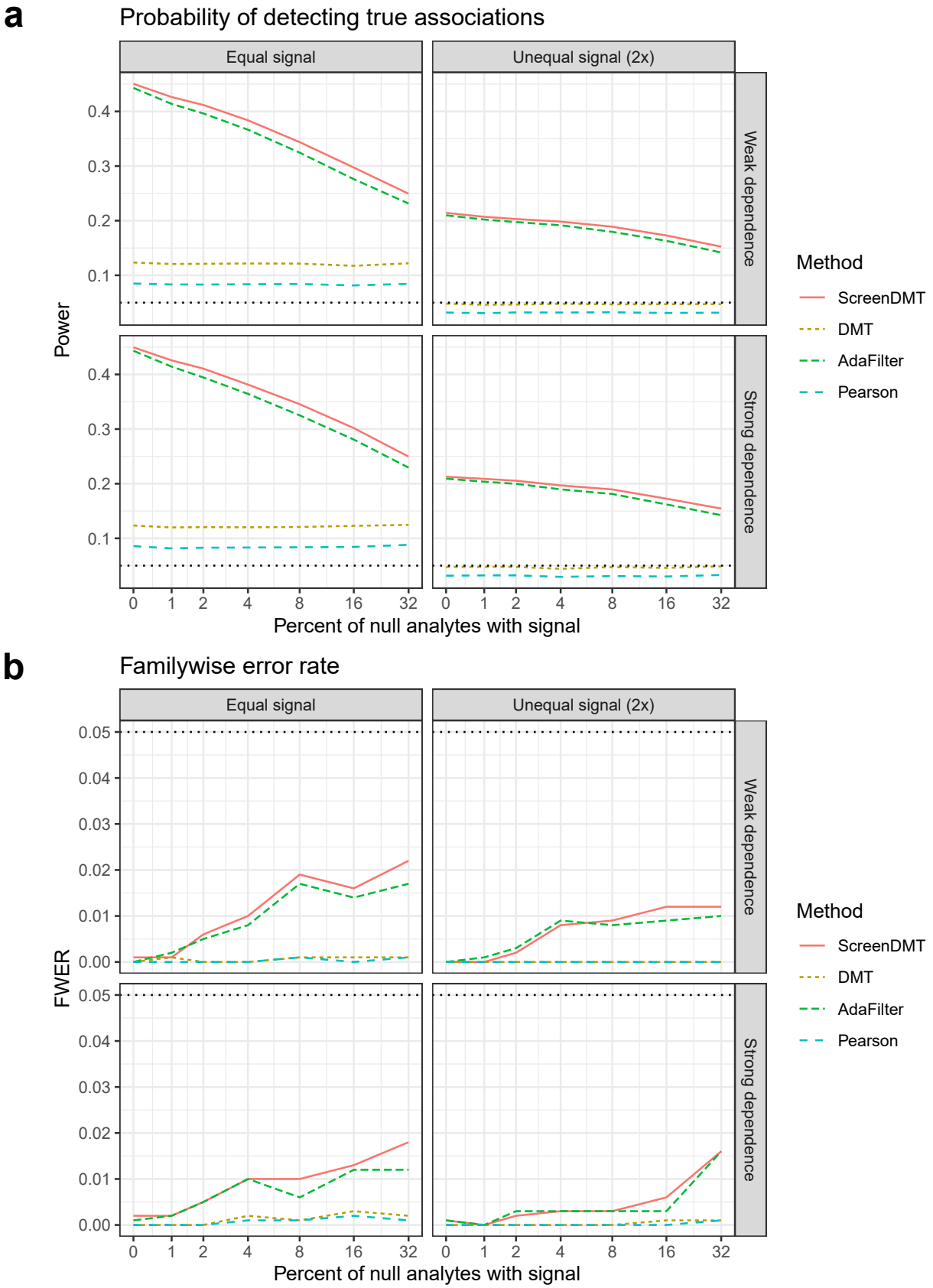


Supplementary Figure 1. Comparison of ScreenDMT's power and family-wise error rate (FWER) to competing approaches in replication of two datasets via simulation. Simulation of two datasets with strong or weak dependence between analytes when the signal strength per analyte is equal between the two datasets and when it is unequal. The x-axis represents the percent of analytes that do not truly directionally replicate but show some effect in one of the studies or show effect in both studies of opposite direction. (a) Probability of detecting true associations (power). (b) FWER. The FWER threshold is 5%.

