Reverse-Bayes Methods for Replication Studies

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Abstract

An important aspect of the credibility of scientific findings is their replicability – the ability that a similar finding can be obtained when the same study is repeated with new subjects. However, various failures to replicate major scientific findings in the social and life sciences indicate that replicability is often lower than expected. This "replication crisis" has led to several methodological reforms in the past decade, an increased conduct of replication studies being one of them. Despite this increase in replication studies, there is no consensus on a fundamental question: How should replication success be defined statistically?

Possible answers to this question are given in the first and largest part of this thesis. It consists of three extensions to a recently proposed reverse-Bayes method for quantifying replication success. The key idea of the method is to challenge the data from the original study with a sceptical prior distribution so that the resulting posterior distribution no longer indicates evidence for an effect. The goal of the replication study is then to show that the sceptical prior is unrealistic, and replication success is achieved if there is sufficient conflict between the prior and the replication data. The procedure can be summarized in a single quantitative measure, termed the sceptical p-value. The first extension recalibrates the sceptical p-value so that replication success takes effect size more appropriately into account. Specifically, the recalibration is chosen such that for original studies which were borderline significant, replication success can only be achieved if the effect estimate from the replication study is larger than the effect estimate from the original study. We find that the recalibrated sceptical p-value also has good frequentist properties comparable to the standard method used in practice. The second extension replaces tail probabilities with Bayes factors as measures of evidence. The procedure can again be summarized in a single measure called the sceptical Bayes factor. The sceptical Bayes factor has similar properties as the sceptical p-value but it avoids a statistical paradox which the sceptical p-value suffers from – in some situations the sceptical p-value may indicate replication success even though the effect estimate from the replication is arbitrarily smaller than the effect estimate from the original study. The third extension provides a framework for Bayesian design of replication studies which allows for combining data from the original study with external knowledge. This approach can lead to potentially more efficient designs compared to classical approaches, and it can be used for replication design based on both the sceptical p-value and the sceptical Bayes factor.

The second part of this thesis also deals with reverse-Bayes methods, but with a broader scope of applications than replication studies. The reverse-Bayes idea was first proposed in the 1950s, but it has mostly been forgotten. To increase awareness and show potential use cases, reverse-Bayes history and methods are summarized in a comprehensive review. The review includes also some new results on connections between reverse-Bayes methods and meta-analysis.

The last part of this thesis takes a meta-scientific perspective on methodological research. Questionable research practices, such as selective reporting of results, are often seen as main cause for replicability issues in the medical and social sciences. These practices can similarly harm methodological research, but are often not recognized. To raise awareness, an illustrative simulation study is conducted in which it is shown how a novel method can easily be presented as superior over established competitor methods if questionable research practices are employed. Finally, several recommendations are given to alleviate these issues.

Key words: Bayesian inference, meta-science, replication studies

Dedicated to my mother Christa.
You are deeply missed.

Thesis outline

Design and analysis of replication studies

Reverse-Bayes methodology

Preface

This thesis is submitted under the PhD program "Epidemiology and Biostatistics" at the University of Zurich for the degree of Doctor of Philosophy. The research contained in this thesis was conducted between October 2019 and December 2022. Financial support was provided by the Swiss National Science Foundation through the project "Reverse-Bayes design and analysis of replication studies" (project #189295) awarded to Leonhard Held.

First and foremost I want to thank my supervisor Leo for giving me the opportunity to do this PhD, for showing me an open-minded and pragmatic approach to statistics, and for giving me the freedom to explore and develop into an independent researcher. I also want to thank the other two members of my PhD committee, Guido and Reinhard, for always providing excellent advice and being great collaborators. Another thanks goes to Robert Matthews who also is a great collaborator and without whom this PhD project would never exist as it was him who resurrected the reverse-Bayes approach from the dead almost twenty years ago. Furthermore, I want to thank Eric-Jan Wagenmakers for giving me the opportunity to do a very interesting and productive six months research stay in Amsterdam.

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Zürich, December 2022

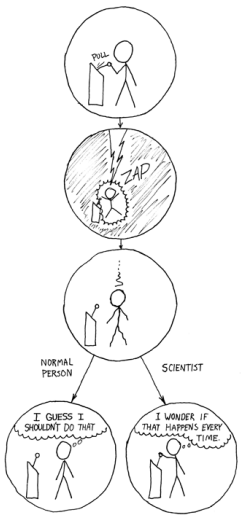
Samuel Pawel

Introduction

> "*Confirmation comes from repetition*. Any attempt to avoid this statement leads at least to failure and more probably to destruction."
>
> J.W. Tukey (1969, p. 84)

1 Replication studies

Being able to trust scientific findings is essential for making evidence-based decisions. But how can we know whether a scientific finding is trustworthy? For instance, how can we know whether the protective effect of a vaccine found in a study is indeed existent? One way to answer this question is through the use of *replication studies*.



Replication studies as illustrated by Randall Munroe (https://xkcd.com/242).

A replication study (or simply replication) involves repeating the original study as closely as possible but with new subjects. If the replication yields similar results to the original study, this increases our confidence in the original finding. However, if the replication study yields conflicting results, this lowers our confidence in the original finding. The concept of replicability has long been a central part of the scientific method. For instance, Fisher (1935, p. 13) noted "*no isolated experiment, however significant in itself, can suffice for the experimental demonstration of any natural phenomenon*". For this reason, "successful" replication is typically a requirement for acceptance of newly proposed scientific theories (e. g., a new physical model). Yet, replication studies are not only important for researchers, but also for decision makers and the

general population, as the implementation of policies based on scientific findings may also depend on whether these findings can be replicated. For instance, for a drug to be approved to the market, the United States food and drug administration requires "*at least two adequate and well-controlled studies, each convincing on its own, to establish effectiveness*" (FDA, 1998, p. 3). The results from replication studies may hence have real-world consequences. It is therefore important that the methodological aspects of replication studies, such as their statistical design and analysis, are well understood.

Despite their importance, the traditional academic system has made it unattractive for researchers to conduct replication studies as publications, citations, and grant money are typically easier to acquire by conducting novel research. This is because until recently, most scientific journals hardly published any replication studies since the emphasis was on "innovation" rather than on "repetition" (Makel et al., 2012; Martin and Clarke, 2017; Coiera and Tong, 2021). As a result, researchers often had no other choice than to focus their efforts on producing novel and eye-catching research results in order to build successful careers (Binswanger, 2013; Moher et al., 2018).

The perceived value of replication studies has changed over the past decade. Earlier criticisms of low research standards (Altman, 1994; Ioannidis, 2005) were backed up by empirical evidence. For instance, pharmaceutical companies reported surprisingly low replication rates from pre-clinical research (Begley and Ellis, 2012) followed by later studies estimating that billions are wasted each year on flawed and non-replicable research in medicine and the life sciences (Chalmers et al., 2014; Freedman et al., 2015; Glasziou and Chalmers, 2018). Similarly, reports of fraud (Wicherts, 2011) and questionable research practices (Wagenmakers et al., 2011; Simmons et al., 2011; John et al., 2012) sparked intense discussion about the need for better research standards in psychology and the social sciences. These discussions eventually led to large-scale replication projects conducted by huge researcher consortia in fields such as psychology (Open Science Collaboration, 2015; Klein et al., 2014, 2018; Protzko et al., 2020), economics (Camerer et al., 2016), the social sciences (Camerer et al., 2018), experimental philosophy (Cova et al., 2018), and cancer biology (Errington et al., 2021).

Most of these large-scale replication projects confirmed what many researchers had feared; carefully conducted replication studies often show less impressive results than their original counterparts, and the replicability of research findings is surprisingly low (how replicability can be defined precisely will soon be discussed in more detail). This realization led many to declare science as being in a "replication crisis". Debates arose about whether or not the crisis really existed and who or what was to blame (Gilbert et al., 2016; Amrhein et al., 2019b). Even the popular press became interested (e. g., Carey, 2015; Kovic, 2016; Achenbach and McGinley, 2017; Devlin, 2018), so that also in the eyes of the public the credibility of science became seriously threatened.

In the midst of this crisis, various reforms were implemented to prevent an escalation of the situation (for an overview see e. g., Munafò et al., 2017). For instance, some journals adopted the "registered report" format (Chambers and Tzavella, 2021) in which a study proposal is peer reviewed *before* the study is conducted, and which, if accepted, gives provisional publication acceptance regardless of the study outcome. Similarly, digital infrastructure platforms, such as Zenodo (`https://zenodo.org`) or the Open Science Framework (`https://osf.io`),

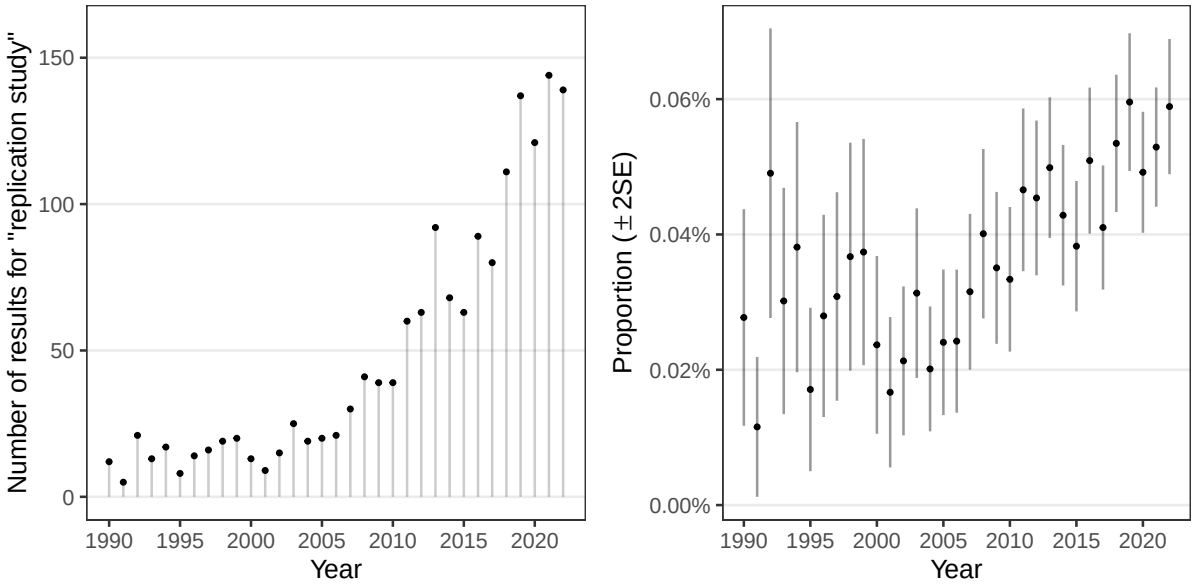


Figure 1: Yearly number of results for search term "replication study" on Web of Science (left), and number of results normalized by the number of results for the search term "study" (right). The search was conducted on 2 December 2022.

were created to facilitate pre-registration, preprints, code and data sharing, all of which have substantially increased over the last decade (Kidwell et al., 2016; Nosek et al., 2018; Rawlinson and Bloom, 2019). The practice of conducting replication studies has also gained popularity. Several academic journals and funders are now explicitly promoting replication research (NWO, 2016; NSF, 2018; Nature Communications, 2022). Figure 1 (left) illustrates this trend by the yearly number of results for the search term "replication study" obtained from the search engine Web of Science. The numbers have been rapidly growing, especially since the mid-2000s. This trend could possibly be explained by the fact that more research results are published each year but also when the numbers are normalized by the number of results for the search term "study", the increasing trend is still visible.

1.1 Statistical aspects of replication studies

Despite the increased interest in replication studies, the research community has not yet agreed on one important question: When is a replication study considered successful? For this reason, replication researchers typically report the results from different methods for assessing replication success. For example, the Open Science Collaboration (2015, p. 11) states "[t]here is no single standard for evaluating replication success. We evaluated [replicability] using significance and P values, effect sizes, subjective assessments of replication teams, and meta-analyses of effect sizes". In the following, I will give an overview about these and other methods which have been used in practice.

Most methods for analyzing replication studies can be formulated in terms of study-level

Table 1: Study-level summary statistics for an original and a replication study. The cumulative distribution function of the standard normal distribution is denoted by $\Phi(\cdot)$, and the $1-\alpha$ quantile of the standard normal distribution is denoted by $\Phi^{-1}(1-\alpha) = z_\alpha$. Confidence intervals and p-values for $H_0 : \theta = 0$ are based on the assumption that an effect estimate $\hat{\theta}_k$ is normally distributed around the unknown effect size θ with (known) variance equal to the squared standard error σ_k^2 for $k \in \{o, r\}$.

	Original study	Replication study
effect estimate	$\hat{\theta}_o$	$\hat{\theta}_r$
standard error	σ_o	σ_r
$(1-\alpha) \times 100\%$ confidence interval	$[\hat{\theta}_o - z_{\alpha/2}\sigma_o,\ \hat{\theta}_o + z_{\alpha/2}\sigma_o]$	$[\hat{\theta}_r - z_{\alpha/2}\sigma_r,\ \hat{\theta}_r + z_{\alpha/2}\sigma_r]$
z-value	$z_o = \hat{\theta}_o / \sigma_o$	$z_r = \hat{\theta}_r / \sigma_r$
p-value (two-sided)	$p_o = 2\{1 - \Phi(\lvert z_o \rvert)\}$	$p_r = 2\{1 - \Phi(\lvert z_r \rvert)\}$

summary statistics as shown in Table 1. All of these are routinely reported in research articles, and if one of them is missing they can typically be calculated from the others. Using summary statistics is also often the only possible way for conducting the replication success analysis as the raw data from the original study may not be available to the researchers conducting the replication study. The most important statistics are the effect estimates $\hat{\theta}_o$ and $\hat{\theta}_r$. They provide an estimate of the underlying effect size θ which quantifies the true effect or association of an intervention/exposure with an outcome variable. Typical effect sizes are mean differences and correlations (for continuous outcomes), odds ratios (for binary outcomes), or hazard ratios (for time-to-event outcomes). Depending on the type of effect size, a transformation might be required so that the assumption of approximately normally distributed effect estimates around the unknown effect size θ (for large enough sample sizes) is justified. This could be, for instance, the Fisher z-transformation for correlations or the log-transformation for odds/hazard ratios (Cooper et al., 2019, chapter 11). The associated standard errors σ_o and σ_r represent the statistical uncertainty of the estimates. Typically, the available standard errors are only estimates of the true standard errors. However, in most parts of this thesis it will be assumed that σ_o and σ_r correspond to the true standard errors. This is the same assumption as in ordinary fixed-effect/random-effects meta-analysis, and typically reasonable if the sample size of the studies is not too small. Under the assumption of (asymptotic) normality, confidence intervals for θ and p-values for testing the null hypothesis $H_0 \colon \theta = 0$ can be computed as shown in Table 1.

Table 2 lists commonly used criteria for replication success in terms of the summary statistics from Table 1. The most popular criterion is listed first and defines replication success by simultaneous statistical significance of original and replication study along with their effect estimates showing the same direction. This approach is also called the "two-trials rule" (Senn, 2008) in drug regulation or "vote-counting" in meta-analysis (Cooper et al., 2019). The criterion can similarly be defined through one-sided p-values, so that the original and replication effect estimate are not explicitly required to show the same direction as this is already taken into account by the one-sided p-values. Some replication projects (Open Science Collaboration, 2015; Errington et al., 2021) also defined replication success via simultaneous non-significance of original and replication study ($p_o > \alpha$ and $p_r > \alpha$). However, with this definition "replication success" can almost always be achieved by conducting original and replication study with

Table 2: Statistical criteria for assessing replication success which have been used in practice (Open Science Collaboration, 2015; Camerer et al., 2016, 2018; Cova et al., 2018; Errington et al., 2021).

Criterion type	Description
Significance	The original and replication p-values are smaller than a threshold α and their effect estimates show the same direction ($p_o < \alpha$, $p_r < \alpha$, and $\text{sign}(\hat{\theta}_o) = \text{sign}(\hat{\theta}_r)$). Usually $\alpha = 5\%$.
Meta-analytic significance	The meta-analytic p-value is smaller than a threshold α ($p_m = 2\{1 - \Phi(\lvert\hat{\theta}_m\rvert/\sigma_m)\} < \alpha$) where $\hat{\theta}_m = (\hat{\theta}_o/\sigma_o^2 + \hat{\theta}_r/\sigma_r^2)\sigma_m^2$ is the pooled effect estimate with standard error $\sigma_m = (1/\sigma_o^2 + 1/\sigma_r^2)^{-1/2}$. There are no established conventions regarding the level α.
Relative effect size	The effect estimate of the replication study goes in the same direction as the original one and is at least d_{min} times as large ($d = \hat{\theta}_r/\hat{\theta}_o \geq d_{\text{min}}$). Usually $d_{\text{min}} = 1$.
Confidence interval	The replication effect estimate is contained in the $(1-\alpha) \times 100\%$ original confidence interval ($\hat{\theta}_r \in [\hat{\theta}_o - z_{\alpha/2}\sigma_o, \hat{\theta}_o + z_{\alpha/2}\sigma_o]$). Sometimes, also defined as the original effect estimate is contained in the $(1-\alpha) \times 100\%$ replication confidence interval ($\hat{\theta}_o \in [\hat{\theta}_r - z_{\alpha/2}\sigma_r, \hat{\theta}_r + z_{\alpha/2}\sigma_r]$). Usually $\alpha = 5\%$.
Prediction interval (Q-test)	The replication effect estimate is contained in its $(1-\alpha) \times 100\%$ prediction interval ($\hat{\theta}_r \in [\hat{\theta}_o - z_{\alpha/2}\sqrt{(\sigma_o^2 + \sigma_r^2)}, \hat{\theta}_o + z_{\alpha/2}\sqrt{(\sigma_o^2 + \sigma_r^2)}]$). Usually $\alpha = 5\%$. This criterion is equivalent to $p_Q \geq \alpha$ where p_Q is the p-value from the meta-analytic Q-test $p_Q = 2\{1 - \Phi(\sqrt{Q})\}$ with Q-statistic $Q = \sum_{i \in \{o,r\}} (\hat{\theta}_i - \hat{\theta}_m)^2/\sigma_i^2 = (\hat{\theta}_o - \hat{\theta}_r)^2/(\sigma_o^2 + \sigma_r^2)$.

very few samples so that the p-values are large. The approach is also logically questionable as it could be seen as an instance of the "absence of evidence fallacy" (Altman and Bland, 1995) meaning the failure to find evidence against the null hypothesis is erroneously interpreted as evidence for the null hypothesis. Meta-analytic extensions of the significance approach define replication success by significance of a combined effect estimate. Typically, the assumption of a common underlying effect size is seen as reasonable so that fixed-effect meta-analysis is used for pooling. Random-effects meta-analysis has primarily been used if more than one replication study of the same original study are conducted since replicators are often interested in understanding between-replication heterogeneity (e. g., in Klein et al., 2018). In contrast to the ordinary significance criterion, it is less established which level α should be used for thresholding the meta-analytic p-value. Some replication projects have used the same level as for the significance approach (Open Science Collaboration, 2015; Camerer et al., 2016; Errington et al., 2021), whereas others have used a smaller level as the pooled estimate is based on

both data sets (e. g., $\alpha = 0.5\%$ in Camerer et al., 2018).

The remaining criteria in Table 2 put more emphasis on compatibility in effect size between the original and the replication study. For example, the relative effect estimate $d = \hat{\theta}_r / \hat{\theta}_o$ quantifies how much the magnitude of the replication effect estimate changed compared to the original, and the smaller d is the smaller the degree of replication success. Some projects also report a confidence interval for d (Camerer et al., 2016, 2018), whereas others ignore its uncertainty and make a binary cut at $d_{\text{min}} = 1$ to define replication success (Errington et al., 2021). The criteria based on confidence and prediction intervals define effect size compatibility on an absolute scale. However, the criterion based on the original confidence interval ignores the uncertainty from the replication, whereas the criterion based on the replication confidence interval ignores the uncertainty from the original study. The prediction interval criterion takes into account both sources of uncertainty (Patil et al., 2016). Yet, declaring "replication success" based on the prediction interval may be logically questionable due to its connection to the meta-analytic Q-test. That is, if the p-value from the Q-test is larger than α this is equivalent to the replication effect estimate $\hat{\theta}_r$ being contained in its $(1 - \alpha) \times 100\%$ prediction interval. The null hypothesis of this test is defined that the underlying effect sizes of original and replication study are the same ($H_0 \colon \theta_o = \theta_r$), so a rejection of this null hypothesis corresponds to demonstrating replication failure and not replication success. Interpreting a failure to reject the null hypothesis as evidence for it is again an instance of the "absence of evidence fallacy" (Hedges and Schauer, 2019). As in the case of defining replication success by simultaneous non-significance of original and replication study, the mismatch of the null hypothesis of the prediction interval criterion results in the undesirable property that "replication success" can almost always be achieved if the sample size of the studies is small enough, because the prediction interval becomes wider with larger standard errors.

Example "Reproducibility Project: Cancer Biology"

I will now illustrate the assessment of replication success on data from the "Reproducibility Project: Cancer Biology" (Errington et al., 2021). This large-scale project attempted to replicate 53 landmark studies from the field of cancer biology (and would perhaps better be named "Replication Project", see Goodman et al., 2016, for the distinction between "replicability" and "reproducibility"). In the end, only 23 of the 53 studies could be repeated due to various difficulties, such as, missing information from the original studies or problems in conducting the experiments. Errington et al. (2021) report that these experiments led to data on 158 quantitative effects. However, from the data which they provide only 132 quantitative effects are provided with original and replication standardized mean difference effect estimates along with standard errors, and only they will be used in the subsequent analyses.

Figure 2 shows the original versus the replication effect estimate (on standardized mean difference scale) with the color indicating whether the replication study was statistically significant at the 5% level (two-sided). As in most other replication projects, the majority of the replications show smaller effect estimates compared to their original counterparts (mean relative effect estimate $\bar{d} = 0.38$). Many of the replications also fail to achieve statistical significance at

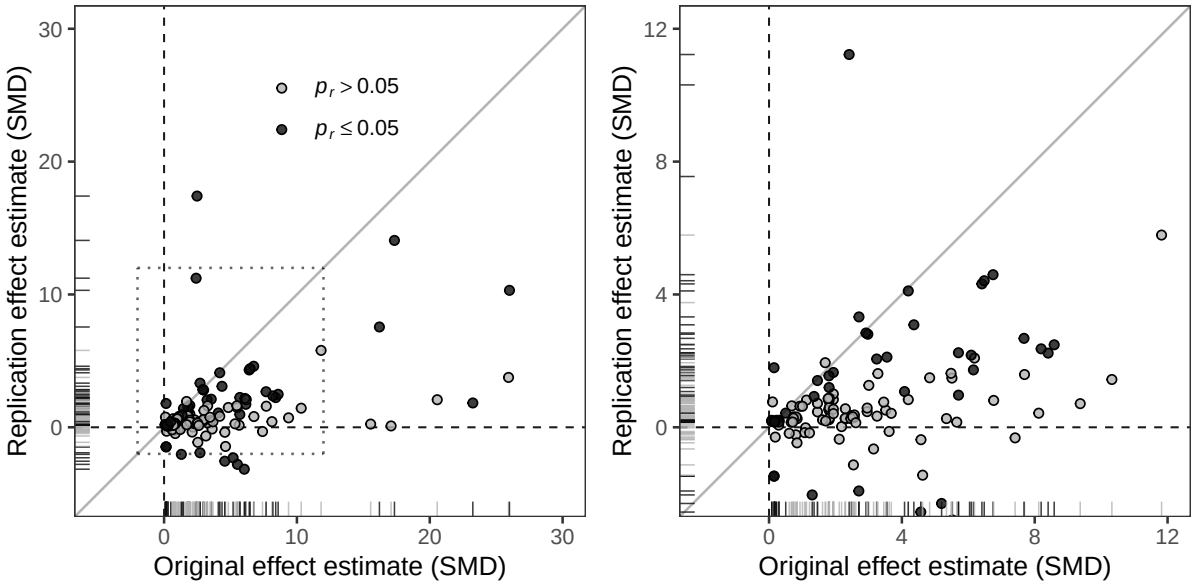


Figure 2: Results for 132 effects from the "Reproducibility Project: Cancer Biology" (Errington et al., 2021) for which effect estimates and standard errors are available on standardized mean difference (SMD) scale. The right plot shows a zoomed-in view of the dotted area in the left plot. The *p*-values are recomputed using a normal approximation. Two study pairs with original effect estimate larger than 80 are not shown.

the 5% level. Specifically, from the 94 effects which were significant in the original study only 32 were also significant in the replication study (in the same direction).

Figure 3 shows how many of the replications are successful according to the criteria from Table 2 (except the confidence interval criteria since they do not take into account the uncertainty from both studies). For the total 132 replications, most successes occur for the meta-analytic significance (83) and the prediction interval criteria (83), followed by significance (32), and relative effect size (9). However, looking at the combinations of the criteria, only in two replications are all criteria satisfied simultaneously (green).

A detailed view for a subset of the data from the project is given in Table 3. The subset is randomly chosen such that from every original study one effect and one replication of that effect is included. For the three replications at the bottom of the table (#18, #19, and #20), all criteria indicate replication failure. For the other replications, the conclusions are more ambiguous as in no single case are all criteria met simultaneously. For instance, the first three replications satisfy the significance criterion ($p_o < 0.05$ and $p_r < 0.05$), the meta analytic significance criterion ($p_m < 0.05$) and the Q-test/prediction interval criterion ($p_Q > 0.05$), yet the replication effect estimate is smaller than the original one so does not satisfy the relative effect size criterion ($d < 1$). The fourth replication, on the other hand, satisfies the relative effect size criterion ($d \geq 1$) but fails to satisfy the significance criterion as the original study was not significant ($p_o > 0.05$).

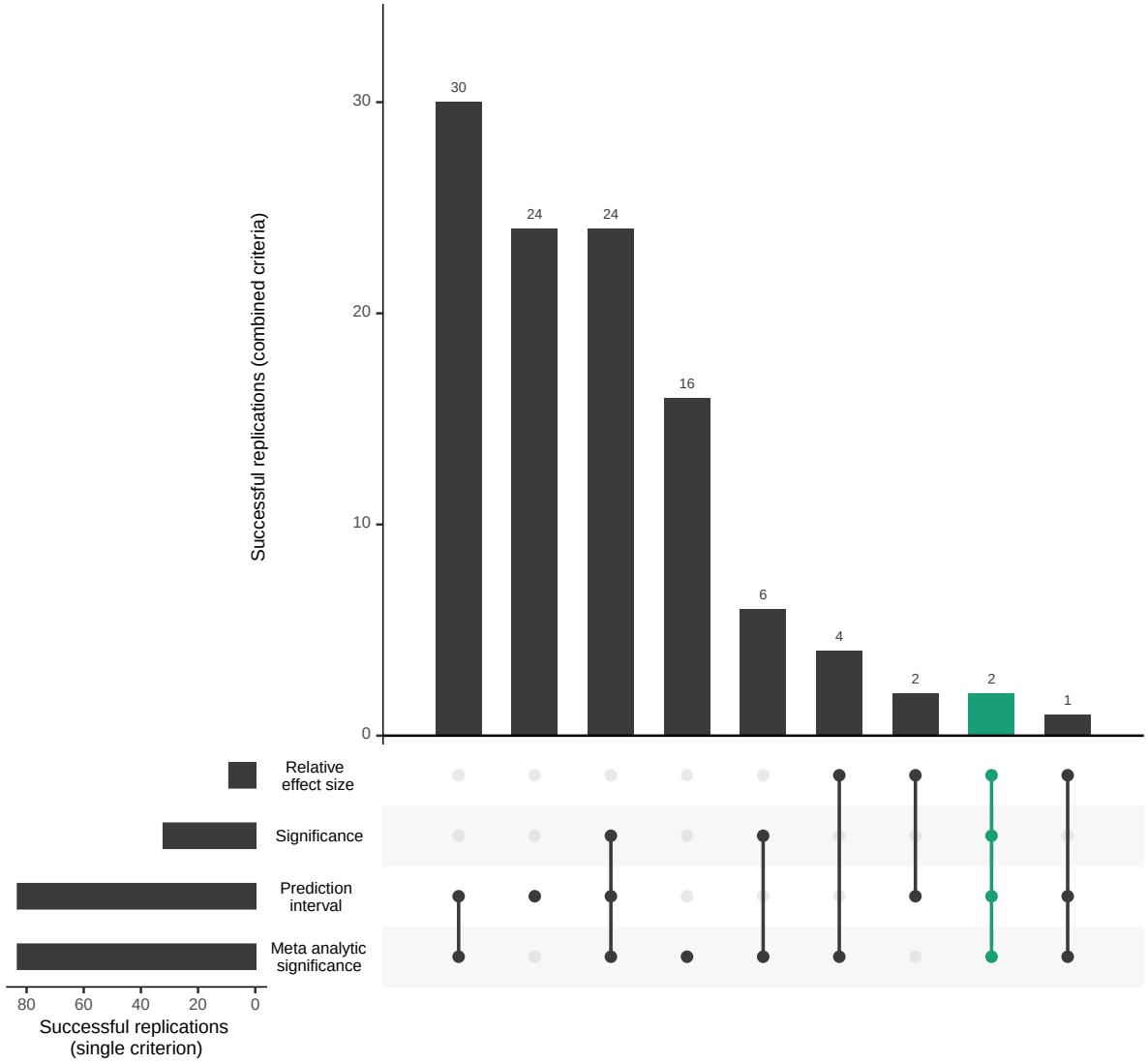


Figure 3: UpSet plot for data on 132 effects from the "Reproducibility Project: Cancer Biology" (Errington et al., 2021) for which effect estimates and standard errors are available on the standardized mean difference scale. Shown are the number of replication successes according to the different criteria from Table 2 and their combinations. A threshold of $\alpha = 5\%$ and a relative effect size threshold of $d_{\text{min}} = 1$ are used for replication success.

Taken together, this analysis demonstrates that conclusions based on commonly used replication success criteria often differ. It is not always clear-cut whether or not a replication is successful. Reducing replicability to a single criterion without mentioning these difficulties, as often done by the popular press (e. g., "more than half of the findings did not hold up when retested" in Carey, 2015), is a simplification of the matter.

Table 3: Subset of results from the "Reproducibility Project: Cancer Biology" (Errington et al., 2021). (P, X, E) denotes effect number E from experiment number X, from original paper number P. Shown are original $\hat{\theta}_o$, replication $\hat{\theta}_r$, and pooled effect estimate $\hat{\theta}_m$ with 95% confidence intervals, variance ratio $c = \sigma_o^2/\sigma_r^2$, relative effect estimate $d = \hat{\theta}_r/\hat{\theta}_o$, original *p*-value p_o, replication *p*-value p_r, meta-analytic *p*-value p_m, Q-test *p*-value p_Q, and one-sided sceptical *p*-value p_S. A replication success (green-bold) threshold of $\alpha = 5\%$ is used for two-sided *p*-values, $\alpha = 2.5\%$ for one-sided p-values, and $d_{\text{min}} = 1$ for the relative effect estimate.

	(P, X, E)	$\hat{\theta}_o$	(95% CI)	$\hat{\theta}_r$	(95% CI)	$\hat{\theta}_m$	(95% CI)	c	d	p_o	p_r	p_m	p_Q	p_S
1	(48, 2, 1)	0.22	(0.15 to 0.30)	0.20	(0.13 to 0.28)	0.21	(0.16 to 0.27)	0.96	0.91	**< 0.0001**	**< 0.0001**	**< 0.0001**	**0.69**	**< 0.0001**
2	(16, 3, 3)	4.36	(2.66 to 6.06)	3.09	(1.42 to 4.75)	3.71	(2.52 to 4.90)	1.04	0.71	**< 0.0001**	**0.00028**	**< 0.0001**	**0.29**	**0.0017**
3	(50, 1, 1)	0.50	(0.29 to 0.71)	0.43	(0.10 to 0.75)	0.48	(0.30 to 0.66)	0.42	0.85	**< 0.0001**	**0.0098**	**< 0.0001**	**0.70**	**0.0079**
4	(19, 1, 2)	2.41	(−0.33 to 5.15)	11.20	(4.21 to 18.24)	3.58	(1.03 to 6.13)	0.15	**4.65**	0.084	**0.0017**	**0.006**	0.022	0.047
5	(20, 2, 2)	1.78	(0.60 to 2.96)	0.87	(−0.28 to 2.01)	1.31	(0.49 to 2.13)	1.06	0.49	**0.0032**	0.14	**0.0018**	**0.28**	0.094
6	(44, 1, 4)	9.37	(7.81 to 10.93)	0.71	(−0.34 to 1.77)	3.43	(2.55 to 4.30)	2.19	0.08	**< 0.0001**	0.19	**< 0.0001**	< 0.0001	0.096
7	(24, 4, 5)	2.92	(−0.36 to 6.20)	2.84	(0.18 to 5.50)	2.87	(0.81 to 4.94)	1.52	0.97	0.081	**0.037**	**0.0065**	**0.97**	0.10
8	(1, 3, 5)	5.70	(0.48 to 10.92)	2.25	(0.39 to 4.10)	2.63	(0.89 to 4.38)	7.94	0.39	**0.032**	**0.018**	**0.0031**	**0.22**	0.12
9	(9, 2, 3)	1.80	(0.62 to 2.99)	0.55	(−0.45 to 1.55)	1.07	(0.31 to 1.84)	1.40	0.30	**0.0028**	0.28	**0.006**	**0.11**	0.16
10	(6, 1, 1)	6.41	(−2.90 to 15.72)	4.32	(0.16 to 8.47)	4.67	(0.87 to 8.46)	5.01	0.67	0.18	**0.042**	**0.016**	**0.69**	0.18
11	(37, 1, 1)	2.96	(1.14 to 4.77)	0.47	(−0.81 to 1.75)	1.30	(0.25 to 2.34)	2.01	0.16	**0.0014**	0.47	**0.015**	0.028	0.24
12	(47, 1, 5)	0.75	(−0.42 to 1.92)	0.31	(−0.49 to 1.12)	0.45	(-0.21 to 1.12)	2.11	0.42	0.21	0.45	0.18	**0.55**	0.28
13	(42, 2, 2)	5.34	(2.14 to 8.54)	0.26	(−0.84 to 1.36)	0.80	(-0.24 to 1.84)	8.42	0.05	**0.0011**	0.64	0.13	0.0033	0.33
14	(15, 2, 1)	1.61	(0.46 to 2.76)	0.22	(−0.83 to 1.28)	0.86	(0.08 to 1.64)	1.19	0.14	**0.006**	0.68	**0.031**	**0.082**	0.34
15	(41, 2, 1)	1.69	(−0.97 to 4.35)	1.95	(−20.93 to 24.82)	1.69	(-0.95 to 4.34)	0.01	**1.15**	0.21	0.87	0.21	**0.98**	0.43
16	(5, 1, 3)	1.10	(−2.06 to 4.26)	−0.02	(−2.33 to 2.29)	0.37	(-1.49 to 2.24)	1.88	−0.01	0.50	0.99	0.70	**0.58**	0.51
17	(21, 1, 3)	0.61	(−0.67 to 1.88)	−0.18	(−0.92 to 0.56)	0.02	(-0.62 to 0.66)	2.94	−0.30	0.35	0.63	0.95	**0.29**	0.65
18	(28, 3, 3)	2.11	(0.08 to 4.15)	−0.36	(−0.86 to 0.15)	−0.21	(-0.70 to 0.28)	16.21	−0.17	**0.042**	0.17	0.39	0.021	0.77
19	(39, 1, 1)	2.54	(0.39 to 4.69)	−1.13	(−2.40 to 0.13)	−0.19	(-1.28 to 0.90)	2.90	−0.45	**0.021**	0.079	0.73	0.0039	0.89
20	(29, 2, 2)	1.30	(−0.24 to 2.84)	−2.04	(−4.02 to −0.05)	0.05	(-1.17 to 1.26)	0.60	−1.57	0.097	**0.044**	0.94	0.0092	0.91

1.2 Reverse-Bayes assessment of replication studies

In response to the lack of a standard criterion for replication success, various methods have been proposed (Verhagen and Wagenmakers, 2014; Simonsohn, 2015; Anderson and Maxwell, 2016; Patil et al., 2016; Johnson et al., 2016; Etz and Vandekerckhove, 2016; van Aert and van Assen, 2017; Ly et al., 2018; Harms, 2019; Hedges and Schauer, 2019; Mathur and VanderWeele, 2020; Held, 2020; Pawel and Held, 2020; Bonett, 2020, among others). The focus of this thesis is to refine and extend the proposal from Held (2020) which combines *reverse-Bayes inference* and *Bayesian model criticism* in a method for assessing replication success. In the following, I will summarize the method and its technical underpinnings.

Reverse-Bayes inference

Bayesian inference is an approach to statistical inference where Bayes' theorem is used to make probability statements about unknown parameters based on the observed data. The central quantity for doing so is the distribution of the parameters conditional on the data, called the *posterior distribution*. It can be obtained from Bayes' theorem,

$$f(\theta \mid \text{data}) = f(\theta) \times \frac{f(\text{data} \mid \theta)}{f(\text{data})},$$

meaning that the *prior distribution* for the parameter θ with probability density/mass function $f(\theta)$ is multiplied by the (normalized) likelihood of the data, also know as *Bayesian updating*. Parameter values which increase the likelihood of the data become more likely *a posteriori* but they are also weighted by their *a priori* plausibility through the prior. As such, Bayesian inference provides a formal way for combining information from the data at hand with external knowledge encoded in the prior.

Many consider the prior to be also the weak point of Bayesian inference since it is unclear how it should be specified in the absence of external knowledge. The *reverse-Bayes* approach, first proposed by Good (1950), is one way of dealing with this issue. The idea is to reverse Bayes' theorem as

$$f(\theta) = f(\theta \mid \text{data}) \times \frac{f(\text{data})}{f(\text{data} \mid \theta)}$$

and instead "downdate" a posterior with the observed data. So, in contrast to the conventional "forward-Bayes" approach where we start with a prior, update it with the data, and end up with a posterior, the reverse-Bayes approach starts with the posterior and ends up with the prior. For example, the posterior may be specified to indicate evidence for/against a particular hypothesis under investigation. Reverse-Bayes inference then revolves around the question of whether the resulting prior is plausible in light of external knowledge, and if so, this indicates support for the specified posterior.

To illustrate reverse-Bayes inference, let us return to the replication setting. Assume we want to conduct inference about the unknown effect size θ based on the effect estimate from the original study $\hat{\theta}_o$ and its standard error σ_o. We will assume that $\hat{\theta}_o$ is normally distributed

around the unknown effect size θ with (known) variance equal to its squared standard error σ_o^2, here and henceforth denoted by $\hat{\theta}_o \,|\, \theta \sim \mathrm{N}(\theta, \sigma_o^2)$. Furthermore, we specify a zero-mean normal prior with variance τ^2 for the effect size θ, representing the position of a sceptic who does not believe in the presence of a genuine effect. The "stubbornness" of the sceptic is determined by how small the variance τ^2 is chosen (the smaller τ^2, the more scepticism). Combining the sceptical prior with the likelihood produces a posterior which is again normal $\theta \,|\, \hat{\theta}_o, \sigma_o \sim \mathrm{N}(\mu_{\text{post}}, \sigma_{\text{post}}^2)$ with mean and variance

$$\mu_{\text{post}} = \frac{\hat{\theta}_o}{1 + \sigma_o^2/\tau^2} \qquad \text{and} \qquad \sigma_{\text{post}}^2 = \frac{1}{1/\sigma_o^2 + 1/\tau^2}.$$

The associated $(1-\alpha) \times 100\%$ highest posterior density credible interval has limits

$$\mu_{\text{post}} \pm z_{\alpha/2}\, \sigma_{\text{post}} \tag{1}$$

and if this credible interval excludes parameter values smaller/larger than zero (depending on the orientation of the effect size) this may be interpreted as evidence for a genuine effect found in the original study. There exist also other definitions of statistical evidence and in subsequent chapters of this thesis (Paper II and Paper IV) we will extend this reverse-Bayes procedure to employ alternative measures of evidence, such as Bayes factors.

Depending on how large the prior variance τ^2 is chosen, the posterior credible interval (1) will either include or exclude zero. Different researchers may have different degrees of scepticism and may thus choose different prior variances τ^2. As a default choice, Held (2020) proposed to use the reverse-Bayes approach from Matthews (2001), that is, to determine the *sufficiently sceptical prior variance* τ_α^2 so that the appropriate limit of the $(1-\alpha) \times 100\%$ credible interval is just fixed to zero. The resulting prior then represents the beliefs of a sceptic who is just stubborn enough to not find the original study convincing at level α.

Figure 4 illustrates the derivation of the sufficiently sceptical prior variance for an original study included in the "Reproducibility Project: Cancer Biology" with standardized mean difference effect estimate $\hat{\theta}_o = 1.46$ and standard error $\sigma_o = 0.57$. We see that the sufficiently sceptical prior with variance $\tau_\alpha^2 = 0.68^2$ produces a posterior with $1 - \alpha = 95\%$ credible interval fixed to zero, so that the original finding is rendered no longer convincing at level $\alpha = 5\%$.

Held (2019a) showed that the sufficiently sceptical prior variance τ_α^2 for a level α is available in closed-form

$$\tau_\alpha^2 = \begin{cases} \dfrac{\sigma_o^2}{\left(z_o^2/z_{\alpha/2}^2\right) - 1} & \text{if } z_o^2 > z_{\alpha/2}^2, \\ \text{undefined} & \text{else.} \end{cases} \tag{2}$$

From (2) we see that convincing original studies (those with large absolute z-values $|z_o|$) require smaller sufficiently sceptical prior variances to render the posterior no longer convincing for the same level α. Conversely, if the original study is not convincing enough (if $|z_o| \leq z_{\alpha/2}$) the sufficiently sceptical prior variance is undefined meaning that the data provide so little evidence that no scepticism is required to make them unconvincing.

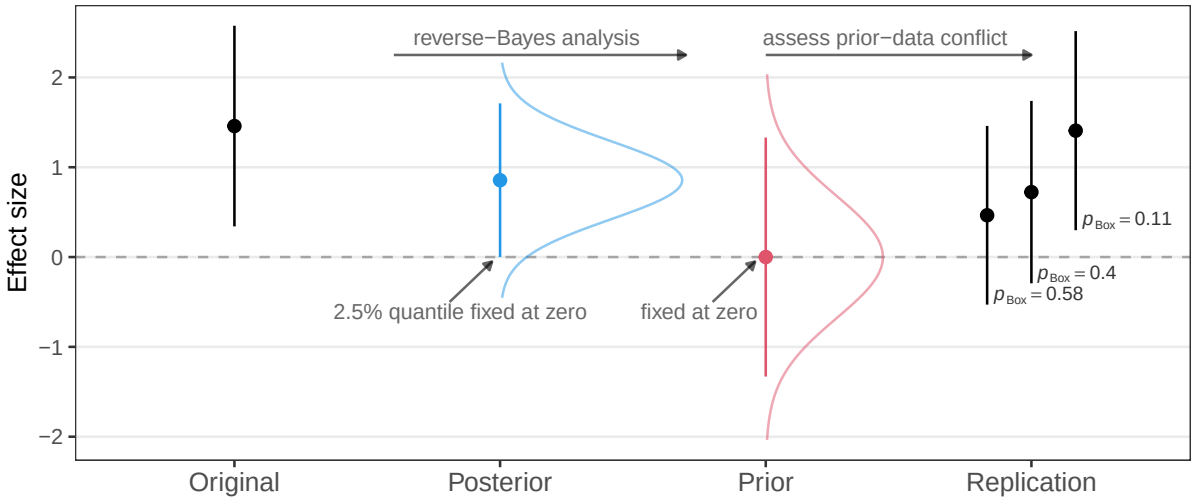


Figure 4: Illustration of reverse-Bayes assessment of replication success using data from the original study (Paper 9, Experiment 2, Effect 5) and its three replication studies from the "Reproducibility Project: Cancer Biology" (Errington et al., 2021). Shown are effect estimates and prior/posterior means with 95% confidence/credible interval. The original finding is challenged with a sceptical prior, sufficiently concentrated around zero so that the resulting posterior is no longer convincing at level $\alpha = 5\%$. Prior predictive *p*-values p_{Box} are computed for quantifying prior-data conflict.

In this way the reverse-Bayes approach based on sceptical priors can be used to formally challenge the finding from an original study. However, once this sceptical prior is determined, the question becomes whether it is plausible in light of external data. A natural candidate for answering the question is data from a replication study. In the following, I will show how Bayesian model criticism can be used for doing so.

Bayesian model criticism

Model criticism describes the assessment of compatibility between observed data and their assumed statistical model. If incompatibility is diagnosed, this alarms the data analyst that inferences based on the model may be invalid and modifications may be required. A formal framework for Bayesian model criticism was first introduced by Box (1980). To understand whether a Bayesian model M consisting of a joint distribution for parameter θ and data is adequate, Box gave the following fundamental decomposition of the joint distribution

$$f(\theta, \text{data} \,|\, \text{M}) = f(\theta \,|\, \text{data}, \text{M}) \times f(\text{data} \,|\, \text{M}).$$

He argued that inferences based on the left factor, the posterior distribution $f(\theta \,|\, \text{data}, \text{M})$, should only be trusted if the right factor, the prior predictive distribution

$$f(\text{data} \,|\, \text{M}) = \int f(\text{data} \,|\, \theta, \text{M})\, f(\theta \,|\, \text{M})\, \text{d}\theta$$

is compatible with the observed data. If the model M was indeed adequate, the empirical distribution of the observed data should be close to its predictive distribution under the model

M. On the other hand, if the empirical distribution differed from the predictive distribution, this would imply that model M is inadequate due to misspecification of the likelihood $f(\text{data} \mid \theta, \text{M})$ and/or misspecification of the prior $f(\theta \mid \text{M})$.

Based on these observations, Box proposed two general approaches for conducting Bayesian model criticism. First, the predictive density of the observed data (or the predictive density of a "checking function" applied to the observed data) can be compared to its reference distribution via a *prior predictive p-value*

$$p_{\text{Box}} = \int_{\mathcal{X}} f(\text{data} = x \mid \text{M}) \, \mathrm{d}x \tag{3}$$

with $\mathcal{X} = \{x : f(\text{data} = x \mid \text{M}) < f(\text{data} = \text{observed data} \mid \text{M})\}$. The p-value p_{Box} is the probability of obtaining data with lower predictive density ("more surprising" data) than the observed data, and the lower p_{Box}, the more incompatibility between the observed data and the assumed model M. This approach was used by Held (2020). However, Box also mentioned a second approach which has mostly been forgotten. If a second "benchmarking" model M_2 alternative to the model under investigation M_1 is available, Box proposed that the *prior predictive ratio*

$$\text{PPR}_{\text{Box}} = \frac{f(\text{data} = \text{observed data} \mid \text{M}_1)}{f(\text{data} = \text{observed data} \mid \text{M}_2)},$$

the ratio of predictive densities from the observed data under both models, could be used to judge the relative adequacy of model M_1. Again, the lower the prior predictive ratio PPR_{Box}, the less compatible the observed data with the model M_1. Bayesian model criticism approaches based on prior predictive ratios will be used in subsequent chapters of this thesis (Paper II and Paper IV).

We now return to the replication setting. Having obtained a sceptical prior $\theta \sim \text{N}(0, \tau_\alpha^2)$ with sufficiently sceptical prior variance τ_α^2 from (2), the aim is to assess its adequacy in light of the data from a replication study. If we are able to show that the prior is inadequate, this would demonstrate that scepticism regarding the original finding is unjustified and that the original study provided evidence for a genuine effect. Under the assumption of a normal likelihood for the replication effect estimate, i. e., $\hat{\theta}_r \mid \theta \sim \text{N}(\theta, \sigma_r^2)$, the prior predictive distribution is given by $\hat{\theta}_r \mid \theta \sim \text{N}(0, \sigma_r^2 + \tau_\alpha^2)$. As the prior predictive distribution is symmetric around zero, the prior predictive p-value (3) is

$$p_{\text{Box}} = 2 \left\{ 1 - \Phi \left(\frac{|\hat{\theta}_r|}{\sqrt{\sigma_r^2 + \tau_\alpha^2}} \right) \right\}. \tag{4}$$

Figure 4 shows the prior predictive p-values from (4) computed for three example replication studies from the "Replication Project: Cancer Biology". We see that larger effect estimates show smaller prior predictive p-values p_{Box}, indicating more prior-data conflict. This is because the standard errors from all three replications are roughly the same size, so that the distance between zero and the replication effect estimate matters most. The p-values suggest that there is hardly any conflict between the sceptical prior and the first two replications (those

with $p_{\text{Box}} = 0.58$ and $p_{\text{Box}} = 0.40$), while the conflict is larger for the third one (the one with $p_{\text{Box}} = 0.11$).

Held (2020) defined replication success at level α by

$$p_{\text{Box}} \leq \alpha.$$

In words, replication success is established if there is more conflict between the sceptical prior and the replication data than there was evidence against the null hypothesis in the original study. For the examples in Figure 4, all prior predictive p-values are larger than the level $\alpha = 5\%$ used for computing the sufficiently sceptical prior variance ($\tau_\alpha^2 = 0.68^2$), so neither of them achieves replication success at level $\alpha = 5\%$. However, at a larger level, e. g., $\alpha = 10\%$, the corresponding sufficiently sceptical prior variance would be smaller ($\tau_\alpha^2 = 0.48^2$). Consequently, there would be more conflict between the prior and the replication data, so that the third replication would be successful at the less convincing level $\alpha = 10\%$ (since the prior predictive p-value would be $p_{\text{Box}} = 0.057 < 10\%$).

The sceptical *p*-value

To remove the dependence on the level α, Held (2020) proposed to determine the smallest level at which replication success can be established. This level is called the *sceptical p-value* p_{S}, and it is available in closed-form

$$p_{\text{S}} = 2\left\{1 - \Phi(|z_{\text{S}}|)\right\} \tag{5}$$

where

$$z_{\text{S}}^2 = \begin{cases} z_{\text{H}}^2/2 & \text{for } c = 1 \\ \left\{\left[z_{\text{A}}^2\left\{z_{\text{A}}^2 + z_{\text{H}}^2(c-1)\right\}\right]^{1/2} - z_{\text{A}}^2\right\}/(c-1) & \text{for } c \neq 1 \end{cases}$$

with arithmetic mean $z_{\text{A}}^2 = (z_o^2 + z_r^2)/2$ and harmonic mean $z_{\text{H}}^2 = 2/(1/z_o^2 + 1/z_r^2)$ of the squared z-statistics, and variance ratio $c = \sigma_o^2/\sigma_r^2$. Replication success at level α is then equivalent to $p_{\text{S}} \leq \alpha$. For instance, the sceptical p-values of the three replication studies in Figure 4 are $p_{\text{S}} = 0.39$, $p_{\text{S}} = 0.23$, and $p_{\text{S}} = 0.075$ (from left to right), so we can see that the third replication is unsuccessful at level $\alpha = 5\%$ but successful at level $\alpha = 10\%$. However, the sceptical p-value does not necessarily have to be dichotomized in this manner, but can also be interpreted as a quantitative measure of replication success; the smaller p_{S}, the higher the degree of replication success.

The sceptical p-value has several interesting properties (Held, 2020, Section 3): First, it is always larger than the maximum of the original and replication p-values ($p_{\text{S}} > \max\{p_o, p_r\}$), meaning that both p-values have to be smaller than α such that replication success at level α is possible. The sceptical p-value hence requires *both* studies to be sufficiently convincing on their own (in terms of their p-values), similar to the significance criterion for replication success. Second, if the p-values p_o and p_r remain fixed but the relative effect estimate $d = \hat{\theta}_r/\hat{\theta}_o$ decreases towards zero, the sceptical p-value increases, meaning that shrinkage of

the replication effect estimate is penalized ($p_S \uparrow 1$ as $d \downarrow 0$ for fixed p_o and p_r). The sceptical p-value thus takes effect shrinkage into account, unlike the significance criterion which can be achieved with any non-zero replication effect estimate $\hat{\theta}_r$ provided the standard error σ_r is small enough. This property is desirable in the replication setting as a smaller replication effect estimate $\hat{\theta}_r$ may not be practically relevant anymore, despite its statistical significance.

There is one problem with the (two-sided) sceptical p-value as defined in (5); It does not take the direction of the effect estimates into account, so replication success may be established even though the effect estimate from the replication goes in the opposite direction of the original one ($\text{sign}(\hat{\theta}_o) \neq \text{sign}(\hat{\theta}_r)$). In fact, the sceptical p-value will decrease with decreasing negative relative effect estimate ($p_S \downarrow p_o$ as $d \downarrow -\infty$ for fixed σ_o and σ_r) which seems contrary to intuitive understandings of replicability as a change in effect direction may diminish the usefulness of a scientific finding (e. g., a negative treatment effect may indicate harm instead of benefit). This "replication paradox" (Ly et al., 2018) can be avoided by defining a one-sided sceptical p-value

$$p_S = \begin{cases} 1 - \Phi(|z_S|) & \text{if } \text{sign}(\hat{\theta}_o) = \text{sign}(\hat{\theta}_r) \\ \Phi(|z_S|) & \text{if } \text{sign}(\hat{\theta}_o) \neq \text{sign}(\hat{\theta}_r) \end{cases}$$

similar to how ordinary one-sided p-values are defined. The one-sided sceptical p-value has similar properties as the two-sided version – it is always larger than the one-sided p-values from original and replication studies, and it penalizes shrinkage of the replication effect estimate. In the subsequent chapters only the one-sided version of the sceptical p-value will be used.

The last column of Table 3 shows the one-sided sceptical p-value for the subset of replications from the "Reproducibility Project: Cancer Biology". The results illustrate the previously discussed properties to require significance from both studies and to penalize effect shrinkage. For example, replication #4 fails to achieve replication success at level $\alpha = 2.5\%$ with the one-sided sceptical p-value, even though the replication study was highly convincing (the effect estimate was almost five times as large as in the original study). Yet, as the approach requires both studies to be convincing on their own – and the original study was not significant at the 2.5% level (one-sided) – replication success at this level is impossible with the sceptical p-value. The second property is illustrated by replication #8. Here both the original and replication studies were significance. However, the effect estimate from the replication was roughly 60% smaller than the one from the original study, and significance is merely achieved because the standard error was much smaller (i. e., around $1/\sqrt{c} \approx 1/2.8$ times smaller). The sceptical p-value is therefore only $p_S = 0.12$, indicating less evidence for replication success.

This concludes the introduction to replication studies and reverse-Bayes methods for their analysis. Some additional properties (e. g., the null distribution of the sceptical p-value) and extensions (e. g., power and sample size calculations) can be found in the original article by Held (2020). The sceptical p-value and related methods are implemented in the R package `ReplicationSuccess` available on CRAN (`https://cran.r-project.org/package=ReplicationSuccess`). In the following, I will discuss open questions and how they are addressed in this thesis.

2 Thesis contributions

This thesis consists of six papers divided into three parts. The first part (Paper I, II, and III) focuses on methodology for design and analysis of replication studies. The second part (Paper IV and V) revolves around reverse-Bayes methodology with a broader scope of applications than replication studies. The last part (Paper VI) deals with integrity issues in methodological research.

2.1 Design and analysis of replication studies

Paper I: The assessment of replication success based on relative effect size
Leonhard Held, Charlotte Micheloud, Samuel Pawel
The Annals of Applied Statistics, 2022, 16(2), 706–720. doi:10.1214/21-AOAS1502.

It is not clear how to interpret the sceptical p-value as it is not an ordinary p-value (which has a uniform distribution under the null hypothesis that the underlying effect size θ is zero). Moreover, when the same level α as for the significance criterion is used for dichotomizing the sceptical p-value, this leads to a much more stringent criterion for replication success than the significance criterion. Many studies which intuitively seem successful will not satisfy it, and frequentist properties such as power and type I error rate will be impacted by it (e. g., power and type I error rate will be much lower compared to the significance criterion).

In this article, we therefore look closer at the "success region" of the sceptical p-value in terms of the relative effect estimate $d = \hat{\theta}_r / \hat{\theta}_o$. This perspective leads to the proposal of a new default level for thresholding the sceptical p-value called the *golden level* α_G (named "golden" because the golden ratio appears in its derivation). The golden level is defined through the property that for an original study which was borderline significant ($p_o = \alpha$), replication success based on $p_S \leq \alpha_G$ is only possible if the replication effect estimate is at least as large as the original one ($d \geq 1$). For instance, for the one-sided significance level $\alpha = 2.5\%$, the corresponding two-sided golden level is $\alpha_G = 6.2\%$. The behavior of the golden level seems to align with common sense: for original studies which were already convincing (in terms of their p-value) the effect estimate in the replication study is allowed to shrink, to some extent, whereas for less convincing original studies (those with p-values around the significance level) shrinkage is more strongly penalized. We find that for replication studies with equal or larger sample size than the original study, replication success based on the golden level controls the type I error rate at the same level as the standard significance criterion. Similarly, if the original study was adequately powered, replication success based on the golden level has comparable or improved "project power"compared to the significance criterion (project power is the probability of replication success conditional on a true effect size based on original and replication study). Case studies from four large-scale replication projects (Open Science Collaboration, 2015; Camerer et al., 2016, 2018; Cova et al., 2018) illustrate the properties of the golden level. In most cases conclusions agree with the significance criterion, but in the differing cases, the golden level seems to produce more appropriate inferences as it takes into

account effect shrinkage. This extension is now implemented as the default option in the R package `ReplicationSuccess`.

L. Held had the idea to apply the sceptical p-value to the data from the four replication projects, which I collected for my master thesis. L. Held and C. Micheloud came up with the golden level. L. Held wrote an initial draft of the manuscript. L. Held, C. Micheloud, and I then iteratively worked on the manuscript.

Paper II: The sceptical Bayes factor for the assessment of replication success

Samuel Pawel, Leonhard Held
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doi:10.1111/rssb.12491.

The reverse-Bayes approach from Held (2020) is based on challenging the original study with a sceptical prior so there is no longer evidence for an effect. Evidence is quantified in terms of credible intervals and tail probabilities. However, there exist also other measures of evidence, and it has been a matter of long debates which is the most appropriate (see e. g., Berger and Sellke, 1987; Casella and Berger, 1987; Royall, 1997; Berger, 2003; Benjamin et al., 2017; Lakens et al., 2018; Amrhein et al., 2019a). In this paper, we extend the reverse-Bayes assessment of replication studies to use Bayes factors (Good, 1958; Jeffreys, 1961) for quantifying evidence and prior-data conflict. Similar to the sceptical p-value, the procedure leads to a single measure for quantifying replication success, *the sceptical Bayes factor*. Systematic comparisons show that the sceptical Bayes factor has similar properties as the sceptical p-value (e. g., it penalizes shrinkage of the replication effect estimate and requires compelling evidence from both studies in terms of p-values and Bayes factors, respectively). However, it is also shown that the sceptical p-value suffers from a certain type of "shrinkage paradox", which is avoided by the sceptical Bayes factor; when the p-value from the original study goes to zero, replication success based on the sceptical p-value can be achieved with any arbitrarily small replication effect estimate, whereas replication success based on the sceptical Bayes factor poses a finite limit on how much shrinkage is allowed. Technically, the procedure is more involved and closed-form solutions for the sceptical Bayes factor are only available in special situations. The method is illustrated on data from the "Social Sciences Replication Project" (Camerer et al., 2018), and implemented in the R package `BayesRep` (`https://gitlab.uzh.ch/samuel.pawel/BayesRep`).

The idea to use Bayes factors instead of tail probabilities was suggested by Consonni (2019) and Pericchi (2020) independently in response to the original article by Held (2020). L. Held then implemented a first version of the procedure for the grant application of this research project (Held, 2019b). I then worked out the technical and implementation details, including closed-form solution for the sceptical Bayes factors, asymptotic properties, type I and type II error rates, and non-normal extensions. I wrote the initial draft of the manuscript and the R package. Throughout, L. Held gave high-level feedback. I presented initial results at the annual meeting of the GMDS and CEN-IBS (German Association for Medical Informatics, Biometry and Epidemiology and the Central European Network of the International Biometric Society) in 2020. L. Held presented the final results at the ISBA (International Society for Bayesian Analysis) world meeting 2021.

Paper III: Bayesian approaches to designing replication studies
Samuel Pawel, Guido Consonni, Leonhard Held
arXiv preprint, 2022. doi:10.48550/arXiv.2211.02552.

An important aspect in the design of replication studies is determining their sample size. How exactly the sample size should be determined depends on which method is used for the analysis of the replication data. Various approaches have been proposed for doing so which are specifically tailored to certain analysis methods. In this article, we provide a general Bayesian framework which applies to any analysis method (including the sceptical *p*-value and the sceptical Bayes factor). We show how the data from the original study and external knowledge can be combined in a *design prior* for the underlying model parameters. Based on this design prior, predictions about the replication data can be computed, and the replication sample size can be chosen such that the probability of replication success becomes as high as desired. We illustrate Bayesian design of replication studies in the normal-normal hierarchical model which provides sufficient flexibility for specification of design priors. Data from a cross-laboratory replication project (Protzko et al., 2020) are used for illustrating our methods, which are available in the R package `BayesRepDesign` (`https://github.com/SamCH93/BayesRepDesign`).

L. Held specified in the grant application of this research project (Held, 2019b) that we will investigate power and sample size calculations for the sceptical *p*-value and the sceptical Bayes factor. In Paper II, I already derived the power function of the sceptical Bayes factor in closed-form for two types of design priors. After its completion, I generalized the result to any design prior in the normal-normal hierarchical model, and started working on this manuscript. I presented a first draft to L. Held and G. Consonni in the beginning of 2021. G. Consonni then helped developing the methodology for multisite replication study design. I continued working on the manuscript in 2022 and also wrote the accompanying R package. Throughout, L. Held and G. Consonni gave high-level feedback.

2.2 Reverse-Bayes methodology

Paper IV: Reverse-Bayes methods for evidence assessment and research synthesis
Leonhard Held, Robert Matthews, Manuela Ott, Samuel Pawel
Research Synthesis Methods, 2022, 13(3), 295–314. doi:10.1002/jrsm.1538.

While the popularity of Bayesian methods has been rapidly increasing since the advent of modern computational methods in the 1990s, reverse-Bayes methods have remained largely unknown to statisticians and users of statistics alike. In this article, we review reverse-Bayes history and methods to increase awareness about the approach. Specifically, we summarize the work on reverse-Bayes by I. J. Good (Good, 1950), who first proposed the idea. We then review methods such as the *Analysis of Credibility* from Matthews (2001, 2018), its extension to Bayes factors, and the *False Positive Risk* from Colquhoun (2017). To illustrate these method, we use data from a meta-analysis on the effect of corticosteroids on COVID-19 mortality.

L. Held and M. Ott started working on this article several years ago. When I discovered the connection between the Analysis of Credibility and the fail-safe N method (Rosenthal, 1979; Rosenberg, 2005), L. Held suggested that it would fit nicely into this manuscript and to add the COVID-19 meta-analysis example. I rewrote and expanded his initial draft, adding also a new section on reverse-Bayes approaches with Bayes factors, largely based on the work from Paper II. We then managed to recruit R. Matthews to also contribute. From that point on the three of us iteratively worked on the manuscript and M. Ott gave high-level feedback.

Paper V: Comment on "Bayesian additional evidence for decision making under small sample uncertainty"

Samuel Pawel, Leonhard Held, Robert Matthews
BMC Medical Research Methodology, 2022, 22(149). doi:10.1186/s12874-022-01635-4.

Shortly after the acceptance of Paper IV, the article by Sondhi et al. (2021) appeared. It proposed a novel reverse-Bayes method called *Bayesian Additional Evidence*, and we noted some flaws in the article. This prompted us to write a commentary. We show that – contrary to the statement by Sondhi et al. – there is a closed form solution for the key quantity in their approach termed "Bayesian Additional Evidence tipping point". The method is also closely related to the Analysis of Credibility by Matthews (2018). We investigate differences and similarities of the two methods, concluding that the priors determined through the Bayesian Additional Evidence method are of limited use due to their restrictive assumption of having equal variance as the data.

R. Matthews alerted us about the article from Sondhi et al. (2021). After reading it, I realized that their statement about closed-form solutions was incorrect and derived a solution. L. Held suggested to write a commentary. I wrote an initial draft of the manuscript, which R. Matthews improved by discussing some logical flaws of the method. The two of us iteratively worked on the manuscript, while L. Held gave high-level feedback.

2.3 Meta-scientific perspectives on methodological research

Paper VI: Pitfalls and Potentials in Simulation Studies

Samuel Pawel, Lucas Kook, Kelly Reeve
arXiv preprint, 2022. doi:10.48550/arXiv.2203.13076.

In methodological research, simulation studies are frequently used for evaluating "how well" statistical methods perform. The conclusions from these studies are therefore often crucial for recommendations when which method should be used. However, several literature review articles identified that the design and reporting standards of simulation studies have remained low over the years (Hoaglin and Andrews, 1975; Burton et al., 2006; Morris et al., 2019). Moreover, some authors have recently argued that methodological research is suffering from reproducibility issues, publication bias, and a "replication crisis" due to researchers engaging in questionable research practices, such as selective reporting (Boulesteix et al., 2020). In this article, draw attention to these issues. We summarize possible questionable research

practices in simulation studies, and show how easy it is to make a method seem superior if various questionable research practices are employed. We also give recommendations to alleviate these issues. Most importantly, we recommend researchers to write and pre-register simulation protocols.

The first authorship of this manuscript is shared with L. Kook. I had the idea to invent a novel method and use questionable research practices that make it seem superior, to draw attention to the low standards in methodological research. I then wrote a first draft of the manuscript and proposed the idea to L. Kook and K. Reeve. L. Kook and myself then invented the regression method "AINET" and started writing the simulation protocol. L. Kook took lead in developing the R package `ainet` (https://github.com/LucasKook/ainet) and simulation study code. Myself, L. Kook, and K. Reeve then designed the final simulation study and continued working on the manuscript together. Recently, I was invited to present the results from this project at the CEN (Central European Network) conference 2023 in Basel.

Data and software

The CC-By 4.0 licensed data from the "Reproducibility Project: Cancer Biology" (Errington et al., 2021) were downloaded from https://doi.org/10.17605/osf.io/e5nvr. The relevant variables were then extracted from the file "`RP_CB Final Analysis - Effect level data.csv`". All analyses from this chapter were conducted in the R programming language version 4.2.2 (R Core Team, 2022). The packages `dplyr` (Wickham et al., 2022), `ggplot2` (Wickham, 2016), `knitr` (Xie, 2022), `ReplicationSuccess` (Held, 2020), `UpSetR` (Gehlenborg, 2019), and `xtable` (Dahl et al., 2019) were used. Code and data to reproduce this thesis are available at https://github.com/SamCH93/thesis. A snapshot of the git repository is archived at https://doi.org/10.5281/zenodo.XXXXXXX.

