Applying Meta-Analytic Predictive Priors with the
R Bayesian evidence synthesis tools

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Abstract

Use of historical data in clinical trial design and analysis has shown various advantages such as reduction of within-study placebo-treated number of subjects and increase of study power. The meta-analytic-predictive (MAP) approach accounts with a hierarchical model for between-trial heterogeneity in order to derive an informative prior from historical (often control) data. In this paper, we introduce the package RBesT (R Bayesian Evidence Synthesis Tools) which implements the MAP approach with normal (known sampling standard deviation), binomial and Poisson endpoints. The hierarchical MAP model is evaluated by MCMC. The numerical MCMC samples representing the MAP prior are approximated with parametric mixture densities which are obtained with the expectation maximization algorithm. The parametric mixture density representation facilitates easy communication of the MAP prior and enables via fast and accurate analytical procedures to evaluate properties of trial designs with informative MAP priors. The paper first introduces the framework of robust Bayesian evidence synthesis in this setting and then explains how RBesT facilitates the derivation and evaluation of an informative MAP prior from historical control data. In addition we describe how the meta-analytic framework relates to further applications including probability of success calculations.

Keywords: Bayesian inference, clinical trial, extrapolation, historical control, operating characteristics, prior, probability of success, robust analysis.

1. Introduction

More efficient clinical trials are of great demand in drug development for all players like pharmaceutical companies, regulatory agencies, health-care organizations and, most importantly, for patients. Use of historical data for quantitative trial design has become more and more attractive for the same reason (Wandel et al. 2015; Neuenschwander and Schmidli forthcoming). Using historical data can reduce the size of the control group, leading to a smaller size of clinical trials which are more ethical and shorten study duration. Therefore, studies utilizing historical data may speed up informative decision making and eventually make better medicines available to patients sooner.

Borrowing information from historical studies has always been a part of the design of clinical
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trials. For example, the definition of a patient population in a new clinical study compared to previous similar studies, or how much of a clinically relevant treatment effect to expect compared to the placebo treatment. Contributions from statisticians in a more quantitative manner started more than 40 years ago, by Pocock (1976). Since then, the relevant statistical approaches have been developed by many, mostly in a Bayesian framework (Chen and Ibrahim 2000; Spiegelhalter \textit{et al.} 2004; Neuenschwander \textit{et al.} 2010; Hobbs \textit{et al.} 2012).

In this paper, we focus on robust meta-analytic-predictive (MAP) priors (Neuenschwander \textit{et al.} 2010; Spiegelhalter \textit{et al.} 2004), which is a hierarchical modeling method allowing heterogeneity between historical trials. As in any meta-analytic approach, it is important to first examine the characteristics of the historical trials with clinical inputs. These include quantitative descriptions of trial population such as subject demographics and baseline characteristics and qualitative features such as concomitant medications. This would help to ensure selected historical controls would be as similar as possible to those in the new trial, such that one of the key assumptions of exchangeability between the trials holds. Secondly the assumption for between-trial heterogeneity needs to be reasonable, which can be checked via sensitivity analysis using different priors for the heterogeneity parameter. This assumption of between-trial heterogeneity should also be agreed with clinical colleagues. Then the MAP prior can be derived from a random-effect meta-analysis of historical data via Markov Chian Monte Carlo (MCMC) algorithms, which is computationally convenient. The predictive distribution will be used to construct the informative prior for the within-study control. The interpretation of using these historical control data can be expressed as the effective sample size of the predictive distribution, i.e. a discounted sample size from the historical control data. Incorporation of this information can therefore save this number of subjects in the control group of the new study. Robustification of the predictive prior (Schmidli \textit{et al.} 2014) is recommended to deal with possible deviation between historical control and the control within the new study.

Application of the MAP approach to incorporate historical data in early phase clinical trials has been more widely accepted, not only by statisticians but also in medical societies (Baeten \textit{et al.} 2013).

In this \textit{R} package, \textsc{R} Bayesian evidence synthesis tools, \textsc{RBesT}, we implement the MAP approach via \texttt{rstan} (Stan Development Team 2018). The package supports endpoints including normal, binary and count and a number of different prior distributions for the between-trial heterogeneity parameter. We approximate the MAP MCMC prior using a parametric mixture distribution which is obtained via the expectation maximization (EM) algorithm. The robustification of the MAP prior is implemented by adding one more weakly-informative component to the mixture. The package also supports inclusion of covariates in the meta-analysis. Functions for running analysis of operating characteristics are built in a very intuitive manner.

Several \textit{R} packages exist for meta-analysis, such as \texttt{netmeta} using a frequentist approach (Rücker 2012), \texttt{bayesmeta} for random-effect meta-analysis (Röver 2017), \texttt{metafor} for mixed-effect meta-analysis and meta-regression (Viechtbauer 2010), and \texttt{MetaStan} (Günhan B. K. and Friede 2018). There are also \textit{R} packages developed for network meta-analysis, which can also deal with the problem discussed here, such as \texttt{gentc} using JAGS for arm-based network meta-analysis (van Valkenhoef and Kuiper 2016), \texttt{pcnetmeta} also using for contrast-based network meta-analysis (L. Lin and Chu 2017) and \texttt{nmaINLA} using integrated nested Laplace approximations (Sauter and Held 2015). One key advantage of \textsc{RBesT} is the EM step and robustification step, which allows easy description of MAP priors and therefore makes analysis easily reproducible. Also, for quantitative trial design and decision making, \textsc{RBesT} provides
functions to evaluate operating characteristics for a new study and to perform the prediction of probability of success at any time.

The organization of this paper is as follows. We will first describe the details of one motivating example from a real clinical study. In Section 3, theoretical background on MAP approach and robustification of MAP will be explained, followed by how these approaches can be applied via \texttt{RBesT} to the example. Finally we close the paper with summary and discussions.

2. Example: Historical control in Phase II

One of the main use-cases of \texttt{RBesT} is the use of historical information in the analysis of clinical trials. The goal is to reduce the trial (usually the control group) sample size while maintaining its target power under the assumed true effect size of an alternative hypothesis. The \texttt{RBesT} package facilitates the (i) prior derivation using MCMC, (ii) parametric (mixture) approximation of the MAP prior and finally (iii) evaluation of the clinical trial design.

