Testing for replicability in a follow-up study when the primary study hypotheses are two-sided

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Abstract

When testing for replication of results from a primary study with two-sided hypotheses in a follow-up study, we are usually interested in discovering the features with discoveries in the same direction in the two studies. The direction of testing in the follow-up study for each feature can therefore be decided by the primary study. We prove that in this case the methods suggested in [1] for control over false replicability claims are valid. Specifically, we prove that if we input into the procedures in [1] the one-sided p-values in the directions favoured by the primary study, then we achieve directional control over the desired error measure (family-wise error rate or false discovery rate).

1 Introduction

In this note we are concerned with the setting where two studies (a primary study and a follow-up study) are available that examine the same problem, and the aim
is to discover the features with true findings with directional consistency from the primary to the follow-up study. So features with true left-sided alternatives in both studies are of interest, and features with true right-sided alternatives in both studies are of interest, but a feature with a true left-sided alternative in one of the studies and a true right-sided alternative in the other study is not.

In [1] we suggested procedures for declaring that findings from a primary study have been replicated in a follow-up study, where a feature has a false replicability claim if the null hypothesis is true in at least one of the studies. Our proposal assigned an r-value to each finding. The false discovery rate (FDR) r-value for feature i is the lowest FDR level at which we can say that the finding is among the replicated ones. We showed that the procedure that declares findings with FDR r-values below q as replicated controls the FDR on replicability claims. For family-wise error-rate (FWER) control on replicability claims, we suggested using FWER r-values with a similar property. In this note, we extend the results in [1] for the setting that the direction of the effects is unknown in advance, and the direction of testing is determined by the data of the primary study. We suggest using for each feature the minimum one-sided primary study p-value, i.e., we consider for replicability the direction the data favours, and in the follow-up the one-sided p-value in the favoured direction determined by the primary study. For example, if in a primary genome-wide association study (GWAS) the direction of association is unknown in advance, the primary study serves to guide two important design decisions for follow-up: first, which hypotheses will be followed-up, and second, the direction of testing in the follow-up study. For replicability analysis, we will need the one-sided p-values in the primary and follow-up studies, in the direction of association determined by the primary study. Although we decide for each feature the direction of testing based on its test statistic in the primary study, if we compute the r-values as in [1], then the procedures that declare as replicated all features with all r-values below the nominal level control the directional FDR/FWER. This is remarkable, since we are used to paying a factor of two for a single study when the direction of testing is unknown: we multiply the (minimal) one-sided p-value for two-sided hypothesis testing. For replicability analysis, there is no cost of not knowing before looking at the results from the primary study the direction of testing for replicability. The reason is that these procedures already have a cost for the fact that we select the promising hypotheses from the primary to the follow-up, and this cost actually covers also the selection of direction of interest. The r-values can be computed using our web application [http://www.math.tau.ac.il/~ruheller/App.html](http://www.math.tau.ac.il/~ruheller/App.html). An R script is also available in RunMyCode [http://www.runmycode.org/companion/view/542](http://www.runmycode.org/companion/view/542).

## 2 Notation

Here we give the formal framework for replicability analysis for two-sided hypotheses, including directional errors. Consider a family of $m \geq 1$ features examined in the
primary study. Feature $j \in \{1, \ldots, m\}$ in study $i \in \{1, 2\}$ has either a true or a false null hypothesis. If the null hypothesis is false, the true left-sided or right-sided alternative is true. We define $H_{ij}$ as follows:

$$H_{ij} = \begin{cases} 
1 & \text{if the right-sided alternative is true for feature } j \text{ in study } i, \\
0 & \text{if the null hypothesis is true for feature } j \text{ in study } i, \\
-1 & \text{if the left-sided alternative is true for feature } j \text{ in study } i.
\end{cases}$$

Let $\mathcal{H} = \{\vec{h} = (h_1, h_2) : h_i \in \{-1, 0, 1\}\}$ be the set of 9 possible configurations of the vector $\vec{H}_j = (H_{1j}, H_{2j})$ for two-sided alternatives. (If interest lies only in detecting left or right sided alternatives, only the relevant subset of 4 possible configurations are considered.) The set of $m$ features can be divided into 9 (unknown) subsets defined by $\mathcal{H} : \{j : \vec{H}_j = \vec{h}\}, \vec{h} \in \mathcal{H}$. Each feature $j$ is in exactly one of the 9 subsets. The subsets of features whose effect is not replicated in the same direction in the two studies are $\{j : \vec{H}_j = \vec{h}\}$, for $\vec{h} \in \mathcal{H}_0 = \{(-1, 1), (-1, 0), (1, 0), (0, 0), (0, 1), (0, -1), (1, -1)\}$. The goal in inference is to discover as many features as possible with $\vec{H}_j \notin \mathcal{H}^0$, i.e., $\vec{H}_j \in \{(1, 1), (-1, -1)\}$.

