Combining independent p-values in replicability analysis: a comparative study

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ABSTRACT
Given a family of null hypotheses $H_1, \ldots, H_s$, we are interested in the hypothesis $H^\gamma_s$ that at most $\gamma - 1$ of these null hypotheses are false. Assuming that the corresponding p-values are independent, we are investigating combined p-values that are valid for testing $H^\gamma_s$. In various settings in which $H^\gamma_s$ is false, we determine which combined p-value works well in which setting. Via simulations, we find that the Stouffer method works well if the null p-values are uniformly distributed and the signal strength is low, and the Fisher method works better if the null p-values are conservative, i.e. stochastically larger than the uniform distribution. The minimum method works well if the evidence for the rejection of $H^\gamma_s$ is focused on only a few non-null p-values, especially if the null p-values are conservative. Methods that incorporate the combination of e-values work well if the null hypotheses $H_1, \ldots, H_s$ are simple. Finally, we also consider nonparametric permutation-based combination methods. They are useful for addressing the conservativity of parametric p-values which are computed under least favourable parameter configurations.

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1. Introduction
Given a set of studies, which are examining related research hypotheses under different conditions, it is often of interest to assess whether findings can be made in at least $\gamma \geq 2$ of the considered studies. Studies may, for example, differ in their underlying populations or in laboratory methods. The search for results in at least two studies is called replicability analysis. It alleviates the possibility that a positive outcome depends on the specific settings of a single study.

Formally, we consider a family of $s \geq 2$ null hypotheses $H_1, \ldots, H_s$ and their corresponding alternative hypotheses $K_1, \ldots, K_s$. For each pair of hypotheses $H_i$ and $K_i$ we assume that a p-value $p_i$ is available and that these p-values $p_1, \ldots, p_s$ are jointly stochastically independent. For $\gamma \leq s$, we are interested in the partial conjunction/replicability null hypothesis

$H^\gamma_s = \{ \text{at least } s - \gamma + 1 \text{ of the null hypotheses } H_1, \ldots, H_s \text{ are true} \}$,

(1)
thus its alternative is that at least \( \gamma \) null hypotheses are false. Our goal is to compare different \( p \)-value combinations for \( p_1, \ldots, p_s \) that are valid for \( H_s^{\gamma} \). A \( p \)-value is called valid for a null hypothesis \( H \) if it is stochastically not smaller than the uniform distribution on \([0, 1]\) (\( \text{Uni}[0, 1] \)) under all parameter values that entail the validity of \( H \).

Since it holds \( H_1^1 \subseteq H_2^1 \subseteq \cdots \subseteq H_s^1 \), valid \( p \)-values for \( H_1^1 \) need not be valid for \( H_s^1 \), \( \gamma \geq 2 \). In [1], the authors investigated the theory of testing the partial conjunction null hypotheses \( H_s^\gamma \). They showed that valid \( p \)-values for \( H_s^\gamma \) can be derived from combination \( p \)-values for \( H_s^{1-\gamma+1} \) by essentially combining the \( s-\gamma+1 \) largest \( p \)-values.

There are several ways to combine the independent \( p \)-values \( p_1, \ldots, p_s \) of a set of null hypotheses \( H_1, \ldots, H_s \) to test for the null hypothesis \( H_s^1 \). In [2], it was shown that for each \( p \)-value combination that is non-decreasing in each \( p \)-value, there exists an alternative hypothesis for which the combination is best. Nevertheless, we consider different null hypothesis setups and identify which of our considered combinations work best in which general situation.

A common way of combining \( p \)-values for \( H_s^1 \) is via averaging, see also [3]. This approach evaluates the sum of the transformed \( p \)-values \( f(p_1, \ldots, p_s) = \sum_i \phi(p_i) \). If the distribution of \( f(U_1, \ldots, U_s) \) is known with cdf \( F_f \), where \( U_i \sim \text{Uni}[0, 1] \), \( i = 1, \ldots, s \), then defining \( F_f^{-1}(f(p_1, \ldots, p_s)) \) leads to a valid \( p \)-value under \( H_s^1 \). Two well-known examples of such are Fisher’s method which uses \( \phi = \log \), and Stouffer’s method, which uses \( \psi(x) = -\Phi^{-1}(1-x) \), where \( \Phi^{-1} \) is the quantile function of the standard normal distribution on \( \mathbb{R} \). If the distribution of \( f(U_1, \ldots, U_s) \) is unknown, one can instead modify \( p = G_0(f(p_1, \ldots, p_s)) \) with a suitable function \( G_0 \) so that \( p \) is at least valid under \( H_s^1 \). This includes for example the arithmetic mean and the harmonic mean, cf. [3–5]. Either way, large \( p \)-values can overshadow small \( p \)-values in averaging methods, which can be problematic if the null \( p \)-values are conservative under nulls, that is, if they are stochastically larger than \( \text{Uni}[0, 1] \). On the other hand, none of the \( p \)-values need to be smaller than a significance level \( \alpha \in (0, 1) \) for the combined \( p \)-value to be smaller than \( \alpha \). Thus averaging methods can be powerful if the evidence for a rejection of the global null hypothesis is spread out between the \( p \)-values. Pearson’s method of averaging via a product of the \( p \)-values is of a similar nature, cf. [6].

On the other hand, there are \( p \)-value combination functions that do not take the size of all \( p \)-values fully into account. For example the combined \( p \)-value \( s \cdot \min\{p_1, \ldots, p_s\} \) resulting from the Bonferroni method is relatively unaffected by conservative \( p \)-values, but the \( p \)-value cannot be smaller than \( \alpha \) if none of the marginal \( p \)-values are. Similarly, since the minimum \( \min\{p_1, \ldots, p_s\} \) of stochastically independent \( \text{Uni}[0, 1] \)-distributed \( p \)-values is Beta-distributed with parameters \( 1 \) and \( s \), Beta\((1, s)\), we can also consider \( p = F_{\text{Beta}(1,s)}(\min\{p_1, \ldots, p_s\}) \) as a valid \( p \)-value for \( H_s^1 \). Another example is the maximum of the \( p \)-values, which is valid for \( H_s^1 \) if the \( p \)-values are independent, cf. [3].

The aforementioned methods require as their input (marginal) \( p \)-values. These are often obtained from a parametric model for the data or for the test statistics pertaining to the null hypotheses of interest. A different approach, which we will consider in Section 4.5, is to utilize permutation-based methods (see, among many others, [7–15]) which directly operate on the data, without imposing a parametric model.

Similarly to the work in [16], we differentiate between alternative hypotheses that have minimally spread evidence and ones that have spread out evidence among all the false null hypotheses. If \( s = 6 \) and \( \gamma = 2 \), the null hypothesis \( H_s^{\gamma} \) is, for example, false if only two
null hypotheses are false or if all null hypotheses are false. However, in [16] only the global null hypotheses \( H^1_s \), that every null hypothesis is true, has been considered. We extend this work by taking the more general partial conjunction hypothesis \( H^p_s \) into account. In [2], the author already noted that in case of \( s = 2 \) studies, the Wilkinson \( p \)-value (case 1) is more sensitive to evidence in one study than the Fisher \( p \)-value, cf. [17]. Furthermore, in [16] only \( \text{Uni}[0,1] \)-distributed null \( p \)-values have been considered. However, it is known that for example in case of composite null hypotheses, conservative null \( p \)-values are more common, cf. [18,19]. In simulations, we investigate how well the different \( p \)-value combination functions deal with conservative null \( p \)-values.