As an example we will use in the following the Novartis Phase II study in ankylosing spondylitis comparing the Novartis test treatment secukinumab with placebo (Baeten \textit{et al.} 2013). The primary efficacy endpoint was a binary responder analysis for the percentage of patients with a 20\% response according to the Assessment of SpondyloArthritis international Society criteria for improvement (ASAS20) at week 6. Eight historical trials, totaling 533 patients as shown in table 1, were used to derive the MAP prior for the control arm.

| Study | 1  | 2  | 3  | 4  | 5  | 6  | 7  | 8  |
|-------|----|----|----|----|----|----|----|----|
| Patients (n) | 107 | 44 | 51 | 39 | 139| 20 | 78 | 35 |
| Responders (r) | 23 | 12 | 19 | 9  | 39 | 6  | 9  | 10 |

Table 1: Historical data used in Novartis Phase II study in ankylosing spondylitis. The data set is available in the \texttt{AS} data frame as part of the \texttt{RBesT} package.

This Novartis Phase II trial was conducted using the MAP approach (before the availability of \texttt{RBesT}). The trial used a Beta(11, 32) prior for the control arm and performed a 4 : 1 randomization ratio of active vs control patients. The final trial compared \( n = 24 \) (\( r = 15 \)) treated vs \( n = 6 \) (\( r = 1 \)) control patients and declared success based on meeting the success criterion defined as requiring that \( P(\delta \leq 0 | y) > 0.95 \) holds. This example is discussed with greater focus on the statistical aspects in the vignette “\texttt{RBesT} for a Binary Endpoint” part of \texttt{RBesT}.

3. Bayesian evidence synthesis and prediction

Important decisions should arguably be evidence based, especially in medicine (Eddy 1990; Wandel and Roychoudhury 2016). For example, decisions regarding design and analysis of clinical trials are important for trial sponsors, patients, physicians and policy makers. To support such decisions, relevant sources of information should be collected, appropriately synthesized through meta-analytic approaches, and used to make predictions on the planned target trial. We use the term meta-analytic-predictive (MAP) approach (Neuen-schwander \textit{et al.} 2010) to denote the synthesis of evidence from various sources, and the prediction/extrapolation to the target. Although the MAP approach is useful in a broad range
of applications, we consider here the medical setting (European Medicines Agency 2013). Methodology for Bayesian evidence synthesis and prediction is well developed. Textbooks on this topic include Stangl and Berry (2000), Spiegelhalter et al. (2004), Welton et al. (2012), and Dias et al. (2018). Robust hierarchical models play a key role here, as explained in the following Sections 3.1 and 3.2. Applications of the MAP approach are very diverse, and we briefly discuss some settings in Section 3.3.

### 3.1. Meta-analytic-predictive methodology

Figure 1 schematically depicts the MAP approach for evidence synthesis and prediction. Suppose that a sponsor plans a new clinical trial (the target, labeled by the star symbol). This trial will generate data $Y_\star$, to be described by a statistical model $p(Y_\star | \theta_\star)$, with parameters $\theta_\star$. Usually, several relevant sources of information will be available, e.g. clinical trials in the same or similar patient population, and with (partly) the same treatments. Each source of information consists of data $Y_j$, modeled by $p(Y_j | \theta_j)$, with corresponding parameters $\theta_j$, $j = 1, ..., J$. To borrow strength from the source information, a model is required that links the parameters from both source and target: $p(\theta_\star, \theta_1, ..., \theta_J | \Psi)$, with hyper-parameters $\Psi$. Such hierarchical models are very natural and convenient for the synthesis of the evidence and the prediction to the target (Spiegelhalter et al. 2004). Within the Bayesian framework, a prior for the hyper-parameters $p(\Psi)$ is needed, which will be specific to the considered setting.

At the planning stage of the target trial, the data $Y_\star$ are not available. Hence the posterior distribution of the parameters $p(\theta_\star, \theta_1, ..., \theta_J, \Psi | Y_1, ..., Y_J)$ is based on the source data only.
The marginal posterior for the target parameter $p_{MAP}(\theta_\star) = p(\theta_\star | Y_1, ..., Y_J)$ is the prior information for the target, called the MAP prior in the following.

Once the target data $Y_\star$ are available, the posterior for $\theta_\star$ is $p(\theta_\star | Y_\star) \propto p(Y_\star | \theta_\star) p_{MAP}(\theta_\star)$.

Exactly the same posterior could also be obtained through a meta-analytic-combined (MAC) approach, from $p(\theta_\star, \theta_1, ..., \theta_J, \Psi | Y_\star, Y_1, ..., Y_J)$ (Schmidli et al. 2014).

An analytical derivation of the MAP prior is typically not possible, and hence Markov chain Monte Carlo (MCMC) methods have to be used (Gelman et al. 2013). These generate a large sample from the posterior distribution of the parameters, including $\theta_\star$. However, an approximate analytical description of the MAP prior facilitates communication and use with standard software. Mixtures of normal distributions generally provide such an analytical approximation (West 1993). When conjugate priors exist, mixtures of conjugate priors may be used (Dallal and Hall 1983; Diaconis and Ylvisaker 1984). These are preferable, as they allow analytical posterior calculations for the target trial in simple settings (O’Hagan and Forster 2004; Schmidli et al. 2014).

### 3.2. Robustness to prior-data conflict

The MAP approach provides the prior for the target parameters as $p_{MAP}(\theta_\star)$. Occasionally, this MAP prior may turn out to be in conflict with the emerging target data $Y_\star$, despite great care in the selection of relevant sources and in the specification of the model. The behavior of the posterior distribution to prior-data conflicts is governed by the tails of the prior (O’Hagan and Pericchi 2012). For example, conjugate priors are not heavy-tailed, and consequently the posterior will always be a compromise between prior and data. However, MAP priors are typically heavy-tailed, and are essentially discarded in case of prior-data conflict. This is a desirable feature in most settings.

Although the MAP prior should be robust to prior-data conflict by accounting for heterogeneity, a faster reaction to prior-data conflicts may be achieved by adding a weakly-informative mixture component $p_V(\theta_\star)$ (Schmidli et al. 2014; Neuenschwander et al. 2016). The robustified MAP prior is:

$$p_{MAPr}(\theta_\star) = (1 - w)p_{MAP}(\theta_\star) + wp_V(\theta_\star),$$

where $w$ may be interpreted as the prior probability that the source information is not relevant for the target, expressing some degree of skepticism towards borrowing strength.

