Smoothed Nested Testing on Directed Acyclic Graphs

Wesley Tansey∗1,2, Jackson H. Loper1,3, Lihua Lei4, and William Fithian4

1Data Science Institute, Columbia University, New York, NY, USA
2Department of Systems Biology, Columbia University Medical Center, New York, NY, USA
3Department of Neuroscience, Columbia University, New York, NY, USA
4Department of Statistics, University of California, Berkeley, CA, USA

Abstract

We consider the problem of multiple hypothesis testing when there is a logical nested structure to the hypotheses. When one hypothesis is nested inside another, the outer hypothesis must be false if the inner hypothesis is false. We model the nested structure as a directed acyclic graph, including chain and tree graphs as special cases. Each node in the graph is a hypothesis and rejecting a node requires also rejecting all of its ancestors. We propose a general framework for adjusting node-level test statistics using the known logical constraints. Within this framework, we study a smoothing procedure that recursively merges each node with all of its descendants to form a more powerful statistic. We prove two classical merging strategies can be used with existing selection procedures to control the familywise error rate, false discovery exceedance rate, or false discovery rate, so long as the original test statistics are independent under the null. When the null statistics are not independent but are derived from positively-correlated normal observations, we prove control for all three error rates when the smoothing method is arithmetic averaging of the observations. Simulations and an application to a real biology dataset demonstrate that smoothing leads to substantial power gains.

∗wesley.tansey@columbia.edu (corresponding author)
1 Introduction

We consider a structured multiple testing problem with a large set of null hypotheses structured along a directed acyclic graph. Each null hypothesis corresponds to a node in the graph and a node contains a false hypothesis only if all ancestors are false. The inferential goal is to maximize power while preserving a target error rate on the entire graph and rejecting hypotheses in a manner that obeys the graph structure. We will focus on boosting power in existing structured testing procedures by using the graph to share statistical strength between the node-level test statistics.

The graph-structured testing problem is motivated by modern biological experiments that collect a large number of samples on which to simultaneously test hundreds or even thousands of hypotheses. In developmental biology, for example, next-generation sequencing enables biologists to measure thousands of gene expression levels across tens of thousands of cells (Potter 2018). The population of measured cells is typically heterogeneous, including samples taken from different subpopulations, such as different tissue locations or different time points in the development of the organism. Biologists studying these subpopulations wish to discover which cellular components are differentially expressed between the groups. Testing each of the thousands of genes for differential expression is a classic multiple hypothesis testing problem. Yet testing typically does not stop here: the biological function of a cell is much richer than individual gene expression.

The full inferential task in modern biology experiments is a structured testing problem involving not just genes but an entire ontology of functionality containing pathways and other higher-order biological units. Pathways represent mechanistic processes in a cell, such as cell division or immune response, and many genes and lower-level pathways may be involved in a single pathway. The set of all genes and pathways involved in human cellular behavior, and their compositional structure, forms an ontology that has been rigorously mapped out through previous experiments (Ashburner et al. 2000). Modern biological experiments aim to test not just the individual genes, but all entries in this ontology. In this structured testing problem, lower-level hypotheses are nested within higher-order hypotheses: if a gene or pathway is differentially expressed, it logically entails that the higher-order pathways in which it participates are also differentially expressed. Here we consider this nested testing problem in the general case, where a directed acyclic graph encodes an ontology of logically nested hypotheses; we will return to the developmental biology example in Section 5.

The key insight in this paper is that knowing the graph structure should increase power in the testing procedure. If every node in the graph represents an independent hypothesis test, then nodes should be able to borrow statistical strength from their ancestors and descendants. The signal at a non-null node may too weak to detect on its own, but the strength of evidence when combined with the evidence from its non-null children may be sufficient to reject the null hypothesis. This strength sharing can also flow in the opposite direction, with non-null parent nodes boosting power to detect non-null children. For instance, if the non-null signal attenuates smoothly as a function of depth in the graph, it may be possible to learn this function. The test statistic for a node can then be adjusted using the estimated signal predicted by the function learned from the ancestors. Whether using the descendants, ancestors, or both, sharing statistical strength creates dependence between test statistics and therefore must be carried out thoughtfully so as to enable control of the target error rate.

This leads us to develop a smoothing approach that implements this sharing of statistical strength between connected test statistics in the directed acyclic graph while still controlling
the target error rate. We explore both descendant merging and ancestor smoothing, but ultimately focus on descendant merging as it requires less prior knowledge of the graph and is thus more broadly applicable. We prove that the descendant smoothing approach yields adjusted \( p \)-values that are compatible with three different selection algorithms from the literature on nested testing with directed acyclic graphs \([\text{Meijer and Goeman, 2015}]
\text{Genovese and Wasserman, 2006} \text{Ramdas et al., 2019}\). Together, these techniques enable us to smooth the \( p \)-values and control familywise (Type I) error, the false discovery rate, or the false exceedance rate. Simulated and real data experiments confirm that smoothing yields substantially higher power across a wide range of alternative distributions and graph structures.

2 Background

There is a wealth of recent work on structured and adaptive testing. We focus on the most relevant work and refer the reader to \([\text{Lynch, 2014}]\) for a comprehensive review of testing with logically nested hypotheses.

The adaptive testing literature deals with the problem of using the data to boost power, as does our smoothing procedure. A suite of methods \([\text{Scott et al., 2015} \text{Xia et al., 2017} \text{Tansey et al., 2018} \text{Lei and Fithian, 2018} \text{Li and Barber, 2019}]\) enable machine learning methods to leverage side information like covariates that learn a prior over the probability of coming from the alternative. In contrast to adaptive testing, in the nested setting we are given the structure in the form a directed acyclic graph encoding logical nesting rather than statistical dependence. While these adaptive methods could potentially be used to increase power in the nested testing problem, they would not admit selection procedures that guarantee the nested structure is preserved. That is, even if the graph structure were used to boost power, they are not able to enforce that rejecting a hypothesis logically entails rejecting all of its ancestors.