Not covered in this paper is the kind of meta analysis that tests \( H^s_1 \) against the alternative of \( H^s_1 \), which is a proper subset of the alternative of \( H^s_1 \) if \( s > 1 \), i.e. each of the null hypotheses \( H_1, \ldots, H_s \) are either all true or all false (for example repetition of an experiment). In [20], the author modelled the marginal \( p \)-values under alternatives as \( \text{Beta}(\alpha, \beta) \)-distributed, Beta-distributed with parameters \( \alpha \) and \( \beta \), and determined which \( p \)-value combinations work well for this question in which subsets of \((0, \infty)^2 \) for the parameters \( (\alpha, \beta) \). Under the assumption that the marginal \( p \)-values are \( \text{Uni}[0,1] \)-distributed under \( H^1_s \), the authors in [21] calculated \( p \)-value combinations by means of likelihood ratio tests and therefore uniformly most powerful test statistics for the above kind of meta analysis under several models.

This work is structured as follows. In Section 2, we introduce our model and notations, and in Section 3 we present the \( p \)-value combinations that we consider. Section 4 contains our comparisons of the \( p \)-value combination functions via simulations. Finally, we conclude with a discussion in Section 5.

### 2. Model setup

Let \((\Omega, \mathcal{F}, (\mathbb{P}_\theta)_{\theta \in \Theta})\) be a statistical model, and let \( X \) be the data and \( \theta \in \Theta \) the parameter of the model and \( \Theta \) the corresponding parameter space. We consider a set of null hypotheses \((H_i)_{i=1,\ldots,s}\) and their corresponding alternatives \((K_i)_{i=1,\ldots,s}\) such that \( H_i \) and \( K_i \) are non-empty subsets of the parameter space \( \Theta \subseteq \mathbb{R}^s \). We assume that \( H_i = \{ \theta : \theta_i \leq 0 \} \) and \( K_i = \{ \theta : \theta_i > 0 \} \) for each \( i = 1, \ldots, s \). Thus each hypothesis pair \( H_i \) and \( K_i \) only depends on the \( i \)-th component of the parameter value \( \theta, i = 1, \ldots, s \).

Let a set of corresponding \( p \)-values \( (p_i)_{i=1,\ldots,s} \) be given, such that for any parameter value \( \theta = (\theta_1, \ldots, \theta_s)^T \in \Theta \)

\[
p_i(X) \sim f_{\theta_i}, \quad i = 1, \ldots, s,
\]

where \( f_{\theta_i} \) is a Lebesgue density with support on \([0, 1]\). More particularly, we assume that the density function \( f_{\theta_i} \) only depends on the \( i \)-th component \( \theta_i \) of \( \theta \). Throughout this paper, we use \( p_i \equiv p_i(X) \) by abuse of notation, and say ’\( p \)-value’ and ’\( p \)-variable’ interchangeably.

We make the following general assumptions to our model:

\begin{enumerate}
   \item[(A1)] The \( p \)-values \( p_1, \ldots, p_s \) are jointly stochastically independent under each parameter value \( \theta \in \Theta \).
   \item[(A2)] Under any \( \theta \in \Theta \) such that \( \theta_i = 0 \), we assume that \( f_0(t) = 1 \{ 0 \leq t \leq 1 \} \), i.e. that \( p_i(X) \) is \( \text{Uni}[0,1] \)-distributed under \( \theta_i = 0, i = 1, \ldots, s \).
\end{enumerate}
(A3) For each $i$, we assume that the $p$-value $p_i(X)$ is stochastically decreasing in $\theta_i$, i.e. $p_i(X)^{(\theta_i)} \leq_{st} p_i(X)^{(\tilde{\theta}_i)}$ if and only if $\theta_i \geq \tilde{\theta}_i$.

Assumption (A1) is for example fulfilled if the null hypotheses $H_1, \ldots, H_s$ are from a set of independent studies. If the parameter space $\Theta$ contains no parameter values $\theta$ with negative $i$th components $\theta_i$, $p_i$ is $\text{Uni}[0,1]$-distributed under each $\theta \in H_i$. Otherwise, $p_i$ may be conservative if $\theta_i < 0$, $i = 1, \ldots, s$.

The relation $\leq_{st}$ in assumption (A3) denotes the usual stochastic order between two random variables, cf. for example [22, Section 1.4]. The notation $p_i(X)^{(\theta_i)}$ refers to the distribution of $p_i(X)$ under $\theta_i$. Under assumptions (A2) and (A3), $p_i$ is a valid $p$-value for $H_i$ and parameters $\theta$ with $\theta_i = 0$ are the least favourable parameter configurations (LFC parameters). See for example Section 2 in [19] for a definition of LFC-based $p$-values.

**Remark 2.1:** Assumption (A3) is for example fulfilled if $p_i$ is an antitone transformation of a test statistic $T_i(X)$ such that $(T_i(X)^{(\theta_i)})_{\theta_i}$ is likelihood ratio ordered, that is, if the distribution of $T_i(X)$ under $\theta$ is smaller under the likelihood ratio order than under $\tilde{\theta}$ if and only if $\theta_i \leq \tilde{\theta}_i$ holds for their $i$th components (cf. for example Section 1.B in [22] for a definition of the likelihood ratio order).

We are interested in the partial conjunction null hypothesis $H^\gamma_s$ from (1), where $1 \leq \gamma \leq s$ is a given constant. The goal of this work is to compare $p$-value combination maps $f : [0,1]^s \rightarrow [0,1]$ for which $f(p_1, \ldots, p_s)$ is a valid $p$-value for $H^\gamma_s$.

**3. Combination functions for $p$-values**

In this section, we introduce the $p$-value combinations $f(p_1, \ldots, p_s)$ that we investigate for the null hypothesis $H^\gamma_s$. Let $U_1, \ldots, U_s$ be stochastically independent and identically $\text{Uni}[0,1]$-distributed random variables.

We first assume the existence of a $p$-value combination function $g : [0, 1]^{s-\gamma+1} \rightarrow [0, 1]$, that is non-decreasing in each argument and valid for the null hypothesis $H^1_{s-\gamma+1}$, i.e.

\begin{equation}
\text{Uni}[0,1] \leq_{st} g \left( U_1, \ldots, U_{s-\gamma+1} \right).
\end{equation}

Let $p_{(1)} \leq \cdots \leq p_{(s)}$ be the ordered $p$-values. According to Lemma 1 in [1], this combination function applied to the $s - \gamma + 1$ largest $p$-values $p_{(\gamma)}, \ldots, p_{(s)}$ among $p_1, \ldots, p_s$ is valid for $H^\gamma_s$, i.e. $f(p_1, \ldots, p_s)$ is valid for $H^\gamma_s$, where $f : [0,1]^s \rightarrow [0,1]$ is a combination function with

\begin{equation}
f (p_1, \ldots, p_s) = g \left( p_{(\gamma)}, \ldots, p_{(s)} \right).
\end{equation}

Hence, in order to find $p$-value combination functions for the partial conjunction null hypothesis $H^\gamma_s$, we only have to consider $p$-value combination functions $g : [0, 1]^{s-\gamma+1} \rightarrow [0,1]$ for $H^1_{s-\gamma+1}$. The functions $g$, that we use in this paper, can be divided into two classes.

(1) We have a component-wise non-increasing function $g_0 : [0,1]^{s-\gamma+1} \rightarrow \mathbb{R}$, such that the distribution of $g_0(U_1, \ldots, U_{s-\gamma+1})$ is known with continuous cdf $F_{g_0}$.
We then define the \( p \)-value \( g(p_1, \ldots, p_{s-\gamma +1}) = 1 - F_{g_0}(g_0(p_1, \ldots, p_{s-\gamma +1})) \). Note, that it holds \( g(U_1, \ldots, U_{s-\gamma +1}) \sim \text{Uni}[0, 1] \) by the principle of probability integral transform.