### 3.3. Applications

Methodology and diverse applications of the MAP approach in medicine are reviewed in Wandel et al. (2015), Schmidli et al. (forthcoming), and Neuenschwander and Schmidli (forthcoming). Specific applications include comparison of several treatments though a network MAP approach (Schmidli et al. 2013), the design and analysis of non-inferiority and biosimilar clinical trials (Gamalo-Siebers et al. 2016; Mielke et al. 2018), and the use of external data in adaptive clinical trials (Gsponer et al. 2014; Mütze et al. 2018). In the following, four common applications are briefly described.

**Random-effects meta-analysis**

Random-effects meta-analyses of clinical trials are very common in medicine (Higgins and Green 2008). These typically synthesize the evidence on the comparative effectiveness of two
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interventions in patients with a specific disease. **Higgins et al.** (2009) emphasize that both the overall effect size and the prediction for the true effect in a new trial are important for decision makers.

Sources of information are often $J$ randomized clinical trials comparing a test and a control treatment, with a continuous clinical endpoint. Data available from the $j$-th source trial are taken from publications, and are usually the estimated effect $y_j$ with standard error $se_j$ (taken as exactly known). These data are modeled as $y_j \sim \text{Normal}(\theta_j, se_j^2)$. The parameters are linked through a model: $\theta_\star, \theta_1, ..., \theta_J \sim \text{Normal}(\mu, \tau^2)$, with overall effect size $\mu$ and between-trial standard deviation $\tau$. The parameter $\theta_\star$ denotes the true effect in a new trial. Priors for the hyper-parameters $\Psi = (\mu, \tau)$ are e.g. a weakly informative Normal prior for $\mu$ and a Half-Normal prior for $\tau$. In case with few trials (i.e. $J < 5$), an appropriate choice of the prior for $\tau$ is crucial (Gelman 2006; Friede et al. 2017,B). After having specified the priors, **RBesT** may be used to obtain a sample from the posterior distribution of the parameters, and to graphically and numerically summarize these.

**Evaluation of probability of success**

Clinical trials aiming to show the superiority of a test treatment over a control treatment are often analyzed using a frequentist approach. The trial is considered a success, if a statistically significant treatment effect is observed, with one-sided significance level $\alpha = 0.025$. The sample size of the trial is chosen such that a power of e.g. 80% is achieved, conditional on a specific treatment effect $\theta_\star$. However, the power does not provide the unconditional probability of success (or assurance), as it ignores the uncertainty on the treatment effect. If relevant source data on the treatment effect are available, the uncertainty on $\theta_\star$ is captured by the MAP prior $p_{MAP}(\theta_\star)$.

The probability of success (PoS) is the prior expectation of the power, averaged over the MAP prior (O’Hagan et al. 2005).

$$\text{PoS} = \int \text{CP}(\theta_\star) \, p_{MAP}(\theta_\star) \, d\theta_\star,$$

where $\text{CP}(\theta_\star)$ is the conditional power function, i.e. the probability of success conditional on an assumed true treatment effect. From a MCMC sample $\theta_\star^{(1)}, ..., \theta_\star^{(M)}$ of the MAP prior the PoS may be calculated as $1/M \sum_{m=1}^{M} \text{CP}(\theta_\star^{(m)})$. Alternatively, the MAP prior may be approximated by a mixture of normal priors with **RBesT**, and PoS can be evaluated by numerical integration.

PoS evaluations are also relevant for decision makers at interim analyses of clinical trials. If the PoS (or predictive power) at interim is low, the trial may be stopped early to avoid unnecessary exposure of patients to ineffective treatments and to save resources (Spiegelhalter et al. 1986; Schmidli et al. 2007; Neuenschwander et al. 2016). For these interim analyses, the MAP prior is updated with the interim data.

**Extrapolation**

New treatments are typically first investigated in adult patients, before starting clinical trials in children. For many diseases and treatments, a similar effect may be expected for children and adults, using a possibly modified children version of the treatment (e.g. dosing based on body weight). Borrowing strength from the available adult trials should therefore always
be considered (FDA’s Center for Devices and Radiological Health (CDRH) and Center for Biologics Evaluation and Research (CBER) 2015; European Medicines Agency 2018). The MAP approach may be used for extrapolation (Wandel et al. 2017; Röver et al. 2019), although alternative methods are also available (Gamalo-Siebers et al. 2017; Wadsworth et al. 2018).

The source data are usually $J$ randomized clinical trials in adults comparing test and control treatment. These can be summarized with a random-effects meta-analysis as described above, which provides the MAP prior for the treatment effect in a new trial in adults $p_{MAP}(\theta_\ast)$. In some settings essentially the same treatment effect in adults and children may be expected, based on a scientific understanding of the disease and the mode-of-action of the treatment. Hence, the MAP prior for adults may also be used for a new trial in children. Skepticism on the relevance of the adult data may be expressed by robustifying the MAP prior (Section 3.2). In simple settings, RBesT can be used to derive the MAP prior, robustify it, evaluate frequentist operating characteristics of the trial in children, and finally obtain the posterior distribution of the treatment effect in children, once results from the children trial are available.

**Historical controls**

In many disease areas, multiple randomized controlled trial (RCT) have been conducted, with the same control group (e.g. placebo) but different test treatments. When planning to investigate a new test treatment in a RCT, the question arised whether one could borrow strength from the historical control data (Viele et al. 2014). In this setting, the sources of information are the control data from $J$ trials. For a clinical endpoint, the control mean from the $j$th trial may be modeled as $Y_j \sim \text{Normal}(\theta_j, s_e^2_j)$, with true control mean $\theta_j$, and standard error $s_e_j$ (taken as exactly known). A model is used to provide the link to the true control mean in the new trial $\theta_\ast$ as: $\theta_\ast, \theta_1, \ldots, \theta_J \sim \text{Normal}(\mu, \tau^2)$. With appropriate priors for the hyper-parameters, the MAP prior $p_{MAP}(\theta_\ast)$ is derived, and used as the informative prior for the control group in the new trial. Again, it is often advisable to robustify the MAP prior in case of some doubt on the relevance of the historical control information (Section 3.2). RBesT may be used for MAP prior derivation, evaluation of frequentist operating characteristics and the final analysis. An example data set is described in Section 2 and in Section 4 we present how RBesT facilitates the use of historical control information in clinical trials.