There is a nascent literature on adaptive testing methods that preserve nested hypothesis structure. \([\text{Lei et al., 2017}]\) describe an interactive adaptive procedure that partially masks \( p \)-values, enabling the scientist to explore the data and unveil its structure, then use the masked bits to perform selection while controlling the false discovery rate at the target level. This interactive approach is able to preserve nested hypothesis structure, but comes at the cost of splitting the \( p \)-values, potentially costing power. Further, the method is only able to control the false discovery rate for independent \( p \)-values; we will consider a much broader class of error metrics and well as some dependent \( p \)-value scenarios. The application of descendant smoothing for familywise error control was also studied in \([\text{Vovk and Wang, 2012}]\), which consider a variant of the Bonferroni-Holm procedure \([\text{Holm, 1979}]\) with a closure principle. However, the procedure does not involve any graph structure and hence cannot be applied to nested testing problems on directed acyclic graphs.

Preserving the logical nesting structure after selection is the domain of structured testing. Methods for structured testing can be categorized based on their assumptions about the structure of the graph and the type of target error rate. Accumulation tests \([\text{Li and Barber, 2017}]\) assume a chain graph and false discovery rate control, where the ordering implies weak prior knowledge about the likelihood of the null hypothesis being false. \([\text{Meinshausen, 2008}]\) considers testing on trees while controlling familywise error. \([\text{Bogomolov et al., 2017}]\) control the false discovery rate for tree-structured graphs. \([\text{Meijer and Goeman, 2015}]\) propose two methods for controlling familywise error on directed acyclic graphs. \([\text{Genovese and} \text{Wasserman, 2006}]\)
Wasserman (2006) show that any familywise error method can be extended to control the false exceedance rate, implying a method to control the false exceedance rate with the Meijer and Goeman (2015) strategy. Lynch (2014) proposes two methods for testing on directed acyclic graphs with false discovery rate control and Ramdas et al. (2019) proposes a more powerful method for the same scenario by extending the Benjamini-Hochberg algorithm (Benjamini and Hochberg, 1995).

Rather than competing with methods for structured testing, our smoothing procedures are complementary. As we will show in Section 4, the descendant smoothing procedure is compatible with controlling familywise error via Meijer and Goeman (2015), the false exceedance rate via an extension to the method of Genovese and Wasserman (2006), and the false discovery rate via Ramdas et al. (2019). In the case of the latter method, we explicitly show that the smoothed \(p\)-values are positive regression dependent each on a subset (Benjamini and Yekutieli, 2001), resolving the issue of dependence under the null after smoothing. The benefit of smoothing is not to enable a new structured hypothesis testing, but to make existing principled methods such as these more powerful by leveraging the structure of the problem.

3 Smoothing Nested Test Statistics

3.1 Smoothed \(q\)-values

Let \(\{H_1, \ldots, H_n\}\) be a large set of null hypotheses. For each \(v \in \{1, \ldots, n\}\) we observe a random variable \(p_v\); if the null hypothesis \(H_v\) holds, we assume that this random variable is uniformly distributed. We will generally assume that all of the null hypotheses are identically and independently drawn from \(\text{Uniform}[0,1]\), though a few exceptions will be considered later. We will use \(V = \{1, \ldots, n\}\) to index all of the null hypotheses, and let

\[
\tilde{S} = \{v \in V : H_v \text{ is true}\}, \quad S = V \setminus \tilde{S} = \{v \in V : H_v \text{ is false}\}
\]

denote the unknown set of null hypotheses which hold and do not hold, respectively. Our task is to produce an estimate \(\hat{S}\) of the set \(S\) from the random variables \(\{p_v\}_{v \in V}\) subject to a target error rate on \(\hat{S}\).

To help estimate \(\hat{S}\), we have access to a directed acyclic graph \(G = (V, E)\) whose edges encode logical constraints on the hypotheses: \(v \rightarrow w \implies (H_v \Rightarrow H_w)\). That is, if \(H_v\) is false, then we know that all of the ancestors of \(v\) must also be false. We would like to use these logical constraints to our advantage in estimating \(\hat{S}\). To use \(G\), we will replace \(\{p_v\}_{v \in V}\) with smoothed values \(\{q_v\}_{v \in V}\).

Assume we are given a graph \(G\) and an arbitrary collection of smoothing functions \(f_v : \mathbb{R}^{|V|} \to \mathbb{R}\). For each \(v \in V\) let \(C_v\) denote the union of \(v\) with all of its descendants in the graph \(G\) and \(f_v(x_{C_v}, x_{V \setminus C_v})\) denote any function. The smoothed \(q\)-value for node \(v\) is then,

\[
F_v(c; x_{V \setminus C_v}) \triangleq \text{pr}(f_v(\tilde{p}_{C_v}, x_{V \setminus C_v}) \leq c), \quad q_v \triangleq F_v(f_v(p_{C_v}, p_{V \setminus C_v}); p_{V \setminus C_v}),
\]

where \(\{\tilde{p}_w\}_{w \in C_v} \overset{i.i.d.}{\sim} \text{Uniform}[0,1]\). Note the value of \(q_v\) can be computed to arbitrary accuracy for any \(f\) using Monte Carlo simulations.

For each \(v\), the resulting random variable \(q_v\) is a valid \(p\)-value for the hypothesis \(H_v\).

**Lemma 1** (\(q\)-values are superuniform). \(\text{pr}(q_v \leq \alpha) \leq \alpha\) for every \(v \in \tilde{S}\).

We defer the proof to the appendix. Lemma 1 allows us to construct a hypothesis test
with Type I error control using the smoothed \( q \)-values. The value at \( q_v \) is a function of \( p_v \) and all its ancestors and descendants. This enables \( q \)-values to borrow statistical strength from each other and, depending on the choice of \( \{ f_v \} \), can lead to more powerful hypothesis tests. The optimal smoothing functions \( \{ f_v \}_{v \in V} \) are application specific. They depend on the structure of the graph, alternative hypothesis, and prior knowledge about the experiments. We focus our investigation on smoothing functions that use only the descendants at each node. Methods using ancestor nodes are left for future work.