Suppose $R$ replicability claims are made by an analysis. Let $R^L$ and $R^R$ be the indicators of whether a replicability claim was made for feature $j$ in the left and right direction, respectively. The number of replicability claims that are true (i.e., that are with true left-sided alternatives in both studies or true right-sided alternatives in both studies) is

$$S = \sum_{\{j : \vec{H}_j = (1, 1)\}} R^R_j + \sum_{\{j : \vec{H}_j = (-1, -1)\}} R^L_j,$$

and $R - S$ is the number of replicability claims that are false (i.e., that are with true left-sided alternatives in at most one study and true right-sided alternatives in at most one study).

The directional FWER criterion is the probability of at least one false directional replicability claim,

$$FWER = \Pr(R - S > 0).$$

The directional FDR for replicability analysis is the expected proportion of false directional replicability claims among all those called replicated:

$$FDR = E\left(\frac{R - S}{\max(R, 1)}\right).$$

For feature $j$ tested in the follow-up study, the left- and right- sided $p$-values for study $i \in \{1, 2\}$ are denoted by $p^L_{ij}$ and $p^R_{ij}$, respectively. For continuous test statistics, $p^R_{ij} = 1 - p^L_{ij}$. For replicability analysis, we will need the one-sided $p$-values only in the direction favoured by the primary study, i.e. the pair $(p^I_{1j}, p^I_{2j})$ defined as follows:

$$p^I_{ij} = \begin{cases} 
p^L_{ij} & \text{if } p^L_{ij} < p^R_{ij}, \\
p^R_{ij} & \text{if } p^L_{ij} > p^R_{ij}.
\end{cases} \quad \text{and} \quad p^J_{1j} = \begin{cases} 
p^L_{1j} & \text{if } p^L_{1j} < p^R_{1j}, \\
p^R_{1j} & \text{if } p^L_{1j} > p^R_{1j}.
\end{cases}$$
Remark 2.1 We implicitly assume that $p'_{1j} \leq 0.5$. This assumption may be violated if the test statistic is discrete. Since features with $p'_{1j} > 0.5$ are obviously not interesting features in the primary study, we suggest including in our selection rule (of which features to follow-up on) the condition that a feature is selected only if $p'_{1j} \leq 0.5$.

3 FDR Replicability from follow-up for two-sided hypotheses

As in [1], we let $f_{00}$ denote the fraction of features, out of the $m$ features examined in the primary study, that are null in both studies. We cannot estimate $f_{00}$ from the data, since only a handful of promising features are followed up in practice. However, $f_{00}$ is typically closer to one than to zero, and we can give a conservative guess for a lower bound on $f_{00}$, call it $l_{00}$. For example, in typical GWAS on the whole genome, $l_{00} = 0.8$ is conservative. We can exploit the fact that $l_{00} > 0$ to gain power.

3.1 Computation of $r$-values for FDR-replicability for two-sided hypotheses

For completeness, we present the procedure for establishing replicability from follow-up, which is identical to the procedure in [1]. The only difference is that the one-sided $p$-values to input into the procedure are the ones favoured by the primary study.

1. Data input:
   (a) $m$, the number of features examined in the primary study.
   (b) $\mathcal{R}_1$, the set of features selected for follow-up based on primary study results. Let $R_1 = |\mathcal{R}_1|$ be their number.
   (c) $\{(p'_{1j}, p'_{2j}) : j \in \mathcal{R}_1\}$, where $p'_{1j}$ and $p'_{2j}$ are, respectively, the primary and follow-up study one-sided $p$-values for feature $j \in \mathcal{R}_1$ in the direction favoured by the primary study.

