**DAGGER : A sequential algorithm for FDR control on DAGs**

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Abstract

We propose a top-down algorithm for multiple testing on directed acyclic graphs (DAGs), where nodes represent hypotheses and edges specify a partial ordering in which hypotheses must be tested. The procedure is guaranteed to reject a sub-DAG with bounded false discovery rate (FDR) while satisfying the logical constraint that a rejected node’s parents must also be rejected. It is designed for sequential testing settings, when the DAG structure is known a priori, but the p-values are obtained selectively (such as sequential conduction of experiments), but the algorithm is also applicable in non-sequential settings when all p-values can be calculated in advance (such as variable/model selection). Our DAGGER algorithm, shorthand for Greedily Evolving Rejections on DAGs, allows for independence, positive or arbitrary dependence of the p-values, and is guaranteed to work on two different types of DAGs: (a) intersection DAGs in which all nodes are intersection hypotheses, with parents being supersets of children, or (b) general DAGs in which all nodes may be elementary hypotheses. The DAGGER procedure has the appealing property that it specializes to known algorithms in the special cases of trees and line graphs, and simplifies to the classic Benjamini-Hochberg procedure when the DAG has no edges. We explore the empirical performance of DAGGER using simulations, as well as a real dataset corresponding to a gene ontology DAG, showing that it performs favorably in terms of time and power.

**Keywords:** false discovery rate, multiple testing, partially ordered hypotheses, directed acyclic graph

1 Introduction

Considerable effort in the field of multiple testing is devoted to incorporating prior knowledge and structural constraints into the testing procedure. Such constraints come in various forms, including groupings of hypotheses, covariates, weights, knowledge of dependence structures, and so on. In this paper, we consider a general setting in which nodes representing hypotheses are organized in a directed acyclic graph (DAG), where the directed edges encode a partial order in which the hypotheses must be tested. We present a sequential top-down algorithm called DAGGER that it is designed to efficiently test hypotheses on such a DAG while providing false discovery rate (FDR) control.

Multiple testing on trees was suggested by two papers published in 2008: Meinshausen [24] discussed control of familywise error rate (FWER) in the setting of hierarchical testing of variable importance, and Yekutieli [35] presenting a method for FDR control for multiresolution testing of quantitative trait loci. In the same year, Goeman and Mansmann [9] proposed an algorithm for FWER control on a DAG, applied to the gene ontology (GO) graph.

The GO graph is an instance of an intersection DAG, in which every node corresponds to an intersection of elementary hypotheses, and the intersection set of a parent node is a superset of the union of the sets of its children. By definition of an intersection DAG, the unknown set of non-null hypotheses must satisfy the

**Strong Heredity Principle (SHP) :** all parents of a non-null node are themselves non-null.

A logical structure that holds in reality need not necessarily hold for the outputs of FDR or FWER procedures, such as the Benjamini-Hochberg or Bonferroni methods. To impose such a logical structure on the output of a multiple-testing procedure, we must explicitly insist that the rejected hypotheses obey the following constraints:
(C1). The rejected nodes must themselves form a DAG (a subgraph of the original DAG).

(C2). All parents of a rejected node must themselves be rejected.

Of course (C2) implies (C1), but not vice versa, and we make the difference explicit to provide intuition. The word “strong” in the SHP is used to differentiate it from its weaker form:

Weak Heredity Principle (WHP): at least one parent of a non-null node is itself non-null.

In this paper, we restrict our attention to the SHP, keeping in mind that it may be of interest in future work to develop algorithms where the rejected nodes satisfy the WHP. Of course, the notions of SHP and WHP coincide for any tree, which is an important special case of a DAG.

While some multiple-testing problems are non-sequential in nature, meaning that all the p-values are available at once, with no cost associated with accessing p-values, we wish to consider the more general problem of sequential multiple testing on arbitrary DAGs (that need not be of the intersection type), where the p-values are not available all at once, but must be obtained in sequence.

As a motivating example, imagine an environmental scientist Alice with access to a suite of chemical compounds. Alice wishes to understand which of these chemicals have an adverse effect on a subject X of interest, such as a human cell, a lab rat, or a species of bacteria. Due to her expertise, Alice is aware of a vast list of logical constraints. For example, she is confident that chemical C can potentially hurt X only if both chemicals A and B definitely hurt X. We assume that she can encode her knowledge as a DAG, with each node representing a different chemical, and an associated null hypothesis stating that this chemical does not hurt X, and she knows that the set of non-nulls satisfy the SHP. However, each test is time-consuming and yields noisy results. We are approached by Alice to design a sequential strategy for testing nodes on her DAG, and returning a set of rejections with bounded false discovery rate (FDR) and satisfy the logical constraints (C1) and (C2).