### 3.2 Descendant smoothing functions

Descendant functions combine the \( p \)-values of all the descendant nodes with the current node. Many different \( p \)-value merging strategies have been proposed in the literature. We consider and analyze two well-known methods for merging \( p \)-values: Stouffer merging ([Stouffer et al., 1949](#)) and Fisher merging ([Fisher, 1992](#)). Stouffer merging converts the \( p \)-values to \( z \)-scores and adds them,

\[
q_v = \sum_{p_c \in C_v} \Phi^{-1}(p_c),
\]

where \( \Phi \) is the CDF of a standard normal. Fisher merging considers the product of the \( p \)-values,

\[
q_v = \Psi_{2|C_v|} \left( \sum_{p_c \in C_v} \log p_c \right),
\]

where \( \Psi_{2|C_v|} \) is the CDF of a \( \chi^2_{2|C_v|} \). Fisher’s method tends to have high power in a wide range of scenarios, though other methods will be more powerful for certain alternative distributions. [Heard and Rubin-Delanchy, 2018](#) provide a survey of other methods and a Neyman-Pearson analysis of optimal alternative hypotheses for each merging function.

Descendant smoothing functions are convenient to work with both computationally and mathematically. Classical merging methods typically have a closed form distribution that enables fast calculation of the smoothed statistic. As we will see, theoretical properties for Stouffer and Fisher merging can also be proven, making them compatible with a broad set of selection methods.

### 4 Testing with Smoothed Statistics

#### 4.1 Target error metric definitions

Once the test statistics have been smoothed, we must select the rejected hypotheses \( \hat{S} \). The selection procedure depends on the type of error metric. We will look at three error rate metrics which the scientist may wish to control: familywise error rate, false discovery rate, and false exceedance rate.

The familywise error rate (FWER), controlled at level \( \alpha \), ensures the probability that even one null hypothesis was rejected is at most \( \alpha \). Mathematically,

\[
\text{pr}(|\hat{S} \cap \hat{\bar{S}}| \geq 1) \leq \alpha.
\]

Controlling the FWER requires a very stringent procedure and generally results in the fewest number of discoveries.
The false discovery rate (FDR), controlled at level $\alpha$, ensures the expected proportion of rejected hypotheses that are actually null is at most $\alpha$. Mathematically,

$$E[|\hat{S} \cap \bar{S}|/(1 \lor |\hat{S}|)] \leq \alpha.$$ 

This is a less stringent requirement, but has some issues if the false discovery proportion has high variance. For example, if 10% of the time a method selects all nulls and 90% of the time it selects zero discoveries, the FDR is still low (only 0.1).

The false exceedance rate (FDX), controlled at level $(\gamma, \alpha)$, ensures the false discovery proportion is greater than $\gamma$ with probability no greater than $\alpha$. Mathematically,

$$\Pr(|\hat{S} \cap \bar{S}|/|\hat{S}| > \gamma) \leq \alpha.$$ 

This is in-between FWER and FDR. For example, $(\gamma = 0.1, \alpha = 0.1)$ requires that 90% of your discoveries are correct, 90% of the time.

For each of the three metrics, we also require that selection preserves the logical nesting structure implied by the graph. We leverage existing DAG testing frameworks for this structured selection, though it is not immediately obvious that this is valid. As we will see, controlling the FWER and FDX is possible for a very general class of smoothing functions; FDR control requires more careful consideration. All proofs are deferred to the appendix.

4.2 Familywise error rate control

To estimate $S$ while controlling the FWER, we can directly apply the algorithm of Meijer and Goeman to the $q$-values (Meijer and Goeman (2015)). Even though the smoothed $q$ values are dependent, this correction is still valid, as formalized in the following lemma.

Lemma 2 (Smoothed Meijer-Goeman). Meijer and Goeman’s estimators for $S$ (cf. Meijer and Goeman (2015)) applied to the smoothed $q$-values still control FWER at the nominal level.

This result is very general. It admits any choice of function over the descendant and ancestor $p$-values. This is possible because the inner-loop of the Meijer and Goeman (2015) algorithm relies on a Bonferroni correction. The union bound strategy of the Bonferroni correction places no requirement on the dependency structure of the statistics, so long as they are marginally all (super-)uniform.

4.3 False exceedance rate control

To estimate $S$ while controlling the FDX, we first apply the FWER control algorithm of Meijer and Goeman (2015). Starting from the roots of the graph $G$, we then reject additional hypotheses until we cross the exceedance rate under the assumption that all our original discoveries were correct and all new discoveries are false. Algorithm 1 outlines the process. The following lemma ensures FDX control.

Lemma 3 (False exceedance control from familywise error control). Let $\hat{S}_{\text{FWER}(\alpha)}$ denote an estimator which controls FWER at the $\alpha$ level. Let $\hat{S}_{\text{FDX}(\alpha)}$ denote any other estimator such that $\hat{S}_{\text{FDX}(\gamma, \alpha)} \supseteq \hat{S}_{\text{FWER}(\alpha)}$ and $|\hat{S}_{\text{FDX}(\gamma, \alpha)} \setminus \hat{S}_{\text{FWER}(\alpha)}| / |\hat{S}_{\text{FDX}(\gamma, \alpha)}| \leq \gamma$. Then $\hat{S}_{\text{FDX}(\gamma, \alpha)}$ controls the false exceedance rate at level $\gamma, \alpha$.  

6
Algorithm 1 FDX extension from FWER

1: procedure $(q\text{-values }q = (q_1, \ldots, q_n), \text{ directed acyclic graph } \mathcal{G}, \text{ exceedance level } \gamma, \text{ estimate } \hat{S}_{\text{FWER}(\alpha)})$

2: $\hat{S}_{\text{FDX}(\alpha, \gamma)} \leftarrow \hat{S}_{\text{FWER}(\alpha)}$

3: for $v \in \text{toposort}(\mathcal{G})$ do

4: if $\gamma \geq |\hat{S}_{\text{FDX}(\alpha, \gamma)} \cup \{v\} - \hat{S}_{\text{FDER}(\alpha)}|/|\hat{S}_{\text{FDX}(\alpha, \gamma)} \cup \{v\}|$ then

5: $\hat{S}_{\text{FDX}(\alpha, \gamma)} \leftarrow \hat{S}_{\text{FDX}(\alpha, \gamma)} \cup \{v\}$

6: else

7: break

8: return $\hat{S}_{\text{FDX}(\alpha, \gamma)}$

The algorithm and lemma extend the result from [Genovese and Wasserman, 2006] to the DAG testing case. This extension ensures that, in addition to overall control of the FDX, the nesting structure is preserved.