2. Parameters input:
   (a) $l_{00} \in [0, 1)$, the lower bound on $f_{00}$ (see above), default value for whole genome GWAS is $l_{00} = 0.8$.
   (b) $c_2 \in (0, 1)$, the emphasis given to the follow-up study (see Section Variations in [1]), default value is $c_2 = 0.5$.

3. Definition of the functions $f_i(x), i \in \mathcal{R}_1, x \in (0, 1)$:
   (a) Compute $c_1(x) = \frac{1-c_2}{1-l_{00}(1-c_2)x}$.
(b) For every feature \( j \in \mathcal{R}_1 \) compute the following \( e \)-values:

\[
e_j(x) = \max \left( \frac{1}{c_1(x)p_{1j}}, \frac{R_1}{mc_2}p_{2j} \right), \quad j \in \mathcal{R}_1.
\]

(c) Let \( f_i(x) = \min_{j : e_j(x) \geq e_i(x), j \in \mathcal{R}_1} e_j(x)^{m \cdot \text{rank}[e_j(x)]} \), where \( \text{rank}[e_j(x)] \) is the rank of the \( e \)-value for feature \( j \in \mathcal{R}_1 \) (with maximum rank for ties).

4. The FDR \( r \)-value for feature \( i \in \mathcal{R}_1 \) is the solution to \( f_i(r_i) = r_i \) if a solution exists in \((0, 1)\), and 1 otherwise. The solution is unique, see Supplementary Information (SI) Lemma S1.1 in [1] for a proof.

3.2 The level \( q \) directional FDR replicability procedure

1. Compute the \( r \)-values as detailed in Section 3.1.

2. The replicability claims at a prefixed level \( q \), say \( q = 0.05 \), are all features with \( r \)-values at most 0.05. Denote this set of features by \( \mathcal{R}_2 \).

3. If feature \( j \in \mathcal{R}_2 \) has \( p'_{1j} = p'^L_{1j} \), then declare the feature as having a replicated true left-sided alternative (i.e., a true effect/signal/association in the left direction) ; If feature \( j \in \mathcal{R}_2 \) has \( p'_{1j} = p'^R_{1j} \), then declare the feature as having a replicated true right-sided alternative (i.e., a true effect/signal/association in the right direction).

The directional FDR for replicability analysis is then controlled at level 0.05, as we show in Theorem 3.1, as long as the selection rule is stable.

Definition [1]. A stable selection rule satisfies the following condition: for any \( j \in \mathcal{R}_1 \), changing \( p'^L_{1j} \) so that \( j \) is still selected while all other primary study \( p \)-values are held fixed, will not change the set \( \mathcal{R}_1 \).

Stable selection rules include selecting the hypotheses with two-sided primary \( p \)-values below a certain cut-off, or by a non-adaptive multiple testing procedure on the primary study two-sided \( p \)-values such as the BH procedure for FDR control or the Bonferroni procedure for FWER control, or selecting the \( k \) hypotheses with the smallest two-sided \( p \)-values, where \( k \) is fixed in advance.

Theorem 3.1 A procedure that declares findings with FDR \( r \)-values at most \( q \) as replicated controls the directional FDR for replicability analysis at level at most \( q \) if the following conditions are satisfied: the rule by which the set \( \mathcal{R}_1 \) is selected is a stable selection rule; \( l_{00} \leq f_{00} \); the \( p \)-values within the follow-up study are jointly independent or are positive regression dependent on the subset of \( p \)-values corresponding to true null
hypotheses (property PRDS\footnote{Property PRDS was introduced in \cite{3}. For example, the PRDS property is satisfied if the test statistics are Gaussian, non-negatively correlated, and the tested hypotheses are one-sided.}); for features with $\vec{H}_j \notin \{(1,1), (-1,-1)\}$ the follow-up study p-values are independent of the primary study p-values; and in addition one of items 1-3 below is satisfied.

1. The p-values within the primary study are independent.

2. Arbitrary dependence among the p-values within the primary study, when in Step 3 in Section \ref{sec:3.1} $m$ is replaced by $m^* = m \sum_{i=1}^{m} 1/i$.