Computational details

```
sessionInfo()
```

```
## R version 4.2.2 Patched (2022-11-10 r83330)
## Platform: x86_64-pc-linux-gnu (64-bit)
## Running under: Ubuntu 20.04.5 LTS
##
## Matrix products: default
## BLAS:   /usr/lib/x86_64-linux-gnu/blas/libblas.so.3.9.0
## LAPACK: /usr/lib/x86_64-linux-gnu/lapack/liblapack.so.3.9.0
##
## locale:
##  [1] LC_CTYPE=en_US.UTF-8       LC_NUMERIC=C
##  [3] LC_TIME=de_CH.UTF-8        LC_COLLATE=en_US.UTF-8
##  [5] LC_MONETARY=de_CH.UTF-8    LC_MESSAGES=en_US.UTF-8
##  [7] LC_PAPER=de_CH.UTF-8       LC_NAME=C
##  [9] LC_ADDRESS=C               LC_TELEPHONE=C
## [11] LC_MEASUREMENT=de_CH.UTF-8 LC_IDENTIFICATION=C
##
## attached base packages:
## [1] stats     graphics  grDevices utils     datasets  methods   base
##
## other attached packages:
## [1] UpSetR_1.4.0           dplyr_1.0.10           ReplicationSuccess_1.2
## [4] xtable_1.8-4           scales_1.2.1           ggpubr_0.4.0
## [7] ggplot2_3.4.0          knitr_1.40
##
## loaded via a namespace (and not attached):
##  [1] Rcpp_1.0.9       plyr_1.8.7       pillar_1.8.1     compiler_4.2.2
##  [5] tools_4.2.2      evaluate_0.18    lifecycle_1.0.3  tibble_3.1.8
##  [9] gtable_0.3.1     pkgconfig_2.0.3  rlang_1.0.6      DBI_1.1.3
## [13] cli_3.4.1        xfun_0.34        gridExtra_2.3    withr_2.5.0
## [17] stringr_1.4.1    generics_0.1.3   vctrs_0.5.0      cowplot_1.1.1
## [21] grid_4.2.2       tidyselect_1.2.0 glue_1.6.2       R6_2.5.1
## [25] rstatix_0.7.1    fansi_1.0.3      carData_3.0-5    farver_2.1.1
## [29] purrr_0.3.5      tidyr_1.2.1      car_3.1-1        magrittr_2.0.3
## [33] backports_1.4.1  assertthat_0.2.1 abind_1.4-5      colorspace_2.0-3
## [37] ggsignif_0.6.4   labeling_0.4.2   utf8_1.2.2       stringi_1.7.8
## [41] munsell_0.5.0    broom_1.0.1
```

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PAPER I

The assessment of replication success based on relative effect size

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Abstract

Replication studies are increasingly conducted in order to confirm original findings. However, there is no established standard how to assess replication success and in practice many different approaches are used. The purpose of this paper is to refine and extend a recently proposed reverse-Bayes approach for the analysis of replication studies. We show how this method is directly related to the relative effect size, the ratio of the replication to the original effect estimate. This perspective leads to a new proposal to recalibrate the assessment of replication success, the golden level. The recalibration ensures that for borderline significant original studies replication success can only be achieved if the replication effect estimate is larger than the original one. Conditional power for replication success can then take any desired value if the original study is significant and the replication sample size is large enough. Compared to the standard approach to require statistical significance of both the original and replication study, replication success at the golden level offers uniform gains in project power and controls the Type I error rate if the replication sample size is not smaller than the original one. An application to data from four large replication projects shows that the new approach leads to more appropriate inferences, as it penalizes shrinkage of the replication estimate compared to the original one, while ensuring that both effect estimates are sufficiently convincing on their own.

Key words: Power, replication studies, sceptical p-value, shrinkage, two-trials rule, Type I error rate

1 Introduction

Replication studies are conducted in order to investigate whether an original finding can be confirmed in an independent study. Although replication has long been a central part of the scientific method in many fields, the so-called replication crisis (Ioannidis, 2005; Begley and Ioannidis, 2015) has led to increased interest in replication over the last decade. These developments eventually culminated in large-scale replication projects that were conducted in various fields (Errington et al., 2014; Klein et al., 2014; Open Science Collaboration, 2015; Ebersole et al., 2016; Camerer et al., 2016, 2018; Cova et al., 2018; Klein et al., 2018).

Declaring a replication as successful is, however, not a straightforward task, and currently used approaches include statistical significance of both the original and replication study, compatibility of their effect estimates, and meta-analysis of the effect estimates. Many of the replication projects listed above also report the relative effect size, the ratio of the replication to the original effect estimate. For example, in Camerer et al. (2018) the replication effect estimates were only half as large as the original ones on average and even smaller in Open Science Collaboration (2015). This gives clear evidence of a systematic bias of the original studies and strongly suggests that the original and replication study should not be treated as exchangeable. However, all the approaches mentioned above will give the same results if the order of studies would be reversed.

In order to address this problem, a new method has recently been proposed in Held (2020b). The approach combines the analysis of credibility (Matthews, 2001a,b) with a prior-data conflict assessment (Box, 1980). Replication success is declared if the replication study is in conflict with a sceptical prior that would make the original study non-significant. This approach penalizes small relative effect sizes as we will see in more detail in the following.

To introduce some notation, let $z_o = \hat{\theta}_o/\sigma_o$ and $z_r = \hat{\theta}_r/\sigma_r$ denote the z-statistic of the original and replication study, respectively. Here $\hat{\theta}_o$ and $\hat{\theta}_r$ are the corresponding effect estimates (assumed to be normally distributed) of the unknown effect θ with standard errors σ_o and σ_r, respectively. The corresponding one-sided p-values are denoted by $p_o = 1 - \Phi(z_o)$ and $p_r = 1 - \Phi(z_r)$, respectively, where $\Phi(\cdot)$ denotes the standard normal cumulative distribution function. Let $c = \sigma_o^2/\sigma_r^2$ denote the variance ratio of the squared standard errors of the original and replication effect estimates. The squared standard errors are usually inversely proportional to the sample size of each study, i. e., $\sigma_o^2 = \kappa^2/n_o$ and $\sigma_r^2 = \kappa^2/n_r$ for some unit variance κ^2. The variance ratio c can then be identified as the relative sample size $c = n_r/n_o$. The relative effect size

$$d = \frac{\hat{\theta}_r}{\hat{\theta}_o} = \frac{1}{\sqrt{c}}\frac{z_r}{z_o} \tag{1}$$

quantifies the size of the replication effect estimate $\hat{\theta}_r$ relative to the original effect estimate $\hat{\theta}_o$. The corresponding shrinkage of the replication effect estimate will be denoted as $s = 1 - d$.

Suppose the original study achieved statistical significance at one-sided level α, so $p_o \leq \alpha$. The standard approach to assess replication success is based on significance of the replication effect estimate at the same level α, i. e., the replication is considered successful if also $p_r \leq \alpha$. This approach is known in drug development as the two-trials rule (Senn, 2008), usually conducted at $\alpha = 0.025$. Let $z_\alpha = \Phi^{-1}(1-\alpha) > 0$ denote the z-value corresponding to the level α, then significance of the replication study is achieved if $z_r \geq z_\alpha$, which is equivalent to the condition

$$d \geq \frac{z_\alpha}{z_o\sqrt{c}} \tag{2}$$

on the relative effect size (1). The right hand-side goes to zero for increasing c, so if the relative sample size c is large enough, significance of the replication study can be achieved with any arbitrarily small (but positive) relative effect size d. However, declaring replication success when there is substantial shrinkage is contrary to common sense, as the replication effect estimate may not reflect an effect size of the same practical relevance as the original one, despite its statistical significance.

In this paper we first review the Held (2020b) approach for the assessment of replication success, followed by showing how it relates to the relative effect size (Section 2.1). This perspective is used in Section 2.2 and 2.3 to propose a recalibration of the method, the *golden level*, which leads to a more appropriate criterion for replication success compared to the two-trials rule (Section 2.4). In Section 3 we study power and Type I error rates of the proposed method and compare it to the two-trials rule. The recalibrated method ensures that conditional power can take any desired value if the original study has been significant and the replication sample size is large enough (Section 3.1), controls the overall Type I error if the replication sample size is not smaller than the original one (Section 3.2), and offers uniform gains in project power

compared to the two-trials rule (Section 3.3). Section 4 describes an application to data from four replication projects and Section 5 closes with some discussion.

2 Replication success

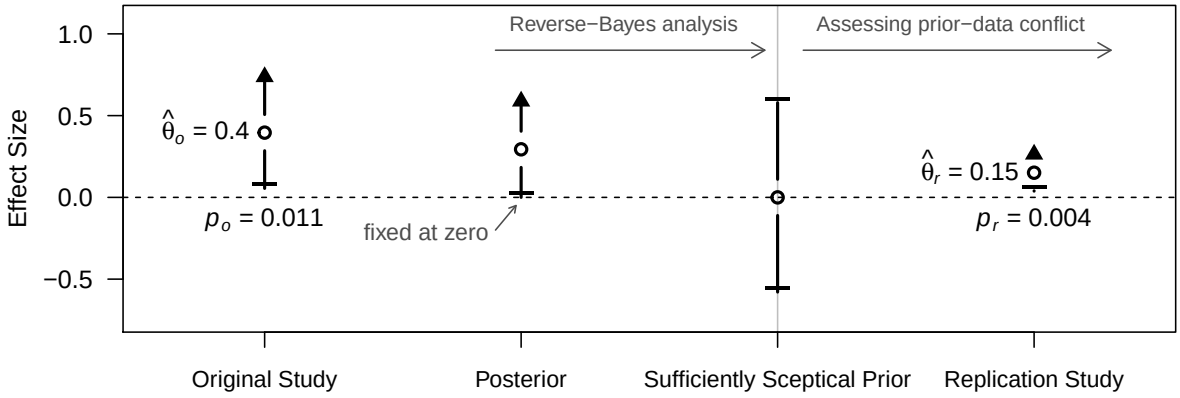

Figure 1: Example of the assessment of replication success. The original study from Pyc and Rawson (2010) has effect estimate $\hat{\theta}_o = 0.4$ on Fisher's z scale (95% CI from 0.05 to 0.74) and one-sided p-value $p_o = 0.011$. The left part of the figure illustrates the reverse-Bayes derivation of the sufficiently sceptical prior based on the original study result and the posterior with lower credible limit fixed at zero. The comparison of the sufficiently sceptical prior with the replication study result ($\hat{\theta}_r = 0.15$, 95% CI from 0.04 to 0.26, $p_r = 0.004$) in the right part of the figure is used to assess potential prior-data conflict.

Hereinafter we focus on the one-sided assessment of replication success to ensure that replication success can only occur if the original and replication effect estimates go in the same direction. Figure 1 illustrates the Held (2020b) approach based on a replication study from the *Social Sciences Replication Project* (Camerer et al., 2018): the significant original finding by Pyc and Rawson (2010) at one-sided level $\alpha = 0.025$ is challenged with a sceptical prior, sufficiently concentrated around zero to make the original study result no longer convincing (Matthews, 2001a,b). Replication success is then defined as conflict between the sceptical prior and the result from the replication study in order to disprove the sceptic. Conflict is quantified by a prior-predictive tail probability p_{Box} (Box, 1980) where a small value $p_{\text{Box}} \leq \alpha$ defines replication success. In Figure 1 the original finding is only borderline significant, so the sufficiently sceptical prior is fairly wide. Furthermore, there is substantial shrinkage ($d = 0.15/0.4 = 0.38$) of the replication effect estimate and therefore hardly any conflict with the sufficiently sceptical prior (one-sided $p_{\text{Box}} = 0.31$). We are thus not able to declare replication success at level 2.5%.

The actual value of p_{Box} is difficult to interpret as it depends on the level α and does not even exist if the original p-value p_o exceeds α. However, Held (2020b) showed that if both $\text{sign}(z_o) = \text{sign}(z_r)$ and

$$\left(z_o^2/z_{\alpha_S}^2 - 1\right)\left(z_r^2/z_{\alpha_S}^2 - 1\right) \geq c \tag{3}$$

hold, replication success at level α_S is achieved, where $z_{\alpha_S} = \Phi^{-1}(1-\alpha_S)$. The requirement (3) can be assessed for any value of $\alpha_S > \max\{p_o, p_r\}$ and of particular interest is the smallest possible value of α_S where (3) holds, the so-called *sceptical p-value* p_S. We are thus interested in the value z_S^2 that fulfills

$$\left(z_o^2/z_S^2 - 1\right)\left(z_r^2/z_S^2 - 1\right) = c. \tag{4}$$

There is a unique solution of (4) which defines the one-sided sceptical p-value $p_S = 1 - \Phi(z_S)$ where $z_S := +\sqrt{z_S^2}$, provided $\text{sign}(z_o) = \text{sign}(z_r)$ holds. Replication success at level α_S is then achieved if $p_S \leq \alpha_S$. In the introductory example based on the original study by Pyc and Rawson (2010), the sceptical p-value turns out to be $p_S = 0.11$.

The sceptical p-value has a number of interesting properties, see Held (2020b, Section 3.1) for details. In particular, $p_S > \max\{p_o, p_r\}$ always holds with $p_S \downarrow \max\{p_o, p_r\}$ for $c \downarrow 0$. Furthermore, if the p-values p_o and p_r are fixed, the sceptical p-value p_S increases with decreasing relative effect size d. The first property ensures that both the original and the replication study have to be sufficiently convincing on their own to achieve replication success. The second property guarantees that shrinkage of the replication effect estimate is penalized.

The level for replication success α_S has to be distinguished from the significance level α associated with the ordinary p-value. Held (2020b) has used the *nominal level* for replication success ($\alpha_S = \alpha$) for convenience, but in the following we will propose a recalibration of the procedure along with a new value for α_S, the *golden level* (Section 2.2). The derivation is based on a property of the required relative effect size for replication success, if the relative sample size is very large (Section 2.1). In a nutshell, the golden level ensures that for original studies which were only borderline significant ($p_o = \alpha$), replication success is only possible if the replication effect estimate is larger than the original one ($d > 1$).

2.1 Relative effect size

Without loss of generality we now assume that $\hat{\theta}_o > 0$ and that $p_o < \alpha_S$ has been observed in the original study, otherwise it would be impossible to achieve replication success at level α_S because p_S is always larger than p_o. The condition (3) for replication success can then be re-written as

$$z_r \geq z_{\alpha_S}\sqrt{1 + c/(K-1)} =: z_r^{\min}, \tag{5}$$

where $K = z_o^2/z_{\alpha_S}^2 > 1$. The right hand-side of (5) is the minimum replication z-value $z_r^{\min}$ required to achieve replication success. Note that $z_r^{\min}$ increases with increasing c, so increasing the replication sample size leads to a more stringent success requirement z_r and the corresponding replication p-value p_r.

Equation (5) can be further transformed to a condition on the relative effect size (1):

$$d \geq \frac{\sqrt{1 + c/(K-1)}}{\sqrt{cK}} =: d_{\min}. \tag{6}$$

To achieve replication success, the relative effect size must be at least as large as the right hand-side of (6), the minimum relative effect size $d_{\min}$, a function of K and the relative sample size c. If the relative sample size becomes very large, i. e., $c \to \infty$, we have $d_{\min} \downarrow d_\infty$ where

$$d_\infty = 1/\sqrt{K(K-1)} \tag{7}$$

is the *limiting relative effect size*. This shows that the minimum relative effect size $d_{\min}$ in (6) does not go to zero for increasing c, so replication success cannot be achieved if the relative effect size d is smaller or equal to d_∞, no matter how large the replication study is. In contrast, the corresponding criterion (2) of the two-trials rule can be achieved for any positive relative effect size, regardless of how small, provided the replication sample size is sufficiently large.

2.2 The golden level

Significance of both the original and the replication study at level α is a necessary but not sufficient requirement for replication success at the nominal level ($\alpha_S = \alpha$). The nominal level may therefore be too stringent. It is more reasonable to calibrate the procedure in such a way that to establish replication success, original and replication study do not both necessarily need to be significant at level α, provided that the replication effect estimate does not shrink compared to the original one. We therefore choose a level α_S such that a borderline significant original study ($p_o = \alpha$) cannot lead to replication success if there is shrinkage $s > 0$ of the replication effect estimate. Mathematically, this translates to setting $d_\infty = 1$ and $K = z_\alpha^2/z_{\alpha_S}^2$ in (7) and leads to the quadratic equation $K(K-1) = 1$ with solution $K = \varphi$ where $\varphi = (\sqrt{5}+1)/2 \approx 1.62$ is known as the golden ratio. Solving for z_{α_S} gives $z_{\alpha_S} = z_\alpha/\sqrt{\varphi}$ and the corresponding *golden level*

$$\alpha_S \quad = \quad 1 - \Phi(z_\alpha/\sqrt{\varphi}) \tag{8}$$

for replication success. This is our recommended default choice to assess replication success and we will study its properties in the following in more detail. For $z_\alpha = 1.96$ (one-sided $\alpha = 0.025$), the golden level is $\alpha_S = 0.062$. In the introductory example shown in Figure 1, the sceptical p-value is $p_S = 0.11 > 0.062$, so the replication of the Pyc and Rawson (2010) study was not successful.

The golden level (8) is derived from (7) with $d_\infty = 1$. However, we may also use a different value for the limiting relative effect size d_∞, say $d_\infty = 0.8$. Then replication success is only possible for a borderline significant result ($p_o = \alpha$) if there is less than $1 - d_\infty$ (20% for $d_\infty = 0.8$) shrinkage of the replication effect estimate. This approach is equivalent to a limiting relative effect size of 1 if the original p-value p_o is equal to a different level α', which can be derived as follows: First, solving (7) for $d_\infty > 0$ gives $K = z_\alpha^2/z_{\alpha_S}^2 = 1/2 + \sqrt{1/4 + 1/d_\infty^2}$. The new level α' fulfills $\varphi = z_{\alpha'}^2/z_{\alpha_S}^2$, so $z_\alpha^2/K = z_{\alpha'}^2/\varphi$ and therefore

$$\alpha' = 1 - \Phi\left(z_\alpha \sqrt{\varphi/K}\right). \tag{9}$$

For example, for $\alpha = 0.025$ and $d_\infty = 0.8$ we obtain $\alpha' = 0.033$.

2.3 Recalibration of the sceptical *p*-value

The condition $p_S \leq \alpha_S$ for replication success at the golden level is equivalent to $z_S \geq z_\alpha / \sqrt{\varphi}$, i. e., $z_S \sqrt{\varphi} \geq z_\alpha$. In practice it may be preferable to recalibrate the sceptical p-value $p_S = 1 - \Phi(z_S)$ to $\tilde{p}_S = 1 - \Phi(z_S \sqrt{\varphi})$, which then needs to be compared to α (rather than α_S) to assess replication success and can thus be interpreted on the same scale as an ordinary p-value. For example, the recalibrated sceptical p-value for the replication of Pyc and Rawson (2010) turns out to be $\tilde{p}_S = 0.061$ and does not lead to replication success at any level $\alpha < 0.061$, including the standard 0.025 level.

2.4 Comparison with the two-trials rule

A useful benchmark for comparison is the two-trials rule in drug development (Kay, 2015, Section 9.4), which requires "at least two adequate and well-controlled studies, each convincing on its own, to establish effectiveness" (FDA, 1998, p. 3). This is usually achieved by independently replicating the result of a first study in a second study, both significant at one-sided level $\alpha = 0.025$. It is worth noting that in practice the two trials are often run in parallel (Senn, 2008), so do not exactly resemble the replication setting.

The main difference between the replication success and the two-trials rule approach concerns how shrinkage of the replication effect estimate is handled. Figure 2 illustrates that shrinkage is penalized in the assessment of replication success, i. e., the original p-value needs to be quite small to achieve replication success for a relative effect size $d < 1$. In contrast, significance of the replication study can be achieved even if there is substantial shrinkage, provided the replication sample size is large enough.

It is interesting to directly compare the two-trials rule and replication success at the golden level in terms of the required relative effect size d to fulfill the criteria (2) and (6), respectively, see Figure 2. If the original p-value is not significant at level α, only replication success can be achieved, but will require a replication effect estimate larger than the original one.

For example, four studies with one-sided $p_o \in (0.025, 0.03)$ have been included in the *Reproducibility Project: Psychology* (Open Science Collaboration, 2015) and one of them achieves replication success (see Section 4 for details). By definition, such non-significant original findings can never fulfill the two-trials rule.

If the original p-value is smaller than α, then the situation depends on the relative sample size c. For example, when the replication sample size is chosen to be the same as in the original study ($c = 1$) and $\alpha = 0.025$, original studies with a p-value larger than 0.006 will require a smaller relative effect size d with the two-trials rule, while p-values smaller than 0.006 will require a smaller relative effect size d with the replication success method. This illustrates that the latter method is less stringent than the two-trials rule if the original study is already sufficiently convincing.

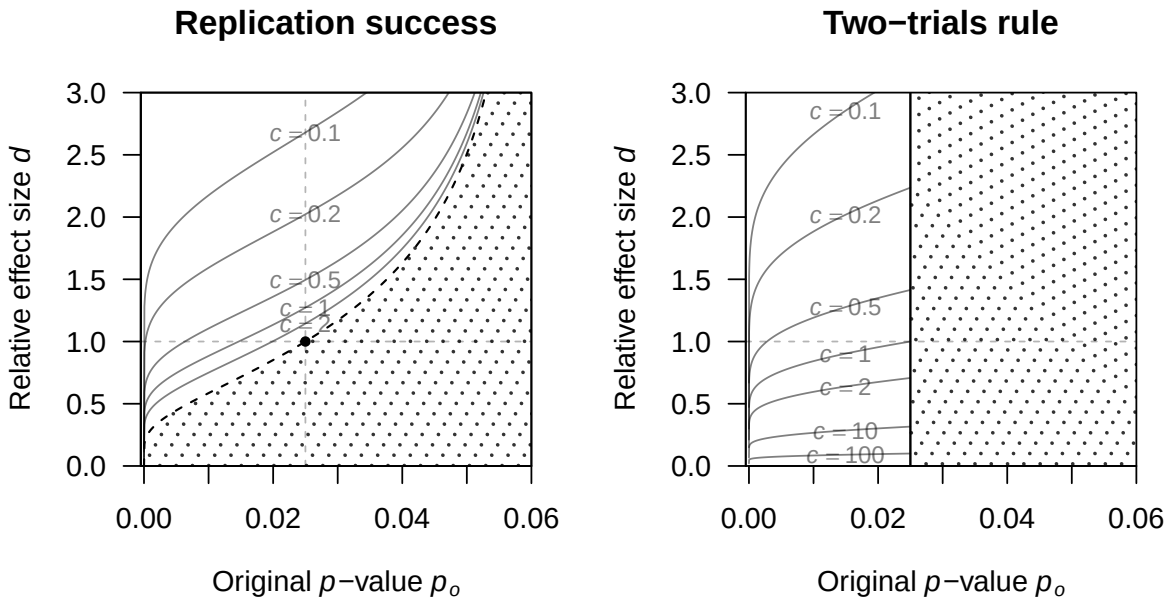

Figure 2: Comparison of replication success at the golden level ($p_S \leq \alpha_S = 0.062$) and the two-trials rule ($p_o \leq 0.025$ and $p_r \leq 0.025$). The dotted areas indicate that success is impossible for original p-value p_o and relative effect size d. In the white areas success is possible and depends on the relative sample size c as indicated by the grey lines. The dashed black line in the left plot indicates the limiting relative effect size d_∞.

3 Power and Type I Error Rate

Although Bayesian methods do not rely on the frequentist paradigm of repeated testing, it is still useful to investigate their frequentist operating characteristics (Dawid, 1982; Rubin, 1984; Grieve, 2016) and this also holds for the proposed reverse-Bayes assessment of replication success. We first condition on the results from the original study and compare the power to achieve replication success with the two-trials rule in Section 3.1. We then assume that none of the two studies have been conducted and investigate the overall Type I error rate (Section 3.2) and the project power (Section 3.3) (Maca et al., 2002) over both studies in combination for fixed relative sample size c.

3.1 Conditional power

Figure 3 compares the power for replication success (see Held, 2020b, Section 4 for details) at the golden and at the nominal level with the power of the two-trials rule for relative sample size $c = 1$ (left) and $c = 5$ (right) as a function of the one-sided p-value p_o from the original study. Shown is the conditional power assuming the unknown parameter θ is equal to the original effect estimate $\hat{\theta}_o$. Then $\hat{\theta}_r \,|\, \hat{\theta}_o \sim \mathrm{N}(\hat{\theta}_o, \kappa^2/n_r)$ and it follows that $d \,|\, \hat{\theta}_o \sim \mathrm{N}(1, 1/(cz_o^2))$.

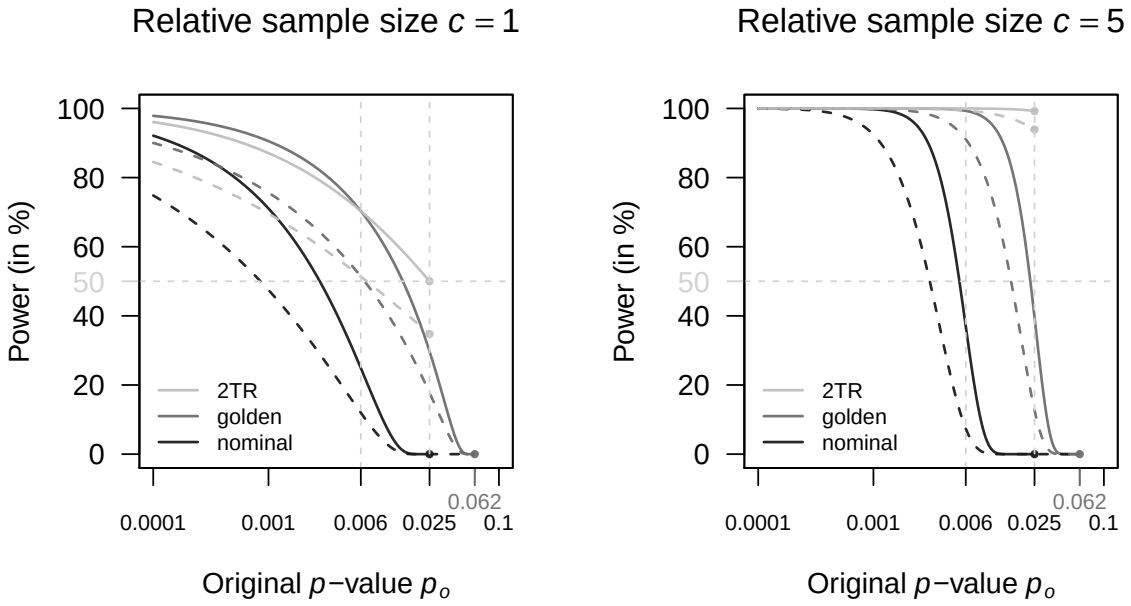

Figure 3: Conditional power as a function of the one-sided p-value of the original study with relative sample size $c = 1$ (left) and $c = 5$ (right). Shown is conditional power assuming the unknown parameter is equal to the original effect estimate (solid) and conditional power based on 20% shrinkage of the original effect estimate (dashed) for the two-trials rule (2TR) at level $\alpha = 0.025$ and for replication success at the corresponding golden and nominal level. Power values of exactly zero are omitted.

The conditional power for replication success can therefore be calculated as

$$\Pr(d \geq d_{\min} \mid \hat{\theta}_o) = \Phi\left[\sqrt{c} z_o (1 - d_{\min})\right], \tag{10}$$

where $d_{\min}$ is given in (6). Predictive power, which is conditional power averaged over a $\mathrm{N}(\hat{\theta}_o, \sigma_o^2)$ distribution for the effect size θ, could also be calculated, then $d \mid \hat{\theta}_o \sim \mathrm{N}(1, (1 + 1/c)/z_o^2)$. Conditional and predictive power of the two-trials rule also depend on z_o, c and α and are given in Micheloud and Held (2022).

The two-trials rule requires a significant original study and hence it is impossible to power a replication study when $p_o > 0.025$. The same applies for replication success at the nominal level, where the power is zero for any $p_o > 0.025$, regardless of the replication sample size. This is different for the golden level, where the conditional power of an original study with $0.025 < p_o < 0.062$ is low, but not zero. However, if the original p-value p_o is slightly smaller than 0.025, the two-trials rule has a larger power, both for $c = 1$ and $c = 5$. But if the original p-value is sufficiently small ($p_o < 0.006$ for $c = 1$), the power for replication success at the golden level is larger than the power of the two-trials rule.

Compared to $c = 1$, the conditional power for $c = 5$ of both the two-trials rule and the replication success approach at the golden level increases if $p_o \leq \alpha$. A remarkable feature of the replication success approach at the golden level is that conditional power can be pushed

towards 100% for large enough c if $p_o < \alpha$, but not otherwise. This can be seen from (10) because $d_{\min} < 1$ for $p_o < \alpha$ and large enough relative sample size c. On the other hand, for $p_o > \alpha$ conditional power for replication success will tend to 0% for increasing c because $d_{\min} > 1$ for all c. Finally, for $p_o = \alpha$ the limit is 50%. The same property can be observed at the nominal level, however at the smaller threshold $1 - \Phi(z_\alpha \sqrt{\varphi})$ which is 0.006 for $\alpha = 0.025$. Only if $p_o < 0.006$ will the conditional power for replication success attain 100% for $c \to \infty$. This further highlights the stringency of the nominal level.

The approach described so far takes the original study at face-value since it assumes that $\hat{\theta}_o$ is equal to the unknown effect size θ. In practice, however, there are often good reasons to believe that original effect estimates have a tendency to be inflated (e. g., due to publication bias). One way to address this issue is to base power calculations on a shrunken version of the original effect estimate, where the amount of shrinkage is guided by domain knowledge and a risk of bias assessment of the original study. For illustration, Figure 3 also shows conditional power based on 20% shrinkage of the original effect estimate which reduces the conditional power for all methods, especially for a relative sample size $c = 1$. Conditional power for replication success at the golden level can now be pushed towards 100% only for $p_o < 0.018$, which can be derived by solving (9) for α with $\alpha' = 0.025$ and $d_\infty = 0.8$. To be able to push conditional power based on 20% shrinkage towards 100% for all $p_o < 0.025$, equation (9) would have to be used directly to relax the level from $\alpha = 0.025$ to $\alpha' = 0.033$.

3.2 Overall Type I error rate

The two studies are assumed to be independent with Type I error rate fixed at α for each of them, so the Type I error rate of the two-trials rule over the entire project is simply α^2 for any value of the relative effect size c. In contrast, the Type I error rate of the proposed replication success assessment depends on the relative sample size c.

For $c = 1$, Held (2020b, Section 3) showed that z_S^2 in (4) simplifies to half the harmonic mean of the squared test statistics z_o^2 and z_r^2. The connection $z_S^2 = z_H^2/4$ to the harmonic mean χ^2-test statistic z_H^2 (Held, 2020a), which has a $\chi^2(1)$-distribution under the null hypothesis, makes it straightforward to compute the Type I error rate at level α_S for $c = 1$ as

$$\text{T1E} = \left\{1 - \Phi\left[2\,\Phi^{-1}\left(1 - \alpha_S\right)\right]\right\}/2. \tag{11}$$

For the golden level $\alpha_S = 0.062$ at $\alpha = 0.025$, the Type I error rate (11) is 0.0515%, slightly less than the Type I error rate $\alpha^2 = 0.0625\%$ of the two-trials rule. For comparison, the Type I error rate at the nominal level $\alpha_S = 0.025$ is 0.0022%, much smaller than 0.0625%.

For $c \neq 1$, the Type I error rate can be calculated through numerical integration:

$$\text{T1E} = \int_{z_{\alpha_S}}^{\infty} \Pr(z_r \geq z_r^{\min} \mid z_o, c, \alpha_S)\, \phi(z_o)\, dz_o, \tag{12}$$

where $\phi(\cdot)$ denotes the standard normal density function. The first term in the integral of (12) is the probability of replication success at level α_S conditional on a fixed original test statistic

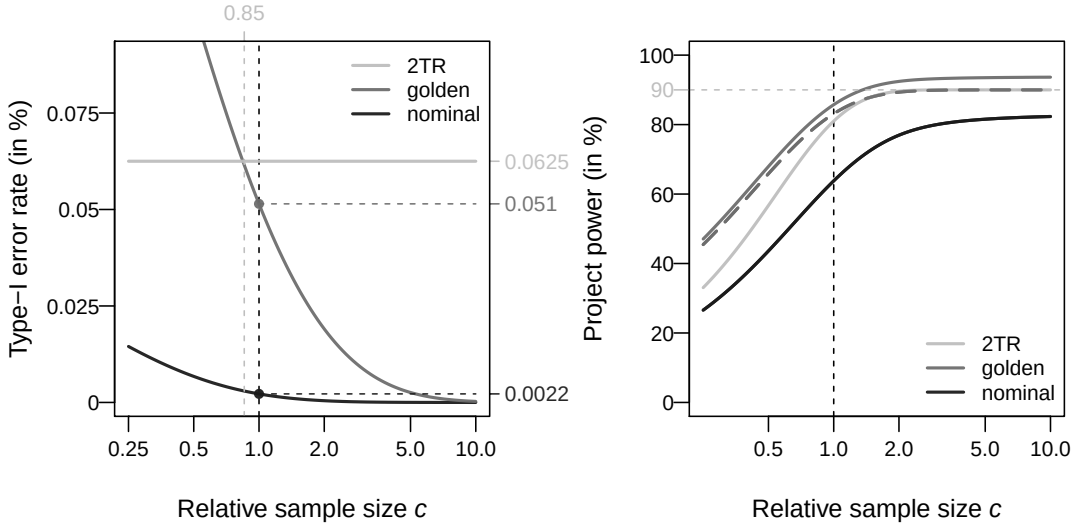

Figure 4: Overall Type I error rate (left) and project power (right) for fixed relative sample size c. Results are given for replication success at the nominal and golden level and compared with the two-trials rule (2TR) at $\alpha = 0.025$. The dashed darkgrey line is the project power at the golden level based on significant original studies ($p_o \leq 0.025$). The power of the original study is 90%.

z_o and a relative sample size c. Now $z_r \sim \mathrm{N}(0,1)$ under the null hypothesis, so this term simplifies to $\Pr(z_r \geq z_r^{\min} \mid z_o, c, \alpha_S) = 1 - \Phi(z_r^{\min})$ where $z_r^{\min}$ in (5) depends on z_o, c, and α_S.

The left plot in Figure 4 displays the Type I error rate for $\alpha = 0.025$ as a function of the relative sample size c. It can be seen that the Type I error of the replication success approach decreases with increasing relative sample size c. This also follows from (12) where $\Pr(z_r \geq z_r^{\min} \mid z_o, c, \alpha_S) = 1 - \Phi(z_r^{\min})$ decreases with increasing c, because $z_r^{\min}$ increases with increasing c, see equation (5).

The Type I error rate of the nominal level is always below the target 0.0625%. Although the Type I error will eventually attain α^2 in the limit $c \downarrow 0$ (Held, 2020b, Section 3.4), the nominal level seems to be too stringent for realistic values of c. The Type I error rate of the golden level is smaller than 0.0625% for $c > 0.85$. Appropriate Type I error control is thus ensured even for replication studies where the sample size is slightly smaller than in the original study.

Figure 5 compares for $c = 1$ the Type I error rate (11) of replication success at the golden and at the nominal level with the two-trials rule for different values of α. The Type I error rate of the two-trials rule is α^2 and the replication success approach at the nominal level always has a much smaller Type I error rate than α^2. At the golden level the Type I error rate of the replication success approach is much closer to α^2, still slightly smaller if $\alpha < 0.058$. For $\alpha = 0.058$ the Type I error rate is equal to the Type I error rate $0.058^2 = 0.34\%$ of the two-trials rule and for $\alpha > 0.058$ the Type I error rate is slightly larger than α^2. The Type I error rate for replication success decreases with increasing c, so as long as the replication sample size is not smaller than the original sample size, Type I error control at α^2 is guaranteed at the golden level for any one-sided level $\alpha < 0.058$.

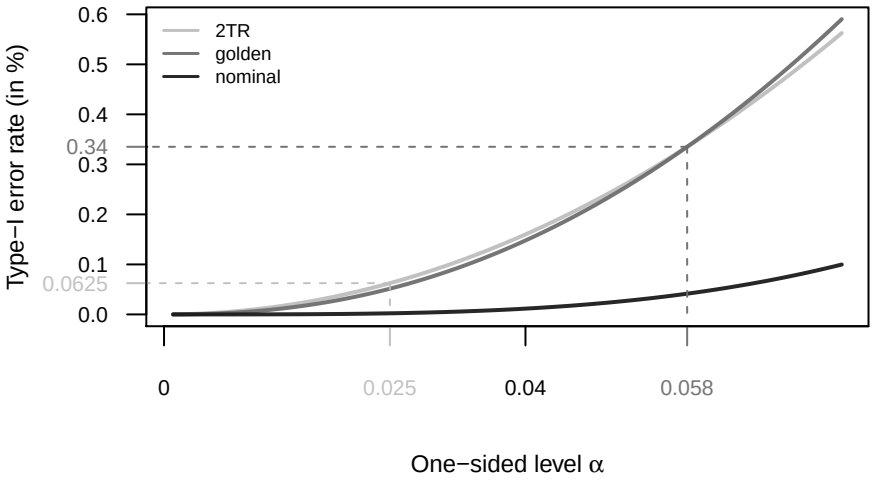

Figure 5: Overall Type I error rate if the replication sample size equal to the original study ($c = 1$). The two-trials rule (2TR) is compared to replication success at the golden and nominal level for different values of α.

3.3 Project power

Under the alternative we have $z_o \sim \mathrm{N}(\mu, 1)$ with $\mu = z_\alpha + z_\beta$ where α is the assumed significance level and $1 - \beta = \Phi(\mu - z_\alpha)$ is the power to detect the assumed effect $\theta = \mu\sigma_o$ in the original study (Matthews, 2006, Section 3.3). In the following $\alpha = 0.025$ and $\beta = 0.1$ are used. The power of a significant replication study with sample size $n_r = cn_o$ is

$$\Phi(\theta/\sigma_r - z_\alpha) = \Phi(\sqrt{c}\mu - z_\alpha),$$

so depends on μ and the relative sample size c. The project power of the two-trials rule is therefore $(1 - \beta)\,\Phi(\sqrt{c}\mu - z_\alpha)$ and increases with increasing c.

The project power for replication success is computed as

$$\mathrm{PP} = \int_{z_{\alpha_\mathrm{S}}}^{\infty} \Pr(z_r \geq z_r^{\min} \,|\, z_o, c, \alpha_\mathrm{S})\, \phi(z_o - \mu)\, dz_o$$

and shown in the right plot of Figure 4 as a function of c. For the golden level, the project power quickly increases to values above 90%, whereas the nominal level only reaches around 80% project power. The project power based on the two-trials rule is shown for comparison, which is always smaller than for the golden level and converges to 90% for large c.

The advantage in power stems partly from replication success still being possible when the original p-value is larger than 0.025, but smaller than 0.062. If we assume that a replication

study is only conducted if the original study is significant (with $p_o \leq 0.025$), then the project power based on the golden level (the dashed line in Figure 4) is slightly smaller and for $c > 1$ barely different than for the two-trials rule. More substantial gains are still visible for $c < 1$. However, the restriction to original studies with $p_o \leq 0.025$ may not reflect current practice in large-scale replication projects. For example, 5 out of 143 replication studies considered in Section 4 do have original p-values between 0.025 and 0.062.

4 Application

In this section, we illustrate the proposed methodology using data from four replication projects. All four projects reported effect estimates that were transformed to correlation coefficients (r). This scale allows for easy comparison of effect estimates from studies that investigate different phenomena and is bounded to the interval between minus one and one. Moreover, the Fisher z-transformation $\hat{\theta} = \tanh^{-1}(r)$ can be applied to the correlation coefficients, resulting in the transformed estimates being asymptotically normal with variance which is only a function of the study sample size n, i. e., $\text{Var}(\hat{\theta}) = 1/(n-3)$ (Fisher, 1921).

The first data set comprises the results from the *Reproducibility Project: Psychology* (Open Science Collaboration, 2015), whose aim was to replicate 100 studies, all of which were published in three major Psychology journals in 2008. For our purpose only the 73 study pairs from the "meta-analytic" subset are considered, since only for these studies the standard error of the Fisher z-transformed effect estimates can be computed (Johnson et al., 2016). The second data set comes from the *Experimental Economics Replication Project* (Camerer et al., 2016) which attempted to replicate 18 experimental economics studies published in two high impact economics journals between 2011 and 2015. The third data stem from the *Social Sciences Replication Project* (Camerer et al., 2018) where 21 replications of studies on the social sciences were carried out, all of which were originally published in the journals *Nature* and *Science* between 2010 and 2015. The last data set originates from the *Experimental Philosophy Replicability Project* (Cova et al., 2018) which involved 40 replications of studies from the emerging field of experimental philosophy. Since only for 31 studies effective sample size for original and replication study were available simultaneously, only these pairs were included. For more information on the data sets see also Pawel and Held (2020).

Table 1: Results for each replication project: Relative effect size d (median with 25% and 75% quantiles on Fisher's z scale), proportion of successful replications with the two-trials rule (2TR) and the replication success (RS) approach (at the golden level), and number of studies where the methods disagree.

Project	relative effect size d	2TR (%)	RS (%)	discrepant
Psychology	0.29 [0.03, 0.77]	28.8	30.1	3/73
Experimental Economics	0.67 [0.35, 0.92]	55.6	55.6	0/18
Social Sciences	0.52 [0.13, 0.65]	61.9	52.4	2/21
Experimental Philosophy	0.86 [0.47, 1.12]	74.2	71.0	1/31

Table 1 presents overall results for each of the replication projects. While the median relative effect size is below one for all of the four projects, there are still large differences. For example, the median relative effect size is only 0.29 in the Psychology project, whereas it is 0.86 in the Philosophy project. The degree of shrinkage is also reflected in the success rates (according to the two-trials rule and the replication success approach at the golden level), which are around 30% for the former and more than 70% for the latter. The proportion of successful replications is similar for the two-trials rule and the replication success approach. In the Experimental Economics project the methods perfectly agree, while in the other three projects the methods disagree for a few studies.

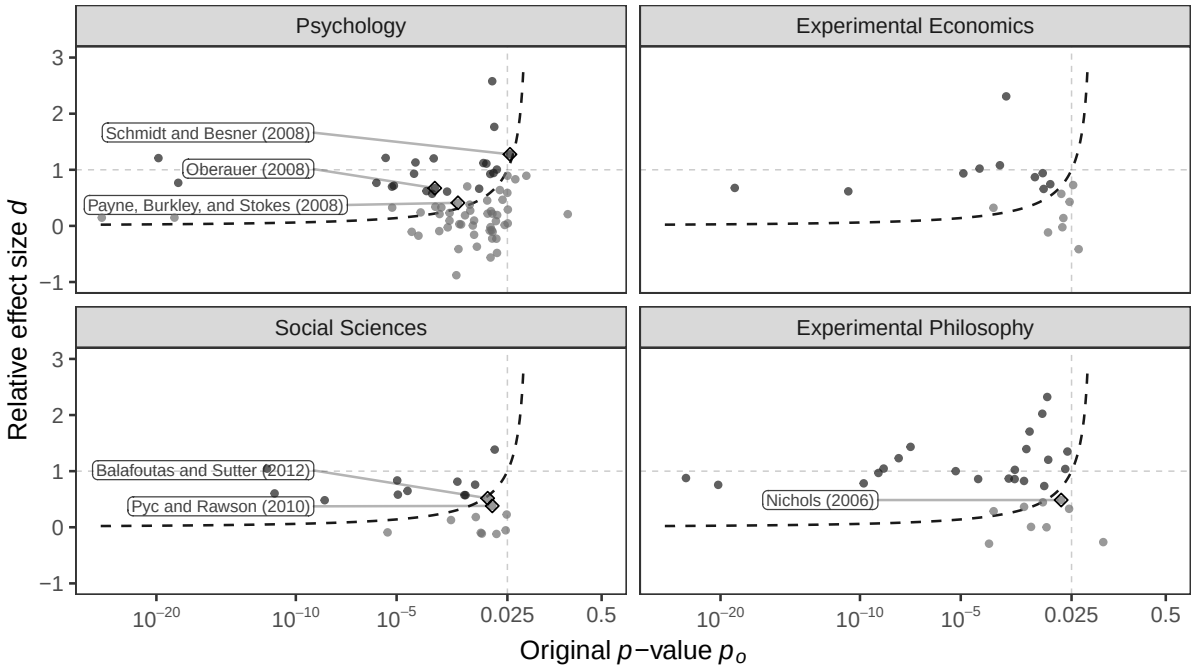

Figure 6: Relative effect size d versus original p-value p_o. Black indicates that replication success was achieved at the golden level while grey indicates that it was not. The diamonds mark studies where the replication success approach (at the golden level) and the two-trials rule disagree. The dashed black line indicates the limiting relative effect size at the golden level with $\alpha = 0.025$.

Figure 6 displays the relative effect size d versus the original p-value p_o for each study pair and stratified by project. Note that one study pair from the Philosophy project is not shown due to extremely small original p-value and another study pair from the Psychology project is not shown due to a very large relative effect size. We can see that for most of the study pairs, the replication success approach and the two-trials rule lead to the same conclusion, only six replications show conflicting results. They are highlighted with diamonds in Figure 6 and their characteristics are summarised in Table 2. Two studies from the Psychology project show replication success but fail the two-trials rule. These studies show p-values that are slightly above the significance threshold in either original or replication study, but do not exhibit much shrinkage; in the replication of Oberauer (2008), the replication p-value was $p_r = 0.035$, a little too large to pass the two-trials rule. However, as the replication effect estimate shrunk only about 30% compared to the original one, replication success is still achieved. Conversely, the

Table 2: Characteristics of studies for which the replication success approach (at the golden level) and the two-trials rule disagree (at one-sided $\alpha = 0.025$). Shown are relative sample size c, relative effect size d, original, replication and recalibrated sceptical p-value p_o, p_r and $\tilde{p}_S$.

Study	Project	c	d	p_o	p_r	$\tilde{p}_S$
Schmidt and Besner (2008)	Psychology	2.58	1.28	**0.028**	< 0.0001	0.024
Oberauer (2008)	Psychology	0.60	0.67	0.0003	**0.035**	0.017
Payne et al. (2008)	Psychology	2.65	0.41	0.001	0.023	**0.031**
Balafoutas and Sutter (2012)	Social Sciences	3.48	0.52	0.009	0.011	**0.04**
Pyc and Rawson (2010)	Social Sciences	9.18	0.38	0.011	0.004	**0.061**
Nichols (2006)	Experimental Philosophy	9.40	0.49	0.015	0.0006	**0.049**

original p-value $p_o = 0.028$ in Schmidt and Besner (2008) was just above the significance level, yet the replication led to a highly significant result $p_r < 0.0001$ with the effect estimate being even 30% larger than the original counterpart, which therefore also resulted in replication success.

The remaining conflicting studies do not show replication success despite passing the two-trials rule. In all cases, there is substantial shrinkage of the replication effect estimate compared to the original one. For instance, in the replication study of Pyc and Rawson (2010), the estimate shrunk by 62% and the replication p-value was only significant because the sample size was increased by a factor of $c = 9.2$.

This analysis was based on the default choice $d_\infty = 1$ at $\alpha = 0.025$ for the golden level as described in Section 2.2. We may also choose a different value for the limiting relative effect size d_∞ at $\alpha = 0.025$ which then corresponds to $d_\infty = 1$ at a different level α' as given in (9). Figure 7 compares the proportion of successful replications with the replication success approach for $d_\infty \in (0.5, 1.1)$ with the two-trials rule at the corresponding levels $\alpha' \in (0.06, 0.022)$ for all four replication projects. We can see that the two proportions agree fairly well for all values of α' considered. The number of discrepant studies in each project varies between 0 and 3. Only in the Psychology project there are some studies which are successful with the replication success approach but not the two-trials rule and some studies successful with the two-trials rule but not the replication success approach. The proportion of studies where both methods are successful (also shown in Figure 7) is then smaller than the proportion of successful replications with either one of the two methods. The three discrepant studies from the Psychology project listed in the top three rows of Table 2 are an example of this particular feature.

5 Discussion

In this paper, we have expanded on the replication success approach introduced in Held (2020b) and demonstrated its advantages over alternative methods such as the two-trials rule. In particular, the method provides an attractive compromise between hypothesis testing and

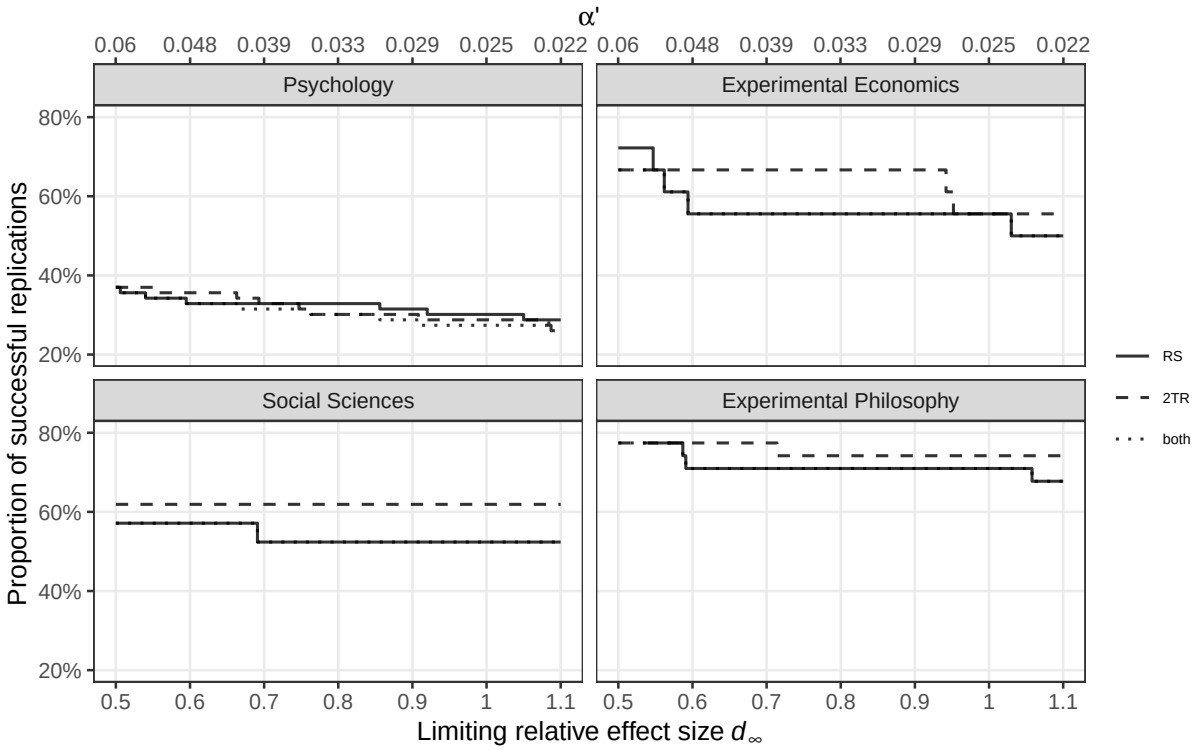

Figure 7: Proportion of successful replications as a function of the limiting relative effect size d_∞ at $\alpha = 0.025$. The upper axis gives the equivalent level α' where the corresponding limiting relative effect size is 1. The replication success (RS) approach is compared with the two-trials rule (2TR).

estimation, as it penalizes shrinkage of the replication effect estimate compared to the original one, while ensuring that both are statistically significant to some extent.

We further refined the method by proposing the golden level, a new threshold for replication success. It guarantees that borderline significant original studies can only be replicated successfully if the replication effect estimate is larger than the original one. Compared to the two-trials rule, the golden level offers uniform gains in project power and controls the Type I error rate at any one-sided level $\alpha < 0.058$ if the replication sample size is not smaller than the original one. Empirical evaluation of data from four replication projects highlights that in most cases the methods are in agreement, however, for the study pairs where the approaches disagree, the replication success approach seems to lead to more sensible conclusions. The good performance has been recently confirmed by a comparison of different replication success metrics through a simulation study in the presence of publication bias (Muradchanian et al., 2021).

Despite a lack of agreement as to which statistical method should be used to evaluate replication studies, conclusions based on different methods usually agree. Nevertheless, in some cases, classical methods such as the two-trials rule may produce anomalies. We argue that the replication success approach improves upon existing methods leading to more appropriate inferences and decisions that better reflect the available evidence. However, in extreme cases the performance of the sceptical p-value may be considered as strange or even counterintuitive.

Specifically, if the original study was only borderline significant, a highly significant replication study can only lead to success if the replication effect estimate is larger than the original one. To understand this behaviour it is important to realize that the proposed approach does not synthesize the evidence from the two studies (like a standard meta-analysis). The sceptical p-value is designed to confirm claims of new discoveries through replication, but will remain "stubborn" (Ly and Wagenmakers, 2020) if the original study was not particularly convincing, even if the replication study provides overwhelming evidence for an effect. It will lead to a different result if the order of studies was reversed, as long as original and replication study do not have the same sample size ($c \neq 1$). The related harmonic mean χ^2-test (Held, 2020a) for evidence synthesis of two or more studies also requires each study to be convincing on its own to a certain degree, but treats them as exchangeable.

With this paper we further advanced the reverse-Bayes methodology for the analysis and design of replication studies, yet certain limitations and opportunities for future research remain: First, assuming normality of the effect estimates may be questionable, especially for small sample sizes, and more robust distributional assumptions could be considered. Second, in some types of analyses (e. g., regression or ANOVA) the effect estimate is a vector and the approach would need suitable adaptations. Third, there is a recent trend to not only conduct one but several replications for one original study (e. g., Klein et al., 2014; Ebersole et al., 2016; Klein et al., 2018). Also for this situation, the method would need to be adapted, e. g., the replication estimates could be first synthesized and an analysis of replication success could be performed subsequently.

Throughout the paper we have assumed that the relative sample size is fixed in advance. In practice the sample size of the replication study is often chosen based on the result of the original study (Anderson and Maxwell, 2017). Power calculations as shown in Figure 3 can then be inverted to determine the appropriate sample size of the replication study. We can also invert equation (6) to obtain the required replication sample size based on the specification of the minimum relative effect size $d_{\min}$ to achieve replication success. This novel way of calculating the sample size requires the specification of the minimum relative effect size which can still be considered as acceptable. Sample size calculations based on the two-trials rule can also be formulated in terms of the minimum relative effect size by inverting equation (2). We will report on a detailed comparison of the different approaches in future work.

Data and Software

Code and data to reproduce the analyses are available at `https://github.com/SamCH93/RSgolden/`. A snapshot of the Git repository at the time of writing is archived at `https://doi.org/10.5281/zenodo.7437689`. The data is available in the R package `ReplicationSuccess` (available on CRAN). Further information can be found on the corresponding help page (with the command `?RProjects`).

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PAPER II

The sceptical Bayes factor for the assessment of replication success

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Abstract

Replication studies are increasingly conducted but there is no established statistical criterion for replication success. We propose a novel approach combining reverse-Bayes analysis with Bayesian hypothesis testing: a sceptical prior is determined for the effect size such that the original finding is no longer convincing in terms of a Bayes factor. This prior is then contrasted to an advocacy prior (the reference posterior of the effect size based on the original study), and replication success is declared if the replication data favour the advocacy over the sceptical prior at a higher level than the original data favoured the sceptical prior over the null hypothesis. The sceptical Bayes factor is the highest level where replication success can be declared. A comparison to existing methods reveals that the sceptical Bayes factor combines several notions of replicability: it ensures that both studies show sufficient evidence against the null and penalises incompatibility of their effect estimates. Analysis of asymptotic properties and error rates, as well as case studies from the Social Sciences Replication Project show the advantages of the method for the assessment of replicability.

Key words: Bayes factor, Bayesian hypothesis testing, replication studies, reverse-Bayes, sceptical *p*-value

1 Introduction

As a consequence of the so-called replication crisis, the scientific community increasingly recognises the value of replication studies, and several attempts have been made to assess replicability on a large scale (Errington et al., 2014; Klein et al., 2014; Open Science Collaboration, 2015; Camerer et al., 2016, 2018; Cova et al., 2018). Despite most researchers agreeing on the importance of replication, there is currently no agreement on a statistical criterion for replication success. Instead, a variety of statistical methods, frequentist (Simonsohn, 2015; Patil et al., 2016; Hedges and Schauer, 2019; Mathur and VanderWeele, 2020), Bayesian (Bayarri and Mayoral, 2002a,b; Verhagen and Wagenmakers, 2014; Johnson et al., 2016; Etz and Vandekerckhove, 2016; van Aert and van Assen, 2017; Ly et al., 2018; Harms, 2019), and combinations thereof (Held, 2020; Pawel and Held, 2020; Held et al., 2022b) have been proposed to quantify replication success.

Due to this lack of an established method, replication projects typically report the results of several methods and it is not uncommon for these to contradict each other. For example, both studies may find evidence against a null effect, but the individual effect estimates may still be incompatible (often the replication estimate is much smaller). Conversely, both estimates may be compatible, but there may not be enough evidence against a null effect in one of the studies.

The objective of this paper is to present a novel Bayesian method for quantifying replication success, which builds upon a previously proposed method (the *sceptical p-value* from Held, 2020) and unifies several notions of replicability. The method combines the natural fit of the reverse-Bayes approach to the replication setting with the use of Bayes factors for hypothesis testing (Jeffreys, 1961; Kass and Raftery, 1995) and model criticism (Box, 1980). In a nutshell,

replication success is declared if the replication data favour an advocacy prior for the effect size, which emerges from taking the original result at face value, over a sceptical prior, which renders the original result unconvincing.

Held (2020) proposed a reverse-Bayes approach for the assessment of replication success: The main idea is to challenge the result from an original study by determining a *sceptical prior* for the effect size, sufficiently concentrated around the null value such that the resulting posterior is rendered unconvincing (Matthews, 2001). An unconvincing posterior at level α is defined by its $(1 - \alpha)$ credible interval just including the null value. Subsequently, the replication data are used in a prior-data conflict assessment (Box, 1980; Evans and Moshonov, 2006) and replication success is concluded if there is sufficient conflict between the sceptical prior and the replication data. Specifically, replication success at level α is established if the prior predictive tail probability of the replication estimate is smaller than α. The smallest level α at which replication success can be declared corresponds to the sceptical p-value.

The method comes with appealing properties: The sceptical p-value is never smaller than the ordinary p-values from both studies, thus ensuring that they both provide evidence against the null. At the same time, it also takes into account the size of their effect estimates, penalising the case when the replication estimate is smaller than the original estimate. Held et al. (2022b) further refined the method with a recalibration that allows the sceptical p-value to be interpreted on the same scale as an ordinary p-value, as well as ensuring appropriate frequentist properties, such as type I error rate control if the replication sample size is not smaller than in the original study.

Despite the methods' Bayesian nature, it relies on tail probabilities as primary inference tool. An alternative is the Bayes factor, the principled Bayesian solution to hypothesis testing and model selection (Jeffreys, 1961; Kass and Raftery, 1995). In contrast to tail probabilities, Bayes factors have a more natural interpretation and allow for direct quantification of evidence for one hypothesis versus another. In this paper we therefore extend the reverse-Bayes procedure from Held (2020) to use Bayes factors for the purpose of quantifying evidence. This extension was suggested by Consonni (2019) and Pericchi (2020) independently. Interestingly, a similar extension of the reverse-Bayes method from Matthews (2001) was already hinted at by Berger (2001), but to date no one has attempted to realise the idea.

The inclusion of Bayes factors leads to a new quantity which we call the *sceptical Bayes factor*. Unlike standard forward-Bayes methods, but similar to the sceptical p-value, the proposed method combines two notions of replication success: It requires from both studies to show sufficient evidence against the null, while also penalising incompatibility of their effect estimates. However, while the sceptical p-value quantifies compatibility only indirectly through conflict with the sceptical prior, the sceptical Bayes factor evaluates directly how likely the replication data are to occur under an advocacy prior (the reference posterior of the effect conditional on the original study). This direct assessment of compatibility allows for stronger statements about the degree of replication success, and it may also lead to different conclusions in certain situations.

This paper is structured as follows: Section 2 presents the derivation of the sceptical Bayes factor. Its asymptotic and finite sample properties are then compared with other measures of

replication success in Section 3. An extension to non-normal models is presented in Section 4. Section 5 illustrates how the method works in practice using case studies from the *Social Sciences Replication Project* (Camerer et al., 2018). Section 6 provides concluding remarks about strengths, limitations and extensions of the method.

Notation and assumptions

Denote the Bayes factor comparing the plausibility of hypotheses H_1 and H_2 with respect to the observed data x by

$$\mathrm{BF}_{1:2}(x) = \frac{f(x \mid H_1)}{f(x \mid H_2)} = \frac{\int_{\Theta_1} f(x \mid \theta_1) f(\theta_1) \, \mathrm{d}\theta_1}{\int_{\Theta_2} f(x \mid \theta_2) f(\theta_2) \, \mathrm{d}\theta_2},$$

where $f(x \mid H_i)$ is the marginal likelihood of the data under H_i obtained by integrating the likelihood $f(x \mid \theta_i)$ with respect to the prior distribution $f(\theta_i)$ of the model parameters $\theta_i \in \Theta_i$ with $i = 1, 2$. Sometimes we will also write $\mathrm{BF}_{1:2}(x; \phi')$ to indicate that the Bayes factor is evaluated for a specific value ϕ' of a hyperparameter ϕ of one of the model priors. To simplify comparison with p-values we will orient Bayes factors such that lower values indicate more evidence against a null hypothesis.

Let θ denote the effect of a treatment on an outcome of interest. Let $\hat{\theta}_o$ and $\hat{\theta}_r$ denote its maximum likelihood estimates obtained from an original (subscript o) and from a replication study (subscript r), respectively. Let the corresponding standard errors be denoted by σ_o and σ_r, the z-values by $z_o = \hat{\theta}_o / \sigma_o$ and $z_r = \hat{\theta}_r / \sigma_r$, and define the variance ratio as $c = \sigma_o^2 / \sigma_r^2$ and the relative effect estimate as $d = \hat{\theta}_r / \hat{\theta}_o = z_r / (z_o \sqrt{c})$. For many effect size types the variances are inversely proportional to the sample size, i. e., $\sigma_o^2 = \kappa / n_o$ and $\sigma_r^2 = \kappa / n_r$ for some unit variance κ. The variance ratio is then the ratio of the replication to the original sample size $c = n_r / n_o$.

We adopt a meta-analytic framework and consider the effect estimates as the data, rather than their underlying samples, and assume that $\hat{\theta}_k \mid \theta \sim \mathrm{N}(\theta, \sigma_k^2)$ for $k \in \{o, r\}$, i. e., normality of the effect estimates around θ, with known variances equal to their squared standard errors. For studies with reasonable sample size, this framework usually provides a good approximation for a wide range of (suitably transformed) effect size types (Spiegelhalter et al., 2004, chapter 2.4). For example, means and mean differences (no transformation), odds ratios, hazard ratios, risk ratios (logarithmic transformation), or correlation coefficients ("Fisher-z" transformation). We refer to the literature of meta-analysis for details about transformations of effect sizes (e. g., Cooper et al., 2019, chapter 11.6). The normal model in combination with conjugate priors enables derivation of closed-form expressions in many cases, which allows us to easily study limiting behaviour and facilitates interpretability. In Section 4, we will present relaxations of the normality assumption, which can lead to more accurate inferences when studies have small sample sizes and/or show extreme results.

2 Reverse-Bayes assessment of replication success with Bayes factors

The idea of reversing Bayes' theorem was first proposed by Good (1950). He acknowledged that in many situations there is no obvious choice for the prior distributions involved in Bayesian analyses. On the other hand, we are often more certain which posterior inferences would convince us regarding the credibility of a hypothesis. For this reason, Good inverted Bayes' theorem and derived priors, which combined with the observed data, would lead to posterior inferences that were specified beforehand (e. g., the data favour one hypothesis over another). His reverse-Bayes inference then centred around the question whether the resulting prior is plausible, and if so, this would legitimise the posterior inference. See Figure 1 for a graphical illustration of this process.

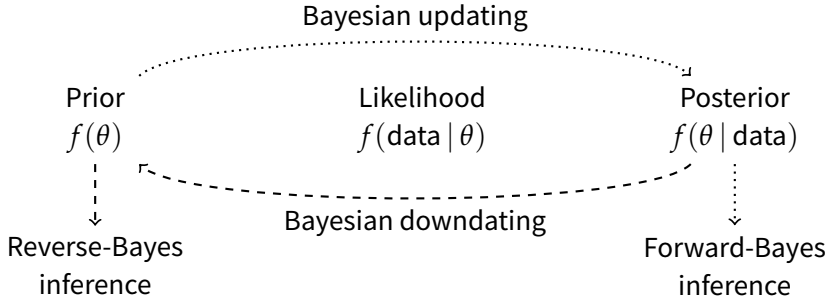

Figure 1: Schematic illustration of reverse-Bayes and forward-Bayes inference for an unknown parameter θ.

Good argued that philosophically there is nothing wrong with inferences resulting from backwards use of Bayes' theorem, since the theorem merely constrains prior and posterior to be consistent with the laws of probability (regardless of their conventional names suggesting a particular temporal ordering). Despite his advocacy, the reverse-Bayes idea remained largely unexplored until Matthews (2001) introduced the *Analysis of Credibility*, which in turn led to new developments in reverse-Bayes methodology (see Held et al. (2022a) for a recent review). Most of these approaches use the reversal of Bayes' theorem in order to challenge or substantiate the credibility of scientific claims. Usually, a posterior inference corresponding to (non-)credibility of a claim is specified, and the associated prior is then derived from the data. Inference is subsequently carried out based on this reverse-Bayes prior, e. g., the interest is often to check whether the prior is plausible in light of external evidence, an obvious candidate being data from a replication study. This can be done, for example, using methods to assess prior-data conflict (Box, 1980; Evans and Moshonov, 2006).