### 4.4 False discovery rate control

To estimate $S$ while controlling the FDR, we apply the DAGGER method of [Ramdas et al., 2019]. The method works with the original test statistics by extending the [Benjamini and Hochberg, 1995] procedure to DAGs. As with BH, it is only guaranteed to control the FDR if the $q$-values satisfy a special property: positive regression dependence on each of a subset (PRDS). Specifically, for any $x, y \in \mathbb{R}^m$ let $x \leq y$ signify that $x_i \leq y_i$ for each $i$. A set $D \subseteq \mathbb{R}^m$ is called non-decreasing if $x \leq y, x \in D \implies y \in D$. A random object $X \in \mathbb{R}^m$ is said to satisfy PRDS on $T \subset \{1, \ldots, m\}$ if $t \mapsto P(X \in D | X_i = t)$ is monotone increasing for every non-decreasing set $D$ and every index $i \in T$.

If the $q$-values satisfy PRDS on $S$, DAGGER can be applied to these smoothed $q$-values. To prove the PRDS property, we first present the following lemma. In spirit it is similar to Lemma 3.1 of [Benjamini and Yekutieli, 2001], but this lemma is designed to help prove the PRDS property for general random variables.

**Lemma 4** (PRDS by coupling). Let $(q_1, \ldots, q_n) \in \mathbb{R}^n$ be a random vector. Suppose that for each $v \in S \subset \{1, \ldots, n\}$ we can exhibit (i) a random object $\varepsilon_v$ satisfying $\varepsilon_v \perp q_v$, and (ii) a collection of functions $\{g_{vw}\}_{w \neq v}$ such that

$$q_w = g_{vw}(\varepsilon_v, q_v) \quad \forall w \neq v$$

and $q_v \mapsto g_{vw}(\varepsilon_v, q_v)$ is monotone increasing. Then $q$ is PRDS on $\hat{S}$.

Using Lemma 4, we demonstrate that the two descendant smoothing function from Section 3.2, Fisher and Stouffer smoothing, yield PRDS $q$-values. The first method is based on Stouffer merging ([Stouffer et al., 1949], which sums $z$-scores.

**Lemma 5** (PRDS for Stouffer smoothing). Let

$$f_v(x) = \sum_{w \in C_v} \Phi^{-1}(x_w; \sigma^2_{vw})$$

where $\Phi^{-1}(x; \sigma^2)$ indicates the quantile function for a Gaussian random variable with variance $\sigma^2$. Then the resulting $q$-values are PRDS on $\hat{S}$. 7
The second method is based on Fisher merging \cite{Fisher1992}, which considers the product of the \( p \)-values,

**Lemma 6** (PRDS for Fisher smoothing). *Let*

\[
f_v(x) = \sum_{w \in C_v} \Psi^{-1}(x_w; k_{vw})
\]

*where \( \Psi^{-1}(x; k) \) indicates the quantile function for a \( \chi^2 \) random variable with \( k \) degrees of freedom. Then the resulting \( q \)-values are PRDS on \( \bar{S} \).*

In practice we find that Fisher smoothing usually has higher power than Stouffer smoothing; we use Fisher smoothing in our simulations. However, Fisher merging is notoriously sensitive to departures from the independence assumption on \( S \). When the independence of the nulls is in doubt, Fisher smoothing is not recommended as it will likely lead to inflated false discovery rates. We briefly turn to the dependent null case next, developing a robust version of Stouffer smoothing.

### 4.5 Dependent null statistics with Gaussian copulas

So far we have assumed that \( p_{\bar{S}} \) \text{i.i.d.} Uniform[0, 1]. If this does not hold, the smoothed \( q \)-values are not guaranteed to be super-uniform. This limits our ability to use these \( q \)-values for hypothesis testing. However, if anything is known about the dependency structure of the \( p \)-values then it may be possible to use this knowledge to create conservative bounds yielding super-uniform \( q \)-values.

In this section we consider the case that \( p_{\bar{S}} \) carries a Gaussian copula with unknown correlation matrix \( R \). In other words, letting \( \Phi^{-1} \) denote the quantile function of the standard normal and letting \( Z_v = \Phi^{-1}(p_v) \), we will assume that \( Z_{\bar{S}} \sim \mathcal{N}(0, R) \). This case arises naturally if the \( p \)-values come from correlated \( z \)-scores.

When the copula is Gaussian, we can still control any of the three target error metrics by using a method we dub **conservative Stouffer smoothing**,

\[
q_v \left\{ \begin{array}{ll}
1 & \text{if } \sum_{w \in C_v} \pi_{vw} Z_w \geq 0 \\
\Phi \left( \sum_{w \in C_v} \pi_{vw} Z_w \right) & \text{otherwise}
\end{array} \right.
\]

where \( \Phi \) is the cumulative distribution function of the standard normal and \( \pi \) satisfies \( \pi_{vw} \geq 0, \sum_{w \in C_v} \pi_{vw} = 1 \).

For FWER, it suffices to show that the smoothed \( q \)-values are marginally super-uniform,

**Lemma 7** (FWER control for Gaussian copulas). *Conservative Stouffer smoothing on marginally uniform \( p \)-values with any Gaussian copula yields super-uniform smoothed \( q \)-values, i.e. \( \text{pr}(q_v \leq \alpha) \leq \alpha \) for all \( v \in \bar{S} \).*

Control of the FDX follows directly from FWER control and Lemma 3.

If we know that the nulls are all non-negatively correlated, we can control the FDR.

