rnmamod: An R Package for Conducting Bayesian Network Meta-analysis with Missing Participants

by Loukia M. Spineli, Chrysostomos Kalyvas, and Katerina Papadimitropoulou

Abstract A plethora of R packages exists for performing network meta-analysis, which has significantly enhanced the popularity of this evidence synthesis methodology. The available R packages facilitate the implementation of the majority of the proposed statistical models to conduct and evaluate network meta-analysis, providing necessary results that conform to the PRISMA-NMA statement. The rnmamod package is a novel contribution to performing aggregate data network meta-analysis using Bayesian methods, as it enables the proper handling of missing participant data in all models, even if a handful of the included studies report this information. Rnmamod is the first R package to offer a rich, user-friendly visualisation toolkit that turns a "parameter-dense" output of network meta-analysis into a collection of comprehensive graphs. The package further facilitates a thorough appraisal and interpretation of the results, allows the cross-comparison of different models and streamlines the preparation of manuscripts for journal submission.

Introduction

Evidence-based medicine forms the backbone of informed decisions for the benefit of the patients, arising from a meticulous and judicious use of the available evidence. This concept incorporates clinical experience and patient values on the basis of the most up-to-date and reliable scientific evidence(Sackett et al. 1996). However, the medical community is confronted daily with vast amount of clinical evidence to keep pace with, which poses challenges to the optimal practice of evidence-based medicine (Lee 2022). Systematic reviews with pairwise meta-analysis summarise the evidence of a pair of interventions, providing fragmented evidence that does not serve the clinical needs of treatment recommendations based on a plethora of available options. Moreover, evidence regarding the comparability of different interventions at the trial level is also fragmented, as it is impractical to compare all intervention options for a particular condition in a single trial. These limitations led to the development and subsequent establishment of network meta-analysis (NMA), also known as multiple treatment comparison — a new generation evidence synthesis tool (Salanti 2012). Network meta-analysis is the extension of pairwise meta-analysis, collating all relevant evidence for a specific condition, patient population, and intervention options. The purpose is to provide coherent evidence for all possible intervention comparisons, and allow the ranking of the investigated interventions from the most to the least effective for a given outcome (Caldwell 2014). Indirect evidence (obtained from different sets of trials sharing a common investigated intervention/comparator) plays a central role in the development and prominence of NMA.

Ever since the introduction of indirect evidence and the initial development of the corresponding methodology (Higgins and Whitehead 1996; Bucher et al. 1997), the NMA framework has made significant conceptual and methodological progress. The rapid publications of pertinent methodological papers and systematic reviews involving multiple interventions bears witness to the growing popularity of NMA within the broad medical and evidence synthesis community (Efthimiou et al. 2016; Petropoulou et al. 2017). The availability of statistical analysis software has been the driving force behind the progress and widespread dissemination of NMA. A comprehensive review of NMA methodology and software (Efthimiou et al. 2016) listed several statistical software tools that have been instrumental in promoting NMA. Among these tools, the **R** software (R Core Team 2023) takes the lead as the most widely utilized, followed by **Stata** (StataCorp 2021) and **SAS software** (SAS Institute 2020). In the past decade, there has been a surge in the development of R packages tailored for NMA, each offering distinct functionalities (Dewey and Viechtbauer 2023).

Most methodological studies and systematic reviews involving NMA have employed Bayesian methods (Efthimiou et al. 2016; Petropoulou et al. 2017), benefiting from the flexibility, uncertainty management, and external data integration of the Bayesian framework (Sutton and Abrams 2001). The BUGS software dominance (Lunn et al. 2009) during the springtime of the NMA framework, may have contributed to the growing popularity of Bayesian NMA. The numerous Bayesian NMA R packages also demonstrate the recognition of Bayesian methods within the evidence synthesis community (Dewey and Viechtbauer 2023). The rest of the section delves into R packages for Bayesian NMA published in the **CRAN Task View 'Meta-Analysis'** (Dewey and Viechtbauer 2023) featuring a wide range of methodological and reporting functionalities: **bnma** (Seo and Schmid 2022), **gemtc** (van

Valkenhoef and Kuiper 2021), **pcnetmeta** (Lin et al. 2017), and **rnmamod** (Spineli 2022) (a recent novel contribution).

The R packages **bnma** (Seo and Schmid 2022), **gemtc** (van Valkenhoef and Kuiper 2021), and **pcnetmeta** (Lin et al. 2017) perform hierarchical NMA using Markov chain Monte Carlo (MCMC) methods through the **JAGS** program (Plummer 2003). However, they differ in terms of their methodological and reporting scope: the former two share a greater common basis in methods and outputs than **pcnetmeta** (Lin et al. 2017). This may be attributed to adoption of difference modelling approaches. **bnma** (Seo and Schmid 2022) and **gemtc** (van Valkenhoef and Kuiper 2021) employ the contrast-based approach, where trial-specific relative effects, such as log odds ratio, are pooled across trials. This is the most established approach to meta-analysis, while **pcnetmeta** (Lin et al. 2017) adopts the arm-based modeling approach, where arm-specific results, such as log odds, are pooled across trials. This approach deviates from the standard meta-analysis practice (Dias and Ades 2016) and is less widespread.

Currently, the **pcnetmeta** (Lin et al. 2017) package lacks functions for performing inconsistency evaluation and meta-regression. Also, it is limited to only rankograms in terms of hierarchy measures (Salanti et al. 2022), and considers solely trace plots as a visual diagnostic tool. On the contrary, **bnma** (Seo and Schmid 2022) and **gemtc** (van Valkenhoef and Kuiper 2021) offer at least one method for inconsistency evaluation and meta-regression, and provide a wider variety of hierarchy measures and diagnostic tools. All three R packages provide a compact toolkit of functions for presenting the relative treatment effects results: a league table for one outcome, typically displayed only in the console, and a forest-plot or table on the relative treatment effects of all comparisons versus a selected reference intervention. Moreover, these packages provide most output using the `print()` function (the results appear in the console) than utilising visualisation. Consequently, the results are often presented in isolation, thereby limiting the ability to gain further insights into the performance of the different NMA models (e.g, assuming consistency versus inconsistency).