(2) For a component-wise non-decreasing function \( g_0 : [0, 1]^{s-\gamma + 1} \rightarrow \mathbb{R} \) we consider \( g_0(p_1, \ldots, p_{s-\gamma +1}) \) and find a constant \( c \in \mathbb{R} \) such that \( \text{Uni}[0, 1] \leq c \cdot g_0(U_1, \ldots, U_{s-\gamma +1}) \). We then define the \( p \)-value \( g(p_1, \ldots, p_{s-\gamma +1}) = c \cdot g_0(p_1, \ldots, p_{s-\gamma +1}) \).

In the following, we take some well-known \( p \)-value combination functions \( g \) for \( H^1_{s-\gamma +1} \) from previous literature. First we consider the Fisher and the Stouffer combination. The combined \( p \)-value by Fisher for \( H^1_{s-\gamma +1} \) applied to \( p(\gamma), \ldots, p(s) \) is defined as

\[
g(p(\gamma), \ldots, p(s)) = 1 - F_{\chi^2_{s-\gamma +1}} \left( -2 \sum_{i=\gamma}^s \log (p(i)) \right),
\]

where \( F_{\chi^2_{s-\gamma +1}} \) is the cdf of the \( \chi^2 \)-distribution with \( 2(s-\gamma + 1) \) degrees of freedom (cf. [23, Section 21.1]). This combination function uses the fact that \( f_0(U_1, \ldots, U_{s-\gamma +1}) = -2 \sum_{i=1}^{s-\gamma +1} \log(U_i) \) is chi-square distributed with \( 2(s-\gamma + 1) \) degrees of freedom.

The combined \( p \)-value by Stouffer for \( H^1_{s-\gamma +1} \) applied to \( p(\gamma), \ldots, p(s) \) is defined as

\[
g(p(\gamma), \ldots, p(s)) = 1 - \Phi \left( \frac{1}{\sqrt{s-\gamma + 1}} \sum_{i=\gamma}^s \Phi^{-1}(1 - p(i)) \right),
\]

where \( \Phi \) is the cdf of the standard normal distribution on \( \mathbb{R} \) (cf. [24, Footnote 14 in Section V of Chapter 4]). This combination function uses the fact that \( g(U_1, \ldots, U_{s-\gamma +1}) = (s-\gamma + 1)^{-1/2} \sum_{i=1}^{s-\gamma +1} \Phi^{-1}(1 - U_i) \) is standard normally distributed. Both combined \( p \)-values require the \( p \)-values \( p_1, \ldots, p_s \) to be stochastically independent.

The next two combined \( p \)-values evaluate only the smallest \( p \)-value. The combined \( p \)-value using the minimum is defined by

\[
g(p(\gamma), \ldots, p(s)) = F_{\text{Beta}(1,s-\gamma +1)} \left( p(\gamma) \right),
\]

where \( F_{\text{Beta}(1,s-\gamma +1)} \) is the cdf of the Beta-distribution with parameters 1 and \( s-\gamma + 1 \). It requires that the \( p \)-values are stochastically independent, and is motivated by the fact that \( g(U_1, \ldots, U_{s-\gamma +1}) = \min\{U_1, \ldots, U_{s-\gamma +1}\} \) is Beta\((1,s-\gamma +1)\)-distributed. The Bonferroni method, which utilizes the Bonferroni inequality, leads to

\[
g(p(\gamma), \ldots, p(s)) = (s-\gamma + 1)p(\gamma).
\]

It also evaluates the minimum but does not require independent \( p \)-values.

Some further \( p \)-value combination functions that we consider make use of so-called \( e \)-values (see [25,26]). Their relation to \( p \)-values is roughly inverse, where higher \( e \)-values entail stronger evidence against the null. In our simulations in Section 4, we calculate a Bayes factor \( e_j \) for each null hypothesis \( H_j, j = 1, \ldots, s \). These are in some cases \( e \)-values, i.e. random variables with expected values not greater than one under \( H_j \). More details on this problem are provided in Section 4.4 and in Appendix A.1 of [3].
Analogously to the problem of $p$-values, we define a combination function $h$ for $H^\gamma_s$ by

$$h(e_1, \ldots, e_s) = h_0(e_{(1)}, \ldots, e_{(s-\gamma+1)}),$$

where $h_0$ is a valid combination function for $H^{1}_{s-\gamma+1}$, i.e. $h_0(e_1, \ldots, e_{s-\gamma+1})$ is a valid $e$-value for $H^{1}_{s-\gamma+1} = \bigcap_{i=1}^{s-\gamma+1} H_i$ if $e_1, \ldots, e_{s-\gamma+1}$ are valid $e$-values for $H_1, \ldots, H_{s-\gamma+1}$, respectively. We explain in the appendix why $h$ is a valid combination function for $H^\gamma_s$.

Finally, to compare the $e$-value approaches to the ones utilizing $p$-values, we transform the $e$-value $h(e_1, \ldots, e_s)$ to a $p$-value, $\max\{h(e_1, \ldots, e_s)^{-1}, 1\}$, for $H^\gamma_s$ (where $0^{-1} = 1$ and $\infty^{-1} = 0$).

Some examples of $e$-value combination functions $h_0$ for $H^{1}_{s-\gamma+1}$ include the arithmetic mean given by

$$h_0(e_1, \ldots, e_{s-\gamma+1}) = \frac{1}{s-\gamma+1} \sum_{i=1}^{s-\gamma+1} e_i,$$

and the product given by

$$h_0(e_1, \ldots, e_{s-\gamma+1}) = \prod_{i=1}^{s-\gamma+1} e_i,$$

cf. [26]. Some reasoning on why we chose these functions for $h_0$ is given in Propositions 3.1 and 4.2 in [3].

4. Simulations

In this section, we compare the $p$-values for $H^\gamma_s$ from Section 3 in simulations. The marginal $p$-values $p_1, \ldots, p_s$ in our simulations are given by two different models.

4.1. Models for $p$-value generation

We consider Beta-distributed $p$-values, which have also been used for example in [16]. For a parameter value $\theta \in \Theta = \mathbb{R}^s$, we define the density function $f_{\theta_i}$ of the $i$th $p$-value as

$$\begin{cases} f_{\theta_i} \sim \text{Beta} \left(1 - \theta_i, 1\right), & \theta_i \leq 0, \\ f_{\theta_i} \sim \text{Beta} \left(1, 1 + \theta_i\right), & \theta_i > 0, \end{cases}$$

where $\text{Beta}(\alpha, \beta)$ denotes the Beta distribution with parameters $\alpha$ and $\beta$.

As the second model, we consider the Normal-Model, where the $p$-values result from a Gaussian shift model with known variance $\sigma^2 > 0$. Here, we define the density function of the $i$th $p$-value as

$$f_{\theta_i}(t) = \frac{\varphi_{(\theta_i, \sigma^2)} \left( \Phi^{-1}_{(0, \sigma^2)} \left( 1 - t \right) \right)}{\varphi_{(0, \sigma^2)} \left( \Phi^{-1}_{(0, \sigma^2)} \left( 1 - t \right) \right)}, \quad t \in [0, 1],$$

where $\varphi_{(\mu, \sigma^2)}$ is the density function, and $\Phi^{-1}_{(\mu, \sigma^2)}$ the quantile function of the normal distribution with expected value $\mu$ and variance $\sigma^2$. 
Table 1. The evidence patterns with uniformly distributed \( p \)-values under nulls.

| Pattern | \( \mu^b_1 \) | \( \mu^b_2 \) | \( \mu^b_3 \) | \( \mu^b_4 \) | \( \mu^b_5 \) | \( \mu^b_6 \) | \( \sum_i (\mu^b_i)^2 \) |
|---------|----------------|----------------|----------------|----------------|----------------|----------------|------------------|
| 1       | 0              | 0              | 0              | 0              | 1              | 5              | 26               |
| 2       | 0              | 0              | 0              | 0              | 3              | 3              | 18               |
| 3       | 0              | 0              | 0              | 0              | 1              | 1              | 18               |
| 4       | 0              | 0              | 0              | 0              | 2              | 2              | 12               |
| 5       | 0              | 0              | 0              | 0              | 1              | 1              | 12               |
| 6       | 0              | 0              | 1.5            | 1.5            | 1.5            | 4              | 17               |
| 7       | 0              | 0.5            | 0.5            | 0.5            | 0.5            | 4              | 17               |
| 8       | 0              | 1              | 1              | 1              | 1              | 2              | 8                |
| 9       | 0              | 1.2            | 1.2            | 1.2            | 1.2            | 1.2            | 12               |
| 10      | 0.2            | 0.2            | 0.2            | 0.2            | 0.2            | 5              | 25.2             |
| 11      | 0.5            | 0.5            | 0.5            | 0.5            | 0.5            | 2              | 9                |
| 12      | 0.5            | 0.5            | 1.25           | 1.25           | 1.25           | 1.25           | 1.25             | 6.75             |
| 13      | 1              | 1              | 1              | 1              | 1              | 1              | 6                |


Lemma 4.1: Both models satisfy Assumptions (A1) – (A3) from Section 2.