Use of the MAP approach in historical control settings has also been described for data modeled by the one-parameter exponential family (Schmidli et al. 2014), count data (Gsteiger et al. 2013), recurrent event data (Holzhauer et al. 2018), time-to-event data (Holzhauer 2017) and variance data (Schmidli et al. 2017).

4. Application

In the following the use of RBesT is explained for the example introduced in section 2. The RBesT package facilitates the (i) prior derivation using MCMC, (ii) parametric (mixture) approximation of the MAP prior and finally (iii) evaluation of the clinical trial design.

4.1. Prior derivation

The statistical models implemented in the package follow the standard generalized linear regression modelling conventions and are implemented with the $gMAP$ function mostly analogous
Applying MAP Priors with \texttt{RBesT} as in the R \texttt{glm} command of the \texttt{stats} package. The supported sampling distributions are normal (with known sampling standard deviation $\sigma$), binomial and Poisson. These use the canonical link functions of the identity, logit and log link, respectively. The \texttt{gMAP} function call for the secukinumab trial is:

```r
set.seed(35667)
map_mcmc <- gMAP(cbind(r, n-r) ~ 1 | study, family=binomial, data=AS,
                 tau.dist="HalfNormal", tau.prior=1, beta.prior=cbind(0, 2))
```

The first argument is the formula argument which specifies a two-column matrix as response for a binary endpoint and contains in the first column the number of responders $r$ and in the second column the number of non-responders $n - r$. The response is modeled using an intercept only here, but covariates can be specified using standard R formulae syntax. The last element of the formula is the grouping factor, separated by a vertical bar. The grouping factor defines what constitutes a trial in the data set. If no grouping factor is specified, then each row in the input data set is interpreted as a group. The next argument is the \texttt{family} argument which specifies the sampling distribution. It is strongly recommended to use \texttt{data} and pass a \texttt{data.frame} to it where all data for the model is stored (otherwise the environment will be searched for the respective columns). Finally, the priors of the model are specified. As the between-trial heterogeneity parameter $\tau$ is of particular importance for a meta-analysis, the \texttt{gMAP} function allows the user to choose the distributional class for the $\tau$ parameter with the \texttt{tau.dist} argument whereas the regression coefficients $\beta$ are restricted to Normal priors. The arguments \texttt{tau.prior} and \texttt{beta.prior} both take a two column argument with the convention that each row corresponds to the respective parameter and the columns correspond to respective parameters of the prior distribution. Whenever a prior distribution for $\tau$ only needs a single parameter, a vector can be given has well, which is the case for the HalfNormal distribution used here with a standard deviation of 1. For the \texttt{beta.prior}, the first and second column correspond to the means and standard deviations of the normal prior distributions, respectively.

Internally the \texttt{gMAP} function uses \texttt{Stan} via the \texttt{rstan} package for sampling from the posterior distribution. The diagnostics of the MCMC sampler as provided by \texttt{Stan} are automatically inspected and potential issues are reported with a warning. The \texttt{gMAP} function returns an \texttt{S3} object, which can then be further processed by standard R modeling functions. The default method

```r
print(map_mcmc)
```

```r
## Generalized Meta Analytic Predictive Prior Analysis
##
## Call:  gMAP(formula = cbind(r, n - r) ~ 1 | study, family = binomial,
##   data = AS, tau.dist = "HalfNormal", tau.prior = 1, beta.prior = cbind(0,
##   2))
##
## Exchangeability tau strata: 1
## Prediction tau stratum : 1
## Maximal Rhat : 1
```
## Between-trial heterogeneity of tau prediction stratum

| mean  | sd    | 2.5% | 50%  | 97.5% |
|-------|-------|------|------|-------|
| 0.3790| 0.2090| 0.0431| 0.3540| 0.8650|

## MAP Prior MCMC sample

| mean  | sd    | 2.5% | 50%  | 97.5% |
|-------|-------|------|------|-------|
| 0.2590| 0.0858| 0.1130| 0.2480| 0.4670|

shows a short summary of the `gMAP` analysis. The derived MAP prior corresponds to the intercept-only model of the fitted statistical model (relevant when using covariates) and is given on the response scale by default as opposed to the link scale of log-odds in this case. More information of the model estimates is available with the `summary` method. Importantly, the `plot` method provides key graphical summaries of the `gMAP` analysis:

```r
model_plots <- plot(map_mcmc)
names(model_plots)
## [1] "densityThetaStar"  "densityThetaStarLink"  "forest_model"
```

The density estimate plot on the response or link scale of the MAP prior shows each fitted chain (by default 4 chains are used) separately. The overlayed display by chain allows to assess graphically the convergence of the MCMC analysis, since each chain must have sampled the same density resulting in very similar densities. As key diagnostic plot we recommend to inspect the `forest_model` as shown in Figure 2(a). The plot gives a graphical summary of the MAP analysis and can serve as a fast check for coding errors.

### 4.2. Parametric mixture prior derivation

The MAP prior, represented numerically with a large MCMC simulation sample, can be approximated with a parametric representation with the `automixfit` function. This function fits a parametric mixture representation using expectation-maximization (EM) algorithm. When calling this function with a `gMAP` analysis object, the EM algorithm is run on the MAP prior MCMC values on the response scale (as opposed to the transformed link scale). The distributional class of the fitted mixture densities depends on the sampling distribution of the `family` argument. For the Gaussian, Binomial and Poisson family a mixture of normal, beta and gamma distributions are fitted with the EM algorithm, respectively. These choices allow RBeST to take advantage of analytical results as the respective likelihood-prior combinations are conjugate to one another.

The EM algorithm requires a pre-specified number of components, which is chosen from `automixfit` automatically through the use of AIC. The function fits parametric mixture models of increasing complexity with up to four components and then selects the one with the lowest AIC. The output below shows the log-likelihood results for the selected mixture model, as well as the mixture components of the beta mixture. All mixtures are represented in RBeST using for each mixture component $k$ a triplet $(w, a, b)_k$ which correspond to the weight $w$ of the component, the first standard parameter $a$ and the second standard parameter $b$ of the respective density. Please refer to the overview table 2 for further details.
Figure 2: Recommended diagnostic plots. (a) Shown are the per-trial point estimates (light dot) and the 95% frequentist confidence intervals (dashed line) and the model derived median (dark point) and the 95% credible interval of the meta-analytic model. In addition the model derived typical parameter estimate and the MAP estimate is shown. (b) Overlay of the MCMC histogram of the MAP prior as obtained from \texttt{gMAP} and the respective parametric mixture approximation as determined from \texttt{automixfit}. 