Supplementary Note 1: ScreenDMT procedure and validation

Problem statement

Let ω_1 and ω_2 be two finite real valued parameters. In the mediation setting ω_1 and ω_2 represent the exposure-mediator and the mediator-outcome effect, while in the replication setting ω_1 and ω_2 represent parameters pertaining to the same biological entity measured in two studies. Whether we are interested in directional mediation or directional replication across two studies, without loss of generality we can consider the problem of detecting mediation in a direction consistent with the exposure increasing the outcome or replication in the same direction across two studies. Thus, we are interested in testing the directional null hypothesis:

$$H_0 : \omega_1\omega_2 \leq 0, \quad \text{against} \quad \bar{H}_0 : \omega_1\omega_2 > 0.$$

The null hypothesis can alternatively be written as:

$$H_0 : \omega_1 = 0 \text{ or } \omega_2 = 0 \text{ or } \operatorname{sign}(\omega_1\omega_2) = -1.$$

We assume that we have $\sqrt{n}_i$-consistent and asymptotically normal estimates $\hat{\omega}_i$ of ω_i for $i = 1, 2$ such that

$$\sqrt{n}_i(\hat{\omega}_i - \omega_i) \xrightarrow{d} N(0, \sigma_i^2)$$

where the convergence is convergence in distribution and $0 < \sigma_i < \infty$ for $i = 1, 2$, where σ_i is known. Then we can define component p-values P_1 and P_2 for testing $H_1 : \omega_1 = 0$ and $H_2 : \omega_2 = 0$, respectively,

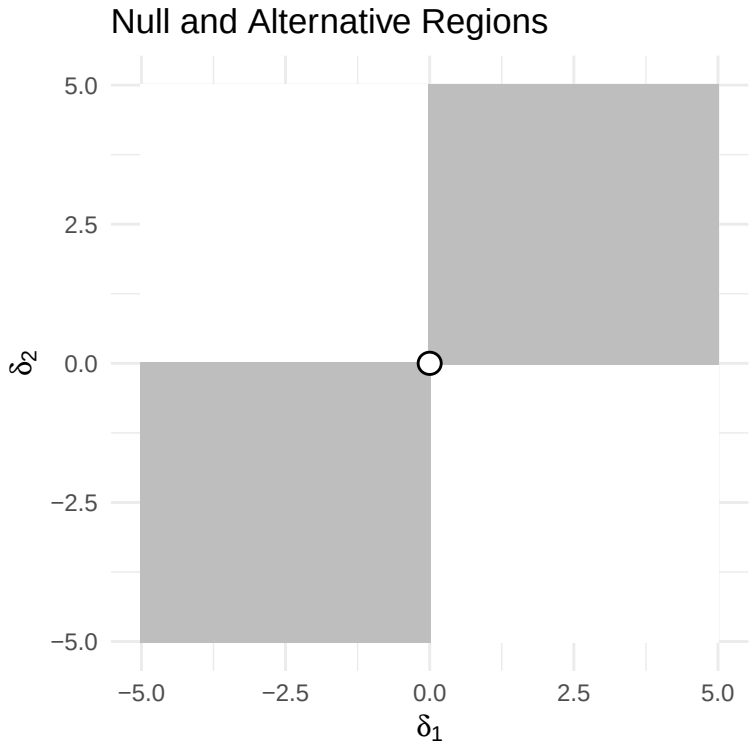
$$P_i = 2\Phi\left(-\frac{\sqrt{n}_i|\hat{\omega}_i|}{\sigma_i}\right) \tag{1}$$

where $\Phi(\cdot)$ is the standard normal cumulative distribution function. The procedures below are valid for large samples if consistent estimates of σ_i are used instead. We further assume that $\hat{\omega}_1$ and $\hat{\omega}_2$ are independent (i.e. $\hat{\omega}_1 \perp\!\!\!\perp \hat{\omega}_2$), a plausible assumption in both the mediation and the replication setting.

To simplify notation we let

$$\delta_i = \frac{\omega_i\sqrt{n}_i}{\sigma_i}$$

for $i = 1, 2$ so that Equation 1 becomes $P_i = 2\Phi\left(-|\hat{\delta}_i|\right)$. This is without loss of generality, since in any dataset $\sqrt{n}_i/\sigma_i$ is a constant coefficient of $\hat{\omega}_i$. The constant is always positive, so δ_i could replace ω_i in the problem statement. We assume ω_i and σ_i are fixed, so $|\delta_i| \to \infty$ implies $\delta_i \neq 0$ and $n_i \to \infty$. This problem's null (white) and alternative (grey) regions are shown in the figure below.



Directional MaxP test

Previous result

The following result given in Dreyfuss et al.[1] regarding the directional MaxP test introduced in the Hitman method specifies how a p-value for H_0 can be obtained from both two-sided p-values associated to the two parameters under study.