Proof: Assumption (A1) is clear. Regarding assumption (A2), the Beta-distribution Beta(1,1) with parameters \( \alpha = \beta = 1 \) is the Uni[0,1] distribution, and therefore \( f_0 = 1_{[0,1]}(t) \). Analogously this is also the case for the Normal-Model.

For assumption (A3), we analyse the cdf of the \( i \)th \( p \)-value. In the Beta-Model, if \( \theta_i \leq 0 \), the \( p \)-value \( p_i(X) \) is Beta\((1 - \theta_i, 1)\)-distributed with cdf \( F_{\theta_i}(t) = t^{\theta_i+1} 1_{[0,1]}(t) + 1_{(1,\infty)}(t) \), which is decreasing in \( \theta_i \) for each fixed \( t \). If \( \theta_i > 0 \), the cdf of \( p_i(X) \) is \( F_{\theta_i}(t) = (1 - (1 - t)^{\theta_i+1}) 1_{[0,1]}(t) + 1_{(1,\infty)}(t) \), which is increasing in \( \theta_i \) for each fixed \( t \). Thus assumption (A3) is fulfilled in the Beta-Model.

In the Normal-Model, we refer to Remark 2.1, where the test statistic \( T_i(X) \) is normally distributed with expected value \( \theta_i \) and (known) variance \( \sigma^2 \).

This concludes the proof of Lemma 4.1. ■

In our simulations below, we draw the true parameter value \( \theta_i \) uniformly from intervals \([\theta_i^b, 0]\) and \((0, \theta_i^b]\) if \( \theta_i^b \leq 0 \) or \( \theta_i^b > 0 \), respectively. Similarly to [16], we write \( \theta_i^b = r \mu_i^b \), \( r > 0 \), \( i = 1, \ldots, s \). Holding each \( \mu_i^b \) constant, we can vary the potential ‘signal strength’ of each \( p \)-value with \( r \), i.e. with increasing \( r \) the \( i \)th \( p \)-value \( p_i \) gets stochastically larger / more conservative under \( H_i \) (assuming \( \mu_i^b \neq 0 \)) and stochastically smaller under \( K_i \) under \( \theta_i^b \).

Table 1 summarizes the different patterns \((\mu_1^b, \ldots, \mu_s^b)^T\) that we use in our simulations, cf. also Table 3 in [16]. We set the number of studies to \( s = 6 \). The patterns are first ordered in their amount of false null hypotheses, i.e. the amount of indices \( i \) with \( \mu_i^b > 0 \). Patterns with the same amount of false null hypotheses are then ordered decreasingly in their order of dispersion \( \sum_i (\mu_i^b)^2 \). Furthermore, we denote by pattern \( j \) the conservative version of pattern \( j \), where we replace each \( \mu_i^b = 0 \) by \( \mu_i^b = -2 \). Patterns 10–13 have no conservative versions.

4.2. Calculation of Bayes factors

We calculate the marginal Bayes factors for the two approaches that utilize \( e \)-value combinations under the same models as in Section 4.1. For this, we need to make some assumptions about the prior distributions of the parameter values under the null hypotheses and under the alternatives.
We assume that it is known beforehand whether the marginal null hypotheses $H_j$, $j = 1, \ldots, s$, are simple (Patterns 1–13) or composite (Patterns 1c–9c). In both cases, we calculate the Bayes factors under the assumption that all parameter values $\theta = (\theta_1, \ldots, \theta_s)^T \in K_i$ are such that the $i$th component $\theta_i$ is drawn uniformly from the interval $(0, 5r]$. Under simple null hypotheses, the resulting Bayes factors are $e$-values, i.e. they have expected values not larger than one, cf. [3]. Under composite null hypotheses, we calculate the Bayes factors under the assumption that $\theta_i$ is uniformly distributed on $[-3r, 0]$ if $\theta \in H_i$. The numbers 5 and $-3$ were chosen such that the true underlying parameter values $\theta_i$ drawn from any of the patterns in Table 1 are included in $(0, 5r]$ or $[-3r, 0]$. 

In the latter case, the resulting Bayes factors are not valid $e$-values for the marginal null hypotheses, i.e. their expected value is larger than one for some parameters under the null. More specifically, the $i$th Bayes factor has an increasing expected value under increasing $\theta_i \in [-3r, 0]$. Therefore, under all parameters $\theta \in H_i$, it has its largest expected value when $\theta_i = 0$. See Appendix for a proof of this. To create valid $e$-values we therefore divide the Bayes factors in Patterns 1c–9c by this expected value. Note that computing this constant requires no extra information beyond the information necessary for calculating the Bayes factors.

### 4.3. Power simulations

The power of a $p$-value $p$ under a parameter value $\theta$ in the alternative given a significance level $\alpha \in (0, 1)$ is defined as $\mathbb{P}_\theta(p \leq \alpha)$. Under various parameter settings, where $H_i^\gamma$ is false, we approximate the relative power (relative to the best performing one in each setting, where we set the significance level to $\alpha = 0.05$) of each $p$-value combination via a Monte-Carlo simulation with 100,000 repetitions.

First, we look at the different evidence structures in Table 1. For a pattern where $H_i^\gamma$ is false, the evidence for its rejection can be focused in few false $p$-values or it can be more evenly spread between the false $p$-values, compare for example Pattern 3 versus Pattern 4. Furthermore, we want to investigate how the choice of $\gamma$ affects the performance of the $p$-value combination functions for different types of evidence structures.

#### 4.3.1. Evidence structures

For the sake of clearness of the graphical displays, we decided to only display the simulation results for the Stouffer, Fisher and minimum $p$-value as well as the product of the $e$-values (called $e$-product). The harmonic mean and the arithmetic mean of the $e$-values (not displayed) performed badly to mediocly throughout.

Figures 1 and 2 have been derived under the Beta-Model of generating the marginal $p$-values. We set $\gamma = 2$ and the significance strengths to $r = 1$ and 5 in Figures 1 and 2, respectively. In Figures 3 and 4, we generated the marginal $p$-values according to the Normal-Model with $\sigma = 1/\sqrt{50}$. We set $\gamma = 2$ and the significance strengths in the figures to $r = 0.5\sigma, 1.5\sigma$, respectively.

At first, we summarize the observations of the two figures with lower signal strength $r$, Figures 1 and 3. If the null $p$-values are Uni[0,1], the Stouffer $p$-value has the highest power to reject $H_2^c$ if the evidence is more focused (lower pattern number). If the evidence is more spread out the $e$-product has the highest power. The power of the Fisher $p$-value is slightly below that of the Stouffer $p$-value and the minimum $p$-value performs badly.
If the null $p$-values are conservative in Figures 1 and 3, the minimum $p$-value performs best if the evidence is focused. If the evidence is more spread out, both the Stouffer and, to a lesser extent, the Fisher $p$-value have the highest power. The $e$-product performs badly in this case.