Given the complexity and the broad scope of NMA, researchers are faced with a substantial volume of results that are essential for understanding the evidence base. This involves evaluating underlying assumptions and assessing the quality of the estimated parameters (via model diagnostics) to properly provide a response to the investigated research question. The aforementioned R packages have limited functionalities when it comes to presentation of NMA results. As a result, meticulously examining and critically appraising the results, a necessary requirement to ensure the transparency of conclusions delivered to the end users of systematic reviews including multiple interventions, presents a considerable challenge. Furthermore, an overreliance on the R console limits the usability of the results. R users are required to resort to tabulation, which hampers comprehension, especially when analysing extensive intervention networks that inherently yield an immense amount of results. Alternatively, R users must write functions to produce thenecessary visualisations, a time-consuming process that heavily relies on the user's programming skills in R. The R package **rnmamod** (Spineli 2022), recently published in the Comprehensive R Archive Network (available at `https://CRAN.R-project.org/package=rnmamod`), aspires to fill this technical gap by offering a rich, dynamic, user-friendly visualisation toolkit that transforms the inherently dense output of NMA into a collection of coherent graphs. Originally, the **rnmamod** package was inspired by the absence of dedicated R packages that properly account for (aggregate) missing participants in the analyses underlying the NMA framework (e.g., core model, inconsistency assessment, and meta-regression).

The article introduces the R package **rnmamod** that performs Bayesian hierarchical NMA in JAGS through the R package **R2jags** (Su and Masanao Yajima 2021) while modeling missing participants using one-stage pattern-mixture models (Little 1993). The package's visualisation functionalities have been developed using the R package **ggplot2** (Wickham 2016), harnessing the flexibility it offers in creating and customising high-quality graphs. The rest of this article is structured as follows. Section 2 provides an overview of the pattern-mixture models for aggregate binary and continuous outcome data within the context of NMA. Section 3 outlines the architecture of **rnmamod**. Section 4 describes the Bayesian network meta-analysis model and introduces the robustness index, a novel approach to investigate the sensitivity of the analysis results to different scenarios about the missing mechanism in the interventions of the investigated network (Spineli, Kalyvas, and Papadimitropoulou 2021c, 2021b). In section 5 we illustrate the various functions of the package on example datasets from published systematic reviews with NMA. Finally, Section 6 concludes with a discussion of the limitations and future developments of the package.

Pattern-mixture model for aggregate binary and continuous outcomes

We briefly introduce the pattern-mixture model, initially proposed by Little (Little 1993), and extend it to aggregate-level binary and continuous outcomes within the evidence synthesis framework. The pattern-mixture model distinguishes participants into two groups: those who completed the assigned

intervention and those who prematurely left the intervention arm for various reasons. The former are referred to as *completers* and the latter as *missing participants*. Information is available only on the outcomes of the completers who remained in the assigned intervention until trial completion. When missing participants are not followed-up after leaving the trial, which is typically the case, their outcome can only be hypothesised with some uncertainty. Hence, we can determine a distribution of possible values to describe the hypothetical outcomes of missing participants in the assigned intervention. Ideally, this distribution should be elicited using an expert opinion regarding the investigated outcome and interventions (White et al. 2007). Then, the weighted average of the observed and hypothesised outcomes, with the proportion of completers and missing participants serving as the corresponding weights, yields the *true* outcome for all randomised participants receiving the investigated intervention. This corresponds to the intention-to-treat analysis and is particularly valuable for assessing the impact of different scenarios regarding the distribution of hypothetical outcome values for the missing participants on the treatment effect. This sensitivity analysis lies at the core of the literature on properly handling missing data (White et al. 2007; *Missing Data in Randomised Controlled Trials: A Practical Guide.* 2007; *The Prevention and Treatment of Missing Data in Clinical Trials Panel on Handling Missing Data in Clinical Trials.* 2010).

Consider a set of N trials collected through a systematic review process. These trials investigate different sets of two or more carefully selected interventions for a specific target population and clinical condition. We extract data on the number randomised participants, the number of completers and missing participants, and the measured outcome from each arm of every trial. The pattern-mixture framework simultaneously models completers and missing participants, while preserving the randomised sample, as follows:

$$\theta_{ik} = \theta^c_{ik} \times (1 - q_{ik}) + \theta^m_{ik} \times q_{ik} \tag{1}$$

where θ_{ik} is the true outcome in arm k of trial i, θ^c_{ik} and θ^m_{ik} are the outcomes among the completers and missing participants, respectively (the superscripts c and m stand for completers and missing), and q_{ik} is the proportion of missing participants. It holds that

$$\begin{aligned}
\theta_{ik} &= P(I_{ikj} = 1 | M_{ikj} = 1 \cup M_{ikj} = 0) \\
\theta^c_{ik} &= P(I_{ikj} = 1 | M_{ikj} = 0) \\
\theta^m_{ik} &= P(I_{ikj} = 1 | M_{ikj} = 1)
\end{aligned}$$

for a binary outcome, and

$$\begin{aligned}
\theta_{ik} &= E(Y_{ikj} | M_{ikj} = 1 \cup M_{ikj} = 0) \\
\theta^c_{ik} &= E(Y_{ikj} | M_{ikj} = 0) \\
\theta^m_{ik} &= E(Y_{ikj} | M_{ikj} = 1)
\end{aligned}$$

for a continuous outcome, with I_{ikj} and M_{ikj} being dummy variables referring to whether a participant j experienced the outcome or left the trial prematurely, respectively, and Y_{ikj} referring to the continuous outcome of participant j.