![Diagnostic plot of gMAP analysis](image1.png)

![Evaluation of parametric mixture approximation](image2.png)
map <- automixfit(map_mcmc)

print(map)

## EM for Beta Mixture Model
## Log-Likelihood = 4471.393
##
## Univariate beta mixture
## Mixture Components:
## comp1    comp2
## w 0.6270981 0.3729019
## a 17.0007087 3.6667131
## b 52.4947716 9.2845241

To consider the quality of the EM fit we recommend to compare the MCMC sample with
the parametric mixture density in a graphical manner. In Figure 2(b) the output of the
plot method is shown for the generated mix plot, which overlays the fitted mixture density
marginal with a histogram of the MCMC sample. In rare cases the response scale can be
inadequate to compare the parametric mixture density appropriately (for example, if the
response rate is very small or very large):

em_diagnostic <- plot(map)
print(em_diagnostic$mix)  ## Shown in Figure 2(b)
print(em_diagnostic$mixdens)  ## Not shown

em_diagnostic_link <- plot(map, link="logit")
print(em_diagnostic_link$mix)  ## Not shown, same as 2(b) on logit scale

Once the user has derived a parametric mixture representation for the MAP prior, the RBesT
package provides additional functions to further investigate as shown in the overview Table 2.
In the following we discuss the key functions needed in the context of informative prior
derivation from historical data.

As the goal is to reduce the required sample size in a future trial, the informative MAP prior
enables unequal randomization of active vs control. In the ankylosing spondylitis example a
4:1 randomization ratio was chosen. The ess function provides approximations to the effective
sample size of a given prior for various methods. The effective sample size of the MAP prior
gives a rough guide by how much the sample size can be reduced when using the respective
frequentist power calculation as a reference, for example.

Instead of using the MAP prior directly in a new study, we recommend to robustify the prior
with a weakly-informative component (equation 1 of Section 3.2) as follows:

map_robust <- robustify(map, weight=0.2, mean=0.5)

RBesT offers many functions which facilitate to explore the implications of an informative
prior. For example, the predictive distribution of the data in a new trial can easily be derived
with the preddist command. While the MAP prior is the predictive distribution of the mean
parameter for a new trial and accounts for parameter uncertainty and between-trial heterogeneity, the predictive distribution of data accounts in addition for sampling uncertainty. For beta mixture densities the respective predictive distribution is the BetaBinomial mixture distribution. This can be used to illustrate possible outcomes in a future trial or to calculate the Bayes factor of observed data with respect to the prior.

Moreover, \texttt{RBesT} provides the \texttt{postmix} command which updates a prior with the data as observed and computes analytically the posterior mixture distribution. For two-sample cases we are often interested in the difference distribution of two densities (representing a treatment difference). In \texttt{RBesT} the difference distribution of mixtures of the same class is supported through the use of the convolution theorem which allows for an accurate evaluation. The table \ref{tab:mixtures} summarizes all functions available for parametric mixtures supported in \texttt{RBesT}. Further details are available in the help files for each function.
| Function Name | Use | Notes |
|---------------|-----|-------|
| c(w, a, b)    | Defines a component of a mixture distribution. Specifies for each component its weight, the first and second standard parameter. | normal densities use mean and standard deviation; beta densities use \( \alpha \) and \( \beta \); gamma densities use shape and rate. |
| mn2norm mn2beta mn2gamma | Maps to standard parametrization given mean and number of observations. | |
| ms2beta ms2gamma | Maps to standard parametrization given mean and standard deviation. | |
| mixnorm mixbeta mixgamma | Creates supported base mixture distribution objects. | for normal densities the attribute sigma sets the known sampling standard deviation; for gamma densities a likelihood attribute sets the likelihood the density is intended to be used with. |
| mixcombine | Combines mixture distributions. | |
| (d/p/q/r)mix | density/distribution/quantile/random number generation | quantile function uses numerical search (optimise and as fallback uniroot). |
| robustify | Add weakly-informative component to mixture. | |
| (d/p/q/r)mixdiff | Difference of two mixture distribution via convolution. | uses convolution theorem; for normal mixtures analytically exact results. |
| ess | Calculates the effective sample size for a mixture prior. | elir (default), moment matching and morita method; refer to appendix B. |
| postmix | Calculates posterior mixture distribution for data and prior mixture. | uses analytically exact results. |
| preddist | Returns the predictive mixture distribution. | |
| decision1S_boundary decision2S_boundary | Calculates critical decision boundary. | refer to appendix C. |
| oclS oc2S | Calculates conditional power. | refer to appendix C. |
| pos1S pos2S | Calculates probability of success. | refer to appendix C. |
| summary | Produces descriptive statistics for mixture. | |
| plot | Produces diagnostic plots of gMAP analyses, EM fits and mixtures distributions. | |

Table 2: Overview on functions in RBesT defined for parametric mixtures.
4.3. Trial design evaluation

Once a parametric mixture MAP prior has been derived, it is crucial to understand its influence on the statistical analysis of a clinical trial. In the context of the historical control example the goal is commonly to reduce the control group sample size while maintaining adequate power for trial success under the alternative hypothesis which assumes some true effect size. The main focus here is the evaluation of the (frequentist) operating characteristics of the trial design with respect to achieving trial success.