Let P_1 and P_2 be the two valid component p-values for testing $H_1 : \omega_1 = 0$ and $H_2 : \omega_2 = 0$ and let $\bar{P} = \max\{P_1, P_2\}$ and $\underline{P} = \min\{P_1, P_2\}$. Further, let $\hat{S} = \mathbb{I}(\text{sign}(\hat{\omega}_1\hat{\omega}_2) = 1)$ indicate if the signs of the estimates $\hat{\omega}_1$ and $\hat{\omega}_2$ are the same, where $\mathbb{I}(\cdot)$ is the indicator function which is one if its argument is true and zero otherwise. Then

$$P_{DMT} = \left(\frac{\bar{P}}{2}\right)^{\hat{S}}$$

is a valid p-value for testing H_0.

We showed this by demonstrating that $\mathbb{P}(P_{DMT} \leq u) \leq u$ for $0 \leq u \leq 1$. The case of $u = 0$ is trivial and we identified that under the null hypothesis $\mathbb{P}(\hat{S} = 1) \leq \frac{1}{2}$ and then focused on the more challenging case of $0 < u < \frac{1}{2}$. We also showed that $\mathbb{P}(\hat{S} = 1) = \frac{1}{2}$ if and only (δ_1, δ_2) is on the boundary of the parameter space where $\delta_1 = 0 \cup \delta_2 = 0$. Since δ_1 and δ_2 are treated symmetrically, without loss of generality we considered the null region $H_0^\star : \delta_1 \leq 0 \cap \delta_2 \geq 0$. On the boundary of $H_0^\star$, we found that $\mathbb{P}(P_{DMT} \leq u | \delta_1 = 0, \delta_2 = 0) = 2u^2 < u$, whereas if one parameter is zero and the magnitude of the other tends to infinity (i.e. the parameter is nonzero and the sample size tends to infinity), we saw that $\mathbb{P}(P_{DMT} \leq u) \to u$, which is the least favorable null. Gail et al.[2] came to the same conclusion, which they proved using Schur-convexity. We also found that when $(\delta_1, \delta_2) \to (-\infty, \infty)$ then $\mathbb{P}(\hat{S} = 1) \to 0$ so $\mathbb{P}(P_{DMT} \leq u) \to 0$, which is the global minimum.

Proposition 1: The directional MaxP test is the Likelihood Ratio Test (LRT)

Proof

This problem is related to the problem of finding subsets of samples with effects of different signs (i.e. qualitative interactions, QI), whose LRT was shown by Gail et al.[2] and nicely presented in Hudson et al.[3]. In that problem, $H_0^{QI} = \omega_1\omega_2 \geq 0$ is tested against $\bar{H}_0^{QI} : \omega_1\omega_2 < 0$, so the null region of the parameter space is $\Omega_0^{QI} = \{(\omega_1, \omega_2) : (\omega_1, \omega_2) \in H_0^{QI}\}$. This is also the form of the problem in directional mediation when the exposure decreases the outcome[1].

For our problem, consider applying a LRT based on the asymptotic sampling distribution of $(\hat{\omega}_1, \hat{\omega}_2)$. The LRT rejects H_0 for large values of:

$$\tau = -2\ln\left[\frac{\max_{(v_1,v_2)\in\Omega_0}\prod_{i\in\{1,2\}}\phi\{\sqrt{n_i}(\hat{\omega}_i - v_i)/\sigma_i\}}{\max_{(u_1,u_2)\in\mathbb{R}^2}\prod_{i\in\{1,2\}}\phi\{\sqrt{n_i}(\hat{\omega}_i - u_i)/\sigma_i\}}\right]$$

where $\Omega_0 = \{(x_1, x_2) : (x_1, x_2) \in H_0\}$ is the null region of the parameter space ($\bar{\Omega}_0$ is the alternative region) and $\phi(\cdot)$ is the standard normal density function. The denominator is maximized at $u_i^\star = \hat{\omega}_i$ for both $i = 1, 2$. Then,

$$\begin{aligned}\tau &= -2\max_{(v_1,v_2)\in\Omega_0}\sum_{i=1}^{2} -\frac{n_i}{2}\left(\frac{\hat{\omega}_i - v_i}{\sigma_i}\right)^2 \\ &= \min_{(v_1,v_2)\in\Omega_0}\sum_{i=1}^{2} n_i\left(\frac{\hat{\omega}_i - v_i}{\sigma_i}\right)^2\end{aligned}$$