To summarize the above discussion, we outline two distinct motivations for algorithms on DAGs:

(M1). A DAG can represent a partial ordering over hypotheses being tested within a lab, where we first conduct tests at all the roots, and depending on their outcomes, we proceed to test hypotheses selectively down the DAG. We can save resources by exploiting constraints (C1) and (C2), by not testing descendants of a node that is not rejected, while further exploring the subgraph of nodes that are rejected. At the end of the adaptive exploration process, we would like a guarantee that not too many rejected nodes are false discoveries.

(M2). A DAG can represent a structural constraint that one might desire for interpretability of the rejected set, even when the p-values at all nodes can be calculated offline from existing data and there is no sequential component to the problem. We encounter this setting when dealing with a gene ontology DAG later in this paper, which is an intersection DAG. Here, logical coherence would require that the unknown underlying truth must satisfy both (C1) and (C2).

Under motivation (M1), the algorithm must be a single-pass and top-down algorithm, due to the nature of the investigative process. However, under motivation (M2), any top-down or bottom-up or combined algorithm would suffice, as long as the set of rejected nodes satisfied requirements (C1) and (C2). We remark that both SHP and WHP represent one-way constraints: a two-way constraint would further require that every rejected parent has at least one rejected child. Note that two-way constraints need not necessarily make sense under motivation (M1); moreover, scientists having motivation (M2) may be interested in group-level findings even without individual-level identification. Accordingly, our analysis here focuses exclusively on one-way constraints.

In this paper, we design a top-down sequentially rejective algorithm, referred to as the DAGGER procedure, for FDR control on DAGs. It was designed based on motivation (M1), but may naturally also be applied in situation (M2). Specifically, the DAGGER procedure can be run in a truly sequential fashion since it does not access child p-values when deciding whether to reject a parent or not. Under motivation (M2) it may be possible to design improved algorithms that consider all p-values simultaneously, but we are not aware of the existence of such algorithms, and as far as we know the DAGGER procedure is the first algorithm that, under either setting (M1) or (M2), is able to explicitly take into account the structure of the DAG, and can provably control FDR on general or intersection DAGs under a variety of dependence assumptions (independence, positive dependence, arbitrary dependence).
Terminology. A directed acyclic graph (DAG) is a graph with directed edges and no directed cycles. Nodes without incoming edges are called roots, while those without outgoing edges are called leaves. The depth of a node is the length of the longest path from a root to the node, plus one. Hence, if $D$ is the maximum depth of the DAG, then roots have depth one while leaves may occur at any depth from 1 to $D$. We use the terms parent and child in the natural way: if $A \rightarrow B$ is an edge, then $A$ is one of the parents of $B$, and $B$ is one of the children of $A$. Hence, leaves have no children, roots have no parents, while other “internal” nodes have both. Analogously, the ancestors of $B$ refer to all nodes, including its parents, that may follow a directed path that leads to $B$, while the descendants of $A$ refer to all nodes, including its children, that it may reach using a directed path. For the purposes of visualization, we imagine roots at the top, leaves at the bottom and all edges pointing downwards; we then use the term top-down to refer to calculations performed from roots to leaves, and bottom-up to mean the opposite.

Error metrics. There are several natural error metrics that one may consider in such a structured setting.

- $t$-FDR/FWER: total errors, includes mistakes made at any node.
- $d$-FDR/FWER: errors at a fixed desired depth $d$.
- $\ell$-FDR/FWER: errors at the leaves.
- $o$-FDR/FWER: errors at “outer” nodes, which are rejected nodes that are not parents of other rejected nodes.
- ML-FDR/FWER: multi-layer control of errors across different depths (various combinations of metrics).

This work focuses on procedures for controlling the $t$-FDR, which we simply refer to as FDR for the rest of this paper, under the strong heredity principle (SHP) in a fully sequential setup.

Special cases. There are several special structures that are of relevance: a tree (with one root, $L$ leaves, and each non-root node having at exactly one parent), a forest (a disjoint collection of trees), a line (with one root, one leaf, and each internal node having one parent and one child), and the empty graph (which corresponds to the standard unconstrained multiple testing problem). Reassuringly, DAGGER specializes to the algorithm for FDR control for trees/forests by Lynch et al. [21], which in turn specializes to the algorithm for a line by Lynch and Guo [20], which in turn simplifies to the Benjamini-Hochberg (BH) procedure [4] for a graph without edges.