In Figures 2 and 4, we used a higher signal strength $r$. If the null hypotheses are simple and the evidence is focused, the Stouffer $p$-value has the highest power under the Beta-Model. If the evidence is more spread out the $e$-product has the highest power. Under the Normal-Model the minimum $p$-value and the Fisher $p$-value are most powerful if the evidence is focused and the Stouffer $p$-value if the evidence is less focused. The $e$-product is most powerful if the evidence is spread out.
Figure 3. Relative power of the combined $p$-values under the Normal Model with $\gamma = 2$ and $r = 0.5\sigma$: (a) Under uniform patterns and (b) Under conservative patterns.

Figure 4. Relative power of the combined $p$-values under the Normal Model with $\gamma = 2$ and $r = 1.5\sigma$: (a) Under uniform patterns and (b) Under conservative patterns.

If the null $p$-values are conservative in Figures 2 and 4, the minimum $p$-value has the highest power in the first patterns. The Stouffer has highest power under the Beta-Model and the Fisher $p$-value has highest power under the Normal-Model in the latter half of the patterns. The $e$-product performs badly throughout all the patterns.

To summarize, the $e$-product works best if we consider the non-conservative versions of the patterns, especially if the null $p$-values are uniformly distributed and the evidence is spread. If the null $p$-values are uniformly distributed and the evidence is focused the Stouffer $p$-value has the highest power. In the conservative patterns, the minimum $p$-value works best for lower pattern numbers. For the higher pattern numbers the Stouffer $p$-value works well if the signal strength is lower, and the Fisher $p$-value works well if the signal strength is higher. The results between the two $p$-value generating models are mostly similar.
4.3.2. The parameter $\gamma$

In this section, we investigate the influence of $\gamma$ on the relative performances of the $p$-value combination functions. More specifically, we chose Patterns 7 and 7c, in which five of the null hypotheses are false, and thus $H_\gamma$ is false for $\gamma = 1, \ldots, 5$. Again, we look at the relative powers of the $p$-value combination functions, relative to the best performing combination function in each setting.

In Figure 5, we employed the Beta-Model. The $p$-value obtained from the $e$-product has the highest power throughout all values of $\gamma = 1, \ldots, 5$ in Pattern 7. With increasing $\gamma$, the power of the other combined $p$-values fall off faster than the power of the $e$-product. Under Pattern 7c, the Fisher and the Stouffer $p$-value have the highest power, the former if $\gamma = 1, 2, 3$ and the latter if $\gamma = 4, 5$. The $e$-value approach, which is adjusted in this case, performs much worse.

In Figure 6, we used the Normal-Model. The $p$-values are close in power for $\gamma = 1$, their power is essentially 1 in absolute values. For $\gamma > 1$ in Pattern 7, the power of all the $p$-values fall relative to the power of the Stouffer $p$-value. The Fisher $p$-value performs relatively well and its power only falls off after $\gamma = 3$. In Pattern 7c, the Fisher $p$-value has the highest power if $\gamma$ is between 2 and 4. For $\gamma = 5$, the minimum $p$-value has the highest power.

While the results under the Beta-Model suggest the superiority of the approach using $e$-values in Pattern 7, the results under the Normal-Model are more diverse. In both models, the Fisher $p$-value has higher power than the Stouffer $p$-value if the null $p$-values are conservative, and vice versa if the null $p$-values are uniformly distributed. Furthermore, the minimum $p$-value works (relatively) well if $\gamma$ is large, especially if $\gamma$ is the true number of false null hypotheses, which is five in Patterns 7 and 7c.

We illustrate this with a short example under the assumption that $H_\gamma$ is false, that is, at least $\gamma$ of the null hypotheses $H_1, \ldots, H_s$ are false. In terms of power, the worst case scenario for a monotonic combination function occurs if the $p$-values are as large as possible, which is the case if $\gamma$ null hypotheses are false with corresponding $p$-values that are
uniformly distributed, and \( s - \gamma \) true null hypotheses with corresponding \( p \)-values that are almost surely 1. Note that the distribution of false \( p \)-values is lower bounded by \( \text{Uni}[0,1] \) due to Assumption (A3). Under this worst case scenario, the ordered, marginal \( p \)-values are \( U(1), \ldots, U(\gamma), 1, \ldots, 1 \), therefore the \( s - \gamma + 1 \) largest \( p \)-values are \( U(\gamma), 1, \ldots, 1 \). Thus, testing for \( H_\gamma^Y \), the minimum \( p \)-value only directly evaluates \( U(\gamma) \), while averaging methods for instance by Fisher and Stouffer evaluate \( U(\gamma), 1, \ldots, 1 \), in this extreme case. Testing for \( H_{\gamma-1}^Y \) (which is also false if \( H_{\gamma}^Y \) is false), the minimum \( p \)-value evaluates \( U(\gamma-1) \) whereas Fisher and Stouffer now consider \( U(\gamma-1), U(\gamma), 1, \ldots, 1 \). The ratio of non-one to one \( p \)-values increases with decreasing \( \gamma \), which favours averaging methods more than the minimum \( p \)-value.

4.4. Null \( p \)-value simulations

In the previous simulations, we only considered the case of false null hypotheses \( H_\gamma^Y \). In this section, we investigate the behaviour of the \( p \)-value combination functions under the null hypothesis \( H_s^\gamma \).

Each of the presented \( p \)-value combination functions in Section 3 is valid for the null hypothesis \( H_s^\gamma \), i.e. they are stochastically at least as large as \( \text{Uni}[0,1] \). Conservative \( p \)-values are common under composite null hypotheses, where the \( p \)-value is only calibrated with respect to the LFC parameter under the null. While still maintaining the type I error control, conservative null \( p \)-values can be problematic in several multiple testing setups that require uniformly distributed null \( p \)-values.

In simulations, we approximate the cdf \( F_\theta(\alpha) \) at point \( \alpha \) of the combined \( p \)-values for \( H_s^\gamma \) under different parameter values \( \theta \) for which the null hypothesis \( H_s^\gamma \) holds. If \( \alpha \) is the significance level, the value \( F_\theta(\alpha) \) for such \( \theta \) is the probability of a false rejection of \( H_s^\gamma \). Since we only consider valid \( p \)-values, it holds \( F_\theta(\alpha) = \alpha \) if the \( p \)-value is \( \text{Uni}[0,1] \)-distributed and \( F_\theta(\alpha) \leq \alpha \) if the \( p \)-value is conservative. It is of interest that
Figure 7. The $p$-values are generated under the Beta-Model. The graphs display the approximations of the cdf at $\alpha$, relative to the (average) maximum estimation in the respective simulation, of the $p$-value combination functions testing the null hypothesis $H_2^\alpha$, via Monte Carlo simulation with 100,000 repetitions. The signal strength $r$ is 5. We replace 0 by $-1$ if conservative, the number of times we do this varies on the horizontal axis. (a) The underlying pattern is $(\mu_{b1}, \ldots, \mu_{bs})^T = (0, \ldots, 0)^T$ and (b) the underlying pattern is $(\mu_{b1}, \ldots, \mu_{bs})^T = (2, 0, \ldots, 0)^T$.

