

Mitigating Publication Bias Using Bayesian Stacking

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1 Introduction

Results from a meta-analysis may be skewed and unreliable in the presence of publication bias, where the publication or non-publication of a study depends on the statistical significance or magnitude of its results (Rothstein et al., 2006). Statistical methods for publication bias have been designed for sensitivity analysis, testing for the presence/magnitude of publication bias, and calculating bias-corrected parameter estimates. Most methods are either based on the funnel plot or selection models.

Methods based on the funnel plot (Light and Pillemer, 1984) – a scatterplot of effect sizes against their standard errors – inspect the plot’s asymmetry to test or correct for bias. Say y_i and $v_i = s_i^2$ are estimated effect sizes and their sampling variances for S studies, $i = 1, \dots, S$. A popular non-parametric test for publication bias (Begg and Mazumdar, 1994) measures the rank correlation between standardized

observed effect sizes y_i^* and the effect sizes' variances v_i , where

$$\begin{aligned} y_i^* &= (y_i - \bar{y}) / (v_i^*)^{1/2} \\ \bar{y} &= \left(\sum_j (v_j^{-1}) / y_j \right) / \left(\sum_j v_j^{-1} \right) \\ v_i^* &= v_i - \left(\sum_j v_j^{-1} \right)^{-1}. \end{aligned}$$

Begg and Mazumdar (1994) measure the correlation between pairs (y_i^*, v_i) with Kendall's tau, where a symmetric funnel plot would have correlation near zero. Egger's test (Egger et al., 1997) fits a linear regression of observed standard normal deviates $\text{SND}_i = y_i / s_i$ against the inverse standard errors $1/s_i$, i.e. $\text{SND}_i = \alpha + \beta \times (1/s_i)$ with the null hypothesis $H_0 : \alpha = 0$. Other regression methods (Macaskill et al., 2001; Rücker et al., 2008; Thompson and Sharp, 1999; Peters et al., 2006) are similar to Egger's test and use regression weights or transformations to improve upon Egger's test in the presence of heterogeneity or for dichotomous outcomes (Jin et al., 2015). Lin and Chu (2018) develops a measure for the severity of publication bias based on the skewness of standardized deviates. The trim-and-fill method (Duval and Tweedie, 2000) calculates an adjusted mean effect estimate in a series of steps, by 1) estimating the number of missing studies k_0 , 2) "trimming" the smaller studies that are causing funnel plot asymmetry, 3) estimating the true mean effect with the remaining studies, and 4) replacing trimmed studies and their missing counterparts and re-estimating the mean effect and its variance. However, Duval and Tweedie (2000) recommend using trim-and-fill as a sensitivity analysis based on the *potential* number of missing studies, with general guidelines for sensitivity analysis given in Shi and Lin (2019). The trim-and-fill method is the only funnel plot-based method that offers an adjusted mean estimate, and it is not recommended if there is heterogeneity in study effects (Jin et al., 2015).

A second class of methods is based on *selection models*, first described in Hedges

(1984). Let Y be a random variable representing effect sizes for all studies in a population. Selection models assume a biased sampling scheme where the probability of a study being observed (published) is represented by a weight function $w(y; \lambda)$, where λ , a scalar or vector parameter, determines how certain studies may be more or less likely to be published. The weighted density for observed effect y_i is then

$$f^*(y_i; \Theta, \lambda) = \frac{f(y_i; \Theta)w(y_i; \lambda)}{\int f(y; \Theta)w(y; \lambda)dy} \quad (1.1)$$

and the likelihood function for all observed studies is

$$L(\Theta, \lambda) = \prod_{i=1}^S f^*(y_i; \Theta, \lambda). \quad (1.2)$$

Some models explicitly model the probability of publication for individual studies as a function of their p-values (Iyengar and Greenhouse, 1988; Hedges, 1992; Givens et al., 1997; Vevea and Hedges, 1995) or as a function of both the effect size and standard error (Copas, 1999; Copas and Shi, 2000, 2001). Earlier selection models were recommended for bias-corrected effect size estimates, and were later recommended only for sensitivity analyses because of identifiability issues in smaller meta-analyses (Veeva and Woods, 2005; Jin et al., 2015). Sensitivity analyses use a grid representing varying levels of publication bias and estimate the mean effect under each assumed scenario. If results do not change much under severe publication bias they are considered robust, and if results do change under mild publication bias they are considered sensitive to publication bias. Bayesian implementations of the Copas selection model (Mavridis et al., 2013; Bai et al., 2020) have again allowed for estimation of mean effect sizes.