If $(\hat{\omega}_1, \hat{\omega}_2) \in \Omega_0$, then we will have $(v_1^\star, v_2^\star) = (\hat{\omega}_1, \hat{\omega}_2)$, yielding $\tau = 0$. So we next consider points under the alternative hypothesis. Without loss of generality, consider that $(\hat{\omega}_1, \hat{\omega}_2)$ is in quadrant I, where both parameters are non-negative. Then the closest (v_1, v_2) can be to $(\hat{\omega}_1, \hat{\omega}_2)$ is to be on the boundary of quadrant I, where for one of $i = 1$ or $i = 2$ we have that $v_i = \hat{\omega}_i$ and for the other $i, v_i = 0$. The minimization of the sum will select the study with the smallest $\hat{\delta}$:

$$\tau = \min_{i\in\{1,2\}} \hat{\delta}_i^2 \mathbb{I}[(\hat{\delta}_1, \hat{\delta}_2) \in \bar{\Omega}_0]$$

where the p-value of the LRT is computed as $\mathbb{P}(\chi_1^2 > \tau)/2$ if $\tau > 0$, otherwise the p-value is one. This is equivalent to computing the p-value as

$$\max_{i\in\{1,2\}} \mathbb{P}(\chi_1^2 > \hat{\delta}_i^2)/2$$

if $(\hat{\delta}_1, \hat{\delta}_2) \in \bar{\Omega}_0$ or otherwise one, which is asymptotically equivalent to the directional MaxP test, so the DMT is the LRT.

ScreenDMT: multiple testing of directional hypotheses with screening

When considering multiple hypotheses (e.g. for many analytes, lipids, genes), we propose the following two-step multiple testing procedure. The ScreenDMT procedure includes an additional step based on AdaFilter[4] to calculate the adjusted p-values.

1. Apply the directional MaxP test per potential analyte to obtain P_{DMT}.
2. Calculate adjusted p-values using AdaFilter with filtering p-value $\Lambda = \underline{P}$ and selection p-value $\Xi = \max\{P_{DMT}, \underline{P}\}$. This can be used for calculating adjusted p-values that control the FDR or the FWER.

Dreyfuss et al. (2021) provided an option in step 1 to calculate valid p-values of these parameters in omics data using the R package Limma[5], which has been found to improve power across omics datasets. The same option is available for ScreenDMT.

The key property that AdaFilter relies on is a form of conditional validity[4]. Assuming that for each analyte P_1 is independent of P_2, the property states that when H_0 is true:

$$\mathbb{P}(\Xi < u | \Lambda < u) \leq u$$

holds for any fixed u > 0 whenever $\mathbb{P}(\underline{P} < u) > 0$.

Proposition 2: ScreenDMT satisfies conditional validity in asymptotic sample sizes

Proof

To demonstrate conditional validity, we first show that this holds on the boundary of the parameter space where $\omega_1 = 0 \cup \omega_2 = 0$ and then off the boundary under $H_0^\star$, which is where $\omega_1 < 0 \cap \omega_2 > 0$. We have,

$$\begin{aligned}
\mathbb{P}(\Xi < u | \Lambda < u) =& \mathbb{P}(\max\{P_{DMT}, \underline{P}\} < u | \underline{P} < u) \\
=& \mathbb{P}(P_{DMT} < u, \underline{P} < u | \underline{P} < u) \\
=& \mathbb{P}(P_{DMT} < u, \underline{P} < u) / \mathbb{P}(\underline{P} < u) \\
=& \mathbb{P}(P_{DMT} < u | \underline{P} < u)
\end{aligned}$$

For $u \geq 1$, we trivially have $\mathbb{P}(P_{DMT} < u | \underline{P} < u) \leq u$. We know that P_{DMT} and $\underline{P}$ are symmetric in ω_1 and ω_2, so without loss of generality we only consider the null region $H_0^\star : \omega_1 \leq 0 \cap \omega_2 \geq 0$. For $0 < u < 1$, using the law of total probability, we continue

$$\begin{aligned}
=& \mathbb{P}(P_{DMT} < u, \hat{S} = 1 | \underline{P} < u) + \mathbb{P}(P_{DMT} < u, \hat{S} = 0 | \underline{P} < u) \\
=& \mathbb{P}(P_{DMT} < u, \hat{S} = 1 | \underline{P} < u), \text{ since } \hat{S} = 0 \implies P_{DMT} = 1, \\
=& \mathbb{P}(\bar{P} < 2u, \hat{S} = 1 | \underline{P} < u) \\
=& \mathbb{P}(P_1 < 2u, P_2 < 2u, \hat{S} = 1 | P_1 < u \cup P_2 < u) \\
=& \frac{\mathbb{P}(P_1 < 2u, P_2 < 2u, P_1 < u \cup P_2 < u, \hat{S} = 1)}{\mathbb{P}(P_1 < u \cup P_2 < u)} \\
=& \frac{\mathbb{P}(P_1 < u, P_2 < 2u, \hat{S} = 1) + \mathbb{P}(P_1 < 2u, P_2 < u, \hat{S} = 1) - \mathbb{P}(P_1 < u, P_2 < u, \hat{S} = 1)}{\mathbb{P}(P_1 < u) + \mathbb{P}(P_2 < u) - \mathbb{P}(P_1 < u, P_2 < u)}.
\end{aligned} \tag{2}$$