In this paper, we consider a reverse-Bayes procedure consisting of two stages that naturally fit the replication setting: We first determine a *sufficiently sceptical prior* for the effect θ such that the original result is no longer convincing in terms of a suitable Bayes factor. Using another Bayes factor, we then quantify replication success by comparing how likely the replication data are predicted by the sufficiently sceptical prior relative to an *advocacy prior*, which is the posterior of the effect θ conditional on the original data and an uninformative/reference prior. Box 1 provides a summary of the procedure, the following sections will explain it in more detail.

1. **Original study**: For the original effect estimate $\hat{\theta}_o \,|\, \theta \sim \mathrm{N}(\theta, \sigma_o^2)$ consider the point null hypothesis $H_0\colon \theta = 0$ vs. $H_\mathrm{S}\colon \theta \neq 0$. Fix a level $\gamma \in (0,1)$ and determine the sufficiently sceptical prior under the alternative $\theta \,|\, H_\mathrm{S} \sim \mathrm{N}(0, g_\gamma \cdot \sigma_o^2)$ such that the Bayes factor contrasting H_0 to H_S is

$$\mathrm{BF}_{0:\mathrm{S}}(\hat{\theta}_o; g_\gamma) = \gamma.$$

   The prior $\theta \,|\, H_\mathrm{S}$ represents a *sceptic* who remains unconvinced about the presence of an effect at level γ.

2. **Replication study**: For the replication effect estimate $\hat{\theta}_r \,|\, \theta \sim \mathrm{N}(\theta, \sigma_r^2)$ compute the Bayes factor contrasting the sceptic $H_\mathrm{S}\colon \theta \sim \mathrm{N}(0, g_\gamma \cdot \sigma_o^2)$ to an advocate $H_\mathrm{A}\colon \theta \sim \mathrm{N}(\hat{\theta}_o, \sigma_o^2)$. Declare *replication success* at level γ if

$$\mathrm{BF}_{\mathrm{S:A}}(\hat{\theta}_r; g_\gamma) \leq \gamma,$$

   i. e., the data favour the advocate over the sceptic at a higher level than the sceptic's initial objection.

→ The *sceptical Bayes factor* BF_S is the smallest level γ at which replication success can be declared.

Box 1: Summary of reverse-Bayes assessment of replication success with Bayes factors.

2.1 Data from the original study

For the effect estimate $\hat{\theta}_o \,|\, \theta \sim \mathrm{N}(\theta, \sigma_o^2)$ from the original study consider a hypothesis test comparing the null hypothesis $H_0\colon\ \theta = 0$ to the alternative $H_\mathrm{S}\colon\ \theta \neq 0$. Specification of a prior distribution for θ under H_S is now required for Bayesian hypothesis testing. A typical choice (Jeffreys, 1961) is a local alternative, a unimodal symmetric prior distribution centred around the null value. We consider the sceptical prior $\theta \,|\, H_\mathrm{S} \sim \mathrm{N}(0, \sigma_s^2 = g \cdot \sigma_o^2)$ with relative sceptical prior variance g for this purpose (relative to the variance from the original estimate $g = \sigma_s^2/\sigma_o^2$), resembling the g-prior known from the regression literature (Zellner, 1986; Liang et al., 2008). The explicit form of the Bayes factor is then given by

$$\mathrm{BF}_{0:\mathrm{S}}(\hat{\theta}_o; g) = \sqrt{1+g} \cdot \exp\left\{-\frac{1}{2} \cdot \frac{g}{1+g} \cdot z_o^2\right\}. \tag{1}$$

The Bayes factor from equation (1) is shown in Figure 2 as a function of g and for different original z-values z_o. For fixed z_o, it is well known that this Bayes factor is bounded from below by

$$\mathrm{minBF}_o = \begin{cases} |z_o| \cdot \exp(-z_o^2/2) \cdot \sqrt{e} & \text{for } |z_o| > 1 \\ 1 & \text{for } |z_o| \leq 1 \end{cases} \tag{2}$$

which is reached at $g_{\text{minBF}_o} = \max\{0, z_o^2 - 1\}$ (Edwards et al., 1963). Further increasing the relative sceptical prior variance increases (1) indefinitely because of the Jeffreys-Lindley paradox, i. e., $\text{BF}_{0:\text{S}}(\hat{\theta}_o; g) \to \infty$ for $g \to \infty$ (Bernardo and Smith, 2000, Section 6.1.4). Hence, for a relative sceptical prior variance $g \in [0, g_{\text{minBF}_o}]$, the resulting Bayes factor will be $\text{BF}_{0:\text{S}}(\hat{\theta}_o; g) \in [\text{minBF}_o, 1]$.

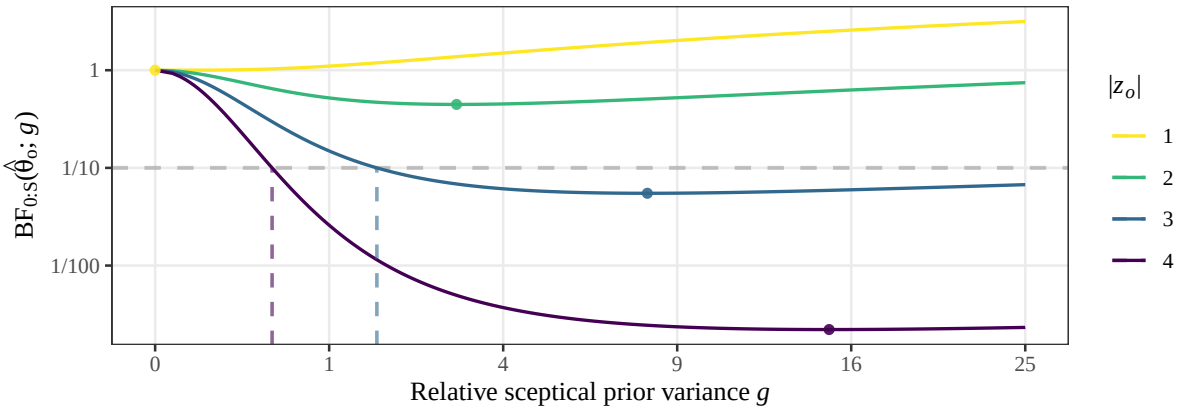

Figure 2: Bayes factor $\text{BF}_{0:\text{S}}(\hat{\theta}_o; g)$ as a function of relative sceptical prior variance g for different values of $|z_o| = |\hat{\theta}_o|/\sigma_o$. Minimum Bayes factors minBF_o are indicated by dots. Dashed vertical lines indicate sufficiently sceptical relative prior variance g_γ at level $\gamma = 1/10$, if they exist.

We now apply the reverse-Bayes idea and challenge the original finding. To do so, we fix a level γ above which the original finding is no longer convincing to us. For example, this could be $\gamma = 1/10$; the threshold for strong evidence against H_0 according to the classification from Jeffreys (1961). Suppose now there exists a $g_\gamma \leq g_{\text{minBF}_o}$ such that $\text{BF}_{0:\text{S}}(\hat{\theta}_o; g_\gamma) = \gamma$. It can be shown (Appendix A) that g_γ can be explicitly computed by

$$g_\gamma = \begin{cases} -\dfrac{z_o^2}{q} - 1 & \text{if } -\dfrac{z_o^2}{q} \geq 1 \\ \text{undefined} & \text{else} \end{cases} \tag{3}$$

$$\text{where } q = \text{W}_{-1}\left(-\frac{z_o^2}{\gamma^2} \cdot \exp\left\{-z_o^2\right\}\right)$$

with $\text{W}_{-1}(\cdot)$ the branch of the Lambert W function (Corless et al., 1996) that satisfies $\text{W}(y) \leq -1$ for $y \in [-e^{-1}, 0)$, see Appendix B for details about the Lambert W function. The sufficiently sceptical prior is then given by $\theta \mid H_\text{S} \sim \text{N}(0, g_\gamma \cdot \sigma_o^2)$ and it can be interpreted as the view of a sceptic who argues that given their prior belief about the effect θ, the observed effect estimate $\hat{\theta}_o$ cannot convince them about the presence of a non-null effect at level γ. An alternative data-based interpretation of sufficiently sceptical priors is to see them as the priors obtained by updating an initial uniform prior with the data from an imaginary study, which was $1/g_\gamma$ times the size of the original study, and which resulted in an effect estimate of exactly zero (Held et al., 2022a).

From Figure 2 we can see that the more compelling the original data (i. e., the larger $|z_o|$), the smaller the sufficiently sceptical relative prior variance g_γ needs to be in order to make

the result no longer convincing at level γ. In the most extreme case, when $|z_o| \to \infty$ and γ remains fixed, the sufficiently sceptical prior variance will converge to zero (Appendix B). On the other hand, if $|z_o|$ is not sufficiently large, $\text{BF}_{0:\text{S}}(\hat{\theta}_o; g)$ will either be always increasing in g (if $|z_o| \leq 1$) or it will reach a minimum above the chosen level γ. In both cases the sufficiently sceptical relative prior variance g_γ is not defined since there is no need to challenge an already unconvincing result.

A side note on the Jeffreys-Lindley paradox is worth being mentioned: If a $g_\gamma < g_{\text{minBF}_o}$ exists, there exists also a $g'_\gamma > g_{\text{minBF}_o}$ as the Bayes factor monotonically increases in $g > g_{\text{minBF}_o}$ and therefore must intersect a second time with γ, due to the paradox. This means that the more compelling the original result, the larger g'_γ needs to be chosen, such that the result becomes no longer convincing at level γ. However, priors which become increasingly diffuse do not represent increasing scepticism but rather increasing ignorance. Using (17) therefore avoids this manifestation of the Jeffreys-Lindley paradox, since it determines sceptical priors only from the class of priors that become increasingly concentrated for increasing evidence (i. e., priors with $g_\gamma \leq g_{\text{minBF}_o}$). In principle, the solution $g'_\gamma > g_{\text{minBF}_o}$ could also be computed by replacing the W_{-1} branch of the Lambert W function in (17) with the W_0 branch, but this will not be of interest to us.

2.2 Data from the replication study

In order to assess whether the original finding can be replicated in an independent study, a replication study is conducted, leading to a new effect estimate $\hat{\theta}_r$. In light of the new data, the sceptic is now challenged by an advocate of the original finding. This is formalised with another Bayes factor, which compares the plausibility of the replication effect estimate $\hat{\theta}_r \,|\, \theta \sim \text{N}(\theta, \sigma_r^2)$ under the sceptical prior $H_\text{S}\colon\ \theta \sim \text{N}(0, g \cdot \sigma_o^2)$ relative to the advocacy prior $H_\text{A}\colon\ \theta \sim \text{N}(\hat{\theta}_o, \sigma_o^2)$. The the view of an advocate is represented by H_A since this is the posterior of θ given the original estimate and a uniform prior (also the reference prior for this model). The Bayes factor is given by

$$\text{BF}_{\text{S:A}}(\hat{\theta}_r; g) = \sqrt{\frac{1/c+1}{1/c+g}} \cdot \exp\left\{-\frac{z_o^2}{2}\left(\frac{d^2}{1/c+g} - \frac{(d-1)^2}{1/c+1}\right)\right\} \tag{4}$$

so it depends on the original z-statistic z_o, the relative sceptical prior variance g, the relative effect estimate $d = \hat{\theta}_r/\hat{\theta}_o$, and the relative variance $c = \sigma_o^2/\sigma_r^2$.

Our goal is now to define a condition for *replication success* in terms of (4). It is natural to consider a replication successful if the replication data favour the advocate over the sceptic to a higher degree than the sceptic's initial objection to the original study. More formally, we say that if the Bayes factor from (4) evaluated at the sufficiently sceptical relative prior variance g_γ is not larger than the corresponding level γ used to define the sufficiently sceptical prior:

$$\text{BF}_{\text{S:A}}(\hat{\theta}_r; g_\gamma) \leq \text{BF}_{0:\text{S}}(\hat{\theta}_o; g_\gamma) = \gamma, \tag{5}$$

we have established *replication success at level* γ.

For example, if we observe $z_o = 3$ (equivalent to minimum Bayes factor $\text{minBF}_o = 1/18$) and choose a level $\gamma = 1/10$ the sufficiently sceptical relative prior variance (17) is $g_\gamma = 1.6$. If a replication is conducted with the same precision ($c = 1$) and we observe $z_r = 2.5$ (equivalent to minimum Bayes factor $\text{minBF}_r = 1/5.5$ and relative effect estimate $d = z_r/(z_o\sqrt{c}) = 0.83$), using equation (4) this would lead to $\text{BF}_{\text{S:A}}(\hat{\theta}_r; 1.6) = 1/3.5$, which means that the replication was not successful at level $\gamma = 1/10$. However, if we had chosen a less stringent level, e. g., $\gamma = 1/3$, the replication would have been considered successful since then $g_\gamma = 0.4$ and $\text{BF}_{\text{S:A}}(\hat{\theta}_r; 0.4) = 1/7.4$.

2.3 The sceptical Bayes factor

Apart from specifying a level γ, the described procedure offers an automated way to assess replication success. One way to remove this dependence is to find the smallest level γ where replication success can be established. We thus call this level the *the sceptical Bayes factor*

$$\text{BF}_\text{S} = \inf\left\{\gamma : \text{BF}_{\text{S:A}}(\hat{\theta}_r; g_\gamma) \leq \gamma\right\}, \tag{6}$$

and replication success at level γ is equivalent with $\text{BF}_\text{S} \leq \gamma$.

Figure 3 shows $\text{BF}_{\text{S:A}}(\hat{\theta}_r; g_\gamma)$ and $\text{BF}_{\text{0:S}}(\hat{\theta}_o; g_\gamma)$ as a function of g_γ for several values of z_o and d along with the corresponding BF_S. Typically, BF_S is given by the height of the intersection between $\text{BF}_{\text{S:A}}(\hat{\theta}_r; g_\gamma)$ and $\text{BF}_{\text{0:S}}(\hat{\theta}_o; g_\gamma)$ in g_γ. It may also happen that $\text{BF}_{\text{S:A}}(\hat{\theta}_r; g_\gamma)$ remains below $\text{BF}_{\text{0:S}}(\hat{\theta}_o; g_\gamma)$ for all values of g_γ, in such situations BF_S is equal to the original minimum Bayes factor minBF_o. Finally, in some pathological cases it may happen that either z_o, d, or both are so small that replication success cannot be established for any level γ and hence BF_S does not exist. This means that the replication study was unsuccessful since it is impossible for the advocate to convince the sceptic at any level of evidence.

In terms of computing the sceptical Bayes factor, it is worth noting that for the special case when the replication is conducted with the same precision as the original study ($c = 1$) and BF_S is located at the intersection of $\text{BF}_{\text{S:A}}(\hat{\theta}_r; g)$ and $\text{BF}_{\text{0:S}}(\hat{\theta}_o; g)$ in g, there is an explicit expression for BF_S

$$\text{BF}_\text{S} = \sqrt{-\frac{z_o^2}{k} \cdot \frac{1+d^2}{2}} \cdot \exp\left\{-\left(\frac{z_o^2}{2} + \frac{k}{1+d^2}\right)\right\} \tag{7}$$

with

$$k = \text{W}\left(-\frac{z_o^2}{\sqrt{2}} \cdot \frac{d^2+1}{2} \cdot \exp\left\{-\frac{z_o^2}{2}\left[1 + \frac{(1-d)^2}{2}\right]\right\}\right),$$

see Appendix C for details.

3 Properties

To study properties of the sceptical Bayes factor and facilitate comparison with other methods we will look at the requirements for replication success based on the relative effect estimate

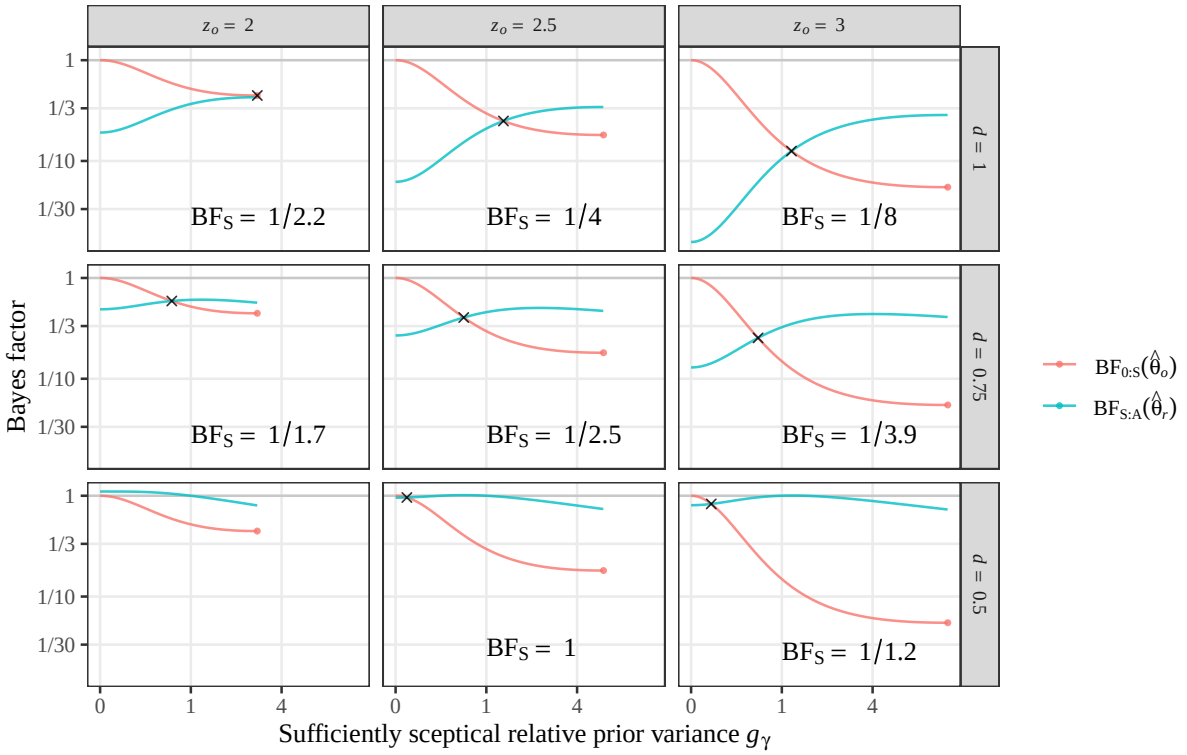

Figure 3: Bayes factors $\text{BF}_{\text{S:A}}(\hat{\theta}_r; g)$ and $\text{BF}_{\text{0:S}}(\hat{\theta}_o; g)$ as a function of the sufficiently sceptical relative prior variance g_γ. In all examples $c = \sigma_o^2/\sigma_r^2 = 1$. Minimum Bayes factors minBF_o are indicated by dots, sceptical Bayes factors BF_S are indicated by crosses where existent.

$d = \hat{\theta}_r/\hat{\theta}_o$, the variance ratio $c = \sigma_o^2/\sigma_r^2$ and the original minimum Bayes factor minBF_o (respectively the original z-value z_o). This perspective is helpful because it disentangles how the method reacts to changes in compatibility of the effect estimates (d), evidence from the original study (minBF_o), and the change in sample size of the replication compared to the original study (c).

The condition for replication success at level γ from (5) is equivalent to

$$\log\left\{\frac{1/c+1}{(1/c+g_\gamma)(1+g_\gamma)}\right\} + \frac{z_o^2}{1+1/g_\gamma} \leq z_o^2\left(\frac{d^2}{1/c+g_\gamma} - \frac{(d-1)^2}{1/c+1}\right). \tag{8}$$

On the right-hand side of (8) the Q-statistic

$$Q = \frac{(\hat{\theta}_o - \hat{\theta}_r)^2}{\sigma_o^2 + \sigma_r^2} = \frac{z_o^2(d-1)^2}{1/c+1} \tag{9}$$

appears. The Q-statistic was proposed as a measure of incompatibility among original and replication effect estimates since its distribution is known for standard meta-analytic models of effect sizes (Hedges and Schauer, 2019). The connection to the sceptical Bayes factor is such that Q acts as a penalty term in (8) and a larger value will lower the degree of replication success possible. However, as we will see, the sceptical Bayes factor goes beyond assessing

effect estimate compatibility as there is also a trade-off with the amount of evidence that the replication study provides against the null.

Applying some algebraic manipulations to (8), one can show that replication success at level γ is achieved if and only if the relative effect estimate d falls within a success region given by

$$\begin{cases} d \notin [M - \sqrt{A/B}, M + \sqrt{A/B}] & \text{if } g_\gamma < 1 \\ d \geq [1 + (1 + 1/c)\{1/2 - \log(2)/z_o^2\}]/2 & \text{if } g_\gamma = 1 \\ d \in [M - \sqrt{A/B}, M + \sqrt{A/B}] & \text{if } g_\gamma > 1 \end{cases} \tag{10}$$

where

$$\begin{aligned} M &= \frac{1/c + g_\gamma}{g_\gamma - 1} \\ A &= \log\left\{\frac{1/c + 1}{(1/c + g_\gamma)(1 + g_\gamma)}\right\} \Big/ z_o^2 + \frac{g_\gamma}{1 + g_\gamma} + \frac{1}{1 - g_\gamma} \\ B &= \frac{1 - g_\gamma}{(1/c + g_\gamma)(1/c + 1)}. \end{aligned}$$

The top-left plot in Figure 4 shows the conditions on d from (10) to achieve replication success at level $\gamma = 1/3$ as a function of the original minimum Bayes factor minBF_o and for different values of the relative variance c. It is important to note that $\gamma = 1/3$ is an arbitrary choice and in practice one should interpret the sceptical Bayes factor as a quantitative measure of replication success. Only the success regions for positive d are shown as replication success in the opposite direction is usually not of interest (see Section 3.2 for a discussion of this issue). We see that with increased precision of the replication study (larger c), the success regions shift closer to zero. This means that the method allows for more shrinkage of the replication effect estimate when the replication provides more evidence against the null (because $|z_r| = d\,|z_o|\,\sqrt{c}$ increases with increasing c). However, the success regions cannot be pushed arbitrarily close to zero but are bounded away. So when $c \to \infty$ the methods still requires the replication estimate to be sufficiently large, despite that the evidence against the null becomes overwhelming (since $|z_r| \to \infty$ as $c \to \infty$).

By definition the sceptical Bayes factor can never be smaller than minBF_o, so replication success at level γ is impossible for original studies with $\text{minBF}_o > \gamma$. This property is visible in the top-left plot in Figure 4 by the cut-off at $\text{minBF}_o = \gamma = 1/3$. In contrast, for more convincing original studies with $\text{minBF}_o < 1/3$ replication success is possible and two cases can be distinguished in terms of the success region: When $1/4.5 < \text{minBF}_o \leq 1/3$ the sufficiently sceptical relative prior variance is $g_\gamma > 1$ and thus by condition (10) the success region consists of an interval $(d_{\text{min}}, d_{\text{max}})$. Hence, in this case the method also penalises too large replication effect estimates. For original studies with $\text{minBF}_o < 1/4.5$, the sufficiently sceptical relative prior variance is $g_\gamma \leq 1$, so due to (10) the success region for positive d is given by $(d_{\text{min}}, d_{\text{max}} = \infty)$. This means that for more convincing original studies there are no upper restrictions for the relative effect estimate, whereas shrinkage of the replication estimate is still penalised.

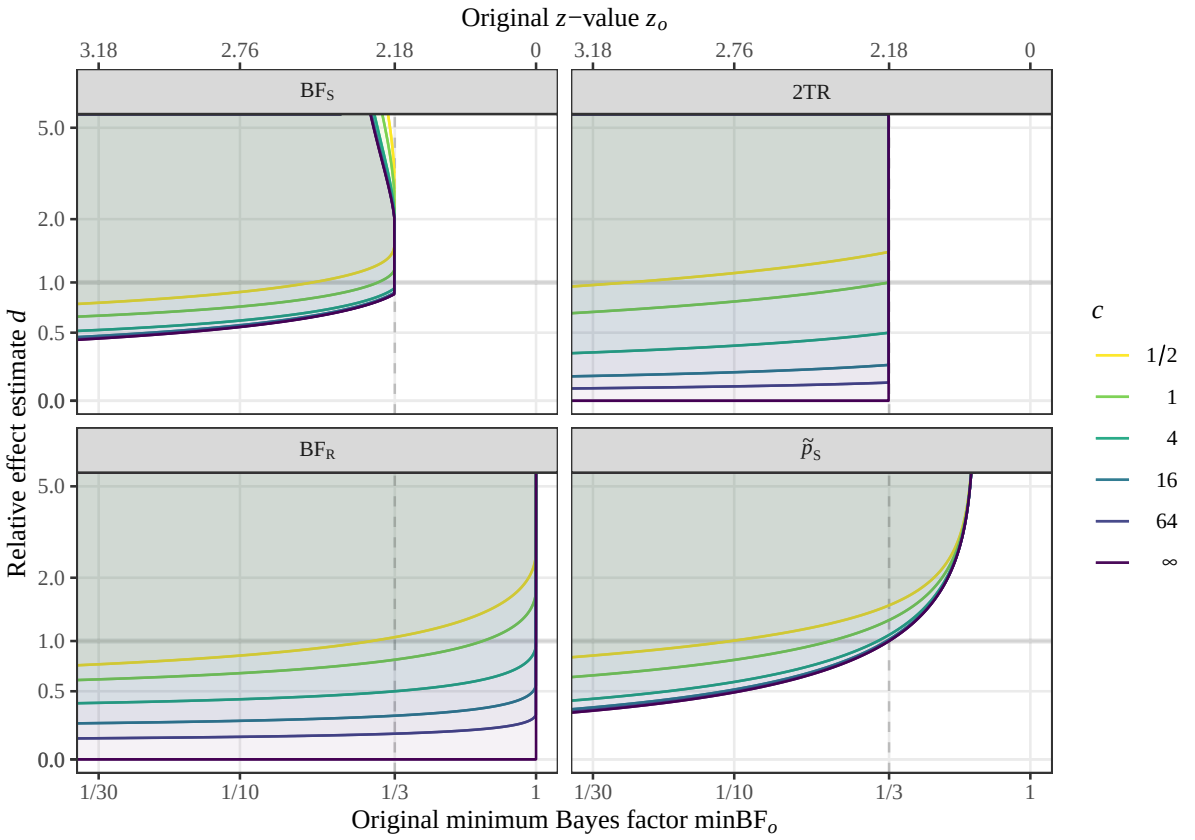

Figure 4: Required relative effect estimate $d = \hat{\theta}_r/\hat{\theta}_o$ to achieve replication success based on the sceptical Bayes factor ($\text{BF}_\text{S} \leq 1/3$), the two-trials rule (2TR: $\text{minBF}_o \leq 1/3$ and $\text{minBF}_r \leq 1/3$), the replication Bayes factor ($\text{BF}_\text{R} \leq 1/3$), and the recalibrated sceptical p-value ($\tilde{p}_\text{S} \leq 1 - \Phi\{z_\gamma\}$ with $\gamma = 1/3$) as a function of the original minimum Bayes factor minBF_o (respectively the corresponding z-value z_o) for different values of the relative variance $c = \sigma_o^2/\sigma_r^2$. Shading indicates regions where replication success is possible. Only positive relative effect estimates d are shown.

3.1 Comparison with other methods

Of interest is the relationship between the sceptical Bayes factor and other measures of replication success. Here, we review and compare a classical (the two-trials rule), a forward-Bayes (the replication Bayes factor from Verhagen and Wagenmakers, 2014) and a reverse-Bayes method (the sceptical p-value from Held, 2020). These methods provide a useful benchmark as they all are based on hypothesis testing, have unique properties, and can be directly compared in terms of their replication success regions as shown in Figure 4.

The two-trials rule

Replication success is most commonly declared when both original and replication study provide compelling evidence against a null effect. This approach is also known as the *two-trials*

rule in drug development and usually a requirement for drug approval (Kay, 2015, Section 9.4). Most replication projects report p-values associated with the effect estimates as measures of evidence against the null, but also default Bayes factors have been used (see e. g., the Bayesian supplement of Camerer et al., 2018). To compare the two-trials rule with methods based on Bayes factors we will study the two-trials rule based on the minimum Bayes factor from (2), i. e., replication success at level γ is established when both $\text{minBF}_k \leq \gamma$ for $k \in \{o, r\}$, as well as $\text{sign}(\hat{\theta}_o) = \text{sign}(\hat{\theta}_r)$. This approach has a one-to-one correspondence to the usual version of two-trials rule as minimum Bayes factors and p-values both only depend on the z-values of original and replication study.

The two-trials rule guarantees that both studies provide compelling evidence against the null. Similarly, the sceptical Bayes factor requires the original study to be compelling on its own since it can never be smaller than minBF_o. However, one can easily construct examples where the sceptical Bayes factor is smaller than the minimum Bayes factor from the replication study (e. g., when $\text{minBF}_o = 1/2$, $\text{minBF}_r = 1/1.5$, and $c = 1$ we obtain $\text{BF}_\text{S} = 1/1.9$). So for the same level of replication success γ the two-trials may not flag replication success whereas the sceptical Bayes factor would.

By definition the two-trials rule can never be fulfilled when the original study was uncompelling. Assuming now that $\text{minBF}_o < \gamma$, replication success with the two-trials rule at level γ is achieved if and only if the relative effect estimate is

$$d \geq \frac{z_\gamma}{z_o \sqrt{c}} \tag{11}$$

with $z_\gamma > 1$ corresponding to $\text{minBF} = z_\gamma \exp(-z_\gamma^2/2)\sqrt{e} = \gamma$. The success region from (11) is displayed in the top-right plot of Figure 4. We see that the success regions shift closer to zero as the relative variance c increases. Also there is a cut-off at $\text{minBF}_o = \gamma = 1/3$ similarly as with the sceptical Bayes factor. In contrast to the sceptical Bayes factor, however, the two-trials can be fulfilled for any arbitrary small (but positive) relative effect estimate d, provided the relative variance c is large enough. Hence, the two-trials rule may flag success even when the replication effect estimate is much smaller than the original one.

The replication Bayes factor

Verhagen and Wagenmakers (2014) proposed the *replication Bayes factor* as a measure of replication success. It is defined as the Bayes factor comparing the point null hypothesis $H_0 \colon \theta = 0$, to the alternative that the effect is distributed according to the posterior distribution of θ after observing the original data. For the normal model considered so far and if an initial reference prior was chosen, this alternative is also the advocacy prior $H_\text{A} \colon \theta \sim \text{N}(\hat{\theta}_o, \sigma_o^2)$ and therefore the replication Bayes factor is given by

$$\text{BF}_\text{R} = \text{BF}_{\text{0:A}}(\hat{\theta}_r) = \sqrt{1+c} \cdot \exp\left\{ -\frac{z_o^2}{2} \left(d^2 \cdot c - \frac{(1-d)^2}{1/c+1} \right) \right\}. \tag{12}$$

Similarly, as with the sceptical Bayes factor, the Q-statistic from (9) appears in (12) and acts as a penalty term, i. e., larger values of Q lower the degree of replication success. However, in

contrast to the sceptical Bayes factor, the replication Bayes factor is not limited by the evidence from the original study because $\text{BF}_\text{R} \downarrow 0$ as $c \to \infty$ provided $z_o \neq 0$ and $d \neq 0$. Moreover, we have that

$$1 \geq \text{BF}_\text{S} \geq \text{BF}_{\text{S:A}}(\hat{\theta}_r; g_{\text{BF}_\text{S}}) = \text{BF}_{\text{S:0}}(\hat{\theta}_r; g_{\text{BF}_\text{S}}) \cdot \underbrace{\text{BF}_{\text{0:A}}(\hat{\theta}_r)}_{=\text{BF}_\text{R}}.$$

So the sceptical Bayes factor is larger than the replication Bayes factor if the replication data favour the sceptical prior $H_\text{S}\colon \theta \sim \text{N}(0, g_{\text{BF}_\text{S}} \cdot \sigma_o^2)$ over the null hypothesis. They can only coincide when $\text{BF}_\text{S} = 1$ since then $g_{\text{BF}_\text{S}} = 0$.

We can also determine conditions on the relative effect estimate in terms of replication success based on $\text{BF}_\text{R} \leq \gamma$. The replication success region is given by

$$d \notin [-\sqrt{J} - H, \sqrt{J} - H] \tag{13}$$

with

$$J = \left\{1 + \frac{\log(1+c) - 2\log\gamma}{z_o^2}\right\} \cdot \frac{1/c + 1}{c}$$
$$H = \frac{1/c + 1}{1 + c}.$$

The condition (13) implies that replication success can also be achieved for negative relative effect estimates d (see Section 3.2 for a discussion of this issue). The bottom-left plot in Figure 4 shows the conditions from (13) for positive relative effect estimates. As with the two-trials rule, the success region of the replication Bayes factor can be pushed arbitrarily close to zero by increasing the relative variance c. In contrast to the two-trials rule, however, replication success can also be achieved for original studies with $\text{minBF}_o > 1/3$.

The sceptical *p*-value

Of particular interest is the relationship between the sceptical Bayes factor and the sceptical p-value (Held, 2020), as it is the outcome of a similar reverse-Bayes procedure. One also considers a sceptical prior for the effect size $\theta \sim \text{N}(0, \tau^2)$, the sufficiently sceptical prior variance at level α is then defined as $\tau^2 = \tau_\alpha^2$ such that the $(1-\alpha)$ credible interval for θ based on the posterior $\theta \,|\, \hat{\theta}_o, \tau_\alpha^2$ does not include zero. Replication success is declared if the tail probability of the replication effect estimate under its prior predictive distribution $\hat{\theta}_r \,|\, \tau_\alpha^2 \sim \text{N}(0, \tau_\alpha^2 + \sigma_r^2)$ is smaller than α. The smallest level α where replication success can be established defines the sceptical p-value. In contrast to the sceptical Bayes factor, the sceptical p-value always exists and there are closed form expressions to compute it for all values of c, i. e., $p_\text{S} = 1 - \Phi(z_\text{S})$ with

$$z_\text{S}^2 = \begin{cases} z_H^2/2 & \text{for } c = 1 \\ \frac{1}{c-1}\left\{\sqrt{z_A^2\left[z_A^2 + (c-1)z_H^2\right]} - z_A^2\right\} & \text{for } c \neq 1 \end{cases}$$

where $z_H^2 = 2/(1/z_o^2 + 1/z_r^2)$ the harmonic mean, $z_A^2 = (z_o^2 + z_r^2)/2$ the arithmetic mean of the squared z-statistics, and provided that $\text{sign}(\hat{\theta}_o) = \text{sign}(\hat{\theta}_r)$ (otherwise $p_\text{S} = \Phi(z_\text{S})$).

Similar to the two-trials rule, the sceptical p-value requires both studies to provide compelling evidence due to the property that $p_S \geq \max\{p_o, p_r\}$. The sceptical p-value also penalises the case when the replication effect estimate shrinks as compared to the original one since it monotonically increases with decreasing relative effect estimate d (Held, 2020, Section 3.1).

Held et al. (2022b) showed that replication success based on $p_S \leq \alpha_S$ is achieved when

$$d \geq \sqrt{\frac{1/c + 1/(K-1)}{K}} \tag{14}$$

with $K = z_o^2/z_{\alpha_S}^2$ where $z_{\alpha_S} = \Phi^{-1}(1-\alpha_S)$. Thresholding the sceptical p-value with the ordinary significance level α for traditional p-values leads to a very stringent criterion for replication success. For example, when $z_o = 2$, $\alpha = 0.025$, and $c = 2$, the replication effect estimate needs to be $d = 4.87$ times larger than the original one. Therefore, Held et al. (2022b) used (14) to determine the *golden level* $\alpha_S = 1 - \Phi(z_\alpha/\sqrt{\varphi})$ with $\varphi = (1+\sqrt{5})/2$ the golden ratio. The golden level ensures that borderline significant original studies ($|z_o| = z_\alpha$) can still achieve replication success provided the replication effect estimate does not shrink compared to the original one ($d \geq 1$). Instead of comparing the sceptical p-value to the golden level ($p_S < \alpha_S$), one can compute a recalibrated sceptical p-value $\tilde{p}_S = 1 - \Phi(z_S\sqrt{\varphi})$ and compare it to the ordinary significance level ($\tilde{p}_S < \alpha$).

The bottom-right plot in Figure 4 shows the success region for the recalibrated sceptical p-value. We see that increasing the precision of the replication study lowers the required minimum relative effect estimate d_{min} as for all other methods. Similarly, as with the sceptical Bayes factor, d_{min} of the sceptical p-value cannot be pushed arbitrarily close to zero. However, its limiting minimum relative effect estimate in c ($\lim_{c\to\infty} d_{\text{min}}$) is smaller than the one from the sceptical Bayes factor when $\text{minBF}_o < 1/5.6$, while for $\text{minBF}_o > 1/5.6$ it is the other way around. So for more convincing original studies the sceptical p-value is less stringent than the sceptical Bayes factor. Due to the recalibration, the sceptical p-value also allows replication success when the $\text{minBF}_o > \gamma$. This is visible in the bottom-right plot of Figure 4 where the success region has no cut-off at $\text{minBF}_o = \gamma = 1/3$, unlike the two-trials rule and the sceptical Bayes factor.

3.2 Paradoxes in the assessment of replication success

The replication setting is different from the classical setting where data from only one study are analysed. As a result, several unique paradoxes may occur.

The replication paradox

The *replication-paradox* (Ly et al., 2018) occurs when original and replication effect estimates go in opposite directions ($\text{sign}(\hat{\theta}_o) \neq \text{sign}(\hat{\theta}_r)$) but a method flags replication success. This is undesired since effect direction is crucial to most scientific theories and research questions.

The two-trials rule and the sceptical p-value both avoid the replication paradox by using one-sided test-statistics. In contrast, the sceptical Bayes factor and the replication Bayes factor

may suffer from the paradox as their success regions from (10) and (13), respectively, include negative relative effect estimates $d < 0$. This is related to the fact that Bayes factors are quantifying relative evidence: When the replication estimate goes in the opposite direction, it will be poorly predicted by the sceptical prior H_S and the advocacy prior H_A, yet when H_S is mostly concentrated around zero (or a point-null in case of the replication Bayes factor), replication estimates going in the opposite direction may still be better predicted by H_A.

In practice, the replication paradox is hardly an issue, since replications rarely show such contradictory results, e. g., to achieve replication success at level $\gamma = 1/3$ with $\text{minBF}_o = 1/10$ and $c = 1$, the relative effect estimate needs to be $d < -7.09$ for the paradox to appear with the sceptical Bayes factor. The replication Bayes factor is more prone to the paradox because its point-null hypothesis fails more strongly to predict estimates in opposite direction, e. g., for the same numbers as before it requires $d < -2.66$.

In both cases the paradox can be overcome by truncating the advocacy prior H_A such that only effects in the same direction as the original estimate $\hat{\theta}_o$ have non-zero probability, i. e., for positive $\hat{\theta}_o$ consider $H_{A'}\colon \theta \sim \text{N}(\hat{\theta}_o, \sigma_o^2)\, \mathbb{1}_{(0,\infty)}(\theta)$, where $\mathbb{1}_B(x)$ is the indicator function of the set B. The Bayes factor contrasting H_S to $H_{A'}$ turns out to be

$$\text{BF}_{\text{S:A}'}(\hat{\theta}_r; g) = \text{BF}_{\text{S:A}}(\hat{\theta}_r; g) \frac{\Phi(|z_o|)}{\Phi\left\{\text{sign}(z_o) \frac{z_o(1+dc)}{\sqrt{1+c}}\right\}} \tag{15}$$

where $\Phi(\cdot)$ is the cumulative distribution function of the standard normal distribution (see Appendix D). Hence, (15) is the Bayes factor under the standard advocacy prior multiplied by a correction term. Determining the smallest level of replication success with (15) leads to a corrected sceptical Bayes factor, while setting $g = 0$ in (15) leads to a corrected replication Bayes factor. The correction term goes to one when the replication estimate goes in the same direction as the original one and the replication sample size increases ($d > 0$ and $c \to \infty$), but it penalises when the replication estimate goes in the opposite direction ($d < 0$ and $c \to \infty$).

This modification guarantees that the replication paradox is avoided and we recommend to compute the sceptical Bayes factor using (15) in cases where the replication paradox is likely to appear. However, truncated priors are unnatural and hard to interpret. Also the non-truncated advocacy prior penalises effect estimate incompatibility and the modification (15) will only make a difference in extreme situations. Due to its easier mathematical treatment we will focus on the standard version of the procedure in the remaining part of the paper.

The shrinkage paradox

The comparison showed that for certain methods replication success is still achievable even when the replication estimate is substantially smaller than the original one. However, a substantially smaller effect estimate in the replication does not reflect an effect size of the same practical importance as the original one and a method should thus not flag replication success. The *shrinkage paradox* occurs if a particular method may flag replication success for any arbitrarily small (but positive) relative effect estimate.

Two forms of the shrinkage paradox can formally be distinguished: the *shrinkage paradox at replication* appears when, for fixed evidence from the original study minBF_o (respectively z_o), the minimum relative effect estimate $d_{\text{min}} > 0$ required for replication success at a fixed level γ becomes arbitrarily small as the relative variance c increases:

$$d_{\text{min}} \downarrow 0 \text{ as } c \to \infty.$$

Held et al. (2022b) found that this form of the paradox occurs for the two-trials rule but not for the sceptical p-value. Similarly, the minimum relative effect estimate d_{min} of the sceptical Bayes factor is bounded away from zero, while it converges to zero for the replication Bayes factor (Appendix E). Hence, among the Bayes factor methods, the sceptical Bayes factor avoids the paradox, whereas the replication Bayes factor suffers from it.

The shrinkage paradox at replication is a serious issue since it depends on the relative variance c which can usually be directly influenced by changing the replication sample size. However, there is also a second form of the paradox which is affected only by evidence from the original study. The *shrinkage paradox at original* appears when, for fixed relative variance c, the minimum relative effect estimate $d_{\text{min}} > 0$ required for replication success at a fixed level γ becomes arbitrarily small as the evidence in the original study increases:

$$d_{\text{min}} \downarrow 0 \text{ as } z_o^2 \to \infty.$$

The replication Bayes factor and the sceptical Bayes factor do not suffer from this form of the paradox, while the two-trials rule and the sceptical p-value do (Appendix E). Hence, with the latter two methods, shrinkage of the replication effect estimate is hardly penalised when the original study was already very convincing.

3.3 Frequentist properties

Despite the fact that Bayesian methods do not rely on repeated testing, it is still often of interest to study their frequentist operating characteristics (Dawid, 1982; Grieve, 2016). This is especially important in the replication setting where regulators and funders usually require from statistical methods to have appropriate error control. We will therefore study and compare type I error rate as well as power of the sceptical Bayes factor and other methods.

Global type I error rate

The probability for replication success at level γ conditional on the original result z_o and the relative variance c can be easily computed as shown in Appendix F. Under the null hypothesis ($H_0 : \theta = 0$) the distribution of the z-values is $z_o, z_r \mid H_0 \sim \text{N}(0, 1)$ and hence the global type I error rate (T1E) based on $\text{BF}_\text{S} \leq \gamma$ is

$$\text{T1E} = 2 \int_{z_\gamma}^{\infty} \Pr(\text{BF}_\text{S} \leq \gamma \mid z_o, c) \phi(z_o) \, \text{d}z_o$$

with $\phi(\cdot)$ the standard normal density function. In a similar fashion one can compute the type I error rate of the sceptical p-value (see Section 3 in Held et al., 2022b), as well as the replication Bayes factor (Appendix G). The type I error rate of the two trials rule is simply $\text{T1E} = 2\{1 - \Phi(z_\gamma)\}^2$.

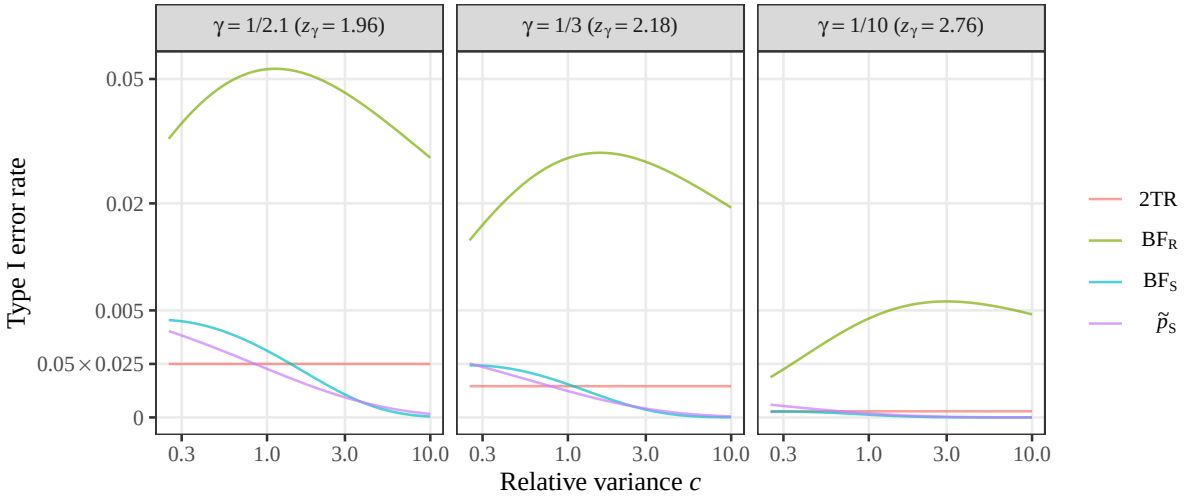

Figure 5: Type I error rate of the two-trials rule (2TR: $\text{minBF}_o \leq \gamma$ and $\text{minBF}_r \leq \gamma$), the replication Bayes factor ($\text{BF}_\text{R} \leq \gamma$), the sceptical Bayes factor ($\text{BF}_\text{S} \leq \gamma$), and the recalibrated sceptical p-value ($\tilde{p}_\text{S} \leq 1 - \Phi\{z_\gamma\}$) as a function of the relative variance $c = \sigma_o^2/\sigma_r^2$ for different levels of replication success γ.

Figure 5 compares the type I error rates of the four methods for different levels γ. The conventional nominal $\text{T1E} = 0.05 \times 0.025$ (two independent experiments with two-sided testing in the first and one-sided testing in the second) along with the corresponding level ($z_\gamma = 1.96$ corresponding to $\gamma = 1/2.1$ and $\alpha = 0.025$) is also indicated. In contrast to the other methods, the type I error rate of the two trials rule does not depend on the relative variance c and therefore does not change for the same level γ. Type I error rates of sceptical p-value and sceptical Bayes factor are decreasing with increasing c, the former usually being slightly smaller than the latter. The point at which both become smaller than the type I error rate from the two-trials rule becomes smaller with more stringent level γ. Roughly speaking the type I error rate of the sceptical Bayes factor is controlled at the conventional level when c is slightly larger than one, while for the sceptical p-value it is controlled when c is slightly below one. Surprisingly, the type I error rate of the replication Bayes factor is non-monotone in c and far higher compared to the other methods. This suggests that a more stringent level γ should be used for the replication Bayes factor compared to the other methods to ensure appropriate type I error control.

Power conditional on the original study

Another frequentist operating characteristic is the probability to establish replication success assuming there is an underlying effect (power). While in principle original and replication

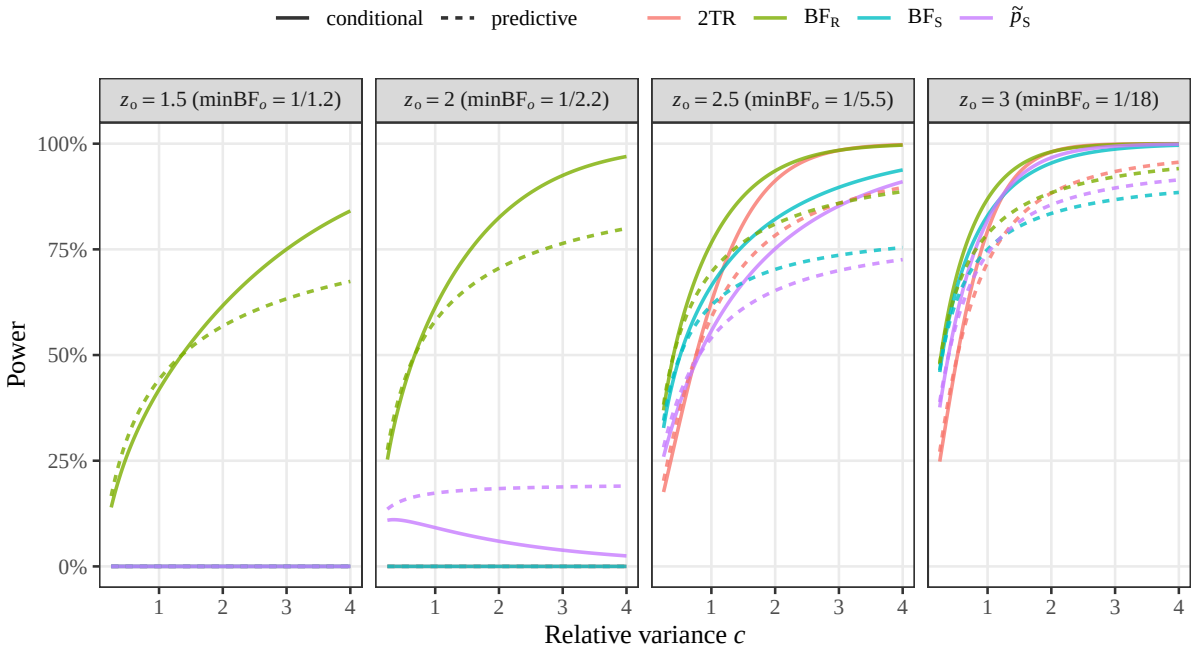

Figure 6: Power of the two-trials rule (2TR: $\text{minBF}_o \leq 1/3$ and $\text{minBF}_r \leq 1/3$), the replication Bayes factor ($\text{BF}_\text{R} \leq 1/3$), the sceptical Bayes factor ($\text{BF}_\text{S} \leq 1/3$), and the recalibrated sceptical p-value ($\tilde{p}_\text{S} \leq 1 - \Phi\{z_\gamma\}$ with $\gamma = 1/3$) as a function of the relative variance $c = \sigma_o^2/\sigma_r^2$ for different original z-values $z_o = \hat{\theta}_o/\sigma_o$ (respectively corresponding minimum Bayes factor minBF_o).

study could be powered simultaneously, we will assume the original study has already been conducted since this is the usual situation. The power to establish replication success $\text{BF}_\text{S} \leq \gamma$ can be computed using the result from Appendix F and either assuming that the underlying true effect corresponds to its estimate from the original study (*conditional power*) or using the predictive distribution of the replication effect estimate based on the advocacy prior (*predictive power*) (Spiegelhalter et al., 1986; Micheloud and Held, 2022). In practice, both forms may be too optimistic as original results are often inflated due to publication bias and questionable research practices. One solution is to shrink the original effect estimate for power calculations (Pawel and Held, 2020; Held et al., 2022b), but we will not focus on this aspect here as this would not provide much more insight but simply lower the power curves of all methods.

Figure 6 shows conditional and predictive power as a function of the relative variance c and for several values of of the original z-value z_o (respectively original minimum Bayes factor minBF_o). In general, uncertainty about replication success is higher for predictive power, leading it to be closer to 50% in all cases. As can also be seen, if the original result was not convincing on its own (e. g., if $z_o = 1.5$ or $z_o = 2$), it is impossible to achieve replication success with the two-trials rule, the sceptical Bayes factor, and the sceptical p-value. This is not the case for the replication Bayes factor, for which high power can also be obtained for small z_o if c is sufficiently large. However, as shown in the previous section, the higher power of the replication Bayes factor comes at the cost of a massive type I error inflation. For $z_o = 2.5$, the sceptical Bayes factor shows higher power than the two-trials rule when $c = 1$,

but the power of the two-trials rule increases faster in c and approaches the power curve of the replication Bayes factor. The power of the sceptical p-value is still a bit lower, likely due to the more stringent requirement on the minimum relative effect estimate. For $z_o = 3$, the power differences between the methods mostly disappear.

3.4 Information consistency

Bayesian hypothesis testing procedures are desired to fulfil certain asymptotic properties (Bayarri et al., 2012). Most notably, they should be *information consistent* in the sense that if data provide overwhelming support for a particular hypothesis, the procedure should indefinitely favour this hypotheses over alternative hypotheses.

There are concerns whether the sceptical Bayes factor is information consistent when we look at the asymptotics only in terms of the replication data (Consonni and La Rocca, 2021; Ly and Wagenmakers, 2022). The sceptical Bayes factor can never be smaller than the original minimum Bayes factor minBF_o. This means that it will be bounded away from zero as the replication sample size grows ($c \to \infty$), even when the data are generated from the same model in both studies. Similarly, the sceptical Bayes factor will be bounded away from zero when the replication effect estimate increases indefinitely. If these two cases constitute overwhelming evidence for replication success, they could be considered instances of the *information paradox* (Liang et al., 2008)

The key to resolving the paradox is to realise that overwhelming evidence for replication success needs to be defined through both studies, not only through the replication. Assume there is a "true" effect size $\theta_* \neq 0$ underlying both effect estimates $\hat{\theta}_i \sim \text{N}(\theta_*, \sigma_i^2)$, $i \in \{o, r\}$. Also assume the variances $\sigma_i^2 = \kappa/n$ are inversely proportional to the sample size $n = n_o = n_r$ for the same unit variance κ in both studies. Letting the sample size n go to infinity is then equivalent to $\sigma_o^2 \downarrow 0$ and $c = \sigma_r^2/\sigma_o^2 = 1$. With decreasing variances the estimates will converge to the true effect size ($\hat{\theta}_i \to \theta_*$), the relative effect estimate will converge to one ($d \to 1$), and the z-values will go to infinity ($|z_i| \to \infty$). Since $c = 1$, the sceptical Bayes factor is given by equation (7). Moreover, we are allowed to use of the approximation $\text{W}_{-1}(x) \approx \log(-x) - \log(-\log(-x))$ as the argument of the Lambert W function is close to zero due to $|z_o| \to \infty$ (Corless et al., 1996, p. 350). Taken together, we have

$$\text{BF}_\text{S} = \sqrt{\frac{1 + d^2}{1 + (1 - d)^2/2 - \mathcal{O}\left\{\log(z_o^2)/z_o^2\right\}}} \cdot \exp\left\{-\frac{z_o^2\left(d^2 + 2d - 1\right)}{4(1 + d^2)} - \mathcal{O}\left(\log z_o^2\right)\right\} \tag{16}$$

Plugging $d = 1$ into (16), we see that $\text{BF}_\text{S} \downarrow 0$ as $|z_o| \to \infty$, so the sceptical Bayes factor is information consistent.

The expression for the sceptical Bayes factor (16) is also valid for other relative effect sizes d. Solving for d such that the multiplicative term of z_o^2 in the exponent changes the sign, we see that the sceptical Bayes factor goes to zero when the underlying true effect size of the replication study is at least $d > \sqrt{2} - 1 \approx 0.41$ times the size of the true effect size from the original study (or $d < -\sqrt{2} - 1 \approx -2.41$ due to the replication paradox if the advocacy prior is not truncated). This means that under the more realistic scenario where the underlying

effect sizes from original and replication are not exactly the same, the sceptical Bayes factor is still consistent when there is not more than 60% shrinkage of the replication effect size.

4 Extension to non-normal models

So far, we have always assumed approximate normality of the effect estimates $\hat{\theta}_o$ and $\hat{\theta}_r$, as well as known variances σ_o^2 and σ_r^2. This may be a problem for studies with small sample size and/or extreme results (e. g., when a study examines a rare disease with death rates close to 0%). One way of dealing with this issue is to consider the exact likelihood of the data underlying the effect estimates, and then marginalise over possible nuisance parameters (Spiegelhalter et al., 2004, chapter 8.2.2). This leads to marginal likelihoods which are again only conditional on the effect size θ, allowing the procedures to be used analogously as described in the proceeding sections. The choice of the likelihood depends on the type of effect size θ. We will illustrate the approach for *standardised mean differences* (SMD) and *log odds ratios* (logOR), two of the most widely used types of effect sizes.

4.1 Standardised mean difference

The SMD quantifies how many standard deviation units σ, the means μ_1 and μ_2 of measurements from two groups differ, i. e.,

$$\theta = \frac{\mu_1 - \mu_2}{\sigma}.$$

Assume now that the measurements come from a normal distribution with common variance σ^2. Knowing the test-statistic t_i from the usual two-sample t-test, as well as the sample sizes in both groups n_{1i} and n_{2i} from study $i \in \{o, r\}$ is sufficient to compute the exact likelihood of the data. It is given by a non-central t-distribution with degrees of freedom $\nu_i = n_{1i} + n_{2i} - 2$ and non-centrality parameter $\theta\sqrt{n_i^*}$ with $n_i^* = (n_{1i}n_{2i})/(n_{1i} + n_{2i})$ (Bayarri and Mayoral, 2002b)

$$T_i \,|\, \theta \sim \text{NCT}_{\nu_i}\left(\theta\sqrt{n_i^*}\right). \tag{17}$$

The same framework is also applicable to test-statistics t_i from paired t-tests based on n_i paired measurements. The SMD θ represents then the standardised mean difference score and $\nu_i = n_i - 1$ and $n_i^* = n_i$ need to be used in (17).

There is no conjugate prior for the SMD θ under model (17), so it is not obvious which prior should be chosen to represent scepticism about it. We will use a zero-mean normal prior $\theta \,|\, H_S \sim \text{N}(0, \tau^2)$ so that the exact procedure is equivalent with the normal approximation as the sample size increases. For the advocacy prior we need to know the posterior distribution of the SMD θ conditional on the original study and a flat prior on θ. Exploiting the fact that the non-central t-distribution can be expressed as a location-scale mixture of a normal with an inverse-gamma distribution (Johnson et al., 1995, chapter 31), the density of the SMD under the advocacy prior is given by

$$f(\theta \,|\, t_o) = \int_0^\infty \text{N}\left(\theta; \frac{t_o}{\sqrt{n_o^*\tau^2}}, \frac{1}{n_o^*}\right) \text{IG}\left(\tau^2; \frac{\nu_o + 1}{2}, \frac{\nu_o}{2}\right) \text{d}\tau^2,$$

where $\mathrm{N}(x; \mu, \phi)$ denotes the density function of the normal distribution with mean μ and variance ϕ evaluated at x, and similarly $\mathrm{IG}(y; a, b)$ denotes the density function of the inverse-gamma distribution with shape and rate parameters a and b evaluated at y.

Taken together, the SMD version of the method proceeds analogously as in Box 1 with the two Bayes factors replaced by

$$\mathrm{BF}_{0:\mathrm{S}}(t_o; \tau^2) = \frac{\mathrm{NCT}_{\nu_o}(t_o; 0)}{\int \mathrm{NCT}_{\nu_o}(t_o; \theta\sqrt{n_o^*})\, \mathrm{N}(\theta; 0, \tau^2)\, \mathrm{d}\theta}$$
$$\mathrm{BF}_{\mathrm{S:A}}(t_r; \tau^2) = \frac{\int \mathrm{NCT}_{\nu_r}(t_r; \theta\sqrt{n_r^*})\, \mathrm{N}(\theta; 0, \tau^2)\, \mathrm{d}\theta}{\int \mathrm{NCT}_{\nu_r}(t_r; \theta\sqrt{n_r^*}) f(\theta \mid t_o)\, \mathrm{d}\theta}$$

and using numerical integration as the integrals cannot be evaluated analytically.

4.2 Log odds ratio

In the case of binary data, we have two independent binomial samples

$$X_{1i} \mid \pi_1 \sim \mathrm{Bin}(n_{1i}, \pi_1) \qquad\qquad X_{2i} \mid \pi_2 \sim \mathrm{Bin}(n_{2i}, \pi_2)$$

for each study $i \in \{o, r\}$, and the effect of the treatment in group 1 relative to the treatment in group 2 is quantified with the logOR

$$\theta = \log \frac{\pi_1/(1-\pi_1)}{\pi_2/(1-\pi_2)}.$$

To obtain a marginal likelihood that only depends on θ, we need to specify a prior for either π_2 or π_1 and marginalise over it. A principled choice is the translation invariant Jeffreys prior, $\pi_1, \pi_2 \sim \mathrm{Be}(1/2, 1/2)$. The exact marginal likelihood for the data from study i is then given by

$$f(x_{1i}, x_{2i} \mid \theta) = \int_0^1 \mathrm{Bin}\left(x_{1i}; n_{1i}, \left\{1 + \exp\left[-\theta - \log\frac{\pi_2}{1-\pi_2}\right]\right\}^{-1}\right) \mathrm{Bin}(x_{2i}; n_{2i}, \pi_2)$$
$$\times\, \mathrm{Be}(\pi_2; 1/2, 1/2)\, \mathrm{d}\pi_2 \tag{18}$$

where $\mathrm{Bin}(x; n, \pi)$ denotes the probability mass function of the binomial distribution with n trials and probability π evaluated at x, and likewise $\mathrm{Be}(y; a, b)$ denotes the density function of the beta distribution with parameters a and b evaluated at y.

There is no conjugate prior for the logOR under model (18), but a pragmatic choice is to specify a zero-mean normal prior $\theta \mid H_{\mathrm{S}} \sim \mathrm{N}(0, \tau^2)$ for the sceptic, to match with the normal approximation as the sample size increases. For the advocacy prior, we need to know the posterior distribution of the logOR θ based on the original study. Using a result from Marshall (1988) combined with a change-of-variables, the exact posterior density of the logOR θ given the original data and Jeffreys priors on π_1 and π_2 is

$$f(\theta \mid x_{1o}, x_{2o}) = \begin{cases} C\, \exp\{e\theta\}\, F\left(e+f, e+g, e+f+g+h, 1-\exp\{\theta\}\right) & \text{for } \theta < 0 \\ C\, \exp\{-f\theta\}\, F\left(e+f, f+h, e+f+g+h, 1-\exp\{-\theta\}\right) & \text{for } \theta > 0 \end{cases}$$

where $F(\cdot)$ is the hypergeometric function, $e = x_{1o} + 1/2$, $f = n_{1o} - x_{1o} + 1/2$, $g = x_{2o} + 1/2$, $h = n_{2o} - x_{2o} + 1/2$, $C = \mathrm{B}(e+g, f+h)/\{\mathrm{B}(e,f)\mathrm{B}(g,h)\}$, and $\mathrm{B}(\cdot,\cdot)$ is the Beta function.

Combining the previous results, we obtain

$$\mathrm{BF}_{0:\mathrm{S}}(x_{1o}, x_{2o}; \tau^2) = \frac{f(x_{1o}, x_{2o} \mid 0)}{\int f(x_{1o}, x_{2o} \mid \theta)\, \mathrm{N}(\theta; 0, \tau^2)\, \mathrm{d}\theta}$$
$$\mathrm{BF}_{\mathrm{S:A}}(x_{1r}, x_{2r}; \tau^2) = \frac{\int f(x_{1r}, x_{2r} \mid \theta)\, \mathrm{N}(\theta; 0, \tau^2)\, \mathrm{d}\theta}{\int f(x_{1r}, x_{2r} \mid \theta) f(\theta \mid x_{1o}, x_{2o})\, \mathrm{d}\theta}$$

as an exact replacement for the Bayes factors in Box 1. Again, there are no closed form expressions for the integrals, but numerical integration needs to be used.

5 Application

The following section will illustrate application of the sceptical Bayes factor using data from the *Social Sciences Replication Project* (Camerer et al., 2018), provided in Table 1. Effect estimates were reported on the correlation scale (r), which is why we applied the Fisher z-transformation $\hat{\theta} = \tanh^{-1}(r)$. This leads to the transformed estimates having approximate variance $\mathrm{Var}(\hat{\theta}) = 1/(n-3)$ (Fisher, 1921), so the relative variance c is roughly the ratio of the replication to the original study sample size $c \approx n_r/n_o$.

For all studies except Janssen et al. (2010) and Derex et al. (2013), the exact approach for either SMD or logOR effect sizes from Section 4 is applicable. In the studies with binary data computing the exact posterior using the hypergeometric function led to numerical issues in some cases and numerical integration was used then. In most cases, the normal approximation of the likelihood seems to lead to similar numerical results for both $\mathrm{BF_S}$ and $\mathrm{BF_R}$ as compared to their counterparts based on exact likelihoods. Qualitative conclusions are the same under both approaches and we will therefore focus on the normal approximation due to better comparability with the remaining measures of replication success as all of them were computed based on approximate normal likelihoods.

For the study pairs where the sceptical Bayes factor suggests a large degree of replication success, all other methods suggest the same in every case. However, there are also cases where there appear to be discrepancies among the methods. For instance, the two-trials rule and the replication Bayes factor may indicate a larger degree of replication success compared to the sceptical p-value and sceptical Bayes factor. This happens for replications that show a substantial increase in sample size but also a much smaller effect estimate compared to the original study. For example, in Balafoutas and Sutter (2012) the sample size was about $c = 3.48$ times larger in the replication, whereas the effect estimate was only $d = 0.52$ the size of the original one. The replication is successful at $\gamma = 1/3$ with the two-trials rule ($\mathrm{minBF}_o = 1/4.2$ and $\mathrm{minBF}_r = 1/3.6$) and the replication Bayes factor ($\mathrm{BF_R} = 1/3.9$), but not with the sceptical Bayes factor ($\mathrm{BF_R} = 1/1.6$) or the sceptical p-value ($\tilde{p}_\mathrm{S} = 0.04 > 1 - \Phi(z_\gamma = 2.18) = 0.01$).

Table 1: Results for data from *Social Sciences Replication Project* (Camerer et al., 2018). Shown are relative variances $c = \sigma_o^2/\sigma_r^2$, relative effect estimates $d = \hat{\theta}_r/\hat{\theta}_o$ (computed on Fisher z-scale), Q-statistic $Q = (\hat{\theta}_o - \hat{\theta}_r)^2/(\sigma_o^2 + \sigma_r^2)$, minimum Bayes factors of original and replication effect estimate (minBF), recalibrated sceptical p-value ($\tilde{p}_S$), sceptical Bayes factors (BF_S) and replication Bayes factors (BF_R), the latter two computed using either a normal approximation or the exact likelihood of the data.