Recent approaches to mitigating publication bias have used Bayesian model averaging (BMA) to consider a set of potential selection functions. Guan and Vandekerckhove (2016) considers four different selection functions, including a no-bias model, an extreme-bias model where results with p-values $p > \alpha$ are never published, a 1-

step function where results with $p > \alpha$ are published with some probability $\pi < 1$, and a model inspired by Givens et al. (1997) where the probability of publication decreases exponentially with p . The authors only implement the models in a fixed-effects framework. Maier et al. (2020) considers a set of 12 models, using a $2 \times 2 \times 2$ factorial design with fixed/random effects, a true null/alternative hypothesis, and the presence/absence of publication bias. The authors consider two-step and three-step selection functions based on p-values when publication bias is assumed, where the probability of publication changes at $p = 0.05$ (two-step) or at both $p = 0.05$ and $p = 0.10$ (three-step).

BMA effectively assumes that one of the considered models is the “true” model, which we call the $\mathcal{M} - \text{closed}$ setting. BMA does not perform as well under the $\mathcal{M} - \text{complete}$ or $\mathcal{M} - \text{open}$ settings, where the true data generating mechanism is too complex to implement or to put into a probabilistic framework (Clyde and Iversen, 2013). Multiple issues arise for BMA in these settings, including a) the need to specify prior model probabilities, which makes little sense when we know the true model is not in our list, and b) the model weights from BMA will converge to the 1 for the model “closest” to the true model in terms of Kullback-Leibler divergence, and 0 for all others. Bayesian stacking (Yao et al., 2018, 2021) is a related method that outperforms BMA and solves the above issues by calculating optimal weights using expected log-predictive densities and leave-one-out (LOO) cross validation.

We propose using Bayesian stacking to mitigate publication bias by incorporating multiple different selection models. Copas and Shi (2001) recommends a sensitivity analysis over a grid of possible patterns of publication bias, each of which returns a bias-adjusted mean effect size estimate. A stacked estimate of the mean effect size can be obtained through a weighted average of estimates with the weights coming from Bayesian stacking. Assumed patterns of publication bias that poorly predict

the observed data with LOO cross validation will be given little weight. We propose stacking over multiple types of models, including step functions (Hedges, 1992; Vevea and Hedges, 1995) and Bayesian Copas selection models Mavridis et al. (2013); Bai et al. (2020).

2 Methods

Say we have S studies indexed by $i = 1, \dots, S$, and each study provides an estimated effect y_i and an associated standard error s_i .

2.1 Selection models based on p -values

The first selection models for publication bias assumed the selection process was based solely on p -values. Here we consider a subset of p -value-based models that split the unit interval $[0, 1]$ into K sub-intervals, where studies with p -values that fall into different intervals have different probabilities of publication (Hedges, 1992; Vevea and Hedges, 1995; Vevea and Woods, 2005). The data model is that of a standard random effects meta-analysis: let y_1, \dots, y_S be observed effect sizes with associated standard errors s_i . We model the observed effects as

$$y_i | \theta_i \sim N(\theta_i, s_i^2) \tag{2.1}$$

$$\theta_i | \theta, \tau^2 \sim N(\theta, \tau^2) \tag{2.2}$$

where θ_i represent random study effects normally distributed around global mean θ and with variance τ^2 . Here we combine the study-specific standard errors s_i and the between-study variability τ^2 into a single residual so that

$$y_i | \theta, \tau^2 \sim N(\theta, s_i^2 + \tau^2). \tag{2.3}$$

We then define a stepped weight function $w(\cdot)$, where $w(p)$ represents the probability that a study with p -value p is observed. Dividing the unit interval into K sub-intervals with descending endpoints a_k in which the weight function $w(p)$ is constant, we have that