For $u > \frac{1}{2}$ we know that $P_i < 2u$ for $i = 1, 2$, so Equation 2 becomes

$$\begin{aligned}
\mathbb{P}(P_{DMT} < u | \underline{P} < u) &= \mathbb{P}(\hat{S} = 1) \frac{\mathbb{P}(P_1 < u) + \mathbb{P}(P_2 < u) - \mathbb{P}(P_1 < u, P_2 < u)}{\mathbb{P}(P_1 < u) + \mathbb{P}(P_2 < u) - \mathbb{P}(P_1 < u, P_2 < u)}, \text{ as } \hat{S} \perp\!\!\!\perp (P_1, P_2), \\
&\leq \frac{1}{2} \\
&< u.
\end{aligned}$$

To see why $\hat{S} \perp\!\!\!\perp (P_1, P_2)$, consider that P_i is only a function of $|\hat{\delta}_i|$ whereas $\hat{S}$ is only a function of $\text{sign}(\hat{\delta}_1)$ and $\text{sign}(\hat{\delta}_2)$. Then we can observe that $|\hat{\delta}_i|$ is the same whether $\hat{\delta}_i = x$ or $\hat{\delta}_i = -x$, and because $\hat{\delta}_1$ and $\hat{\delta}_2$ are both continuous, they are never zero, so $x \neq -x$, implying that $\text{sign}(\hat{\delta}_i) \perp\!\!\!\perp |\hat{\delta}_i|$. Finally, we have assumed above that $\hat{\delta}_1 \perp\!\!\!\perp \hat{\delta}_2$, so $\Big(\text{sign}(\hat{\delta}_1), \text{sign}(\hat{\delta}_2)\Big) \perp\!\!\!\perp \Big(|\hat{\delta}_1|, |\hat{\delta}_2|\Big)$, which proves the claim.

The second line follows because we showed the bound $\mathbb{P}(\hat{S} = 1) \leq \frac{1}{2}$ previously[1].

We now consider $\mathbb{P}(P_{DMT} < u | \underline{P} < u)$ under $H_0^\star$ for $0 < u \leq \frac{1}{2}$ both on the boundary of the parameter space where $\omega_1 = 0 \cup \omega_2 = 0$ and then over the whole parameter space.

Boundary of parameter space

Under $H_0^\star$ for $0 < u \leq \frac{1}{2}$ when $\omega_1 = 0 \cup \omega_2 = 0$ we know that $\mathbb{P}(\hat{S} = 1 | \omega_1 = 0 \cup \omega_2 = 0) = \frac{1}{2}$ and $\mathbb{P}(P_i < u | \omega_i = 0) = u$. Without loss of generality, let $\omega_2 = 0$ and $\omega_1 \leq 0$, so $\mathbb{P}(P_2 < u | \omega_2 = 0) = u$ and $\mathbb{P}(P_1 < u | \omega_1 \leq 0) = F(u) \geq u$. For these parameter values, Equation 2 becomes

$$\begin{aligned}
\mathbb{P}(P_{DMT} < u | \underline{P} < u, \omega_2 = 0) &= u \frac{2F(u) + F(2u) - F(u)}{2[u + F(u) - uF(u)]} \\
&= u \frac{F(u) + F(2u)}{2[u + F(u) - uF(u)]} \\
&\to u, \text{ as } F(u) \to 1 \\
&\text{and} \\
\mathbb{P}(P_{DMT} < u | \underline{P} < u, \omega_1 = \omega_2 = 0) &= \frac{3u}{2(2-u)} \\
&\leq u, \text{ for } 0 < u \leq \frac{1}{2}.
\end{aligned}$$

$F(u) \to 1$ for $\delta_2 = 0$ as $\delta_1 \to -\infty$ as per Equation 1 which occurs as $n_1 \to \infty$.