Original study	c	d	Q	minBF_o	minBF_r	$\tilde{p}_S$	BF_S	BF_S (exact)	BF_R	BF_R (exact)
Hauser et al. (2014)	0.51	1.04	0.03	< 1/1000	< 1/1000	< 0.0001	< 1/1000	< 1/1000	< 1/1000	< 1/1000
Aviezer et al. (2012)	0.92	0.60	3.49	< 1/1000	1/347	< 0.0001	1/78	1/10	1/284	1/41
Wilson et al. (2014)	1.33	0.83	0.28	< 1/1000	1/659	0.0001	1/45	1/35	< 1/1000	< 1/1000
Derex et al. (2013)	1.29	0.65	1.14	1/520	1/17	0.002	1/8.5		1/31	
Gneezy et al. (2014)	2.31	0.81	0.22	1/18	1/157	0.004	1/6.9	1/7.5	1/474	1/551
Karpicke and Blunt (2011)	1.24	0.58	1.75	< 1/1000	1/9.6	0.002	1/5.6	1/5	1/12	1/12
Morewedge et al. (2010)	2.97	0.76	0.30	1/7.3	1/65	0.011	1/3.9	1/4	1/160	1/156
Kovacs et al. (2010)	4.38	1.38	0.59	1/3.2	< 1/1000	0.009	1/3.2	1/3.8	< 1/1000	< 1/1000
Duncan et al. (2012)	7.42	0.57	1.29	1/12	< 1/1000	0.011	1/3.1	1/3.1	< 1/1000	< 1/1000
Nishi et al. (2015)	2.42	0.57	1.05	1/12	1/6.1	0.016	1/2.5	1/2.2	1/8.2	1/7.6
Janssen et al. (2010)	0.65	0.48	3.51	< 1/1000	1/3.3	0.003	1/1.6		1/1.6	
Balafoutas and Sutter (2012)	3.48	0.52	1.02	1/4.2	1/3.6	0.04	1/1.6	1/1.6	1/3.9	1/3.9
Pyc and Rawson (2010)	9.18	0.38	1.79	1/3.5	1/7.3	0.061	1/1.2	1/1.2	1/4	1/4
Rand et al. (2012)	6.27	0.18	3.96	1/7.1	1	0.13			9.6	9.7
Ackerman et al. (2010)	11.69	0.23	2.15	1/2.2	1/1.3	0.15			3.2	3.2
Sparrow et al. (2011)	3.50	0.13	5.80	1/26	1	0.19			29	32
Shah et al. (2012)	11.62	-0.05	4.08	1/2.2	1	0.66			25	26
Kidd and Castano (2013)	8.57	-0.10	6.83	1/5.7	1	0.77			72	69
Gervais and Norenzayan (2012)	9.78	-0.12	5.44	1/3	1	0.78			36	37
Lee and Schwarz (2010)	7.65	-0.11	6.80	1/5.4	1	0.79			65	69
Ramirez and Beilock (2011)	4.47	-0.09	19.29	< 1/1000	1	0.85			> 1000	> 1000

Discrepancies between the sceptical p-value and the sceptical Bayes factor happen in situations where the replication shows an effect estimate that, although incompatible with the sceptical prior, is also incompatible with the advocacy prior. For example in the Janssen et al. (2010) replication, both effect estimates are substantially larger than zero ($\hat{\theta}_o = 0.74$ with $\text{minBF}_o < 1/1000$ and $\hat{\theta}_r = 0.36$ with $\text{minBF}_r = 1/3.3$), yet the Q-statistic indicates some incompatibility ($Q = 3.51$), which explains why $\tilde{p}_S = 0.003$, but $\text{BF}_S = 1/1.6$ only.

Discrepancies between the replication Bayes factor and the sceptical Bayes factor arise when the replication finding provides overwhelming evidence against the null, whereas the original finding was less compelling. The replication of Kovacs et al. (2010) illustrates this situation. The original study provided only moderate evidence against the null ($\hat{\theta}_o = 0.49$ and $\text{minBF}_o = 1/3.2$), whereas the replication finding was more compelling ($\hat{\theta}_r = 0.67$ and $\text{minBF}_r < 1/1000$). By construction the sceptical Bayes factor can only be as small as the minimum Bayes factor from the original study minBF_o, which is actually attained in this case ($\text{BF}_S = 1/3.2$). The replication Bayes factor, on the other hand, is not limited by the moderate level of evidence from the original study and indicates decisive evidence for the advocate ($\text{BF}_R < 1/1000$). This illustrates that in order to achieve a reasonable degree of replication success, the sceptical Bayes factor requires the original study to be convincing, whereas the replication Bayes factor only requires a compelling replication result.

6 Discussion

We proposed a novel method for the statistical assessment of replicability combining reverse-Bayes analysis with Bayesian hypothesis testing. Compared to other methods, the sceptical Bayes factor poses more stringent requirements but also allows for stronger statements about replication success. It ensures that both studies provide sufficient evidence against a null effect, while also penalising incompatibility of their effect estimates. If the replication sample size is not too small, the sceptical Bayes factor comes with appropriate frequentist error rates, which is often a requirement from research funders and regulators. Asymptotic analysis of the method showed that it is information consistent in the sense that if the sample size in both studies increases, the sceptical Bayes factor will indicate overwhelming replication success when the underlying effect size of the replication is not much smaller than the underlying effect size of the original study. Finally, the sceptical Bayes factor is the only method in our comparison which does not suffer from any form of the shrinkage paradox, i. e., replication success can never be achieved with arbitrarily small replication effect estimates, not even when the replication sample size becomes very large or the evidence from the original study overwhelming.

In extreme scenarios the sceptical Bayes factor can suffer from the replication paradox, which means that it may flag success when the replication estimate goes in opposite direction of the original one. However, the paradox can be avoided by truncating the advocacy prior to the direction of the original estimate. It may also happen that the result of the replication is so inconclusive that replication success cannot be established at any level, so the sceptical Bayes factor does not exist. Other methods, such as the sceptical p-value or the replication Bayes factor, can be used in this situation.

The proposed method could be extended in many ways. First, in many cases not just one but several replication studies are conducted for one original study (e. g., as in Klein et al., 2014). The Bayesian framework allows to easily extend the sceptical Bayes factor to the "many-to-one" replication setting as the likelihoods are also straightforward to compute for a sample of replication effect estimates. Second, a multivariate generalisation would allow for effects in the form of a vector with approximate multivariate normal likelihood which is then combined with a sceptical g-prior (Liang et al., 2008). The normal prior could also be replaced with other distributions, for example the (multivariate) Cauchy distribution which is often the preferred prior choice for default Bayes factor hypothesis tests (Jeffreys, 1961). The g parameter of the g-prior or the scale parameter of the Cauchy prior would then take over the role of the relative sceptical prior variance. Third, based on the replication result one could also compute a posterior distribution for the effect size based on a model-average of the advocacy prior and the sceptical prior (using the variance at the sceptical Bayes factor). This distribution would provide a formal compromise between scepticism and advocacy of the original finding. Fourth, while Bayes factors are an important part in Bayesian hypothesis testing, they do not take into account the prior probabilities of the hypotheses under consideration. It would be interesting to investigate whether the reverse-Bayes approach could be used in a framework where priors are assigned jointly to the hypothesis and parameter space (Dellaportas et al., 2012). Finally, an important aspect is the design of new replication studies. An appropriate sample size is of particular importance for a replication to be informative. We will report in the future on sample size planning based on the sceptical Bayes factor.

For a thorough assessment of replication attempts, no single metric seems to be able to answer all important questions completely. Instead, we recommend that researchers conduct a comprehensive statistical evaluation of replication success. Reverse-Bayes methods naturally fit to the replication setting, they avoid various paradoxes from which other methods suffers, and they combine different notions of replicability. The reverse-Bayes approach therefore leads to sensible inferences and decisions, which is why we advocate it as a key part in the assessment of replication success.

Software and data

All analyses were performed in the R programming language version 4.2.2 (R Core Team, 2022). The code to reproduce this manuscript is available at `https://gitlab.uzh.ch/samuel.pawel/BFScode`. We used the implementation of the Lambert W function from the package `lamW` (Adler, 2015), graphics were created with the `ggplot2` package (Wickham, 2016), the sceptical p-value and related calculations were conducted using the package `ReplicationSuccess` available on the Comprehensive R Archive Network (Held, 2020). All methods are implemented in the R package `BayesRep` which is available at `https://gitlab.uzh.ch/samuel.pawel/BayesRep`.

Data on effect estimates from the *Social Sciences Replication Project* (Camerer et al., 2018) were downloaded from `https://osf.io/abu7k/`, respectively, taken from `https://osf.io/nsxgj/` for exact calculations.

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A Sufficiently sceptical relative prior variance

The sufficiently sceptical relative prior variance at level γ is the value $g_\gamma \in [0, g_{\text{minBF}_o}]$ that fulfils the condition

$$\text{BF}_{0:\text{S}}(\hat{\theta}_o; g_\gamma) = \gamma. \tag{19}$$

Substituting (19) and rearranging terms, we obtain

$$\begin{aligned}\sqrt{1+g_\gamma} \cdot \exp\left\{-\frac{1}{2} \cdot \frac{g_\gamma}{1+g_\gamma} \cdot z_o^2\right\} &= \gamma \\ \iff \frac{1}{\gamma} \cdot \exp\left\{-\frac{z_o^2}{2}\right\} &= \frac{1}{\sqrt{1+g_\gamma}} \exp\left\{-\frac{1}{2} \cdot \frac{z_o^2}{1+g_\gamma}\right\}.\end{aligned}$$

Squaring both sides and multiplying by $-z_o^2$, this becomes

$$\iff -\frac{z_o^2}{\gamma^2} \cdot \exp\left\{-z_o^2\right\} = -\frac{z_o^2}{1+g_\gamma} \exp\left\{-\frac{z_o^2}{1+g_\gamma}\right\}. \tag{20}$$

This is a transcendental equation that cannot be explicitly solved in terms of elementary functions. However, if we set $q = -z_o^2/(1+g_\gamma)$ then (20) becomes

$$-\frac{z_o^2}{\gamma^2} \cdot \exp\left\{-z_o^2\right\} = q \cdot \exp\left\{q\right\}.$$

The solution for q (and consequently for g_γ) can be explicitly computed with

$$\begin{aligned} q &= \text{W}_{-1}\left(-\frac{z_o^2}{\gamma^2} \cdot \exp\left\{-z_o^2\right\}\right) \\ g_\gamma &= \begin{cases} -\dfrac{z_o^2}{q} - 1 & \text{if } -\dfrac{z_o^2}{q} \geq 1 \\ \text{undefined} & \text{else} \end{cases} \end{aligned} \tag{21}$$

where $\text{W}_{-1}(\cdot)$ is the branch of the Lambert W function that satisfies $\text{W}(y) \leq -1$ for $y \in [-e^{-1}, 0)$, ensuring that $g_\gamma \leq g_{\text{minBF}_o}$. See Appendix B for details about the Lambert W function. For some z_o, equation (20) can also be satisfied for negative g_γ, which is why we need to add the condition $-z_o^2/q \geq 1$ in equation (21), such that g_γ is a valid relative variance.

As z_o^2 becomes larger, the argument to the Lambert W function $x = -z_o^2 \exp(-z_o^2)/\gamma^2$ will approach zero, so the approximation $W_{-1}(x) \approx \log(-x) - \log(-\log(-x))$ can be applied (Corless et al., 1996, p. 350). This leads to

$$g_\gamma \approx \frac{z_o^2}{z_o^2 + \log \gamma^2 - \log z_o^2 + \log\{z_o^2 + \log \gamma^2 - \log z_o^2\}} - 1.$$

We can see that $g_\gamma \downarrow 0$ when γ remains fixed and $z_o^2 \to \infty$, which means that the sufficiently sceptical relative prior variance converges to zero for increasingly compelling evidence from the original study.

B The Lambert W function

The Lambert W function (Corless et al., 1996) is defined as the function $W(\cdot)$ satisfying

$$W(y) \cdot \exp\{W(y)\} = y$$

and it is also known as "product logarithm" since it returns the number which plugged in the exponential function and then multiplied by itself produces y. For real y, $W(y)$ is only defined for $y \geq -e^{-1}$ and for $y \in [-e^{-1}, 0)$ the function has two branches that are commonly denoted by $W_0(\cdot)$, the branch with $W(y) \geq -1$, and $W_{-1}(\cdot)$, the branch with $W(y) \leq -1$ (see Figure 7 for an illustration).

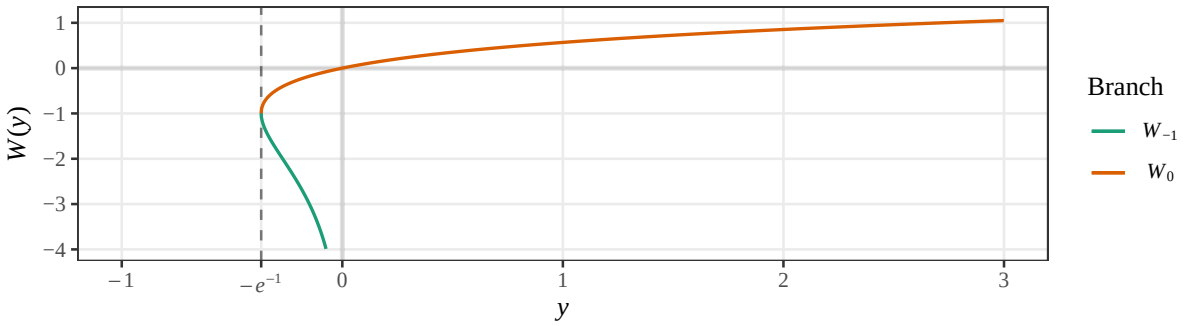

Figure 7: Lambert W function for real argument y.

C Computation of the sceptical Bayes factor

From the definition of the sceptical Bayes factor it is apparent that BF_S is either

1. undefined, if $BF_{S:A}(\hat{\theta}_r; g) > BF_{0:S}(\hat{\theta}_o; g)$ for all $g \in [0, g_{\text{minBF}_o}]$
2. $BF_S = \text{minBF}_o$, if $BF_{S:A}(\hat{\theta}_r; g_{\text{minBF}_o}) \leq BF_{0:S}(\hat{\theta}_o; g_{\text{minBF}_o})$

3. $\text{BF}_\text{S} = \inf_{g_\gamma}\left\{\gamma : \text{BF}_{\text{S:A}}(\hat{\theta}_r; g_\gamma) = \gamma\right\}$, the height of the lowest intersection of $\text{BF}_{\text{0:S}}(\hat{\theta}_o; g_\gamma) = \gamma$ and $\text{BF}_{\text{S:A}}(\hat{\theta}_r; g_\gamma)$ in g_γ otherwise

Whether BF_S attains the lower bound minBF_o (condition 2) can be checked by evaluating if $\text{BF}_{\text{S:A}}(\hat{\theta}_r; g_{\text{minBF}_o}) \leq \text{minBF}_o$ and setting $\text{BF}_\text{S} = \text{minBF}_o$ if it is the case. For condition 3, we know that the intersections satisfy

$$\begin{gathered}\text{BF}_{\text{S:A}}(\hat{\theta}_r; g_*) = \text{BF}_{\text{0:S}}(\hat{\theta}_o; g_*) \\ \sqrt{\frac{1/c+1}{1/c+g_*}} \cdot \exp\left\{-\frac{z_o^2}{2}\left(\frac{d^2}{1/c+g_*} - \frac{(1-d)^2}{1/c+1}\right)\right\} = \sqrt{1+g_*} \cdot \exp\left\{-\frac{1}{2} \cdot \frac{g_*}{1+g_*} \cdot z_o^2\right\}\end{gathered}$$

which is equivalent to

$$\begin{aligned}&\sqrt{\frac{1}{(1+g_*)(1/c+g_*)}} \cdot \exp\left\{-\frac{z_o^2}{2}\left(\frac{1}{1+g_*} + \frac{d^2}{1/c+g_*}\right)\right\} \\ &\qquad = \sqrt{\frac{1}{1/c+1}} \cdot \exp\left\{-\frac{z_o^2}{2}\left(1 + \frac{(1-d)^2}{1/c+1}\right)\right\}. \end{aligned} \tag{22}$$

This is a transcendental equation that has no closed-form solution for g_* in terms of elementary functions, but root-finding algorithms can be used to compute it. However, when $c = 1$, equation (22) simplifies

$$\frac{1}{1+g_*} \cdot \exp\left\{-\frac{z_o^2}{2} \cdot \frac{1+d^2}{1+g_*}\right\} = \frac{1}{\sqrt{2}} \cdot \exp\left\{-\frac{z_o^2}{2}\left(1 + \frac{(1-d)^2}{2}\right)\right\}. \tag{23}$$

Multiplying (23) by $-z_o^2(1+d^2)/2$ and applying the Lambert W function leads to

$$\begin{aligned}k &= W\left(-\frac{z_o^2}{\sqrt{2}} \cdot \frac{1+d^2}{2} \cdot \exp\left\{-\frac{z_o^2}{2}\left[1 + \frac{(1-d)^2}{2}\right]\right\}\right) \\ g_* &= \begin{cases} -\dfrac{z_o^2}{k} \cdot \dfrac{1+d^2}{2} - 1 & \text{if } -\dfrac{z_o^2}{k} \cdot \dfrac{1+d^2}{2} \geq 1 \\ \text{undefined} & \text{else,} \end{cases}\end{aligned} \tag{24}$$

with the condition that $-z_o^2(1+d^2)/(2k) \geq 1$ such that g_* is a valid relative variance, as the equation may otherwise be satisfied for negative g_*. Since the argument to $\text{W}(\cdot)$ is real and negative (if $z_o \neq 0$), the branches $\text{W}_{-1}(\cdot)$ and $\text{W}_0(\cdot)$ both provide solutions that can fulfil the equation (assuming the argument is not smaller than $-e^{-1}$ which would mean that there are no intersections). It must also hold that $g_* \leq g_{\text{minBF}_o} = \max\{z_o^2 - 1, 0\}$ for g_* to be a valid sufficiently sceptical prior variance. Hence, when $|d| \leq 1$, the g_* from (24) can only be computed with the $\text{W}_{-1}(\cdot)$ branch, whereas for $|d| > 1$ and when $-k \geq (1+d^2)/2$ the solution g_* is computed from the $\text{W}_0(\cdot)$ branch. Plugging the relative prior variance g_* from (24) into the Bayes factor from (1), we obtain the expression for the sceptical Bayes factor in (7).

D Bayes factor with truncated advocacy prior

For now assume $\hat{\theta}_o > 0$. The marginal likelihood of the replication effect estimate $\hat{\theta}_r \mid \theta \sim \mathrm{N}(\theta, \sigma_r^2)$ under the truncated advocacy prior $H_{\mathrm{A}'}\colon \theta \sim \mathrm{N}(\hat{\theta}_o, \sigma_o^2)\mathbb{1}_{(0,\infty)}(\theta)$ is

$$\begin{aligned}
f(\hat{\theta}_r \mid H_{\mathrm{A}'}) &= \int_{-\infty}^{+\infty} f(\hat{\theta}_r \mid \theta) f(\theta \mid H_{\mathrm{A}'}) \, \mathrm{d}\theta \\
&= \int_{-\infty}^{+\infty} \frac{\mathbb{1}_{(0,\infty)}(\theta)}{2\pi\sigma_r\sigma_o\Phi(z_o)} \exp\left\{-\frac{1}{2}\left[\frac{(\hat{\theta}_o - \theta)^2}{\sigma_r^2} + \frac{(\theta - \hat{\theta}_o)^2}{\sigma_o^2}\right]\right\} \mathrm{d}\theta \\
&= \frac{1}{2\pi\sigma_r\sigma_o\Phi(z_o)} \exp\left\{-\frac{1}{2}\frac{(\hat{\theta}_r - \hat{\theta}_o)^2}{\sigma_r^2 + \sigma_o^2}\right\} \underbrace{\int_0^{+\infty} \exp\left\{-\frac{1}{2}\frac{(\theta - \frac{\hat{\theta}_o/\sigma_o^2 + \hat{\theta}_r/\sigma_r^2}{1/\sigma_o^2 + 1/\sigma_r^2})^2}{(1/\sigma_o^2 + 1/\sigma_r^2)^{-1}}\right\} \mathrm{d}\theta}_{= \sqrt{\frac{2\pi}{1/\sigma_o^2 + 1/\sigma_r^2}}\Phi\left(\frac{z_o(1+dc)}{\sqrt{1+c}}\right)} \\
&= \frac{1}{\sqrt{2\pi(\sigma_r^2 + \sigma_o^2)}} \exp\left\{-\frac{1}{2}\frac{(\hat{\theta}_r - \hat{\theta}_o)^2}{\sigma_r^2 + \sigma_o^2}\right\} \frac{\Phi\left(\frac{z_o(1+dc)}{\sqrt{1+c}}\right)}{\Phi(z_o)}. \qquad (25)
\end{aligned}$$

With a similar argument one can show that this result holds for any $\hat{\theta}_o$ if the last factor in (25) is changed to

$$\frac{\Phi\left\{\mathrm{sign}(z_o)\frac{z_o(1+dc)}{\sqrt{1+c}}\right\}}{\Phi\left\{|z_o|\right\}}.$$

By dividing the marginal likelihood of the replication data under the sceptical prior by the marginal likelihood under the truncated advocacy prior, the Bayes factor in (15) is obtained.

E The shrinkage paradox

We want to investigate what happens to the replication success regions as the relative variance c and the squared original z-value z_o^2 (a monotone transformation of the original minimum Bayes factor minBF_o) become larger. Ignoring the success regions on the wrong side of zero (due to the replication paradox), the minimum relative effect estimates d_{min} as shown in Section 3 are given by

$$d^{\text{BF}_\text{S}}_{\text{min}} = \frac{1/c + g_\gamma}{g_\gamma - 1} + \sqrt{\frac{\log\left[\frac{1/c+1}{(1/c+g_\gamma)(1+g_\gamma)}\right]/z_o^2 + \frac{g_\gamma}{1+g_\gamma} + \frac{1}{1-g_\gamma}}{(1-g_\gamma)/\left[(1/c+g_\gamma)(1/c+1)\right]}} \quad \text{(sceptical Bayes factor)}$$

$$d^{\text{2TR}}_{\text{min}} = \frac{z_\gamma}{z_o\sqrt{c}} \quad \text{(two-trials rule)}$$

$$d^{\text{BF}_\text{R}}_{\text{min}} = \sqrt{\left[1 + \frac{\log(1+c) - 2\log\gamma}{z_o^2}\right]\frac{1/c+1}{c}} - \frac{1/c+1}{1+c} \quad \text{(replication Bayes factor)}$$

$$d^{p_\text{S}}_{\text{min}} = \sqrt{\frac{1/c + 1/(z_o^2/z_\gamma^2 - 1)}{z_o^2/z_\gamma^2}} \quad \text{(sceptical } p\text{-value)}$$

where for the sceptical Bayes factor it was assumed that $g_\gamma > 1$ (otherwise the plus before the square root term needs to be replaced by a minus).

For the sceptical Bayes factor, we obtain

$$\lim_{c\to\infty} d^{\text{BF}_\text{S}}_{\text{min}} = \frac{g_\gamma}{g_\gamma - 1} + \sqrt{\frac{\log\left[\frac{1}{g_\gamma(1+g_\gamma)}\right]/z_o^2 + \frac{g_\gamma}{1+g_\gamma} + \frac{1}{1-g_\gamma}}{(1-g_\gamma)/g_\gamma}} \quad \text{and} \quad \lim_{z_o^2\to\infty} d^{\text{BF}_\text{S}}_{\text{min}} = \sqrt{\frac{1/c+1}{c}} - \frac{1}{c}$$

where for the second limit we used that $\lim_{z_o^2\to\infty} g_\gamma = 0$ for a fixed level γ (Appendix A). So the sceptical Bayes factor does not suffer from any form of the shrinkage paradox. The limits for the two-trials rule are given by

$$\lim_{c\to\infty} d^{\text{2TR}}_{\text{min}} = 0 \qquad \text{and} \qquad \lim_{z_o^2\to\infty} d^{\text{2TR}}_{\text{min}} = 0$$

so the two-trials rule suffers from both forms of the shrinkage paradox. For the sceptical p-value, we obtain

$$\lim_{c\to\infty} d^{p_\text{S}}_{\text{min}} = \sqrt{\frac{z_\gamma^2}{z_o^2(z_o^2/z_\gamma^2 - 1)}} \qquad \text{and} \qquad \lim_{z_o^2\to\infty} d^{p_\text{S}}_{\text{min}} = 0$$

thus, the sceptical p-value suffers from the shrinkage paradox at original. Finally, the limits for the replication Bayes factor are

$$\lim_{c\to\infty} d^{\text{BF}_\text{R}}_{\text{min}} = 0 \qquad \text{and} \qquad \lim_{z_o^2\to\infty} d^{\text{BF}_\text{R}}_{\text{min}} = \sqrt{\frac{1/c+1}{c}} - \frac{1/c+1}{1+c}$$

which means that the replication Bayes factor suffers from the shrinkage paradox at replication.

F Probability of replication success with the sceptical Bayes factor

Conditional on the original study, the probability for replication success at level γ is given by the probability of (8). This event involves $z_r = dz_o\sqrt{c}$ as the only random quantity if the

original study has been completed. Assuming a normal distribution

$$z_r \,|\, z_o, c \sim \mathrm{N}(\mu_{z_r}, \sigma^2_{z_r})$$

which may depend on z_o and c encompasses the typical scenarios under which one would want to compute the probability for replication success. For example, under the null hypothesis ($H_0\colon \theta = 0$), we have $\mu_{z_r} = 0$ and $\sigma^2_{z_r} = 1$. For conditional power we assume the underlying effect size equals the original effect estimate ($\theta = \hat{\theta}_o$) and therefore $\mu_{z_r} = z_o\sqrt{c}$ and $\sigma^2_{z_r} = 1$. Finally, predictive power is obtained by using the predictive distribution based on the advocacy prior ($H_\mathrm{A}\colon \theta \sim \mathrm{N}(\hat{\theta}_o, \sigma^2_o)$) and thus $\mu_{z_r} = z_o\sqrt{c}$ and $\sigma^2_{z_r} = 1 + c$.

Applying some algebraic manipulations to (8), the probability for replication success at level γ can be computed by

$$\Pr\left(\mathrm{BF_S} \leq \gamma \,|\, z_o, c\right) = \begin{cases} \Pr(\chi^2_{1,\lambda} \geq A/[B\sigma^2_{z_r}]) & \text{for } g_\gamma < 1 \\ \Phi(\mathrm{sign}(z_o)\left\{\mu_{z_r} - D\right\}/\sigma_{z_r}) & \text{for } g_\gamma = 1 \\ \Pr(\chi^2_{1,\lambda} \leq A/[B\sigma^2_{z_r}]) & \text{for } g_\gamma > 1 \end{cases} \tag{26}$$

with non-centrality parameter $\lambda = (\mu_{z_r} - M)^2/\sigma^2_{z_r}$ and

$$\begin{aligned} A &= \log\left\{\frac{1/c + 1}{(1/c + g_\gamma)(1 + g_\gamma)}\right\} + z_o^2\left\{\frac{g_\gamma}{1 + g_\gamma} + \frac{1}{1 - g_\gamma}\right\}, \\ B &= \frac{1 - g_\gamma}{(1 + cg_\gamma)(1/c + 1)}, \\ D &= \frac{z_o^2\{1/2 + 1/(1/c + 1)\} - \log 2}{2z_o\sqrt{c}}(1 + c) \\ M &= \frac{z_o(1 + cg_\gamma)}{\sqrt{c}(g_\gamma - 1)}. \end{aligned}$$

The probability is zero, if the original z-value $|z_o|$ is not large enough such that the sufficiently sceptical relative prior variance g_γ can be computed for level γ with (17).

G Probability of replication success with the replication Bayes factor

The probability of $\mathrm{BF_R} \leq \gamma$ is equivalent to the probability of

$$\log(1 + c) - z_r^2 + \frac{(z_r - z_o\sqrt{c})^2}{1 + c} \leq 2\log\gamma \tag{27}$$

Applying some algebraic manipulations to (27) and assuming a normal distribution for z_r as in Appendix F leads to

$$\Pr\left(\mathrm{BF_R} \leq \gamma \,|\, z_o, c\right) = \Pr\left(\chi^2_{1,\lambda} \geq \left\{z_o^2 + \log(1 + c) - \log\gamma^2\right\}[1 + 1/c]/\sigma^2_{z_r}\right)$$

with non-centrality parameter $\lambda = (\mu_{z_r} + z_o/\sqrt{c})^2/\sigma^2_{z_r}$.

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PAPER III

Bayesian approaches to designing replication studies

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Abstract

Replication studies are essential for assessing the credibility of claims from original studies. A critical aspect of designing replication studies is determining their sample size; a too small sample size may lead to inconclusive studies whereas a too large sample size may waste resources that could be allocated better in other studies. Here we show how Bayesian approaches can be used for tackling this problem. The Bayesian framework allows researchers to combine the original data and external knowledge in a design prior distribution for the underlying parameters. Based on a design prior, predictions about the replication data can be made, and the replication sample size can be chosen to ensure a sufficiently high probability of replication success. Replication success may be defined through Bayesian or non-Bayesian criteria, and different criteria may also be combined to meet distinct stakeholders and allow conclusive inferences based on multiple analysis approaches. We investigate sample size determination in the normal-normal hierarchical model where analytical results are available and traditional sample size determination is a special case where the uncertainty on parameter values is not accounted for. An application to data from a multisite replication project of social-behavioral experiments illustrates how Bayesian approaches help to design informative and cost-effective replication studies. Our methods can be used through the R package `BayesRepDesign`.

Key words: Bayesian design, design prior, multisite replication, sample size determination

1 Introduction

The replicability of research findings is a cornerstone for the credibility of science. However, there is growing evidence that the replicability of many scientific findings is lower than expected (Ioannidis, 2005; Open Science Collaboration, 2015; Camerer et al., 2018; Errington et al., 2021). This "replication crisis" has led to methodological reforms in various fields of science, one of which is an increased conduct of replication studies (Munafò et al., 2017). Statistical methodology plays a key role in the evaluation of replication studies, and various methods have been proposed for quantifying how "successful" a replication study was in replicating the original finding (Bayarri and Mayoral, 2002; Verhagen and Wagenmakers, 2014; Simonsohn, 2015; Anderson and Maxwell, 2016; Patil et al., 2016; Johnson et al., 2016; Etz and Vandekerckhove, 2016; van Aert and van Assen, 2017; Ly et al., 2018; Harms, 2019; Hedges and Schauer, 2019; Mathur and VanderWeele, 2020; Held, 2020; Pawel and Held, 2020; Bonett, 2020; Held et al., 2022b; Pawel and Held, 2022, among others). Yet, as with ordinary studies, statistical methodology is not only important for analyzing replication studies but also for designing them, in particular for their *sample size determination* (SSD). Optimal SSD is important since too small sample sizes may lead to inconclusive studies, whereas too large sample sizes may waste resources which could have been allocated better in other research projects.

SSD for replication studies comes with unique opportunities and challenges; the data from the original study can be used to inform SSD, at the same time the analysis of replication success based on original and replication study is typically different from an analysis of a single

study for which traditional SSD methodology was developed. Since analysis and design of replication studies should be in accordance, a relatively small literature has emerged which specifically deals with replication study power calculations and SSD (Bayarri and Mayoral, 2002; Goodman, 1992; Senn, 2002; Anderson and Maxwell, 2017; Micheloud and Held, 2022; van Zwet and Goodman, 2022; Held, 2020; Pawel and Held, 2022; Hedges and Schauer, 2021; Anderson and Kelley, 2022). However, most of these articles only deal with selected analysis methods and data models. An exception is the excellent article by Anderson and Kelley (2022) which discusses more general principles of replication SSD in the context of psychological research, mostly from a frequentist perspective. As they state "the literature on Bayesian sample size planning is still nascent, particularly with respect to Bayes Factors (Schönbrodt and Wagenmakers, 2017), and has not yet been clearly optimized for the context of most replication goals" (Anderson and Kelley, 2022, p. 18). Our goal is therefore to complement their article by developing a unified framework of replication SSD (schematically illustrated in Figure 1) based on principles from Bayesian design approaches (Spiegelhalter et al., 1986; Spiegelhalter and Freedman, 1986; Weiss, 1997; O'Hagan and Stevens, 2001; Gelfand and Wang, 2002; De Santis, 2004; Spiegelhalter et al., 2004; Schönbrodt and Wagenmakers, 2017; Pek and Park, 2019; Kunzmann et al., 2021; Park and Pek, 2022; Grieve, 2022). We aim to provide both a theoretical basis for methodologists developing new methods for design and analysis methods of replication studies, and also to illustrate how Bayesian design approaches can practically be used by researchers planning a replication study.

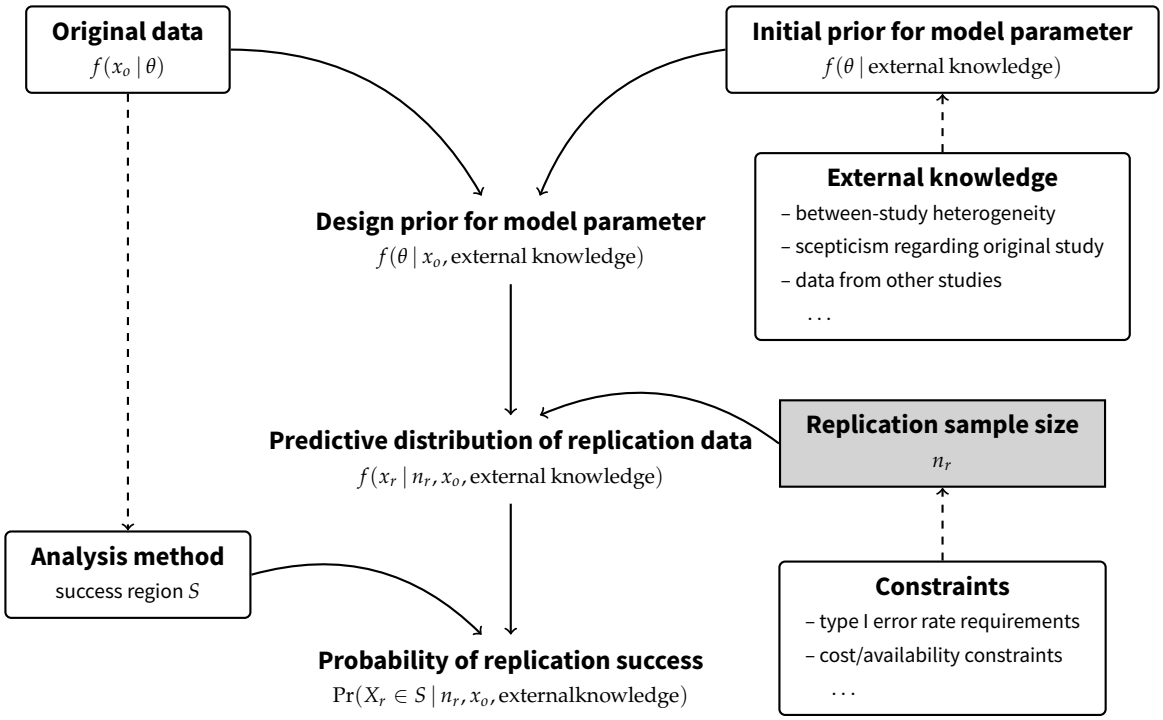


Figure 1: Schematic illustration of Bayesian sample size determination for replication studies. The original and replication data are denoted by x_o and x_r, respectively. Both are assumed to come from a distribution with density/probability mass function denoted by $f(x_i \mid \theta)$ for $i \in \{o, r\}$. An initial prior with density function $f(\theta \mid \text{external knowledge})$ is assigned to the model parameter θ.

The design of replication studies is a natural candidate for Bayesian knowledge updating as it allows to combine uncertain information from different sources –for instance, the data from the original study and/or expert knowledge– in a so-called *design prior* distribution for the underlying model parameters. If the analysis of the replication data is also Bayesian, the design prior may be different from the so-called *analysis prior* which, unlike the design prior, is usually desired to be objective or "uninformative" (O'Hagan and Stevens, 2001). Based on the design prior, predictions about the replication data can then be made, and the sample size can be chosen such that the probability of replication success becomes sufficiently high. Importantly, Bayesian design approaches can also be used if the planned analysis of the replication study is non-Bayesian, which is the more common situation in practice. Bayesian design based on a frequentist analysis is known under various names, such as "hybrid classical-Bayesian design" (Spiegelhalter et al., 2004) or "Bayesian assurance" (O'Hagan et al., 2005), and has also been used before for psychological applications (Pek and Park, 2019; Park and Pek, 2022) and replication studies (Anderson and Maxwell, 2017; Micheloud and Held, 2022).

This paper is structured as follows: We start with presenting a general framework for Bayesian SSD of replication studies which applies to any kind of data model and analysis method. We then investigate design priors and SSD in the normal-normal hierarchical model framework which provides sufficient flexibility for incorporating the original data and external knowledge in replication design. No advanced computational methods, such as (Markov Chain) Monte Carlo sampling, are required for conducting Bayesian SSD in this framework, and in many cases there are even simple formulae which generalize classical power and sample size calculations. We illustrate the methodology for several Bayesian and non-Bayesian analysis methods, and for both singlesite and multisite replication studies. Since multisite replication studies are becoming increasingly popular in psychology (e. g., Klein et al., 2018), we also discuss how to choose the optimum allocation of samples within and between sites from a Bayesian design point of view. As a running example we use data from a multisite replication project of social-behavioral experiments (Protzko et al., 2020). Finally, we close with concluding remarks, limitations, and open questions.

2 General framework

Suppose an original study has been conducted and resulted in a data set x_o. These data are assumed to come from a distribution characterized by an unknown parameter θ and with density function $f(x_o \mid \theta)$. To assess the replicability of a claim from the original study, an independent and identically designed (apart from the sample size) replication study is conducted, and the goal of the design stage is to determine its sample size n_r.

As the observed original data x_o, the yet unobserved replication data X_r are assumed to come from a distribution depending on the parameter θ. The parameter θ thus provides a link between the two studies, and the knowledge obtained from the original study can be used to make predictions about the replication. The central quantity for doing so is the so-called *design prior* of the parameter θ, which we write as the posterior distribution of θ based on the

original data and an *initial prior* for θ

$$f(\theta \mid x_o, \text{external knowledge}) = \frac{f(x_o \mid \theta)\, f(\theta \mid \text{external knowledge})}{f(x_o \mid \text{external knowledge})}. \tag{1}$$

The initial prior of θ may depend on external knowledge (e. g., data from other studies) and it represents the uncertainty about θ before observing the original data. We will discuss common types of external knowledge in the replication setting in the next Section. The design prior (1) hence represents the state of knowledge and uncertainty about the parameter θ before the replication is conducted, and, along with an assumed replication sample size n_r, it can be used to compute a predictive distribution for the replication data

$$f(x_r \mid n_r, x_o, \text{external knowledge}) = \int f(x_r \mid n_r, \theta)\, f(\theta \mid x_o, \text{external knowledge})\, \mathrm{d}\theta. \tag{2}$$

After completion of the replication, the observed data x_r will be analyzed in some way to quantify to what extent the original result could be replicated. The analysis may involve the original data (for example, a meta-analysis of the two data sets) or it may only use the replication data. Typically, there is a *success region* S which implies that if the replication data fall within it ($x_r \in S$), the replication is successful. The *probability of replication success* can thus be computed by integrating the predictive density (2) over S. To ensure a sufficiently conclusive replication design, the sample size n_r is determined such that the probability of replication success is at least as large as a desired target probability of success, here and henceforth denoted by $1 - \beta$. The required sample size n_r^* is then the smallest sample size which leads to a probability of replication success of at least $1 - \beta$, i. e.,

$$n_r^* = \inf \{ n_r : \Pr(X_r \in S \mid n_r, x_o, \text{external knowledge}) \geq 1 - \beta \}. \tag{3}$$

Often, replication studies are analyzed using several methods which quantify different aspects of replicability, and which have different success regions (e. g., one method for quantifying parameter compatibility and another for quantifying evidence against a null hypothesis). In this case, the sample size may be chosen such that the probability of replication success is as large as desired for all planned analysis methods.

There may sometimes be certain constraints which the replication sample size needs to satisfy. For instance, in most cases there is an upper limit on the possible sample size due to limited resources and/or availability of samples. Moreover, funders and regulators may also require methods to be *calibrated* (Grieve, 2016), that is, to have appropriate type I error rate control. The sample size n_r^* may thus also need to satisfy a type I error rate not larger than some required level.

3 Sample size determination in the normal-normal hierarchical model

We will now illustrate the general methodology from the previous section in the *normal-normal hierarchical model* where predictive distributions and the probability of replication success can

often be expressed in closed-form, permitting further insight. It is pragmatic to adopt a meta-analytic perspective and use only study level summary statistics instead of the raw study data since the raw data from the original study are not always available to the replicators. Typically, the underlying parameter θ is a univariate effect size quantifying the effect on the outcome variable (e. g., a mean difference, a log odds ratio, or a log hazard ratio). The original and replication study can then be summarized through an effect estimate $\hat{\theta}$, possibly the maximum likelihood estimate, and a corresponding standard error σ, i. e., $x_o = \{\hat{\theta}_o, \sigma_o\}$ and $x_r = \{\hat{\theta}_r, \sigma_r\}$. Effect estimates and standard errors are routinely reported in research articles or can, under some assumptions, be computed from p-values and confidence intervals. As in the conventional meta-analytic framework (Sutton and Abrams, 2001), we further assume that for study $k \in \{o, r\}$ the (suitably transformed) effect estimate $\hat{\theta}_k$ is approximately normally distributed around a study specific effect size θ_k and with (known) variance equal to its squared standard error σ_k^2, here and henceforth denoted by $\hat{\theta}_k \,|\, \theta_k \sim \mathrm{N}(\theta_k, \sigma_k^2)$. The standard error σ_k is typically of the form $\sigma_k = \lambda / \sqrt{n_k}$ with λ^2 some unit variance and n_k the sample size. The ratio of the original to the replication variance is thus the ratio of the replication to the original sample size

$$c = \sigma_o^2 / \sigma_r^2 = n_r / n_o,$$

which is often the main focus of SSD as it quantifies how much the replication sample n_r size needs to be changed compared to the original sample size n_o. Depending on the effect size type, this framework might require slight modifications (see e. g., Spiegelhalter et al., 2004, chapter 2.4).

Assuming a normal sampling model for the effect estimates (4a), as described previously, and specifying an initial hierarchical normal prior for the study specific effect sizes (4b) and the effect size (4c), leads then to the normal-normal hierarchical model

$$\hat{\theta}_k \,|\, \theta_k \sim \mathrm{N}(\theta_k, \sigma_k^2) \tag{4a}$$
$$\theta_k \,|\, \theta \sim \mathrm{N}(\theta, \tau^2) \tag{4b}$$
$$\theta \sim \mathrm{N}(\mu_\theta, \sigma_\theta^2). \tag{4c}$$

By marginalizing over the study specific effects sizes, the model (4) can alternatively be expressed as

$$\hat{\theta}_k \,|\, \theta \sim \mathrm{N}(\theta, \sigma_k^2 + \tau^2) \tag{5a}$$
$$\theta \sim \mathrm{N}(\mu_\theta, \sigma_\theta^2) \tag{5b}$$

which is often more useful for derivations and computations. In the following we will explain how the normal-normal hierarchical model can be used for SSD of the replication study.

3.1 Design prior and predictive distribution

The observed original data $x_o = \{\hat{\theta}_o, \sigma_o\}$ can be combined with the initial prior (5b) by standard Bayesian theory for normal prior and likelihood (Spiegelhalter et al., 2004, ch. 3.7) to

obtain a posterior distribution for the effect size θ

$$\theta \mid \hat{\theta}_o, \sigma_o^2 \sim \mathrm{N}\left(\frac{\hat{\theta}_o}{1+1/g} + \frac{\mu_\theta}{1+g}, \frac{\sigma_o^2 + \tau^2}{1+1/g}\right) \tag{6}$$

where $g = \sigma_\theta^2 / (\sigma_o^2 + \tau^2)$ is the *relative prior variance*. This posterior serves then as the design prior for predicting the replication data.

It is interesting to contrast the design prior (6) to the "conditional" design prior (Micheloud and Held, 2022), that is, to assume that the unknown effect size θ corresponds to the original effect estimate $\hat{\theta}_o$. This is a standard approach in practice, for instance, Open Science Collaboration (2015) determined the sample sizes of its 100 replications under this assumption. In our framework it implies that the normal design prior (6) becomes a point mass at the original effect estimate $\hat{\theta}_o$, which can either be achieved through overwhelmingly informative original data ($\sigma_o^2 \downarrow 0$) along with no heterogeneity ($\tau^2 = 0$), or through an overwhelmingly informative initial prior ($g \downarrow 0$) centered around the original effect estimate ($\mu_\theta = \hat{\theta}_o$). Both cases show that from a Bayesian perspective the standard approach is unnatural as it either corresponds to making the standard error σ_o smaller than it actually was, or to cherry-picking the prior based on the data.

Based on the design prior (6), the predictive distribution of the replication effect estimate $\hat{\theta}_r$ can then be computed by assuming a replication standard error σ_r and integrating the marginal density of the replication effect estimate (5a) with respect to the prior density, leading to

$$\hat{\theta}_r \mid \hat{\theta}_o, \sigma_o^2, \sigma_r^2 \sim \mathrm{N}\left(\mu_{\hat{\theta}_r} = \frac{\hat{\theta}_o}{1+1/g} + \frac{\mu_\theta}{1+g}, \sigma_{\hat{\theta}_r}^2 = \sigma_r^2 + \tau^2 + \frac{\sigma_o^2 + \tau^2}{1+1/g}\right) \tag{7}$$

which can again be shown using standard Bayesian theory (Spiegelhalter et al., 2004, ch. 3.13.3). The design prior (6) and the resulting predictive distribution (7) depend on the parameters of the initial prior (τ^2, μ_θ, σ_θ^2). We will now explain how these parameters can be specified based on external knowledge.

3.2 Incorporating external knowledge in the initial prior

At least three common types of external knowledge can be distinguished in the replication setting: (i) expected heterogeneity between original and replication study due to differences in study design, execution, and population, (ii) prior knowledge about the effect size either from theory or from related studies, (iii) scepticism regarding the original study due to the possibility of exaggerated results.

Between-study heterogeneity

The expected degree of between-study heterogeneity can be incorporated via the variance τ^2 in (4b). As τ^2 decreases, the study specific effect sizes become more similar, whereas for increasing τ^2 they become more unrelated. If the replicators do not expect any heterogeneity they can thus set $\tau^2 = 0$ which will lead to the model collapsing to a fixed effects model.

If heterogeneity is expected, there are different approaches for specifying τ^2. A domain expert may subjectively assess how much heterogeneity is to be expected due to the change in laboratory, study population, and other factors. An alternative is to take an estimate from the literature, e. g., from multisite replication projects or from systematic reviews. Finally, one can also specify an upper limit of "tolerable heterogeneity". This approach is similar to specifying a minimal clinically relevant difference in classical power analysis in the sense that a true replication effect size which is intolerably heterogeneous from the original effect size is not relevant to be detected. An absolute (Spiegelhalter et al., 2004, chapter 5.7.3) and a relative approach (Held and Pawel, 2020) can be considered. In the absolute approach, a value of τ^2 is chosen such that a suitable range of study-specific effect sizes is not larger than an effect size difference considered negligible. For example, when 95% of the study specific effect sizes should not vary more than a small effect size e. g., $d = 0.2$ on standardized mean difference scale based on the Cohen (1992) effect size classification, this would lead to $\tau = d/(2 \cdot 1.96) \approx 0.05$. In the relative approach, τ^2 is specified relative to the variance of the original estimate σ_o^2 using field conventions for tolerable relative heterogeneity. For example, in the Cochrane guidelines for systematic reviews (Deeks et al., 2019) a value of $I^2 = \tau^2/(\tau^2 + \sigma_o^2) = 40\%$ is classified as "negligible", which translates to $\tau^2 = \sigma_o^2/(1/I^2 - 1) = (2\sigma_o^2)/3$.

We note that one can also assign a prior distribution to τ^2 (for an overview of prior distributions for heterogeneity variances in the normal-normal hierarchical model see Röver et al., 2021). In this case there is no closed-form expression for the predictive distribution of the replication effect estimate but numerical or Monte Carlo integration need to be used. We illustrate in the supplement how the probability of replication success can in this case be computed. The derived closed-form expressions conditional on τ^2 are still useful as they enable computation of the predictive distribution up to a single one-dimensional integral which can be computed numerically.

Knowledge about the effect size

Prior knowledge about the effect size θ can be incorporated via the prior mean μ_θ and the prior variance σ_θ^2 in (4c). For instance, the parameters may be specified based on a meta-analysis of related studies (McKinney et al., 2021) or based on expert elicitation (O'Hagan, 2019). The resulting design prior will then contain more information than what was provided by the original data alone, leading to potentially more efficient designs. If there is no prior knowledge available, a standard approach is to specify an (improper) flat prior by letting the variance go to infinity ($\sigma_\theta^2 \to \infty$). The resulting design prior will then only contain the information from the original study.

Exaggerated original results

Potentially exaggerated original results can be counteracted by setting $\mu_\theta = 0$ which shrinks the design prior towards smaller effect sizes (in absolute value) than the observed effect estimate $\hat{\theta}_o$. For instance, replicators could believe that the results from the original study are exaggerated because there is no pre-registered study protocol available. Even without such

beliefs, weakly informative shrinkage priors may also be motivated from a "regularization" point of view as they can correct for statistical biases (Copas, 1983; Firth, 1993) or prevent unreasonable parameter values from taking over the posterior in settings with uninformative data (Gelman, 2009).

The amount of shrinkage is determined via the prior variance σ_θ^2. A diffuse prior ($\sigma_\theta^2 \to \infty$) will lead to no shrinkage, while a highly concentrated prior ($\sigma_\theta^2 \downarrow 0$) will completely shrink the design prior to a point mass on zero. One option for specifying σ_θ^2 is to use an estimate from a corpus of related studies. For instance, Zwet et al. (2021) used the Cochrane library of systematic reviews to specify design priors for hypothetical replication studies of RCTs. If no corpus is available, a pragmatic alternative is to use the empirical Bayes estimate based on the original data

$$\hat{\sigma}_\theta^2 = \max\{(\hat{\theta}_o - \mu_\theta)^2 - \tau^2 - \sigma_o^2, 0\}. \tag{8}$$

The estimate (8) will lead to adaptive shrinkage (Pawel and Held, 2020) in the sense that shrinkage is large for unconvincing original studies (those with small effect estimates in absolute value $|\hat{\theta}_o|$ and/or large standard errors σ_o), but disappears as the data become more convincing (through larger effect estimates in absolute value $|\hat{\theta}_o|$ and/or smaller standard errors σ_o).

3.3 Example: Cross-laboratory replication project

We will now illustrate the construction of design priors based on data from a recently conducted replication project (Protzko et al., 2020), see Figure 2 for a summary of the data. The data were collected in four laboratories which, over the course of five years, conducted their typical social-behavioral experiments on topics such as psychology, communication, or political science. From the experiments conducted in this period, each lab submitted four original findings to be replicated. For instance, the original finding from the "Labels" experiment was: "When a researcher uses a label to describe people who hold a certain opinion, he or she is interpreted as disagreeing with those attributes when a negative label is used and agreeing with those attributes when a positive label is used" (Protzko et al., 2020, p. 17), which was based on an effect estimate $\hat{\theta}_o = 0.205$ with 95% confidence interval from 0.11 to 0.3. For each submitted original finding, four replication studies were then carried out, one by the same lab (a *self-replication*) and three by the other three labs (three *external-replications*).

Most studies used simple between-subject designs with two groups and a continuous outcome so that for a study $i \in \{o, r\}$ the standardized mean difference (SMD) effect estimate $\hat{\theta}_i$ can be computed from the group means $\bar{y}_{i1}, \bar{y}_{i2}$, group standard deviations s_{i1}, s_{i2}, and group sample sizes n_{i1}, n_{i2} by

$$\hat{\theta}_i = \frac{\bar{y}_{i1} - \bar{y}_{i2}}{s_i}$$

with $s_i^2 = \{(n_{i1} - 1)s_{i1}^2 + (n_{i2} - 1)s_{i2}^2\}/(n_{i1} + n_{i2} - 2)$ the pooled sample variance. Under a normal sampling model and assuming equal variances in both groups, the approximate

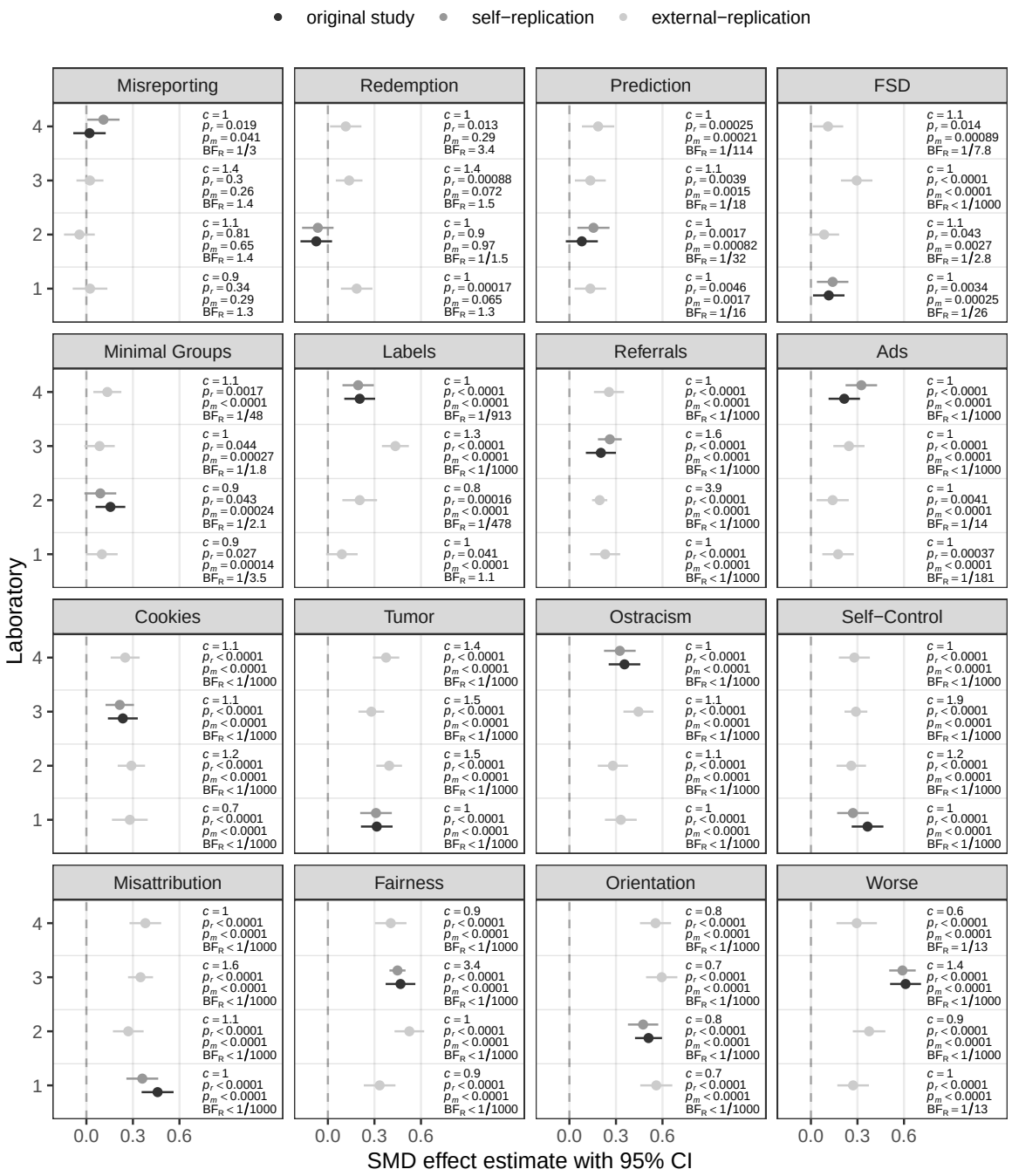


Figure 2: Data from cross-laboratory replication project by Protzko et al. (2020). Shown are standardized mean difference (SMD) effect estimates with 95% confidence intervals stratified by experiment and laboratory. For each replication study, the relative sample size $c = n_r/n_o$, the one-sided replication p-value p_r, the one-sided meta-analytic p-value p_m, and the replication Bayes factor $\mathrm{BF_R}$ are shown. Experiments are ordered (left to right, top to bottom) by their original one-sided p-value $p_o = 1 - \Phi(|\hat{\theta}_o|/\sigma_o)$

variance of $\hat{\theta}_i$ is

$$\sigma_i^2 = \frac{n_{i1} + n_{i2}}{n_{i1} n_{i2}} + \frac{\hat{\theta}_i^2}{2(n_{i1} + n_{i2})} \tag{9}$$

(Hedges, 1981). A cruder, but for SSD more useful, approximation $\sigma_i^2 \approx 4/n_i$ is obtained by assuming the same sample size in both groups $n_{i1} = n_{i2} = n_i/2$, with n_i the total sample size, and neglecting the second term in (9) which will be close to zero for small effect estimates and/or large sample sizes (Hedges and Schauer, 2021). We thus have the approximate unit variance $\lambda^2 = 4$ and the relative variance $c = \sigma_o^2/\sigma_r^2 = n_r/n_o$, which can be interpreted as the ratio of the replication to the original sample size.

Suppose now the original studies have been finished, and we want to conduct SSD for the not yet conducted replication studies. We start by specifying the design priors (one for each replication). Since the original studies have been preregistered, we do not expect an exaggeration of their effect estimates due to selective reporting or other questionable research practices. Therefore, we choose an uninformative initial prior ($\sigma_\theta^2 \to \infty$), which leads to design prior and predictive distribution both centered around the original effect estimate $\hat{\theta}_o$.

For specifying the between-study heterogeneity variance τ^2, a distinction needs to be made between self-replications and external-replications. For self-replications it is reasonable to set $\tau^2 = 0$ because we would expect no between-study heterogeneity as the experimental conditions will be nearly identical in both studies. In contrast, one would expect some between-study heterogeneity for external-replications as the experimental conditions may slightly differ between the labs. In the following, we will use $\tau^2 = 0.05^2$ elicited via the "absolute" approach as discussed previously, so that the range between the 2.5% and the 97.5% quantile of the study specific effect size distribution is equal to a small effect size $d = 0.2$.

Taken together, we obtain the design prior $\theta \mid \hat{\theta}_o, \sigma_o^2 \sim \mathrm{N}(\hat{\theta}_o, \sigma_o^2)$ for self-replications and the design prior $\theta \mid \hat{\theta}_o, \sigma_o^2 \sim \mathrm{N}(\hat{\theta}_o, \sigma_o^2 + \tau^2)$ with $\tau^2 = 0.05^2$ for external-replications. For example, for the experiment "Labels", the design prior would be centered around the original effect estimate $\hat{\theta}_o = 0.205$ with variance $\sigma_o^2 = 0.05^2$ for a self-replication, and with variance $\sigma_o^2 + \tau^2 = 0.05^2 + 0.05^2 \approx 0.07^2$ for an external-replication. Figure 3 (dark-gray solid lines) shows the densities of the two priors.

While these two priors seem sensible for the Protzko et al. (2020) data, it is interesting to think about alternative scenarios. If there had been reasons to believe that the original result might be exaggerated, we could have specified an initial shrinkage prior ($\mu_\theta = 0$ and $\sigma_\theta^2 < \infty$). For instance, the empirical Bayes estimate for the prior variance σ_θ^2 from (8) leads to a prior whose mean and variance are shrunken towards zero by 12% (medium-gray dashed lines in Figure 3). In contrast, if we had prior knowledge about the effect size θ from another study, we could have specified an initial "optimistic" prior. For example, if the self-replication of the "Labels" experiment had been a pilot study and we used its effect estimate $\hat{\theta}_p = 0.195$ and standard error $\sigma_p = 0.05$ to specify the initial prior, this would lead to a design prior centered around the weighted mean of original and pilot study, and a prior precision equal to the sum of the precision of both estimates (light-gray dot-dashed lines in Figure 3). Due to the inclusion of the external data, this design prior is much more concentrated than the other two.

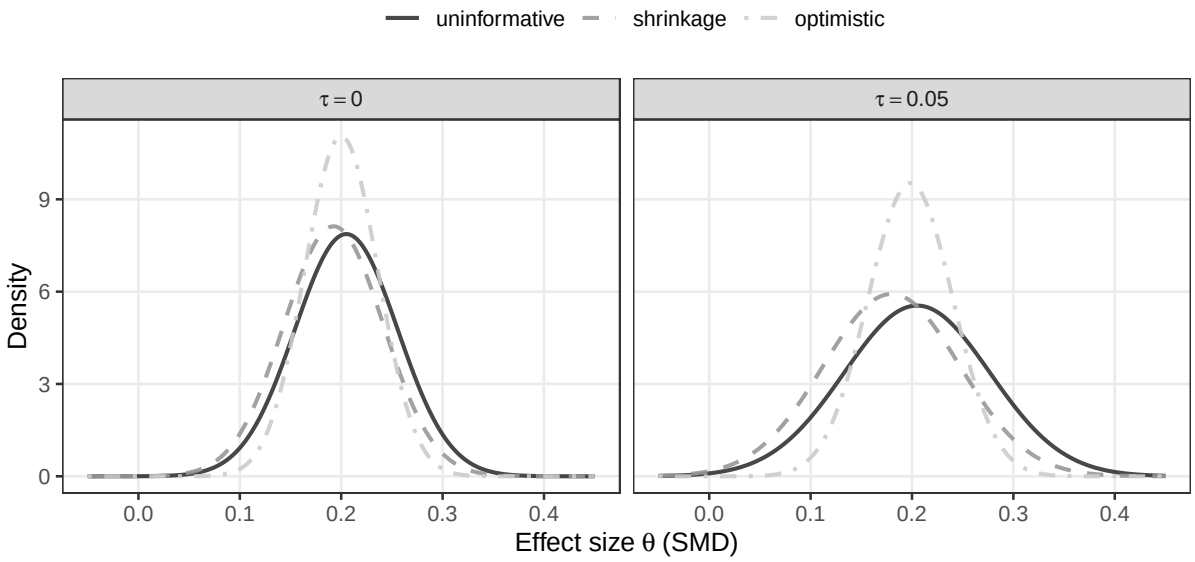


Figure 3: Design priors for the effect size θ (SMD) in the experiment "Labels" based on the original effect estimate $\hat{\theta}_o = 0.205$ with standard error $\sigma_o = 0.051$. Shown are different choices for the between-study heterogeneity τ and the initial prior for the effect size θ, "uninformative" corresponds to a flat prior, "shrinkage" corresponds to a zero-mean normal prior with empirical Bayes variance estimate (8), and "optimistic" corresponds to a flat prior updated by the data from a pilot study with effect estimate $\hat{\theta}_p = 0.195$ and standard error $\sigma_p = 0.052$.

3.4 Probability of replication success and required sample size

To compute the probability of replication success one needs to select an analysis method and integrate the predictive distribution (7) over the associated success region S. There is no universally accepted method for quantifying replicability and here we do not intend to contribute to the debate about the most appropriate method. We will simply show the success regions of different methods, and how the replication sample size can be computed from them. Some methods depend on the direction of the original effect estimate $\hat{\theta}_o$ and throughout we will assume that it was positive ($\hat{\theta}_o > 0$). Functions for computing the probability of replication success and the required sample size are implemented in the R package `BayesRepDesign` (see Appendix A) for all analysis methods discussed in the following.

The two-trials rule

The most common approach for the analysis of replication studies is to declare replication success when both the original and replication study lead to a p-value for testing the null hypothesis $H_0\colon \theta = 0$ smaller than a pre-specified threshold α, usually $\alpha = 5\%$ for two-sided tests and $\alpha = 2.5\%$ for one-sided tests. This procedure is known as the *two-trials rule* in drug regulation (Senn, 2008).

We now assume that the one-sided original p-value was significant at some level α, i. e., $p_o = 1 - \Phi(\hat{\theta}_o/\sigma_o) \leq \alpha$. Replication success at level α is then achieved if the replication p-value is also significant, i. e., $p_r = 1 - \Phi(\hat{\theta}_r/\sigma_r) \leq \alpha$, which implies a success region

$$S_{\text{2TR}} = [z_\alpha \sigma_r, \infty),$$

where z_α is the $1-\alpha$ quantile of the standard normal distribution. The probability of replication success is thus given by

$$\Pr(\hat{\theta}_r \in S_{\text{2TR}} \mid \hat{\theta}_o, \sigma_o, \sigma_r) = \Phi\left(\frac{\mu_{\hat{\theta}_r} - z_\alpha \sigma_r}{\sigma_{\hat{\theta}_r}}\right) \tag{10}$$

with $\Phi(\cdot)$ the standard normal cumulative distribution function and $\mu_{\hat{\theta}_r}$ and $\sigma_{\hat{\theta}_r}$ the mean and standard deviation of the predictive distribution (7). Importantly, by decreasing the standard error σ_r (through increasing the sample size n_r), the probability of replication success (10) cannot become arbitrarily large but is bounded from above by

$$\text{lim}\Pr_{\text{2TR}} = \Phi\left(\frac{\mu_{\hat{\theta}_r}}{\sqrt{\tau^2 + (\sigma_o^2 + \tau^2)/(1 + 1/g)}}\right). \tag{11}$$

The required replication standard error σ_r^* to achieve a target probability of replication success $1 - \beta < \text{lim}\Pr_{\text{2TR}}$ can now be obtained by equating (10) to $1 - \beta$ and solving for σ_r. This leads to

$$\sigma_r^* = \frac{\mu_{\hat{\theta}_r} z_\alpha - z_\beta \sqrt{(z_\alpha^2 - z_\beta^2)\left\{\tau^2 + (\sigma_o^2 + \tau^2)/(1 + 1/g)\right\} + \mu_{\hat{\theta}_r}^2}}{z_\alpha^2 - z_\beta^2} \tag{12}$$

for $\alpha < \beta$. The standard error σ_r^* can subsequently be translated in a sample size. The translation depends on the type of effect size, for instance, for SMD effect sizes we can use the approximation $n_r^* \approx 4/(\sigma_r^*)^2$ from earlier. Moreover, by assuming a standard error of the form $\sigma_r = \lambda/\sqrt{n_r}$ and plugging in the parameters of the "conditional" design prior ($\tau^2 = 0$, $\mu_\theta = \hat{\theta}_o$, $g \downarrow 0$), we obtain the well-known sample size formula (Matthews, 2006, chapter 3.3)

$$n_r^* = \frac{(z_\alpha + z_\beta)^2}{(\hat{\theta}_o/\lambda)^2}$$

for a one-sided significance test at level α with power $1 - \beta$ to detect the original effect estimate $\hat{\theta}_o$. The formula (12) thus generalizes standard sample size calculation to take into account the uncertainty of the original estimate, between-study heterogeneity and other types of external knowledge.