$$w(p_i) = \begin{cases} \omega_1 & \text{if } a_1 < p_i < 1 \\ \omega_j & \text{if } a_j < p_i < a_{j-1} \\ \omega_K & \text{if } 0 < p_i < a_{K-1} \end{cases} \quad (2.4)$$

where $a_0 = 1$ and $a_K = 0$. Say $\boldsymbol{\omega} = (\omega_1, \dots, \omega_K)$. We then have that the likelihood contribution for each observation y_i given θ , τ^2 and weight function $w(\cdot)$ is

$$f(y_i|\theta, \tau^2, \boldsymbol{\omega}) = \frac{\phi(y_i; \theta, \tau^2 + s_i^2) \times w(p_i)}{\int \phi(x; \theta, \tau^2 + s_i^2) \times w(1 - \Phi(x/2)) dx}, \quad (2.5)$$

where $\phi(x)$ and $\Phi(x)$ represent the standard normal probability density and cumulative density functions, respectively. Maier et al. (2020) place a ‘‘cumulative-Dirichlet’’ prior distribution on the weights $\boldsymbol{\omega}$, which effectively means placing a symmetric Dirichlet prior on an auxiliary parameter $\tilde{\boldsymbol{\omega}} \in (0, 1)^K$ and taking the cumulative sum

$$\begin{aligned} \tilde{\boldsymbol{\omega}} &\sim \text{Dirichlet}(\text{rep}(1, K)) \\ \boldsymbol{\omega} &= \text{cumulative-sum}(\tilde{\boldsymbol{\omega}}). \end{aligned} \quad (2.6)$$

This restricts $\boldsymbol{\omega}$ so that the K intervals in (2.4) have increasing probability of publication with decreasing p -values, and $\omega_K = 1$. The symmetric Dirichlet prior on $\tilde{\boldsymbol{\omega}}$ leads to prior means $(\frac{1}{K}, \frac{2}{K}, \dots, 1)$ for $\boldsymbol{\omega}$. Restricting $\omega_K = 1$ means each other ω_j represents the probability of publication for a study in interval j relative to the probability of publication in the lowest interval. We consider a range of possible structures for the weight function $w(p)$ by varying both the number of intervals K and the choice of cut-points a_j .

2.2 Copas selection model

The Copas selection model (Copas, 1999; Copas and Shi, 2000, 2001) assumes that the selection mechanism for publication depends study effects y_i and associated standard errors s_i instead of p -values. The data model is

$$y_i = \theta_i + s_i \epsilon_i \quad (2.7)$$

$$z_i = \gamma_0 + \frac{\gamma_1}{s_i} + \delta_i \quad (2.8)$$

$$\theta_i \sim N(\theta, \tau^2) \quad (2.9)$$

where θ_i is again study i 's true effect, θ is the global mean effect, and τ^2 describes between-study heterogeneity. The latent factor z_i models the publication process, where study i is selected (published) only if $z_i > 0$. The parameter γ_0 controls the baseline probability of publication, and γ_1 defines the relationship between the observed standard deviation s_i and the probability of publication. Usually γ_1 is assumed to be positive, so that studies with smaller standard errors are more likely to be published. The random effects (ϵ_i, δ_i) are modeled as bivariate normal

$$\begin{pmatrix} \epsilon_i \\ \delta_i \end{pmatrix} \sim N \left(\begin{pmatrix} 0 \\ 0 \end{pmatrix}, \begin{pmatrix} 1 & \rho \\ \rho & 1 \end{pmatrix} \right) \quad (2.10)$$

where $\text{corr}(\epsilon_i, \delta_i) = \rho$ measures how the probability of selection changes with observed effect sizes.

Interpretation of the parameters $(\gamma_0, \gamma_1, \rho)$ can be difficult. The marginal probability that a study with standard error s_i is published is

$$P(z_i > 0 | s_i) = \Phi\left(\gamma_0 + \frac{\gamma_1}{s_i}\right).$$

Thus, if γ_0 is large and positive then all studies are published with high probability regardless of the value of s_i . We restrict γ_1 to be positive under the assumption that larger studies are more likely to be published for various reasons (e.g. more

funding, quality of writing, etc.). Larger values of γ_1 lead to larger differences in publication probabilities for studies with different standard errors. The correlation parameter ρ is the main driver in how unadjusted estimates of θ are biased from the truth. If $\rho = 0$, then the selection process does not depend on observed effect sizes and unadjusted estimates are unbiased. Positive values of ρ indicate that observed effects y_i influence the selection process such that larger values of y_i (relative to their true mean θ_i) are being selected for, while negative values of ρ would show selection favoring larger negative values of y_i .