**Lemma 8** (PRDS for conservative Stouffer smoothing). *Let \( R \) be a correlation matrix with no negative entries. Conservative Stouffer smoothing on marginally uniform \( p \)-values with any Gaussian copula of correlation \( R \) yields smoothed \( q \)-values which are PRDS on \( \bar{S} \).*

It follows that DAGGER can be applied to these conservatively smoothed \( q \)-values.
5 Results

5.1 Simulations

To benchmark Fisher smoothing, we run a set of simulations under different graph structures, alternative hypotheses, and target error metrics. We consider the following DAG structures:

- Deep tree. A tree graph with depth 8 and branching factor 2.
- Wide tree. A tree graph with depth 3 and branching factor 20.
- Bipartite graph. A two-layer graph with 100 roots and 100 leaves. Each root is randomly connected to 20 leaves.
- Hourglass graph. A three-layer graph with 30 roots, 10 middle nodes, and 30 leaves. Each (root, middle) and (middle, leaf) edge is added with probability 0.2. The graph is then post-processed to ensure each node is connected to at least one node, with middle nodes having at least one incoming and one outgoing node.

We generate one-sided $p$-values from $z$-scores with the null $z$-scores drawn from a standard normal. For each structure, we consider two scenarios:

- Global alternative. The alternative distribution at each non-null node is $\mathcal{N}(2, 1)$. DAGs are populated starting at the leaves and null nodes are flipped to non-null with probability 0.5.
- Incremental alternative. The alternative distribution at each non-null node is $\mathcal{N}(1 + 0.3 \times (D - d), 1)$, where $d$ is the depth of the node and $D$ is the maximum depth of the DAG. The graph is populated starting at the leaves with non-null probability 0.5 and internal nodes are intersection hypotheses that are null if and only if all their child nodes are null.

For each simulation, we run 100 independent trials and report empirical estimates of power, FWER, FDX, and FDR at $
alpha = (0.01, 0.02, 0.03, 0.04, 0.05, 0.08, 0.1, 0.15, 0.2, 0.25).

For the FDX, we fix $\gamma = 0.1$ for all experiments. We compare performance with and without Fisher smoothing using the method of Meijer and Goeman (2015) for FWER control, Meijer and Goeman (2015) with Algorithm 1 for FDX control, and Ramdas et al. (2019) for FDR control. Both structured testing methods are the current state of the art for testing on DAGs, with both showing the highest power to-date relative to other methods targeting the same error rate. We also compare to the structureless method of Benjamini and Hochberg (1995), which will generally not be admissible since it does not preserve nesting structure. However, performance relative to this baseline illustrates how smoothing turns the graph structure into an advantage rather than just a constraint.

Figure 1 presents empirical estimates of power for each simulation. In each scenario, Fisher smoothing boosts the power of all three methods. Moreover, in all simulations DAGGER actually performs as well or better than BH. This is particularly promising since Ramdas et al. (2019) found that the BH method almost always had higher power and only in very limited scenarios would the structured method outperform. This is completely reversed
Figure 1: Empirical power in each simulation as a function of target error rate. Gray lines are unsmoothed results, black lines are smoothed results; dashed lines use Meijer and Goeman (2015), dashed lines with arrows use Meijer and Goeman (2015) with Algorithm 1, and dotted lines use Ramdas et al. (2019); the solid gray line is the structureless (i.e. inadmissible) method of Benjamini and Hochberg (1995).

Figure 2: Empirical target error rates in each simulation. Lines match those in Fig. 1; the solid black line is the (0, 1) line (maximum allowable error).

in the smoothed case, with the BH method generally having lower power due to being unaware of the structure of the method.

Figure 2 confirms that indeed all methods conserve their target error rates empirically. In general, smoothing makes each method less conservative but not to the point of violating the target rate. This is precisely the desired outcome: given a budget for errors, one would
Figure 3: Performance comparison of raw $p$-values versus smoothed $q$-values on a biological dataset. Left: total discoveries reported by each method at varying error rates. Right: relative gain of using smoothed $q$-values over raw $p$-values. Solid gray line: BH; dotted black line: Fisher smoothing with DAGGER, dashed dark gray line: Fisher smoothing with the method of Meijer and Goeman (2015); light gray lines at bottom are the same two methods without smoothing.

prefer to make full use of the budget in order to maximize the number of discoveries.

5.2 Application to Single-Cell Developmental Trajectories

We demonstrate the gains of smoothed testing on a real dataset of gene expression gathered on developing mouse cells (Schiebinger et al., 2019). The data measure how the gene activity of those cells changed over time. The scientific goal is to discover differentially expressed genes and higher-order processes (e.g., pathways and regulatory networks) between hour zero and hour twelve. These hypotheses form a DAG, with genes at the leaves and more complex processes as internal nodes; we use the Gene Ontology (Ashburner et al., 2000) to define the DAG. For each node, we consider the null hypothesis that the activity of the member gene(s) was independent of the time of measurement. Each hypothesis is tested by constructing a classifier to predict the time (hour zero versus hour twelve) from the constituent gene(s). The $p$-values are computed using Fisher’s exact test for the confusion matrix on held-out data. The resulting DAG has 18197 nodes with 80703 edges.

We use Fisher smoothing and perform selection with FWER control via Meijer and Goeman (2015) and FDR control via Ramdas et al. (2019), each at the target error levels, $\alpha = (0.01, 0.02, 0.05, 0.1, 0.15, 0.2, 0.25, 0.3, 0.35)$.

Figure 3 shows the results and comparison to the same methods on the original test statistics. As in the simulations, the power gains are substantial: 25x more discoveries for the method of Meijer and Goeman (2015) and 28x more for the method of Ramdas et al. (2019). Further, the performance of DAGGER is similar to BH, though slightly lower power since this particular graph has many unconnected leaf nodes. Since the latter method does not preserve nesting, and is therefore inadmissible, smoothing has the important effect of recovering the power of BH while preserving the logical nesting structure.
6 Discussion

6.1 Reshaping for false discovery rate control under dependence

When targeting control of the FDR, we relied on DAGGER for selection after smoothing. There are actually two variants of this method, each extending structureless testing methods to the DAG testing scenario. We focused on the version which extends BH and requires PRDS. Another version extends the Benjamini and Yekutieli (2001) procedure to DAGs by reshaping the node-level test statistics.