Whole parameter space

We continue Equation 2 for $0 < u \leq \frac{1}{2}$ using the definition of our component p-values from Equation 1,

$$\begin{aligned}
&\mathbb{P}(P_{DMT} < u | \underline{P} < u) \\
=&\Bigg\{ \mathbb{P}\left(2\Phi\left(-|\hat{\delta}_1|\right) < u, 2\Phi\left(-|\hat{\delta}_2|\right) < 2u, \hat{S} = 1\right) + \mathbb{P}\left(2\Phi\left(-|\hat{\delta}_1|\right) < 2u, 2\Phi\left(-|\hat{\delta}_2|\right) < u, \hat{S} = 1\right) \\
&- \mathbb{P}\left(2\Phi\left(-|\hat{\delta}_1|\right) < u, 2\Phi\left(-|\hat{\delta}_2|\right) < u, \hat{S} = 1\right) \Bigg\} / \\
&\left\{ \mathbb{P}\left(2\Phi\left(-|\hat{\delta}_1|\right) < u\right) + \mathbb{P}\left(2\Phi\left(-|\hat{\delta}_2|\right) < u\right) - \mathbb{P}\left(2\Phi\left(-|\hat{\delta}_1|\right) < u, 2\Phi\left(-|\hat{\delta}_2|\right) < u\right) \right\} \\
=&\Bigg\{ \mathbb{P}\left(-|\hat{\delta}_1| < \Phi^{-1}\left(\frac{u}{2}\right), -|\hat{\delta}_2| < \Phi^{-1}(u), \hat{S} = 1\right) + \mathbb{P}\left(-|\hat{\delta}_1| < \Phi^{-1}(u), -|\hat{\delta}_2| < \Phi^{-1}\left(\frac{u}{2}\right), \hat{S} = 1\right) - \\
&\mathbb{P}\left(-|\hat{\delta}_1| < \Phi^{-1}\left(\frac{u}{2}\right), -|\hat{\delta}_2| < \Phi^{-1}\left(\frac{u}{2}\right), \hat{S} = 1\right) \Bigg\} / \\
&\left\{ \mathbb{P}\left(-|\hat{\delta}_1| < \Phi^{-1}\left(\frac{u}{2}\right)\right) + \mathbb{P}\left(-|\hat{\delta}_2| < \Phi^{-1}\left(\frac{u}{2}\right)\right) - \mathbb{P}\left(-|\hat{\delta}_1| < \Phi^{-1}\left(\frac{u}{2}\right), -|\hat{\delta}_2| < \Phi^{-1}\left(\frac{u}{2}\right)\right) \right\}.
\end{aligned} \tag{3}$$

We calculate these probabilities according to the law of total probability by integrating over the realized values (x_1, x_2) of the random estimates $(\hat{\omega}_1, \hat{\omega}_2)$. This involves the joint density

$$f\left(\hat{\delta}_1 = x_1, \hat{\delta}_2 = x_2\right) = \phi\left(x_1 - \delta_1\right)\phi\left(x_2 - \delta_2\right)$$

which follows from $\hat{\delta}_1 \perp\!\!\!\perp \hat{\delta}_2$, where $\phi(\cdot)$ is the standard normal density. For example, for the first term in the numerator of Equation 3 with fixed δ_i for $i = 1, 2$,