Related work. Table summarizes our contributions relative to existing work. Below, we briefly clarify how the LORD and $p$-filter procedures are connected to DAGs.

The LORD algorithm [14] was recently introduced for the “online multiple testing” setting where we observe the p-value for a single hypothesis at each instance, and must immediately decide whether to reject it or not. Such an online FDR algorithms can be applied in settings (M1) and (M2) as follows: we test the root-level p-values one at a time in any chosen order, then, at the next level, we only test those hypotheses whose parents have been rejected in any chosen order, and so on. If the p-values are constructed to be independent, there is no concern of selection bias introduced by choosing which hypotheses to test, but otherwise corrections can be introduced that deal with arbitrarily dependent p-values. The power of the LORD algorithm was recently improved [26], and it is this algorithm that we use in the simulation section, with the same name for simplicity. There exist other online FDR algorithms that control a “modified” FDR, as first introduced by Foster and Stine [8] and generalized by Aharoni and Rosset [1], but the experiments by [14] demonstrate that LORD is often more powerful than these, and hence we compare to only this online FDR algorithm in our experiments section.

The original multi-layer $p$-filter algorithm by Barber and Ramdas [3] can control the FDR simultaneously over arbitrary non-hierarchical partitions, resulting in layers that resemble neither trees nor DAGs. However, as a special case, one may also consider hierarchical FDR control by choosing partitions of increasingly coarse resolutions, and hence it can applied to tree-structured settings. The generalized $p$-filter algorithm by Ramdas et al. [25] can even handle overlapping groups within each partition, and when this flexibility is utilized in the hierarchical setting, a group in one partition may have several parent groups in a coarser partition, effectively making the structure a DAG.

1 Recall that leaves may occur at many different depths.
2 These nodes are jointly determined by the graph and by the procedure.
| Error metric | Dependence | Setting | Graph and logical constraints | Style | Algorithm name (for DAGs) and reference |
|--------------|------------|---------|--------------------------------|-------|-----------------------------------------|
| FWER         | Sequential | Line    |                                | top-down | Rosenbaum [27]                        |
| FWER         | Sequential | Tree    |                                | top-down | Meinshausen [24]                      |
| FWER         | Batch      | DAG : SHP (two-way) | simultaneous | Focus-level: Goeman and Mansmann [9] |
| FWER         | Batch      | DAG : WHP, SHP (one, two-way) | top-down | MG-b1, MG-b2: Meijer and Goeman [22] |
| FWER         | Batch      | DAG : WHP, SHP (one, two-way) | top-down | structured-Holm: Meijer and Goeman [23] |
| t, o, d-FDR | Sequential | Tree    |                                | top-down | Yekutieli [35]                        |
| FDR          | Sequential | Line    |                                | top-down | Lynch et al. [21], Lynch [19]         |
| FDR          | Sequential | Tree    |                                | top-down | Lynch and Guo [20], Lynch [19]        |
| FDR          | Batch      | DAG : SHP | simultaneous | SCR-DAG: Lynch [19] |
| FDR          | Batch      | DAG : SHP | simultaneous | BH-DAG: Lynch [19] |
| FDR          | Batch      | DAG : SHP, WHP (one-way) | bottom-up | STAR: Lei, Ramdas and Fithian [18]   |
| FDR          | Sequential | DAG : SHP, WHP (one, two-way) | top-down | LORD: Javanmard and Montanari [14], Ramdas et al. [26] |
| ML-FDR       | Batch      | Tree    |                                | simultaneous | p-filter (original): Barber and Ramdas [3] |
| ML-FDR       | Batch      | Tree    |                                | simultaneous | p-filter (generalized): Katsevich and Sabatti [16] |
| ML-FDR       | Sequential | Tree    |                                | top-down | TreeBH: Bogomolov et al. [7]          |
| ML-FDR       | Batch      | DAG : SHP, WHP (two-way) | simultaneous | p-filter (generalized): Ramdas et al. [25] |
| FDR          | Sequential | DAG : SHP (one-way) | top-down | DAGGER: This paper, Theorem 1         |

Table 1. A summary of our contributions relative to related work, grouped by error metric. Naturally, any algorithm for general DAGs also applies to trees and to intersection DAGs. The traffic lights ●, ○ and ○ respectively represent results that work under some variant of independence, positive dependence, and arbitrary dependence between the p-values (the size and color representing strongest to weakest assumption). The red light with a green border ● means that the procedure needs some form of independence, but some amount of arbitrary dependence can also be handled. Please refer to the original papers for the exact error metrics and assumptions. We compare several of these algorithms using simulations in Section 4.
Paper organization. The rest of the paper is organized as follows. In Section 2, we formalize the notion of a canonical form of a DAG, and define the relevant terminology needed to set up the formal problem statement. In Section 3, we present the main class of algorithms in this paper that work under independence, positive dependence or arbitrary dependence. In Section 4, we run simulations to explore some aspects of our procedure's performance. On a real gene ontology DAG described in Section 5, we demonstrate our algorithm’s greater power compared to an existing FWER-control algorithm for DAGs. Finally, we provide the proof of our main theorem in Section 6 and conclude with a discussion of some open problems in Section 7.