As in the structureless procedure, reshaping controls the FDR regardless of any dependency structure among the statistics, so long as they are marginally (super-)uniform. This reshaping procedure can be applied directly to the smoothed $q$-values to control the FDR. However, the reshaping procedure raises the bar for rejection, often leading to low power, and will always lead to strictly lower power than the BH extension. Nevertheless, the reshaping variant could be used to control the FDR when using smoothing functions for which no PRDS guarantee is available.

6.2 Ancestor smoothing functions

We described a general framework for smoothing test statistics on DAGs by sharing statistical strength between related nodes. Our current work focused on descendant merging functions, which ignore the information contained in ancestor nodes. An alternative class of smoothing functions uses ancestor nodes to smooth the node statistics. These ancestor smoothing functions use prior knowledge about the experiment to adapt their test statistic based on the data in ancestral nodes. Ancestor smoothing functions construct $q_v$ by fixing all ancestor $p$-values of $p_v$ and fitting a model to the ancestor values. The model requires prior knowledge of the alternative hypothesis, such as knowing that the alternative signal attenuates with the depth of the graph. We expect this to be the case for many real-world scenarios where shallower nodes represent more complex mechanisms or stronger interventions.

Ancestor functions have the appeal of potentially incorporating prior knowledge to gain higher power, but come with substantial trade-offs. First, they typically do not have a closed form null distribution. This makes them computationally expensive, as they require many Monte Carlo simulations in which for every trial the adaptive procedure must be re-run. They are also much more difficult to analyze theoretically. When a selection method requires us to guarantee something about the joint distribution of the $q$-values under the null, adaptive methods will likely be inadmissible. Pragmatically, we have not found any practical examples where the prior knowledge is so strong that it leads to meaningful increases in performance over descendant merging. We leave investigation of ancestor smoothing and hybrid ancestor-descendant smoothing functions to future work.

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**Proofs**

We here recall some notation for the benefit of the reader. For each $v \in \{1, \cdots, n\} = \mathcal{V}$ we can observe a random variable $p_v$. Let $\tilde{\mathcal{S}} \subset \mathcal{V}$; we assume $\{p_v\}_{v \in \tilde{\mathcal{S}}} \overset{\text{i.i.d.}}{\sim} \text{Uniform}[0, 1]$. $\mathcal{G} = (\mathcal{V}, \mathcal{E})$
Algorithm 2  Goeman and Solari’s Threshold-Based Sequential Rejection Procedure

1:  procedure (p-values $p = (p_1, \ldots, p_n)$, a weight-function $w$)
2:    $R \leftarrow \emptyset$
3:  repeat
4:    $R \leftarrow \{v : p_v \leq w(v, R)\}$
5:  until convergence
6:  return $R$

whose edges encode logical constraints on the hypotheses: $v \rightarrow w \implies (v \in \bar{S} \implies w \in \bar{S})$. For each $v$ we have that $C_v$ denotes the union of $v$ with all of its descendants in the graph $G$ and $f_v(x_{C_v}, x_{\bar{V}\setminus C_v})$ denotes any function. The smoothed $q$-value for node $v$ is then,

$$F_v(c; x_{\bar{V}\setminus C_v}) \triangleq \Pr(f_v(\tilde{p}_{C_v}, x_{\bar{V}\setminus C_v}) \leq c), \quad q_v \triangleq F_v(f_v(p_{C_v}, p_{\bar{V}\setminus C_v}); p_{\bar{V}\setminus C_v}),$$

where $\{\tilde{p}_w\}_{w \in C_v} \overset{i.i.d.}{\sim} \text{Uniform}[0, 1]$.

.1 Smoothed test statistics

The starting point for this work is Lemma 1 which we prove here.

Proof. Fix any $v \in \bar{S}$. The meaning of the graph structure indicates that $C_v \subset \bar{S}$, so $\{q_w\}_{w \in C_v}$ are independent uniforms. Now conditioned on any values of $p_{\bar{V}\setminus C_v}$, the variable $q_v$ is calculated as the cumulative distribution function of $f_v(x_{C_v}, x_{\bar{V}\setminus C_v})$ applied to itself, which must be super-uniform. Since it is super-uniform conditioned on any fixed value of $p_{\bar{V}\setminus C_v}$, it must also be marginally super-uniform. \qed

.2 Familywise error rate control

Lemma 1 enables us to use standard false-discovery procedures such as the one introduced by Meijer and Goeman (2015). Their procedure is a specific example of the Sequential Rejection Procedure developed in Goeman and Solari (2010). This procedure uses a weight-function $w$ to discover nonnull hypotheses while controlling false discovery rates. The weight function takes two arguments: a hypothesis $v \in \{1 \cdots n\}$ and a subset $R \subset \{1 \cdots n\}$ of hypotheses which have already been rejected. The algorithm proceeds iteratively. For each hypothesis $v$, an initial thresholds is computed as $w(v, \emptyset)$. Hypotheses with $p$-values below the thresholds are then collected into a set $R$. Next, for each hypothesis $v$ a new threshold are computed using $w(v, R)$, and any $p$-values which are below the new thresholds are now added to $R$. This process is repeated until convergence. We give an outline in Alg. 2.

As shown in Goeman and Solari (2010), Alg. 2 will control familywise error rate at level $\alpha$ as long as two conditions hold on the weight function $w$. The first is monotonicity,

$$R \subset R' \implies w(v, R) \leq w(v, R').$$

This requires that it must get easier to reject more hypotheses as the rejection set increases. The second requirement is the one-step condition,

$$\Pr(S = \{v : p_v \leq w(v, S)\}) \geq 1 - \alpha,$$
where $S = \mathcal{V} \setminus \hat{S}$. If we let $R \leftarrow S$, the true set of of nonnull hypotheses, then the update

$$R \leftarrow \{v : p_v \leq w(v, R)\}$$

from Alg. 2 should do nothing, leading to the successful termination of the algorithm.