RBesT follows a modular, step-wise approach for design evaluation. First, a success criterion is defined, then the design of the trial is specified and finally the desired evaluation of the trial can be conducted for possible scenarios of interest. The success criterion supported are restricted to one-sided criterion’s which are referred to as decision functions. These can be set up for one-sample (decision1S) and two-sample (decision2S) situations. In RBesT the decision functions can be set up to require that multiple critical probability thresholds and quantiles for the difference distribution have to be met in the two-sample case while these thresholds are applied directly to the posterior density in the one-sample case. This enables evaluation of so-called dual criterion designs (Roychoudhury et al. 2018) which evaluate a statistical confidence criterion (high confidence in a positive/negative difference) and a minimally observed treatment difference (observed median difference being greater/smaller than some value). For the ankylosing spondylitis trial, success was declared whenever the posterior treatment difference is positive with a probability which exceeds 95%. In RBesT this is expressed as:

```r
# decision function as used in the trial
success <- decision2S(0.95, 0)
# an alternative which demands in addition to see at least
# a median difference of at least 10%
success_dual <- decision2S(c(0.95, 0.5), c(0, 0.1))
```

The returned object represents the decision function and is a binary function. It takes as arguments two mixture densities (those will be the mixture posteriors) and returns 1 whenever the condition for success on the difference distribution of the two mixture densities is fulfilled and 0 otherwise. Optionally, the success criterion allows for transformation of the input mixture distributions prior to forming the difference distribution using the link argument. The log and logit link enable relative risk and log odds-ratio success criterion to be evaluated with RBesT.

The next step is to define the design of the trial using the operating characteristics function oc2S (or oc1S for a one-sample case). The design of the trial includes the priors for each arm, the total sample size per arm and the decision function for trial success. To evaluate, for example, the impact a robust MAP prior has on the frequentist operating characteristics compared to the respective non-robust design, one can may use:

```r
## prior used for treatment in trial
treat_prior <- mixbeta(c(1,1/2,1))
## explore different trial designs
design_nonrobust <- oc2S(map , treat_prior, 6, 24, success)
design_robust <- oc2S(map_robust, treat_prior, 6, 24, success)
```
The oc2S function returns a binary function which is finally used to calculate the frequency of trial success as a function of an assumed truth for each arm. For the binomial sampling distribution, the function takes assumed true response rates \( \theta_1 \) and \( \theta_2 \). Whenever these two are set to the same numerical value \( \theta = \theta_1 = \theta_2 \), the scenario of no treatment difference is evaluated which would be referred to a type-I error in respective Frequentist trial analysis. Setting \( \theta_1 \) to a plausible control response rate and varying \( \theta_2 \) as a function of the difference \( \delta = \theta_2 - \theta_1 \) gives the desired power of the trial. The functions take vectors of equal length as arguments so that we can evaluate the type-I over large parameter ranges as:

```r
ground <- c(0.25, 0.5, 0.75)
round(design_nonrobust(theta, theta), 3)
## [1] 0.020 0.341 0.795
round(design_robust(theta, theta), 3)
## [1] 0.018 0.190 0.173
```

Here we see that the Bayesian design with informative priors does not control the type-I error and that the error rate depends on the actual parameter value. However, the 97.5% quantile of the MAP prior is approximately 0.48 such that response rates greater than this would be very unusual. Given that RBesT is fast and accurate for these calculations, it is recommended to use graphical plots in addition to tables to visualize the (error) rates of interest as demonstrated in the vignettes of RBesT.

In addition to the operating characteristics functions RBesT also provides respective functions to evaluate the probability of success with pos2S and pos1S. These functions allow to account for uncertainty in the assumed true parameter values. They pos2S (pos1S) require as arguments the same trial design specification arguments as the oc2S (oc1S) functions. The returned functions take as arguments mixture densities which represent uncertainty in the respective parameter of each arm.

Internally, all trial design calculations use analytical results wherever possible. This makes RBesT very accurate and fast in evaluating the design properties of trials. A key quantity calculated is the critical decision boundary determined by the success criterion and the trial design. At the critical outcome boundary the success criterion changes its value between 0 and 1. While in the one-sample case this corresponds to a single value, it is a function of the outcome in the second sample in the two-sample case. As the decision boundary can be useful for other applications, the boundary can be obtained with the functions decision2S_boundary (decision1S_boundary). These are also useful when communicating various data scenarios and their respective decisions to non-statisticians like clinical teams. For more details please refer to the appendix.

## 5. Summary

In this paper, we introduced the RBesT package which implements the MAP approach via MCMC sampling algorithms for a number of common sampling and prior distributions. Incorporating historical data in clinical studies has various advantages, such as reducing the
number of subjects randomized to a control arm or getting more precise information for decision making. Incorporation of historical data should lead to more ethical and efficient clinical trials.

The MAP approach is a hierarchical modeling method allowing heterogeneity between historical trials, which can incorporate historical data in a meta analytic framework. The RBesT package allows for easier implementation of MAP priors. After selection of appropriate historical information, RBesT facilitates the prior derivation using MCMC, the parametric (mixture) approximation of the MAP prior and finally the evaluation of the clinical trial design.

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A. Parametric mixture inference

In RBesT the expectation maximization (EM) algorithm is used to find parametric mixture approximations to the numerical representation of the MAP prior. Thus, we consider in this section as data \( Y \) the MCMC sample representing the MAP prior (or any other MCMC sample). Direct application of maximum likelihood is numerically problematic, since the log-likelihood for a mixture prior, \( \log p(Y|\mathbf{w}, \mathbf{a}, \mathbf{b}) = \sum_{i=1}^{N} \sum_{k=1}^{K} w_k \log p_k(Y_i|a_k, b_k) \), involves the sum over the log of the component densities \( w_k p_k(Y_i|a_k, b_k) \). The inner summation is on the natural scale and is required as we do not know the component \( k \) which a data item \( Y_i \) is a member of. However, extending the observed data \( (Y) \), also referred to as incomplete data, to the so-called complete data \( (Y,Z) \) leads to a numerically stable problem. The unobserved data \( Z \) is defined as the latent component indicator such that \( Z_{i,k} = 1 \) whenever data item \( i \) is part of component \( k \) and 0 otherwise. The extended problem is related to the original through marginalization, \( p(Y|\mathbf{w}, \mathbf{a}, \mathbf{b}) = E_Z[p(Y, Z|\mathbf{w}, \mathbf{a}, \mathbf{b})] \). However, the extended log-likelihood factorizes in the usual way

\[
\log p(Y, Z|\mathbf{w}, \mathbf{a}, \mathbf{b}) = \sum_{i=1}^{N} \sum_{k=1}^{K} Z_{i,k} \left[ \log(w_k) + \log p_k(Y_i|a_k, b_k) \right].
\]

The EM algorithm begins with a fixed number of mixture components \( K \) and an initial guess of all parameters. The initial guess of the parameters is achieved with the k nearest neighbors (knn) algorithm in RBesT with the exception of the normal mixture case as detailed below. The parameter vector \( (\mathbf{w}, \mathbf{a}, \mathbf{b}) \) is then updated iteratively. The \( n \)th iteration of the EM consists of first performing the expectation (E) step and then the maximization (M) step which updates the parameter vector for the next iteration. These EM steps are then repeated until convergence to a maximum of the log-likelihood. While it is guaranteed that in each iteration the log-likelihood is always increased, the EM algorithm may only find a local rather than a global extremum.