$$\begin{aligned}
&\mathbb{P}\left(-|\hat{\delta}_1| < \Phi^{-1}\left(\frac{u}{2}\right), -|\hat{\delta}_2| < \Phi^{-1}(u), \hat{S} = 1\right) \\
&= \int_{-\infty}^{\infty}\int_{-\infty}^{\infty} \mathbb{P}\left(-|\hat{\delta}_1| < \Phi^{-1}\left(\frac{u}{2}\right), -|\hat{\delta}_2| < \Phi^{-1}(u), \hat{S} = 1 \middle| \hat{\delta}_1 = x_1, \hat{\delta}_2 = x_2\right) f\left(\hat{\delta}_1 = x_1, \hat{\delta}_2 = x_2\right) \mathrm{d}x_1 \mathrm{d}x_2 \\
&= \int_{-\infty}^{\infty}\int_{-\infty}^{\infty} \mathbb{P}\left(-|x_1| < \Phi^{-1}\left(\frac{u}{2}\right), -|x_2| < \Phi^{-1}(u), \hat{S} = 1\right) \phi\left(x_1 - \delta_1\right)\phi\left(x_2 - \delta_2\right) \mathrm{d}x_1 \mathrm{d}x_2 \\
&= \int_{-\infty}^{\infty}\int_{-\infty}^{\infty} \mathbb{I}\left(-|x_1| < \Phi^{-1}\left(\frac{u}{2}\right), -|x_2| < \Phi^{-1}(u), \hat{S} = 1\right) \phi\left(x_1 - \delta_1\right)\phi\left(x_2 - \delta_2\right) \mathrm{d}x_1 \mathrm{d}x_2 \\
&= \int_{-\Phi^{-1}\left(\frac{u}{2}\right)}^{\infty} \phi\left(x_1 - \delta_1\right) \mathrm{d}x_1 \int_{-\Phi^{-1}(u)}^{\infty} \phi\left(x_2 - \delta_2\right) \mathrm{d}x_2 + \int_{-\infty}^{\Phi^{-1}\left(\frac{u}{2}\right)} \phi\left(x_1 - \delta_1\right) \mathrm{d}x_1 \int_{-\infty}^{\Phi^{-1}(u)} \phi\left(x_2 - \delta_2\right) \mathrm{d}x_2 \\
&= \lim_{\psi \to \infty} \left\{ \Phi\left(x_1 - \delta_1\right) \Big|_{-\Phi^{-1}\left(\frac{u}{2}\right)}^{\psi} \Phi\left(x_2 - \delta_2\right) \Big|_{-\Phi^{-1}(u)}^{\psi} + \Phi\left(x_1 - \delta_1\right) \Big|_{-\psi}^{\Phi^{-1}\left(\frac{u}{2}\right)} \Phi\left(x_2 - \delta_2\right) \Big|_{-\psi}^{\Phi^{-1}(u)} \right\} \\
&= \left[1 - \Phi\left(-\Phi^{-1}(u/2) - \delta_1\right)\right]\left[1 - \Phi\left(-\Phi^{-1}(u) - \delta_2\right)\right] + \Phi\left(\Phi^{-1}(u/2) - \delta_1\right)\Phi\left(\Phi^{-1}(u) - \delta_2\right) \\
&= \Phi\left(\Phi^{-1}(u/2) + \delta_1\right)\Phi\left(\Phi^{-1}(u) + \delta_2\right) + \Phi\left(\Phi^{-1}(u/2) - \delta_1\right)\Phi\left(\Phi^{-1}(u) - \delta_2\right), \text{ since } \Phi(-x) = 1 - \Phi(x).
\end{aligned}$$

The fourth line (involving the indicator function) holds because (x_1, x_2) are realizations of random variables, rather than being random themselves, so the probabilities evaluate to zero where their event is false and one where it is true. Following this example, we can simplify Equation 3 by removing the $\hat{S}$ terms,