Meijer and Goeman (2015) introduce two options for this weight function (the “any-parent” and “all-parent” procedures) based on a directed acyclic graph $\mathcal{G}$. They show that both of their weight functions satisfy the monotonicity property and guarantee that $\sum_{v \in R} w(v, R) \leq \alpha$. Thus, to show that their method can be applied to the smoothed $q$-values proposed in this paper, it suffices to use these properties to show that the one-step condition is satisfied. This leads to Lemma 2 from the main text of this paper, which we prove below.

**Lemma 2 (Smoothed Meijer-Goeman).** Meijer and Goeman’s estimators for $S$ (cf. Meijer and Goeman (2015)) applied to the smoothed $q$-values still control FWER at the nominal level.

**Proof.** As discussed above, it suffices to show the one-step condition. This can be verified directly using a union bound, Lemma 1, and the weight control property above:

$$\Pr(S = \{v : q_v \leq w(v, S)\}) = \Pr(q_v > w(v, S) \quad \forall v \in S) \\
\geq 1 - \sum_{v \in \bar{S}} \Pr(q_v \leq w(v, S)) \\
\geq 1 - \sum_{v \in \bar{S}} w(v, S) \geq 1 - \alpha.$$ 

\[\square\]

.3 False exceedance control

FDX*

**Proof.** Let $E$ denote the event that every discovery in $\hat{S}_{\text{FWER}(\alpha)}$ is valid. When this happens, the number of false discoveries in $\hat{S}_{\text{FDX}(\gamma, \alpha)}$ is at most $|\hat{S}_{\text{FDX}(\gamma, \alpha)} \setminus \hat{S}_{\text{FWER}(\alpha)}|$. The corresponding false discovery proportion is thus at most $|\hat{S}_{\text{FDX}(\gamma, \alpha)} \setminus \hat{S}_{\text{FWER}(\alpha)}| / |\hat{S}_{\text{FDX}(\gamma, \alpha)}|$. If we bound this quantity by $\gamma$, the false discovery proportion is guaranteed to be less than $\gamma$ whenever the event $E$ happens. Since we have assumed $\hat{S}_{\text{FWER}(\alpha)}$ controls FWER at the $\alpha$ level, we know that $E$ happens with probability at most $1 - \alpha$. Thus the false discovery proportion exceeds $\gamma$ with probability at most $\alpha$. \[\square\]

.4 False discovery rate control

To use the unreshaped version of DAGGER on our $q$-values, we must show that these satisfy the PRDS property. To show this, we will use Lemma 4 from the main text of this paper, which we prove below.

**Lemma 4 (PRDS by coupling).** Let $(q_1, \cdots, q_n) \in \mathbb{R}^n$ be a random vector. Suppose that for each $v \in \bar{S} \subset \{1, \cdots, n\}$, we can exhibit (i) a random object $\varepsilon_v$ satisfying $\varepsilon_v \perp \setminus q_v$, and (ii) a collection of functions $\{g_{vw}\}_{w \neq v}$ such that

$$q_w = g_{vw}(\varepsilon_v, q_v) \quad \forall w \neq v$$
and \( q_v \mapsto g_{vw}(\epsilon, q_v) \) is monotone increasing. Then \( q \) is PRDS on \( \bar{S} \).

**Proof.** Fix any non-decreasing set \( D \) and any index \( v \in \bar{S} \). For notational convenience we will denote \( q_v = q_v(\epsilon, q_v) \). Using the independence of \( \epsilon_v \) from \( q_v \), we then obtain the following equivalence,

\[
pr(q \in D \mid q_v = y) = pr(g_v(\epsilon, y) \in D),
\]

where \( g_v(\cdot) \) denotes the vector \((g_{vw}(\cdot))_{w \neq v}\). It thus suffices to show that the right hand side is monotone as a function of \( y \). Fix any \( y_1 \leq y_2 \). By construction \( g_v(\epsilon, y_1) \preceq g_v(\epsilon, y_2) \). Using the nondecreasingness of \( D \) we obtain that

\[
g_v(\epsilon, y_1) \in D \implies g_v(\epsilon, y_2) \in D.
\]

Thus \( y \mapsto pr(g_v(\epsilon, y) \in D) \) is monotonic nondecreasing as desired.\( \Box \)

This allows us to prove Lemmas 5 and 6 from the main text of this paper, which we do below.

**Lemma 5** (PRDS for Stouffer smoothing). Let

\[
f_v(x) = \sum_{w \in C_v} \Phi^{-1}(x_w; \sigma_{vw}^2)
\]

where \( \Phi^{-1}(x; \sigma^2) \) indicates the quantile function for a Gaussian random variable with variance \( \sigma^2 \). Then the resulting \( q \)-values are PRDS on \( \bar{S} \).

**Proof.** Fix any \( v \in \bar{S} \). To apply Lemma 4 we must be able to write the distribution of \((q_v, q_{\bar{v}})\) such that \( q_{\bar{v}} \) is deterministic as a function of \( q_v \), our value of interest, and \( \epsilon_v \), some source of randomness with \( q_v \perp \perp \epsilon_v \). We achieve this by first showing that the original \( p \)-values can be written as a deterministic monotone function of \( q_v \) and independent noise, and then noting that the smoothed \( q \)-values are monotone functions of the \( p \)-values. That is, we define

\[
e_{vw} = p_w \quad w \notin C_v
\]

\[
h_{vw}(e_{vw}) = e_{vw} \quad w \notin C_v
\]

\[
\epsilon_{vw} \sim \mathcal{N}(0, \Sigma) \quad w \in C_v
\]

\[
h_{vw}(\epsilon, q_v) = \epsilon_{vw} + q_v \sum_{w \in C_v} \frac{|\sigma_{vw}|}{\sigma_{vw}} \quad w \in C_v,
\]

where \( \Sigma \) denotes the covariance of \((p_{C_v} \mid q_v)\). It is straightforward to verify that \((q_v, h_{vw}(\epsilon_v, q_v))\) carries the same distribution as \((q_v, p)\). Indeed, \( h_{vw}(\epsilon, q_v) = p_w \) for \( w \notin C_v \) and \( h_{vw}(\epsilon_v, q_v) \) yields the conditional distribution of \( p_{C_v} \mid q_v \). Finally, recall that since \( v \in \bar{S} \) we have \( p_{C_v} \perp \perp p_{\bar{v} \setminus C_v} \), so the overall distribution matches. We can therefore construct the joint on \((q_v, p, \epsilon)\) such that \( p = h_v(\epsilon_v, q_v) \).