**E-step** The E-step calculates the posterior probability for the latent indicators \( p(Z|Y, \mathbf{w}, \mathbf{a}, \mathbf{b}) \) in order to compute the expected posterior mean weights

\[
E[Z_{i,k}] = \frac{w_k p(Y_i|a_k, b_k)}{\sum_k w_k p(Y_i|a_k, b_k)} = \gamma(Z_{i,k}).
\]

The expression \( \gamma(Z_{i,k}) \) is often referred to as the responsibility of mixture component \( k \) for data item \( i \). The overall responsibility of mixture component \( k \)

\[
N_k = \sum_{i=1}^{N} \gamma(Z_{i,k})
\]

can be interpreted as the number of data items belonging to mixture component \( k \). Finally, the E-step computes the expectation of the complete log-likelihood with respect to \( Z \) conditional on the parameter vector of the current \( n \)th iteration,

\[
E_{Z|\mathbf{w}^n, \mathbf{a}^n, \mathbf{b}^n}[\log p(Y, Z|\mathbf{w}, \mathbf{a}, \mathbf{b})] = \sum_{i=1}^{N} \sum_{k=1}^{K} \gamma(Z_{i,k}) \left[ \log(w_k) + \log p_k(Y_i|a_k, b_k) \right] = Q(\mathbf{w}, \mathbf{a}, \mathbf{b}|\mathbf{w}^n, \mathbf{a}^n, \mathbf{b}^n)
\]

\( Q(\mathbf{w}, \mathbf{a}, \mathbf{b}|\mathbf{w}^n, \mathbf{a}^n, \mathbf{b}^n) \)
M-step  The M-step then proceeds by finding a new parameter vector through maximization

\[(w^{n+1}, a^{n+1}, b^{n+1}) = \arg \max_{w, a, b} Q(w, a, b|w^n, a^n, b^n).\]

The updated weights are constrained to sum to one. Maximization with this constraint is achieved through Lagrange multipliers and leads for the updated weights to the solution

\[w_k^{n+1} = \frac{N_k}{N} \cdot \]

To find the maximum with respect to the parameters of each component \(k\), we take the gradient \(\frac{\partial}{\partial a_k, \partial b_k} Q(w, a, b|w^n, a^n, b^n)\) and equate these to zero.

**Normal mixtures**  For normal mixtures RBesT implements internally a multi-variate normal EM, but only exposes the uni-variate functionality at the moment. Empirically we observed that the normal EM algorithm is easily trapped into local extrema which is caused by the commonly heavy tailed distributions of MAP priors. For this reason, we initialize the normal EM with the result of a Student-t EM procedure as described in Peel and McLachlan (2000). The Student-t EM is itself initialized with \(k\) nearest neighbors. The maximization equations can be solved analytically in the normal mixture case,

\[\mu_k = \frac{1}{N_k} \sum_{i=1}^{N} \gamma(Z_{i,k}) Y_i\]

\[\Sigma_k = \frac{1}{N_k} \sum_{i=1}^{N} \gamma(Z_{i,k}) (Y_i - \mu_k) (Y_i - \mu_k)'.\]

The analytical solution is a weighted mean and covariance estimate with the weight for each data item \(Y_i\) equal to \(\gamma(Z_{i,k})/N_k\).

**Beta mixtures**  For beta mixture distributions we are lead to the joint equation system of (see also Ma and Leijon 2009)

\[\psi(a_k) - \psi(a_k + b_k) = \frac{1}{N_k} \sum_{i=1}^{N} \gamma(Z_{i,k}) \log(Y_i)\]

\[\psi(b_k) - \psi(a_k + b_k) = \frac{1}{N_k} \sum_{i=1}^{N} \gamma(Z_{i,k}) \log(1 - Y_i).\]

Here \(\psi(x)\) is defined as \(\frac{\partial}{\partial x} \log(\Gamma(x))\). This equation system is solved simultaneously for \(a_k\) and \(b_k\) through numerical minimization.

**Gamma mixtures**  With gamma mixtures the algebraic equation system

\[\psi(a_k) - \log(b_k) = \frac{1}{N_k} \sum_{i=1}^{N} \gamma(Y_{i,k}) \log(Y_i)\]

\[a_k = \frac{1}{N_k} \sum_{i=1}^{N} \gamma(Z_{i,k}) Y_i\]
is obtained. This system can be reduced to a single equation, which is again solved through numerical minimization.

**B. Effective sample size**

The effective sample size is an approximate measure for the number of observations a prior is equivalent to. In the setting of conjugate likelihood-prior pairs without mixtures the standard parameters can be cast into an effective sample size. However, this is not the case for mixture priors and **RBesT** implements three approaches:

**elir** The expected local information ratio has been proposed in Neuenschwander *et al.* (2019) and is a predictively consistent effective sample size measure. The predictive consistency requires that the effective sample size of the prior is equal to the average effective sample size of the respective posterior of this prior after simulation of $m$ samples from the predictive prior distribution and subtracting $m$ from the averaged posterior effective sample size. The method is neither liberal nor conservative and is the default method in **RBesT**.

**morita** The method from Morita *et al.* (2008) evaluates the curvature of the prior at a reference point (mode, median or mode) and compares this against the expected curvature of a posterior of a variance inflated prior which is updated with $m$ samples from the prior predictive of the prior. The $m$ is chosen to minimize the difference in curvature. Since the Morita method evaluates the prior at a single point, the approach can be sensitive to the curvature at this point and has been observed to report relatively liberal effective sample sizes when used with mixture priors.

**moment** The moment based approach matches the mean and the variance of a given prior to its respective canonical prior from which the effective sample size can be obtained directly from the standard parameters. This approach has been found empirically to report very conservative (low) effective sample sizes.