Informative missingness parameters

It has been suggested in the relevant published literature to express the missingness parameter θ^m_{ik} as a function of an informative missingness parameter ϕ_{ik}, a difference of the outcome in completers and missing participants (White, Higgins, and Wood 2008; Mavridis et al. 2015; Turner et al. 2015):

$$\phi_{ik} = logit(\theta^m_{ik}) - logit(\theta^c_{ik})$$

the informative missingness odds ratio (IMOR) in the logarithmic scale for binary outcomes (White, Higgins, and Wood 2008; Turner et al. 2015), and

$$\psi_{ik} = \theta^m_{ik} - \theta^c_{ik}$$

the informative missingness difference of means (IMDoM) for continuous outcomes (Mavridis et al. 2015). Additional informative missingness parameters proposed for binary outcomes include the response probability ratio (Magder 2003; Turner et al. 2015), which is defined as the ratio of the probability of completing the trial given the event being experienced to the probability of completing the trial given the event not being experienced,

$$\omega_{ik} = \frac{P(M_{ikj} = 0|I_{ikj} = 1)}{P(M_{ikj} = 0|I_{ikj} = 0)}$$

and the success probability ratio (Akl et al. 2013; Turner et al. 2015) as the ratio of the probability of experiencing the outcome given the missing participants to the probability of experiencing the outcome given the completers,

$$\rho_{ik} = \frac{\theta^m_{ik}}{\theta^c_{ik}} = \frac{P(I_{ikj} = 1|M_{ikj} = 1)}{P(I_{ikj} = 1|M_{ikj} = 0)}.$$

Finally, the informative missingness ratio of means (IMRoM) has also been proposed for continuous outcomes (Mavridis et al. 2015), which is defined as the mean outcome given the missing participants to the mean outcome given the completers,

$$e^{\zeta_{ik}} = \frac{\theta^m_{ik}}{\theta^c_{ik}} = \frac{E(Y_{ikj}|M_{ikj} = 1)}{E(Y_{ikj}|M_{ikj} = 0)}.$$

The response probability ratio (Magder 2003; Turner et al. 2015) aligns better with a different approach for dealing with missing data, i.e., the selection model. This model distinguishes the participants based on their outcome and categorises them into those who completed the assigned intervention and those who left prematurely (Little 1995). On the other hand, the success probability ratio (Akl et al. 2013; Turner et al. 2015) is more suited for use with the risk ratio, as it represents a ratio of risks. IMRoM is intuitively related to the ratio of means (Mavridis et al. 2015). Finally, IMOR and IMDoM are more commonly used in conjunction with the OR and the mean difference (MD) and standardised mean difference, respectively.

The informative missingness parameters, IMDoM and IMOR, in the logarithmic scale (log IMOR), can take values in $\mathbb{R}$, where a value zero implies the missing-at-random assumption (ignorable missingness), while non-zero values indicate the missing-not-at-random assumption (non-ignorable missingness). Essentially, these informative missingness parameters quantify deviations from the missing-at-random assumption. As these parameters are typically unknown, the analysts can consider one of the following situations:

- assign a fixed value, which corresponds to imputation (Higgins, White, and Wood 2008; Turner et al. 2015; Spineli 2019),
- assume a distribution with suggested parameter values and proceed with a two-stage approach to synthesise the trials using their adjusted treatment effects and variances for missing participants obtained through the Taylor series approximation in the first stage (White, Higgins, and Wood 2008; Mavridis et al. 2015), or
- use the Bayesian framework to estimate their posterior distribution via an one-stage approach to synthesise the trials (Turner et al. 2015; Spineli 2019; Spineli, Kalyvas, and Papadimitropoulou 2021a).

Typically, a normal distribution is assigned on log IMOR, IMDoM and log IMRoM with mean and variance implying our belief and its corresponding uncertainty, respectively, about the missingness mechanism on average (Higgins, White, and Wood 2008; White, Higgins, and Wood 2008; Mavridis et al. 2015; Turner et al. 2015; Spineli 2019; Spineli, Kalyvas, and Papadimitropoulou 2021a):

$$\phi_{ik}, \psi_{ik}, \zeta_{ik} \sim N(b_{ik}, \kappa^2_{ik})$$

In the Bayesian framework, the analysts assign a prior normal distribution on these parameters and can determine the mean (b_{ik}) and variance (κ^2_{ik}) to be common across the trials and intervention arms, specific to the interventions or trials, as well as identical, hierarchical or independent (Turner et al. 2015; Spineli 2019; Spineli, Kalyvas, and Papadimitropoulou 2021a). Table 1 presents the different structural specifications of log IMOR, IMDoM and log IMRoM. Informative structure makes the least strong assumption but it yields the most parameters to estimate. Identical is the most parsimonious structure but makes the strongest assumption. Lastly, hierarchical structure is the most flexible for allowing information to be 'borrowed', improving estimation. Deciding on the prior structure of the informative missingness parameter is not straightforward: the analysts need to consider the trade-off between clinical plausibility and model fit to avoid overfitting. There is already an empirical and simulation study on the properties of the aforementioned structural assumptions (Spineli 2019; Spineli, Kalyvas, and Pateras 2019). The authors provide recommendations to assist in selecting the proper structure, and they emphasise consulting expertise on the investigative health-field and intervention when determining the structure of the informative missingness parameter, ideally during the protocol stage of the systematic review (Spineli 2019; Spineli, Kalyvas, and Pateras 2019). The authors also

highlight that further research is needed to demystify the properties of these structural assumptions (Spineli 2019; Spineli, Kalyvas, and Pateras 2019). The **rnmamod** package allows the user to apply all structural specifications for log IMOR, IMDoM and log IMRoM.

