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

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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 collecction 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 daily confronted 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 signle 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). The advantages of the Bayesian framework (e.g., flexible modeling, allowing uncertainty in all model parameters, incorporation of external relevant information and facilitation of probabilistic statements) (Sutton and Abrams 2001), coupled with the dominance of the BUGS software (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 the necessary 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 has 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 on the limitations and future developments of the package.

Pattern-mixture model for aggregate binary and continuous outcomes

We briefly introduce the pattern-mixture model, originally proposed by Little (Little 1993), and extend it to a summary binary and continuous outcome in the evidence synthesis framework. The pattern-

mixture model distinguishes the participants to those completing and those leaving the assigned intervention arm prematurely for several reasons. The former are called *completers* and the latter *missing participants*. There is information only on the outcome of the completers for remaining to the assigned intervention until trial completion. If missing participants are not followed-up after leaving the trial, which is usually the case, their outcome can only be hypothesised with some uncertainty; hence, we can determine a distribution of possible values to describe the hypothetical outcome of missing participants in the assigned intervention. Ideally, this distribution should be elicited using an expert opinion for the investigated outcome and interventions (White et al. 2007). Then, the weighted average of the observed and hypothesised outcomes, using the proportion of completers and missing participants 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 it is of particular interest to investigate the impact to the treatment effect of different scenarios about the distribution of hypothetical outcome values for the missing participants. This sensitivity analysis is at the core of the literature on handling missing data properly (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 using 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 information on the number randomised, the number of completers and missing participants, and the measured outcome from each arm of every trial. The pattern-mixture framework models completers and missing participants simultaneously, maintaining 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 replace the missingness parameter θ^m_{ik} with the following parameters to measure the informative missingness as a function 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). Other informative missingness parameters that have been suggested for binary outcomes are the response probability ratio (Magder 2003; Turner et al. 2015) defined as the ratio of the probability of completing the trial given the outcome being experienced to the probability of completing the trial given the outcome 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 suggested for the continuous outcomes (Mavridis et al. 2015) 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 selection model that distinguishes the participants based on their outcome and then further distinguishes between those completing and those leaving the assigned intervention prematurely (Little 1995). The success probability ratio (Akl et al. 2013; Turner et al. 2015) is more likely to be used with the risk ratio for also being a ratio of risks. The IMRoM is intuitively related to the ratio of means (Mavridis et al. 2015). Finally, IMOR and IMDoM are more likely to be used in conjunction to the OR and the mean difference (MD) and standardised mean difference (SMD), respectively.

The informative missingness parameters in the logarithmic scale (log IMOR and log IMRoM, respectively) take values in $\mathbb{R}$ with zero implying the missing at random (MAR) assumption (ignorable missingness) and non-zero values indicating the missing not at random assumption (non-ignorable missingness). Essentially, the informative missingness parameters quantify departures from the missing at random assumption. Since these parameters are 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 about the missingness mechanism on average and our uncertainty about this belief, respectively (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 investigate 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). They authors also highlight that further research is needed in demystifying further 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 consider only the IMOR and IMDoM due to their intuitive relation to the aforementioned effect measures which are also the most frequently used 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 from 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 experience 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 precious 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 has a central role in the architecture of the **rnmamod** package. It is the function of conducting the core NMA model and related analyses to assess the underlying assumptions of NMA. It also comprises the object of most functions to create the necessary visualisations. Initially, `run_model()` calls the `data_preparation()` function to prepare the dataset in the proper format to fit the model in JAGS. The dataset is provided in the one-study-per-row format, typical for codes written in the BUGS language. Then `run_model()` bundles the dataset and the necessary parameters (they have been 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 to conduct a hierarchical one-stage NMA, as 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, to be read by JAGS. The `baseline_model()` function is relevant only in the case of a binary outcome. It processes the baseline risk defined by the user or the default option before conducting 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

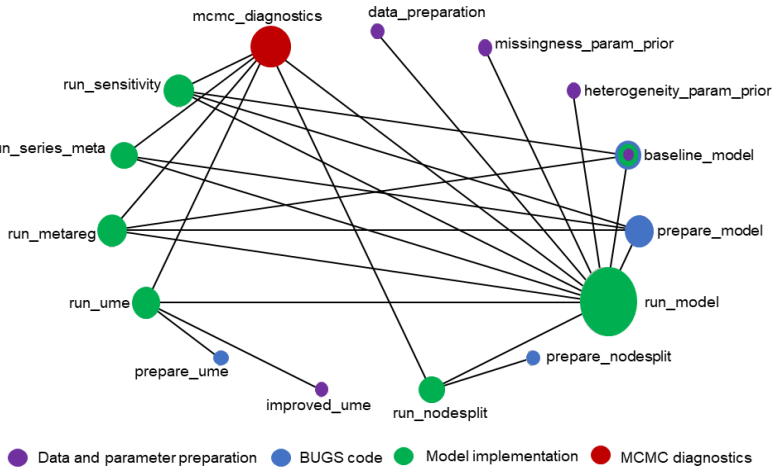

Figure 1: Network of functions for data preparation and model implementation

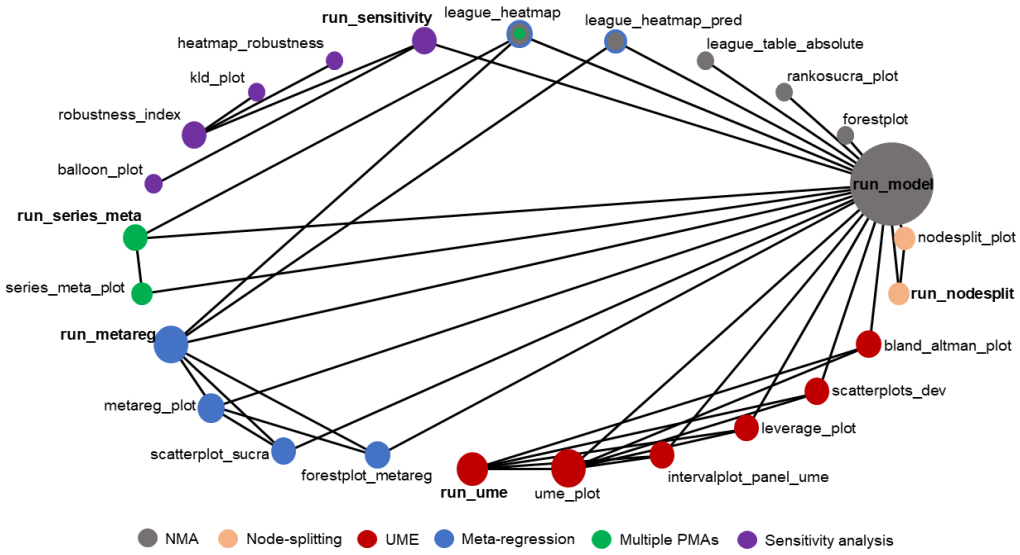

Figure 2: Network of functions for summarising and presenting the analysis results

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**.

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