; EU, European Union; LABA, long-acting β_2-agonist.

This is the PRISMA diagram. K=31, I=5, 65 trial arms.

Moher et al., B.M.J. 2009; Buhl et al., poster ATS 2013

(4) Results and comparison

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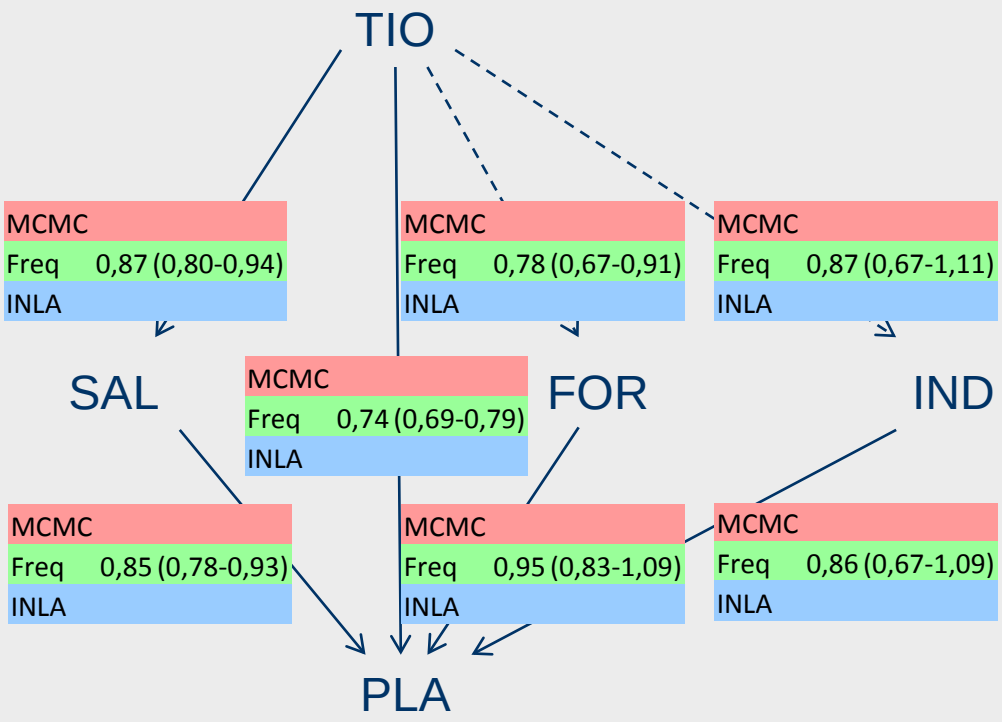
In the network diagram, the results for the odds ratios are as follows:



ML: Effect estimates and SEs.

Buhl et al., poster ATS 2013

(4) Results and comparison

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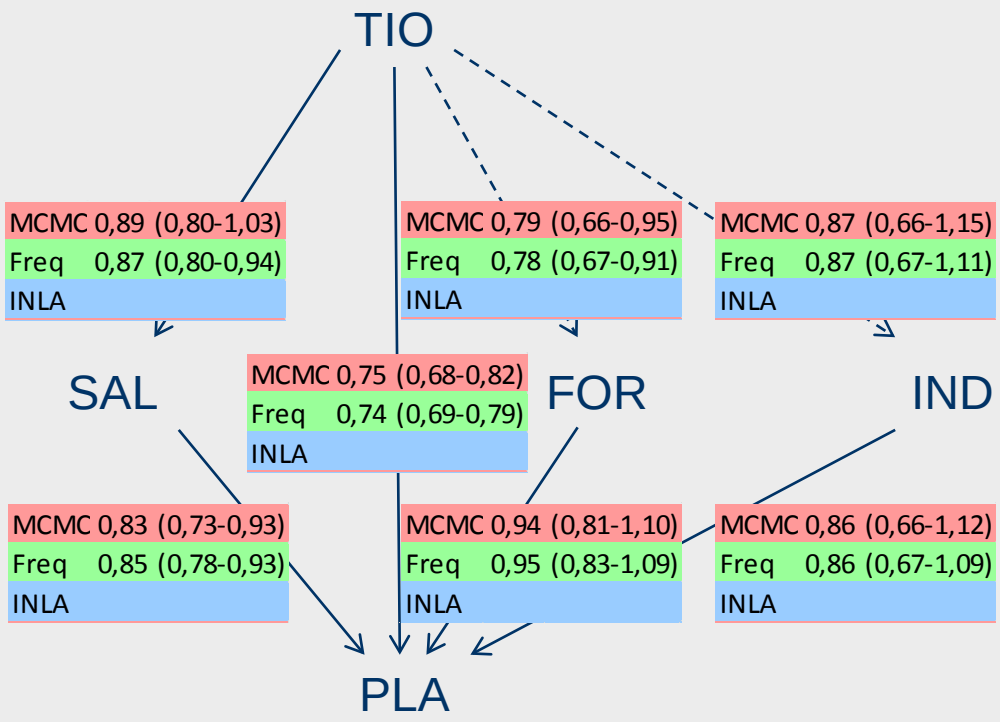

MCMC: The number of iterations was 10000 + 200000/20, which is more than sufficient for convergence and mixing. No problems with widely dispersed starting values.