In this article, we will only consider IMOR and IMDoM due to their intuitive relationship to the aforementioned effect measures, which are also the most frequently employed in published systematic reviews and relevant methodological literature (Friedrich, Adhikari, and Beyene 2008; Nikolakopoulou et al. 2014; Bakbergenuly, Hoaglin, and Kulinskaya 2019).

Bayesian network meta-analysis model

Suppose the N trials compare different sets of T interventions $A, B, C, ..., T$: the network of interventions is made up of two-arm trials and probably multi-arm trials, as well, and the network is connected; namely, there is no intervention or group of interventions forming a separate network. For a binary outcome, we extract information on the number of participants who experienced the outcome in arm k ($k \geq 1$) of trial i and completed the trial, r^c_{ik}, and the number of missing participants, m_{ik}, out of the total randomised, n_{ik}. Following the notation from the previous section, r^c_{ik} and m_{ik} are assumed to be sampled from the corresponding binomial distributions:

$$r^c_{ik} \sim Binomial(\theta^c_{ik}, c_{ik})$$

and

$$m_{ik} \sim Binomial(q_{ik}, n_{ik})$$

with θ^c_{ik} and c_{ik} being the underlying probability of event among the completers and the number of completers, respectively, in arm k of trial i. In the case of a continuous outcome, the extracted information pertains to the average outcome and variance thereof among those completing arm k of trial i, y^c_{ik} and v^c_{ik}, respectively, and m_{ik} out of n_{ik}. Then, it can be assumed that y^c_{ik} is samples from the following normal distribution:

$$y^c_{ik} \sim N(\theta^c_{ik}, v^c_{ik})$$

with θ^c_{ik} being the underlying mean of the continuous outcome among the completers in arm k of trial i.

Returning to the binary outcome, the underlying logit of an event in the experimental arm k of trial i, $logit(\theta_{ik})$, is a function of the baseline logit of an event in trial i, $u_i = logit(\theta_{i1})$, and the odds ratio of event between arm k and the baseline arm in the logarithmic scale, δ_{ik}:

$$logit(\theta_{ik}) = u_i + \delta_{ik} \times I\{k \neq 1\}$$

The parameter θ_{ik} has been adjusted for missing participants using the pattern-mixture model (equation (1)) with ϕ_{ik} for informative missingness parameter under a specific prior structure and assumption about the missingness mechanism reflected by the mean of the prior distribution (see Table 1).

The link function for the continuous outcome is the following:

$$\theta_{ik} = u_i + \delta_{ik} \times I\{k \neq 1\}$$

with θ_{ik} and $u_i = \theta_{i1}$ being the underlying mean outcome in arm k and baseline arm of trial i, respectively, and δ_{ik} being the MD between arm k and baseline arm of the trial. When SMD is the effect measure, the link function is written as follows:

$$\theta_{ik} = u_i + S_i \times \delta_{ik} \times I\{k \neq 1\}$$

with S_i being the pooled standard deviation under the MAR assumption when trial i has missing participants. In this case, the variance of the outcome among the completers is assumed to be equal to the variance of the outcome among the missing participants (Spineli, Kalyvas, and Papadimitropoulou 2021a). To acknowledge the uncertainty about this assumption, S_i is assumed to be sampled from the following gamma distribution (Stevens 2011; Spineli, Kalyvas, and Papadimitropoulou 2021a):

$$S^2_i \sim \Gamma\left(\frac{\sum_{k=1}^{a_i}(n_{ik}-1)}{2}, \frac{\sum_{k=1}^{a_i}(n_{ik}-1)}{2 \times v^c_{ik}}\right)$$

Table 1: Prior specification structure of the informative missingness parameters log IMOR, IMDoM, and log IMRoM