The key expressions involved in the effective sample size calculations is the prior information

$$i(p(\theta)) = -\partial^2_\theta \log(p(\theta))$$

and the Fisher information

$$i_F(\theta) = E_{Y_1|\theta} [i(p(Y_1|\theta))] = -E_{Y_1|\theta} \left[ \partial^2_\theta \log(p(Y_1|\theta)) \right].$$

The Fisher information is derived from the sampling distribution, but the second derivative of the log mixture prior density with $K$ components, defined as

$$p(\theta|w, a, b) = \sum_{k=1}^{K} w_k p_k(\theta|a_k, b_k),$$

needs some considerations for a numerically stable evaluation. It is key to evaluate the log density instead of the density on the natural scale whenever possible. We will in the following
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suppress the weights and standard parameters of $p(\theta)$ and $p_k(\theta)$ for simplicity. Using the equality $\partial_\theta p(\theta) = p(\theta) \partial_\theta \log(p(\theta))$ one finds that the prior information for a mixture is

$$i(p(\theta)) = \frac{1}{p(\theta)^2} \left( \sum_{k=1}^{K} w_k p_k(\theta) \partial_\theta \log(p_k(\theta)) \right)^2 - \frac{1}{p(\theta)} \sum_{k=1}^{K} w_k p_k(\theta) \left( (\partial_\theta \log(p_k(\theta)))^2 + \partial_\theta^2 \log(p_k(\theta)) \right).$$

(3)

The table 3 lists all the main expressions required for the supported conjugate likelihood-prior pairs in \textsc{RBesT}.

| Sampling distribution | Fisher information | Prior density | Prior information |
|-----------------------|--------------------|---------------|-------------------|
| $p(Y|\theta)$         | $i_F(\theta)$      | $p_k(\theta|a, b)$ | $i(p_k(\theta))$ |
| Normal $\mathcal{N}(\theta, \sigma^2)$ | $\sigma^{-2}$ | Normal $\mathcal{N}(\theta|m, s^2)$ | $s^{-2}$ |
| Binomial $\mathcal{B}(Y, n)$ | $n^{-1}$ | Beta $\mathcal{B}(\theta|a, b)$ | $\frac{a-1}{\sigma^2} + \frac{b-1}{(1-\theta)^2}$ |
| Poisson $\mathcal{P}(Y|\theta)$ | $\theta^{-1}$ | Gamma $\mathcal{G}(\theta|a, b)$ | $\frac{a-1}{\theta^2}$ |
| Exp $\mathcal{E}(Y|\theta)$ | $\theta^{-2}$ | Gamma $\mathcal{G}(\theta|a, b)$ | $\frac{a-1}{\theta}$ |

Table 3: Overview on supported conjugate likelihood-prior pairs supported in \textsc{RBesT}. \(^1\)Note that for the exponential sampling distribution only the effective sample size calculations are supported as of \textsc{RBesT} 1.4-0.

C. Informative prior evaluation

In \textsc{RBesT} one-sided decision functions with multiple criteria are supported for one and two sample cases. The decision functions are indicator functions through thresholding density distributions such that critical quantiles must exceed predefined probability thresholds. Denoting with $H(x)$ the Heaviside step function, which is 0 for $x \leq 0$ and 1 otherwise, the decision functions are defined as

$$D(p(\theta)) = \prod_i H(P(\theta \leq q_{i,c}) - p_{i,c})$$

one sample,

$$D(p_1(\theta_1), p_2(\theta_2)) = \prod_i H(P(\theta_1 - \theta_2 \leq q_{i,c}) - p_{i,c})$$

two sample.

In the two-sample case the difference distribution of $p_1(\theta_1)$ and $p_2(\theta_2)$ is thresholded.

**Critical decision boundary** With the design of a trial the priors and the sample size per sample is defined and these determine the critical decision boundary of the decision function,

$$D_c = \sup_y \{ D(p(\theta|y)) = 1 \} = y_c$$

one sample,

$$D_{c,1}(y_2) = \sup_{y_1} \{ D(p_1(\theta_1|y_1), p_2(\theta_2|y_2)) = 1 \}$$

two sample.

While for the one sample cases the decision boundary is a single value, $D_c = y_c$, the decision boundary is a function of the outcome in one of the samples (by convention the second sample), $D_{c,1}(y_2)$. 
Conditional power  The critical decision boundary is used in RBesT to simplify the conditional power calculation in the following manner,

\[ CP(\theta) = \int D(p(\theta'|y)) p(y|\theta) \, dy = \int_{-\infty}^{y_c} p(y|\theta) \, dy \]

\[ CP(\theta_1, \theta_2) = \int \int D(p_1(\theta_1'|y_1), p_2(\theta_2'|y_2)) p_1(y_1|\theta_1) p_2(y_2|\theta_2) \, dy_1 \, dy_2 \]

\[ = \int P_1(y_1 \leq D_{c,1}(y_2)|\theta_1) p_2(y_2|\theta_2) \, dy_2 \]

Therefore, the conditional power simplifies in the one sample case to evaluation of the cumulative density function corresponding to the sampling distribution and in the two sample case the integration is simplified to a one dimensional integral instead of a two dimensional one. For the case of a binomial sampling distribution the calculations are carried out exactly. With normal and Poisson endpoints the respective integrals are evaluated with quadrature integration on a domain which corresponds to \( 1 - \epsilon \) (\( \epsilon = 10^{-6} \) by default) of probability mass.

Probability of success  The probability of success as defined in equation 2 of Section 3.3.2 results in a double (triple) integral for the one (two) sample case. To simplify this, the prior predictive distribution of the prior \( p(\theta) \),

\[ p(y) = \int p(y|\theta) p(\theta) \, d\theta, \]

is used. The prior predictive distribution is available in analytic form and allows to re-arrange the evaluation of the equation 2 as

\[ \text{PoS} = \int \int \int D(p(\theta'|y)) p(y|\theta) p(\theta) \, d\theta \, dy = \int \int D(p(\theta'|y)) p(y) \, dy. \]

This re-arrangement holds for the two sample case respectively. This leads to the same calculations as previously for the operating characteristics with the only difference in that the sampling distribution, \( p(y|\theta) \), is replaced by the predictive distribution of the prior, \( p(y) \).

For the two sample case the integration is performed using numerical integration while for the one sample case the cumulative distribution function of the predictive is evaluated.

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