$F_\theta(\alpha)$ is as close to $\alpha$ as possible. One example is the problem of estimating the proportion $\pi_0$ of true null hypotheses in a multiple testing setup with the Schweder–Spjøtvoll estimator $\hat{\pi}_0(\alpha)$, cf. [27]. The estimator $\hat{\pi}_0(\alpha)$ utilizes the marginal $p$-values, and its bias $E_\theta[\hat{\pi}_0(\alpha)] - \pi_0 \geq 0$ increases with decreasing $F_\theta(\alpha)$ for any of the marginal $p$-values, cf. [19]. The choice $\lambda = \alpha$ in the Schweder–Spjøtvoll estimator $\hat{\pi}_0(\lambda)$ was proposed in [28]. For arbitrary parameter values $\lambda \in [0, 1]$ in the Schweder–Spjøtvoll estimator we have to look at the entire cdf $F_\theta$. If the $p$-value is Unif$[0, 1]$-distributed, its cdf is a straight line between $(0, 0)$ and $(1, 1)$, and more conservative $p$-values have a cdf below that line. For selected parameter values $\theta$, we approximate the cdf of some of the $p$-values.

Figures 7 and 8 plot the empirical cumulative distribution functions (ecdfs) of the $p$-value combinations at point $\alpha$, relative to the largest one in each setting, generated by a Monte-Carlo simulation with 100,000 repetitions, where we test for the rejection of $H_2^\alpha$, i.e. that at least two null hypotheses are false. We use $(\mu_{b1}^b, \ldots, \mu_{bs}^b)^T = (0, \ldots, 0)^T$ on the left and $(\mu_{b1}^b, \ldots, \mu_{bs}^b)^T = (2, 0, \ldots, 0)^T$ on the right graphs. Furthermore, we replace 0 by $-1$ in $(\mu_{b1}^b, \ldots, \mu_{bs}^b)^T$ if the respective null is conservative. The number of times we do this is indicated on the horizontal axis.

In Figure 7, we used the Beta-Model and in Figure 8 we used the Normal-Model. The results are similar. The Stouffer $p$-value has the highest ecdf at $\alpha$ if the number of conservative nulls is low (below 2 or 3), the minimum $p$-value has the highest ecdf at $\alpha$ if that number is higher. The Fisher $p$-value has mediocre performances and comes closer to the best $p$-values on the right graphs. The $e$-product has the lowest ecdf values at $\alpha$.

In Figure 9, we display the ecdfs of the Stouffer, the Fisher and the minimum $p$-value in the cases of 1 and 4 conservative null $p$-values under the Beta-Model like in the right plot of Figure 7. The values for $(\mu_{b1}^b, \ldots, \mu_{bs}^b)^T$ are provided in the figure captions, $r$ is 5. First, we
Figure 8. The \( p \)-values are generated under the Normal-Model with standard deviation \( \sigma = 1/\sqrt{50} \). The graphs display the approximations of the cdf at \( \alpha \), relative to the (average) maximum estimation in the respective simulation, of the \( p \)-value combination functions testing the null hypothesis \( H_0 \) via Monte Carlo simulation with 100,000 repetitions. The signal strength \( r \) is 1.5\( \sigma \). We replace 0 by \(-1\) if conservative, then the number of times we do this varies on the horizontal axis. (a) The underlying pattern is \( (\mu_1^b, \ldots, \mu_s^b)^T = (0, \ldots, 0)^T \sigma \) and (b) the underlying pattern is \( (\mu_1^b, \ldots, \mu_s^b)^T = (2, 0, \ldots, 0)^T \sigma \).

Figure 9. The ecdfs from a Monte-Carlo simulation with 10,000 repetitions of the Fisher, Stouffer and minimum \( p \)-values in \( H_6^2 \). The marginal \( p \)-values have been generated under the Beta-Model with signal strength \( r = 5 \). (a) The underlying pattern is \( (\mu_1^b, \ldots, \mu_6^b)^T = (2, -1, 0, \ldots, 0)^T \) and (b) the underlying pattern is \( (\mu_1^b, \ldots, \mu_6^b)^T = (2, -1, \ldots, -1, 0)^T \).

notice that the ecdfs are closer to the identity line on the left plot than they are on the right. On the left plot, the ecdfs are close to each other, whereas on the right one the ecdf of the minimum \( p \)-value is noticeably closer to the identity line compared to the other two ecdfs. Another difference is that the ecdfs are not ordered consistently at each point \( t \in [0, 1] \) on the left plot, which implies that the corresponding \( p \)-values are not stochastically ordered. On the right plot, however, the ecdf of the minimum \( p \)-value seems to be the largest at each
point \( t \in [0, 1] \), and therefore the minimum \( p \)-value is stochastically closest to \( \text{Uni}[0, 1] \) in this more conservative setting.

### 4.5. Utilizing permutations

In case that the marginal null distributions, which are necessary to calculate the marginal \( p \)-values, are unknown or uncertain, one can instead consider nonparametric permutation testing methods. An added benefit of a non-parametric approach is that one potentially comes closer to the true null distribution than with a parametric approach that typically evaluates the \( p \)-values at LFC parameters. In particular, the method of nonparametric combination (NPC) of dependent permutation tests has been proposed in [10]; see also [12–15] and Chapter 4 in [11], among others. Here we briefly describe the NPC approach.

Let \( X_{1,i}, \ldots, X_{n_i,i} \) denote the random data of the studies \( i = 1, \ldots, s \). Under the null hypothesis \( H_i \), we assume that \( X_{1,i}, \ldots, X_{n_i,i} \) are exchangeable. Let the alternative hypothesis \( K_i \) be such that \( X_{1,i}, \ldots, X_{n_i,i} \) are not exchangeable, for example, the first \( n_{i,1} \) data points have a smaller expected value than the remaining \( n_{i,2} = n_i - n_{i,1} \) data points (two-sample means comparison). For cases in which the data cannot be assumed to be exchangeable under the null hypothesis (like in test problems of Behrens–Fisher-type, for example), we refer to [29] and references therein which deal with Studentized versions of permutation tests. Let \( T_i \) be a test statistic for the \( i \)th testing problem \( H_i \) vs. \( K_i \) such that \( T_i \) tends to larger values under the alternative \( K_i \). In our notation, the NPC algorithm is then given by Algorithm 4.2.

**Algorithm 4.2 (The NPC algorithm):**

1. Let \( x_{j,i}, \ i = 1, \ldots, s, \ j = 1, \ldots, n_i \) be the observed data, and \( T_i^{(0)} = T_i(x_{1,i}, \ldots, x_{n_i,i}) \) the observed test statistic, \( i = 1, \ldots, s \).
2. Let \( S_{n_i} \) denote the set of all possible permutations of \( \{1, \ldots, n_i\} \). For every \( \pi \in S_{n_i} \), calculate \( T_i(x_{\pi(1),i}, \ldots, x_{\pi(n_i),i}) \).
3. Determine the \( p \)-value \( p_i^{(0)} \) as the proportion
   \[
   p_i^{(0)} = \frac{|\{ \pi \in S_{n_i} : T_i(x_{\pi(1),i}, \ldots, x_{\pi(n_i),i}) \geq T_i^{(0)} \}|}{|S_{n_i}|},
   \]
   \( i = 1, \ldots, s \). Alternatively, one can approximate this proportion with a Monte-Carlo simulation.
4. Combine the \( p \)-values into a \( p \)-value for \( H_i^{\gamma} \) with one of the combination functions from Section 3, \( p^{(0)} = f(p_1^{(0)}, \ldots, p_s^{(0)}) \).
5. Generate an \((s \times B)\)-matrix \( M \) whose first \( s - \gamma + 1 \) rows are permutations of \(0, 1/B, \ldots, (B - 1)/B\), and the last \( \gamma - 1 \) rows are \((0, \ldots, 0)\).
6. Denote by \( p^{(j)} \) the combined \( p \)-value (using the same combination function \( f \)) resulting from the \( j \)th column in \( M, j = 1, \ldots, B \). Define the final \( p \)-value \( p \) as
   \[
   p = \frac{|\{ j \in \{1, \ldots, B\} : p^{(j)} \leq p^{(0)} \}|}{B}.
   \]

The \( p \)-value \( p^{(0)} \) from Step 4 is valid for \( H_i^{\gamma} \) already. However, it may be conservative even under LFC parameters in \( H_i^{\gamma} \). The \( p \)-value \( p \) that results after applying Steps 5 and 6 is valid for \( H_i^{\gamma} \) and (close to being) uniformly distributed under LFC parameters in \( H_i^{\gamma} \). Steps 5 and 6 are not necessary if the combination function \( f \) already provides...
uniformly distributed $p$-values under LFC parameters in $H_2^s$. For instance, this is the case if $f$ is the Fisher, Stouffer or the minimum combination function. Furthermore, if the exact cdf $F_0$ of $f(U_1, \ldots, U_{s-\gamma+1}, 0, \ldots, 0)$ is known, where $U_1, \ldots, U_{s-\gamma+1}$ are i.i.d. Uni[0,1]-distributed, one can skip Steps 5 and 6 and define $p = F_0(p^{(0)})$.