Fixed effects meta-analysis

The data from the original and replication studies are sometimes pooled via fixed-effects meta-analysis. The pooled effect estimate $\hat{\theta}_m$ and standard error σ_m are then given by

$$\hat{\theta}_m = \left(\hat{\theta}_o/\sigma_o^2 + \hat{\theta}_r/\sigma_r^2\right)\sigma_m^2 \qquad \text{and} \qquad \sigma_m = \left(1/\sigma_o^2 + 1/\sigma_r^2\right)^{-1/2},$$

and they are also equivalent to the mean and standard deviation of a posterior distribution for the effect size θ based on the data from both studies and an initial flat prior for θ. The success region

$$S_{\text{MA}} = \left[\sigma_r z_\alpha \sqrt{1 + \sigma_r^2/\sigma_o^2} - (\hat{\theta}_o \sigma_r^2)/\sigma_o^2, \infty\right) \tag{13}$$

then corresponds to both replication success defined via a one-sided meta-analytic p-value being smaller than level α, i. e., $p_m = 1 - \Phi(\hat{\theta}_m/\sigma_m) \leq \alpha$, or to replication success defined via a Bayesian posterior probability $\Pr(\theta > 0 \,|\, \hat{\theta}_o, \hat{\theta}_r, \sigma_o, \sigma_r) \geq 1 - \alpha$. Based on the success region (13) and an assumed standard error σ_r, the probability of replication success can be computed by

$$\Pr(\hat{\theta}_r \in S_{\text{MA}} \,|\, \hat{\theta}_o, \sigma_o, \sigma_r) = \Phi\left(\frac{\mu_{\hat{\theta}_r} - \sigma_r z_\alpha \sqrt{1 + \sigma_r^2/\sigma_o^2} + (\hat{\theta}_o \sigma_r^2)/\sigma_o^2}{\sigma_{\hat{\theta}_r}}\right). \tag{14}$$

As for the two-trials rule, the probability (14) cannot be made arbitrarily large by decreasing the standard error σ_r but is bounded from above by $\text{limPr}_{\text{2TR}}$ defined in (11). The required standard error σ_r^* to achieve a target probability of replication success $1 - \beta < \text{limPr}_{\text{2TR}}$ can be computed numerically using root finding algorithms.

Effect size equivalence test

Anderson and Maxwell (2016) proposed a method for quantifying replicability based on effect size equivalence. Under normality, replication success at level α is achieved if the $(1 - \alpha)$ confidence interval for the effect size difference $\theta_r - \theta_o$

$$\hat{\theta}_r - \hat{\theta}_o \pm z_{\alpha/2} \sqrt{\sigma_r^2 + \sigma_o^2}$$

is fully inside an equivalence region $[-\Delta, \Delta]$ defined via the pre-specified margin $\Delta > 0$. This procedure corresponds to rejecting the null hypothesis $H_0 \colon |\theta_r - \theta_o| > \Delta$ in an equivalence test, and it implies a success region for the replication effect estimate $\hat{\theta}_r$ given by

$$S_{\text{E}} = \left[\hat{\theta}_o - \Delta + z_{\alpha/2} \sqrt{\sigma_o^2 + \sigma_r^2}, \hat{\theta}_o + \Delta - z_{\alpha/2} \sqrt{\sigma_o^2 + \sigma_r^2}\right] \tag{15}$$

for $\Delta \geq z_{\alpha/2} \sqrt{\sigma_o^2 + \sigma_r^2}$. For too small margins ($\Delta < z_{\alpha/2} \sqrt{\sigma_o^2 + \sigma_r^2}$), the success region (15) becomes the empty set meaning that replication success is impossible. Assuming now that the margin is large enough, the probability of replication success can be computed by

$$\begin{aligned} \Pr(\hat{\theta}_r \in S_{\text{E}} \,|\, \hat{\theta}_o, \sigma_o, \sigma_r) = \Phi&\left(\frac{\hat{\theta}_o + \Delta - z_{\alpha/2} \sqrt{\sigma_o^2 + \sigma_r^2} - \mu_{\hat{\theta}_r}}{\sigma_{\hat{\theta}_r}}\right) \\ - \Phi&\left(\frac{\hat{\theta}_o - \Delta + z_{\alpha/2} \sqrt{\sigma_o^2 + \sigma_r^2} - \mu_{\hat{\theta}_r}}{\sigma_{\hat{\theta}_r}}\right). \end{aligned} \tag{16}$$

As with the previous methods, the probability (16) cannot be made arbitrarily large by decreasing the replication standard error σ_r, but is bounded by

$$\text{limPr}_\text{E} = \Phi\left(\frac{\hat{\theta}_o + \Delta - z_{\alpha/2}\sigma_o - \mu_{\hat{\theta}_r}}{\sqrt{\tau^2 + (\sigma_o^2 + \tau^2)/(1 + 1/g)}}\right) - \Phi\left(\frac{\hat{\theta}_o - \Delta + z_{\alpha/2}\sigma_o - \mu_{\hat{\theta}_r}}{\sqrt{\tau^2 + (\sigma_o^2 + \tau^2)/(1 + 1/g)}}\right).$$

The required replication standard error σ_r^* to achieve a target probability of replication success $1 - \beta < \text{limPr}_\text{E}$ can again be computed numerically.

The replication Bayes factor

A Bayesian hypothesis testing approach for assessing replication success was proposed by Verhagen and Wagenmakers (2014) and further developed by Ly et al. (2018). They define a "replication Bayes factor"

$$\text{BF}_\text{R} = \frac{f(x_r \mid H_0)}{f(x_r \mid H_1)}$$

which is the ratio of the marginal likelihoods of the replication data x_r under the null hypothesis $H_0 \colon \theta = 0$ to the marginal likelihood of x_r under the alternative hypothesis $H_1 \colon \theta \sim f(\theta \mid x_o)$, that is the posterior of the effect size θ based on the original data x_o. If the original study provides evidence against the null hypothesis, replication Bayes factor values $\text{BF}_\text{R} < 1$ indicate replication success, and the smaller the value the higher the degree of success.

Under normality and assuming no heterogeneity, the success region for achieving $\text{BF}_\text{R} \leq \gamma$ is given by

$$S_{\text{BF}_\text{R}} = \left(-\infty, -\sqrt{A} - (\hat{\theta}_o\sigma_r^2)/\sigma_o^2\right] \bigcup \left[\sqrt{A} - (\hat{\theta}_o\sigma_r^2)/\sigma_o^2, \infty\right) \tag{17}$$

with $A = \sigma_r^2(1 + \sigma_r^2/\sigma_o^2)\{\hat{\theta}_o^2/\sigma_o^2 - 2\log\gamma + \log(1 + \sigma_o^2/\sigma_r^2)\}$. Details of this calculation are given in the supplement. The fact that the success region (17) is defined on both sides around zero shows that replication success is also possible if the replication effect estimate goes in opposite direction of the original one, which is known as the "replication paradox" (Ly et al., 2018). The paradox can be avoided using a modified version of the replication Bayes factor but the success region is no longer available in closed-form (Pawel and Held, 2022, Appendix D). Based on the success region (17), the probability of replication success can be computed by

$$\Pr(\hat{\theta}_r \in S_{\text{BF}_\text{R}} \mid \hat{\theta}_o, \sigma_o, \sigma_r) = \Phi\left(\frac{\mu_{\hat{\theta}_r} - \sqrt{A} + (\hat{\theta}_o\sigma_r^2)/\sigma_o^2}{\sigma_{\hat{\theta}_r}}\right) + \Phi\left(\frac{-\sqrt{A} - (\hat{\theta}_o\sigma_r^2)/\sigma_o^2 - \mu_{\hat{\theta}_r}}{\sigma_{\hat{\theta}_r}}\right). \tag{18}$$

One may want to compute the probability of replication success only for the part of the success region with the same sign as the original effect estimate to avoid the replication paradox. As for the other methods, the probability (18) is bounded from above by a constant $\text{limPr}_{\text{BF}_\text{R}} = \lim_{\sigma_r \downarrow 0} \Pr(\hat{\theta}_r \in S_{\text{BF}_\text{R}} \mid \hat{\theta}_o, \sigma_o, \sigma_r)$, and root finding algorithms can be used to numerically determine the required standard error σ_r^* for achieving a target probability of replication success $1 - \beta < \text{limPr}_{\text{BF}_\text{R}}$.

The sceptical *p*-value

Held (2020) proposed a reverse-Bayes approach for quantifying replication success. The main idea is to determine the variance of a "sceptical" zero-mean normal prior for the effect size θ such that its posterior distribution based on the original study is no longer credible. Replication success is then achieved if the replication data are in conflict with the sceptical prior. The procedure can be summarized by a "sceptical p-value" p_S, and the lower the p-value the higher the degree of replication success. Held et al. (2022b, sec. 2.1) showed that the success region for replication success defined by $p_S \leq \alpha$ is given by

$$S_{p_S} = \left[z_\alpha \sqrt{\sigma_r^2 + \frac{\sigma_o^2}{(z_o^2/z_\alpha^2) - 1}}, \infty \right). \tag{19}$$

From the success region (19) the probability of replication success at level α is

$$\Pr(\hat{\theta}_r \in S_{p_S} \,|\, \hat{\theta}_o, \sigma_o, \sigma_r) = \Phi\left(\frac{\mu_{\hat{\theta}_r} - z_\alpha \sqrt{\sigma_r^2 + \sigma_o^2 / \{(z_o^2/z_\alpha^2) - 1\}}}{\sigma_{\hat{\theta}_r}} \right),$$

and also bounded from above by a constant $\text{limPr}_{p_S} = \lim_{\sigma_r \downarrow 0} \Pr(\hat{\theta}_r \in S_{p_S} \,|\, \hat{\theta}_o, \sigma_o, \sigma_r)$. As for the two-trials rule, the required standard error σ_r^* to achieve a probability of replication success $1 - \beta < \text{limPr}_{p_S}$ can be computed analytically for $\alpha < \beta$:

$$\sigma_r^* = \sqrt{x^2 - \frac{\sigma_o^2}{(z_o/z_\alpha)^2 - 1}}$$

with

$$x = \frac{z_\alpha \mu_{\hat{\theta}_r} - z_\beta \sqrt{\mu_{\hat{\theta}_r}^2 - (z_\alpha^2 - z_\beta^2)[\tau^2 + (\sigma_o^2 + \tau^2)/(1 + 1/g) - \sigma_o^2 / \{(z_o/z_\alpha)^2 - 1\}]}}{z_\alpha^2 - z_\beta^2}.$$

The sceptical Bayes factor

Pawel and Held (2022) modified the previously described reverse-Bayes assessment of replication success from Held (2020) to work with Bayes factors instead of tail probabilities as measures of evidence and prior data conflict. Again, the procedure can be summarized in a single measure termed the "sceptical Bayes factor" BF_S, with lower values of BF_S pointing to higher degrees of replication success. Also for this method, the success region and the probability of replication success can be expressed in closed-form but the derivations are more involved than for the other methods. For this reason, they are only given in the supplement.

3.5 Example: Cross-laboratory replication project (continued)

We will now revisit the experiment "Labels" and compute the probability of replication success. The parameters of the analysis methods are specified as follows: For the two-trials rule

we use the conventional one-sided significance level $\alpha = 0.025$, while for meta-analysis we use the more stringent level $\alpha = 0.025^2$ as the method is based on two data sets rather than one. We use a $1 - \alpha = 90\%$ confidence interval which is conventionally used in equivalence testing, along with a margin $\Delta = 0.2$ corresponding to a small SMD effect size according to the classification from Cohen (1992). For the sceptical p-value we use the recommended "golden" level $\alpha = 0.062$ as it guarantees that for original studies which where just significant at $\alpha = 0.025$ replication success is only possible if the replication effect estimate is larger than the original one (Held et al., 2022b). Finally, for the replication Bayes factor and the sceptical Bayes factor we use the "strong evidence" level $\gamma = 1/10$ from Jeffreys (1961).

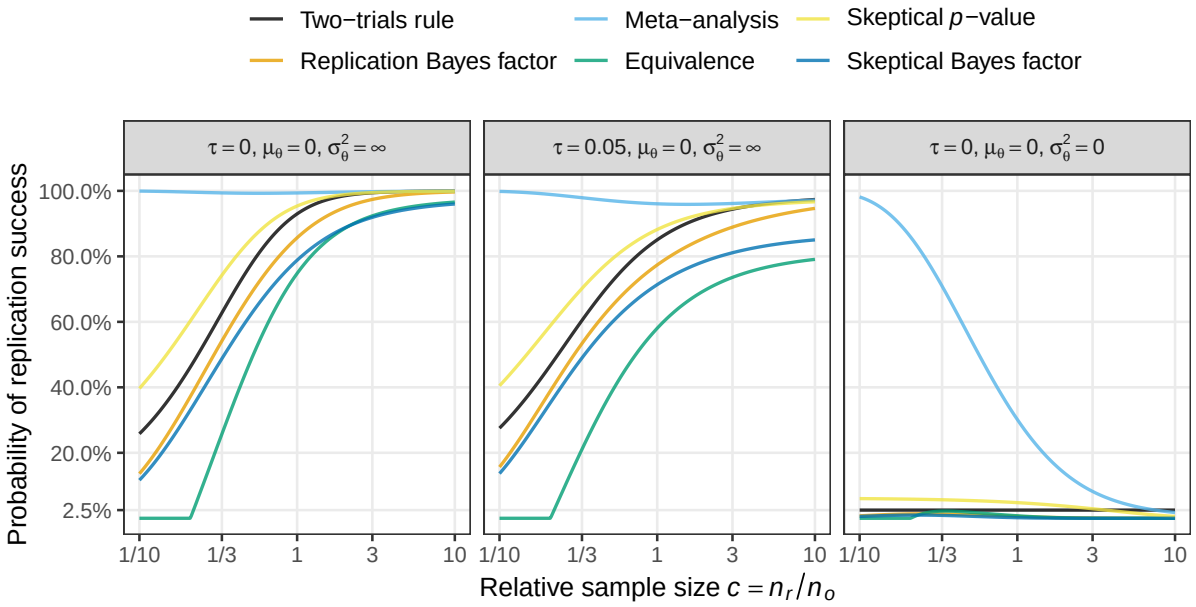


Figure 4: Probability of replication success as a function of relative sample size $c = n_r/n_o$ for experiment "Labels" with original effect estimate $\hat{\theta}_o = 0.205$ and standard error $\sigma_o = 0.051$ for different initial prior parameters $(\tau, \mu_\theta, \sigma_\theta^2)$. The probability of replication success with the design prior $\tau = 0, \mu_\theta = 0$, and $\sigma_\theta^2 = 0$ (right plot) corresponds to the type I error rate under the fixed effects null hypothesis ($H_0 \colon \theta = 0, \tau^2 = 0$). Replication success is defined by the two-trials rule at level $\alpha = 0.025$, the replication Bayes factor at level $\gamma = 1/10$, fixed effects-meta analysis at level $\alpha = 0.025^2$, effect size equivalence based on 90% confidence interval and with margin $\Delta = 0.2$, sceptical p-value at level $\alpha = 0.062$, and sceptical Bayes factor at level $\gamma = 1/10$.

Figure 4 shows the probability of replication success as a function of the relative sample size $c = n_r/n_o$ and for different initial priors. The left and middle plot are based on an uninformative prior for the effect size ($\sigma_\theta^2 \to \infty$) without heterogeneity ($\tau^2 = 0$) and with heterogeneity ($\tau^2 = 0.05^2$), respectively. The right plot shows the prior corresponding to the "fixed effects null hypothesis" $H_0 \colon \theta = 0, \tau^2 = 0$, so that the probability of replication success is the type I error rate which some stakeholders might require to be "controlled" at some adequate level.

We see from the left and middle plots that increasing the relative sample size monotonically

increases the probability of replication success for all methods but meta-analysis (light blue). Meta-analysis shows a non-monotone behavior because the original study was already highly significant so that the pooled effect estimate is significant even for replication studies with very small sample size (Micheloud and Held, 2022). The uncertainty regarding the replication effect estimate $\hat{\theta}_r$ may therefore even reduce the probability of replication success for meta-analysis if the sample size is increased. If heterogeneity is taken into account (middle plot) the probability of replication success becomes closer to 50% for all methods but the equivalence test, reflecting the larger uncertainty about the effect size θ. To achieve 80% probability of replication success the fewest samples are required with meta-analysis, followed by the sceptical p-value, the two-trials rule, the replication Bayes factor, the sceptical Bayes factor, and lastly the equivalence test. If the chosen sample size should guarantee a sufficiently conclusive replication study with all these methods, the replication sample size has to be slightly larger than the original one in the situation of no heterogeneity ($\tau^2 = 0$), while it has to be increased more than ten-fold if there is heterogeneity ($\tau^2 = 0.05^2$). However, this is mostly due to the equivalence test which requires by far the most samples. If the equivalence test sample size is ignored, the relative sample size $c = 2.5$ ensures at least 80% probability of replication success with the remaining methods.

The right plot in Figure 4 shows that the type I error rate of the two-trials rule (black) stays constant at $\alpha = 0.025$, as expected by definition of the method. In contrast, the type I error rates of the other methods vary with the relative sample size c but most of them stay below $\alpha = 0.025$ for all c with the exception of meta-analysis and the sceptical p-value. Meta-analysis (light blue) has an extremely high type I error rate as the pooling with the highly significant original data leads to replication success if the replication sample size is not drastically increased. The type I error rate of the sceptical p-value (yellow) is only slightly larger than $\alpha = 0.025$ which is expected since the level $\alpha = 0.062$ is used for declaring replication success with the sceptical p-value, and its type I error rate is always smaller than the level for thresholding it (Held, 2020). The type I error rate of the sceptical p-value decreases to values smaller than $\alpha = 0.025$ of the two-trials rule at approximately $c = 3$.

We now conduct SSD for all studies from the replication project of Protzko et al. (2020). Figure 5 shows the required relative sample size and the associated type I error rates if a sample size can be computed for a probability of replication success of $1 - \beta = 80\%$. If there is no sample size for which a probability of 80% can be achieved the space is left blank. This is, for instance, the case for the meta-analysis method for all studies below the "Labels" experiment as the probability stays above 80% for any relative sample size.

We see that for all methods but the equivalence test the required relative sample size c decreases with decreasing original p-value p_o, and original studies with very small p-values require much fewer samples in the replication study. For the equivalence test, the required sample size depends instead on the size of the original standard error σ_o, and smaller standard errors leads to smaller required sample sizes in the replication. We also see that taking into account heterogeneity (triangle) increases the required sample size for all methods compared to not taking it into account (dot). At the same time, a larger required sample size reduces the type I error rate for most methods. We see again the pattern that the type I error rate of the equivalence test and the sceptical p-value is larger than the type I error rate 2.5% of the

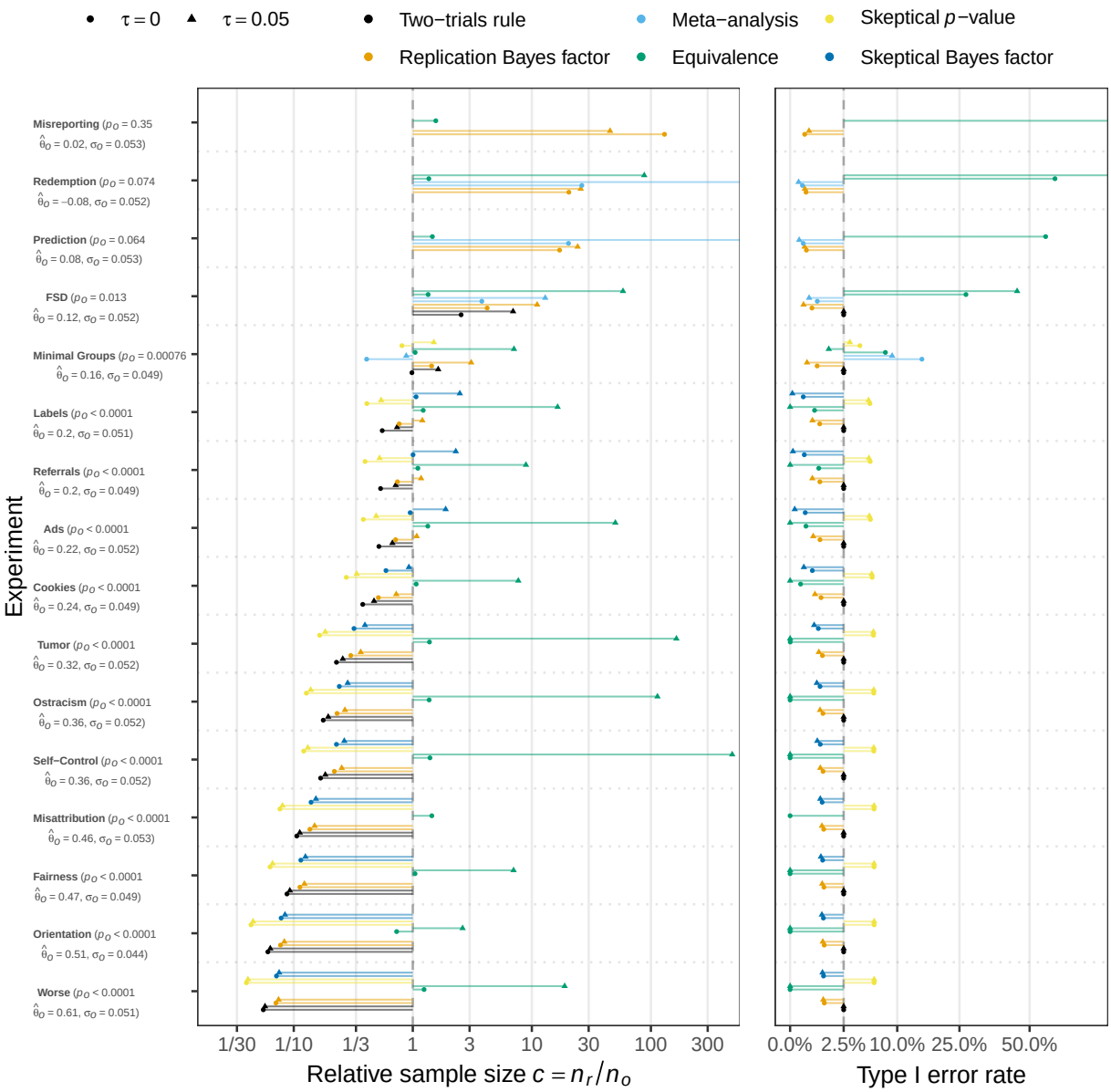


Figure 5: The left plot shows the required relative sample size $c = n_r/n_o$ to achieve a target probability of replication success of $1 - \beta = 80\%$ (if possible). Replication success is defined through the two-trials rule at level $\alpha = 0.025$, replication Bayes factor at level $\gamma = 1/10$, fixed effects-meta analysis at level $\alpha = 0.025^2$, effect size equivalence at level $\alpha = 0.1$ with margin $\Delta = 0.2$, sceptical p-value at level $\alpha = 0.062$, and sceptical Bayes factor at level $\gamma = 1/10$ for data from the replication project by Protzko et al. (2020). A flat initial prior ($\mu_\theta = 0, \sigma_\theta^2 \to \infty$) is used for the effect size θ is used either without ($\tau = 0$) or with heterogeneity ($\tau = 0.05$). The right plot shows the type I error rate associated with the required sample size. Experiments are ordered (top to bottom) by their original one-sided p-value $p_o = 1 - \Phi(|\hat{\theta}_o|/\sigma_o)$.

two-trials rule. However, while the type I error rate of the sceptical p-value decreases when replication studies require larger sample sizes, the type I error rate of the equivalence test

may also be large if the replication requires very large sample sizes (e. g., for the experiment "FSD") since it depends on whether the original effect estimate $\hat{\theta}_o$ is sufficiently different from zero. If the original effect estimate $\hat{\theta}_o$ is close to zero, the type I error rate of the equivalence test is drastically increased as equivalence can also be established if the effect estimates from original and replication studies are close to zero (as under the null hypothesis).

Taken together, for most of the experiments all methods but the equivalence test require fewer samples in the replication than in the original study to achieve a target probability of replication success $1 - \beta = 80\%$. This is still the case if heterogeneity is taken into account in the design prior (triangles), which generally increases the required sample size compared to when heterogeneity is not taken into account (dots), especially for studies with large original p-value. Larger replication sample sizes are required for some original studies. In some cases these are unrealistically large (e. g., in the experiment "Prediction" an almost 30 times increase in sample size for the replication Bayes factor), but in other cases they seem more realistic and could be reallocated from the other studies which require fewer samples (e. g., in the experiment "Referrals" an almost three times increase for the sceptical Bayes factor). On the other hand, the equivalence test typically requires larger sample sizes in the replication because the original standard errors are large relative to the specified margin. If one anticipates to analyze the original and replication pair with an equivalence test, this should therefore be taken into account already at the design stage of the original study.

3.6 Sample size determination for multisite replication projects

So far we considered the situation where a pair of a single original and a single replication study are analyzed in isolation. However, if multiple replications per single original study are conducted (so-called *multisite* replication studies) the ensemble of replications can also be analyzed jointly. In this case, some adaptations of the SSD methodology are required.

The replication effect estimate and its standard error are now vectors $\hat{\boldsymbol{\theta}}_r = (\hat{\theta}_{r1}, \ldots, \hat{\theta}_{rm})^\top$ and $\boldsymbol{\sigma}_r^2 = (\sigma_{r1}^2, \ldots, \sigma_{rm}^2)^\top$ consisting of m replication effect estimates, respectively, their standard errors. The normal hierarchical model for the replication estimates $\hat{\boldsymbol{\theta}}_r$ then becomes

$$\hat{\boldsymbol{\theta}}_r \,|\, \boldsymbol{\theta}_r \sim \mathrm{N}_m \left\{ \boldsymbol{\theta}_r, \mathrm{diag}\left(\boldsymbol{\sigma}_r^2\right) \right\} \tag{20a}$$

$$\boldsymbol{\theta}_r \,|\, \theta \;\sim \mathrm{N}_m \left\{ \theta\, \mathbf{1}_m, \tau^2 \mathrm{diag}(\mathbf{1}_m) \right\}, \tag{20b}$$

where $\boldsymbol{\theta}_r$ is a vector of m study specific effect sizes, $\mathbf{1}_m$ is a vector of m ones, and $\mathrm{N}_m(\boldsymbol{\mu}, \boldsymbol{\Sigma})$ denotes the m-variate normal distribution with mean vector $\boldsymbol{\mu}$ and covariance matrix $\boldsymbol{\Sigma}$. By marginalizing over the study specific effect size $\boldsymbol{\theta}_k$, the model can alternatively be expressed by

$$\hat{\boldsymbol{\theta}}_r \,|\, \theta \sim \mathrm{N}_m \left\{ \theta\, \mathbf{1}_m, \mathrm{diag}\left(\boldsymbol{\sigma}_r^2 + \tau^2 \mathbf{1}_m\right) \right\}, \tag{21}$$

so the predictive distribution of $\hat{\boldsymbol{\theta}}_r$ based on the design prior (6) is given by

$$\hat{\boldsymbol{\theta}}_r \,|\, \hat{\theta}_o, \sigma_o^2, \boldsymbol{\sigma}_r^2 \sim \mathrm{N}_m \left\{ \mu_{\hat{\theta}_r} \mathbf{1}_m, \mathrm{diag}\left(\boldsymbol{\sigma}_r^2 + \tau^2 \mathbf{1}_m\right) + \left(\frac{\tau^2 + \sigma_o^2}{1 + 1/g} \right) \mathbf{1}_m \mathbf{1}_m^\top \right\} \tag{22}$$

with $\mu_{\hat{\theta}_r}$ the mean of the predictive distribution of a single replication effect estimate from (7). Importantly, the replication effect estimates are correlated as the covariance matrix in (22) has $(\tau^2 + \sigma_o^2)/(1 + 1/g)$ in the off-diagonal entries.

Often the assessment of replication success can be formulated in terms of a weighted average of the replication effect estimates $\hat{\theta}_{r*} = (\sum_{i=1}^{m} w_i \hat{\theta}_{ri})/(\sum_{i=1}^{m} w_i)$ with w_i the weight of replication i. For instance, several multisite replication projects (e. g., Klein et al., 2018) have defined replication success by the fixed or random effects meta-analytic effect estimate of the replication effect estimates achieving statistical significance. Based on the predictive distribution of the replication effect estimate vector (22), the predictive distribution of the weighted average $\hat{\theta}_{r*}$ is given by

$$\hat{\theta}_{r*} \,|\, \hat{\theta}_o, \sigma_o^2, \sigma_r^2 \sim \mathrm{N}\left\{ \mu_{\hat{\theta}_r}, \sigma^2_{\hat{\theta}_{r*}} = \left(\sum_{i=1}^{m} w_i^2 \sigma^2_{\hat{\theta}_{ri}} + \sum_{i=1}^{m} \sum_{\substack{j=1 \\ j \neq i}}^{m} w_i w_j \frac{\tau^2 + \sigma_o^2}{1 + 1/g} \right) \Big/ \left(\sum_{i=1}^{m} w_i \right)^2 \right\} \tag{23}$$

with $\sigma^2_{\hat{\theta}_{ri}}$ the predictive variance of a single replication effect estimate with standard error σ_{ri} as in (7). In particular when the studies receive equal weights ($w_i = w$ for $i = 1, \ldots, m$) and the standard errors of the replication effect estimates are equal ($\sigma_{ri} = \sigma_r$ for $i = 1, \ldots, m$), the predictive variance becomes

$$\sigma^2_{\hat{\theta}_{r*}} = \frac{\sigma_r^2 + \tau^2}{m} + \frac{\tau^2 + \sigma_o^2}{1 + 1/g}. \tag{24}$$

The probability of replication success can now be obtained by integrating (22), respectively (23), over the corresponding success region S. This may be more involved if the success region is defined in terms of the replication effect estimate vector $\hat{\boldsymbol{\theta}}_r$, whereas it is as simple as in the singlesite replication case if the success region is formulated in terms of the weighted average $\hat{\theta}_{r*}$.

Optimal allocation within and between sites

A key challenge in SSD for multisite replication studies is the optimal allocation of samples within and between sites, that is, how many sites m and how many samples n_{ri} per site i should be used. A similar problem exists in SSD for cluster randomized trials and we can adapt the common solution based on cost functions (Raudenbush, 1997). That is, the optimal configuration is determined so that the probability of replication success is maximized subject to a constrained cost function which accounts for the (typically different) costs of additional samples and sites.

For example, assume a balanced design ($n_{ri} = n_r$ for $i = 1, \ldots, m$) and that the standard errors of the replication effect estimates are inversely proportional to the square-root of the sample size $\sigma_{ri} = \lambda/\sqrt{n_r}$ for some unit variance λ^2. Further assume that maximizing the probability of replication success corresponds to minimizing the variance of the weighted average $\sigma^2_{\hat{\theta}_{r*}}$ in (24). Let K_s denote the cost of an additional site, and K_c the cost of an additional sample/case.

The total cost of the project is then $K = m(K_c\, n_r + K_s)$, and constrained minimization of the predictive variance (24) leads to the optimal sample size per site

$$n_r^* = \frac{\lambda}{\tau}\sqrt{\frac{K_s}{K_c}}$$

which is equivalent to the optimal cluster sample size known from cluster randomized trials (Raudenbush and Liu, 2000). Note that the optimal sample size per site may be different for other analysis approaches where maximizing the probability of replication success does not correspond to minimizing the variance of the weighted average. Moreover, there are also practical considerations which affect the choice of how many sites should be included in a project. For instance, there may simply not be enough labs available with the required expertise to perform the replication experiments.

3.7 Example: Cross-laboratory replication project (continued)

Figure 6 illustrates multisite SSD for the experiment "Labels" from Protzko et al. (2020) for planned analyses based on the two-trials rule and the replication Bayes factor (see the supplement for details on the multisite extension of these two methods). As for singlesite SSD, we use the design prior based on an initial flat prior for the effect size and taking into account heterogeneity ($\tau = 0.05$). The top plots show the probability of replication success as a function of the total sample size $m \times n_r$ for different number of sites m. We see that for the same total sample size a larger number of sites increases the probability of replication success. For instance, a total sample size of roughly 3000 is required to achieve an 80% target probability with one site for the two-trials rule, whereas only approximately half as many samples are required for two sites.

However, focusing only on the total sample size ignores the fact that the cost of an additional site is usually larger than the cost of an additional observation. The bottom plot shows the total cost K of a design (relative to the cost of one sample K_c) whose sample size is determined for a target probability of replication success $1 - \beta = 80\%$. We see that if the cost of an additional site K_s is not much larger than the cost of an additional sample K_c, e. g., $K_S/K_c = 30$ the optimal number of sites is $m = 5$ for the two-trials rule and $m = 8$ for the replication Bayes factor. If an additional site is more costly the optimal number of sites is lower, e. g., if the cost ratio is $K_S/K_c = 300$, the optimal number of sites is $m = 2$ for the two trials rule and $m = 3$ for the replication Bayes factor. This is similar to the actually used number of sites $m = 3$ (counting only external-replications), respectively, $m = 4$ (counting also the internal-replication) from Protzko et al. (2020).

4 Discussion

We showed how Bayesian approaches can be used to determine the sample size of replication studies based on all the available information and the associated uncertainty. A key strength of the approach is that it can be applied to any kind of replication analysis method, Bayes or

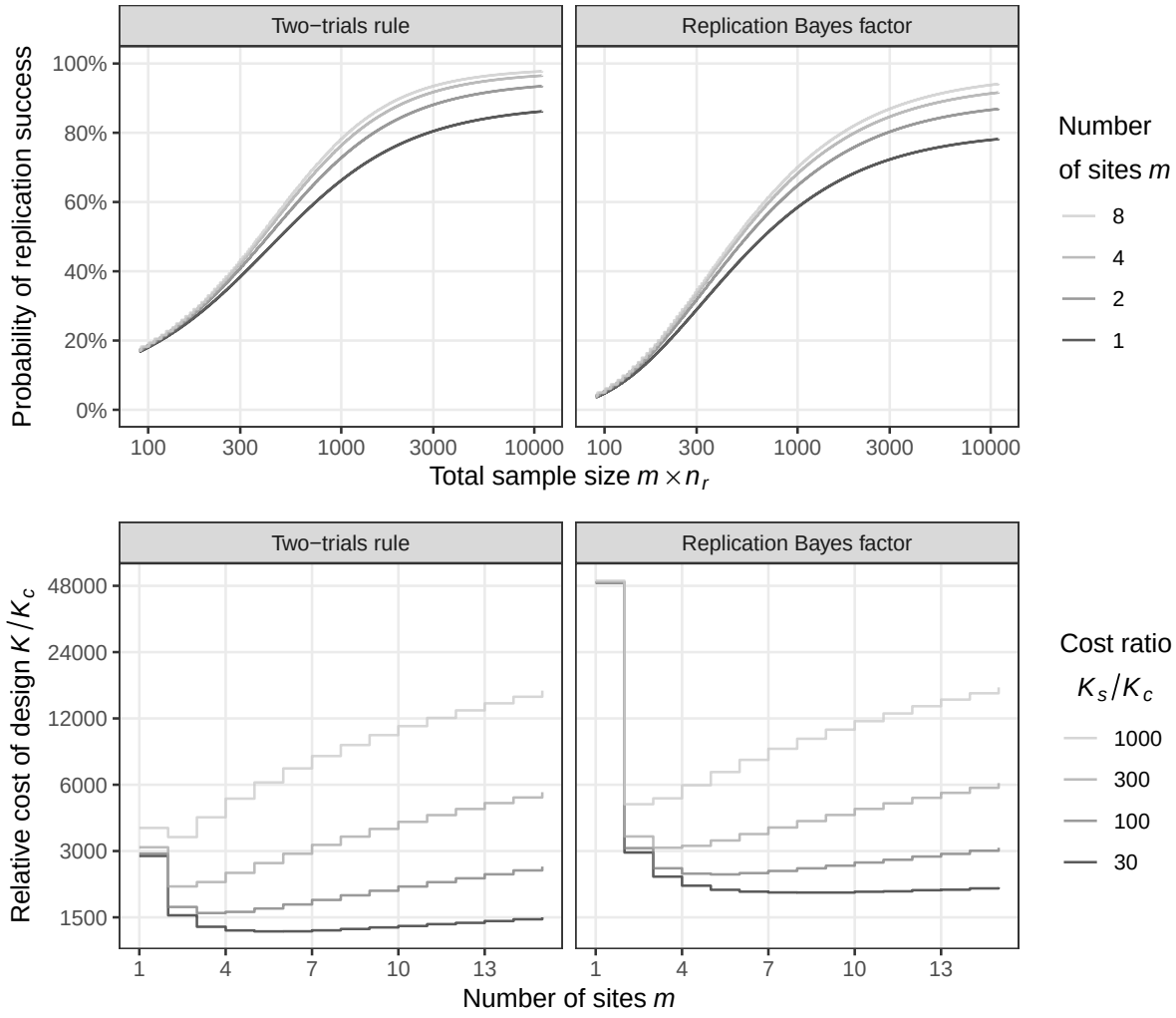


Figure 6: Top plots show the probability of replication success based on the replication Bayes factor at level $\gamma = 1/10$ (left) and the two-trials rule at level $\alpha = 0.025$ (right) as a function of the total sample size and for different number of sites m for data from the experiment "Labels". A design prior with heterogeneity $\tau = 0.05$ and flat initial prior for the effect size θ is used. The same heterogeneity value is assumed in the analysis of the replications. design (relative to the cost of a single sample K_c) as a function of the number of sites m and for different site costs K_s. The sample size of each design corresponds to a target probability of replication success $1 - \beta = 80\%$.

non-Bayes, as long as there is a well-defined success region for the replication effect estimate. Methods for assessing replication success which have not yet been adapted to Bayesian design approaches in the normal-normal hierarchical model (or which have not even been proposed) can thus benefit from our methodology. For instance, our methods could be straightforwardly applied to the "dual-criterion" from Rosenkranz (2021) which defines replication success via simultaneous statistical significance and practical relevance of the effect estimates from original and replication study.

There are some limitations and possible extensions: we have developed the methodology for

"direct" replication studies (Simons, 2014) which attempt to replicate the conditions from the original study as closely as possible; yet SSD methodology is also needed for "conceptual" replication and for "generalization" studies which may show systematic deviations from the original study. While the heterogeneity variance in the design prior allows to take effect size heterogeneity into account for SSD, to some extent, further research is needed for investigating how systematic study deviations and external knowledge can be incorporated. Furthermore, as is standard in meta-analysis we assumed that the variances of the effect estimates are known, which can sometimes be inadequate (Jackson and White, 2018). Specifying priors also for the variances could better reflect the available uncertainty but would come at the price of lower interpretability and higher computational complexity. We did also not consider designs where the replication data are analyzed in a sequential manner. Ideas from the Bayesian sequential design (Schönbrodt and Wagenmakers, 2017; Stefan et al., 2022) or from the adaptive trials literature (Bretz et al., 2009) could be adapted to the replication setting as in Micheloud and Held (2022). A sequential analysis of the replication data could possibly increase the efficiency of the replication. An additional point is that we assumed that the original study has been completed when planning the replication study. One could also consider a scenario where both the original and replication study are planned simultaneously and adopt a "project" perspective (Maca et al., 2002; Held et al., 2022b). However, in this case no information from the original study is available and the design prior needs to be specified entirely based on external knowledge. Finally, researchers have only limited resources and it may happen that they cannot afford a large enough sample size to obtain their desired probability of replication success. In this situation a reverse-Bayes approach (Held et al., 2022a) could be applied in order to determine the prior for the effect size which is required to achieve the desired probability of replication success based on the maximally possible sample size. Researchers can then judge whether or not such prior beliefs are scientifically sensible, and decide whether they should conduct the replication study with their limited resources.

Software and data

All our analyses were conducted in the R programming language version 4.2.2 (R Core Team, 2022). Code to reproduce this manuscript is available at `https://github.com/SamCH93/BAtDRS`. A snapshot of the Git repository at the time of writing is archived at `https://doi.org/10.5281/zenodo.7291076`. Methods for Bayesian design of replication studies are implemented in the R package BayesRepDesign which is available at `https://github.com/SamCH93/BayesRepDesign`. The CC-By 4.0 licensed data were downloaded from `https://osf.io/42ef9/`. The R markdown script "Decline effects main analysis.Rmd" was executed and the relevant variables from the objects "ES_experiments" and "decline_effects" were saved.

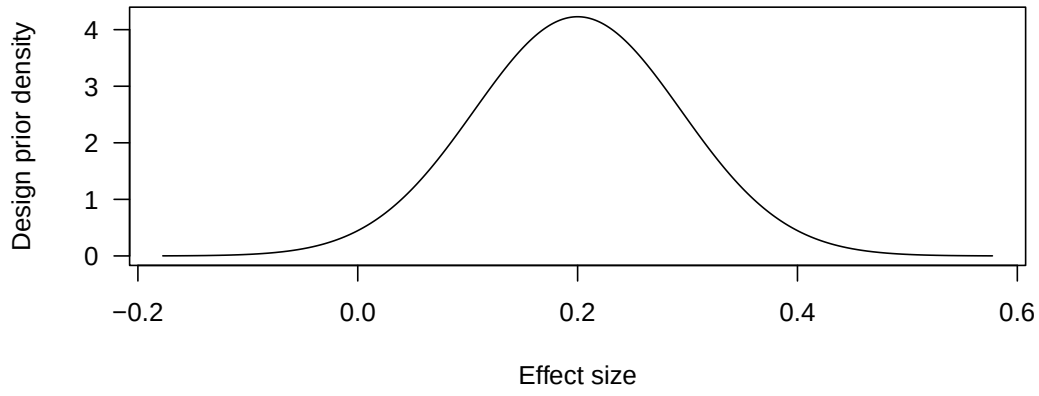
Acknowledgments

We thank Protzko et al. (2020) for publicly sharing their data. We thank Charlotte Micheloud and Angelika Stefan for helpful comments on drafts of the manuscript. Our acknowledgment of these individuals does not imply their endorsement of this article.

A The BayesRepDesign R package

```r
library("BayesRepDesign")

## design prior (flat initial prior for effect size + heterogeneity)
dp <- designPrior(to = 0.2, so = 0.05, tau = 0.08)
plot(dp)
```




```r
## compute replication standard error for achieving significance at 2.5%
ssdSig(level = 0.025, dprior = dp, power = 0.8)


##        Bayesian sample size calculation for replication studies
##        ========================================================
##
## success criterion and computation
## ---------------------------------------------------------------------------
##   replication p-value <= 0.025 (exact computation)
##
## original data and initial prior for effect size
## ---------------------------------------------------------------------------
##   to = 0.2 : original effect estimate
##   so = 0.05 : standard error of original effect estimate
##   tau = 0.08 : assumed heterogeneity standard deviation
##   N(mean = 0, sd = Inf) : initial normal prior
##
```

```
## design prior for effect size
## ------------------------------------------------------------------------
##   N(mean = 0.2, sd = 0.094) : normal design prior
##
## probability of replication success
## ------------------------------------------------------------------------
##   PoRS = 0.8 : specified
##   PoRS = 0.8 : recomputed with sr
##
## required sample size
## ------------------------------------------------------------------------
##   sr = 0.045 : required standard error of replication effect estimate
##   c = so^2/sr^2 ~= nr/no = 1.2 : required relative variance / sample size


## compute numerically via success region and method agnostic function
sregFun <- function(sr) {
    ## success region is [1.96*sr, Inf)
    successRegion(intervals = cbind(qnorm(p = 0.975)*sr, Inf))
}
ssd(sregionfun = sregFun, dprior = dp, power = 0.8)


##        Bayesian sample size calculation for replication studies
##        ========================================================
##
## success criterion and computation
## ------------------------------------------------------------------------
##   method agnostic success region (numerical computation)
##
## original data and initial prior for effect size
## ------------------------------------------------------------------------
##   to = 0.2 : original effect estimate
##   so = 0.05 : standard error of original effect estimate
##   tau = 0.08 : assumed heterogeneity standard deviation
##   N(mean = 0, sd = Inf) : initial normal prior
##
## design prior for effect size
## ------------------------------------------------------------------------
##   N(mean = 0.2, sd = 0.094) : normal design prior
##
## probability of replication success
## ------------------------------------------------------------------------
##   PoRS = 0.8 : specified
##   PoRS = 0.8 : recomputed with sr
##
## required sample size
## ------------------------------------------------------------------------
##   sr = 0.045 : required standard error of replication effect estimate
##   c = so^2/sr^2 ~= nr/no = 1.2 : required relative variance / sample size
```

B Supplementary material

Here, we provide additional information on computing the predictive distribution of the replication effect estimate when a prior is assigned to the heterogeneity variance τ^2 (Section B.1). We also provide additional information on methods for analyzing replication data. For each method we derive the *success region* in terms of the effect estimate of the replication study $\hat{\theta}_r$, which is required for sample size determination as illustrated in the main manuscript (Section B.2 to B.8). For the two-trials rule and the replication Bayes factor methods we additionally provide derivations on how these methods can be generalized to the multisite replication setting. We show then how the optimal number of samples per site can be derived for multisite SSD (Section B.9). Finally, we show SSD for the Protzko et al. (2020) project but using an adaptive shrinkage prior instead of the flat prior as in the main manuscript (Section B.10).

B.1 Prior on the heterogeneity variance

When also a prior is assigned to the heterogeneity variance τ^2, the predictive distribution of the replication effect estimate $\hat{\theta}_r$ is given by

$$f(\hat{\theta}_r \mid \hat{\theta}_o, \sigma_o, \sigma_r) = \int_0^{+\infty} f(\hat{\theta}_r \mid \sigma_r, \hat{\theta}_o, \sigma_o, \tau^2)\, f(\tau^2 \mid \hat{\theta}_o, \sigma_o)\, \mathrm{d}\tau^2.$$

That is, it is the predictive distribution of the replication effect estimate $\hat{\theta}_r$ integrated with respect to the marginal posterior of τ^2 based on the original data $x_o = \{\hat{\theta}_o, \sigma_o^2\}$. If the initial prior for θ is normal $\theta \sim \mathrm{N}(\mu_\theta, \sigma_\theta^2)$, and the initial prior for τ^2 has density $f(\tau^2)$, we have

$$\begin{aligned}
f(\tau^2 \mid \hat{\theta}_o, \sigma_o) &= \int_{-\infty}^{+\infty} f(\theta, \tau^2 \mid \hat{\theta}_o, \sigma_o)\, \mathrm{d}\theta \\
&= \frac{\int_{-\infty}^{+\infty} f(\hat{\theta}_o \mid \theta, \tau^2, \sigma_o^2)\, f(\theta \mid \tau^2)\, f(\tau^2)\, \mathrm{d}\theta}{\int_0^{+\infty} \int_{-\infty}^{+\infty} f(\hat{\theta}_o \mid \theta_*, \tau_*^2, \sigma_o^2)\, f(\theta_* \mid \tau_*^2)\, f(\tau_*^2)\, \mathrm{d}\theta_*\, \mathrm{d}\tau_*^2} \\
&= \frac{f(\tau^2) \int_{-\infty}^{+\infty} \mathrm{N}(\hat{\theta}_o \mid \theta, \tau^2 + \sigma_o^2)\ \mathrm{N}(\theta \mid \mu_\theta, \sigma_\theta^2)\, \mathrm{d}\theta}{\int_0^{+\infty} f(\tau_*^2) \int_{-\infty}^{+\infty} \mathrm{N}(\hat{\theta}_o \mid \theta_*, \tau_*^2 + \sigma_o^2)\ \mathrm{N}(\theta_* \mid \mu_\theta, \sigma_\theta^2)\, \mathrm{d}\theta_*\, \mathrm{d}\tau_*^2} \\
&= \frac{f(\tau^2)\ \mathrm{N}(\hat{\theta}_o \mid \mu_\theta, \tau^2 + \sigma_o^2 + \sigma_\theta^2)}{\int_0^{+\infty} f(\tau_*^2)\, \mathrm{N}(\hat{\theta}_o \mid \mu_\theta, \tau_*^2 + \sigma_o^2 + \sigma_\theta^2)\, \mathrm{d}\tau_*^2}.
\end{aligned}$$

To compute the marginal posterior density of τ^2 one numerical integration is hence required. The updating of the prior depends on the distance between prior mean μ_θ and the original effect estimate $\hat{\theta}_o$ relative to the prior variance σ_θ^2 and the squared standard error σ_o^2. If an

improper uniform prior is assigned to θ ($\sigma_\theta^2 \to \infty$), the posterior reduces to the prior

$$\begin{aligned}
\lim_{\sigma_\theta^2 \to \infty} f(\tau^2 \mid \hat{\theta}_o, \sigma_o) &= \lim_{\sigma_\theta^2 \to \infty} \frac{f(\tau^2)\, \mathrm{N}(\hat{\theta}_o \mid \mu_\theta, \tau^2 + \sigma_o^2 + \sigma_\theta^2)}{\int_0^{+\infty} f(\tau_*^2)\, \mathrm{N}(\hat{\theta}_o \mid \mu_\theta, \tau_*^2 + \sigma_o^2 + \sigma_\theta^2)\, \mathrm{d}\tau_*^2} \\
&= \lim_{\sigma_\theta^2 \to \infty} \int_0^{+\infty} \frac{f(\tau^2)}{f(\tau_*^2)} \underbrace{\sqrt{\frac{\tau_*^2 + \sigma_o^2 + \sigma_\theta^2}{\tau^2 + \sigma_o^2 + \sigma_\theta^2}}}_{\to 1} \\
&\qquad \times \exp\left[-\frac{1}{2} \left\{ \underbrace{\frac{(\hat{\theta}_o - \mu_\theta)^2}{\tau^2 + \sigma_o^2 + \sigma_\theta^2}}_{\downarrow 0} - \underbrace{\frac{(\hat{\theta}_o - \mu_\theta)^2}{\tau_*^2 + \sigma_o^2 + \sigma_\theta^2}}_{\downarrow 0} \right\} \right] \mathrm{d}\tau_*^2 \\
&= f(\tau^2),
\end{aligned}$$

the limit can be interchanged with the integral because of the monotone convergence theorem. This means that with a uniform prior nothing can be learned about the variance τ^2 which intuitively makes sense as estimation of a variance requires at least two observations. The phenomenon is illustrated in Figure 7 for the data from the experiment "Labels" (Protzko et al., 2020) as also used in the main manuscript. We see that as the prior standard deviation increases (making the prior more uniform), the marginal posterior density becomes closer to the prior density.

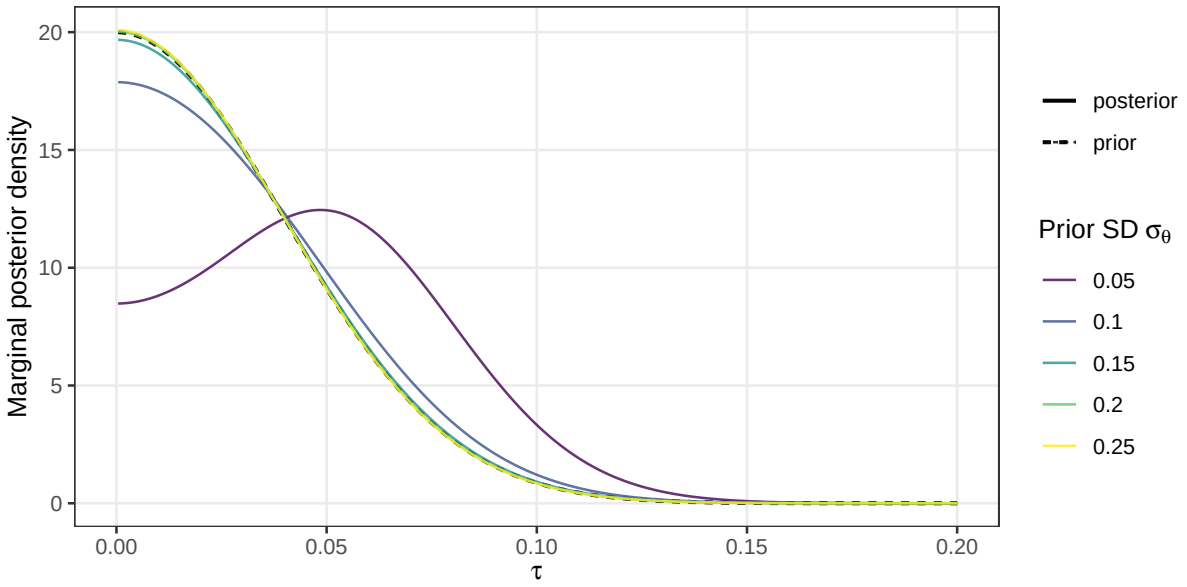


Figure 7: Marginal posterior distribution of heterogeneity variance τ^2 based on data from experiment "Labels" from Protzko et al. (2020) with original effect estimate $\hat{\theta}_o = 0.205$ and standard error $\sigma_o = 0.051$. A $\theta \sim \mathrm{N}(0, \sigma_\theta^2)$ prior is assigned to the effect size θ and a half normal prior with standard deviation 0.04 is assigned to τ.

Combining all the previous results, we obtain the probability of replication success as

$$\begin{aligned}\Pr(\hat{\theta}_r \in S \mid \hat{\theta}_o, \sigma_o, \sigma_r) &= \int_S \int_0^{+\infty} f(\hat{\theta}_r \mid \hat{\theta}_o, \sigma_o, \sigma_r, \tau^2)\, f(\tau^2 \mid \hat{\theta}_o, \sigma_o)\, \mathrm{d}\hat{\theta}_r\, \mathrm{d}\tau^2 \\ &= \int_0^{+\infty} \Pr(\hat{\theta}_r \in S \mid \hat{\theta}_o, \sigma_o, \sigma_r, \tau^2)\, f(\tau^2 \mid \hat{\theta}_o, \sigma_o)\, \mathrm{d}\tau^2.\end{aligned}$$

This mean computing the probability of replication success with a prior on τ^2 requires two-dimensional numerical integration. However, in the common case when a uniform prior is assigned to θ, the marginal posterior distribution of τ^2 reduces to the prior, and only one numerical integration is required.

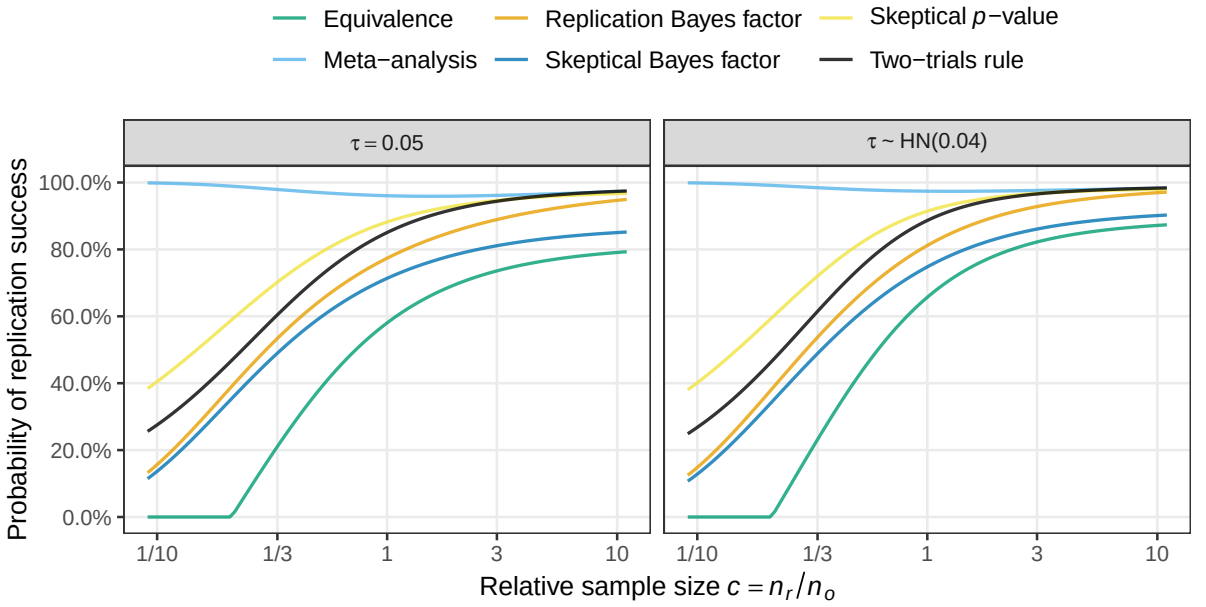


Figure 8: Probability of replication success as a function of relative sample size $c = n_r/n_o$ for experiment "Labels" with original effect estimate $\hat{\theta}_o = 0.205$ and standard error $\sigma_o = 0.051$ for uniform initial prior for effect size θ and either fixed $\tau = 0.05$ (as in main manuscript) or half normal prior with standard deviation 0.04 assigned to τ. Replication success is defined by the two-trials rule at level $\alpha = 0.025$, the replication Bayes factor at level $\gamma = 1/10$, fixed effects-meta analysis at level $\alpha = 0.025^2$, effect size equivalence based on 90% confidence interval and with margin $\Delta = 0.2$, sceptical p-value at level $\alpha = 0.062$, and sceptical Bayes factor at level $\gamma = 1/10$.

Figure 8 shows the probability of replication success based on data from the "Labels" experiment, as in the main manuscript. A half normal prior with is assigned to the heterogeneity τ which is a typical prior distribution used for heterogeneity modeling in meta-analysis (Röver et al., 2021). The standard deviation of the prior is set to 0.04 so that the mean of the prior equals the value of the fixed heterogeneity $\tau = 0.05$ elicited in the main manuscript. We see that the probability of replication success is only slightly higher compared to the fixed $\tau = 0.05$ from the main manuscript.

B.2 The two-trials rule

The two-trials rule is the most common analysis approach for replication studies. Replication success is declared if both original and replication study achieve statistical significance at some level α (and both estimates go in the same direction which can be taken into account by using one-sided p-values). We will study the two-trial under normality using the data model $\hat{\theta}_i \,|\, \theta \sim \mathrm{N}(\theta, \sigma_i^2)$ with $\hat{\theta}_i$ the estimate of the unknown effect size θ from study i and σ_i is the corresponding standard error (assumed to be know). The p-values for testing $H_0 \colon \theta = 0$ versus $H_1 \colon \theta > 0$ are then $p_i = 1 - \Phi(\hat{\theta}_i / \sigma_i)$ whereas for the alternative $H_1 \colon \theta < 0$ they are $p_i = \Phi(\hat{\theta}_i / \sigma_i)$. Suppose the original effect estimate was statistically significant at level α, i. e., $p_o \leq \alpha$. Replication success at level α is then established if the replication effect estimate $\hat{\theta}_r$ is also statistically significant at level α, i. e., $p_r \leq \alpha$. By applying some algebraic manipulations to the success condition, one can show that this implies that replication success is achieved if the replication effect estimate $\hat{\theta}_r$ is contained in the success region

$$S_{\text{2TR}} = \begin{cases} [z_\alpha \, \sigma_r, \infty) & \text{for } \hat{\theta}_o > 0 \\ [-\infty, -z_\alpha \, \sigma_r) & \text{for } \hat{\theta}_o < 0. \end{cases}$$

The multisite two-trials rule

If multiple replication studies are conducted for one original study (a *multisite* replication), the two-trials rule is typically modified by meta-analyzing the effect estimates from all replications and then using the combined estimate as usual in the two-trials rule (see e. g., the "Many labs" projects from Klein et al., 2014, 2018). Suppose m replication studies are conducted and produce m effect estimates $\hat{\theta}_{r1}, \ldots, \hat{\theta}_m$ with standard errors $\sigma_{r1}, \ldots, \sigma_{rm}$. Subsequently, a weighted average $\hat{\theta}_{r*} = \{\sum_{i=1}^m \hat{\theta}_{ri} / (\sigma_{ri}^2 + \tau_r^2)\} \, \sigma_{r*}^2$ with standard error $\sigma_{r*} = 1 / \sqrt{\{\sum_i^m 1 / (\sigma_{ri}^2 + \tau_r^2)\}}$ can be computed. If the between-replication heterogeneity variance τ_r^2 is set to zero this corresponds to the fixed effects estimate of θ, while estimating τ_r^2 from the data corresponds to the random effects estimate. Replication success at level α is then established if the replication p-value is smaller than α, i. e., $p_{r*} = 1 - \Phi(\hat{\theta}_{r*} / \sigma_{r*}) \leq \alpha$. With some algebra one can show that this implies a success region for the weighted average replication effect estimate $\hat{\theta}_{r*}$ given by

$$S_{\text{2TR}} = \begin{cases} [z_\alpha \, \sigma_{r*}, \infty) & \text{for } \hat{\theta}_o > 0 \\ [-\infty, -z_\alpha \, \sigma_{r*}) & \text{for } \hat{\theta}_o < 0. \end{cases}$$

B.3 Fixed effects meta-analysis

Assume again the data model $\hat{\theta}_i \,|\, \theta \sim \mathrm{N}(\theta, \sigma_i^2)$ where $\hat{\theta}_i$ is an estimate of the effect size θ from study $i \in \{o, r\}$ and σ_i is the corresponding standard error (assumed to be know). In the fixed effects meta-analysis approach replicability is assessed in terms of the pooled effect estimate $\hat{\theta}_m$ and standard error σ_m which are

$$\hat{\theta}_m = \left(\hat{\theta}_o / \sigma_o^2 + \hat{\theta}_r / \sigma_r^2\right) \sigma_m^2 \qquad \text{and} \qquad \sigma_m = \left(1/\sigma_o^2 + 1/\sigma_r^2\right)^{-1/2},$$

which are also equivalent to the mean and standard deviation of a posterior distribution for the effect size θ based on the data from original and replication study and an initial flat prior for θ. Fixed effects meta-analysis is typically used because estimating a heterogeneity variance from two studies is highly unstable. Replication success at level α is established if the one-sided meta-analytic p-value (in the direction of the original effect estimate $\hat{\theta}$) is significant at level α, i. e., $p_m = 1 - \Phi(\hat{\theta}_m/\sigma_m) \leq \alpha$ for $\hat{\theta}_o > 0$ and $p_m = \Phi(\hat{\theta}_m/\sigma_m) \leq \alpha$ for $\hat{\theta}_o < 0$. With some algebraic manipulations one can show that this criterion implies a success region S_{MA} for the replication effect estimate $\hat{\theta}_r$ given by

$$S_{\text{MA}} = \begin{cases} [\sigma_r z_\alpha \sqrt{1 + \sigma_r^2/\sigma_o^2} - (\hat{\theta}_o \sigma_r^2)/\sigma_o^2, \infty) & \text{for } \hat{\theta}_o > 0 \\ (-\infty, -\sigma_r z_\alpha \sqrt{1 + \sigma_r^2/\sigma_o^2} - (\hat{\theta}_o \sigma_r^2)/\sigma_o^2] & \text{for } \hat{\theta}_o < 0. \end{cases}$$

B.4 Effect size equivalence

The effect size equivalence approach (Anderson and Maxwell, 2016) defines replication success via compatibility of the effect estimates from both studies. Under normality we may assume the data model $\hat{\theta}_i \,|\, \theta_i \sim \text{N}(\theta_i, \sigma_i^2)$ for study $i \in \{o, r\}$, and we are interested in the true effect size difference $\delta = \theta_r - \theta_o$. A $(1 - \alpha)$ confidence interval for δ is then given by

$$C_\alpha = \left[\hat{\theta}_r - \hat{\theta}_o - z_{\alpha/2}\sqrt{\sigma_r^2 + \sigma_r^2}, \hat{\theta}_r - \hat{\theta}_o + z_{\alpha/2}\sqrt{\sigma_r^2 + \sigma_r^2}\right]$$

Effect size equivalence is established if the confidence interval is fully included in an equivalence region $C_\alpha \subseteq [-\Delta, \Delta]$ with $\Delta > 0$ a pre-specified margin. Applying some algebraic manipulations to the success conditions one can show that the equivalence test replication success criterion implies a success region S_{E} for the replication estimate $\hat{\theta}_r$ given by

$$S_{\text{E}} = \left[\hat{\theta}_o - \Delta + z_{\alpha/2}\sqrt{\sigma_o^2 + \sigma_r^2}, \hat{\theta}_o + \Delta - z_{\alpha/2}\sqrt{\sigma_o^2 + \sigma_r^2}\right].$$

B.5 The replication Bayes factor

The replication Bayes factor approach uses the replication data x_r to quantify the evidence for the null hypothesis $H_0 \colon \theta = 0$ relative to the alternative hypothesis $H_1 \colon \theta \sim f(\theta \,|\, x_o)$, which postulates that the effect size θ is distributed according to its posterior distribution based on the original data x_o. Assume again a normal model $\hat{\theta}_i \,|\, \theta \sim \text{N}(\theta, \sigma_i^2)$ with $\hat{\theta}_i$ an estimate of the effect size θ from study $i \in \{o, r\}$ and σ_i the corresponding standard error (assumed to be know), and that we use the alternative $H_1 \colon \theta \sim \text{N}(\hat{\theta}_o, \sigma_o^2)$ which arises from updating an initial flat prior for θ the original data $x_o = \{\hat{\theta}_o, \sigma_o\}$. The replication Bayes factor is then

$$\text{BF}_{\text{R}} = \frac{f(\hat{\theta}_r \,|\, H_0)}{f(\hat{\theta}_r \,|\, H_1)} = \sqrt{1 + \sigma_o^2/\sigma_r^2}\, \exp\left[-\frac{1}{2}\left\{\frac{\hat{\theta}_r^2}{\sigma_r^2} - \frac{(\hat{\theta}_r - \hat{\theta}_o)^2}{\sigma_o^2 + \sigma_r^2}\right\}\right]. \tag{25}$$

Replication success at level $\gamma \in (0, 1)$ is achieved if $\text{BF}_\text{R} \leq \gamma$. By applying some algebra to $\text{BF}_\text{R} \leq \gamma$, one can show that it is equivalent to the replication effect estimate $\hat{\theta}_r$ falling in the success region

$$S_{\text{BF}_\text{R}} = \left(-\infty, -\sqrt{A} - (\hat{\theta}_o\sigma_r^2)/\sigma_o^2\right] \bigcup \left[\sqrt{A} - (\hat{\theta}_o\sigma_r^2)/\sigma_o^2, \infty\right)$$

where $A = \sigma_r^2(1 + \sigma_r^2/\sigma_o^2)\{\hat{\theta}_o^2/\sigma_o^2 - 2\log\gamma + \log(1 + \sigma_o^2/\sigma_r^2)\}$.