We consider two Bayesian adaptations of the Copas model (Mavridis et al., 2013; Bai et al., 2020), which put prior distributions on all parameters including γ_0 and γ_1 . Mavridis et al. (2013) instead places priors on the lower and upper bounds for the probability of publication, P_{low} and P_{high} , as

$$\begin{aligned} P_{\text{low}} &\sim \text{Uniform}(L_1, L_2) \\ P_{\text{high}} &\sim \text{Uniform}(U_1, U_2), \end{aligned} \tag{2.11}$$

where (L_1, L_2) and (U_1, U_2) represent plausible ranges for the probability of publication for the studies with the largest and smallest standard errors, respectively. They then transform $(P_{\text{low}}, P_{\text{high}})$ to (γ_0, γ_1) with a 1-to-1 transformation using

$$\begin{aligned} \gamma_0 + \frac{\gamma_1}{s_{\text{max}}} &= \Phi^{-1}(P_{\text{low}}) \\ \gamma_0 + \frac{\gamma_1}{s_{\text{min}}} &= \Phi^{-1}(P_{\text{high}}) \end{aligned} \tag{2.12}$$

where s_{min} and s_{max} are the smallest and largest observed standard errors in the sample of S studies. Bai et al. (2020) place priors directly on γ_0 and γ_1 as

$$\begin{aligned} \gamma_0 &\sim \text{Uniform}(-2, 2) \\ \gamma_1 &\sim \text{Uniform}(0, s_{\text{max}}). \end{aligned} \tag{2.13}$$

They reason that this range of values allows for selection probabilities between 2.5% and 99.7% by restricting most of the mass for latent variables z_i to the range

$(-2, 3)$. Priors (2.13) are meant to be default prior distributions, while (2.11) may require more problem-specific tuning, and the two priors lead to surprisingly different posterior distributions for the mean parameter θ .

2.3 Bayesian stacking

We use \mathcal{M} -open to refer to the setting in which our list of candidate models does not include the true data generating mechanism (Bernardo and Smith, 2009). Bayesian stacking (Yao et al., 2018) is an alternative to BMA that has superior performance in the \mathcal{M} -open setting. If we have K candidate models, the goal is to find the set of optimal weights $w \in \mathcal{S}_1^K$, $\mathcal{S}_1^K = \{w \in [0, 1]^K : \sum_{k=1}^K w_k = 1\}$, that maximizes a score S comparing weighted predictive distributions $p_k(\tilde{y}|y, M_k)$ to the true distribution $p_t(\tilde{y}|y)$. Rather than requiring holdout data \tilde{y} and Yao et al. (2018) replace $p(\tilde{y}|y)$ with observed values y_i and replace $p(\tilde{y}|y, M_k)$ with its corresponding leave-one-out (LOO) predictive distribution $\hat{p}_{k,-i}(y_i) = \int p(Y_i|\theta_k, M_k)p(\theta_k|y_{-i}, M_k)d\theta_k$, where M_k is model k , $k = 1, \dots, K$, and θ_k are the parameters in model k . The authors recommend the logarithmic scoring rule, which reduces the stacking problem to solving for weights w in

$$\max_{w \in \mathcal{S}_1^K} \frac{1}{n} \sum_{i=1}^n \log \sum_{k=1}^K w_k p(y_i|y_{-i}, M_k) \quad (2.14)$$

via optimization. Instead of refitting each model n times to obtain LOO distributions $p_k(y_i|y_{-i}M_k)$, Yao et al. (2018) use Pareto smoothed importance sampling (PSIS) (Vehtari et al., 2017) to obtain approximations.

After stacking weights w have been optimized, the stacked posterior distribution of θ can be obtained by taking $w_k \times T$ samples from each model k 's posterior distribution $p(\theta|y)$ for a total of T posterior samples.