For the simulation part of this section, we employ the parameter patterns from Table 1. Again, we distinguish between the uniform versions and the conservative versions of the patterns, when there is at least one true null hypothesis.

We consider a two-sample means comparison model. Let $n_i = 20$ and $n_{i,1} = n_{i,2} = 10$ for all $i$. We assume that $X_{1,i}, \ldots, X_{n_i,i}$ are i.i.d. $N(0,1)$ and $X_{n_{i,1}+1,i}, \ldots, X_{n,i}$ are i.i.d. $N(\mu_{i}^b,1)$ distributed, where $\mu_{i}^b$ is from Table 1, $i = 1, \ldots, s$. We test $H_i = \{\mu_{i}^b \leq 0\}$ versus $K_i = \{\mu_{i}^b > 0\}$ and employ the NPC algorithm as described above, where $T_i(x_{1,i}, \ldots, x_{n,i}) = n_{i,2}^{-1} \sum_{j=n_{i,1}+1}^{n_i} x_{j,i} - n_{i,1}^{-1} \sum_{j=1}^{n_{i,1}} x_{j,i}$. Figures 10 and 11 display the relative powers of the Fisher, the Stouffer, the harmonic, the arithmetic and the minimum $p$-values for $H_2^s$, where the signal strength $r$ was chosen as 0.5 and 0.25, respectively.

The results are similar to our simulations from Section 4.3. However, the power of the harmonic mean and the arithmetic mean $p$-value increased considerably compared to before. Especially if the signal strength is low, the harmonic mean $p$-value dominates the other considered combination functions. The improvements of these two combination functions come from Steps 5 and 6 of Algorithm 4.2, because they were conservative even under LFC parameters in the simulations presented before.

5. Discussion

We compared a number of $p$-value combination functions for independent $p$-values and compared their power under the alternative hypothesis and their degree of conservativity under the null hypothesis when testing the partial conjunction hypothesis $H_2^s$. Among the
Figure 11. Relative power of some combination functions for $H_2^2$ when using the NPC algorithm on the model as described. Parameter patterns are taken from Table 1, and $r = 0.25$: (a) under uniform patterns and (b) under conservative patterns.

$p$-value combination functions that we considered in this paper, we can roughly distinguish between two classes. One are the $p$-values that rely on a weighted average of the $s - \gamma + 1$ largest $p$-values and one that only evaluates the $(s - \gamma + 1)$th largest $p$-value. They mainly differ in how they deal with spread out evidence versus focused evidence, and conservative versus uniformly distributed null $p$-values.

Among the considered $p$-value combination functions, the approaches that utilize Bayes factors as $e$-values, work best if the null hypotheses $H_1, \ldots, H_s$ are simple, and the Stouffer, the Fisher and the minimum $p$-values have the best results, if the null hypotheses are composite. The three latter $p$-values excel in different situations under the alternative and the null hypothesis. Under the alternative, the Stouffer $p$-value appears to have the highest power if the marginal $p$-values are uniformly distributed and the signal strength is low. The Fisher $p$-value works better than the other combination functions if the marginal null $p$-values are conservative and the evidence is spread out between several false null hypotheses. The minimum method works best if the evidence is focused on few false null hypotheses, especially when the null $p$-values are conservative. Under the null hypothesis $H_2^\gamma$, the Stouffer $p$-value is closest to uniformity if the marginal null $p$-values are Uni[0,1]-distributed. However, if there is at least one conservative null $p$-value, the minimum method works better than the other combination methods. The Fisher $p$-value is stochastically closer to Uni[0,1] than the Stouffer $p$-value if some of the marginal null $p$-values are conservative. One major difference between the Stouffer and the Fisher $p$-value is that the latter emphasizes the smallest $p$-values more and is thus less affected by conservative $p$-values, cf. [30], which coincides with our results. Furthermore, the NPC algorithm, in particular its Steps 5 and 6, can increase the power of certain combination methods. While our selection of combination functions for $H_2^\gamma$ is not exhaustive, the overall conclusion in this paper can be generalized to $p$-values that evaluate an average of all $p$-values versus $p$-values that place more weight on the smallest $p$-values.
Since this paper is concerned about replicability analyses, we limited our research to $p$-values from independent tests. It is interesting to see how the results differ, if the $p$-values are dependent. Methods that are designed for combining independent $p$-values, like the Fisher, Stouffer and minimum $p$-value, tend to fail to work properly if the marginal $p$-values are positively correlated, cf. [31]. Introducing weights can be helpful in this matter. Furthermore, we only consider two models for the generation of the marginal $p$-values. The Beta-Model was also used in [16] and our results are similar when $\gamma = 1$. The Normal-Model had similar results as well. In both models, the $p$-values have non-decreasing densities under the null hypothesis and non-increasing ones under the alternative. Deviation from this assumption is not considered here and is an attractive topic for future research.

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References
[1] Benjamini Y, Heller R. Screening for partial conjunction hypotheses. Biometrics. 2008;64(4): 1215–1222.
[2] Birnbaum A. Combining independent tests of significance. J Am Stat Assoc. 1954;49(267): 559–574.
[3] Vovk V, Wang R. Combining $p$-values via averaging. Biometrika. 2020;107(4):791–808.
[4] Rüschendorf L. Random variables with maximum sums. Adv Appl Probab. 1982;14(3):623–632.
[5] Wilson DJ. The harmonic mean $p$-value for combining dependent tests. Proc Natl Acad Sci USA. 2019;116(4):1195–1200. https://doi.org/10.1073/pnas.1814092116.
[6] Pearson ES. The probability integral transformation for testing goodness of fit and combining independent tests of significance. Biometrika. 1938;30(1/2):134–148.
[7] Westfall PH, Young SS. Resampling-based multiple testing: examples and methods for $p$-value adjustment. New York: Wiley; 1993. (Wiley Series in Probability and Mathematical Statistics. Applied Probability and Statistics).
[8] Meinshausen N, Maathuis MH, Bühlmann P. Asymptotic optimality of the Westfall–Young permutation procedure for multiple testing under dependence. Ann Stat. 2011;39(6):3369–3391. https://doi.org/10.1214/11-AOS946.

[9] Hemerik J, Goeman J. Exact testing with random permutations. Test. 2018;27(4):811–825. https://doi.org/10.1007/s11749-017-0571-1.

[10] Pesarin F. Multivariate permutation tests. Chichester: John Wiley & Sons, Ltd.; 2001. (With applications in biostatistics).

[11] Pesarin F, Salmaso L. Permutation tests for complex data: theory, applications and software. Chichester: John Wiley & Sons, Ltd.; 2020. (Wiley Series in Probability and Statistics).

[12] Giancristofaro RA, Bonnini S. Moment-based multivariate permutation tests for ordinal categorical data. J Nonparametr Stat. 2008;20(5):383–393. https://doi.org/10.1080/10485250802195440.