B.6 The multisite replication Bayes factor

The generalization of the replication Bayes factor to the multisite setting is straightforward. The data are represented by vector of replication effect estimates $\hat{\boldsymbol{\theta}}_r = (\hat{\theta}_{r1}, \ldots, \hat{\theta}_{rm})^\top$ with corresponding standard error vector $\boldsymbol{\sigma}_r = (\sigma_{r1}, \ldots, \sigma_{rm})^\top$, and we assume the data model $\hat{\boldsymbol{\theta}}_r \mid \theta \sim \text{N}_m\{\theta\,\mathbf{1}_m, \text{diag}(\boldsymbol{\sigma}^2 + \tau_r^2\,\mathbf{1}_m\}$ where $\mathbf{1}_m$ is a vector of m ones and τ_r^2 is a heterogeneity variance for the replication effect sizes (not to be confused with the heterogeneity variance τ^2 used in the design prior).

As in the singlesite case, the replication Bayes factor quantifies the evidence that the data provide for the null hypothesis $H_0\colon \theta = 0$ relative to the alternative hypothesis $H_1\colon \theta \sim \text{N}(\hat{\theta}_o, \sigma_o^2)$. The marginal density of the replication data under the null hypothesis is simply $\hat{\boldsymbol{\theta}}_r \mid H_0 \sim \text{N}_m\{0\,\mathbf{1}_m, \text{diag}(\boldsymbol{\sigma}^2 + \tau_r^2\,\mathbf{1}_m\}$, whereas the marginal likelihood under the alternative H_1 is obtained from integrating the likelihood with respect to the prior distribution of θ under the alternative H_1. Let $\text{N}(x; m, v)$ denote the normal density function mean m and variance v evaluated at x. Define also $\hat{\theta}_{r*} = \left\{\sum_{i=1}^n \hat{\theta}_{ri}/(\sigma_{ri}^2 + \tau_r^2)\right\}\sigma_{r*}^2$ and $\sigma_{r*}^2 = 1/\left\{\sum_{i=1}^n 1/(\sigma_{ri}^2 + \tau_r^2)\right\}$, i. e., the weighted average of the replication effect estimates based on the heterogeneity τ_r^2 and its variance. The marginal density is then

$$\begin{aligned}
f(\hat{\boldsymbol{\theta}}_r \mid H_1) &= \int f(\hat{\boldsymbol{\theta}}_r \mid \theta) f(\theta \mid H_1)\,\text{d}\theta \\
&= \int \frac{\exp\left[-\frac{1}{2}\left\{\sum_{i=1}^n \frac{(\hat{\theta}_{ri}-\theta)^2}{\sigma_{ri}^2+\tau_r^2} + \frac{(\theta-\hat{\theta}_o)^2}{\sigma_o^2}\right\}\right]}{\left\{2\pi\sigma_o^2\prod_{i=1}^n 2\pi\left(\sigma_{ri}^2+\tau_r^2\right)\right\}^{1/2}}\,\text{d}\theta \\
&= \int \frac{\exp\left[-\frac{1}{2}\left\{\sum_{i=1}^n \frac{(\hat{\theta}_{ri}-\hat{\theta}_{r*})^2}{\sigma_{ri}^2+\tau_r^2} + \frac{(\hat{\theta}_{r*}-\theta)^2}{\sigma_{r*}^2} + \frac{(\theta-\hat{\theta}_o)^2}{\sigma_o^2}\right\}\right]}{\left\{2\pi\sigma_o^2\prod_{i=1}^n 2\pi\left(\sigma_{ri}^2+\tau_r^2\right)\right\}^{1/2}}\,\text{d}\theta \\
&= \frac{\exp\left[-\frac{1}{2}\left\{\sum_{i=1}^n \frac{(\hat{\theta}_{ri}-\hat{\theta}_{r*})^2}{\sigma_{ri}^2+\tau_r^2}\right\}\right]}{\left\{2\pi\sigma_o^2\prod_{i=1}^n 2\pi\left(\sigma_{ri}^2+\tau_r^2\right)\right\}^{1/2}} \underbrace{\int \exp\left[-\frac{1}{2}\left\{\frac{(\hat{\theta}_{r*}-\theta)^2}{\sigma_{r*}^2} + \frac{(\theta-\hat{\theta}_o)^2}{\sigma_o^2}\right\}\right]\text{d}\theta}_{=\text{N}(\hat{\theta}_{r*}; m, \sigma_o^2+\sigma_{r*}^2)2\pi\sigma_o\sigma_{r*}} \\
&= \left\{(1 + \sigma_o^2/\sigma_{r*}^2)\prod_{i=1}^n 2\pi\left(\sigma_{ri}^2+\tau_r^2\right)\right\}^{-1/2} \exp\left[-\frac{1}{2}\left\{\sum_{i=1}^n \frac{(\hat{\theta}_{ri}-\hat{\theta}_{r*})^2}{\sigma_{ri}^2+\tau_r^2} + \frac{(\hat{\theta}_{r*}-\hat{\theta}_o)^2}{\sigma_{r*}^2+\sigma_o^2}\right\}\right].
\end{aligned}$$

Dividing the marginal density of $\hat{\boldsymbol{\theta}}_r$ under H_0 by the marginal density of $\hat{\boldsymbol{\theta}}_r$ under H_1 leads to cancellation of several terms, and produces the replication Bayes factor

$$\text{BF}_{01}(\hat{\boldsymbol{\theta}}_r) = \frac{f(\hat{\boldsymbol{\theta}}_r \mid H_0)}{f(\hat{\boldsymbol{\theta}}_r \mid H_1)} = \sqrt{1 + \sigma_o^2/\sigma_{r*}^2} \exp\left[-\frac{1}{2}\left\{\frac{\hat{\theta}_{r*}^2}{\sigma_{r*}^2} - \frac{(\hat{\theta}_{r*} - \hat{\theta}_o)^2}{\sigma_{r*}^2 + \sigma_o^2}\right\}\right].$$

The multisite replication Bayes factor is therefore equivalent to the singlesite replication Bayes factor from (25) but using the weighted average $\hat{\theta}_{r*}$ and its standard error σ_{r*} as the replication effect estimate $\hat{\theta}_r$ and standard error σ_r.

B.7 The sceptical *p*-value

Held (2020) proposed a reverse-Bayes approach for assessing replicability. One assumes again the data model $\hat{\theta}_i \mid \theta \sim \text{N}(\theta, \sigma_i^2)$ with $i \in \{o, r\}$, along with a zero-mean "sceptical" prior $\theta \sim \text{N}(0, \sigma_\text{S}^2)$ for the effect size. In a first step, a level $\alpha \geq p_o = 1 - \Phi(|\hat{\theta}_o|/\sigma_o)$ is fixed and the "sufficiently sceptical" prior variance σ_S^2 is computed

$$\sigma_\text{S}^2 = \frac{\sigma_o^2}{(z_o^2/z_\alpha^2) - 1}$$

where $z_o = \hat{\theta}_o/\sigma_o$. The sufficiently sceptical prior variance σ_S^2 has the property that it renders the resulting posterior of θ no longer "credible" at level α, that is, the posterior tail probability is fixed to $\Pr(\theta \geq 0 \mid \hat{\theta}_o, \sigma_o, \sigma_\text{S}) = 1 - \alpha$ for positive estimates and $\Pr(\theta \leq 0 \mid \hat{\theta}_o, \sigma_o, \sigma_\text{S}) = 1 - \alpha$ for negative estimates. In a second step, the conflict between the sceptical prior and the observed replication data is quantified, larger conflict indicating a higher degree of replication success. For doing so, a prior predictive tail probability

$$p_\text{Box} = \begin{cases} 1 - \Phi\left\{\hat{\theta}_r/(\sigma_r^2 + \sigma_\text{S}^2)\right\} & \text{if } \hat{\theta}_o > 0 \\ \Phi\left\{\hat{\theta}_r/(\sigma_r^2 + \sigma_\text{S}^2)\right\} & \text{if } \hat{\theta}_o < 0 \end{cases}$$

is computed and replication success at level α is declared if $p_\text{Box} \leq \alpha$. The smallest level α at which replication success is achieved is called the *the sceptical p-value* p_S and replication success at level α is equivalent with $p_\text{S} \leq \alpha$ (see Held, 2020; Held et al., 2022b, for more details on p_S). By applying some algebraic manipulations to the condition $p_\text{Box} \leq \alpha$, one can show that it is equivalent to the replication effect estimate $\hat{\theta}_r$ falling in the success region

$$S_{p_\text{S}} = \begin{cases} [z_\alpha\sqrt{\{\sigma_r^2 + \frac{\sigma_o^2}{(z_o^2/z_\alpha^2)-1}\}}, \infty) & \text{if } \hat{\theta}_o > 0 \\ (-\infty, -z_\alpha\sqrt{\{\sigma_r^2 + \frac{\sigma_o^2}{(z_o^2/z_\alpha^2)-1}\}}] & \text{if } \hat{\theta}_o < 0. \end{cases}$$

B.8 The sceptical Bayes factor

Pawel and Held (2022) modified the reverse-Bayes assessment of replication success from Held (2020) to use Bayes factors (Jeffreys, 1961; Kass and Raftery, 1995) instead of tail probabilities as measures of evidence and prior data conflict. The procedure assumes again the data model

$\hat{\theta}_i \,|\, \theta \sim \mathrm{N}(\theta, \sigma_i^2)$ for study $i \in \{o, r\}$. In the first step the original data are used to contrast the evidence for the point null hypothesis $H_0\colon \theta = 0$ relative to the "sceptical" alternative $H_\mathrm{S}\colon \theta \sim \mathrm{N}(0, \sigma_\mathrm{S}^2)$ with the Bayes factor

$$\mathrm{BF}_{0\mathrm{S}} = \frac{f(\hat{\theta}_o \,|\, H_0)}{f(\hat{\theta}_o \,|\, H_\mathrm{S})} = \sqrt{1 + \sigma_\mathrm{S}^2/\sigma_o^2}\, \exp\left\{ - \frac{z_o^2}{2(1 + \sigma_o^2/\sigma_\mathrm{S}^2)} \right\}.$$

where $z_o = \hat{\theta}/\sigma_o^2$. One then determines the sufficiently sceptical prior variance σ_S^2 so that the Bayes factor is fixed to a level $\gamma \in (0, 1)$ meaning that there is no longer evidence against the null hypothesis at level γ. The sufficiently sceptical prior variance can be computed by

$$\sigma_\mathrm{S}^2 = \begin{cases} -\dfrac{\hat{\theta}_o^2}{q} - \sigma_o^2 & \text{if } -\dfrac{\hat{\theta}_o^2}{q} \geq \sigma_o^2 \\ \text{undefined} & \text{else} \end{cases} \tag{26}$$

$$\text{where } q = \mathrm{W}_{-1}\left\{ -\frac{z_o^2}{\gamma^2}\, \exp\left(-z_o^2\right) \right\} \tag{27}$$

with $\mathrm{W}_{-1}(\cdot)$ the branch of the Lambert W function with $\mathrm{W}(y) \leq -1$ for $y \in [-1/e, 0)$.

In a second step the conflict between the sceptical prior and the replication data is quantified. To do so, the sceptic is contrasted to the "advocacy" alternative $H_\mathrm{A}\colon \theta \sim \mathrm{N}(\hat{\theta}_o, \sigma_o^2)$ which represents the position of an advocate as the prior corresponds to the posterior distribution based on the original data $\{\hat{\theta}_o, \sigma_o\}$ and a flat prior for the effect size θ. This is done by computing the Bayes factor

$$\mathrm{BF}_{\mathrm{SA}} = \frac{f(\hat{\theta}_r \,|\, H_\mathrm{S})}{f(\hat{\theta}_r \,|\, H_\mathrm{A})} = \sqrt{\frac{\sigma_o^2 + \sigma_r^2}{\sigma_\mathrm{S}^2 + \sigma_r^2}}\, \exp\left[-\frac{1}{2} \left\{ \frac{\hat{\theta}_r^2}{\sigma_\mathrm{S}^2 + \sigma_r^2} - \frac{(\hat{\theta}_r - \hat{\theta}_o^2)}{\sigma_o^2 + \sigma_r^2} \right\} \right]$$

and replication success at level γ is defined by $\mathrm{BF}_{\mathrm{SA}} \leq \gamma$ as the data favor the advocate over the sceptic at a higher level than the sceptic's initial objection to the null hypothesis. The smallest level γ at which replication success is achievable is then called *the sceptical Bayes factor* BF_S, and replication success at level γ is equivalent to $\mathrm{BF}_\mathrm{S} \leq \gamma$ (see Pawel and Held, 2022, for details on how to compute BF_S). To derive the success region of the sceptical Bayes factor one can apply algebraic manipulations to $\mathrm{BF}_{\mathrm{SA}} \leq \gamma$, the condition for replication success at level γ, which leads to

$$S_{\mathrm{BF}_\mathrm{S}} = \begin{cases} (-\infty, -\sqrt{B} - M] \bigcup [\sqrt{B} - M, \infty) & \text{for } \sigma_\mathrm{S}^2 < \sigma_o^2 \\ [\hat{\theta}_o - \{(\sigma_o^2 + \sigma_r^2) \log \gamma\}/\hat{\theta}_o, \infty) & \text{for } \sigma_\mathrm{S}^2 = \sigma_o^2 \\ [-\sqrt{B} - M, \sqrt{B} - M] & \text{for } \sigma_\mathrm{S}^2 > \sigma_o^2 \end{cases} \tag{28}$$

with

$$B = \left\{ \frac{\hat{\theta}_o^2}{\sigma_o^2 - \sigma_\mathrm{S}^2} + 2 \log\left(\frac{\sigma_o^2 + \sigma_r^2}{\sigma_\mathrm{S}^2 + \sigma_r^2} \right) - 2 \log \gamma \right\} \frac{(\sigma_\mathrm{S}^2 + \sigma_r^2)(\sigma_o^2 + \sigma_r^2)}{\sigma_o^2 - \sigma_\mathrm{S}^2}$$

$$M = \frac{\hat{\theta}_o(\sigma_\mathrm{S}^2 + \sigma_r^2)}{\sigma_o^2 - \sigma_\mathrm{S}^2}$$

and the sufficiently sceptical prior variance σ_S^2 computed by (26).

B.9 Optimal number of sites

The total cost of the design are $K = m(K_c n_r + K_s)$ so that we can write the number of sites m for a given total cost as

$$m = K(K_c n_r + K_s)^{-1}. \tag{29}$$

We now want to minimize the predictive variance of the weighted average $\hat{\theta}_{r*}$ which, for a balanced design, is given by

$$\sigma^2_{\hat{\theta}_{r*}} = \frac{\sigma_r^2 + \tau^2}{m} + \frac{\tau^2 + \sigma_o^2}{1 + 1/g}. \tag{30}$$

Plugging in (29) into (30) and minimizing it with respect to n_r, leads to the optimal sample size

$$n_r^* = \frac{\lambda}{\tau}\sqrt{\frac{K_s}{K_c}}$$

for a given cost ratio K_s/K_c.

B.10 Sample size determination with adaptive shrinkage prior

Figure 9 shows sample size determination for all studies from the Protzko et al. (2020) project as in the main manuscript but using an "adaptive shrinkage prior" for the effect size θ where the variance of the shrinkage prior is estimated by empirical Bayes. We see that the required sample size increases for studies with large p-values compared to the analysis based on a flat prior for θ as in the main manuscript, whereas it stays about the same for studies with small p-values. This is because studies with large p-values receive more shrinkage.

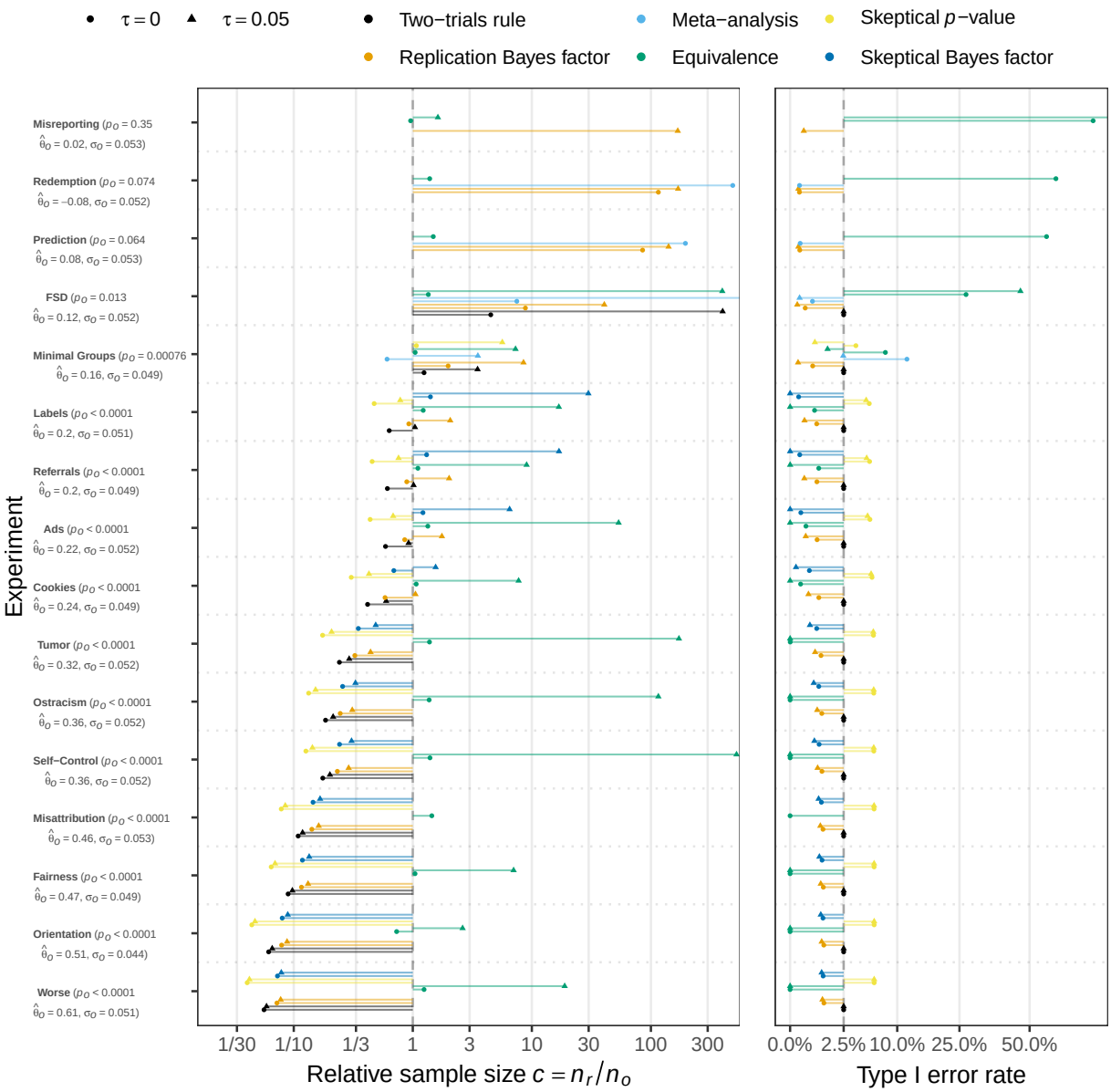


Figure 9: The left plot shows the required relative sample size $c = n_r/n_o$ to achieve a target probability of replication success of $1 - \beta = 80\%$ (if possible). Replication success is defined through the two-trials rule at level $\alpha = 0.025$, replication Bayes factor at level $\gamma = 1/10$, fixed effects-meta analysis at level $\alpha = 0.025^2$, effect size equivalence at level $\alpha = 0.1$ with margin $\Delta = 0.2$, sceptical p-value at level $\alpha = 0.062$, and sceptical Bayes factor at level $\gamma = 1/10$ for data from the replication project by Protzko et al. (2020). An adaptive shrinkage prior is used for the effect size θ either without ($\tau = 0$) or with between-study heterogeneity ($\tau = 0.05$). The right plot shows the type I error rate associated with the required sample size. Experiments are ordered (top to bottom) by their original one-sided p-value $p_o = 1 - \Phi(|\hat{\theta}_o|/\sigma_o)$.

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PAPER IV

Reverse-Bayes methods for evidence assessment and research synthesis

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Abstract

It is now widely accepted that the standard inferential toolkit used by the scientific research community – null-hypothesis significance testing (NHST) – is not fit for purpose. Yet despite the threat posed to the scientific enterprise, there is no agreement concerning alternative approaches for evidence assessment. This lack of consensus reflects long-standing issues concerning Bayesian methods, the principal alternative to NHST. We report on recent work that builds on an approach to inference put forward over 70 years ago to address the well-known "Problem of Priors" in Bayesian analysis, by reversing the conventional prior-likelihood-posterior ("forward") use of Bayes's Theorem. Such Reverse-Bayes analysis allows priors to be deduced from the likelihood by requiring that the posterior achieve a specified level of credibility. We summarise the technical underpinning of this approach, and show how it opens up new approaches to common inferential challenges, such as assessing the credibility of scientific findings, setting them in appropriate context, estimating the probability of successful replications, and extracting more insight from NHST while reducing the risk of misinterpretation. We argue that Reverse-Bayes methods have a key role to play in making Bayesian methods more accessible and attractive for evidence assessment and research synthesis. As a running example we consider a recently published meta-analysis from several randomized controlled trials (RCTs) investigating the association between corticosteroids and mortality in hospitalized patients with COVID-19.

Key words: Analysis of Credibility, Bayes factor, false positive risk, meta-analysis, prior-data conflict, reverse-Bayes

1 Introduction: the origin of Reverse-Bayes methods

> "We can make judgments of initial probabilities and infer final ones, or we can equally make judgments of final ones and infer initial ones by *Bayes's theorem in reverse*."
>
> Good (1983, p. 29)

There is now a common consensus that the most widely-used methods of statistical inference have led to a crisis in both the interpretation of research findings and their replication (Gelman and Loken, 2014; Wasserstein and Lazar, 2016). At the same time, there is a lack of consensus on how to address the challenge (Matthews, 2017), as highlighted by the plethora of alternative techniques to null-hypothesis significance testing now being put forward, see for example Wasserstein et al. (2019) and the references therein. Especially striking is the relative dearth of alternatives based on Bayesian concepts. Given their intuitive inferential basis and output (Wagenmakers et al., 2008; McElreath, 2018), these would seem obvious candidates to supplant the prevailing frequentist methodology. However, it is well-known that the adoption of Bayesian methods continues to be hampered by several factors, such as the belief that advanced computational tools are required to make Bayesian statistics practical (Green et al., 2015). The most persistent of these is that the full benefit of Bayesian methods demands

specification of a prior level of belief, even in the absence of any appropriate insight. This "Problem of Priors" has cast a shadow over Bayesian methods since their emergence over 250 years ago (McGrayne, 2011), and has led to a variety of approaches, such as prior elicitation, prior sensitivity analysis, and objective Bayesian methodology; all have their supporters and critics.

One of the least well-known was suggested over 70 years ago (Good, 1950) by one of the best-known proponents of Bayesian methods during the 20th century, I.J. Good. It involves reversing the conventional direction of Bayes's Theorem and determining the level of prior belief required to reach a specified level of posterior belief, given the evidence observed. This reversal of Bayes's Theorem allows the assessment of new findings on the basis of whether the resulting prior is reasonable in the light of existing knowledge. Whether a prior is plausible in the light of existing knowledge can be assessed informally or more formally using techniques for comparing priors with existing data as suggested by Box (1980) and further refined by Evans and Moshonov (2006), see also Nott et al. (2020, 2021) for related approaches. Good stressed that despite the routine use of the adjectives "prior" and "posterior" in applications of Bayes's Theorem, the validity of any resulting inference does not require a specific temporal ordering, as the theorem is simply a constraint ensuring consistency with the axioms of probability. While reversing Bayes's Theorem is still regarded as unacceptable by some on the grounds it allows "cheating" in the sense of choosing priors to achieve a desired posterior inference (O'Hagan and Forster, 2004, p. 143), others point out this is not an ineluctable consequence of the reversal (Cox, 2006, pp. 78–79). As we shall show, recent technical advances further weaken this criticism.

Good's belief in the value of Reverse-Bayes methods won support from E.T. Jaynes in his well-known treatise on probability. Explaining a specific manifestation of the approach (to be discussed shortly) Jaynes remarked: "We shall find it helpful in many cases where our prior information seems at first too vague to lead to any definite prior probabilities; it stimulates our thinking and tells us how to assign them after all" (Jaynes, 2003, p. 126). Yet despite the advocacy of two leading figures in the foundations of Bayesian methodology, the potential of Reverse-Bayes methods has remained largely unexplored. Most published work has focused on their use in putting new research claims in context, with Reverse-Bayes methods being used to assess whether the prior evidence needed to make a claim credible is consistent with existing insight (Carlin and Louis, 1996; Matthews, 2001a,b; Spiegelhalter et al., 2004; Greenland, 2006, 2011; Held, 2013; Colquhoun, 2017, 2019; Held, 2019a, 2020; Pawel and Held, 2022; Best et al., 2021).

The purpose of this paper is to highlight recent technical developments of Good's basic idea which lead to inferential tools of practical value in the analysis of summary measures as reported in meta-analysis. As a running example we consider a recently published meta-analysis investigating the association between corticosteroids and mortality in hospitalized patients with COVID-19. Specifically, we show how Reverse-Bayes methods address the current concerns about the interpretation of new findings and their replication. We begin by illustrating the basics of the Reverse-Bayes approach for both hypothesis testing and parameter estimation. This is followed by a discussion of Reverse-Bayes methods for assessing effect estimates in Section 2. These allow the credibility of both new and existing research findings reported in

terms of NHST to be evaluated in the context of existing knowledge. This enables researchers to go beyond the standard dichotomy of statistical significance/non-significance, extracting further insight from their findings. We then discuss the use of the Reverse-Bayes approach in the most recalcitrant form of the Problem of Priors, involving the assessment of research findings which are unprecedented and thus lacking any clear source of prior support. We show how the concept of intrinsic credibility resolves this challenge, and puts recent calls to tighten p-value thresholds on a principled basis (Benjamin et al., 2017). In Section 3 we describe Reverse-Bayes methods with Bayes factors, the principled solution for Bayesian hypothesis testing. Finally, we describe in Section 4 Reverse-Bayes approaches to interpretational issues that arise in conventional statistical analysis based on p-values, and how they can be used to flag the risk of inferential fallacies. We close with some extensions and final conclusions.

1.1 Reverse-Bayes for hypothesis testing

The subjectivity involved in the specification of prior distributions is often seen as a weak point of Bayesian inference. The Reverse-Bayes approach can help to resolve this issue both in hypothesis testing and parameter estimation, we will start with the former.

Consider a null hypothesis H_0 with prior probability $\pi = \Pr(H_0)$, so $\Pr(H_1) = 1 - \pi$ is the prior probability of the alternative hypothesis H_1. Computation of the posterior probability of H_1 is routine with Bayes' theorem:

$$\Pr(H_1 \,|\, \text{data}) = \frac{\Pr(\text{data} \,|\, H_1)\Pr(H_1)}{\Pr(\text{data} \,|\, H_0)\Pr(H_0) + \Pr(\text{data} \,|\, H_1)\Pr(H_1)}.$$

Bayes' theorem can be written in more compact form as

$$\frac{\Pr(H_1 \,|\, \text{data})}{\Pr(H_0 \,|\, \text{data})} = \frac{\Pr(\text{data} \,|\, H_1)}{\Pr(\text{data} \,|\, H_0)} \frac{\Pr(H_1)}{\Pr(H_0)}, \tag{1}$$

i. e., the posterior odds are the likelihood ratio times the prior odds. The standard 'forward-Bayes' approach thus fixes the prior odds (or one of the underlying probabilities), determines the likelihood ratio for the available data, and takes the product to compute the posterior odds. Of course, the latter can be easily back-transformed to the posterior probability $\Pr(H_1 \,|\, \text{data})$, if required. The Problem of Priors is now apparent: in order for us to update the odds in favour of H_1, we must first specify the prior odds. This can be problematic in situations where, for example, the evidence on which to base the prior odds is controversial or even non-existent.

However, as Good emphasised it is entirely justifiable to "flip" Bayes's theorem around, allowing us to ask the question: Which prior, when combined with the data, leads to our specified posterior?

$$\frac{\Pr(H_1)}{\Pr(H_0)} = \frac{\Pr(H_1 \,|\, \text{data})}{\Pr(H_0 \,|\, \text{data})} \Big/ \frac{\Pr(\text{data} \,|\, H_1)}{\Pr(\text{data} \,|\, H_0)}. \tag{2}$$

For illustration we re-visit an example put forward by Good (1950, p. 35), perhaps the first published Reverse-Bayes calculation. It centres on a question for which the setting of an

initial prior is especially problematic: does an experiment provide convincing evidence for the existence of extra-sensory perception (ESP)? The substantive hypothesis H_1 is that ESP exists, so that H_0 asserts it does not exist. Imagine an experiment in which a person has to make n consecutive guesses of random digits (between 0 and 9) and all are correct, as the ESP hypothesis H_1 would predict. The likelihood ratio is therefore

$$\frac{\Pr(\text{data} \mid H_1)}{\Pr(\text{data} \mid H_0)} = \frac{1}{(1/10)^n} = 10^n. \tag{3}$$

It is unlikely that sceptics and advocates of the existence of ESP would ever agree on what constitutes reasonable priors from which to start a standard Bayesian analysis of the evidence. However, Good argued that Reverse-Bayes offers a way forward by using it to set bounds on the prior probabilities for H_1 and H_0. This is achieved via the outcome of a thought (Gedanken) experiment capable of demonstrating H_1 is more likely than H_0, that is, of leading to posterior probabilities such that $\Pr(H_1 \mid \text{data}) > \Pr(H_0 \mid \text{data})$. Using this approach, which Good termed the *Device of Imaginary Results*, we see that if the ESP experiment produced $n = 20$ correct consecutive guesses, (2) combined with (3) implies that ESP may be deemed more likely than not to exist by anyone whose priors satisfy $\Pr(H_1)/\Pr(H_0) > 10^{-20}$. In contrast, if only $n = 3$ correct guesses emerged, then the existence of ESP could be rejected by anyone whose priors satisfy $\Pr(H_1)/\Pr(H_0) < 10^{-3}$. Using Bayes's Theorem in reverse has thus led to a quantitative statement of the prior beliefs that either advocates or sceptics of ESP must be able to justify in the face of results from a real experiment. The practical value of Good's approach was noted by Jaynes in his treatise: "[I]n the present state of development of probability theory, the device of imaginary results is usable and useful in a very wide variety of situations, where we might not at first think it applicable" (Jaynes, 2003, p. 125–126).

It is straightforward to extend (1) and (2) to hypotheses that involve unknown parameters θ. The likelihood ratio $\Pr(\text{data} \mid H_1)/\Pr(\text{data} \mid H_0)$ is then called a Bayes factor (Jeffreys, 1961; Kass and Raftery, 1995) where

$$\Pr(\text{data} \mid H_i) = \int \Pr(\text{data} \mid \theta, H_i) f(\theta \mid H_i) d\theta$$

is the marginal likelihood under hypothesis H_i, $i = 0, 1$, obtained be integration of the ordinary likelihood with respect to the prior distribution $f(\theta \mid H_i)$. We will apply the Reverse-Bayes approach to Bayes factors in Section 3 and 4.

1.2 Reverse-Bayes for parameter estimation

We can also apply the Reverse-Bayes idea to continuous prior and posterior distributions of a parameter of interest θ. Reversing Bayes' theorem

$$f(\theta \mid \text{data}) = \frac{f(\text{data} \mid \theta) f(\theta)}{f(\text{data})}$$

then leads to

$$f(\theta) = f(\text{data}) \frac{f(\theta \mid \text{data})}{f(\text{data} \mid \theta)}. \tag{4}$$

So the prior is proportional to the posterior divided by the likelihood with proportionality constant $f(\text{data})$.

Consider Bayesian inference for the mean θ of a univariate normal distribution, assuming the variance σ^2 is known. Let x denote the observed value from that $\mathrm{N}(\theta, \sigma^2)$ distribution and suppose the prior for θ (and hence also the posterior) is conjugate normal. Each of them is determined by two parameters, usually the mean and the variance, but two distinct quantiles would also work. If we fix both parameters of the posterior, then the prior in (4) is – under a certain regularity condition – uniquely determined. For ease of presentation we work with the observational precision $\kappa = 1/\sigma^2$ and denote the prior and posterior precision by δ and δ', respectively. Finally let μ and μ' denote the prior and posterior mean, respectively.

Forward-Bayesian updating tells us how to compute the posterior precision and mean:

$$\delta' = \delta + \kappa, \tag{5}$$

$$\mu' = \frac{\mu\delta + x\kappa}{\delta'}. \tag{6}$$

For example, fixed-effect (FE) meta-analysis is based on iteratively applying (5) and (6) to the summary effect estimate x_i with standard error σ_i from the i-th study, $i = 1, \ldots, n$, starting with an initial precision of zero. Reverse-Bayes simply inverts these equations, which leads to the following:

$$\delta = \delta' - \kappa, \tag{7}$$

$$\mu = \frac{\mu'\delta' - x\kappa}{\delta}, \tag{8}$$

provided $\delta' > \kappa$, i. e., the posterior precision must be larger than the observational precision.

We will illustrate the application of (7) and (8) as well as the methodology in the rest of this paper using a recent meta-analysis combining information from $n = 7$ randomized controlled trials investigating the association between corticosteroids and mortality in hospitalized patients with COVID-19 (WHO REACT Working Group, 2020); its results are reproduced in Figure 1 (here and henceforth, odds ratios (ORs) are expressed as log odds ratios to transform the range from $(0, \infty)$ to $(-\infty, +\infty)$, consistent with the assumption of normality). Let $x_i = \hat{\theta}_i$ denote the maximum likelihood estimate (MLE) of the log odds ratio θ in the i-th study with standard error σ_i. The meta-analytic odds ratio estimate under the fixed-effect model (the pre-specified primary analysis) is $\widehat{\mathrm{OR}} = 0.66$ [95% CI 0.53 to 0.82], respectively $\hat{\theta} = -0.42$ [95% CI -0.63 to -0.20] for the log odds ratio θ, indicating evidence for lower mortality of patients treated with corticosteroids compared to patients receiving usual care or placebo. The pooled effect estimate $\hat{\theta}$ represents a posterior mean μ' with posterior precision $\delta' = 83.8$.

With a meta-analysis such as this, it is of interest to quantify potential conflict among the effect estimates from the different studies. To do this, we follow Presanis et al. (2013) and compute a prior-predictive tail probability (Box, 1980; Evans and Moshonov, 2006) for each study-specific estimate $\hat{\theta}_i$, with a meta-analytic estimate based on the remaining studies serving as the prior. As discussed above, fixed-effect meta-analysis is standard forward-Bayesian updating for normally distributed effect estimates with an initial flat prior. Hence, instead

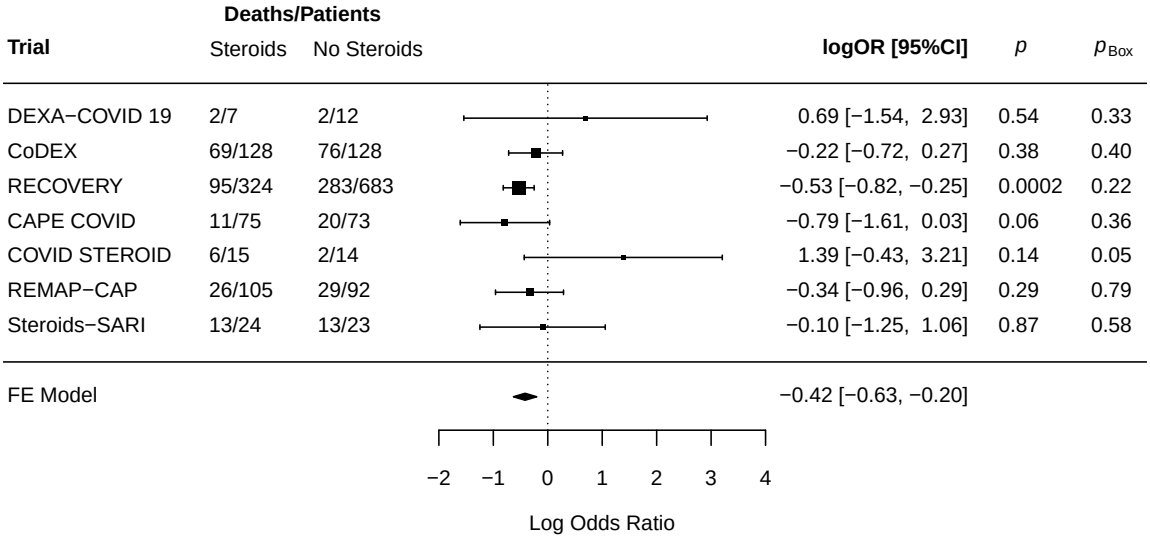

Figure 1: Forest plot of fixed-effect meta-analysis of 7 randomized controlled trials investigating association between corticosteroids and mortality in hospitalized patients with COVID-19 (WHO REACT Working Group, 2020). Shown are number of deaths among total number of patients for treatment/control group, log odds ratio effect estimates with 95% confidence interval, two-sided p-values p, and prior-predictive tail probabilities p_{Box} with a meta-analytic estimate based on the remaining studies serving as the prior.

of fitting a reduced meta-analysis for each study, we can simply use the the Reverse-Bayes equations (7) and (8) together with the overall estimate to compute the parameters of the prior in the absence of the i-th study (denoted by the index $-i$):

$$\begin{aligned} \delta_{-i} &= \delta' - 1/\sigma_i^2, \\ \mu_{-i} &= \frac{\mu'\delta' - \hat{\theta}_i/\sigma_i^2}{\delta_{-i}}. \end{aligned}$$

For example, through omitting the RECOVERY trial result $\hat{\theta}_i = -0.53$ with standard error $\sigma_i = 0.145$ we obtain $\delta_{-i} = 36.1$ and $\mu_{-i} = -0.26$. A prior predictive tail probability using the approach from Box (1980) is then obtained by computing $p_{\text{Box}} = \Pr(\chi_1^2 \geq t_{\text{Box}}^2)$ with

$$t_{\text{Box}} = \frac{\hat{\theta}_i - \mu_{-i}}{\sqrt{\sigma_i^2 + 1/\delta_{-i}}} = -1.24.$$

This leads to $p_{\text{Box}} = 0.22$ for the RECOVERY trial, indicating very little prior-data conflict. The tail probabilities for the other studies are even larger, with the exception of the COVID STEROID trial ($p_{\text{Box}} = 0.05$), see Figure 1. The lack of strong conflict can be seen as an informal justification of the assumptions of the underlying fixed-effect meta-analysis (Presanis et al., 2013; Ferkingstad et al., 2017). A related method in network meta-analysis is to assess

consistency via "node-splitting" (Dias et al., 2010). Reverse-Bayes methods may also be useful for conflict assessment in more general evidence synthesis methods where multiple distinct sources of data are combined (Goudie et al., 2019; Cunen and Hjort, 2021), but this may require more advanced numerical techniques.

Instead of determining the prior completely based on the posterior, one may also want to fix one parameter of the posterior and one parameter of the prior. This is of particular interest in order to challenge "significant" or "non-significant" findings through the Analysis of Credibility, as we will see in the following section.

2 Reverse-Bayes methods for the assessment of effect estimates

A more general question amenable to Reverse-Bayes methods is the assessment of effect estimates and their statistical significance or non-significance. This issue has recently attracted intense interest following the public statement of the American Statistical Association about the misuse and misinterpretation of the NHST concepts of statistical significance and non-significance (Wasserstein and Lazar, 2016). First investigated 20 years ago by Matthews (2001a,b), Reverse-Bayes methods for assessing both statistically significant and non-significant findings have been termed the Analysis of Credibility, or in short AnCred (Matthews, 2018), whose principles and practice we now briefly review.

2.1 The Analysis of Credibility

Suppose the study gives rise to a conventional confidence interval for the unknown effect size θ at level $1-\alpha$ with lower limit L and upper limit U. Assume that L and U are symmetric around the point estimate $\hat{\theta}$ (assumed to be normally distributed with standard error σ). AnCred then takes this likelihood and uses a Reverse-Bayes approach to deduce the prior required in order to generate credible evidence for the existence of an effect, in the form of a posterior that excludes no effect. As such, AnCred allows evidence deemed *statistically significant/non-significant* in the NHST framework to be assessed for its *credibility* in the Bayesian framework. As the latter conditions on the data rather than the null hypothesis, it is inferentially directly relevant to researchers. After a suitable transformation AnCred can be applied to a large number of commonly used effect measures such as differences in means, odds ratios, relative risks and correlations. We refer to the literature of meta-analysis for details about conversion among effect size scales, e. g., Cooper et al. (2019, chapter 11.6). The inversion of Bayes's Theorem needed to assess credibility requires the form and location of the prior distribution to be specified. This in turn depends on whether the claim being assessed is statistically significant or non-significant; we consider each below.

Challenging statistically significant findings

A statistically significant finding at level α is characterized by both L and U being either positive or negative. Equivalently $z^2 > z^2_{\alpha/2}$ is required where $z = \hat{\theta}/\sigma$ denotes the corresponding

test statistic and $z_{\alpha/2}$ the $(1-\alpha/2)$-quantile of the standard normal distribution.

For significant findings, the idea is to ask how sceptical we would have to be not to find the apparent effect estimate convincing. To this end, a *sceptical prior* is derived such that the corresponding posterior credible interval just includes zero, the value of no effect. This critical prior interval can then be compared with internal or external evidence to assess if the finding is credible or not, despite being "statistically significant".

More specifically, a Reverse-Bayes approach is applied to significant confidence intervals (at level α) based on a normally distributed effect estimate. The sceptical prior is a mean-zero normal distribution with variance $\tau^2 = g \cdot \sigma^2$, so the only free parameter is the relative prior variance $g = \tau^2/\sigma^2$. The posterior is hence also normal and either its lower $\alpha/2$-quantile (for positive $\hat{\theta}$) or upper $1-\alpha/2$-quantile (for negative $\hat{\theta}$) is fixed to zero, so just represents "non-credible". The sufficiently sceptical prior then has relative variance

$$g = \begin{cases} \dfrac{1}{z^2/z^2_{\alpha/2} - 1} & \text{if } z^2 > z^2_{\alpha/2} \\ \text{undefined} & \text{else} \end{cases} \tag{9}$$

see the Appendix in Held (2019a) for a derivation. The corresponding *scepticism limit* (Matthews, 2018), the upper bound of the equal-tailed sceptical prior credible interval at level $1-\alpha$, is

$$\text{SL} = \frac{(U-L)^2}{4\sqrt{UL}}, \tag{10}$$

which holds for any value of α provided the effect is significant at that level.

The left plot in Figure 2 illustrates the AnCred procedure for the finding from the RECOVERY trial, the only statistically significant result (at the conventional $\alpha = 0.05$ level) shown in Figure 1. The trial found a decrease in COVID-19 mortality for patients treated with corticosteroids compared to usual care or placebo ($\hat{\theta} = -0.53$ [95% CI -0.82 to -0.25]. The sufficiently sceptical prior has relative variance $g = 0.39$, so the sufficiently sceptical prior variance needs to be roughly 2.5 times smaller than the variance of the estimate to make the result non-credible. The scepticism limit on the log odds ratio scale turns out to be SL $= 0.18$, which corresponds to a critical prior interval with limits 0.84 and 1.19 on the odds ratio scale. Thus sceptics may still reject the RECOVERY trial finding as lacking credibility despite its statistical significance if external evidence suggests mortality reductions (in terms of odds) are unlikely to exceed $1 - 0.84 \approx 16\%$.

It is also possible to apply the approach to the meta-analytic log odds ratio estimate $\hat{\theta} = -0.42$ [95% CI -0.63 to -0.20] from all 7 studies combined. Then SL $= 0.13$, so the meta-analytic estimate can be considered as non-credible if external evidence suggests that mortality reductions are unlikely to exceed $1 - \exp(-\text{SL}) = 1 - 0.88 \approx 12\%$. This illustrates that the meta-analytic estimate has gained credibility compared to the result from the RECOVERY study alone, despite the reduction in the effect estimate ($\widehat{\text{OR}} = \exp(\hat{\theta}) = 0.66$ vs. 0.59 in the RECOVERY study).

Challenging statistically non-significant findings

It is also possible to challenge "non-significant" findings (i. e., those for which the CI now includes zero, so $z^2 < z^2_{\alpha/2}$) using a prior that pushes the posterior towards being credible in the Bayesian sense, with posterior credible interval no longer including zero, corresponding to no effect.

Matthews (2018) proposed the "advocacy prior" for this purpose, a normal prior with positive mean μ and variance τ^2 chosen such that the $\alpha/2$-quantile is fixed to zero (for positive effect estimates $\hat{\theta} > 0$). He showed that the "advocacy limit" AL, the $(1-\alpha/2)$-quantile of the advocacy prior is

$$\text{AL} = -\frac{U+L}{2\,UL}(U-L)^2 \tag{11}$$

to reach credibility of the corresponding posterior at level α. We show in Appendix A that the corresponding relative prior mean $f = \mu/\hat{\theta}$ is

$$f = \begin{cases} \dfrac{2}{1 - z^2/z^2_{\alpha/2}} & \text{if } z^2 < z^2_{\alpha/2} \\ \text{undefined} & \text{else.} \end{cases} \tag{12}$$

There are two important properties of the advocacy prior. First, the coefficient of variation CV is

$$\text{CV} = \tau/\mu = z^{-1}_{\alpha/2}.$$

The advocacy prior $\theta \sim \text{N}(\mu, \tau^2 = \mu^2\,\text{CV}^2)$ is hence characterized by a fixed coefficient of variation, so this prior has equal evidential weight (quantified in terms of $\mu/\tau = z_{\alpha/2}$) as data which are "just significant" at level α. Second, the advocacy limit AL defines the family of normal priors capable of rendering a "non-significant" finding credible at the same level. Such priors are summarized by the credible interval (L_o, U_o) where $L_o \geq 0$, $U_o \leq \text{AL}$. Thus when confronted with a "non-significant" result – often, and wrongly, interpreted as indicating no effect – advocates of the existence of an effect may still claim the existence of the effect is credible to the same level if there exists prior evidence or insight compatible with the credible interval (L_o, U_o). If the evidence for an effect is strong (weak), the resulting advocacy prior will be broad (narrow), giving advocates of an effect more (less) latitude to make their case under terms of AnCred. Note that (11) and (12) also hold for negative effect estimates, where we fix the $(1-\alpha/2)$-quantile of the advocacy prior to zero and define the advocacy limit AL as the $\alpha/2$-quantile of the advocacy prior.

For illustration we consider the data from the REMAP-CAP trial that supported the RECOVERY trial finding of decreased COVID-19 mortality from corticosteroid use. However, this trial involved far fewer patients, and despite the point estimate showing efficacy, the relatively large uncertainty rendered the overall finding non-significant at the 5% level ($\hat{\theta} = -0.34$ [95% CI -0.96 to 0.29]). Such an outcome is frequently (and wrongly) taken to imply no effect. The use of AnCred leads to a more nuanced conclusion. The advocacy limit AL on the log odds ratio scale for REMAP-CAP is -1.89, i. e., 0.15 on the odds ratio scale, see also the right plot in Figure 2. Thus advocates of the effectiveness of corticosteroids can regard the trial as providing credible evidence of effectiveness despite its non-significance if external

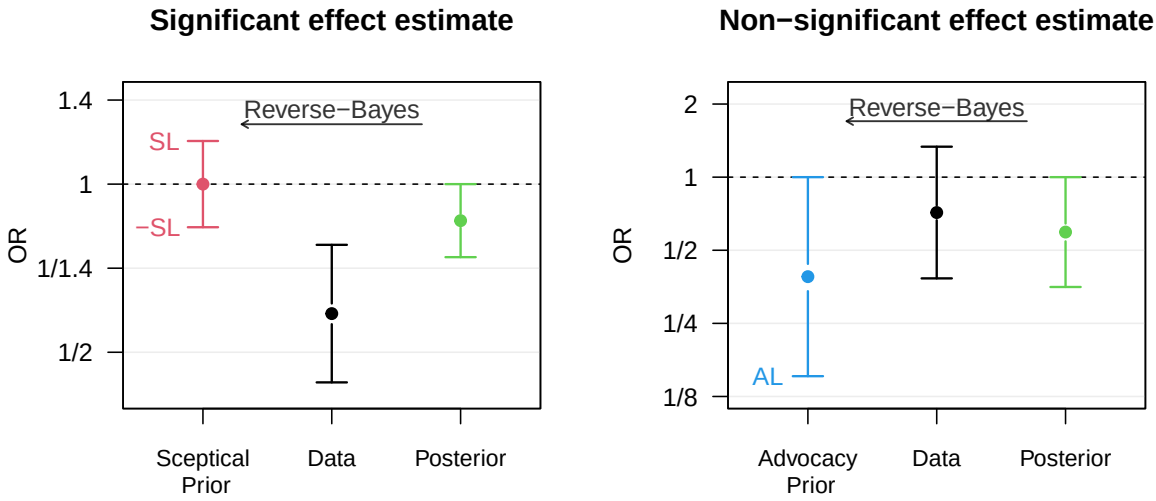

Figure 2: Two examples of the Analysis of Credibility. Shown are point estimates within 95% confidence/credible intervals. The left plot illustrates how a sceptical prior is used to challenge the significant finding from the RECOVERY trial (RECOVERY Collaborative Group, 2020). The right plot illustrates how an advocacy prior is used to challenge a non-significant finding from the REMAP-CAP trial (REMAP-CAP Investigators, 2020). In both scenarios the posterior is fixed to be just non-credible/credible.

evidence supports mortality reductions (in terms of odds) in the range 0% to 85%. So broad an advocacy range reflects the fact that this relatively small trial provides only modest evidential weight, and thus little constraint on prior beliefs about the effectiveness of corticosteroids.

Another way to push non-significant findings towards credibility is to use a prior based on data from another study or a different subgroup. For example, Best et al. (2021) consider results from the MENSA trial (Ortega et al., 2014) on the efficacy of Mepolizumab against placebo in 551 adult and 25 adolescent patients with severe asthma. The treatment effect was estimated to be positive in both subgroups but lacked significance among adolescents. Best et al. combine the data in the adolescent subgroup with a mixture prior based on a weak and an informative component. The weak component is a minimally informative normal prior with mean zero and large variance. The variance is chosen such that the information content of the prior is equivalent to that provided by a single subject or event (*unit-information prior*, Kass and Wasserman, 1995). The other component is an informative prior based on the (significant) results from the adolescent subgroup. A Reverse-Bayes approach is used to determine how much prior weight one needs to assign to the informative component to obtain a credible posterior result with a 95% highest posterior credible interval no longer including zero. In the MENSA trial the required prior weight on the informative component was 0.7 (and thus 0.3 on the weak prior component) to achieve a credible result (Best et al., 2021). This illustrates that a considerable amount of "Bayesian borrowing" is required to extrapolate the results from adults to adolescents.

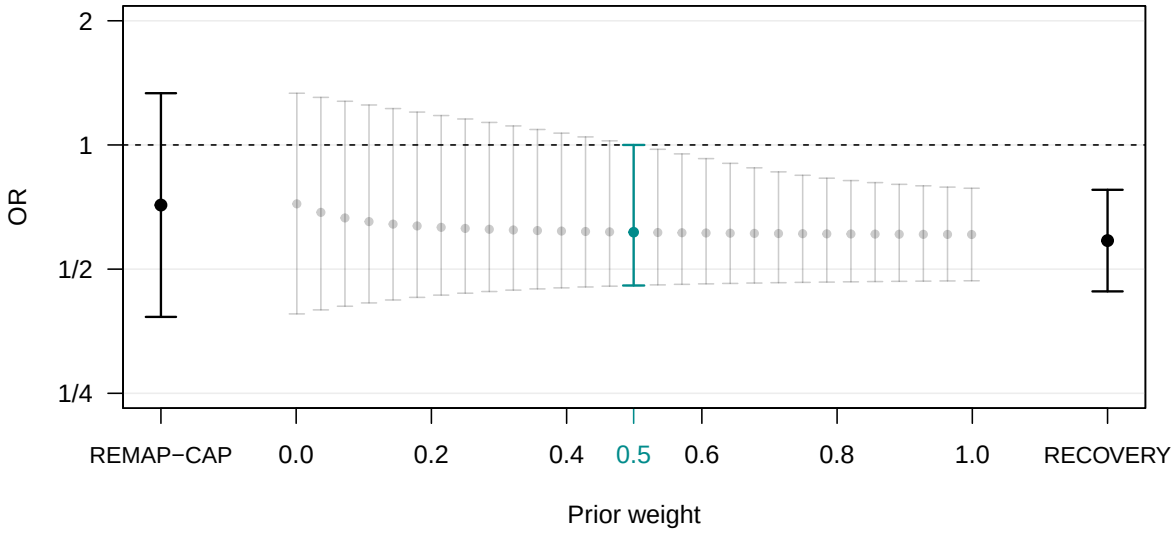

Figure 3: Illustration of the Reverse-Bayes borrowing method. The data from the (non-significant) REMAP-CAP trial are combined with a mixture prior consisting of the (significant) RECOVERY trial data and a unit-information prior (both estimates shown with 95% confidence interval). The resulting posterior medians with equal-tailed 95% credible intervals are shown for a range of mixing weights. The Reverse-Bayes mixing weight $w = 0.5$ leads to the highlighted posterior with upper credible interval limit fixed at one.

In the meta-analytic setting we may ask a similar question: Suppose we want to combine the REMAP-CAP study results with a fraction of the RECOVERY trial data, how much weight do we need to assign to the RECOVERY trial to make the REMAP-CAP study credible? The unit-information prior for a logOR has variance $\tau^2 = 4$ (Spiegelhalter et al., 2004, section 2.4.1), so the mixture prior is

$$\theta \sim w \cdot \mathrm{N}\left(0, \tau^2 = 4\right) + (1 - w) \cdot \mathrm{N}\left(\hat{\theta}_{\mathrm{REC}}, \sigma^2_{\mathrm{REC}}\right)$$

with w the mixing weight and point estimate $\hat{\theta}_{\mathrm{REC}}$ and squared standard error σ^2_{REC} of the RECOVERY trial, respectively. The resulting posterior is again a mixture of two normals with the posterior mean and variance of each component being the usual ones obtained from conjugate Bayesian updating, while the weights are proportional to the marginal likelihood of the data under each component (Best et al., 2021, section 3.5).

Figure 3 shows posterior medians with 95% equal-tailed credible intervals for a range of mixing weights. We see that a weight of at least $w = 0.5$ is required to render the resulting posterior credible. Advocates of corticosteroids thus need to be able to justify such levels of prior beliefs, in order to conclude efficacy of corticosteroids also in the REMAP-CAP trial.

Assessing credibility via equivalent prior study sizes

Reverse-Bayes credibility assessments can also be formulated in terms of the size and content of a prior study capable of challenging a claim of statistical significance/non-significance. This approach puts the weight of prior evidence in the context of the observed data, expressed as participant numbers. Greenland (2006) demonstrated the value of this approach in assessing the credibility of statistically significant findings from large observational studies in epidemiology. The same concept can, however, be extended to the assessment of both significant and non-significant outcomes more widely, such as small randomized controlled trials. For any study generating binary data in the form of event/non-event counts under two different conditions, the comparative effect measure can be expressed as a log-odds ratio with variance (squared standard error)

$$1/m_1 + 1/n_1 + 1/m_2 + 1/n_2. \tag{13}$$

where m_i and n_i are the numbers of events and non-events, respectively, in study arm $i = 1, 2$. This provides the link between the Reverse-Bayes prior distribution and the corresponding numbers of prior study participants. Using the simplifying assumptions of equal numbers of events $m = m_1 = m_2$ and large numbers of non-events n_1 and n_2 in each arm ($n_i > 100\, m_i$, say), the variance (13) reduces to $2/m$. The Reverse-Bayes sceptical prior defined in Section 2.1 has variance $\tau^2 = \mathrm{SL}^2/z^2_{\alpha/2}$, where SL is the sceptical limit. Equating the two implies that such a prior is equivalent to a (large) hypothetical study with

$$m = 2/\tau^2 = 2\, z^2_{\alpha/2}/\mathrm{SL}^2$$

events in both arms. The more compelling the data – that is, the smaller the value of SL – the larger the number of events m required in both arms of the hypothetical large prior study to render the result non-credible at level α.

While the assumption of large studies can be appropriate with epidemiological studies involving rare events, it can be harder to justify for RCTs. Fortunately, the theory can be extended to encompass these and also the case of non-significant findings with little additional complexity. In the case of the sceptical prior, we simply require that the numbers of event m and non-events n are the same in both arms to constrain the mean to zero; the variance (13) then simplifies to $2/m + 2/n$. Adding the constraint that the event rate of the sceptical prior $R = m/(m+n)$ matches that of the study under assessment, we then find

$$m = \frac{2}{\tau^2(1-R)} \quad \text{and} \quad n = \frac{m(1-R)}{R}.$$

For example, from Figure 1 the RECOVERY trial has an overall mortality rate $R = (95+283)/(324+683) = 37.54\%$ and SL $= 0.178$ at the $\alpha = 5\%$ level ($z_{\alpha/2} = 1.96$) corresponds to $\tau^2 = 0.091^2$, so $m = 389$ and $n = 648$ (these are integer approximations of exact computations), and thus a prior study capable of challenging the credibility of the RECOVERY trial requires 1037 patients and 389 deaths in each arm. At more than twice the size of the RECOVERY trial (2074 vs. 1007) patients and considerably more deaths in both arms, this level of sceptical prior evidence highlights the robustness of the trial finding.

A similar approach determines the characteristics of the hypothetical prior study needed to turn a "negative" non-significant finding into one that is credible to a specific α level. The

Reverse-Bayes advocacy prior from Matthews (2018) described in Section 2.1 has a mean $\mu = \mathrm{AL}/2$ and variance $\tau^2 = \mathrm{AL}^2/(2z_{\alpha/2})^2$. Under the large study assumption and equating the latter with (13) as before, the corresponding number of events needed to be observed in both arms of the hypothetical study is $m = 2/\tau^2 = 8\,z^2_{\alpha/2}/\mathrm{AL}^2$. To incorporate the non-zero mean by which this prior represents advocacy, these m events are taken to have been observed among participants allocated to the two study arms in the ratio $1 : K$ where $K = \exp(\mu) = \exp(\mathrm{AL}/2)$, the allocation being such that it increases the relative evidential weight for the hypothesis "negated" by the non-significance.

As before, while the large study approximation may be justified in epidemiological examples, this is less likely to be true for RCTs. In such cases, we can adapt the approach used for sceptical priors, the size and composition of the advocacy prior being found by setting the numbers of events m in each arm the same, but this time allowing for different numbers of non-events in each arm via the allocation ratio K. The resulting variance is then

$$\tau^2 = \frac{2}{m} + \frac{K+1}{n}$$

where n is the number of non-events in the arm used to support the null hypothesis (e. g., the control arm in an RCT). With the control arm event rate $R = m/(m+n)$ constrained to match that of the actual study, we find

$$m = \frac{2 - R(1-K)}{\tau^2(1-R)} \quad \text{and} \quad n = \frac{m(1-R)}{R}.$$

As an example, we return to the REMAP-CAP trial, whose findings were consistent with a reduction of mortality but failed to reach statistical significance. As noted above, its advocacy limit ($\mathrm{AL} = -1.89$) implies this trial has relatively little evidential weight, and gives considerable scope for prior studies to make its outcome credible at the 95% level. With $K = \exp(\mu) = \exp(\mathrm{AL}/2) = 0.39$, $R = 29/92$ and $z_{\alpha/2} = 1.96$ we find $m = 11$ and $n = 25$. Thus the hypothetical prior study comprises 11 deaths from 11 + 25 = 36 patients in the control arm and the same number of deaths from $11 + (25/0.4) = 75$ patients in the treatment arm. At barely half the total size of REMAP-CAP but a considerably more impressive mortality reduction from $R = 29/92 = 32\%$ in the control arm to $11/75 = 15\%$ in the treatment arm (rather than $26/105 = 25\%$ in REMAP-CAP), the nature of this hypothetical prior study confirms the paucity of evidence in the original trial.

The fail-safe *N* method

Another data representation of a sceptical prior forms the basis of the well-known "fail-safe N" method, sometimes also called "file-drawer analysis". This method, first introduced by Rosenthal (1979) and later refined by Rosenberg (2005), is commonly applied to the results from a meta-analysis and answers the question: "How many unpublished negative studies do we need to make the meta-analytic effect estimate non-significant?" A relatively large N of such unpublished studies suggests that the estimate is robust to potential null-findings, for

example due to publication bias. Calculations are made under the assumption that the unpublished studies have an average effect of zero and a precision equal to the average precision of the published ones.

While the method does not identify nor adjust for publication bias, it provides a quick way to assess how robust the meta-analytic effect estimate is. The method is available in common software packages such as `metafor` (Viechtbauer, 2010) and its simplicity and intuitive appeal have made it very popular among researchers.

AnCred and the fail-safe N are both based on the idea to challenge effect estimates such that they become "non-significant/not credible", and it is easy to show that the methods are under some circumstances also technically equivalent. To illustrate this, we consider again the meta-analysis on the association between corticosteroids and COVID-19 mortality (WHO REACT Working Group, 2020) which gave the pooled log odds ratio estimate $\hat{\theta} = -0.42$ with standard error $\sigma = 0.11$, posterior precision $\delta' = 83.8$ and test statistic $z = \hat{\theta}/\sigma = -3.81$.

Using the Rosenberg (2005) approach (as implemented in the `fsn()` function from the `metafor` package) we find that at least $N = 20$ additional but unpublished non-significant findings are needed to make the published meta-analysis effect non-significant. If instead, we challenge the overall estimate with AnCred, we obtain the relative prior variance $g = 0.36$ using equation (9), so $\tau^2 = 0.0043$. Taking into account the average precision $\delta'/n = 11.98$ of the different effect estimates estimates in the meta-analysis leads to $N = n/(\delta' \cdot \tau^2) = 19.5$ which is equivalent to the fail-safe N result after rounding to the next larger integer.

2.2 Intrinsic credibility

The Problem of Priors is at its most challenging in the context of entirely novel "out of the blue" effects for which no obviously relevant external evidence exist. By their nature, such findings often attract considerable interest both within and beyond the research community, making their reliability of particular importance. Given the absence of external sources of evidence, Matthews (2018) proposed the concept of *intrinsic credibility*. This requires that the evidential weight of an unprecedented finding is sufficient to put it in conflict with the sceptical prior rendering it non-credible. In the AnCred framework, this implies a finding possesses intrinsic credibility at level α if the estimate $\hat{\theta}$ is outside the corresponding sceptical prior interval $[-\text{SL}, \text{SL}]$ extracted using Reverse-Bayes from the finding itself, i. e., $\hat{\theta}^2 > \text{SL}^2$ with SL given in (10). Matthews showed this implies an unprecedented finding is intrinsically credible at level $\alpha = 0.05$ if its p-value does not exceed 0.013.

Held (2019a) refined the concept by suggesting the use of a prior-predictive check (Box, 1980; Evans and Moshonov, 2006) to assess potential prior-data conflict. With this approach the uncertainty of the estimate $\hat{\theta}$ is also taken into account since it is based on the prior-predictive distribution, in this case $\hat{\theta} \sim \text{N}(0, \sigma^2 + \tau^2 = \sigma^2(1+g))$ with g as given in (9). Intrinsic credibility is declared if the (two-sided) tail-probability

$$p_{\text{Box}} = \Pr\left(\chi^2_1 \geq \hat{\theta}^2/(\sigma^2 + \tau^2)\right) = \Pr\left(\chi^2_1 \geq z^2/(1+g)\right)$$

of $\hat{\theta}$ under the prior-predictive distribution is smaller than α. It turns out that the p-value associated with θ needs to be at least as small as 0.0056 to obtain intrinsic credibility at level $\alpha = 0.05$, providing another principled argument for the recent proposition to lower the p-value threshold for the claims of new discoveries to 0.005 (Benjamin et al., 2017). A simple check for intrinsic credibility is based on the *credibility ratio*, the ratio of the upper to the lower limit (or vice versa) of a confidence interval for a significant effect size estimate. If the credibility ratio is smaller than 5.8 then the result is intrinsically credible (Held, 2019a). This holds for confidence intervals at all possible values of α, not just for the 0.05 standard. For example, in the RECOVERY study the 95% confidence interval for the log-odds ratio ranges from -0.82 to -0.25, so the credibility ratio is $-0.82/-0.25 = 3.27 < 5.8$ and the result is intrinsically credible at the standard 5% level.

Replication of effect direction

Whether intrinsic credibility is assessed based on the prior or the prior-predictive distribution, it depends on the level α in both cases. To remove this dependence, Held (2019a) proposed to consider the smallest level at which intrinsic credibility can be established, defining the p-value for intrinsic credibility

$$p_{\text{IC}} = 2\left\{1 - \Phi\left(\frac{|z|}{\sqrt{2}}\right)\right\}, \tag{14}$$

see section 4 in Held (2019a) for the derivation. Now $z = \hat{\theta}/\sigma$, so compared to the standard p-value $p = 2\{1 - \Phi(|z|)\}$, the p-value for intrinsic credibility is based on twice the variance σ^2 of the estimate $\hat{\theta}$. Although motivated from a different perspective, inference based on intrinsic credibility thus mimics the *doubling the variance rule* advocated by Copas and Eguchi (2005) as a simple means of adjusting for model uncertainty.

Moreover, Held (2019a) showed that p_{IC} is connected to p_{rep} of Killeen (2006), the probability that a replication will result in an effect estimate $\hat{\theta}_r$ in the same direction as the observed effect estimate $\hat{\theta}$, by $p_{\text{rep}} = 1 - p_{\text{IC}}/2$. Hence, an intrinsically credible estimate at a small level α will have high chance of replicating since $p_{\text{rep}} \geq 1 - \alpha/2$. Note that p_{rep} lies between 0.5 and 1 with the extreme case $p_{\text{rep}} = 0.5$ if $\hat{\theta} = 0$.

As an example, the p-value for intrinsic credibility for the RECOVERY trial finding (with p-value $p = 0.0002$) cited earlier is $p_{\text{IC}} = 0.01$ and thus the probability of the replication effect going in the same direction (i. e., reduced mortality in this case) is 0.995. In contrast, the finding from the smaller REMAP-CAP trial (with $p = 0.29$) leads to $p_{\text{IC}} = 0.46$, and the probability of effect direction replication is hence only 0.77.

