

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 conducting aggregate network meta-analysis using Bayesian methods, as it allows addressing missing participants properly in all models, even if a handful of the included studies report this information. Importantly, 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 several comprehensive graphs. The rnmamod package aids the thorough appraisal and interpretation of the results, the cross-comparison of different models and the manuscript preparation for journal submission.

Introduction

Evidence-based medicine is the backbone of informed decisions for the benefit of the patients, stemming from a meticulous and judicious use of the available evidence, while taking into account also the clinical experience and patient values (Sackett et al. 1996). However, the medical community is faced daily with several intervention options and dosages, challenging the optimal practice of evidence-based medicine (Lee 2022). Systematic reviews with pairwise meta-analysis summarise the evidence of pairs of interventions, providing fragmented evidence that does not serve the clinical needs. Moreover, evidence in the comparability of different interventions at the trial level is also fragmented, as it is not feasible to compare all intervention options for a condition in one trial. These limitations led to the development and later establishment of network meta-analysis (NMA), also known as multiple treatment comparison, a new generation evidence synthesis tool (Salanti 2012). Network meta-analysis is an extension of pairwise meta-analysis for collecting all relevant pieces of evidence for a specific condition, patient population, and intervention options to provide coherent evidence for all possible intervention comparisons, and allow ordering the investigated interventions from the best to worst option for a specific outcome (Caldwell 2014). Indirect evidence (obtained from different sets of trials sharing a common comparator) plays a central role in the development and prominence of NMA.

Since the introduction of indirect evidence and early development of the relevant methodology (Higgins and Whitehead 1996; Bucher et al. 1997), the NMA framework has undergone substantial progress conceptually and methodologically. The fast-paced publications of relevant methodological articles and systematic reviews with multiple interventions attest to the increasing popularity of NMA in the wide medical and evidence synthesis community (Efthimiou et al. 2016; Petropoulou et al. 2017). Needless to say that the availability of statistical analysis software has been the driving force to the advances and wide dissemination of NMA. A review of the methodology and software for NMA (Efthimiou et al. 2016) listed several statistical software tools used to promote NMA, with the **R** software (R Core Team 2023) being the most popular, followed by **Stata** (StataCorp 2021) and **SAS software** (SAS Institute 2020). In the last decade, there has been a rise in the R packages for NMA with various functionalities (Dewey and Viechtbauer 2023).

Most methodological studies on and systematic reviews with NMA have implemented Bayesian methods (Efthimiou et al. 2016; Petropoulou et al. 2017). The advantages of the Bayesian framework (e.g., flexible modeling, allowance of uncertainty in all model parameters, incorporation of external relevant information and facilitation of probabilistic statements) (Sutton and Abrams 2001), in conjunction with the dominance of the BUGS software (Lunn et al. 2009) during the springtime of the NMA framework, may have contributed to the rising popularity of Bayesian NMA. The numerous R packages on Bayesian NMA also demonstrate the acclaim of Bayesian methods from the evidence synthesis community (Dewey and Viechtbauer 2023). The rest of the section pertains to R packages on Bayesian NMA published in the **CRAN Task View ‘Meta-Analysis’** (Dewey and Viechtbauer 2023) that feature a wide methodological and reporting scope: **bnma** (Seo and Schmid 2022), **CRANpkg(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) conduct hierarchical NMA using Markov chain Monte Carlo (MCMC) methods through the **JAGS** program (Plummer 2003). However, they differ in their methodological and reporting breadth: **bnma** (Seo and Schmid 2022) and **gemtc** (van Valkenhoef and Kuiper 2021) have a greater common basis on methods and outputs than **pcnetmeta** (Lin et al. 2017). This may be ascribed to using the contrast-based modeling approach (trial-specific relative effects, such as log odds ratio, are pooled across the trials), which is the established approach to meta-analysis, whilst **pcnetmeta** (Lin et al. 2017) considers the arm-based modeling approach (arm-specific results, such as log odds, are pooled across the trials), which deviates from the standard meta-analysis practice (Dias and Ades 2016) and is less widespread.

Currently, the package **pcnetmeta** (Lin et al. 2017) does not contain any function to conduct inconsistency evaluation and meta-regression, is limited only to rankograms in terms of hierarchy measures (Salanti et al. 2022), and considers only the 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, allow conducting meta-regression, and consider a wider variety of hierarchy measures and diagnostic tools. However, all three R packages provide a small-sized toolkit with functions regarding the presentation of the relative treatment effects: a league table for one outcome that appears only in the console, and a forest-plot or table on the relative treatment effects of all comparisons with the selected intervention. Moreover, they rely more on the function `print()` (the results appear in the console) than visualisation, and present the results mostly in isolation, restricting the ability to gain further insights into the performance of different NMA models (for instance, assuming consistency versus inconsistency).

Due to the complexity and the wide scope of NMA, the researchers are faced with a large volume of results, necessary to understand the evidence base, assess the underlying assumptions, and evaluate the quality of the estimated parameters (model diagnostics) in order to properly answer the investigated research question. The aforementioned R packages have limited functionalities concerning the presentation of the NMA results, therefore, hindering thorough scrutiny, and critical appraisal, necessary for the transparency of conclusions delivered to the end-users of systematic reviews with multiple interventions. Furthermore, undue reliance on the console limits the usability of the results as the R users have to resort to tabulation, afflicting comprehension, especially, when analysing large intervention networks that are naturally associated with an immense amount of results. Alternatively, the R users have to create the functions to obtain the necessary visualisations, a time-consuming process, depending on the R user experience, whilst time and energy could have been put into appraising the results. The R package **rnmamod** (Spineli 2022), published recently 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 turns an inherently dense output of NMA into several coherent graphs. Originally, the **rnmamod** package was inspired by the absence of 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 present 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 visualisation toolkit of the package has been developed using the R package **ggplot2** (Wickham 2016) to benefit from the flexibility offered in creating and customising quality graphs. The article has the following structure. Section 2 provides an overview of the pattern-mixture models for aggregate binary and continuous outcome data in NMA. Section 3 delineates the architecture of **rnmamod**, and section 4 exemplifies the several functions of the package using examples from published systematic reviews with NMA. Finally, Section 5 concludes with a discussion on the limitations and future developments of the package.