2 Problem setup and semantics

We consider a directed acyclic graph (DAG) with \( N \) nodes, each representing one hypothesis associated with a single p-value. The hypothesis at a node may either correspond to (a) the intersection hypothesis of its children; or (b) a separate, possibly unrelated hypothesis. A DAG where every node corresponds to the first type is called an intersection DAG. Our algorithms will apply to intersection DAGs as well as more general DAGs.

Let us call the \( N \) hypotheses \( H_1, \ldots, H_N \), and the set of all hypotheses as \( \mathcal{H} \), and these are associated with corresponding p-values \( P_1, \ldots, P_N \). Naturally, when any of the hypotheses is a true null, we assume that its p-value is super-uniform, meaning that it satisfies the inequality

\[
\Pr\{P \leq t\} \leq t \text{ for all } t \in [0, 1].
\]  

We define the depth of a node \( a \), denoted \( \text{Depth}(a) \), in a top-down manner. All roots are initialized to have depth 1. Any node that has all parents being roots has depth 2, and so on recursively. Then, the depth of a node is always one larger than the maximum depth of any of its parents. More formally, using \( \text{Par}(a) \) to refer to the set of parents of node \( a \), we have

\[
\text{Depth}(a) = 1 + \max_{b \in \text{Par}(a)} \text{Depth}(a).
\]

In other words, a node’s depth is the length of the longest possible path one could take from a root to the node. Let \( D \) denote the maximum depth of any node in the DAG and let \( \mathcal{L} \) denote the set of all leaves. Note that all roots have depth 1, but not all leaves have depth \( D \)—there might be leaves at depths smaller than \( d \), and in fact a node that is isolated from the graph is both a root and a leaf at depth 1. Let \( \mathcal{H}_d \) denote the set of all hypotheses at depth \( d \), and let us arbitrarily name these as \( H_{d,1}, \ldots, H_{d,|\mathcal{H}_d|} \) with associated p-values \( P_{d,1}, \ldots, P_{d,|\mathcal{H}_d|} \). Let \( \mathcal{H}_{1:d} \) denote the set of all nodes with depth \( \leq d \). Then \( \{\mathcal{H}_d\}_{d=1}^D \) is a partition of the hypotheses, that naturally satisfy \( \mathcal{H}_d \cup \mathcal{H}_{1:d-1} = \mathcal{H}_{1:d} \) and also \( \mathcal{H}_{1:D} = \mathcal{H} \).

Note that we sometimes refer to nodes in the graph with the subscripts \( a \equiv (d, i) \). Consequently, if we explicitly refer to an arbitrary hypothesis while making its depth explicit, we may use the label \( H_{d,i} \), but if its depth is implicit then we may simply refer to the node as \( H_a \). For an example to aid visualization, the reader may refer to Figure 1.

2.1 Testing protocol and goal

Recall that we assume the scientist creates, or knows, the structure of the DAG in advance to performing any tests. The goal of the scientist is to design testing levels \( \alpha_{d,i} \) at which to test each \( P_{d,i} \), so that the false discovery rate (FDR) over the entire DAG is controlled at a predefined level \( \alpha \). The process is inherently constrained by the DAG to be sequential in nature—before testing a node, the scientist must have already tested and rejected all of its parents. In other words, we assume that the testing proceeds in \( D \) steps:

1. Test all root hypotheses at some predefined constant levels \( \{\alpha_{1,i}\}_{i \in \mathcal{H}_1} \), and let \( \mathcal{R}_1 \) denote the corresponding set of rejections.

2. For each depth \( d = 2, \ldots, D \), repeat the following: test all hypotheses at depth \( d \) at levels \( \{\alpha_{d,i}\}_{i \in \mathcal{H}_d} \), and let \( \mathcal{R}_d \) denote the corresponding set of rejections.