Structure	Assumption	log IMOR	IMDoM	log IMRoM
Identical	Common	$$\phi_{ik}=\phi, \phi \sim N(0,1)$$	$$\psi_{ik}=\psi, \psi \sim N(0,1)$$	$$\gamma_{ik}=\gamma, \gamma \sim N(0,0.2^{2})$$
	Trial-specific	$$\phi_{ik}=\phi_{i}, \phi_{i} \sim N(0,1)$$	$$\psi_{ik}=\psi_{i}, \psi_{i} \sim N(0,1)$$	$$\gamma_{ik}=\gamma_{i}, \gamma_{i} \sim N(0,0.2^{2})$$
	Intervention-specific	$$\phi_{ik}=\phi_{t_{ik}}, \phi_{t_{ik}} \sim N(0,1)$$	$$\psi_{ik}=\psi_{t_{ik}}, \psi_{t_{ik}} \sim N(0,1)$$	$$\gamma_{ik}=\gamma_{t_{ik}}, \gamma_{t_{ik}} \sim N(0,0.2^{2})$$
Hierarchical	Common	$$\phi_{ik} \sim N(\Delta, \sigma^{2}), \Delta \sim N(0,1), \sigma \sim U(0,1)$$	$$\psi_{ik} \sim N(\Delta, \sigma^{2}), \Delta \sim N(0,1), \sigma \sim U(0,1)$$	$$\gamma_{ik} \sim N(\Delta, \sigma^{2}), \Delta \sim N(0,0.2^{2}), \sigma \sim U(0,0.2)$$
	Trial-specific	$$\phi_{ik} \sim N(\Delta_{i}, \sigma_{i}^{2}), \Delta_{i} \sim N(0,1), \sigma_{i} \sim U(0,1)$$	$$\psi_{ik} \sim N(\Delta_{i}, \sigma_{i}^{2}), \Delta_{i} \sim N(0,1), \sigma_{i} \sim U(0,1)$$	$$\gamma_{ik} \sim N(\Delta_{i}, \sigma_{i}^{2}), \Delta_{i} \sim N(0,0.2^{2}), \sigma_{i} \sim U(0,0.2)$$
	Intervention-specific	$$\phi_{ik} \sim N(\Delta_{t_{ik}}, \sigma_{t_{ik}}^{2}), \Delta_{t_{ik}} \sim N(0,1), \sigma_{t_{ik}} \sim U(0,1)$$	$$\psi_{ik} \sim N(\Delta_{t_{ik}}, \sigma_{t_{ik}}^{2}), \Delta_{t_{ik}} \sim N(0,1), \sigma_{t_{ik}} \sim U(0,1)$$	$$\gamma_{ik} \sim N(\Delta_{t_{ik}}, \sigma_{t_{ik}}^{2}), \Delta_{t_{ik}} \sim N(0,0.2^{2}), \sigma_{t_{ik}} \sim U(0,0.2)$$
Independent	Uncorrelated	$$\phi_{ik} \sim N(0,1)$$	$$\psi_{ik} \sim N(0,1)$$	$$\gamma_{ik} \sim N(0,1)$$
	Correlated	$$\mathbf{\phi_{i}} \sim MVN_{a_{i}} \left(\begin{pmatrix} 0 \\ \vdots \\ 0 \end{pmatrix}, \begin{pmatrix} 1 \quad \cdots \quad 0.5 \\ \cdots \quad \ddots \quad \cdots \\ 0.5 \quad \cdots \quad 1 \end{pmatrix}\right)$$	$$\mathbf{\psi_{i}} \sim MVN_{a_{i}} \left(\begin{pmatrix} 0 \\ \vdots \\ 0 \end{pmatrix}, \begin{pmatrix} 1 \quad \cdots \quad 0.5 \\ \cdots \quad \ddots \quad \cdots \\ 0.5 \quad \cdots \quad 1 \end{pmatrix}\right)$$	$$\mathbf{\phi_{i}} \sim MVN_{a_{i}} \left(\begin{pmatrix} 0 \\ \vdots \\ 0 \end{pmatrix}, \begin{pmatrix} 0.2^{2} \quad \cdots \quad 0.5 \\ \cdots \quad \ddots \quad \cdots \\ 0.5 \quad \cdots \quad 0.2^{2} \end{pmatrix}\right)$$

Note.
\begin{equation} MVN_{a_{i}} \text{: multivariate normal distribution for trial} \quad i \quad \text{with} \qu

Like with the binary outcome, θ_{ik} has been adjusted for missing participants using the pattern-mixture model (equation (1)) with ψ_{ik} for informative missingness parameter under a specific prior structure and assumption about the missingness mechanism reflected by the mean of the prior distribution (see Table 1).

Robustness index for sensitivity analysis

blah blah

The architecture of rnmamod

Functions on data preparation and model implementation

The `run_model()` function plays a central role in the architecture of the **rnmamod** package. It is responsible for fitting the core NMA model and related analyses to assess the underlying assumptions of NMA. It also comprises the R object for most functions used to create the necessary visualisations. Initially, `run_model()` calls the `data_preparation()` function to prepare the format of the dataset for JAGS modelling appropriately. The dataset is provided in the one-study-per-row format, which is typical for code written in the BUGS language. Then `run_model()` bundles the dataset along with the necessary parameters (previously processed through the `missingness_param_prior()`, `heterogeneity_param_prior()`, and `baseline_model()` functions) to conduct NMA through the `prepare_model()` function. The `prepare_model()` function contains the code in BUGS language for performing a hierarchical one-stage NMA, following the methodology published by the NICE Decision Support Unit in a series of tutorial papers on evidence synthesis methods for decision-making (Dias et al. 2013). The `missingness_param_prior()` and `heterogeneity_param_prior()` functions process the hyperparameters of the selected prior distribution for the informative missingness parameter and the between-study heterogeneity parameter, respectively, preparing them for use by JAGS. The `baseline_model()` function is relevant only when dealing with binary outcomes. It processes the baseline risk defined by the user or the default option before performing NMA.

Subsequent analyses associated with the underlying assumptions of NMA are performed by specially devised functions that inherit most arguments from `run_model()`. Therefore, careful specification of the arguments in `run_model()` is essential for the contingent functions to yield sensible results and ensure meaningful comparison with the NMA results. These functions refer to the local and global consistency evaluation (`run_nodesplit()` and `run_ume()`), network meta-regression (`run_metareg()`), multiple pairwise meta-analyses (`run_series_meta()`) and sensitivity analysis to different missingness scenarios (`run_sensitivity()`) when the number of missing participants has been extracted for all study-arms. The functions `run_nodesplit()` and `run_ume()` call the `prepare_nodesplit()` and `prepare_ume()` functions, respectively, to fit the node-splitting and the unrelated mean effects models in JAGS. The function `improved_ume()` is also called to ensure a proper accommodation of the multi-arm trials in the unrelated mean effects model. In line with `run_model()`, network meta-regression, multiple pairwise meta-analyses, and sensitivity analysis are fitted in JAGS through the `prepare_model()` function. All model-related functions can be passed as an object to the `mcmc_diagnostics()` function to generate the diagnostic plots and measures for the monitored model parameters.