3. Arbitrary dependence among the p-values within the primary study, and the selection rule is such that the primary study p-values of the features that are selected for follow-up are at most a fixed threshold $t \in (0,1)$, when $c_1$ computed in Step 3(a) is replaced by

$$
\tilde{c}_1(x) = \max\{a : a(1 + \sum_{i=1}^{[tm/(ax)-1]} 1/i) = c_1(x)\}.
$$

Steps 3(b) and 3(c) remain unchanged. In step 4, the FDR $r$-value for feature $i \in \mathcal{R}_1$ is $r_i = \min\{x : f_i(x) \leq x\}$ if a solution exists in $(0,1)$, and one otherwise.

See Appendix \ref{app:A} for a proof. The implication of item 3 is that for FDR-replicability at level $q$, if $t < c_1(q)/m$, no modification is required, so the procedure that declares as replicated all features with $r$-values at most $q$ controls the FDR at level $q$ on replicability claims for any type of dependency in the primary study. Note that the modification in item 3 will lead to more discoveries than the modification in item 2 only if $t < \frac{c_1(q)q}{1+\sum_{i=1}^{m} 1/i}$.

We conjecture from empirical investigations that even if the primary study p-values are not independent, the conservative modifications of the $r$-value computation in items 2-3 are unnecessary for FDR control in replicability analysis of GWAS studies, see \cite{1} for details.

\section{FWER Replicability from follow-up for two-sided hypotheses}

\subsection{Computation of $r$-values for FWER-replicability for two-sided hypotheses}

The directional FWER criterion,

$$FWER = \Pr(R - S > 0),$$


\begin{thebibliography}{1}
\bibitem{1} Property PRDS was introduced in \cite{3}. For example, the PRDS property is satisfied if the test statistics are Gaussian, non-negatively correlated, and the tested hypotheses are one-sided.
\end{thebibliography}
is more stringent than the directional FDR, yet it may sometimes be desired. The directional FWER $r$-value is the lowest directional FWER level at which we can say that the finding has been replicated. The $r$-value can be compared to any desired level of directional FWER. For feature $j \in \mathcal{R}_1$,
\[
    f_{j}^{Bonf}(x) = m \cdot e_{j}(x),
\]
where $e_{j}(x)$ is the $e$-value defined in Step 3(b) of Section 3.1. The Bonferroni $r$-value for feature $j$ is the solution to $f_{j}^{Bonf}(r_{j}) = r_{j}$ if a solution exists in $[0, 1)$, and one otherwise. It can be shown that the solution is unique similarly to the case with FDR $r$-values.

4.2 The level $\alpha$ directional FWER-replicability procedure

1. Compute the $r$-values as detailed in Section 4.1.

2. The replicability claims at a prefixed level $\alpha$, say $\alpha = 0.05$, are all features with $r$-values at most $\alpha$. Denote this set of features by $\mathcal{R}_2$.

3. If feature $j \in \mathcal{R}_2$ has $p_{Lj} \leq p_{Rj}$, then declare the feature as having a replicated true left-sided alternative; If feature $j \in \mathcal{R}_2$ has $p_{Rj} \leq p_{Lj}$, then declare the feature as having a replicated true right-sided alternative.

The directional FWER for replicability analysis is then controlled at level 0.05, as stated in the following theorem.

**Theorem 4.1** The procedure above controls the directional FWER for replicability analysis at level $\alpha$ if $l_{00} \leq f_{00}$, and if for features with $\vec{H}_j \notin \{(1, 1), (-1, -1)\}$ the follow-up study $p$-values are independent of the primary study $p$-values.

See Appendix B for the proof.

References

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### A Proof of Theorem 3.1

We first show that the following procedure is identical to that of declaring the set of findings with FDR-replicability $r$-values at most $q$ as replicated. First, compute the number of replicability claims at level $q$ as follows:

\[ R_2 \equiv \max \left\{ r : \sum_{j \in R_1} \mathbf{1}[ (p'_{1j}, p'_{2j}) \leq \left( \frac{r}{m} c_1(q) q, \frac{r}{R_1} c_2 q \right) ] = r \right\}. \]

Next, declare as replicated findings the set

\[ \mathcal{R}_2 = \left\{ j : (p'_{1j}, p'_{2j}) \leq \left( \frac{R_2}{m} c_1(q) q, \frac{R_2}{R_1} c_2 q \right), j \in \mathcal{R}_1 \right\}. \]

It was shown in Lemma S1.1 in [1] that when the hypotheses are one-sided, this procedure is identical to declaring the set of findings with FDR-replicability $r$-values at most $q$ as replicated, when the one-sided $p$-values replace $(p'_{1j}, p'_{2j})$ both in the above procedure and in the computation of FDR-replicability $r$-values. It is straightforward to see that the proof of Lemma S1.1 in [1] remains unchanged when the one-sided $p$-values are replaced by $(p'_{1j}, p'_{2j})$, therefore the above procedure is identical to that of declaring the set of findings with FDR-replicability $r$-values at most $q$ as replicated for two-sided hypotheses.