\[
p_w = h_{vw}(\epsilon_v, q_v)
\]

\[
q_w = f_w(p) = (f_w \circ h_v)(\epsilon_v, q_v).
\]

Lemma 4 now yields our result; each \( f_w \circ h_v \) is monotone as a function of \( q_v \), because \( h_v \) is
monotone as a function of \( q_v \) and \( f_w \) is monotone in all its arguments, and \( \varepsilon_v \perp q_v \) because \( p_{\cdot\mid C_v} \perp q_v \).

**Lemma 6** (PRDS for Fisher smoothing). Let

\[
f_v(x) = \sum_{w \in C_v} \Psi^{-1}(x_w; k_{vw})
\]

where \( \Psi^{-1}(x; k) \) indicates the quantile function for a \( \chi^2 \) random variable with \( k \) degrees of freedom. Then the resulting \( q \)-values are PRDS on \( \mathcal{S} \).

**Proof.** The structure of the proof is the same as above. The only difference is how we write the distribution of \( p \mid q_v \). In this case it takes the form of a scaled Dirichlet distribution:

\[
\varepsilon_{vw} = p_w \quad w \not\in C_v
\]

\[
h_{vw}(\varepsilon_{vw}) = \varepsilon_{vw} \quad w \not\in C_v
\]

\[
\varepsilon_{vC_v} \sim \text{Dirichlet}(2k_v)
\]

\[
h_{vw}(\varepsilon_v, q_v) = \varepsilon_{vw}q_v \quad w \in C_v.
\]

This follows because the conditional distribution of several \( \chi^2 \) distributions conditioned on its sum follows a scaled Dirichlet distribution. \( \square \)

### 5 Dependency

Let \( \Phi^{-1} \) denote the quantile function of the standard normal. We here consider the case that \( Z_v = \Phi^{-1}(p_v) \) satisfies \( Z_{\mathcal{S}} \sim \mathcal{N}(0, R) \) for some correlation matrix \( R \). In this case the methods above may fail due to the correlation between the \( p \)-values. However, we can account for this dependency, even if we do not know \( R \). Throughout this section we consider this case, and apply what we call conservative Stouffer smoothing.

\[
q_v \left\{ \begin{array}{ll}
1 & \text{if } \sum_{w \in C_v} \pi_{vw} Z_w \geq 0 \\
\Phi \left( \sum_{w \in C_v} \pi_{vw} Z_w \right) & \text{otherwise},
\end{array} \right.
\]

where \( \Phi \) denotes the standard normal CDF and \( \pi \) satisfies \( \pi_{vw} \geq 0, \sum_{w \in C_v} \pi_{vw} = 1 \). As in the independent case, the existing techniques of Meijer and Goeman (2015) and Ramdas et al. (2019) can be now be applied to these smoothed values. The target error rate will still be controlled, even though the null \( p \)-values are no longer independent.

**Lemma 7** (FWER control for Gaussian copulas). Conservative Stouffer smoothing on marginally uniform \( p \)-values with any Gaussian copula yields super-uniform smoothed \( q \)-values, i.e. \( \Pr(q_v \leq \alpha) \leq \alpha \) for all \( v \in \mathcal{S} \).

**Proof.** Fix any \( v \in \mathcal{S} \). Let \( Y_v = \sum_{w \in C_v} \pi_{vw} Z_w \). The assumption of Gaussian copula tells us that \( Y_v \sim \mathcal{N}(0, \sigma^2) \). We can get an upper bound for \( \sigma^2 \) using the observation that \( R_{w, w'} \in [-1, 1] \) and \( \pi \) lies on the simplex:

\[
\text{var}(Y_v) = \sum_w \pi_w \left( \sum_{w'} R_{w, w'} \pi_{w'} \right) \leq \sum_w \pi_w(1) = 1.
\]
Thus $\sigma \leq 1$. We can now prove the Lemma, considering three different cases. First, let $\alpha \leq 1/2$. Then
\[
\Pr(q_v \leq \alpha) = \Pr(Y_v \leq \Phi^{-1}(\alpha)) = \Phi(\Psi^{-1}(\alpha)/\sigma) \\
\leq \Phi(\Phi^{-1}(\alpha)) = \alpha.
\]
This only works because we can assume $\Phi^{-1}(\alpha) \leq 0$; otherwise the inequality goes the other way. Second, let $1/2 < \alpha < 1$. Then
\[
\Pr(q_v \leq \alpha) = \Pr(q_v \leq 1/2) + \Pr(q_v \in (1/2, \alpha)) \\
= \Pr(q_v \leq 1/2) + 0 \leq 1/2 \leq \alpha.
\]
Finally, let $\alpha = 1$. Then $\Pr(q_v \leq 1) = 1 = \alpha$.

Lemma 8 (PRDS for conservative Stouffer smoothing). Let $R$ be a correlation matrix with no negative entries. Conservative Stouffer smoothing on marginally uniform $p$-values with any Gaussian copula of correlation $R$ yields smoothed $q$-values which are PRDS on $\bar{S}$.

Proof. As in the previous proof, let $Y_v = \sum_{w \in C_v} \pi_{vw} Z_w$. Note that $Y_\bar{S}$ is jointly Gaussian. Since $R$ has no negative entries and $\pi$ is also non-negative, the covariance of $Y_\bar{S}$ is positive. It follows that $Y$ are PRDS (Benjamini and Yekutieli, 2001). Moreover, $q$ is an elementwise monotone nondecreasing transformation of $Y$; each $q_v$ can be expressed as a monotone nondecreasing function of $Y_v$; it follows that $q$ are also PRDS.