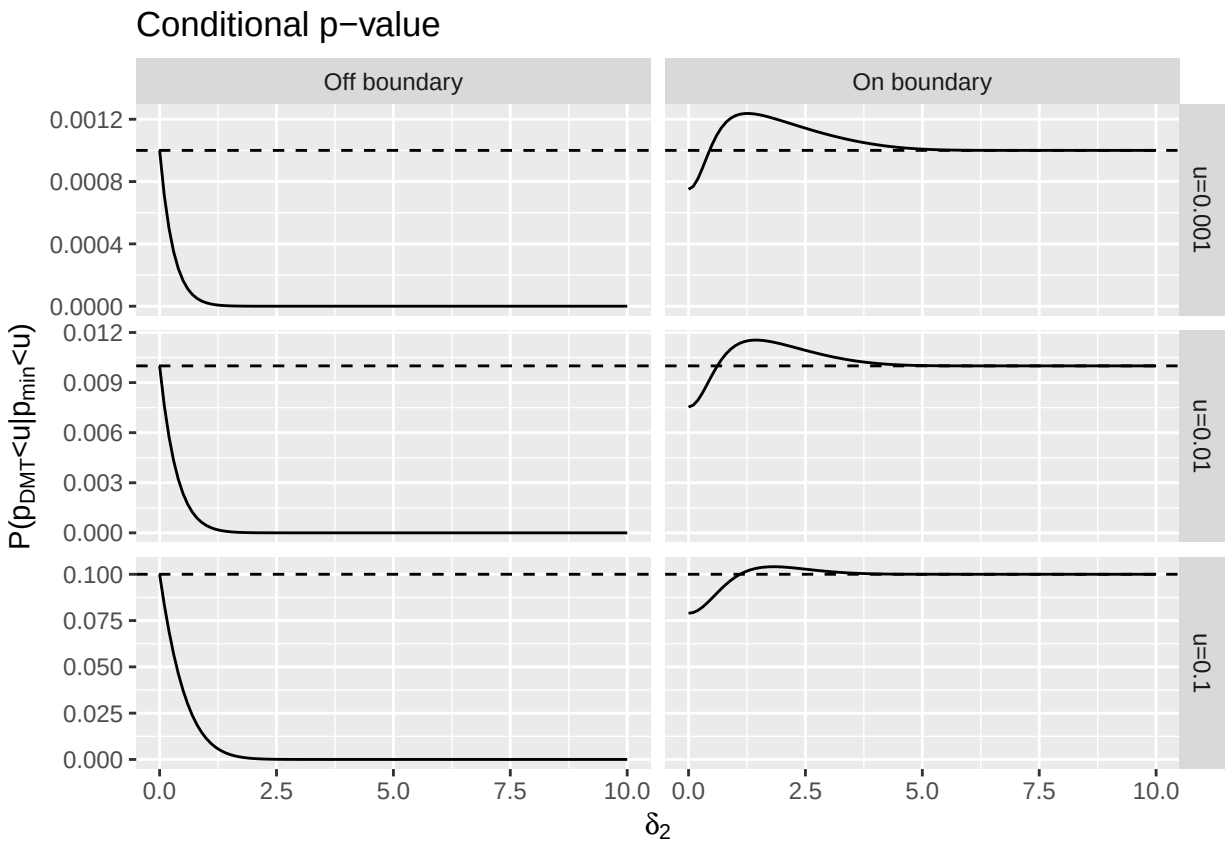
$$\begin{aligned}
&\mathbb{P}(P_{DMT} < u | \underline{P} < u) \\
=&\big\{\Phi\left(\Phi^{-1}(u/2) + \delta_1\right)\Phi\left(\Phi^{-1}(u) + \delta_2\right) + \Phi\left(\Phi^{-1}(u/2) - \delta_1\right)\Phi\left(\Phi^{-1}(u) - \delta_2\right) + \\
&\Phi\left(\Phi^{-1}(u) + \delta_1\right)\Phi\left(\Phi^{-1}(u/2) + \delta_2\right) + \Phi\left(\Phi^{-1}(u) - \delta_1\right)\Phi\left(\Phi^{-1}(u/2) - \delta_2\right) - \\
&\Phi\left(\Phi^{-1}(u/2) + \delta_1\right)\Phi\left(\Phi^{-1}(u/2) + \delta_2\right) - \Phi\left(\Phi^{-1}(u/2) - \delta_1\right)\Phi\left(\Phi^{-1}(u/2) - \delta_2\right)\big\} / \\
&\big\{\Phi\left(\Phi^{-1}(u/2) + \delta_1\right) + \Phi\left(\Phi^{-1}(u/2) - \delta_1\right) + \Phi\left(\Phi^{-1}(u/2) + \delta_2\right) + \Phi\left(\Phi^{-1}(u/2) - \delta_2\right) - \\
&\Phi\left(\Phi^{-1}(u/2) + \delta_1\right)\Phi\left(\Phi^{-1}(u/2) + \delta_2\right) - \Phi\left(\Phi^{-1}(u/2) - \delta_1\right)\Phi\left(\Phi^{-1}(u/2) - \delta_2\right) - \\
&\Phi\left(\Phi^{-1}(u/2) - \delta_1\right)\Phi\left(\Phi^{-1}(u/2) + \delta_2\right) - \Phi\left(\Phi^{-1}(u/2) + \delta_1\right)\Phi\left(\Phi^{-1}(u/2) - \delta_2\right)\big\}.
\end{aligned} \tag{4}$$

To evaluate Equation 4 off the boundary in the large sample limit where δ_1 and δ_2 are no longer finite, consider that for fixed x with $0 < x < 1$, $\lim_{\delta \to \infty} \Phi\left(\Phi^{-1}(x) + \delta\right) = 1$ and $\lim_{\delta \to \infty} \Phi\left(\Phi^{-1}(x) - \delta\right) = 0$. Using these limits off the boundary as the sample sizes n_1 and n_2 grow unbounded, we find that Equation 4 converges to zero, so $\mathbb{P}(P_{DMT} < u | \underline{P} < u) \to 0$, which is the global minimum. Thus, the asymptotic maximum under $H_0^\star$ is reached on the boundary when only one parameter is zero where $\mathbb{P}(P_{DMT} < u | \underline{P} < u) \to u$, which completes the proof.

Conditional p-value in finite sample sizes

We have the closed form expression of the conditional p-value $\mathbb{P}(P_{DMT} < u | \underline{P} < u)$ in Equation 4 for finite sample sizes, so we plot it below. We see that when δ_1 is off the boundary in the left panels (here we show $\delta_1 = -10$) and $\delta_2 > 0$, conditional validity is easily satisfied, since the curve is far below the dashed line at u. When $\delta_1 = 0$ is on the boundary in the right panels and δ_2 takes on some small values there is slight

inflation but conditional validity holds when δ_2 is near zero and when $\delta_2 > 0$ for large sample sizes, which is concordant with our mathematical proof.



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