Figure 1 illustrates the network of the functions developed to prepare the data and conduct NMA and related analyses. Nodes and links refer to functions and the synergy of two functions. The node's size indicates the usability of the corresponding function. For instance, `run_model()` is an over-represented node for having a dual role in the network: it is an object to most functions (e.g., `run_nodesplit()` and `mcmc_diagnostics()`) and depends on other functions to operate (e.g., `data_preparation()` and `prepare_model()`). The node's colour indicates the operationality of the function: most functions perform model implementation (green nodes), followed by functions that contain the BUGS code (blue nodes) or process the dataset and prepare specific arguments (purple nodes) for the corresponding model. The `baseline_model()` function contains all three operationalities, whilst `mcmc_diagnostics()` offers only a set with MCMC diagnostics.

The visualisation toolkit

Figure 2 presents the network of visualisation-related functions alongside `run_model()` and several model-related functions. The functions associated with summarising and presenting the results have a common structure: `run_model()` and the model-related function of interest are passed as objects into the corresponding arguments. Hence, `run_model()` comprises the backbone of the network and forms

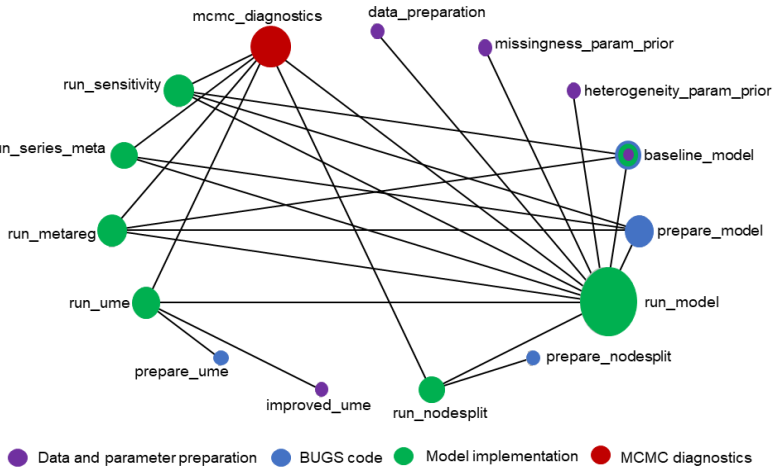

Figure 1: Network of functions for data preparation and model implementation

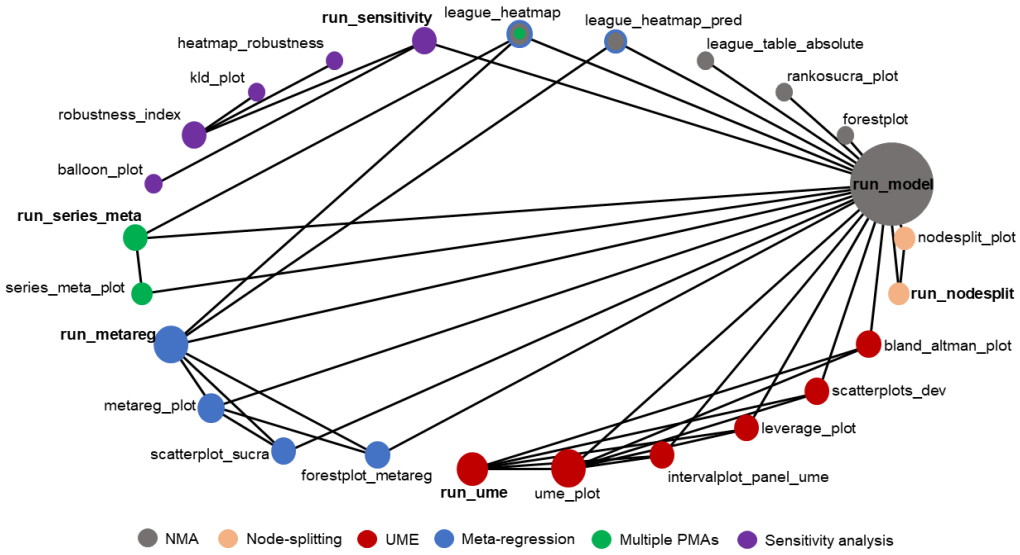

Figure 2: Network of functions for summarising and presenting the analysis results

the largest node (Figure 2). The visualisation-related functions are distinguished into the *stand-alone* and the *platform* functions. The stand-alone functions are immediately related to generating the relevant graphs. For instance, `forestplot_metareg()`, and `interval_panel_ume()` constitute stand-alone functions and return only the intended graph using `run_model()` together with `run_metareg()` and `run_ume()`, respectively, as objects in their arguments. Other stand-alone functions depend on a single function to operate; for example, `rankosucra_plot()` and `kld_plot()` use only the `run_model()` and `robustness_index()`, respectively, in their arguments. The platform functions host the stand-alone functions and generate complementary tables and further graphs. They are easy to spot in Figure 2, as they are named after the related model, with the *plot* affixed at the end: `nodesplit_plot()`, `ume_plot()`, `metareg_plot()`, and `series_meta_plot()`. For instance, `metareg_plot()` calls `scatterplot_sucra()` and `forestplot_sucra()` to return the corresponding intended graphs and prints tables in the console where the effect estimates and predictions from NMA are juxtaposed with those from network meta-regression. Every analysis has an individualised visualisation toolkit, indicated by the functions sharing the same colour node (Figure 2). Only network meta-regression (blue nodes) and conducting separate pairwise meta-analyses (green nodes) share a few stand-alone functions with NMA (grey nodes), namely, `league_heatmap()` and `league_heatmap_pred()`.

Using the rnmamod R package

Discussion

We have displayed various tooltips that are available in the package **ToOoOlTiPs**.

Acknowledgments

Loukia M Spineli received funding from the German Research Foundation (Deutsche Forschungsgemeinschaft; grant SP 1664/2-1). The sponsor had no influence on the study design, collection, analysis, interpretation of data, reporting, and decision to submit the article for publication. Chrysostomos Kalyvas is employed by Merck Sharp & Dohme. Katerina Papadimitropoulou is employed by Amaris Consulting. The authors alone are responsible for the views expressed in this article, and they should not be construed with the views, decisions, or policies of the institutions with which they are affiliated.