We shall prove that under the conditions of items 1-3 of Theorem 3.1 the above procedure controls the FDR for replicability analysis at a level which is smaller or equal to

\[
\begin{align*}
&c_1(q) c_2 q^2 \| \{ j : \vec{H}_j \in \{(-1,0), (1,0), (0,0) \} \} \| / m + \\
&c_1(q) q \| \{ j : \vec{H}_j \in \{(0,1), (0,-1), (-1,-1), (1,1), (-1,1), (1,-1) \} \| / m + \\
&c_2 q E[|\mathcal{R}_1 \cap \{ j : \vec{H}_j \in \{(-1,0), (1,0), (-1,1), (1,-1), (0,1), (0,-1), (0,0) \} |]/|\mathcal{R}_1|, 
\end{align*}
\]

(1)
where the cardinalities are over the sets containing all \( m \) features, i.e. \( j = 1, \ldots, m \).
Note that this expression is at most \( q \) if \( l_{00} \leq f_{00} \). To see this, note that

\[
|j : \vec{H}_j \in \{(-1, 0), (1, 0), (0, 0)\}|/m = f_0,
\]

and

\[
|j : \vec{H}_j \in \{(0, 1), (0, -1), (-1, -1), (1, 1), (-1, 1), (1, -1)\}|/m = 1 - f_0.
\]

Moreover,

\[
E[|\mathcal{R}_1 \cap \{j : \vec{H}_j \in \{(-1, 0), (1, 0), (-1, 1), (1, -1), (0, 1), (0, -1), (0, 0)\}|/|\mathcal{R}_1|] \leq 1.
\]

Therefore, expression (1) is at most

\[
\begin{align*}
&c_1(q)c_2q^2f_0 + c_1(q)q(1 - f_0) + c_2q \\
&= c_1(q)q - f_0c_1(q)q(1 - c_2q) + c_2q \\
&\leq c_1(q)q - l_{00}c_1(q)(1 - c_2q) + c_2q \\
&= c_1(q)q[1 - l_{00}(1 - c_2q)] + c_2q \\
&= (1 - c_2)q + c_2q = q.
\end{align*}
\]

We shall now prove that the expression in (1) is an upper bound for the directional FDR for replicability analysis, which is

\[
E \left( \frac{R - S}{\max(R, 1)} \right) = \sum_{\{j : \vec{H}_j \in \{0, -1, (0, 0), (1, 0), (0, 1), (1, 1), (0, -1), (-1, 1), (-1, -1)\}\}} E \left( \frac{R_j^L}{\max(R, 1)} \right) + \sum_{\{j : \vec{H}_j = (1, 1)\}} E \left( \frac{R_j^L}{\max(R, 1)} \right) + \sum_{\{j : \vec{H}_j = (-1, -1)\}} E \left( \frac{R_j^R}{\max(R, 1)} \right).
\]

(2)

For each \( j \in \{1, \ldots, m\} \), we define \( C_{r}^{(j)} \) as the event in which if \( j \) is declared replicated, \( r \) hypotheses are declared replicated including \( j \), which amounts to the definition given in the proof of Theorem 1 in Supplementary Material of [1], where the one-sided \( p \)-values \((p_{1j}, p_{2j})\) are replaced by \((p'_{1j}, p'_{2j})\). Note that for any given realization of \(|\mathcal{R}_1|\) and value of \( r \) such that \( r > |\mathcal{R}_1|, \, C_{r}^{(j)} = \emptyset \).