Dias et al. 2011/2014; Jansen et al., Value in Health 2008; Rücker/Schwarzer, Stat.Med. 2014

(4) Results and comparison

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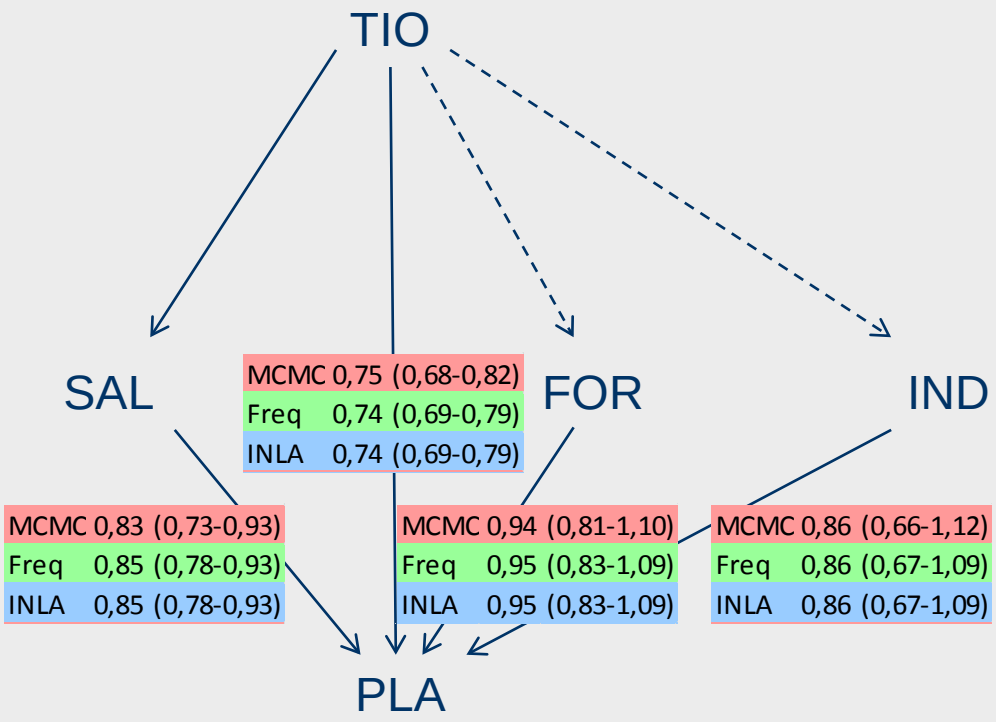

INLA: Only the distributions of these 4 differences are reported. Results for the comparisons other than with PLA need to be simulated from them separately.

www.imbei.uni-mainz.de/bayes/programm/2009-Rue-Lecture1.pdf

(4) Results and comparison

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The sampled points from the MCMC sequence can be post-processed to obtain a ranking.
Calculate the degree of certainty that treatment i assumes rank m:

Treatment	Degree of certainty for rank				
	1	2	3	4	5
PLA					
SAL					
FOR					
IND					
TIO					

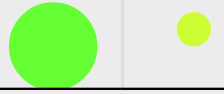
Circle areas are proportional to degree of certainty.

Salanti et al., J.Clin.Epi. 2011; Woods et al., BMC 2010; Novick/Grizzle, J.A.S.A. 1965

(4) Results and comparison

Boehringer Ingelheim

The i.i.d. sampled points from the INLA results can be post-processed in the same way.
Calculate the degree of certainty that treatment i assumes rank m:

Treatment	Degree of certainty for rank				
	1	2	3	4	5
PLA					
SAL					
FOR					
IND					
TIO					

Circle areas are proportional to degree of certainty.

There is no relevant difference to the MCMC-based ranking.

(5) Discussion, conclusion

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In this example we see no fundamental problems; the distribution of the logit-transformed π_{ik}'s and of the a_{ik}'s is approximately normal and therefore both the ML estimation and the INLA method perform well.

Some small divergences in the CI could not be resolved. One possible explanation is MCMC simulation error.

It is worth-while to move the investigation closer to the limits, namely to let the r_i's (numerators) go closer towards zero.

Medically, the drop-out question needs more attention, see recent discussions about i-t-t / follow-up and estimands. The time to drop-out (including unspecific mortality) should be considered as censoring time. This comes in addition to the consideration of event times (➔ HR models). The transformation of Woods et al. (2010) projects counted events onto a time scale. Note however that this assumes a constant hazard over the observation time, equivalent to an exponential distribution for the event times.

Fong et al., Biostatistics 2010; Capanu et al., Stat.Med. 2013; Woods et al., BMC 2010

(5) Discussion, conclusion

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In the process of drug development, network meta-analysis will probably have most of its value

- in Phase 4 (e.g. reimbursement discussions)
- in Marketing (ranking)
- in the early stages of a project (internal planning and decision making).

We currently see less application in Phase 3 and registration-related discussions.

Schmidli et al., S.M.M.R. 2013; Di Scala et al., Stat. Med. 2013

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