3 Reverse-Bayes methods with Bayes factors

The AnCred procedure as described above uses posterior credible intervals as a means of quantifying evidence. However, quantification of evidence with Bayes factors is a more principled solution for hypothesis testing in the Bayesian framework (Jeffreys, 1961; Kass and

Raftery, 1995). Bayes factors enable direct probability statements about null and alternative hypothesis and they can also quantify evidence *for* the null hypothesis, both are impossible with indirect measures of evidence such as p-values (Held and Ott, 2018). Reverse-Bayes approaches combined with Bayes factor methodology was pioneered by Carlin and Louis (1996) but then remained unexplored until Pawel and Held (2022) proposed an extension of AnCred where Bayes factors are used as a means of quantifying evidence. Rather than determining a prior such that a finding becomes "non-credible" in terms of a posterior credible interval, this approach determines a prior such that the finding becomes "non-compelling" in terms of a Bayes factor. In the second step of the procedure, the plausibility of this prior is quantified using external data from a replication study. Here, we will illustrate the methodology using only an original study; we mention extensions for replications in Section 5.1.

3.1 Sceptical priors

As before, $\hat{\theta}$ denotes the estimate of the unknown mean θ of a $\mathrm{N}(\theta, \sigma^2)$ distribution with known variance σ^2. A standard hypothesis test compares the null hypothesis $H_0\colon\ \theta = 0$ to the alternative $H_1\colon\ \theta \neq 0$. Bayesian hypothesis testing requires specification of a prior distribution of θ under H_1. A typical choice is a local alternative, a unimodal symmetric prior distribution centred around the null value (Johnson and Rossell, 2010). We consider again the conjugate sceptical prior $\theta \,|\, H_1 \sim \mathrm{N}(0, \tau^2 = g \cdot \sigma^2)$ with relative prior variance g for this purpose. This leads to the Bayes factor comparing H_0 to H_1 being

$$\mathrm{BF}_{01} = \sqrt{1+g} \cdot \exp\left\{-\frac{g}{1+g} \cdot \frac{z^2}{2}\right\}, \tag{15}$$

where $z = \hat{\theta}/\sigma$. Yet again, the amount of evidence which the data provide against the null hypothesis depends on the prior parameter g; As g becomes smaller ($g \downarrow 0$), the null hypothesis and the alternative will become indistinguishable, so the data are equally likely under both ($\mathrm{BF}_{01} \to 1$). On the other hand, for increasingly diffuse priors ($g \to \infty$), the null hypothesis will always prevail ($\mathrm{BF}_{01} \to \infty$) due to the Jeffreys-Lindley paradox (Robert, 2014). In between, the BF_{01} reaches a minimum at $g = \max\left\{z^2 - 1, 0\right\}$ leading to

$$\mathrm{minBF}_{01} = \begin{cases} |z| \cdot \exp\left\{-z^2/2\right\} \cdot \sqrt{e} & \text{if } |z| > 1 \\ 1 & \text{else} \end{cases} \tag{16}$$

which is an instance of a *minimum Bayes factor*, the smallest possible Bayes factor within a class of alternative hypotheses, in this case zero-mean normal alternatives (Edwards et al., 1963; Berger and Sellke, 1987; Sellke et al., 2001; Held and Ott, 2018).

Reporting of minimum Bayes factors is one attempt of solving the Problem of Priors in Bayesian inference. However, this bound may be rather small and the corresponding prior unrealistic. In contrast, the Reverse-Bayes approach makes the choice of the prior explicit by determining the relative prior variance parameter g such that the finding is no longer compelling, followed by assessing the plausibility of this prior. To do so, one first fixes $\mathrm{BF}_{01} = \gamma$, where γ is a cut-off above which the result is no longer convincing, for example $\gamma = 1/10$, the

level for strong evidence according to the classification from Jeffreys (1961). The sufficiently sceptical relative prior variance is then given by

$$g = \begin{cases} -\frac{z^2}{q} - 1 & \text{if } -\frac{z^2}{q} \geq 1 \\ \text{undefined} & \text{else} \end{cases} \tag{17}$$
$$\text{where } q = \mathrm{W}\left(-\frac{z^2}{\gamma^2} \cdot \exp\left\{-z^2\right\}\right)$$

where $\mathrm{W}(\cdot)$ is the branch of the Lambert W function that satisfies $\mathrm{W}(y) \leq -1$ for $y \in [-e^{-1}, 0)$ (Corless et al., 1996), see the Appendix in (Pawel and Held, 2022) for a proof.

The sufficiently sceptical relative prior variance g exists only for a cut-off γ if $\text{minBF}_{01} \leq \gamma$, similar to standard AnCred where it exists only at level α if the original finding was significant at the same level. In contrast to standard AnCred, however, if the sufficiently sceptical relative prior variance g exists, there are always two solutions, a consequence of the Jeffreys-Lindley paradox: If BF_{01} decreases in g below the chosen cut-off γ, after attaining its minimum it will monotonically increase and intersect a second time with γ, admitting a second solution for the sufficiently sceptical prior.

We now revisit the meta-analysis example considered earlier: The left plot in Figure 4 shows the Bayes factor BF_{01} from (15) as a function of the relative prior variance g for each finding included in the meta-analysis. Most of them did not include a great number of participants and thus provide little evidence against the null hypothesis for any value of the relative prior variance g. In contrast, the finding from the RECOVERY trial provides more compelling evidence and can be challenged up to $\text{minBF}_{01} = 1/148.9$. For example, we see in Figure 4 that the relative sceptical prior variance needs to be $g \leq 0.59$ such that the finding is no longer compelling at level $\gamma = 1/10$. This translates to a 95% prior credible interval from 0.8 to 1.24 for the OR (or any narrower interval around 1). Hence, a sceptic might still consider the RECOVERY finding to be unconvincing, despite its minimum BF being very compelling, if external evidence supports ORs in that range. By applying the prior-to-data conversion method described in Section 2.1 we can further see that the evidential value of this prior is equivalent to a trial with 258 events and 429 non-events in both arms (so that the overall mortality rate is equivalent with the RECOVERY trial). For comparison, the sceptical prior from standard AnCred at $\alpha = 0.05$ was equivalent to a trial with 389 events and 648 non-events, respectively.

The plausibility of the sufficiently sceptical prior can be evaluated in light of external evidence, but what should we do in the absence of such? We could again use the Box (1980) prior-predictive check as in Section 2.2, however, the resulting tail probability is difficult to compare to the Bayes-factor cut-off γ. When a specific alternative model to the null is in mind, Box (1980, p. 391) also suggested to use a Bayes factor for model criticism of the null model. Following this approach, Pawel and Held (2022) proposed to define a second Bayes factor contrasting the sufficiently sceptical prior to an optimistic prior, which they defined as $\theta \mid H_2 \sim \mathrm{N}(\hat{\theta}, \sigma^2)$ the posterior of θ based on the data and the reference prior $f(\theta) \propto 1$. The optimistic prior therefore represents the position of a proponent who takes the original claim

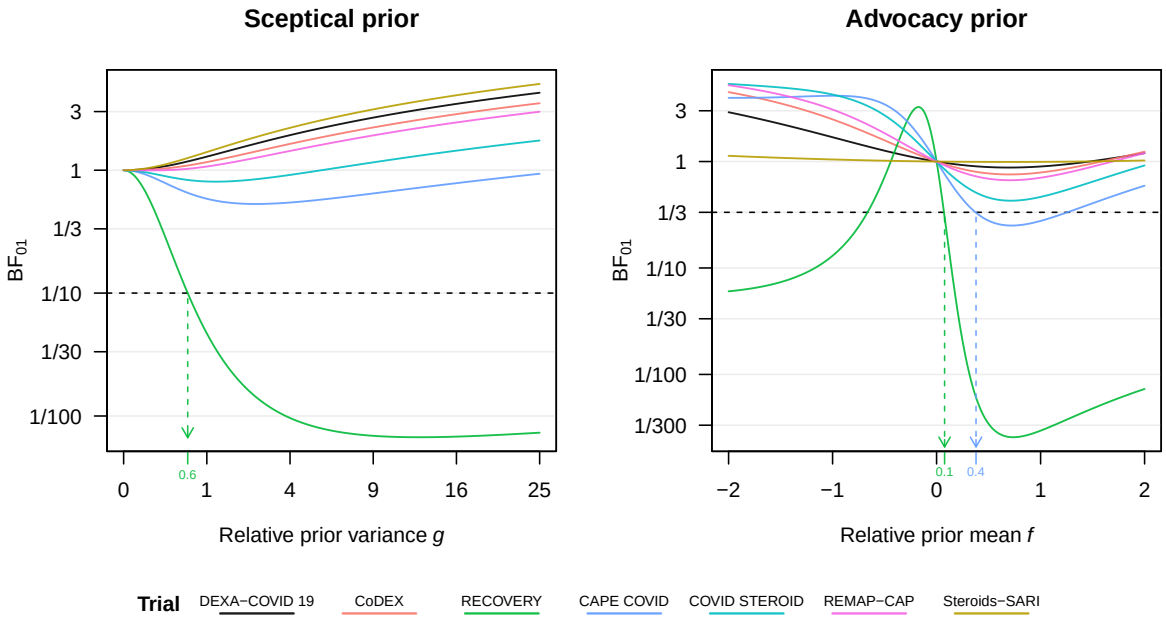

Figure 4: Illustration of the AnCred with Bayes factors procedure using the findings from the meta-analysis on the association of COVID-19 mortality and corticosteroids. The left plot shows the Bayes factor BF_{01} as a function of the relative variance g of the sceptical prior. The result from the RECOVERY trial is challenged with a sceptical prior such that $\text{BF}_{01} = 1/10$, for the other trials such a prior does not exist. The right plot shows the Bayes factor BF_{01} as a function of the relative mean $f = \mu/\hat{\theta}$ of the advocacy prior where the coefficient of variation from the prior is fixed to $\text{CV} = \tau/\mu = 1/z(\gamma = 1/3) = 0.67$, where $z(\gamma)$ is given in (20). The RECOVERY and the CAPE COVID findings are challenged such that $\text{BF}_{01} = 1/3$, for the other trials such a prior does not exist.

at face value. This leads to the second Bayes factor being

$$\text{BF}_{12} = \sqrt{\frac{2}{1+g}} \cdot \exp\left\{-\frac{1}{2} \cdot \frac{z^2}{1+g}\right\}. \tag{18}$$

Analogously to the tail probability approach from Section 2.2, intrinsic credibility is established if the data support the optimistic over the sceptical prior at a higher level than they support the sceptical prior over the null hypothesis, i. e., if

$$\text{BF}_{12} \leq \text{BF}_{01}$$

with sufficiently sceptical relative prior variance g from (17) used in both Bayes factors. For example, if we challenge the RECOVERY trial finding such that the resulting Bayes factor is only $\text{BF}_{01} = 1/10$, we obtain with (9) the sufficiently sceptical relative prior variance $g = 0.59$ and in turn with (18) the Bayes factor $\text{BF}_{12} = 1/64$, so the finding is intrinsically credible at $\gamma = 1/10$.

To remove the dependence on the choice of the level γ, one can determine the smallest level γ where intrinsic credibility can be established. This defines a Bayes factor for intrinsic credibility BF_{IC} similar to the definition of the p-value for intrinsic credibility p_{IC} from (14). Intrinsic

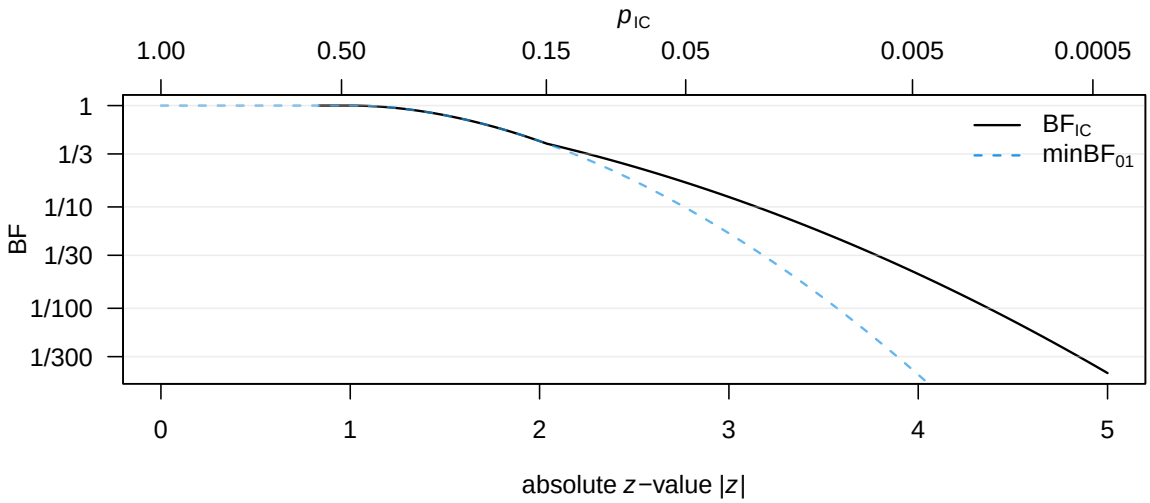

Figure 5: Comparison of the Bayes factor for intrinsic credibility BF_{IC}, the minimum Bayes factor $minBF_{01}$, and the p-value for intrinsic credibility p_{IC} as a function of the absolute z-value $|z|$. The value $p_{IC} = 0.15$ is at the breakpoint at $|z| = 2.04$.

credibility at level γ is then equivalent with $BF_{IC} \leq \gamma$. Details on the computation of BF_{IC} are given in Appendix B. For the RECOVERY finding, the Bayes factor for intrinsic credibility is $BF_{IC} = 1/25$. This means the data favour the optimistic prior over any sceptical prior that is capable of rendering the original result no longer convincing at $\gamma = 1/25$. For comparison the p-value for intrinsic credibility (14) is $p_{IC} = 0.009$.

Figure 5 shows the Bayes factor for intrinsic credibility BF_{IC} as a function of the z-value along with a comparison to the p-value for intrinsic credibility p_{IC} and the minimum Bayes factor $minBF_{01}$ from (16). We see that the BF_{IC} is undefined when $|z| < \sqrt{\log 2} \approx 0.83$. In this case the data are so unconvincing that any sceptical prior is better supported by the data than the optimistic prior. For z-values between $\sqrt{\log 2} \leq |z| < 2.04$, the BF_{IC} equals the minimum Bayes factor $minBF_{01}$, whereas for larger z-values $|z| \geq 2.04$, the BF_{IC} is always larger (more conservative) than the $minBF_{01}$. In the absence of any prior information, it may therefore be a useful evidential summary which formally takes into account both scepticism and optimism about the observed data.

A p-value less than 0.05 is usually regarded as sufficient evidence against the null hypothesis, but how much evidence does $p = 0.05$ mean in terms of the Bayes factor for intrinsic credibility? From Figure 5, we see that the $BF_{IC} = 1/2.1$ for $|z| = 1.96$, so at most "worth a bare mention" according to the classification from Jeffreys (1961). Thus, also from this perspective, the conventional p-value threshold of 0.05 for the claim of new discoveries seems too lax in terms of the evidential value that a finding at this threshold provides. We saw in Section 2.2 that an ordinary p-value needs to be at least as small as $p \leq 0.0056$ for a finding to be intrinsically credible in terms of the p-value for intrinsic credibility $p_{IC} \leq 0.05$. A p-value of 0.0056 corresponds to $|z| = 2.77$ where the Bayes factor for intrinsic credibility is $BF_{IC} = 1/5.7$, in-

dicating at least "substantial" evidence against the null hypothesis according to Jeffreys. To achieve intrinsic credibility at the level for strong evidence ($\gamma = 1/10$) the requirements are even more stringent as the z-value needs to be at least $|z| \geq 3.15$ (equivalent to minBF $\leq 1/27$, $p \leq 0.002$, or $p_{\text{IC}} \leq 0.026$).

3.2 Advocacy priors

A natural question is whether we can also define an advocacy prior, a prior which renders an uncompelling finding compelling, in the AnCred framework with Bayes factors. In traditional AnCred, advocacy priors always exist since one can always find a prior that, when combined with the data, can overrule them. This is fundamentally different to inference based on Bayes factors, where the prior is not synthesized with the data, but rather used to predict them. A classical result due to Edwards et al. (1963) states that if we consider the class of all possible priors under H_1, the minimum Bayes factor is given by

$$\text{minBF}_{01} = \exp\left\{-z^2/2\right\} \tag{19}$$

which is obtained for H_1: $\theta = \hat{\theta}$. This implies that a non-compelling finding can not be "rescued" further than to this bound. For example, for the finding from the REMAP-CAP trial the bound is unsatisfactorily $\text{minBF}_{01} = 1/1.7$, so at most "worth a bare mention" according to the classification from Jeffreys (1961).

Putting these considerations aside, we may still consider the class of $\text{N}(\mu, \tau^2)$ priors under the alternative H_1. The Bayes factor contrasting H_0 to H_1 is then given by

$$\text{BF}_{01} = \sqrt{1 + \tau^2/\sigma^2} \cdot \exp\left\{-\frac{1}{2}\left[\frac{\hat{\theta}^2}{\sigma^2} - \frac{(\hat{\theta} - \mu)^2}{\sigma^2 + \tau^2}\right]\right\}.$$

The Reverse-Bayes approach now determines the prior mean μ and variance τ^2 which lead to the Bayes factor BF_{01} being just at some cut-off γ. However, if both parameters are free, there are infinitely many solutions to $\text{BF}_{01} = \gamma$, if any exist at all. The traditional AnCred framework resolves this by restricting the class of possible priors to advocacy priors with fixed coefficient of variation of $\text{CV} = \tau/\mu = 1/z_{\alpha/2}$. We can translate this idea to the Bayes factor AnCred framework and fix the prior's coefficient of variation to $\text{CV} = 1/z(\gamma)$, where

$$z(\gamma) = \sqrt{-2 \log \gamma}, \tag{20}$$

obtained by solving (19) for z with $\text{minBF}_{01} = \gamma$. The advocacy prior thus carries the same evidential weight as data with $\text{minBF}_{01} = \gamma$. Moreover, the determination of the prior parameters becomes more feasible since there is only one free parameter left (either μ or τ^2).

The right plot in Figure 4 illustrates application of the procedure on data from the meta-analysis on association between COVID-19 mortality and corticosteroids. The coefficient of variation of the advocacy prior is fixed to $\text{CV} = 1/z(\gamma = 1/3) = 0.67$ (for comparison, the CV of the advocacy prior in traditional AnCred at $\alpha = 0.05$ is $\text{CV} = 1/z_{\alpha/2} = 0.51$) and thus the Bayes factor BF_{01} only depends on the relative mean $f = \mu/\hat{\theta}$. Under the sceptical prior only the RECOVERY finding could be challenged at $\gamma = 1/3$ (where $z(\gamma) = 1.5$ corresponds

to $\alpha = 13\%$). With the advocacy prior this is now also possible for the CAPE COVID finding (Dequin et al., 2020), where a prior with mean $\mu = f \cdot \hat{\theta} = 0.37 \cdot (-0.79) = -0.29$ and standard deviation $\tau = \text{CV} \cdot \mu = 0.2$ is able to make the finding compelling at $\gamma = 1/3$. The corresponding prior credible interval for the OR at level $1 - \alpha$ ranges from 0.55 to 1, so advocates may still consider the "non-compelling" finding as providing moderate evidence in favour of a benefit, if external evidence supports mortality reductions in that range. Using the prior-to-data conversion described in Section 2.1, the prior can be translated to a trial with 69 events in both arms, but 206 non-events in the treatment and 182 non-events in the control arm (such that the mortality rate in the control arm is the same as in the CAPE COVID trial). Note that the advocacy prior may not be unique, e. g., for the CAPE COVID finding the prior with relative mean $f' = 1.26$ and standard deviation $\tau' = 0.67$ also renders the data as just compelling at $\gamma = 1/3$. We recommend to choose the prior with f closer to zero, as it is the more conservative choice.

4 Reverse-Bayes analysis of the False Positive Risk

Application of the Analysis of Credibility with Bayes factors as described in Section 3 assumes some familiarity with Bayes factors as measures of evidence. Colquhoun (2019) argued that very few nonprofessional users of statistics are familiar with the notion of Bayes factors or likelihood ratios. He proposes to quantify evidence with the *false positive risk*, "if only because that is what most users still think, mistakenly, that that is what the p-value tells them". More specifically, Colquhoun (2019) defines the FPR as the posterior probability that the point null hypothesis H_0 of no effect is true given the observed p-value p, i. e., $\text{FPR} = \Pr(H_0 \mid p)$. As before, H_0 corresponds to the point null hypothesis $H_0 \colon \theta = 0$. Note also that we take the exact (two-sided) p-value p as the observed "data", regardless of whether or not it is significant at some pre-specified level, the so-called "p-equals" interpretation of NHST (Colquhoun, 2017).

FPR can be calculated based on the Bayes factor associated with p. For ease of presentation we invert Bayes' theorem (1) and obtain

$$\frac{\text{FPR}}{1 - \text{FPR}} = \frac{\Pr(H_0 \mid p)}{\Pr(H_1 \mid p)} = \text{BF}_{01} \frac{\Pr(H_0)}{\Pr(H_1)}, \tag{21}$$

where $\text{BF}_{01} = 1/\text{BF}_{10}$ is the Bayes factor for H_0 against H_1, computed directly from the observed p-value p.

The common 'forward-Bayes' approach is to compute the FPR from the prior probability $\Pr(H_0)$ and the Bayes factor with (21). However, the prior probability $\Pr(H_0)$ is usually unknown in practice and often hard to assess. This can be resolved via the Reverse-Bayes approach (Colquhoun, 2017, 2019): Given a p-value and a false positive risk value, calculate the corresponding prior probability $\Pr(H_0)$ that is needed to achieve that false positive risk. Of specific interest is the value FPR = 5%, because many scientists believe that a Type I error of 5% is equivalent to a FPR of 5% (Greenland et al., 2016). This is of course not true and we

follow Example 1 from Berger and Sellke (1987) and use the Reverse-Bayes approach to derive the necessary prior assumptions on $\Pr(H_0)$ to achieve FPR = 5% with Equation (21):

$$\Pr(H_0) = \left[1 + \frac{1 - \text{FPR}}{\text{FPR}} \cdot \text{BF}_{01}\right]^{-1}. \tag{22}$$

Colquhoun (2017) uses a Bayes factor based on the t-test, but for compatibility with the previous sections we assume normality of the underlying test statistic. We consider Bayes factors under all simple alternatives, but also Bayes factors under local normal priors, see Held and Ott (2018) for a detailed comparison.

Instead of working with a Bayes factor for a specific prior distribution, we prefer to work with the minimum Bayes factor minBF_{01} as introduced in Section 3.1. In what follows we will use the minimum Bayes factor based on the z-test, see Section 2.1 and 2.2 in Held and Ott (2018).

Let minBF_{01} denote the minimum Bayes factor over a specific class of alternatives. From equation (22) we obtain the inequality

$$\Pr(H_0) \leq \left[1 + \frac{1 - \text{FPR}}{\text{FPR}} \cdot \text{minBF}_{01}\right]^{-1}. \tag{23}$$

The right-hand side is thus an upper bound on the prior probability $\Pr(H_0)$ for a given p-value to achieve a pre-specified FPR value.

There are also minBFs not based on the z-test statistic as (16), but directly on the (two-sided) p-value p, the so-called "$-e\,p\log p$" (Sellke et al., 2001) calibration

$$\text{minBF} = \begin{cases} -e\,p\log p & \text{for } p < 1/e \\ 1 & \text{otherwise,} \end{cases} \tag{24}$$

and the "$-e\,q\log q$" calibration, where $q = 1 - p$, see Section 2.3 in Held and Ott (2018):

$$\text{minBF} = \begin{cases} -e\,(1-p)\log(1-p) & \text{for } p < 1 - 1/e \\ 1 & \text{otherwise.} \end{cases} \tag{25}$$

For small p, equation (25) can be simplified to $\text{minBF} \approx e\,p$, which mimics the Good (1958) transformation of p-values to Bayes factors (Held, 2019b).

The two p-based calibrations carry less assumptions than the minimum Bayes factors based on the z-test under normality and can be used as alternative expressions in (23). The "$-e\,p\log p$" provides a general bound under all unimodal and symmetrical local priors for p-values from z-tests, see Section 3.2 in Sellke et al. (2001). The "$-e\,q\log q$" calibration is more conservative and gives a smaller bound on the Bayes factor than the "$-e\,p\log p$" calibration. It can be viewed as a general lower bound under simple alternatives where the direction of the effect is taken into account, see Section 2.1 and 2.3 in Held and Ott (2018).

The left plot in Figure 6 shows the resulting upper bound on the prior probability $\Pr(H_0)$ as a function of the two-sided p-value if the FPR is fixed at 5%. For $p = 0.05$, the "$-e\,p\log p$" bound is around 11% and 28% for the "$-e\,q\log q$" calibration. The corresponding values based on the z-test are slightly smaller (10% and 15%, respectively). All the probabilities are

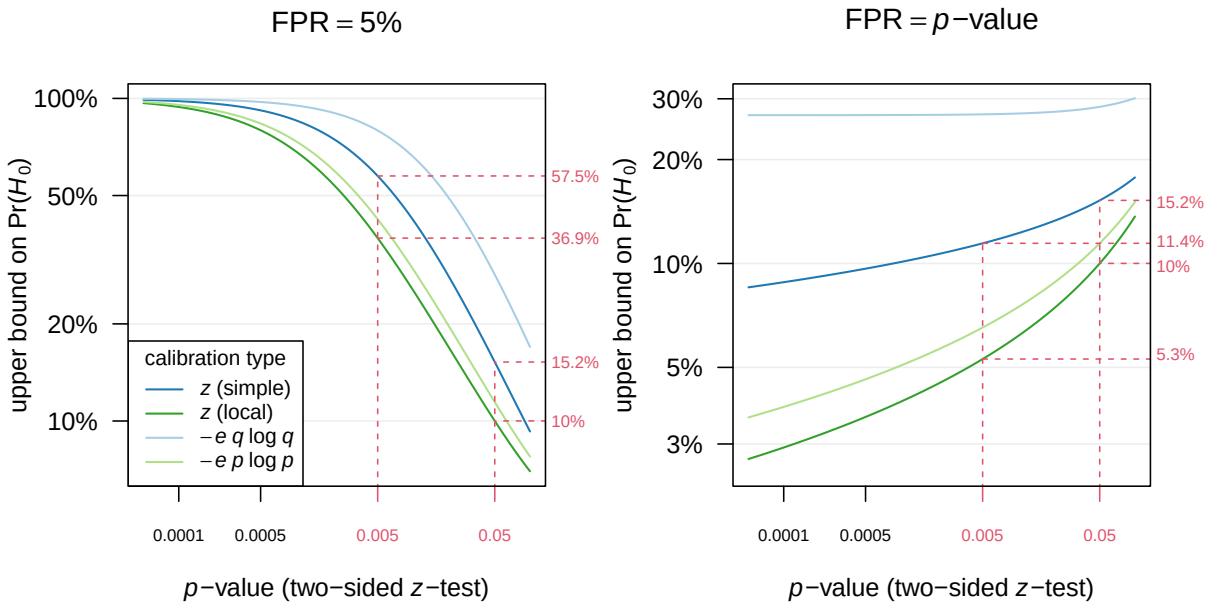

Figure 6: The left plot shows the upper bound on the prior probability $\Pr(H_0)$ to achieve a false positive risk of 5% as a function of the p-value calibrated with either a z-test calibration (simple or local alternatives) or with the "$-e\,p\log p$" or "$-e\,q\log q$" calibrations, respectively. The right plot shows the upper bound on $\Pr(H_0)$ as a function of the p-value using the same calibrations but assuming the p-value equals the FPR.

below the 50% value of equipoise, illustrating that borderline significant result with $p \approx 0.05$ do not provide sufficient evidence to justify an FPR value of 5%. For $p = 0.005$, the upper bounds are closer to 50% (37% for local and 57% for simple alternatives).

Turning again to the example from the RECOVERY trial, the p-value associated with the estimated treatment effect is $p = 0.0002$. The left plot in Figure 6 shows that the false positive risk can safely be assumed to be around 5% (or lower), since the upper bound on $\Pr(H_0)$ are all very large for such a small p-value.

Fixing FPR at the 5% level may be considered as arbitrary. Another widespread misconception is the belief that the FPR is equal to the p-value. Held (2013) used a Reverse-Bayes approach to investigate which prior assumptions are required such that FPR $= p$ holds. Combining (22) with the "$-e\,p\log p$" calibration (24) gives the explicit condition

$$\Pr(H_0) \leq 1/\left\{1 - e\,(1-p)\,\log(p)\right\}$$

whereas the "$-e\,q\log q$" calibration (25) leads to

$$\Pr(H_0) \leq 1/\left\{1 - e\,\frac{(1-p)^2}{p}\,\log(1-p)\right\} \approx 1/\left\{1 + e\,(1-p)\right\},$$

which is approximately $1/(1+e) = 26.9\%$ for small p.

The right plot in Figure 6 compares the bounds based on these two calibrations with the ones obtained from simple respectively local alternatives. We can see that strong assumptions on $\Pr(H_0)$ are needed to justify the claim FPR $= p$: $\Pr(H_0)$ cannot be larger than 15.2% if the p-value is conventionally significant ($p < 0.05$). For $p < 0.005$, the bound drops further to 11.4%. Even under the conservative "$-e\,q\log q$" calibration, the upper bound on $\Pr(H_0)$ is 26.9% for small p and increases only slightly for larger values of p. This illustrates that the misinterpretation FPR $= p$ only holds if the prior probability of H_0 is substantially smaller than 50%, an assumption which is questionable in the absence of strong external knowledge.

5 Discussion

5.1 Extensions, work in progress and outlook

The Reverse-Bayes methods described above have focused on the comparison of the prior needed for credibility with findings from other studies and/or more general insights. However, replication studies make an obvious additional source of external evidence, as these are typically conducted to confirm original findings by repeating their experiments as closely as possible. The question is then whether the original findings have been successfully "replicated", currently of considerable concern to the research community. To date, there remains no consensus on the precise meaning of replication in a statistical sense. The proposal of Held (2020) (see also Held et al., 2022) was to challenge the original finding using AnCred, as described in Section 2.1, and then evaluate the plausibility of the resulting prior using a prior-predictive check on the data from a replication study. A similar procedure but using AnCred based on Bayes factors as in Section 3 was proposed in Pawel and Held (2022). Reverse-Bayes inference seems to fit naturally into this setting as it provides a formal framework to challenge and substantiate scientific findings.

Apart from using data from a replication study, there are also other possible extensions of AnCred: We proposed to derive Reverse-Bayes priors using posterior tail probabilities (or credible intervals) or Bayes factors as measures of evidence, but also other measures such as relative belief ratios (Evans, 2015) could be used. When testing point null hypotheses, relative belief ratios are equivalent to Bayes factors due to the Savage-Dickey density ratio (Evans, 2015, p. 98). Therefore, determining the sceptical prior variance through fixing the resulting Bayes factor is equivalent to fixing the resulting relative belief ratio. However, there is no connection to relative belief in prior-data conflict assessment based on the Bayes factor contrasting the sceptical to the optimistic prior since both are composite. Further research is needed on Reverse-Bayes procedures in the relative belief framework, candidate methods for prior-data conflict assessment are prior to posterior divergence (Nott et al., 2020) and prior expansions (Nott et al., 2021) as these methods have an interpretation in terms of relative beliefs. Moreover, we either used prior-predictive checks (Box, 1980; Evans and Moshonov, 2006) or Bayes-factors (Jeffreys, 1961; Kass and Raftery, 1995) for the formal evaluation of the plausibility of the priors derived through Reverse-Bayes. Other methods could be used for this purpose, for example, Bayesian measures of surprise (Bayarri and Morales, 2003). Furthermore, AnCred in its current state is derived assuming a normal likelihood for the effect

estimate $\hat{\theta}$. This is the same framework as in standard meta-analysis and provides a good approximation for studies with reasonable sample size (Carlin, 1992). For the comparison of binomial outcomes with small counts, the normal approximation of the log odds ratio could be improved with a Yates continuity correction (Spiegelhalter et al., 2004, section 2.4.1) or replaced with the exact profile likelihood of the log odds ratio (Held and Sabanés Bové, 2014, section 5.3), see also Section 4 in Pawel and Held (2022) which shows AnCred with Bayes factors using either a non-central t or a Binomial likelihood. Likewise, the conjugate normal prior could be replaced by a more robust prior distribution such as a mixture of normals (as considered in Section 2.1), a double-exponential, or a Student t-distribution (Pericchi and Smith, 1992). For example, Fúquene et al. (2009) investigate the use of robust priors in an application to binomial data from a randomized controlled trial. In general, any distribution from the location-scale family can be used, whereby the scale parameter takes over the role of the sceptical prior standard deviation, while the location parameter is fixed to the null value.

5.2 Conclusions

The inferential advantages of Bayesian methods are increasingly recognised within the statistical community. However, among the majority of working researchers they have failed to make any serious headway, and retain a reputation for complex and "controversial". We have outlined how an idea that began with Jack Good's proposal for resolving the "Problem of Priors" over 70 years ago (Good, 1950) has experienced a renaissance over recent years. The basic idea is to invert Bayes' theorem: a specified posterior is combined with the data to obtain the Reverse-Bayes prior, which is then used for further inference. This approach is useful in situations where it is difficult to decide what constitutes a reasonable prior, but easy to specify the posterior which would lead to a particular decision. A subsequent prior-to-data conversion (Greenland, 2006) helps to assess the weight of the Reverse-Bayes prior in relation to the actual data.

We have shown that the Reverse-Bayes methodology is useful to extract more insights from the results typically reported in a meta-analysis. It facilitates the computation of prior-predictive checks for conflict diagnostics (Presanis et al., 2013) and has been shown capable of addressing many common inferential challenges, including assessing the credibility of scientific findings (Spiegelhalter et al., 2004; Greenland, 2011), making sense of "out of the blue" discoveries with no prior support (Matthews, 2018; Held, 2019a), estimating the probability of successful replications (Held, 2019a, 2020), and extracting more insight from standard p-values while reducing the risk of misinterpretation (Held, 2013; Colquhoun, 2017, 2019). The appeal of Reverse-Bayes techniques has recently been widened by the development of inferential methods using both posterior probabilities and Bayes Factors (Carlin and Louis, 1996; Pawel and Held, 2022).

These developments come at a crucial time for the role of statistical methods in research. Despite the many serious – and now well-publicised – inadequacies of NHST (Wasserstein and Lazar, 2016), the research community has shown itself to be remarkably reluctant to abandon NHST. Techniques based on the Reverse-Bayes methodology of the kind described

in this review could encourage the wider use of Bayesian inference by researchers. As such, we believe they can play a key role in the scientific enterprise of the 21$^{\text{th}}$ century.

Software and Data Availability

All analyses were performed in the R programming language version 4.2.2 (R Core Team, 2022). Minimum Bayes factors were computed using the package `pCalibrate` (Held and Ott, 2018). The package `metafor` (Viechtbauer, 2010) was used for meta-analysis and forest plots. Data and code to reproduce all analyses are available at `https://gitlab.uzh.ch/samuel.pawel/Reverse-Bayes-Code`.

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A Mean of the advocacy prior

Suppose that the estimate $\hat{\theta}$ is not significant at level α, so $z^2/z^2_{\alpha/2} < 1$. With $U, L = \hat{\theta} \pm z_{\alpha/2}\,\sigma$ we have $U + L = 2\,\hat{\theta}$, $UL = \hat{\theta}^2 - z^2_{\alpha/2}\,\sigma^2$ and $U - L = 2\,z_{\alpha/2}\,\sigma$.

We therefore obtain with (11):

$$\mu = \frac{\text{AL}}{2} = -\frac{2\,\hat{\theta}}{2\,(\hat{\theta}^2 - z^2_{\alpha/2}\,\sigma^2)}\frac{(2\,z_{\alpha/2}\,\sigma)^2}{2} = \frac{2\,\hat{\theta}\,z^2_{\alpha/2}\,\sigma^2}{z^2_{\alpha/2}\,\sigma^2 - \hat{\theta}^2} = \frac{2\,\hat{\theta}}{1 - z^2/z^2_{\alpha/2}}.$$

Dividing by the effect estimate $\hat{\theta}$ leads to the relative mean $f = \mu/\hat{\theta}$ as in (12). The advocacy standard deviation is $\tau = \text{AL}/(2\,z_{\alpha/2}) = \mu/z_{\alpha/2}$ and the coefficient of variation is therefore $\text{CV} = \tau/\mu = z^{-1}_{\alpha/2}$.

B Bayes factor for intrinsic credibility

Intrinsic credibility at level γ is established when

$$\text{BF}_{12} \leq \text{BF}_{01} = \gamma \tag{26}$$

and we are interested in the Bayes factor for intrinsic credibility BF_{IC} which is the smallest level $\gamma \in (0, 1]$ where (26) holds. The BF_{IC} is therefore a special case of the sceptical Bayes

factor from Pawel and Held (2022) where the same data is used in both Bayes factors (instead of the data from a replication study for BF_{12}). It is hence given by

$$BF_{IC} = \begin{cases} \sqrt{-z^2/k} \cdot \exp\left\{-(z^2+k)/2\right\} & \text{if } |z| \geq \sqrt{\left\{-2W\left(-e^{-1}/\sqrt{2}\right)\right\}} \\ \text{minBF}_{01} & \text{if } \sqrt{\log 2} \leq |z| < \sqrt{\left\{-2W\left(-e^{-1}/\sqrt{2}\right)\right\}} \\ \text{undefined} & \text{if } |z| < \sqrt{\log 2} \end{cases} \tag{27}$$

with $k = W(-z^2 \exp\{-z^2/2\}/\sqrt{2})$ and $W(\cdot)$ the branch of the Lambert W function that satisfies $W(y) \leq -1$ for $y \in [-e^{-1}, 0)$. If $|z| \geq \sqrt{-2W(-e^{-1}/\sqrt{2})} \approx 2.04$, BF_{IC} is located at the intersection between BF_{12} and BF_{01} in the relative prior variance g, so equation (7) from Pawel and Held (2022) can be used. For $|z| \geq \sqrt{\log 2} \approx 0.83$, BF_{12} remains below BF_{01} for all g and hence BF_{IC} is given by minBF_{01}, the minimum of BF_{01} from (16). Finally, when $|z| < \sqrt{\log 2}$, equation (26) cannot be satisfied for any valid sufficiently sceptical relative prior variance g, hence the BF_{IC} is undefined.

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PAPER V

Comment on "Bayesian additional evidence for decision making under small sample uncertainty"

Samuel Pawel, Leonhard Held, Robert Matthews

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Abstract

We examine the concept of Bayesian Additional Evidence (BAE) recently proposed by Sondhi et al. We derive simple closed-form expressions for BAE and compare its properties with other methods for assessing findings in the light of new evidence. We find that while BAE is easy to apply, it lacks both a compelling rationale and clarity of use needed for reliable decision-making.

Key words: Advocacy prior, analysis of credibility, Bayesian additional evidence, reverse-Bayes

1 Introduction

We read with great interest the article by Sondhi et al. (2021), which introduces the concept of *Bayesian Additional Evidence* (BAE). The authors use a reverse-Bayes argument to define BAE, and apply it to the important issue of how new evidence affects the overall credibility of an existing finding. As they state, BAE is thus closely related to another reverse-Bayes approach known as *Analysis of Credibility* (AnCred) proposed by Matthews (2018); see also the recent review of Reverse-Bayes methods (Held et al., 2022). In what follows, we comment on the similarities and differences of the two approaches and their inferential consequences. We find that decision making based on the BAE approach is limited by the restrictive assumption that the additional evidence must have equal or smaller variance than the variance of the observed data.

2 Bayesian additional evidence

We begin by showing that fortunately – and contrary to the statement by Sondhi et al. on page 4 of their article – there is a closed-form solution for what they term the BAE "tipping point", which is key to their approach.

Assume, as per Sondhi et al., that both the likelihood of an effect estimate $\hat{\theta}$ (the "data") and the prior of the underlying effect size θ are represented by normal distributions $\hat{\theta} \mid \theta \sim \mathrm{N}(\theta, \sigma^2)$ and $\theta \sim \mathrm{N}(\mu, \tau^2)$, with the latter evidence coming either from pre-existing insight/studies or from a subsequent replication. Bayes's Theorem then implies a posterior distribution $\theta \mid \hat{\theta} \sim \mathrm{N}(\mu_p, \tau_p^2)$ whose mean and variance satisfy

$$\frac{\mu_p}{\tau_p^2} = \frac{\hat{\theta}}{\sigma^2} + \frac{\mu}{\tau^2} \qquad \text{and} \qquad \frac{1}{\tau_p^2} = \frac{1}{\sigma^2} + \frac{1}{\tau^2}$$

Sondhi et al. further assume that $\tau^2 = \sigma^2$, that is, the prior variance τ^2 is equal to the data variance σ^2 which itself is equal to the squared (known) standard error σ of the effect estimate

$\hat{\theta}$. It then follows that the posterior mean is the mean of the data and the prior mean, and that the posterior variance is half the data variance

$$\mu_p = \frac{\hat{\theta} + \mu}{2} \qquad \text{and} \qquad \tau_p^2 = \frac{\sigma^2}{2} \tag{1}$$

The BAE "tipping point" is then defined as the least extreme prior mean that results in a posterior credible interval which excludes the null value. If the substantive hypothesis is for positive effect estimates (e. g., $\log(\text{HR}) > 0$) the BAE is the prior mean which leads to the lower limit L_p of the $100(1-\alpha)\%$ posterior credible interval being zero

$$L_p = \mu_p - z_{\alpha/2}\,\tau_p = 0 \tag{2}$$

while for negative effect estimates the upper limit U_p is fixed to zero

$$U_p = \mu_p + z_{\alpha/2}\,\tau_p = 0 \tag{3}$$

with $z_{\alpha/2}$ the $1-\alpha/2$ quantile of the standard normal distribution. Combining Eq. (1) with Eq. (2), respectively Eq. (3), leads to

$$\text{BAE} = \text{sign}(\hat{\theta})\sqrt{2}\,z_{\alpha/2}\,\sigma - \hat{\theta} \tag{4}$$

where $\text{sign}(\hat{\theta}) = 1$ when $\hat{\theta} > 0$ and $\text{sign}(\hat{\theta}) = -1$ otherwise. Re-written in terms of the upper and lower $100(1-\alpha)\%$ confidence interval (CI) limits U and L of the effect estimate $\hat{\theta}$ we obtain

$$\text{BAE} = \frac{\text{sign}(\hat{\theta})\sqrt{2}(U-L) - (U+L)}{2} \tag{5}$$

We see from Eq. (4) that Sondhi et al.'s proposal has the intuitive property that as the study becomes more convincing (through larger effect sizes $|\hat{\theta}|$ and/or smaller standard errors σ), the BAE will decrease (increase) for positive (negative) $\hat{\theta}$, indicating that less additional evidence is needed to push a non-significant study towards credibility. Eq. (4) and Eq. (5) also hold for significant studies but the BAE then represents the mean of a "sceptical" prior which renders the study non-significant.

These closed-form solutions greatly simplify the use of the BAE methodology. For example, Sondhi et al. use a comparison of monoclonals to show how it identifies additional evidence which, when combined with a non-significant finding, leads to overall credibility. The trial estimated the hazard ratio of the bevacizumab+chemo patients compared to the cetuximab+chemo patients as HR $= 0.42$ (95% CI: 0.14 to 1.23), a non-significant finding with $p = 0.11$. Expressed as log(HR), we have $L = -1.97$ and $U = 0.21$. We use Eq. (5) and find that on log hazard ratio scale BAE $= -0.66$ equivalent to an HR of 0.52. Figure 1 shows the corresponding prior mean with 95% prior credible interval.

Thus additional evidence in the form of prior insight or a subsequent replication supporting an HR at least as impressive as this (i. e., an HR < 0.52 in this case), and a CI at least as tight as that of the original study will render this non-significant result credible at the 95% level. Sondhi et al. cite prior evidence from Innocenti et al. (2019) who found an HR $= 0.13$ (95% CI: 0.06 to 0.30) which meets both criteria set by the BAE, and renders the original study credible.

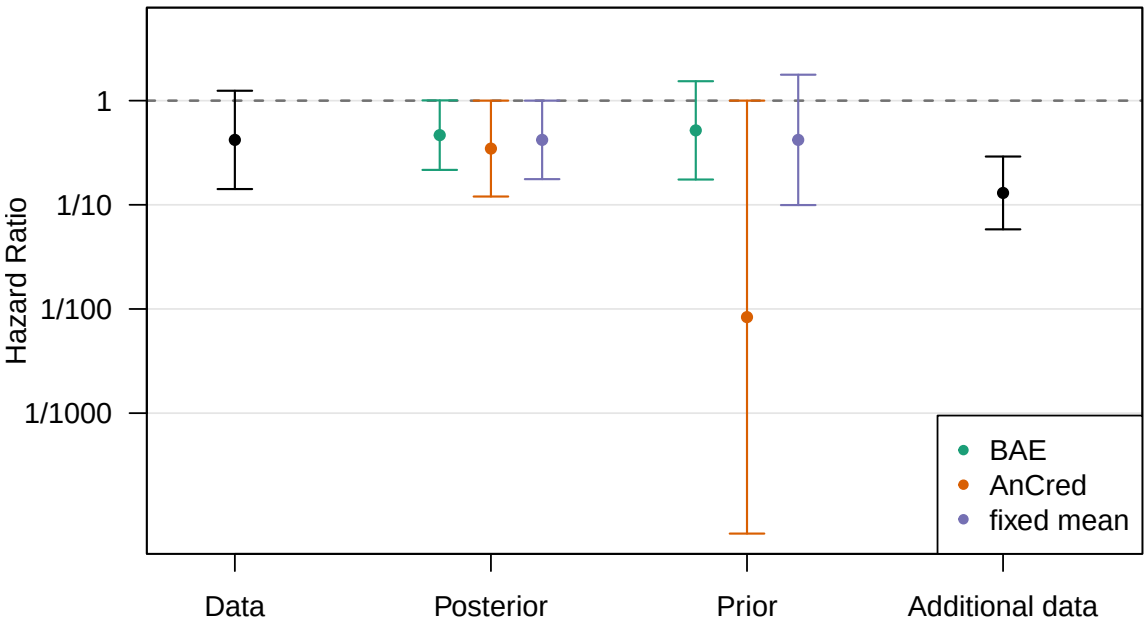

Figure 1: Comparison of BAE, AnCred, and fixed mean 95% prior and posterior credible intervals for the data from Sondhi et al. (2021). Additional data from Innocenti et al. (2019) are also shown.

3 Alternatives approaches

In order to get a unique solution for the BAE, Sondhi et al. make the assumption that the prior variance equals the data variance, but also other possibilities exist. An alternative rationale would be to set the mean of the additional evidence, rather than variance, to that of the original finding (i. e., $\mu = \hat{\theta}$), and determining the prior variance τ^2 such that the posterior credible interval includes the null value. Under this approach, the prior variance is given by

$$\tau^2 = \frac{\sigma^2}{z_{\alpha/2}^2/z^2 - 1}$$

with $z = \hat{\theta}/\sigma$. The resulting prior represents a study with identical effect estimate but different precision compared to the observed one. As the observed study becomes more convincing (with larger effect estimates $|\hat{\theta}|$ and/or smaller standard errors σ), the prior will become more diffuse, so less additional evidence is needed to render the finding credible. We see in Figure 1 that prior and posterior are similar to BAE for the clinical trial data from Sondhi et al.

Figure 1 also illustrates that the BAE and the fixed mean approach can lead to priors which support effect sizes opposing that of the original finding. This is not possible with the AnCred

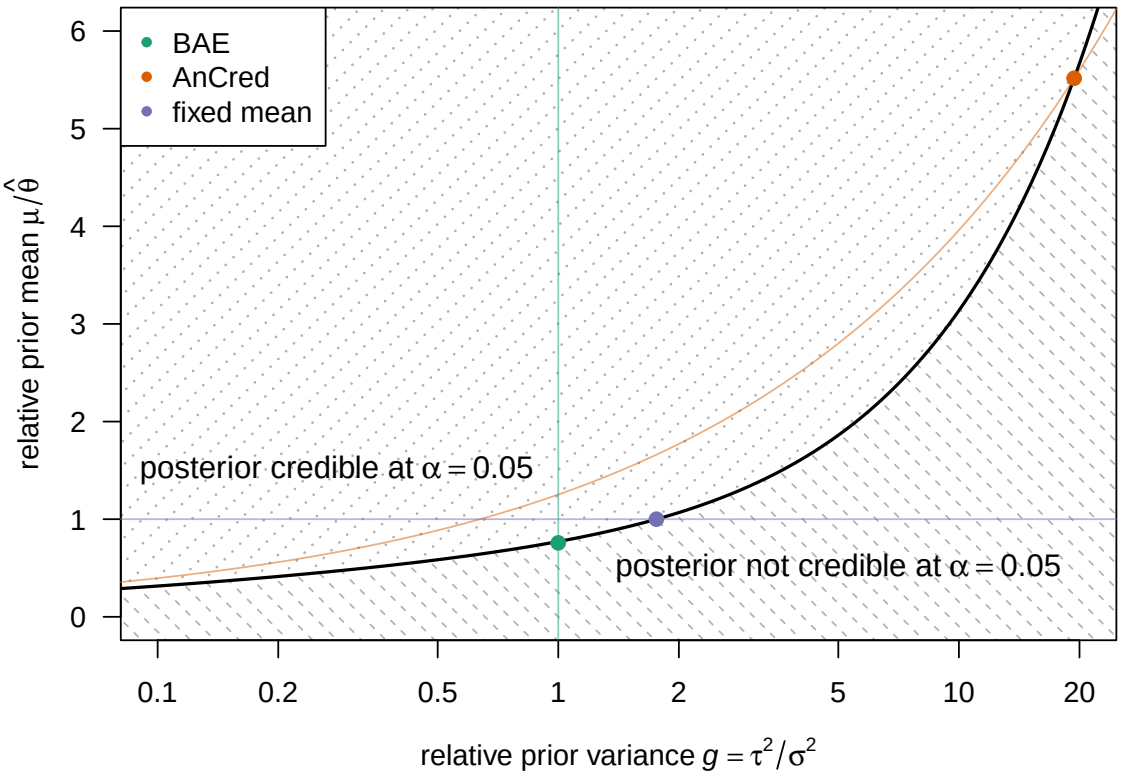

Figure 2: Relative prior mean vs. relative prior variance for the data from Sondhi et al. The dashed region represents parameter values, which do not lead to posterior credibility, whereas values in the dotted region lead to posterior credibility (at $\alpha = 5\%$). The colored lines indicate the parameters which fulfil the side-constraints of the respective method.

advocacy prior whose prior credible interval is fixed to the null value so that the prior adheres to the Principle of Fairminded Advocacy (Matthews, 2018). Held et al. (2022) showed that this constraint is equivalent to fixing the coefficient of variation from the prior to $\tau/\mu = z_{\alpha/2}^{-1}$. Hence, its mean and variance are given by

$$\mu = \frac{2\,\hat{\theta}}{1 - z^2/z_{\alpha/2}^2} \qquad \text{and} \qquad \tau^2 = \frac{\mu^2}{z_{\alpha/2}^2}.$$

We see that – as with the fixed mean approach – the AnCred prior becomes more diffuse for increasingly convincing studies. However, at the same time the prior mean also increases (decreases) for positive (negative) effect estimates, so that only effect sizes in the correct direction are supported.

Figure 1 shows that the AnCred advocacy prior credible interval is far wider compared to the other approaches. Perhaps this observation led Sondhi et al. to state that AnCred is harder to

interpret than BAE, and that it can lead to prior intervals "wide enough to effectively contain any effect size, which is unhelpful for decision making". We would argue that broad priors are a valuable diagnostic of when little additional evidence is needed to achieve posterior credibility, as it is the case with the example Sondhi et al. consider. Moreover, we would argue that AnCred priors are very helpful in decision making since any additional evidence whose confidence interval is contained in the AnCred prior credible interval will *necessarily* lead to posterior credibility when combined with the observed data (Held et al., 2022). In contrast, the BAE approach requires decision makers to keep in mind the variance of the additional evidence, since only additional evidence with a point estimate that is more extreme as the BAE and with confidence interval at least as tight as the observed confidence interval from the study is guaranteed to lead to posterior credibility. Assume, for example, the additional data from Innocenti et al. had been more impressive, say, HR $= 0.05$, with a 95% CI from 0.015 to 0.16. Intuition suggests, and direct calculation confirms, that this would be even more capable of making the original finding credible. However, this would not be clear to a decision maker using the BAE approach as currently formulated, as the confidence interval is wider than the one of the observed study (on the log scale).

While Sondhi et al. acknowledge the dependence of the BAE on the choice of the prior variance, they do not give clear guidance on when it should be set to a value different from the observed data variance. Fortunately, when the prior and data variances differ, there is again a closed form solution for the BAE "tipping point"

$$\mathrm{BAE}(g) = \mathrm{sign}(\hat{\theta})\sqrt{g\,(1+g)\,z_{\alpha/2}\,\sigma - g\,\hat{\theta}} \tag{6}$$

with relative prior variance $g = \tau^2/\sigma^2$. We see from Figure 2 that Eq. (6) substantially depends on the chosen prior variance and that the BAE based on $g = 1$ only captures a limited range of priors which lead to posterior credibility. Unfortunately, Sondhi et al. do not give a clear rationale for the default choice of $g = 1$. It may therefore be more helpful for decision makers to base their decision on the more principled AnCred advocacy prior or on a visualisation of the prior parameter space as in Figure 2.

4 Conclusion

In summary, we welcome BAE as an interesting application of reverse-Bayes methods, and we hope our derivation of closed-form solutions will encourage further research. However, as currently formulated BAE lacks both a clear rationale for the constraints on which it is based, and a sufficiently detailed explanation allowing reliable decision-making.

Software and data

Summary statistics on the case study were taken from Sondhi et al. (2021). The code to reproduce our analyses is available at `https://github.com/SamCH93/BAEcomment`. A snapshot of the Git repository at the time of writing is archived at `https://doi.org/10.5281/zenodo.7437722`.

Acknowledgments

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PAPER VI

Pitfalls and Potentials in Simulation Studies

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Abstract

Comparative simulation studies are workhorse tools for benchmarking statistical methods. As with other empirical studies, the success of simulation studies hinges on the quality of their design, execution and reporting. If not conducted carefully and transparently, their conclusions may be misleading. In this paper we discuss various questionable research practices which may impact the validity of simulation studies, some of which cannot be detected or prevented by the current publication process in statistics journals. To illustrate our point, we invent a novel prediction method with no expected performance gain and benchmark it in a pre-registered comparative simulation study. We show how easy it is to make the method appear superior over well-established competitor methods if questionable research practices are employed. Finally, we provide concrete suggestions for researchers, reviewers and other academic stakeholders for improving the methodological quality of comparative simulation studies, such as pre-registering simulation protocols, incentivizing neutral simulation studies and code and data sharing.

Key words: Benchmarking studies, Monte Carlo experiments, overoptimism, reproducibility, replicability, transparency

1 Introduction

Simulation studies are to a statistician what experiments are to a scientist (Hoaglin and Andrews, 1975). They have become a ubiquitous tool for the evaluation of statistical methods, mainly because simulation can be used for studying the statistical properties of methods under conditions that would be difficult or impossible to study theoretically. In this paper we focus on simulation studies where the objective is to compare the performance of two or more statistical methods (*comparative simulation studies*). Such studies are needed to ensure that previously proposed methods work as expected under various conditions, and to identify conditions under which they fail. Moreover, evidence from comparative simulation studies is often the only guidance available to data analysts for choosing from the plethora of available methods (Boulesteix et al., 2013, 2017). Proper design and execution of comparative simulation studies is therefore important, and results of methodologically flawed studies may lead to misinformed decisions in scientific and medical practice.

Figure 1 shows a schematic illustration of an example comparative simulation study. We see that, just like non-simulation based studies, comparative simulation studies require many decisions to be made, for instance: How will the data be generated? How often will a simulation condition be repeated? Which statistical methods will be compared and how are their parameters specified? How will the performance of the methods be evaluated? The degree of flexibility, however, is much higher for simulation studies than for non-simulation based studies as they can often be rapidly repeated under different conditions at practically no additional cost. This is why numerous recommendations and best practices for design, execution and reporting of simulation studies have been proposed (Hoaglin and Andrews, 1975; Holford et al., 2000; Burton et al., 2006; Smith and Marshall, 2010; O'Kelly et al., 2016; Monks et al.,

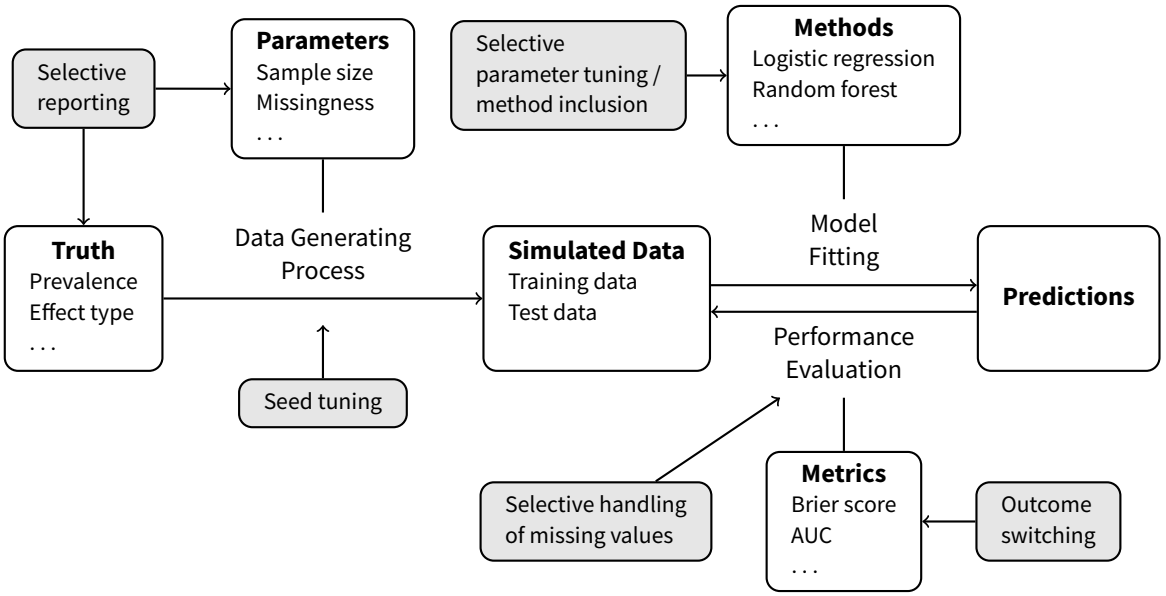

Figure 1: Schematic illustration of a comparative simulation study for evaluating performance of methods for predicting binary outcomes, such as the example study in Section 3. Questionable research practices (in gray) can affect all aspects of the study.

2018; Elofsson et al., 2019; Morris et al., 2019; Boulesteix et al., 2020). We recommend Morris et al. (2019) for an introduction to state-of-the-art simulation study methodology.

Despite wide availability of such guidelines, statistics articles often provide too little detail about the reported simulation studies to enable quality assessment and replication (see the literature reviews in Burton et al., 2006; Morris et al., 2019). Journal policies sometimes require the computer code to reproduce the results, but they rarely require or promote rigorous simulation methodology (for instance, the preparation of a simulation protocol). This leaves researchers with considerable flexibility in how they conduct and present simulations studies. As a consequence, readers of statistics papers can rarely be sure of the quality of evidence that a simulation study provides.

Unfortunately, there are many questionable research practices (QRPs) which may undermine the validity of comparative simulations studies and which can easily go undetected under current publishing standards. Figure 1 shows several QRPs that may occur in the exemplary simulation study. There is often a fine line between QRPs and legitimate research practices. For instance, a researcher may choose to selectively report the most relevant simulation conditions, methods and outcomes in order to streamline the results for the reader. These practices only become questionable when they serve to confirm the hopes and beliefs of researchers regarding a particular method. For instance, if only conditions and outcomes are reported where the researcher's favored method appears superior over competitor methods. Consequently, the results and conclusions of the study will be biased in favor of this method (Nießl et al., 2021).

The aim of this paper is to raise awareness about the issue of QRPs in comparative simulation studies, and to highlight the need for the adoption of higher standards. While researchers

may make decisions that can make the conclusions of simulation studies misleading, we are not accusing them of doing so intentionally or maliciously. Instead, we highlight how QRPs can occur and possibly be prevented. External pressures, for example, to publish novel and superior methods (Boulesteix et al., 2015) or to concisely report large amounts of simulation results, may also lead honest researchers to (unknowingly) employ QRPs. As we will argue, it is not only up to the researchers but also other academic stakeholders to improve on these issues.

This article is structured as follows: We first give an illustrative list of QRPs related to comparative simulation studies (Section 2). With an exemplary simulation study, we then show h?ow easy it is to present a novel, made-up method as an improvement over others if QRPs are employed and *a priori* simulation plans remain undisclosed (Section 3). The main inspiration for this work is drawn from similar illustrative studies which have been conducted by Yousefi et al. (2009) and Jelizarow et al. (2010) for benchmarking studies, and by Simmons et al. (2011) in the context of *p*-hacking in psychological research. Recently, Nießl et al. (2021) and Ullmann et al. (2022) expanded on QRPs in benchmarking studies with the latter also including simulation studies. In Section 4, we then provide concrete suggestions for researchers, reviewers, editors and funding bodies to alleviate the issues of QRPs and improve the methodological quality of comparative simulation studies. Section 5 closes with limitations and concluding remarks.

2 Questionable research practices in comparative simulation studies

There are various QRPs which threaten the validity of comparative simulation studies (see Table 1 for an overview). QRPs can be categorized with respect to the stage of research at which they can occur and which other QRPs they are related to (Wicherts et al., 2016). Typically, QRPs becomes more problematic if they are combined with related QRPs. For example, adapting the data-generating process to achieve a desired outcome (E2) is more problematic when the results based on the adapted process are selectively reported (R2) compared to reporting the results based on both the original and the adapted process. In the following, we describe QRPs from all phases of a simulation study, namely, design, execution and reporting.

2.1 QRPs in the design of comparative simulation studies

The *a priori* specification of research hypotheses, study design and analytic choices is what separates *confirmatory* from *exploratory* research. Evidence from confirmatory research is typically considered more robust because study hypotheses, design, and analysis are independent of the observed data (Tukey, 1980). The line between the two types of research is, however, blurry in simulation studies since they are often iteratively conducted, with each iteration including newly simulated data and building on the results of the previous study. The first simulation study in a sequence of studies may thus be exploratory whereas the subsequent studies may be confirmatory. Yet, one may argue that in many cases a single confirmatory

Table 1: Types of questionable research practices (QRPs) in comparative simulation studies at different stages of the research process. A QRP becomes more problematic if combined with a related QRP, especially a reporting QRP.

Tag	Related	Type of QRP
Design		
D1	E1, R1	Not/vaguely defining objectives of simulation study
D2	E2, R1	Not/vaguely defining data-generating process
D3	E3, E4, R1	Not/vaguely defining which methods will be compared and how their parameters are specified
D4	E1, E5, R1	Not/vaguely defining estimands of interest
D5	E1, E5, R1	Not/vaguely defining evaluation criteria
D6	E6, R1	Not/vaguely defining how to handle missing values (for example, due to non-convergence of methods)
D7	E7, E8, R3	Not justifying number of simulations
Execution		
E1	D1, R2	Changing objective of the study to achieve desired outcomes
E2	D2, R2	Adapting data-generating process to achieve desired outcomes
E3	D3, R2	Adding/removing comparison methods to achieve desired outcomes
E4	D3, R2	Selective tuning of method hyperparameters to achieve desired outcomes
E5	D4, D5, R2	Choosing evaluation criteria to achieve desired outcomes
E6	D6, R2	Adapting inclusion/exclusion/imputation rules to achieve desired outcomes
E7	D7, R3	Choosing number of simulations to achieve desired outcomes
E8	D7, R3	Choosing random number generator seed to achieve desired outcomes
Reporting		
R1	D1–D6	Justifying design decisions which lead to desired outcomes *post hoc*
R2	E1–E6	Selective reporting of results from simulations that lead to desired outcomes
R3	D7, E7, E8	Failing to report Monte Carlo uncertainty
R4		Failing to assure computational reproducibility (for example, not sharing code and sufficient details about computing environment)
R5		Failing to assure replicability (for example, not sufficiently reporting design and execution methodology)

simulation study which is carefully designed and whose design is justified based on external knowledge provides more relevant evidence than a sequence of simulation studies which are iteratively tweaked based on previous results.

To allow readers to distinguish between confirmatory and exploratory research, many non-methodological journals require pre-registration of study design and analysis protocols. For

instance, pre-registration is common practice in randomized controlled clinical trials (Angelis et al., 2004), and increasingly adopted in experimental psychology (Nosek et al., 2018) and epidemiology (Lawlor, 2007; Loder et al., 2010). It is also generally recommended to write and pre-register simulation protocols in simulation studies (Morris et al., 2019). Well-defined study aims and methodology are arguably at least as important as in simulation studies compared to non-simulation based studies because the space of possible design and analysis choices is typically much larger (Hoffmann et al., 2021). If researchers are vague or fail to define the study goals (D1), the data-generating process (D2), the methods under investigation (D3), the estimands of interest (D4), the evaluation metrics (D5), or how missing values should be handled (D6) *a priori* a high number of *researcher degrees of freedom* (Simmons et al., 2011) are left open. Researchers can then generate a multiplicity of possible results which may foster overoptimistic impressions if they report only the subset of results aligning with their hopes and beliefs (R2), and for which they can find plausible justifications *post hoc* (R1).