From the equivalent procedure above the following equality follows.

\[
E \left( \frac{R_{1j}^L}{\max(R, 1)} \right) = \sum_{r=1}^{m} \frac{1}{r} \Pr \left( j \in \mathcal{R}_1, P_{1j}^L \leq \min \left( \frac{rc_1(q)q}{m}, 0.5 \right), P_{2j}^L \leq \frac{rc_2q}{\max(|\mathcal{R}_1|, 1)}, C_{r}^{(j)} \right) \\
\leq \sum_{r=1}^{m} \frac{1}{r} \Pr \left( P_{1j}^L \leq \frac{rc_1(q)q}{m}, P_{2j}^L \leq c_2q, C_{r}^{(j)} \right),
\]

(3)

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where the equality follows from the fact that a replicability claim is made in the left
direction only if \( P_{ij}^L \leq P_{ij}^R \), i.e. only if \( P_{ij}^L < 0.5 \). Similarly,

\[
E \left( \frac{R_{ij}^R}{\max(R, 1)} \right) \leq \sum_{r=1}^m \frac{1}{r} \Pr \left( P_{ij}^R \leq \frac{rc_1(q)q}{m}, P_{2j}^R \leq c_2q, C^{(j)}_r \right). \tag{4}
\]

Using inequalities (3) and (4), and the facts that \( P_{ij}^L \) and \( P_{ij}^R \) are uniform for \( j \in \{j : H_{1j} = 0\} \) and are stochastically larger than uniform for \( j \in \{j : H_{1j} = 1\} \) and \( j \in \{j : H_{1j} = -1\} \) respectively, we obtain the following inequalities:

\[
E \left( \frac{R_{ij}^R}{\max(R, 1)} \right) \leq \begin{cases} 
  c_1(q)q/m & \text{if } \bar{H}_j \in \{(0, -1), (1, -1), (1, 1)\}, \\
  c_2qE[I(j \in \mathcal{R}_1)/|\mathcal{R}_1|] & \text{if } \bar{H}_j \in \{(-1, 0), (0, 1), (-1, 1)\}, \\
  c_1(q)c_2q^2/m & \text{if } \bar{H}_j \in \{(0, 0), (1, 0)\}, 
\end{cases}
\]

\[
E \left( \frac{R_{ij}^L}{\max(R, 1)} \right) \leq \begin{cases} 
  c_1(q)q/m & \text{if } \bar{H}_j \in \{(0, 1), (-1, 1), (-1, -1)\}, \\
  c_2qE[I(j \in \mathcal{R}_1)/|\mathcal{R}_1|] & \text{if } \bar{H}_j \in \{(1, 0), (0, -1), (1, -1), (0, 0)\}, \\
  c_1(q)c_2q^2/m & \text{if } \bar{H}_j \in \{(-1, 0)\}.
\end{cases}
\]

These upper bounds for items 1-3 of Theorem 3.1 follow from similar derivations to
given in the proof of items (i)-(iii) of Theorem 1 in [1], respectively. Specifically,
for each of the items, the upper bounds \( c_1(q)q/m \), \( c_2qE[I(j \in \mathcal{R}_1)/|\mathcal{R}_1|] \) and \( c_1(q)c_2q^2/m \) are derived similarly to inequalities [S3], [S4], and [S5] in the proof of Theorem 1 in [1], respectively. Thus we obtain

\[
E \left( \frac{R_{ij}^R + R_{ij}^L}{\max(R, 1)} \right) \leq \begin{cases} 
  c_2qE[I(j \in \mathcal{R}_1)/|\mathcal{R}_1|] + c_1(q)c_2q^2/m & \text{if } \bar{H}_j = (0, 0), \\
  c_2qE[I(j \in \mathcal{R}_1)/|\mathcal{R}_1|] + c_1(q)c_2q^2/m & \text{if } \bar{H}_j \in \{(1, 0), (-1, 0)\}, \\
  c_1(q)q/m + c_2qE[I(j \in \mathcal{R}_1)/|\mathcal{R}_1|] & \text{if } \bar{H}_j \in \{(0, 1), (0, -1)\}, \\
  c_2qE[I(j \in \mathcal{R}_1)/|\mathcal{R}_1|] + c_1(q)q/m & \text{if } \bar{H}_j \in \{(1, -1), (-1, 1)\}, 
\end{cases}
\]

and for the directional error terms:

\[
E \left( \frac{R_{ij}^L}{\max(R, 1)} \right) \leq \frac{c_1(q)q}m, \text{ for } j \text{ with } \bar{H}_j = (1, 1)
\]
\[
E \left( \frac{R_{ij}^R}{\max(R, 1)} \right) \leq \frac{c_1(q)q}m, \text{ for } j \text{ with } \bar{H}_j = (-1, -1).
\]

The result follows from using expression (2) for the directional FDR for replicability
analysis, and summing up over the above upper bounds.