Let \( \mathcal{R}_{1:d} = \bigcup_{k=1}^d \mathcal{R}_k \) be the total set of rejections up to depth \( d \). Then, we formally require that the level \( \alpha_{d,i} \) at which \( P_{d,i} \) is tested must be solely a function of \( \mathcal{R}_{1:d-1} \) and the p-values in \( \mathcal{H}_d \).
Denote the set of discoveries over the DAG as the rejected set \( R = \bigcup_{d=1}^{D} R_d \), of size \( R = |R| \). If \( H_0 \) is the unknown set of true null hypotheses, then let the set of false discoveries by \( V = H_0 \cap R \), of size \( V = |V| \). Clearly, both \( R \) and \( V \) are random variables, and we define the false discovery rate as their expected ratio. In order to handle the ratio \( \frac{0}{0} \) that often arises in FDR control results, we adopt the convenient notation

\[
\frac{a}{b} = \begin{cases} 
\frac{a}{b}, & \text{if } b \neq 0, \\
0, & \text{if } b = 0.
\end{cases}
\]

With this notation, the false discovery rate is given by \( \text{FDR} = \mathbb{E} \left[ \frac{V}{R} \right] \), and our goal is to ensure \( \text{FDR} \leq \alpha \).

Since we only test nodes whose parents have been rejected, the set of nodes that is tested is itself random and a-priori unknown. This model intuitively mimics the adaptive process of science, allowing for the subset of hypotheses to be tested in the future to depend on which hypotheses are currently being tested, which in turn is a function of which hypotheses have been tested and rejected in the past. We wish to design algorithms to set the testing levels \( \alpha_i \) in an adaptive manner, so that no matter which nodes are null and non-null, and no matter the randomness in the corresponding p-values, the false discovery rate over the whole DAG is controlled. It turns out the algorithm design, as well as power, depend heavily on what assumptions one is willing to impose on the dependence structure between the various p-values, an issue which we now discuss.

### 2.2 Positive dependence (PRDS)

In this paper, we analyze four possible settings of dependence between the p-values, which are defined in terms of sets and functions that are nonincreasing with respect to a partial ordering. For a pair of vectors \( x, y \in [0, 1]^K \), we use the notation \( x \preceq y \) to denote the partial ordering defined by the orthant cone: i.e., we have \( x \preceq y \) if and only if \( x_i \leq y_i \) for all \( i \in \{1, \ldots, K\} \).

**Definition 1** (Nonincreasing sets and functions). A function \( f : [0, 1]^K \to \mathbb{R}_+ \) is **nonincreasing with respect to the orthant ordering** if \( x \preceq y \) implies \( f(x) \geq f(y) \). Similarly, a subset \( D \) of \( [0, 1]^K \) is **nondecreasing with respect to the orthant ordering** if \( x \in D \) implies \( y \in D \) for all \( y \succeq x \).

Equipped with this definition, we can now define a particular notion of positive dependence, called positive regression dependence on a subset, or PRDS for short, for a vector of p-values \( P \).
Definition 2 (PRDS). For any \( i \in \mathcal{H}^i \) and nondecreasing set \( D \subseteq [0,1]^n \), the function \( t \mapsto \Pr\{ P \in D \mid P_i \leq t \} \) is nondecreasing on the interval \( (0,1] \).

When the PRDS condition is met for a particular null \( P_i \), we then say that \( P \) is PRDS on \( P_i \). The original positive regression dependence assumption introduced by Lehmann [17] as well as the PRDS assumption first made by Benjamini and Yekutieli [5] both had \( P_i = t \) instead of \( P_i \leq t \) in the definition, but one can prove that both conditions are essentially equivalent.

The PRDS condition holds trivially if the p-values are independent, but also allows for some amount of “positive” dependence. Consider the following simple example for intuition. Let \( Z = (Z_1, \ldots, Z_n) \) be a multivariate Gaussian vector with covariance matrix \( \Sigma \); the null components correspond to Gaussian variables with zero mean. Letting \( \Phi \) be the CDF of a standard Gaussian, the vector \( P = (\Phi(Z_1), \ldots, \Phi(Z_n)) \) is PRDS on \( P_i \) for every null index \( i \) if and only if all entries of the covariance matrix \( \Sigma \) are non-negative. See Benjamini and Yekutieli [5] for additional examples of this type. Note that the PRDS assumption is closely related to the assumption of log-supermodularity, or equivalently multivariate total positivity of order two (MTP2), as studied by Karlin and Rinott [15]. In the Gaussian setting, MTP2 corresponds to the off-diagonal entries of the covariance matrix being equal. Since MTP2 is known to imply PRDS, results that hold under PRDS also immediately also hold under MTP2.