[13] Pesarin F, Salmaso L. Finite-sample consistency of combination-based permutation tests with application to repeated measures designs. J Nonparametr Stat. 2010;22(5–6):669–684. https://doi.org/10.1080/10485250902807407.

[14] Pesarin F, Salmaso L. A review and some new results on permutation testing for multivariate problems. Stat Comput. 2012;22(2):639–646. https://doi.org/10.1007/s11222-011-9261-0.

[15] Pesarin F, Salmaso L. On the weak consistency of permutation tests. Commun Stat Simul Comput. 2013;42(6):1368–1379.

[16] Loughin TM. A systematic comparison of methods for combining p-values from independent tests. Comput Stat Data Anal. 2004;47(3):467–485.

[17] Wilkinson B. A statistical consideration in psychological research. Psychol Bull. 1951;48(2):156.

[18] Hoang AT, Dickhaus T. On the usage of randomized p-values in the Schweder–Spjøtvoll estimator. Forthcoming Ann Inst Stat Math. 2021.

[19] Hoang AT, Dickhaus T. Randomized p-values for multiple testing and their application in replicability analysis. Biometr J. 2021. early view.

[20] Kocak M. Meta-analysis of univariate p-values. Commun Stat Simul Comput. 2017;46(2):1257–1265.

[21] Heard NA, Rubin-Delanchy P. Choosing between methods of combining-values. Biometrika. 2018;105(1):239–246.

[22] Shaked M, Shanthikumar JG. Stochastic orders. New York: Springer; 2007. (Springer Series in Statistics). https://doi.org/10.1007/978-0-387-34675-5.

[23] Fisher RA. Statistical methods for research workers. 5th ed., Edinburgh and London: Oliver and Boyd; 1934.

[24] Stouffer SA, Suchman EA, DeVinney LC, et al. The American soldier: adjustment during army life. Princeton: Princeton University Press; 1949. (Studies in social psychology in World War II; 1).

[25] Grünwald P, de Heide R, Koolen WM. Safe testing. Preprint 2019. Available from: [arxiv:1906.07801].

[26] Vovk V, Wang R. E-values: Calibration, combination, and applications. Ann Stat. 2021;49(3):1736–1754.

[27] Schweder T, Spjøtvoll E. Plots of p-values to evaluate many tests simultaneously. Biometrika. 1982;69(3):493–502.

[28] Blanchard G, Roquain E. Adaptive false discovery rate control under independence and dependence. J Mach Learn Res. 2009;10:2837–2871.

[29] Schildknecht K, Olek S, Dickhaus T. Simultaneous statistical inference for epigenetic data. PLOS One. 2015;10(5):e0125587.

[30] Owen AB, et al. Karl Pearsons meta-analysis revisited. Ann Stat. 2009;37(6B):3867–3892.

[31] Alves G, Yu YK. Accuracy evaluation of the unified p-value from combining correlated p-values. PLoS One. 2014;9(3):e91225.
Appendix. Some results regarding e-variables and Bayes factors in our models

The following lemma is analogous to Lemma 1 in [1], for e-variables instead of p-values.

**Lemma A.1:** Let $e_1, \ldots, e_s$ be valid e-variables for $H_1, \ldots, H_s$, respectively. If $h_0 : [0, \infty]^{s-\gamma+1} \rightarrow [0, \infty]$ is a valid, symmetric and monotonically non-decreasing e-variable combination function for $H_{s-\gamma+1}^1$, then

$$ h(e_1, \ldots, e_s) = h_0(e_{(1)}, \ldots, e_{(s-\gamma+1)}) $$

is a valid e-variable for $H_s^\gamma$.

**Proof:** We have to show that

$$ \mathbb{E}_\theta [h(e_1, \ldots, e_s)] \leq 1 $$

(A1)

holds for all $\theta \in H_s^\gamma$. We determine the parameters $\theta \in H_s^\gamma$ for which $\mathbb{E}_\theta [h(e_1, \ldots, e_s)]$ is largest and show that (A1) holds. Since $h_0$ is monotonically non-decreasing in all its arguments, so is $h$. Under $H_s^\gamma$, there at least $s - \gamma + 1$ of the null hypotheses $H_1, \ldots, H_s$ are true, the worst case for (A1) occurs, when exactly $s - \gamma + 1$ of the null hypotheses $H_1, \ldots, H_s$ are true, since e-variables are unbounded under alternatives. The $\gamma - 1$ e-variables that correspond to the false null hypotheses are as large as possible in the worst case, for simplicity they are $\infty$.

Without loss of generality, assume that the null hypotheses $H_1, \ldots, H_{s-\gamma+1}$ are the true ones. The ordered e-values

$$(e_{(1)}, \ldots, e_{(s)}) = (\tau(e_1, \ldots, e_{s-\gamma+1}), \infty, \ldots, \infty),$$

where $\tau$ is a permutation map, are such that the $s - \gamma + 1$ smallest e-variables correspond to the true null hypotheses. Therefore, in the worst case, the combination of these e-variables

$$ h(e_{(1)}, \ldots, e_{(s-\gamma+1)}, \infty, \ldots, \infty) = h_0(e_1, \ldots, e_{s-\gamma+1}) $$

has an expected value not greater than 1, according to the definition of $h_0$.

The next result helps us construct valid e-variables under composite null hypotheses. We assume that a p-value model as in Section 2 is given. Furthermore, we assume that for all $i$ the Lebesgue density $f_{0_i}$ of $p_i$ is monotonically decreasing if $\theta_i \leq 0$ and monotonically increasing if $\theta_i > 0$. This latter assumption is for example fulfilled under the conditions in Remark 2.1. To see this, we use Assumption (A2) and note that if the distributions $(p_i(X)^{(-\theta_i)})_{0_i}$ are likelihood ratio ordered, then $f_{0_i}(t)/f_{\bar{0}_i}(t)$ is non-decreasing in $t$, if $\theta_i \leq \bar{\theta}_i$.

Let $i$ be fixed. For given Bayes marginal probability distributions $P_0$ under $H_i$ and $P_1$ under $K_i$ for the parameter values, we define the Bayes factor as

$$ BF(p) := \frac{\int f_{0_i}(p) \, dP_1(\theta_i)}{\int f_{0_i}(p) \, dP_0(\theta_i)}. $$

(A2)

Its expected value under $\theta_i$ is

$$ \mathbb{E}_{\theta_i} [BF] = \int BF(p) f_{\theta_i}(p) \, dp, $$

which is required to not be larger than 1 under each $\theta_i \in H_i$ for BF to be a valid e-variable for $H_i$. The following result helps determine whether BF is an e-variable.

**Lemma A.2:** Under the assumptions from above and for the Bayes factor BF as in (A2), the expected value $\mathbb{E}_{\theta_i} [BF]$ of BF is non-decreasing in $\theta_i$.

**Proof:** With the assumptions we made, the Bayes factor BF($p$) is non-decreasing in $p$. Thus the expected value of (the distribution) $[BF(p_i(X))]^{(\theta_i)}$ decreases with stochastically increasing $p_i(X)^{(-\theta_i)}$ and therefore with decreasing $\theta_i$. 

$\blacksquare$
Both the Beta-Model and the Normal-Model fulfill the assumptions of the latter lemma. As a consequence, the Bayes factor BF has its largest expected value under $H_i$ if $\theta_i = 0$, regardless of the priors. Therefore, $BF/E_0[BF]$ is an $e$-variable for $H_i$ with expected value 1 under $\theta_i = 0$.

Under the same assumptions, it is also easy to see that the Bayes factor

$$BF_0(p) := \frac{\int f_{\theta_i}(p) \, dP_1(\theta_i)}{f_0(p)} = \int f_{\theta_i}(p) \, d\mathbb{P}_1(\theta_i)$$

that assumes a simple null hypothesis is an $e$-variable with expected value 1 under $\theta_i = 0$ even if $H_i$ is composite.