References

Akl, Elie A, Bradley C Johnston, Pablo Alonso-Coello, Ignacio Neumann, Shanil Ebrahim, Matthias Briel, Deborah J Cook, and Gordon H Guyatt. 2013. "Addressing Dichotomous Data for Participants Excluded from Trial Analysis: A Guide for Systematic Reviewers." *PLoS One* 8 (2): e57132. https://doi.org/10.1371/journal.pone.0057132.

Bakbergenuly, Ilyas, David C Hoaglin, and Elena Kulinskaya. 2019. "Pitfalls of Using the Risk Ratio in Meta-Analysis." *Res Synth Methods* 10 (3): 398–419. https://doi.org/10.1002/jrsm.1347.

Caldwell, Deborah M. 2014. "An Overview of Conducting Systematic Reviews with Network Meta-Analysis." *Syst Rev* 3: 109. https://doi.org/10.1186/2046-4053-3-109.

Dewey, Michael, and Wolfgang Viechtbauer. 2023. *CRAN Task View: Meta-Analysis*. https://CRAN.R-project.org/view=MetaAnalysis.

Dias, Sofia, and A E Ades. 2016. "Absolute or Relative Effects? Arm-Based Synthesis of Trial Data." *Res Synth Methods* 7 (1): 23–28. https://doi.org/10.1002/jrsm.1184.

Dias, Sofia, Alexander J Sutton, A E Ades, and N J Welton. 2013. "Evidence Synthesis for Decision Making 2: A Generalized Linear Modeling Framework for Pairwise and Network Meta-Analysis of Randomized Controlled Trials." *Med Decis Making* 33 (5): 607–17.

Efthimiou, Orestis, Thomas P. A. Debray, Gert van Valkenhoef, Sven Trelle, Klea Panayidou, Karel G. M. Moons, Johannes B. Reitsma, Aijing Shang, Georgia Salanti, and GetReal Methods Review Group. 2016. "GetReal in Network Meta-Analysis: A Review of the Methodology." *Res Synth Methods* 7 (3): 236–63. https://doi.org/10.1002/jrsm.1195.

Friedrich, Jan O, Neill K J Adhikari, and Joseph Beyene. 2008. "The Ratio of Means Method as an Alternative to Mean Differences for Analyzing Continuous Outcome Variables in Meta-Analysis: A Simulation Study." *BMC Med Res Methodol* 8: 32. https://doi.org/10.1186/1471-2288-8-32.

Higgins, Julian P T, Ian R White, and Angela M Wood. 2008. "Imputation Methods for Missing Outcome Data in Meta-Analysis of Clinical Trials." *Clin Trials* 5 (3): 225–39. https://doi.org/10.1177/1740774508091600.

Lee, Andrew. 2022. "The Development of Network Meta-Analysis." *J R Soc Med* 115 (8): 313–21. https://doi.org/10.1177/01410768221113196.

Lin, Lifeng, Jing Zhang, James S. Hodges, and Haitao Chu. 2017. "Performing Arm-Based Network Meta-Analysis in R with the pcnetmeta Package." *Journal of Statistical Software* 80 (5): 1–25. https://doi.org/10.18637/jss.v080.i05.

Little, RJA. 1993. "Pattern-Mixture Models Formultivariate Incomplete Data." *J Am Stat Assoc* 88 (421): 125–34. https://doi.org/doi.org/10.2307/2290705.

———. 1995. "Modeling the Drop-Out Mechanism in Repeated-Measures Studies." *J Am Stat Assoc* 90 (431): 1112–21. https://doi.org/10.2307/2291350.

Lunn, David, David Spiegelhalter, Andrew Thomas, and Nicky Best. 2009. "The BUGS Project: Evolution, Critique and Future Directions." *Stat Med* 28 (25): 3049–67. https://doi.org/10.1002/sim.3680.

Magder, Laurence S. 2003. "Simple Approaches to Assess the Possible Impact of Missing Outcome Information on Estimates of Risk Ratios, Odds Ratios, and Risk Differences." *Control Clin Trials* 24 (4): 411–21. https://doi.org/10.1016/s0197-2456(03)00021-7.

Mavridis, Dimitris, Ian R White, Julian P T Higgins, Andrea Cipriani, and Georgia Salanti. 2015. "Allowing for Uncertainty Due to Missing Continuous Outcome Data in Pairwise and Network Meta-Analysis." *Stat Med* 34 (5): 721–41. https://doi.org/10.1002/sim.6365.

Missing Data in Randomised Controlled Trials: A Practical Guide. 2007. Health Technology Assessment Methodology Programme: Birmingham. https://researchonline.lshtm.ac.uk/id/eprint/4018500.

Nikolakopoulou, Adriani, Anna Chaimani, Areti Angeliki Veroniki, Haris S Vasiliadis, Christopher H Schmid, and Georgia Salanti. 2014. "Characteristics of Networks of Interventions: A Description of a Database of 186 Published Networks." *PLoS One* 9 (1): e86754. https://doi.org/10.1371/journal.pone.0086754.

Petropoulou, Maria, Adriani Nikolakopoulou, Areti-Angeliki Veroniki, Patricia Rios, Afshin Vafaei, Wasifa Zarin, Myrsini Giannatsi, et al. 2017. "Bibliographic Study Showed Improving Statistical Methodology of Network Meta-Analyses Published Between 1999 and 2015." *J Clin Epidemiol* 82: 20–28. https://doi.org/10.1016/j.jclinepi.2016.11.002.