2.3 Arbitrary dependence and reshaping

In order to deal with arbitrarily dependent p-values, we first need to define reshaping functions \( \beta \), as introduced by Blanchard and Roquain [6].

Definition 3 (Reshaping). Let \( T \) denote the set of all probability measures \( \tau \) with domain \( \mathbb{R}^+ \). Given any user-chosen \( \tau \in T \), we define the reshaping function \( \beta = \beta_\tau \) as

\[
\beta_\tau(r) = \int_0^r x d\tau(x).
\]

We let \( \beta(T) := \{ \beta_\tau \mid \tau \in T \} \) refer to the set of all such reshaping functions. Alternatively, one may also choose \( \beta(r) = r \) if one wishes to avoid reshaping, as is done when dealing with independent or positively dependent p-values. We often drop the subscript \( \tau \) for ease of notation.

When no assumptions are made about the joint distribution of p-values, FDR-controlling procedures must generally be guarded while proclaiming a discovery. Noting that \( \beta_\tau(r) \leq r \) for any \( \tau \in T \) by construction, the function \( \beta \) is guaranteed to reshape vectors and hence the thresholds by lowering them, rendering the associated procedure more conservative. Indeed, the argument \( r \) has been used suggestively, since \( \beta \) conservatively undercounts the number of rejections. Benjamini and Yekutieli [5] suggested the specific choice of \( \beta \) being the normalized discrete measure assigning mass \( 1/k \) to each positive integer \( k \in \{1, \ldots, K\} \). Effectively, the Benjamini-Yekutieli (BY) procedure uses the function \( \beta_{BY}(r) = \frac{r}{\sum_{k=1}^{K} \frac{1}{k}} \). See Ramdas et al. [25] for further discussion on the uses and interpretation of reshaping, as well as associated references.

2.4 The Simes’ p-value

Given a subset \( \mathcal{S} \) of hypotheses \( H_1, \ldots, H_S \) and associated p-values \( P_1, \ldots, P_S \), the generalized Simes’ p-value is given by \( \text{Simes}(\mathcal{S}) := \min_{(k)} \frac{P_{(k)}|\mathcal{S}}{\beta_{(k)}} \), where \( P_{(1)}, \ldots, P_{(S)} \) denotes the sequence of ordered p-values. It is well known that if \( \mathcal{S} \) is null, meaning that it consists only of true null hypotheses, then \( \text{Simes}(P) \) is a bonafide p-value for the intersection hypothesis \( H_1 \cap \cdots \cap H_S \). More precisely, this statement means that under the global null hypothesis for subset \( \mathcal{S} \), we have \( \Pr\{ \text{Simes}(P) \leq t \} \leq t \) for all \( t \in [0,1] \). This guarantee holds for three settings of p-values: (a) independent, using \( \beta(x) = x \); (b) positively dependent, using \( \beta(x) = x \); and (c) arbitrary dependence, using \( \beta \in \beta(T) \). For a proof of the above claims, we refer the reader to the papers [31, 5, 6, 25].
The Simes’ p-value will be of special interest for intersection DAGs, because they yield bonafide p-values under positive dependence, even without reshaping. We remark that we may use other methods for combining p-values within a group to test the intersection null for that group, such as Fisher’s or Rosenthal’s, as long as the appropriate independence assumptions within the group are satisfied, and as long as we employ reshaping to guard against arbitrary dependence between the resulting group p-values.

3 An algorithm for general DAGs

The settings of dependence addressed that can be handled by our algorithm are:

(D1). For arbitrary and intersection DAGs: all p-values are independent.

(D2). For arbitrary and intersection DAGs: all p-values are PRDS.

(D3). For arbitrary and intersection DAGs: all p-values are arbitrarily dependent.

(D4). For intersection DAGs: the leaf p-values are PRDS, and other p-values are formed using Simes’ procedure.

(D5). For intersection DAGs: the leaf p-values are independent, and other p-values are formed using Fisher’s procedure, or the one by Stouffer et al. [33], commonly called Rosenthal’s method.

(D6). For intersection DAGs: the leaf p-values are arbitrarily dependent, and other p-values are formed using the procedures by Rüschendorf [29], Vovk [34] or Rüger [28].