Pattern-mixture models 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 of different scenarios about the missingness mechanism (implied by the distribution of hypothetical outcome values for the missing participants) to the treatment effect. 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:

$$\theta_{ik} = \theta_{ik}^c \times (1 - q_{ik}) + \theta_{ik}^m \times q_{ik}$$

where θ_{ik} is the true outcome in arm k of trial i , θ_{ik}^c and θ_{ik}^m 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

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

for a binary outcome, and

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

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 .

It has been suggested in the relevant published literature to replace the missingness parameter θ_{ik}^m 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):

$$\phi_{ik} = \text{logit}(\theta_{ik}^m) - \text{logit}(\theta_{ik}^c)$$

the informative missingness odds ratio in the logarithmic scale for binary outcomes, and

$$\psi_{ik} = \theta_{ik}^m - \theta_{ik}^c$$

the informative missingness difference of means for continuous outcomes. Other informative missingness parameters that have been suggested are X ; however, IMOR and IMDOM XX . Both informative missingness parameters take values in \mathbb{R} with zero implying the missing at random 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 (White, Higgins, and Wood 2008; Mavridis et al. 2015), or - use the Bayesian framework to estimate their posterior distribution (Turner et al. 2015; Spineli 2019).

Typically, a normal distribution is assigned on both informative missingness parameters (Higgins, White, and Wood 2008; White, Higgins, and Wood 2008; Mavridis et al. 2015; Turner et al. 2015; Spineli 2019). In the Bayesian framework, the analysts assign a prior normal distribution on these parameters and can determine the mean and variance of the normal distribution to be specific to the interventions, trials or trial-arms, fixed, exchangeable or independent across the interventions, trials, or trial-arms (Turner et al. 2015; Spineli 2019).

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 operability 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 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()`

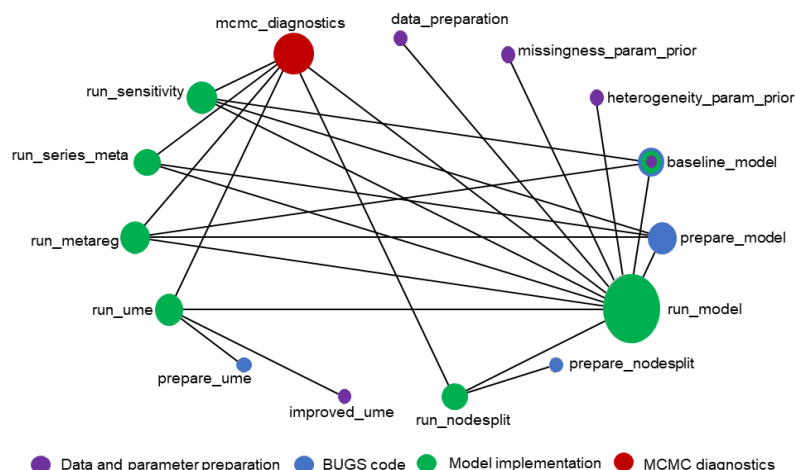


Figure 1: Network of functions for data preparation and model implementation

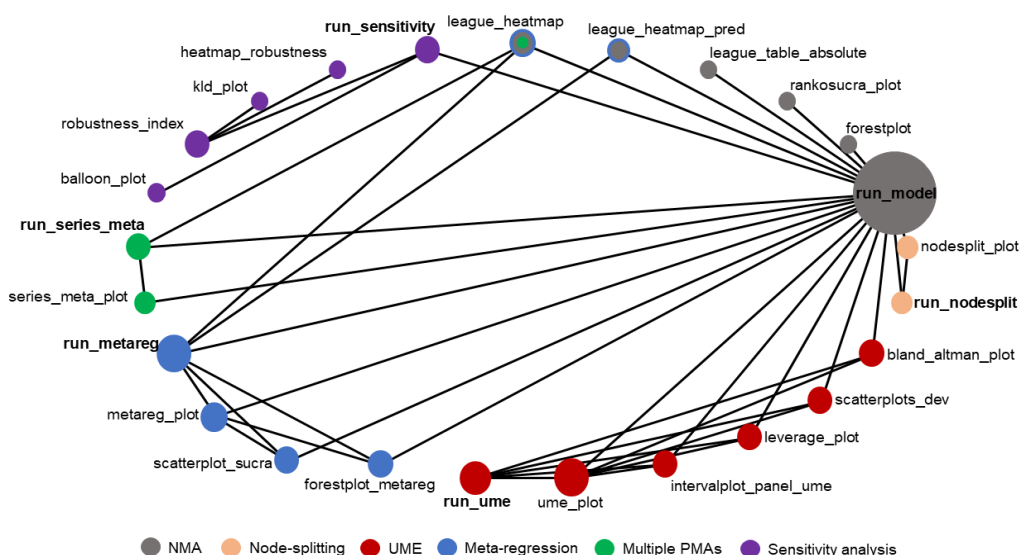


Figure 2: Network of functions for summarising and presenting the analysis results

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()`.

A gallery of tooltips examples

Summary

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

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