Plummer, Martyn. 2003. *JAGS: A Program for Analysis of Bayesian Graphical Models Using Gibbs Sampling*. Edited by Kurt Hornik, Friedrich Leisch, and Achim Zeileis. Technische Universität Wien, Vienna, Austria. https://www.R-project.org/conferences/DSC-2003/Proceedings/Plummer.pdf.

Sackett, David L, William M Rosenberg, J A Gray, R B Haynes, and W S Richardson. 1996. "Evidence Based Medicine: What It Is and What It Isn't." *BMJ* 312 (7023): 71–72. https://doi.org/10.1136/bmj.312.7023.71.

Salanti, Georgia. 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." *Res Synth Methods* 3 (2): 80–97. https://doi.org/10.1002/jrsm.1037.

Salanti, Georgia, Adriani Nikolakopoulou, Orestis Efthimiou, Dimitris Mavridis, Matthias Egger, and Ian R White. 2022. "Introducing the Treatment Hierarchy Question in Network Meta-Analysis." *Am J Epidemiol* 191 (5): 930–38. https://doi.org/10.1093/aje/kwab278.

Seo, Michael, and Christopher Schmid. 2022. *Bnma: Bayesian Network Meta-Analysis Using 'JAGS'*. https://CRAN.R-project.org/package=bnma.

Spineli, Loukia M. 2019. "An Empirical Comparison of Bayesian Modelling Strategies for Missing Binary Outcome Data in Network Meta-Analysis." *BMC Med Res Methodol* 19 (1): 86. https://doi.org/10.1186/s12874-019-0731-y.

———. 2022. *Rnmamod: Bayesian Network Meta-Analysis with Missing Participants*. https://CRAN.R-project.org/package=rnmamod.

Spineli, Loukia M, Chrysostomos Kalyvas, and Katerina Papadimitropoulou. 2021a. "Continuous(ly) Missing Outcome Data in Network Meta-Analysis: A One-Stage Pattern-Mixture Model Approach." *Stat Methods Med Res* 30 (4): 958–75. https://doi.org/10.1177/0962280220983544.

———. 2021b. "How Robust Are Findings of Pairwise and Network Meta-Analysis in the Presence of Missing Participant Outcome Data?." *BMC Med* 19 (1): 323. https://doi.org/0.1186/s12916-021-02195-y.

———. 2021c. "Quantifying the Robustness of Primary Analysis Results: A Case Study on Missing Outcome Data in Pairwise and Network Meta-Analysis." *Res Synth Methods* 12 (4): 475–90. https://doi.org/10.1002/jrsm.1478.

Spineli, Loukia M, Chrysostomos Kalyvas, and Konstantinos Pateras. 2019. "Participants' Outcomes Gone Missing Within a Network of Interventions: Bayesian Modeling Strategies." *Stat Med* 38 (20): 3861–79. https://doi.org/10.1002/sim.8207.

Stevens, John W. 2011. "A Note on Dealing with Missing Standard Errors in Meta-Analyses of Continuous Outcome Measures in WinBUGS." *Pharm Stat* 10 (4): 374–78. https://doi.org/10.1002/pst.491.

Su, Yu-Sung, and Masanao Yajima. 2021. *R2jags: Using r to Run 'JAGS'*. https://CRAN.R-project.org/package=R2jags.

Sutton, Alex J, and Keith R Abrams. 2001. "Bayesian Methods in Meta-Analysis and Evidence Synthesis." *Stat Methods Med Res* 10 (4): 277–303. https://doi.org/10.1177/096228020101000404.

The Prevention and Treatment of Missing Data in Clinical Trials Panel on Handling Missing Data in Clinical Trials. 2010. Division of Behavioral; Social Sciences; Education, Washington, DC: The National Academies Press. www.nap.edu.

Turner, N. L., S. Dias, A. E. Ades, and N. J. Welton. 2015. "A Bayesian Framework to Account for Uncertainty Due to Missing Binary Outcome Data in Pairwise Meta-Analysis." *Stat Med* 34 (12): 2062–80. https://doi.org/10.1002/sim.6475.

van Valkenhoef, Gert, and Joel Kuiper. 2021. *Gemtc: Network Meta-Analysis Using Bayesian Methods*. https://CRAN.R-project.org/package=gemtc.

White, Ian R, James Carpenter, Stephen Evans, and Sara Schroter. 2007. "Eliciting and Using Expert Opinions about Dropout Bias in Randomized Controlled Trials." *Clin Trials* 4 (2): 125–39. https://doi.org/10.1177/1740774507077849.

White, Ian R, Julian P T Higgins, and Angela M Wood. 2008. "Allowing for Uncertainty Due to Missing Data in Meta-Analysis—Part 1: Two-Stage Methods." *Stat Med* 27 (5): 711–27. https://doi.org/10.1002/sim.3008.

Wickham, Hadley. 2016. *Ggplot2: Elegant Graphics for Data Analysis*. Springer-Verlag New York. https://ggplot2.tidyverse.org.

Loukia M. Spineli
Midwifery Research and Education Unit
Hannover Medical School
Carl-Neuber-Strasse 1, 30625, Hannover, Germany
https://www.github.com/LoukiaSpin
ORCiD: 0000-0001-9515-582X
Spineli.Loukia@mh-hannover.de

Chrysostomos Kalyvas
Biostatistics and Research Decision Sciences
MSD Europe Inc., Brussels, Belgium
https://www.github.com/ckalyvas
ORCiD: 0000-0003-0606-4518
chrysostomos.kalyvas@merck.com

Katerina Papadimitropoulou
Health Economics and Market Access
Amaris Consulting, Lyon, France
https://www.github.com/Katerina-Pap
ORCiD: 0000-0002-5732-4044
katerina.papadimitropoulou@gmail.com