In order to describe our algorithm, we need some further DAG-related notation. The descendants of a node a is the set of nodes that can be reached from a along a path of directed edges. We use \( \text{Sub}(a) \) to denote the subgraph formed by taking a as the root, along with all descendants of node a. The effective number of nodes and effective number of leaves in \( \text{Sub}(a) \), denoted by \( m_a \) and \( \ell_a \) respectively, are defined as follows. We calculate \( \ell_a \) and \( m_a \) for each node a in a bottom-up fashion: we first instantiate each leaf node \( a \in \mathcal{L} \) with the value \( m_a = \ell_a = 1 \), and then proceed up the tree, from leaves to roots, recursively calculating

\[
\ell_a^{(i)} = \sum_{b \in \text{Child}(a)} \frac{\ell_b}{|\text{Par}(b)|}, \quad \text{and} \quad m_a^{(i)} = 1 + \sum_{b \in \text{Child}(a)} \frac{m_b}{|\text{Par}(b)|}.
\]

In other words, the counts at each node are split evenly between its parents, and so on. By construction, these counts satisfy the following identities at the roots:

\[
\sum_{a \in \mathcal{H}_1} \ell_a^{(i)} = L, \quad \text{and} \quad \sum_{a \in \mathcal{H}_1} m_a^{(i)} = N.
\]

The above calculation is analogous to a water-filling procedure [19, 22]: imagine pouring a unit of water into all the leaf nodes, and then turning the graph upside down so that the leaves are at the top and roots at the bottom. Then, water will flow due to gravity from leaves to roots according to the dynamics (3)(i), whereas equation (4) corresponds to the conservation of water at the roots at the end of the process.

3.1 Generalized step-up procedures

For the moment, suppose that we are only testing a batch of \( K \) hypotheses. A threshold function for \( P_i \) is mapping of the form \( \alpha_i : \{1, \ldots, K\} \rightarrow [0, 1] \). Each function \( \alpha_i \) is also implicitly a function of the constant target FDR level \( \alpha \), but we leave this dependence implicit. A generalized step-up procedure associated with a sequence of threshold functions \( \{\alpha_i(r)\}_{i=1}^K \) works as follows. It first calculates the number of rejections as

\[
R = \arg \max_{r=1,\ldots,K} \left\{ \sum_{i=1}^K 1 \{ P_i \leq \alpha_i(r) \} \geq r \right\},
\]

and then rejects all \( i \) such that \( P_i \leq \alpha_i(R) \). For example, the BH procedure is recovered by using \( \alpha_i(r) = \alpha r / K \) for all \( i \). Our algorithm **DAGGER** will employ a generalized step-up procedure to test the hypotheses within \( \mathcal{H}_d \) for each \( d = 1, \ldots, D \).
3.2 The DAGGER algorithm

We are now ready to describe the DAGGER algorithm. We first choose reshaping functions $\beta_1, \ldots, \beta_D \in \beta(\mathcal{T})$ to protect against arbitrary dependence, or alternately $\beta_d(u) = u$ for all $d$ under positive dependence or independence. We then run a step-up procedure on $\mathcal{H}_d$, for each $d = 1, \ldots, D$, with threshold functions $\{\alpha_{d,i}(r)\}_{i=1}^{\mathcal{H}_d}$ defined by

$$\alpha_{d,i}(r) = \begin{cases} \min \left\{ \sum_{j \in \text{Par}(i)} H_{d,j} \in \mathcal{R}_{1:d-1} \right\} & \frac{\ell_i \beta_d(m_i + r + \mathcal{R}_{1:d-1} - 1)}{m_i} \leq \alpha \left\{ \sum_{i=1}^{\mathcal{H}_d} 1 \{P_i \leq \alpha_{d,i}(r)\} \geq r \right\}. \end{cases} \tag{6}$$

More explicitly, we set $R_{1:0} := 0$ and update $R_{1:d} = R_d + \mathcal{R}_{1:d-1}$, where $R_d$ is determined by

$$R_d = \max\{1 \leq r \leq \mathcal{H}_d : \sum_{i=1}^{\mathcal{H}_d} 1 \{P_i \leq \alpha_{d,i}(r)\} \geq r \}. \tag{7}$$

We refer to this procedure as greedily evolving rejections on DAGs, or DAGGER for short. The exact choice of reshaping function $\beta_d$ does not affect FDR control, but the power is certainly affected. A reasonable choice for $\beta_d$ would only use an underlying measure $\tau$ that puts mass only on the values that its argument could possibly take. For example, in order to mimic By, the reshaping function $\beta_d$ would assign mass proportional to $1/k$ to each of the real numbers $k \in \{m_i + d - 1, m_i + d, \ldots, m_i + |\mathcal{H}_{1:d}| - 1\}$. This assignment occurs because whenever there are any rejections at level $d$, we must have $d \leq \mathcal{R}_{1:d-1} \leq |\mathcal{H}_{1:d}|$. Special cases of DAGGER include:

- First, suppose that the DAG is trivial, with $N$ nodes and no edges. Then all the hypotheses are leaves, and the DAGGER procedure reduces to the BH procedure under independence or positive dependence, and to the BY procedure under arbitrary dependence. More generally, we recover the generalized BHY procedure [25].
- Second, suppose that the DAG is a line graph. On this DAG, the hypotheses are fully ordered, and our procedure reduces to the fixed sequential testing procedure of Lynch et al. [21].
- Third, consider a DAG in which each node has at most one parent, such as a tree. In such a DAG, our procedure reduces to the hierarchical testing procedure of Lynch and Guo [20].