Implementation of Bayesian stacking can be done using the R package 'loo'.

2.4 Stacking selection models for publication bias

It would be naive to think that either the stepped selection functions in Section 2.1 or the Copas models in Section 2.2 represent the true data generating mechanism for publication bias. As Bayesian stacking is designed to perform well in the event that our model list does not contain the true model, we propose stacking over a variety of stepped selection functions and Copas models to obtain a more robust posterior distribution for the mean parameter θ . We fit both Bayesian Copas selection models (Mavridis et al., 2013; Bai et al., 2020) and a set of stepped selection models with varying numbers of steps. As a default, we use a 1-step function with the step at $p = 0.05$, a two-step function with steps at $p = (0.05, 0.10)$, and a three-step function with steps $p = (0.05, 0.10, 0.20)$.

We fit the Copas models in JAGS (Plummer et al., 2003) as there is a straightforward Gibbs sampling routine. Writing model (2.7) - (2.9) as

$$\begin{pmatrix} y_i \\ z_i \end{pmatrix} \sim N \left(\begin{pmatrix} \theta \\ u_i \end{pmatrix}, \begin{pmatrix} \tau^2 + s_i^2 & \rho s_i \\ \rho s_i & 1 \end{pmatrix} \right) \mathbb{1}_{z_i > 0} \quad (2.15)$$

we see that we can first sample z_i from a truncated normal $z_i \sim N(u_i, 1) \mathbb{1}_{z_i > 0}$, and then sample $y_i | z_i \sim N(E(y_i | z_i), \text{Var}(y_i | z_i))$ where $E(y_i | z_i) = \theta + \rho s_i(z_i - u_i)$ and $\text{Var}(y_i | z_i) = \tau^2 + s_i^2(1 - \rho^2)$. We also need to extract the log-likelihood for each observation (y_i, s_i) in order to stack models. The model construction leads to a simple form for the log-likelihood

$$\begin{aligned} L(\theta, \tau^2, \rho, \gamma_0, \gamma_1) &= \sum_{i=1}^S \log[p(y_i | z_i > 0, s_i)] \\ &= \sum_{i=1}^S \log \left[\frac{p(z_i > 0 | y_i, s_i) f(y_i)}{p(z_i > 0 | s_i)} \right] \\ &= \sum_{i=1}^S \log(\phi(y_i; \theta, \tau^2)) - \log \Phi(u_i) + \log \Phi(v_i) \end{aligned} \quad (2.16)$$

where $\phi(y_i; \theta, \tau^2)$ represents the density at the point y_i of a normal distribution with mean θ and variance τ^2 , $\Phi(\cdot)$ represents the standard normal cumulative density function, and

$$\begin{aligned} u_i &= \gamma_0 + \frac{\gamma_1}{s_i} \\ v_i &= \frac{u_i + \tilde{\rho}_i \frac{y_i - \theta}{\sqrt{\tau^2 + s_i^2}}}{\sqrt{(1 - \tilde{\rho}_i^2)}} \\ \tilde{\rho}_i &= \frac{s_i}{(\tau^2 + s_i^2)^{1/2}} \rho. \end{aligned}$$

We fit the stepped selection models in Stan (Gelman et al., 2015) because of the ability to easily code the custom probability distribution (2.5).

3 Simulation

We assess model performance using bias, 95% interval coverage, 95% interval length, and root-mean squared error (RMSE). We use a factorial design with $\theta = (0, 0.4)$ and $\tau = 0.2$, sample $S = 30, 60, 100$ values s_i , $i = 1, \dots, S$ from a Uniform(0.2, 0.8) distribution as study-specific standard errors, and sample $\theta_i \sim N(\theta, \tau^2)$ or $\theta \sim t(\theta, \tau^2, df = 4)$ as true study effects. We then sample $y_i \sim N(\theta_i, s_i^2)$ as observed study effects. Because we propose stacking models when the true model is not in our list, we use several complex selection mechanisms that endow each study i with a probability α_i of being observed as $f(y_i, s_i, p_i)$, where $p_i = 2 \times (1 - \Phi(|y_i|/s_i))$ and a selection indicator for each study i is drawn from Bernoulli(α_i).

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