\section*{B Proof of Theorem 4.1}

It is easy to show that the procedure in Section 4.2 is unchanged if we replace Step 2 by the following: the replicability claims are all features with \( f_j^{Bonf}(\alpha) \leq \alpha \). The
equivalence follows from the facts that $f^\text{Bonf}_j(x)$ is a continuous function of $x$ and $f^\text{Bonf}_j(x)/x$ is strictly monotone decreasing (this result follows from the proof of Lemma S1.1 in the SI of [1] and it is straightforward to show that it continues to hold in the directional replicability analysis).

We shall now prove that the expression in (1) with $q$ replaced by $\alpha$ is an upper bound for the directional FWER for replicability analysis, which is $\Pr(R - S > 0)$. It was shown in the proof of Theorem S6.1 that this expression is at most $\alpha$ if $l_00 \leq f_00$. Note that

$$\Pr(R - S > 0) \leq E(R - S) \leq \sum_{\{j: \vec{H}_j = (1,1)\}} E(R^L_j) + \sum_{\{j: \vec{H}_j = (-1,-1)\}} E(R^R_j) + \sum_{\{j: \vec{H}_j \in \{(0,-1),(0,1),(0,0),(1,0),(-1,0),(1,-1),(-1,-1)\}\}} E(R^R_j + R^L_j)$$

We consider the equivalent procedure that replaces Step 2 by counting as replicability claims all features with $f^\text{Bonf}_j(\alpha) \leq \alpha$ (as discussed above). The directional error terms in the first two sums contribute the following:

$$E(R^L_j) \leq \frac{c_1(\alpha)\alpha}{m}, \text{ for } j \text{ with } \vec{H}_j = (1,1)$$

$$E(R^R_j) \leq \frac{c_1(\alpha)\alpha}{m}, \text{ for } j \text{ with } \vec{H}_j = (-1,-1)$$

To see how these upper bounds were derived, we consider only the first (since the second is derived similarly). For $j$ with $\vec{H}_j = (1,1)$

$$E(R^L_j) \leq \Pr(P^L_{1j} \leq \min(c_1(\alpha)\alpha/m, \alpha/2), P^L_{2j} \leq c_2\alpha / R_1) \leq \Pr(P^L_{1j} \leq c_1(\alpha)\alpha/m) \leq \frac{c_1\alpha}{m},$$

where the first inequality follows from the fact that a replicability claim is made in the left direction only if $P^L_{1j} \leq P^L_{1j}, i.e., only if $P^L_{1j} < 0.5$, and the last inequality follows that the fact that for $H_{1j} = 1, P^L_{1j}$ is stochastically larger than uniform.

All remaining errors are false replicability claims, not only directional errors. Clearly, $E(R^R_j + R^L_j) = \Pr(\min(P^L_{1j}, P^R_{1j}) \leq c_1(\alpha)\alpha/m, P^L_{2j} \leq c_2\alpha / |R_1|, j \in R_1)$. It is simple to show (using similar derivations to those in the proof of Theorem S6.1 in the SI of [1]) that the right hand side is at most the following upper bounds:

$$E(R^R_j + R^L_j) \leq \begin{cases} 
  c_2\alpha E[I(j \in R_1)/|R_1|] + c_1(\alpha)\alpha/m \times c_2\alpha & \text{if } \vec{H}_j = (0,0), \\
  c_2\alpha E[I(j \in R_1)/|R_1|] + c_1(\alpha)\alpha/m \times c_2\alpha & \text{if } \vec{H}_j \in \{(1,0),(-1,0)\}, \\
  c_1(\alpha)\alpha/m + c_2\alpha E[I(j \in R_1)/|R_1|] & \text{if } \vec{H}_j \in \{(0,1),(0,-1)\}, \\
  c_2\alpha E[I(j \in R_1)/|R_1|] + c_1(\alpha)\alpha/m & \text{if } \vec{H}_j \in \{(1,-1),(-1,1)\}. 
\end{cases}$$

The result follows from summing over these upper bounds.