Another crucial part of rigorous design is simulation size calculation (see Section 5.3 in Morris et al., 2019, for an overview). While an arbitrarily chosen, often too small, number of simulations can be executed faster, they yield noisier results. The additional noise is not necessarily problematic if one is only concerned with estimation. However, if the goal is to establish method superiority through statistical tests (for instance, through a confidence interval for the difference in method performance excluding zero), simulation studies with too few repetitions come with undesirable properties, just as any other study with an insufficiently large sample size. For instance, "true" differences in method performance are more likely to remain undetected (increased type II errors), detected differences are more likely to be in the wrong direction (increased "type S" errors, see Gelman and Tuerlinckx, 2000), and their magnitude is more likely to be overestimated (increased "type M" errors, see Zwet et al., 2021). Additionally, a researcher may start with a small simulation size and continue to add newly simulated data until superiority is established (*optional stopping*). This is similar to early stopping of a trial without correction for the interim analysis. Without specialized corrections, optional stopping leads to biased estimates and increased type I error rates (Robertson et al., 2022). These biases may also occur when the entire simulation study is rerun with a larger sample size and the seed of the random number generator is left unchanged. The simulated data will be the same up to the additional data (provided the simulation runs deterministically conditional on a seed). From this perspective, researchers should thus change the seed if they want rerun the study and increase the simulation size adaptively.

2.2 QRPs in the execution of comparative simulation studies

During the execution of a simulation study researchers may (often unknowingly) engage in various QRPs that can lead to overoptimism. For instance, the objective of the simulation study may be changed depending on the outcome (E1). For example, an initial comparison of predictive performance may be changed to comparing estimation performance if the results suggest that the favored method performs better at estimation tasks rather than prediction. The data-generating process may also be adapted until conditions are found in which the favored method appears superior (E2). For example, the noise levels, the number of covariates, or the effect sizes could be changed. Competitor methods that are superior to the

proposed method may also be excluded from the comparison altogether, or methods which perform worse under the (adapted) data-generating process may be added (E3). The methods under comparison may come with hyperparameters (for instance, regularization parameters in penalized regression models). In this case, the hyperparameters of a favored method may be tuned until the method appears superior, or the hyperparameters of competitor methods may be tuned selectively, for example, left at their default values (E4). Finally, the evaluation criteria for comparing the performance of the investigated methods may also be changed to make a particular method look better than the others (E5). For example, even though the original aim of the study may have been to compare predictive performance among methods using the Brier score, the evaluation criterion of the simulation study may be switched to area under the curve if the results suggest that the favored method performs better with respect to the latter metric. This QRP parallels the well-known *outcome-switching* problem in clinical trials (Altman et al., 2017). It is usually not difficult to find reasonable justification for such modifications and then present them as if they were specified during the planning of the study (R1). As emphasized earlier, iteratively changing simulation goals, conditions, methods under comparison and evaluation criteria can be part of finding out how a method works. These practices become mostly problematic if only the simulations in line with the researchers hopes and beliefs are reported (R2).

There are, however, practices which are considerably more problematic on their own. For instance, in some simulations a method may fail to converge and thus produce missing values in the estimates. If it is not pre-specified how these situations will be handled, different inclusion/exclusion or imputation strategies may be tried out until a favored method appears superior (E6). Choosing an inadequate strategy can result in systematic bias and misleading conclusions. If no *a priori* simulation size calculation was conducted, the simulation size may also be changed until favorable results are obtained (E7). If in that case the number of simulations is too small, true performance differences are more likely to be missed, their estimated direction is more likely to be incorrect and their magnitude is more likely overestimated, as explained previously. Finally, if only few simulations are conducted (for instance, because the methods under investigation are computationally very expensive), the initializing seed for generating random numbers may have a substantial impact on the result. A particularly questionable practice in this situation is to tune the seed until a value is found for which a preferred method seems superior (E8).

2.3 QRPs in the reporting of comparative simulation studies

In the reporting stage, researchers are faced with the challenge of reporting the design, results, and analyses of their simulation study in a digestible manner. Various QRPs can occur at this stage. For instance, reporting may focus on results in which the method of interest performs best (R2). Failing to mention conditions in which the method was inferior (or at least not superior) to competitors creates overoptimistic impressions, and may lead readers to think that the method uniformly outperforms competitors. Similarly, presenting simulation conditions which were added based on the observed results as pre-planned and justified (R1) fosters overconfidence in the results.

Another crucial aspect of reporting is to adequately show the uncertainty related to the simulation results (Hoaglin and Andrews, 1975; Van der Bles et al., 2019). Failing to report Monte Carlo uncertainty (R3), such as error bars or confidence intervals reflecting uncertainty in the simulation, hampers the readers' ability to assess the accuracy of the results from the simulation study and it allows one to present random differences in performance as if they were systematic.

Finally, by failing to assure computational reproducibility of the simulation study (R4), for example, by not sharing code and software versions to run the simulation, it is more likely that coding errors remain undetected. By not reporting the design and execution of the study in enough detail (R5), other researchers are unable to replicate and expand on the simulation study. Unclear reporting also makes it harder for readers to identify potentially overoptimistic statements. For instance, if it is reported that all but one method are left at their default parameters, readers can better contextualize this method's apparent superior performance.

3 Empirical study: The Adaptive Importance Elastic Net (AINET)

To illustrate the application of QRPs from Table 1 we conducted a simulation study. The objective of the study was to evaluate the predictive performance of a made-up regression method termed the *adaptive importance elastic net* (AINET). The main idea of AINET is to use variable importance measures from a random forest for a weighted penalization of the variables in an elastic net regression model. The hope is that this *ad hoc* modification of the elastic net model improves predictive performance in clinical prediction modeling settings where penalized regression models are frequently used. Superficially, AINET may seem sensible, however, for the data-generating process considered in our simulation study no advantage over the classical elastic net is expected. For more details on the method, we refer the reader to the simulation protocol (Appendix A). We report the pre-registered simulation study results in the online supplement (we use the term *pre-registered* throughout to refer to simulation analyses conducted as pre-specified in the protocol). As expected, the performance of AINET was virtually identical to standard elastic net regression. AINET also did not yield any improvements over logistic regression for the data-generating process that we considered sensible *a priori* (that is, specified based on typical conditions in clinical prediction modeling and simulation studies from other researchers).

We now show how application of QRPs changes the above pre-registered conclusions. Figure 2 illustrates different types of QRPs sequentially applied to simulation-based evaluation of AINET. The top row depicts the pre-registered differences in Brier score (horizontal axis) between AINET and competitor methods (vertical axis) for a representative subset of the simulation conditions. A negative difference indicates superior performance of AINET. In the second row, the arrows depict the change in the pre-registered results after changing the data-generating process (E2). The third row shows the result after removal of the elastic net competitor (E3). Finally, the bottom row shows the end result where selective reporting of simulation conditions and competitor methods (R2) is applied to give a more favorable impression of AINET. We will now discuss these QRPs in more detail.

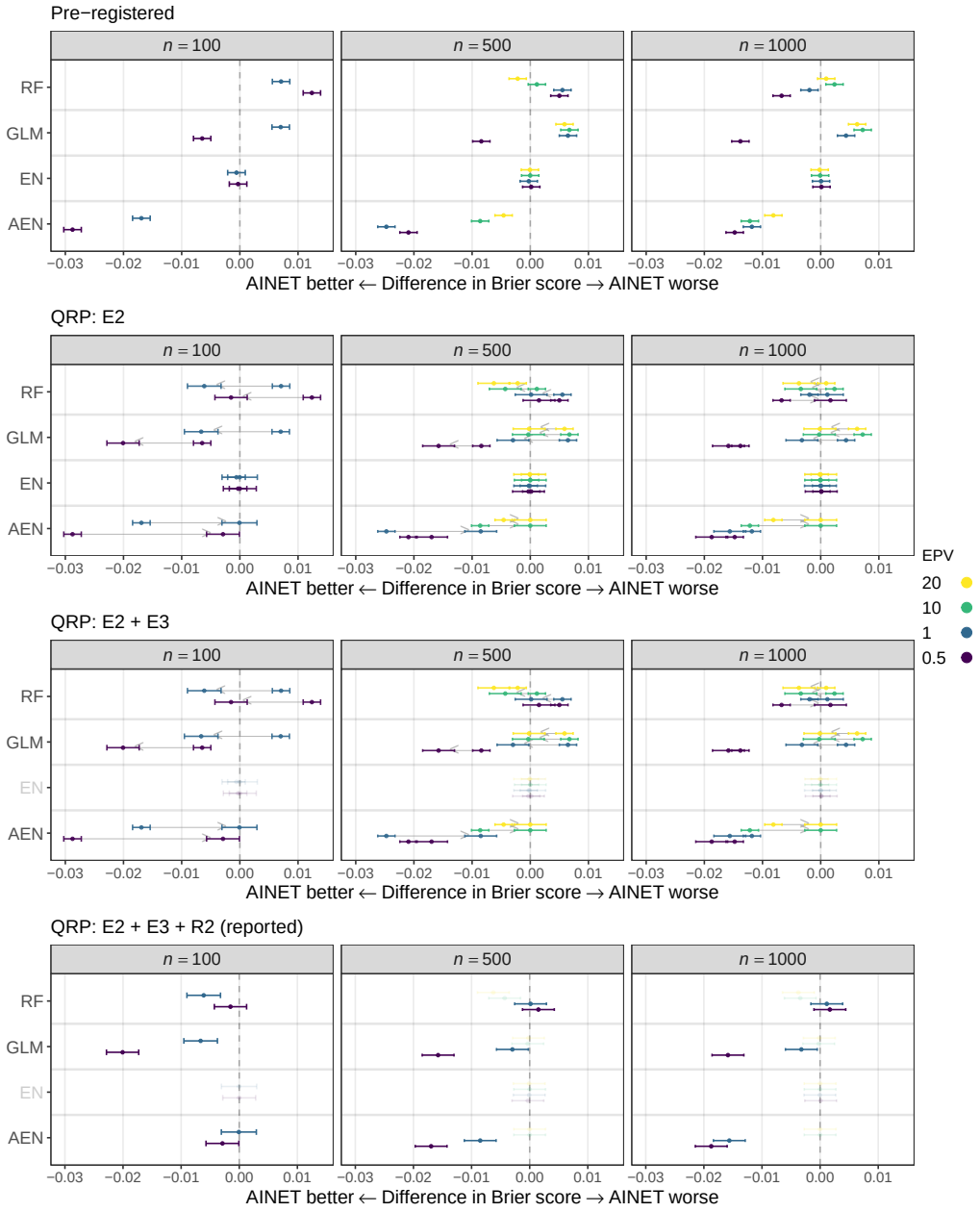

Figure 2: Differences in Brier score with 95% adjusted confidence intervals between AINET and random forest (RF), logistic regression (GLM), elastic net (EN) and adaptive elastic net (AEN) are shown for representative simulation conditions (correlated covariates $\rho = 0.95$, prevalence $\text{prev} = 0.05$, a range of sample sizes n and events per variable (EPV), in each simulation the Brier score is computed for 10'000 test observations; for details see Appendix A). The top row depicts the pre-registered results in which AINET does not outperform any competitor uniformly, except AEN. In the second row, we apply QRP E2: Altering the data-generating process by adding a non-linear effect and sparsity. The gray arrows point from the pre-registered result to the results under the tweaked simulation. In the third row, QRP E3 is applied: EN is removed as a competitor. In the bottom row, selective reporting R2 is applied: Only low EPV settings are reported to give a more favorable impression for AINET. Arrows are depicted only for non-overlapping confidence intervals.

Altering the data-generating process (E2) We could not detect a systematic performance benefit of AINET over standard logistic regression, elastic net regression, or random forest for the scenarios specified in the protocol. For this reason, we tweaked the data-generating process by adding different sparsity conditions and a non-linear effect. We then found that AINET outperforms logistic regression under the following conditions: Only few variables being associated with the outcome (sparsity), a non-linear effect and a low number of events per variable (EPV). Figure 2 (second row) shows the changes in Brier score difference between the pre-registered and the tweaked simulation. As can be seen, the tweaked data-generating process leads to AINET being superior to competitors in some conditions, and at least not inferior in others.

Removing competitor methods (E3) Despite the adapted data-generating process, we still observed only minor (if any) improvements of AINET over the elastic net. In order to present AINET in a better light we could omit the comparisons with the elastic net (E3), as shown in Figure 2 (third row). This could be justified, for example, by arguing that for neutral comparison it is sufficient to compare a less flexible method (logistic regression, which has no tuning parameters and captures linear effects), a more flexible method (random forest, which has tuning parameters and captures nonlinear relationships), and a comparably flexible method (adaptive elastic net, which has the same tuning parameters as AINET, but differs in the way the penalization weights are chosen).

Selective reporting of simulation results (R2) After the removal of the competitor elastic net, there are still some simulation conditions under which AINET is not superior to the remaining competitors. To make AINET appear more favorable, we thus report only simulation conditions with low EPV, as shown in Figure 2 (fourth row). This could be justified by the fact that journals require authors to be concise in their reporting. Otherwise, further conditions with low EPV values could be simulated to make the results seem more exhaustive. Focusing primarily on low EPV settings could be justified in hindsight by framing AINET as a method designed for high-dimensional data (low sample size relative to the number of variables).

4 Recommendations

The previous sections painted a rather negative picture of how undisclosed changes in simulation design, analysis and reporting may lead to overoptimistic conclusions. In the following, we summarize what we consider to be practical recommendations for improving the methodological quality of simulation studies; see Table 2 for an overview. Our recommendations are grouped with regards to which stakeholder they concern.

4.1 Recommendations for researchers

Adopting pre-registered simulation protocols is an important measure that researchers can take to prevent themselves from subconsciously engaging in QRPs. Pre-registration enables

Table 2: Recommendations for improving quality of comparative simulation studies and preventing QRPs.

Researchers
– Write (and possibly pre-register) simulation protocols
– Adopt good computational practices (code review, packaging, unit-tests)
– Share code and data (possibly in intermediate/summary form to enable secondary analysis)
– Report the process of the simulation study fully and transparently (for instance, time-stamped protocol amendments to disclose pilot studies and *post hoc* modifications)
– Perform simulation analysis in a blinded manner
– Collaborate with other research groups (possibly familiar with "competing" methods)
– Disclose multiplicity and uncertainty of results (for example, with sensitivity analyses)
– Teach simulation study methodology in statistics (post)graduate courses
Editors and reviewers
– Encourage exploration of conditions where methods should be inferior or break down
– Encourage (pre-registered) simulation protocols
– Provide enough space for description of simulation methodology
Journals and funding bodies
– Provide incentives for rigorous simulation methodology (such as badges on papers)
– Require code and data
– Promote standardized reporting
– Adopt reproducibility checks
– Promote/fund research and software to improve simulation study methodology
– Shift focus away from outperforming state-of-the-art methods

readers to distinguish between confirmatory and exploratory findings, and it lowers the risk of potentially flawed methods being promoted as an improvement over competitors. While pre-registered simulation protocols may at first seem disadvantageous due to the additional work and possibly lower chance of publication, they provide researchers with the means to differentiate their high-quality simulation studies from the numerous unregistered and possibly less trustworthy simulation studies in the literature. Platforms such as GitHub (`https://github.com/`), OSF (`https://osf.io/`), or Zenodo (`https://zenodo.org/`) can be used for archiving and time-stamping documents. Moreover, pre-registration can also save researchers from some work later on. For instance, large parts of the methodology description can usually be copied from the protocol to the final manuscript.

When pre-registering and conducting simulation studies, we recommend using a robust computational workflow. Such a workflow encompasses packaging the software, writing unit tests and reviewing code (see Schwab and Held, 2021). Other researchers and the authors themselves then benefit from improved computational reproducibility and less error-prone code. Of course, there are also certain practical limits to computational reproducibility. For instance, if a simulation study requires high performance computing and/or several weeks of running time, the authors should not expect reviewers and journals to replicate their simulation study from scratch. The authors should nevertheless provide the code to run the simulation and, if possible, they should also provide intermediate simulation results (for instance, fitted model objects) so that the simulation study can at least be partially reproduced. Similarly, authors can share the simulated data, either in raw and/or some summarized form (for example, sharing simulated data sets and parameter estimates of fitted models). This allows interested readers and reviewers to do additional analyses. Unlike experiments with human subjects, there are no privacy concerns for sharing simulation data. Furthermore, online tools, such as INTEREST (INteractive Tool for Exploring REsults from Simulation sTudies, Gasparini et al., 2021), can be used for interactive exploration of the data set.

While planning a simulation study, it is impossible to think of all potential weaknesses or problems that may arise when conducting the planned simulations. In turn, researchers may be reluctant to tie their hands in a pre-registered protocol. However, a transparently conducted and reported preliminary simulation can obviate most of these problems. We recommend researchers to disclose preliminary results and any resulting changes to the protocol, for example, in a revised and time-stamped version of the protocol. This approach is similar to conducting a small pilot study, as is often done in non-simulation based research. Even if researchers realize that further changes are required after the main simulation study has begun, transparent reporting of when and why *post hoc* modifications were made allows the reader to better assess the quality of evidence provided by the study. Researchers designing simulation studies may draw inspiration from clinical trials by tracking their protocol modifications and time-stamping versions of their protocol.

A different approach for making *post hoc* changes to the protocol is to use blinding in the analysis of the simulation results (Dutilh et al., 2021). Blinded analysis is a standard procedure in particle physics to prevent data analysts from biasing their result towards their own beliefs (Klein and Roodman, 2005), and it lends legitimacy to *post hoc* modifications of the simulation study. For instance, researchers might shuffle the method labels and only unblind themselves after the necessary analysis pipelines are set in place. An alternative blinding approach is to carry out data generation and analysis by different researchers. For instance, the study from Kreutz et al. (2020) involved two independent research groups, one who simulated and one who analyzed the data. A related way for improving simulation studies is to collaborate with other researchers, possibly ones familiar with "competing" methods. This helps to design simulation studies which are more objective and whose results are more useful for making a decision about which method to choose under which circumstances.

We also recommend researchers to disclose the multiplicity and uncertainty inherent to the design and analysis of their simulation studies (Hoffmann et al., 2021). For instance, researchers can report sensitivity analyses that show how the study results change for different

analysis decisions (for example, Table 4 in van Smeden et al. (2016) shows how the evaluation metrics for different estimators change depending on how convergence of a method is defined). Methods from multivariate statistics can be used for visualizing the influence of different design choices, such as the multidimensional unfolding approach in Nießl et al. (2021).

One reason for the low standards of simulation studies in the statistics literature may be that rigorous simulation methodology is usually not taught in graduate or postgraduate courses (with a few exceptions, such as the course "Using simulation studies to evaluate statistical methods" from the MRC Clinical Trials Unit). To improve training of current and future generations of statisticians, researchers who are involved in teaching should therefore also include simulation study methodology in their curricula. The standards of simulation studies in many statistics related fields (for instance, machine learning, psychometrics, econometrics, or ecology) are arguably not much different. One possible avenue for future research is thus to also promote education and adaptation of simulation study methodology for the special needs in these fields.

4.2 Recommendations for editors and reviewers

Peer review is an important tool for identifying QRPs in research results submitted to methodological journals. For instance, reviewers may demand researchers to include competitor methods which are not part of their comparison yet (or which might have been excluded from the comparison). However, reviewers can only identify a subset of all QRPs since some types are impossible to spot if no pre-registered simulation protocol is in place (for example, a reviewer cannot know whether the evaluation criterion was switched). Even QRPs which can be detected by peer review may be difficult to spot in practice. It is thus important that reviewers and editors promote that authors make simulation protocols and computer code available alongside the manuscript. Moreover, by providing enough space and encouraging authors to provide detailed descriptions of their simulation studies, replicability of the simulation studies can be improved. Finally, reviewers should not be satisfied with manuscripts showing that a method is uniformly superior; they should also encourage authors to explore conditions in which their method is expected to be inferior to other methods or to break down entirely.

4.3 Recommendations for journals and funding bodies

Journals and funding bodies can improve on the status quo by either actively requiring or passively incentivizing more rigorous and neutral simulation study methodology. Actively, journals can make (pre-registered) simulation protocols mandatory for all articles featuring a simulation study. A more passive and less extreme measure would be to indicate with a badge whether an article contains a pre-registered simulation study, or to introduce article types dedicated to neutral comparison studies. Such an approach rewards researchers who take the extra effort. Similar initiatives have led to a large increase in the adoption of pre-registered study protocols in the field of psychology (Kidwell et al., 2016). Another measure

could be to require standardized reporting of simulation studies, for example, the "ADEMP" reporting structure proposed by Morris et al. (2019). Journals may also employ reproducibility checks to ensure computational reproducibility of the published simulation studies. This is already done, for example, by the Journal of Open Source Software or the Journal of Statistical Software. Moreover, journals and funding bodies can promote or fund research and software to improve simulation study methodology. For instance, a journal might have special calls for papers on simulation methodology. Similarly, a funding body could have special grants dedicated to software development that facilitates sound design, execution and reporting of simulation studies (as White, 2010; Gasparini, 2018; Chalmers and Adkins, 2020). Finally, journals and funding bodies often exert a strong incentive on researchers to publish novel and superior methods. This may lead to articles with non-systematic simulation studies that mainly highlight settings beneficial to the proposed methods. We believe that the above recommendations can shift the incentive structure towards more transparent and neutral simulation studies, and away from the "one method fits all data sets" philosophy (Strobl and Leisch, 2022).

5 Conclusions

Simulation studies should be viewed and treated analogously to (empirical) experiments from other fields of science. Transparent reporting of methodology and results is essential to contextualize the outcome of such a study. As in other empirical sciences, QRPs in simulation studies can obfuscate the usefulness of a novel method and lead to misleading and non-replicable results.

By deliberately using several QRPs we were able to present a method with no expected benefits and little theoretical justification – invented solely for this article – as an improvement over theoretically and empirically well-established competitors. While such intentional engagement in these practices is far from the norm, unintentional QRPs may have the same detrimental effect. We hope that our illustration will increase awareness about the fragility of findings from simulation studies and the need for higher standards.

While this article focuses on comparative simulation studies, many of the issues and recommendations also apply to neutral comparison studies with real data sets as discussed in Nießl et al. (2021). Some of the noted problems even exist in theoretical research; due to the incentive to publish positive results, researchers often selectively study optimality conditions of methods rather than conditions under which they fail.

Again, it is imperative to note that researchers rarely engage in QRPs with malicious intent but because humans tend to interpret ambiguous information self-servingly, and because they are good at finding reasonable justifications that match their expectations and desires (Simmons et al., 2011). As in other domains of science, it is easier to publish positive results in methodological research, that is, novel and superior methods (Boulesteix et al., 2015). Thus, methodological researchers will typically desire to show the superiority of a method rather than to neutrally disclose its strengths and weaknesses.

We provide several recommendations involving various stakeholders in the research community which we believe may help incentivize researchers to perform well-designed simulation studies. Most importantly, we think that reviewers, journals and funders should raise the standards for simulation studies by promoting pre-registered simulation protocols and rewarding researchers who invest the extra effort. Although there is evidence for the effectiveness of protocols in preventing QRPs in other fields, it is unclear whether this effect translates to simulation studies. Indeed, there are many reasons to believe that simulation studies will not benefit in a similar way as studies with human or animal subjects, due to the nature of simulations studies. For instance, requiring pre-registered protocols cannot prevent researchers engaging in QRPs until they find their desired results and only then writing and registering a protocol. In addition, there is currently no tradition of pre-registration in simulation studies, no best-practices guidance and no dedicated platform to publish protocols. For example, Kipruto and Sauerbrei (2022) published the pre-registration of their simulation protocol as a journal article, whereas the pre-registration of the protocol from our study was uploaded to GitHub. Both protocols use the ADEMP reporting structure from Morris et al. (2019), yet the field could benefit from reporting guidelines developed by a consortium of simulation experts similar to the guidelines for health research promoted by the EQUATOR Network (Altman et al., 2008). Similarly, the field could benefit from a centralized pre-registration platform tailored to simulation studies (similar to `https://clinicaltrials.gov` for clinical trials). Regardless of the (unknown) effectiveness of pre-registered simulation protocols, we personally think that they are an important step toward improving simulation studies since they promote a minimum degree of transparency and credibility. For this reason, we think that they are especially important for "late-stage" methodological studies (Heinze et al., 2022) where the objective is to neutrally compare different methods and generate robust evidence.

Software and data

The simulation study was conducted in the R language for statistical computing (R Core Team, 2022) using the version 4.1.1. The method AINET is implemented in the `ainet` package and available on GitHub (`https://github.com/LucasKook/ainet`). We provide scripts for reproducing the different simulation studies on the GitHub repository (`https://github.com/SamCH93/SimPaper`). Due to the computational overhead, we also provide the resulting data so that the analyses can be conducted without rerunning the simulations. We used `pROC` version 1.18.0 to compute the AUC (Robin et al., 2011). Random forests were fitted using `ranger` version 0.13.1 (Wright and Ziegler, 2017). For penalized likelihood methods, we used `glmnet` version 4.1.2 (Friedman et al., 2010; Simon et al., 2011). The `SimDesign` package version 2.7.1 was used to set up simulation scenarios (Chalmers and Adkins, 2020).

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A Simulation protocol

Below, we include an excerpt of the final version of the protocol for the simulation-based evaluation of AINET. All time-stamped versions of the protocol are available at https://doi.org/10.5281/zenodo.6364575.

A.1 Aims

The aim of this simulation study is to systematically study the predictive performance of AINET for a binary prediction task. The simulation conditions should resemble typical conditions found in the development of prediction models in biomedical research. In particular we want to evaluate the performance of AINET conditional on

- low- and high-dimensional covariates
- (un-)correlated covariates
- small and large sample sizes
- varying baseline prevalences

AINET will be compared to other (penalized) binary regression models from the literature, namely

- Binary logistic regression: the simplest and most popular method for binary prediction
- Elastic net: a generalization of LASSO and ridge regression, the most widely used penalized regression methods
- Adaptive elastic net: a generalization of the most popular weighted penalized regression method (adaptive LASSO)
- Random forest: a popular, more flexible method. This method is related to AINET, see Section A.4.

These cover a wide range of established methods with varying flexibility and serve as a reasonable benchmark for AINET. There are many more extensions of the adaptive elastic net in the literature (see e. g., the review by Vidaurre et al., 2013). However, most of these extensions focus on variable selection and estimation instead of prediction, which is why we restrict our focus only on the four methods above.

A.2 Data-generating process

In each simulation $b = 1, \ldots, B$, we generate a data set consisting of n realizations, i. e., $\{(y_i, \boldsymbol{x}_i)\}_{i=1}^{n}$. A datum $(Y, \boldsymbol{X})$ consists of a binary outcome $Y \in \{0, 1\}$ and p-dimensional covariate vector $\boldsymbol{X} \in \mathbb{R}^p$. The binary outcomes are generated by

$$Y \mid \boldsymbol{x} \sim \text{Bernoulli}\left(\text{expit}\left\{\beta_0 + \boldsymbol{x}^\top \boldsymbol{\beta}\right\}\right)$$

with $\text{expit}(z) = (1 + \exp(-z))^{-1}$ and the covariate vectors are generated by

$$\boldsymbol{X} \sim \text{N}_p\left(0, \Sigma\right)$$

with covariance matrix Σ that may vary across simulation conditions (see below). The baseline prevalence is $\text{prev} = \text{expit}(\beta_0)$. The coefficient vector $\boldsymbol{\beta}$ is generated from

$$\boldsymbol{\beta} \sim \text{N}_p(0, \text{Id})$$

once per simulation. Finally, the simulation parameters are varied fully factorially (except for the removal of some unreasonable conditions) as described below, leading to a total of 128 scenarios, see below.

Sample size

The sample size used in the development of predictions models varies widely (Damen et al., 2016). We will use $n \in \{100, 500, 1000, 5000\}$, which span typical values occurring in practice. Note that previous simulation studies usually chose sample size based on the implied number of events together with the number of covariates in the model for easier interpretation (van Smeden et al., 2018; Riley et al., 2018). We will use this approach in reverse to determine the dimensionality of the parameters below.

Dimensionality

Previous simulation studies showed that events per variable (EPV) rather than the absolute sample size n and dimensionality p influences the predictive performance of a method. We will therefore define the dimensionality p via EPV by

$$p = \frac{n \cdot \text{prev}}{\text{EPV}}$$

and $2 \leq p \leq 100$. If the above formula gives non-integer values, the next larger integer will be used for p. When the formula gives values above 100 or below 2, this simulation condition will be removed from the design. This is done because prediction models are in practice only multivariable models ($p \geq 2$), but at the same time the number of predictors is rarely larger than $p \geq 100$ (Kreuzberger et al., 2020; Seker et al., 2020; Wynants et al., 2020). The exception are studies considering complex data, such as images, omics, or text data which are not the focus here. The values $\text{EPV} \in \{20, 10, 1, 0.5\}$ are chosen to cover scenarios with small to large number of covariates (see van Smeden et al., 2018).

Collinearity in X

We distinguish between no, low, medium and high collinearity. The diagonal elements of Σ are given by $\Sigma_{ii} = 1$ and the off-diagonal elements are set to $\Sigma_{ij} = \rho$, $\rho \in \{0, 0.3, 0.6, 0.95\}$. These values cover the typical (positive) range of correlations.

Baseline prevalence

Different baseline prevalences $\text{expit}(\beta_0) \in \{0.01, 0.05, 0.1\}$ are considered, reflecting a reasonable range of prevalences for rare to common diseases/adverse events.

Test data

In order to test the out-of-sample predictive performance, we generate a test data set of $n_{\text{test}} = 10000$ data points in each simulation b.

A.3 Estimands

We will estimate different quantities to evaluate overall predictive performance, calibration, and discrimination, respectively. All methods will be evaluated on independently generated test data.

Primary estimand

- **Brier score.** We compute the Brier score as

$$\overline{\text{BS}} = n_{\text{test}}^{-1} \sum_{i=1}^{n_{\text{test}}} (y_i - \hat{y}_i)^2,$$

  where $\hat{y} = \widehat{\mathbb{P}}(Y = 1 \mid \boldsymbol{x})$. Lower values indicate better predictive performance in terms of calibration and sharpness. A prediction is well-calibrated if the observed proportion of events is close to the predicted probabilities. Sharpness refers to how concentrated a predictive distribution is (e. g., how wide/narrow a prediction interval is), and the predictive goal is to maximize sharpness subject to calibration (Gneiting, 2008). The Brier score is a proper scoring rule, meaning that it is minimized if a predicted distribution is equal to the data-generating distribution (Gneiting and Raftery, 2007). Proper scoring rules thus encourage honest predictions. The Brier score is therefore a principled choice for our primary estimand.

Secondary estimands

- **Scaled Brier score.** The scaled Brier score (also known as Brier skill score) is computed as
$$\overline{\text{BS}}^* = 1 - \overline{\text{BS}} \,/\, \overline{\text{BS}}_0$$
with $\overline{\text{BS}}_0 = \bar{y}(1-\bar{y})$ and $\bar{y}$ the observed prevalence in the data set. The scaled Brier score takes into account that the prevalence varies across simulation conditions. Hence, the scaled Brier score can be compared between conditions (Schmid and Griffith, 2005; Steyerberg, 2019).

- **Log-score.** We compute the log-score on independently generated test data,
$$\overline{\text{LS}} = -n_{\text{test}}^{-1} \sum_{i=1}^{n_{\text{test}}} \{y_i \log(\hat{y}_i) + (1-y_i)\log(1-\hat{y}_i)\},$$
will be used as a secondary measure of overall predictive performance. Lower values indicate better predictive performance in terms of calibration and sharpness. The log-score is a strictly proper scoring rule, however, it is more sensitive to extreme predicted probabilities compared to the Brier score (Gneiting and Raftery, 2007).

- **AUC.** The AUC is given by
$$\text{AUC} = \max\{\text{PI}, 1-\text{PI}\}$$
with
$$\text{PI} = \widehat{\mathbb{P}}(Y_i \geq Y_j \,|\, \boldsymbol{x}_i, \boldsymbol{x}_j),\ i,j = 1,\ldots,n_{\text{test}},$$
where Y_i and Y_j denote case and non-case, respectively. The AUC is related to the area under the receiver-operating-characteristic (ROC) curve (Steyerberg, 2019). It will be used as a measure of discrimination and values closer to one indicate better discriminative ability. Discrimination describes the ability of a prediction model to discriminate between cases and non-cases. Other discrimination measures, such as accuracy, sensitivity, specificity, etc., are not considered because we want to evaluate predictive performance in terms of probabilistic predictions instead of point predictions/classification.

- **Calibration slope $\hat{b}$.** The calibration slope $\hat{b}$ is obtained by regressing the test data outcomes y_{test} on the models' predicted logits $\text{logit}(\hat{y})$, i. e.,
$$\text{logit}\,\mathbb{E}[Y \,|\, \hat{y}] = a + b\,\text{logit}(\hat{y}).$$
This measure will be used to assess calibration and deviations of $\hat{b}$ from one indicate miscalibration (Steyerberg, 2019).

- **Calibration in the large $\hat{a}$.** We inspect calibration in the large $\hat{a}$ on independently generated test data, from the model
$$\text{logit}\,\mathbb{E}[Y \,|\, \hat{y}] = a + \text{logit}(\hat{y}).$$
This measure will also be used to assess calibration and deviations of $\hat{a}$ from zero indicate miscalibration (Steyerberg, 2019).

To facilitate comparison between simulation conditions, all estimands will also be corrected by the oracle version of the estimand, e. g., the Brier score will be computed from the ground truth parameters and the simulated data $\boldsymbol{x}$, subsequently the oracle Brier score will be subtracted from the estimated Brier score.

A.4 Methods

AINET

We now present the mock-method and give a superficial motivation why it could lead to improved predictive performance: Choosing the vector of penalization weights in the adaptive LASSO becomes difficult in high-dimensional settings. For instance, using absolute LASSO estimates as penalization weights omits the importance of several predictors by not selecting them, especially in the case of highly correlated predictors (Algamal and Lee, 2015). The adaptive importance elastic net (AINET) circumvents this problem by employing a random forest to estimate the penalization weights via an *a priori* chosen variable importance measure. In this way, the importance of all variables enter the penalization weights simultaneously.

The penalized log-likelihood for AINET for a single observation $(y, \boldsymbol{x})$ is defined as

$$\ell_{\text{AINET}}(\beta_0, \boldsymbol{\beta}; y, \boldsymbol{x}, \alpha, \lambda, \boldsymbol{w}) = \ell(\beta_0, \boldsymbol{\beta}; y, \boldsymbol{x}) + \lambda \left(\alpha \sum_{j=1}^{p} w_j |\beta_j| + \frac{1}{2}(1-\alpha) \sum_{j=1}^{p} w_j \beta_j^2 \right)$$

where

$$\ell(\beta_0, \boldsymbol{\beta}; y, \boldsymbol{x}) = y \log \left(\text{expit} \left\{ \beta_0 + \boldsymbol{x}^\top \boldsymbol{\beta} \right\} \right) + (1-y) \log \left(1 - \text{expit} \left\{ \beta_0 + \boldsymbol{x}^\top \boldsymbol{\beta} \right\} \right)$$

denotes the log-likelihood of a binomial GLM and $\boldsymbol{w}$ is derived from a random forest variable importance measure IMP as

$$w_j = 1 - \left(\frac{\text{IMP}_j}{\sum_{k=1}^{p} \text{IMP}_k} \right)^{\gamma},$$

where we transform IMP to be non-negative via

$$\text{IMP}_j = \max\{0, \widetilde{\text{IMP}}_j\}$$

and γ is a hyperparameter for the influence of the weights similar to γ hyperparameter of the adaptive elastic net. AINET is fitted by maximizing its penalized log-likelihood assuming i.i.d. observations $\{(y_i, \boldsymbol{x}_i)\}_{i=1}^{n}$, i. e.,

$$\arg\max_{\beta_0, \boldsymbol{\beta}} \sum_{i=1}^{n} \ell_{\text{AINET}}(\beta_0, \boldsymbol{\beta}; y_i, \boldsymbol{x}_i, \alpha, \lambda, \boldsymbol{w}).$$

Per default, we choose mean decrease in the Gini coefficient for $\widetilde{\text{IMP}}$. Hyperparameters of the random forest are not tuned, but kept at their default values (e. g., `mtry`, `ntree`). The hyperparameter $\gamma = 1$ will stay constant for all simulations.

AINET is supposed to seem like a reasonable method at first glance. However, AINET cannot be expected to share desirable theoretical properties with the usual adaptive LASSO, such as oracle estimation (Zou, 2006). This is because the penalization weights $\boldsymbol{w}$ do not meet the required consistency assumption. Also in terms of prediction performance, AINET is not expected to outperform methods of comparable complexity.

Benchmark methods

- **Binary logistic regression** (McCullagh and Nelder, 1989) with and without ridge penalty for high- and low-dimensional settings, respectively. In case a ridge penalty is needed, it is tuned via 5-fold cross-validation by following the "one standard error" rule as implemented in **glmnet** (Friedman et al., 2010).
- **Elastic net** (Zou and Hastie, 2005), for which the penalized log-likelihood is given by

$$\ell_{\text{EN}}(\beta_0, \boldsymbol{\beta}; y, \boldsymbol{x}, \alpha, \lambda) = \ell(\beta_0, \boldsymbol{\beta}; y, \boldsymbol{x}) + \lambda \left(\alpha \sum_{j=1}^{p} |\beta_j| + \frac{1}{2}(1-\alpha) \sum_{j=1}^{p} \beta_j^2 \right).$$

  Here, α and λ are tuned via 5-fold cross-validation by following the "one standard error" rule.
- **Adaptive elastic net** (Zou, 2006), with penalized loss function

$$\ell_{\text{adaptive}}(\beta_0, \boldsymbol{\beta}; y, \boldsymbol{x}, \alpha, \lambda, \boldsymbol{w}) = \ell(\beta_0, \boldsymbol{\beta}; y, \boldsymbol{x}) + \lambda \left(\alpha \sum_{j=1}^{p} w_j |\beta_j| + \frac{1}{2}(1-\alpha) \sum_{j=1}^{p} w_j \beta_j^2 \right).$$

  Here, the penalty weights $\boldsymbol{w}$ are inverse coefficient estimates from a binary logistic regression

$$\hat{w}_j = |\hat{\vartheta}_j|^{-\gamma},$$

  where λ and α are tuned via 5-fold cross-validation by following the "one standard error" rule. The hyperparameter $\gamma = 1$ will stay constant for all simulations. In case $p > n$, we estimate the penalty weights using a ridge penalty, tuned via an additional nested 5-fold cross-validation by following the "one standard error" rule.
- **Random forests** (Breiman, 2001) for binary outcomes without hyperparameter tuning. The default parameters of **ranger** will be used (Wright and Ziegler, 2017).

A.5 Performance measures

The distribution of all estimands from Section A.3 will be assessed visually with box- and violin-plots that are stratified by method and simulation conditions. We will also compute mean, median, standard deviation, interquartile range, and 95% confidence intervals for each of the estimands. Moreover, instead of "eye-balling" differences in predictive performance across methods and conditions, we will formally assess them by regressing the estimands on

the method and simulation conditions (see Skrondal, 2000). To do so, we will use a fully interacted model with the interaction between the methods and the 128 simulations conditions, i. e., in R notation: `estimand ~ 0 + method:scenario`. We will rank pairwise comparison between two methods within a single condition by their p-values, to more easily identify conditions where methods show differences in predictive performance. The choice of a significance level at which a method is deemed superior will be determined based on preliminary simulations. We set this level to 5%, where p-values will be adjusted using the single-step method (Hothorn et al., 2008) within a single simulation condition for comparisons between AINET and any other method.

A.6 Determining the number of simulations

We determine the number of simulation B such that the Monte Carlo standard error of the primary estimand, the mean Brier score $\overline{\text{BS}}$, is sufficiently small. The variance of $\overline{\text{BS}}$ is given by

$$\text{Var}\left(\overline{\text{BS}} / B\right) = \frac{\text{Var}\left\{(y - \hat{y})^2\right\}}{B \cdot n_{\text{test}}}$$

and $\text{Var}\left\{(y_{ib} - \hat{y}_{ib})^2\right\}$ could be decomposed further (Bradley et al., 2008). However, the resulting expression is difficult to evaluate for our data-generating process as it depends on several of the simulation parameters. We therefore follow a similar approach as in Morris et al. (2019) and estimate $\widehat{\text{Var}}\left\{(y_{ib} - \hat{y}_{ib})^2\right\} < V$ from an initial small simulation run with 100 simulations per condition to get an upper bound V for worst-case variance across all simulation conditions. Therefore, the number of simulations is then given by

$$B = \frac{V}{n_{\text{test}} \text{Var}\left(\overline{\text{BS}}\right)}.$$

Since $\overline{\text{BS}} \in [0, 1]$ we decide that we require the Monte Carlo standard error of $\overline{\text{BS}}$ to be lower than four significant digits, 0.0001.

The initial simulation run led to an estimated worst case variance of $\widehat{V} = 0.2$. Therefore, we compute that

$$B = 0.2 / (10000 \times 0.0001^2) = 2000$$

replications are required to obtain Brier score estimates with the desired precision.

A.7 Handling exceptions

It is inevitable that convergence issues and other problems will arise in the simulation study. We will handle them as follows:

- If a method fails to converge, the simulation will be excluded from the analysis. The failing simulations will not be replaced with new simulations that successfully converge as convergence may be impossible for some scenarios.

- We will report the proportion of simulations with convergence issues for each method and discuss the potential reasons for their emergence.
- In case of severe convergence issues or other problems (more than 10% of the simulations failing within a setting), we may adjust the simulation parameters post hoc. This will be indicated in the discussion of the results.
- Convergence may be possible for certain tuning parameters of a method (e. g., cross-validation of LASSO may fail for some values λ while it could work for others). In this case we will choose a parameter value where the method still converges, as one would usually do with a real data set.

B Pre-registered simulation results

Here, we describe the outcomes of the pre-registered simulations. Overall, the performance of AINET was virtually identical to elastic net regression. The adaptive penalization weights of AINET do not seem to make a difference for the data generating mechanism considered in our simulations. Moreover, since the data were generated under a process equivalent to a logistic regression model, it is no surprise that for reasonably large sample sizes, logistic regression also performed the best. The only exception are conditions with small sample size and low number of events per variable. Here, AINET and elastic net led to more stable and better calibrated predictions than logistic regression. The random forest was outperformed by AINET in most simulation conditions, with exception of very small sample size and prevalence, as well as when a high correlation between covariates was present. Finally, the performance of the adaptive elastic net was generally worse compared to AINET and elastic net. In the following, we summarize the results for each estimand.

B.1 Brier score (primary estimand)

Figure 3 shows the differences in mean Brier score between AINET and the other methods stratified by simulation conditions. We see that there is hardly any difference between AINET and the elastic net (EN) across all simulation conditions meaning that predictive performance of both methods seems to be very similar in the investigated scenarios.

The random forest (RF) shows better predictive performance than AINET in conditions with very low sample size ($n = 100$) and prevalence (prev $= 0.01$). For increasing sample size and prevalence, the performance of AINET seems to become more similar or improve over RF when the correlation of the covariates is not too large ($\rho \leq 0.6$) especially for low events per variable (EPV ≤ 1). For highly correlated covariates ($\rho = 0.95$), the performance of AINET is similar or worse across most simulation conditions.

Logistic regression (GLM) showed better predictive performance compared to AINET in most simulation conditions. An exception are the conditions with small sample size ($n = 100$), medium to large prevalence (prev ≥ 0.05) and low events per variable (EPV ≤ 1), where AINET performed better than GLM.

The adaptive elastic net (AEN) method performed worse than AINET in almost all simulation conditions. Only in conditions with very large sample size ($n = 5000$), very small prevalence (prev $= 0.01$), and high events per variable (EPV $= 20$), AEN showed predictive performance on par with AINET.

B.2 Scaled Brier score (secondary estimand)

Figure 4 shows the differences in scaled Brier score between AINET and the other methods stratified by simulation conditions. The scaled Brier score is useful to compare the actual values of Brier scores across conditions with different prevalence, but not so much to compare Brier scores of different methods within a simulation condition with fixed prevalence.

We see that for most conditions the plots look like a flipped version of the original Brier scores from Figure 3. Therefore, conclusions are mostly the same. For very small sample sizes coupled with low prevalence and low events per variable (the topleft plots), the scaled Brier score indicates superiority of AINET over RF and GLM, which is opposite the conclusion based on the raw Brier score. We advise to interpret these conditions cautiously since the prevalence prediction which is used for scaling is based on the much larger test data set.

B.3 Log-score (secondary estimand)

Figure 5 shows the differences in log-score between AINET and the other methods stratified by simulation conditions. We see that in certain conditions, the error bars of certain methods are much larger. This is due to the log-score's sensitivity to extreme predictions, which often happen under the RF (and sometimes under the GLM). Despite the larger variability of the log-score, conclusion regarding the comparison between AINET and the other methods are largely the same as under the Brier score.

B.4 Area under the curve (secondary estimand)

Figure 5 shows the differences in area under the curve (AUC) between AINET and the other methods stratified by simulation conditions. As with the other estimands, AINET shows virtually identical performance as EN regression across all simulation conditions. AINET seems to outperform RF across most simulation conditions, with the exception of a conditions with low sample size ($n = 100$), medium prevalence (prev $= 0.05$), and low events per variable (EPV ≤ 1). GLM, typically outperforms AINET conditions with small to medium sample size ($n \leq 500$), and also in conditions with larger sample size when the events per variable is normal to high (EPV ≥ 10) and the prevalence is small (prev $= 0.01$). Finally, the AEN is worse with respect to AUC than AINET across all simulation conditions.

B.5 Calibration slope (secondary estimand)

Figure 6 shows boxplots of calibration slopes stratified by simulation condition and method. For each condition the percentage of simulations where no estimate could be obtained is indicated. This usually happened because of extreme (close to zero or one) predictions, or non-convergence of the method itself. We caution against interpretation of the random forest (RF) calibration slopes because this method often resulted in predicted probabilities of zero or one, so that a calibration slope could not be fitted.

We see that logistic regression (GLM) shows on average optimal calibration slopes in most simulation condition. In cases where it is off one, its calibration slopes are usually too small indicating overoptimistic predictions. In general, worse calibration slopes are obtained for lower event per variable (EPV).

The penalized methods (AINET, EN, AEN) show a more stable behavior, and on average larger calibration slopes than GLM. This is likely confounded by the simulation conditions in which no GLM calibration slope can be estimated, but estimation of the penalized methods' calibration slope is still possible. Among the penalized method's AINET and EN shows relatively similar calibration slopes whereas the AEN shows worse calibration slopes that are more off the value of one.

B.6 Calibration in the large (secondary estimand)

Figure 7 shows boxplots of calibration in the large estimates stratified by simulation condition and method. For each condition also the percentage of simulations where no estimate could be obtained is indicated. This usually happened because of extreme (close to zero or one) predictions.

We see that the number of simulations with non-estimable calibration is substantially larger when the sample size is small, whereas it decreases for larger sample sizes. An exception is the RF where the number of non-estimable calibrations stays high across most conditions.

While all methods seem to be marginally well calibrated, the penalized methods (AINET, EN, and AEN) show lower numbers of simulations with non-estimable calibration compared to GLM, especially for low to medium sample sizes and low events per variables.

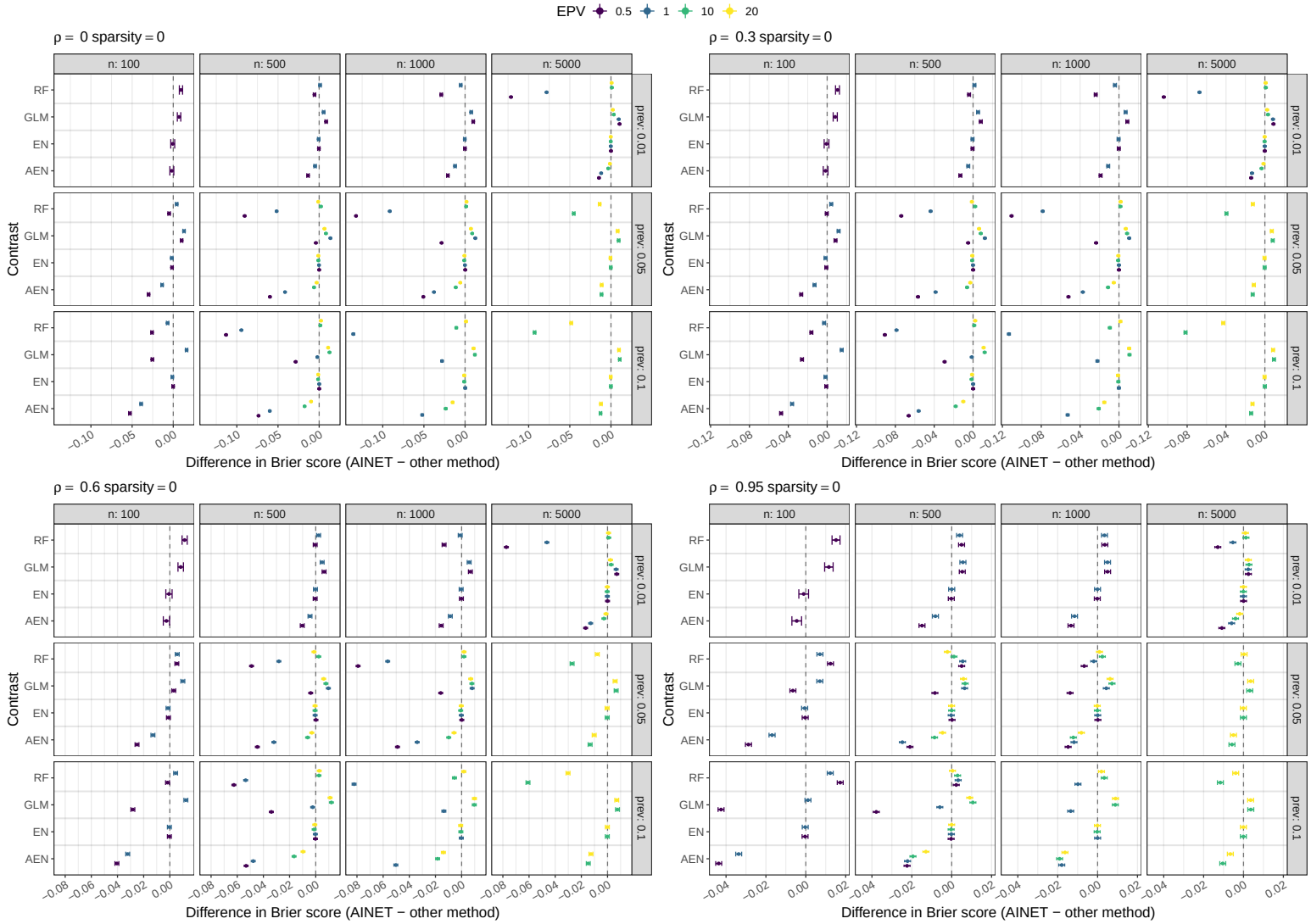

Figure 3: Tie-fighter plot for the difference in Brier score between any method on the y-axis and AINET. The 95% confidence intervals are adjusted per simulation condition using the single-step method. Lower values indicate better performance of AINET.

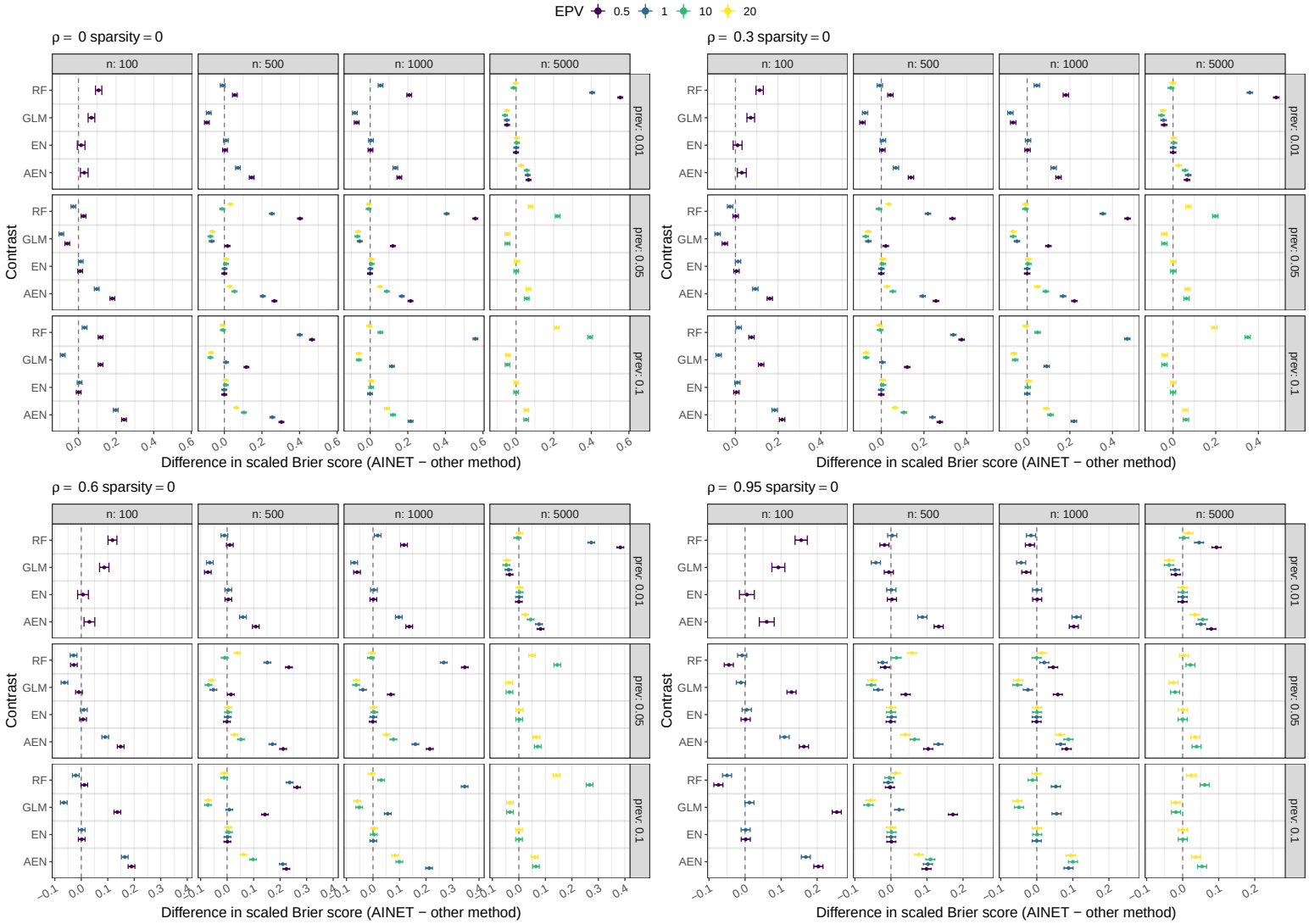

Figure 4: Tie-fighter plot for the difference in scaled Brier score between any method on the y-axis and AINET. The 95% confidence intervals are adjusted per simulation condition using the single-step method. Larger values indicate better performance of AINET.

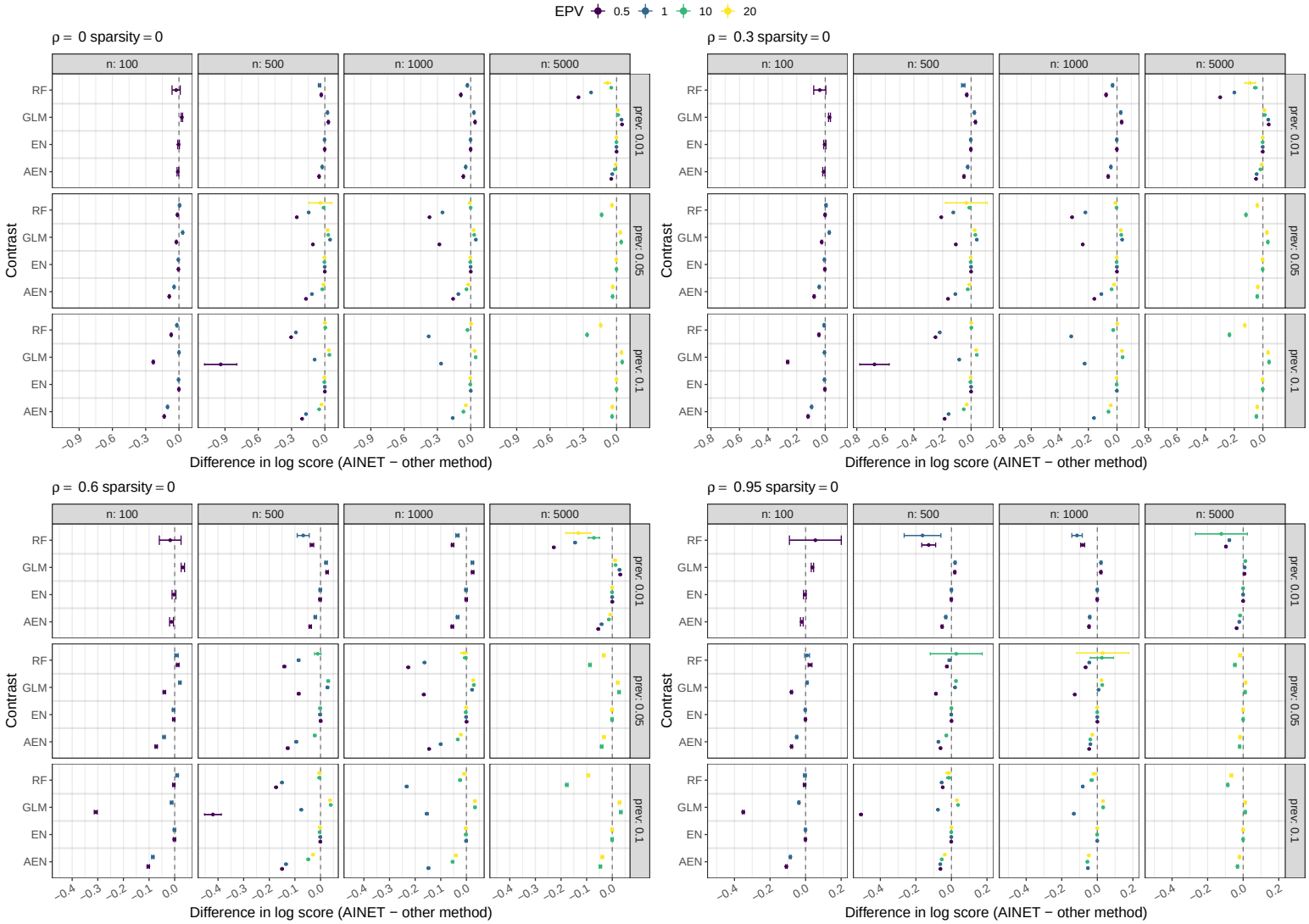

Figure 5: Tie-fighter plot for the difference in log-score between any method on the y-axis and AINET. The 95% confidence intervals are adjusted per simulation condition using the single-step method. Lower values indicate better performance of AINET.

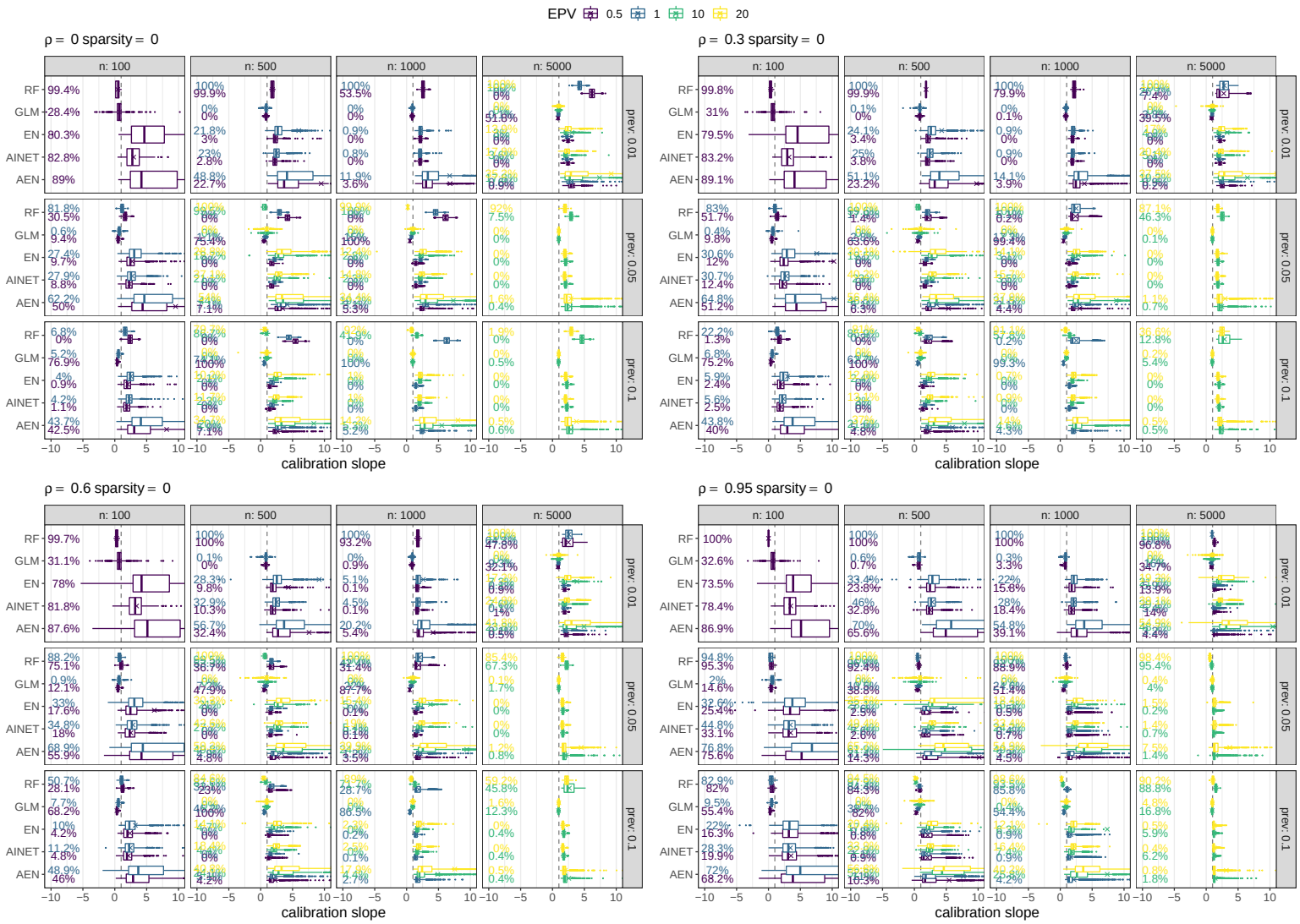

Figure 6: Boxplots of calibration slopes stratified by method and simulation conditions. Mean calibration slope is indicated by a cross. A value of one indicates optimal calibration. Percentage of simulations where calibration slope could not be estimated (due to extreme predictions or complete separation) are also indicated.

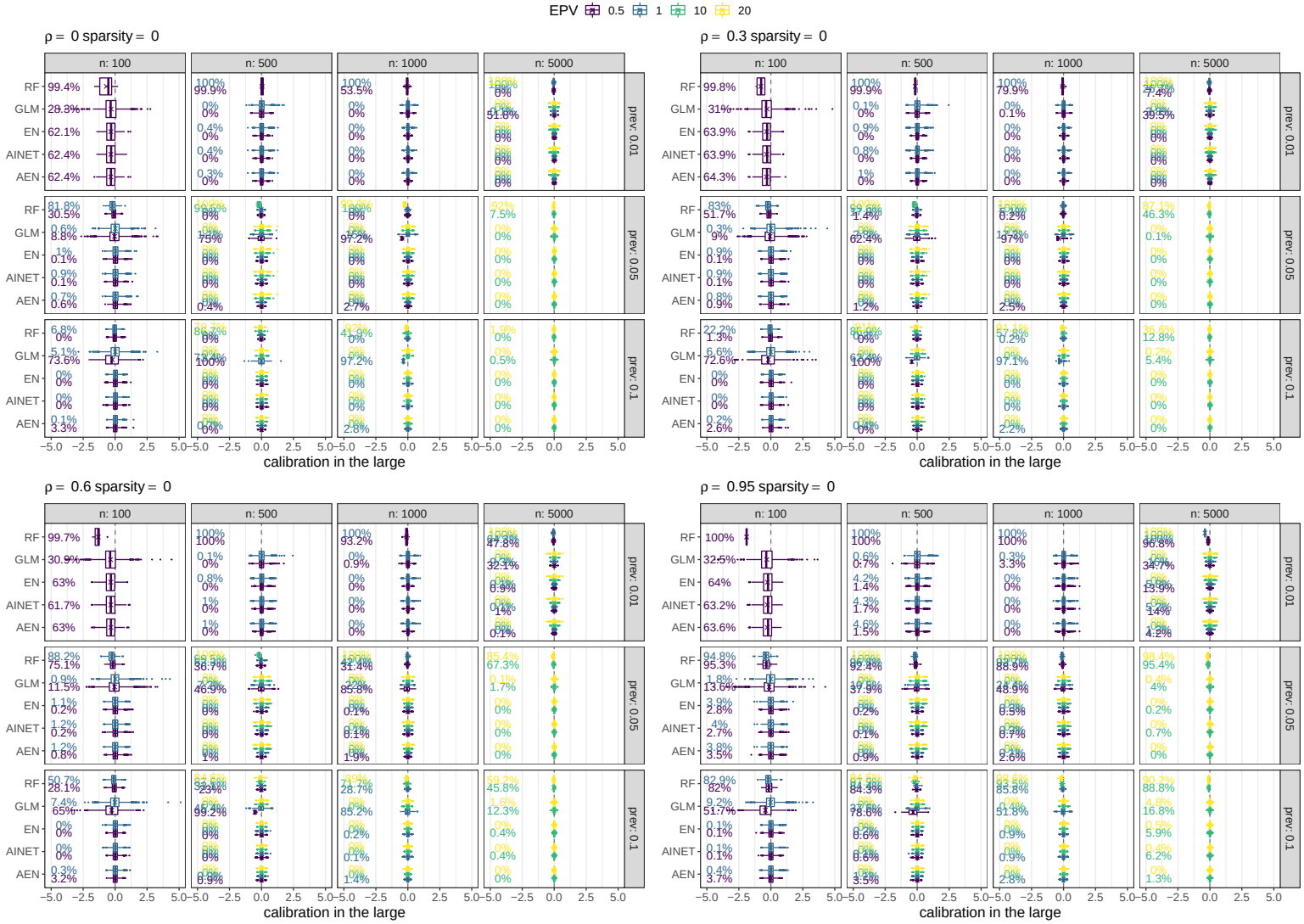

Figure 7: Boxplots of calibration in the large stratified by method and simulation conditions. Mean calibration in the large is indicated by a cross. A value of zero indicates optimal calibration in the large. Percentage of simulations where calibration in the large could not be estimated (due to extreme predictions or complete separation) are also indicated.

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