The following theorem lists some conditions under which DAGGER controls FDR. Below, let FDR($\mathcal{H}_{1:d}$) refer to the FDR achieved after the first $d$ rounds of DAGGER, so that FDR = FDR($\mathcal{H}_{1:D}$).

**Theorem 1.** The DAGGER procedure has the following guarantees:

(a) (All DAGs) If all the p-values are either independent or positively dependent, then choosing $\beta_d(r) = r$ for all $d$ guarantees that FDR($\mathcal{H}_{1:d}$) $\leq \alpha$ for all $d$.

(b) (All DAGs) If the p-values are arbitrarily dependent, then choosing $\beta_d \in \beta(\mathcal{T})$ for all $d$ guarantees that FDR($\mathcal{H}_{1:d}$) $\leq \alpha$ for all $d$.

(c) (Intersection DAGs) If the p-values at the leaves are positively dependent, and p-values at all other nodes are formed using Simes’ procedure (either on the leaves of the node’s sub-DAG, or directly on the node’s children), then choosing $\beta_d(r) = r$ for all $d$ guarantees that FDR($\mathcal{H}_{1:d}$) $\leq \alpha$ for all $d$.

(d) (Intersection DAGs) If the p-values at the leaves are independent or arbitrarily dependent, and all other p-values are formed using any valid global null test on the leaves (such as Fisher’s, Rosenthal’s, Rüger’s or Rüschendorf’s methods, then choosing $\beta_d \in \beta(\mathcal{T})$ for all $d$ guarantees that FDR($\mathcal{H}_{1:d}$) $\leq \alpha$ for all $d$.

The proof of this theorem, which is based on a bottom-up induction, is provided in Section 5. The algorithm and proof combine the structure of the DAG with ideas from batch FDR procedures as well as online FDR procedures. Naturally, the use of generalized step-up procedures is reminiscent of batch FDR procedures like the BH method. Further, if we make more rejections earlier in the algorithm, then we get to test later hypotheses at more lenient thresholds, because $\alpha_{d,i}(r)$ increases with $\mathcal{R}_{1:d-1}$, reminiscent of online FDR procedures earning alpha-wealth on making rejections, to spend on later tests [8]. Also, note that for trees, Meinhausen’s FWER procedure [24] tests each node whose parents were rejected at a level $\alpha \frac{r}{L}$, and hence the last term in the expression for $\alpha_{d,i}(r)$ intuitively captures the more lenient thresholds that DAGGER enjoys. On a technical note, the proof employs some super-uniformity lemmas developed in both the offline context [6] [25], as well as the online context [14] [26].
4 Simulations

In this section, we compare the performance of the proposed algorithms with other existing algorithms including

- the Focus-level method by Goeman and Mansmann [9];
- generalizations of Meinshausen’s procedure to DAGs by Meijer and Goeman [22], called MG-b1, MG-b2;
- a structured-Holm procedure by Meijer and Goeman [23];
- the two top down procedures called SCR-DAG and BH-DAG by Lynch [19];
- the LORD algorithm by Javanmard and Montanari [14], specifically its improvement by Ramdas et al. [26].

Note that the first four algorithms control FWER, while the last three algorithms control FDR in the case of independent p-values. Code for reproducing our empirical results is available for free online.

An important caveat. We remind the reader that except for DAGGER and LORD, there is no other algorithm which is both sequential and controls FDR on a DAG under setting (M1). Therefore, in order to compare these algorithms, all the experiments are carried out in the batch/offline setting (M2) when all the p-values are available in advance and algorithms may take multiple passes over the p-values in order to determine rejections.

Summary of results under (M2). DAGGER is very efficient computationally, requiring only sort operations, and queries to the DAG structure. LORD is slightly faster, since it does not sort, but the other FDR algorithms, in particular SCR-DAG, BH-DAG, are slower by several orders of magnitude, taking several hundred times the amount of time that DAGGER does. This is because each iteration of these algorithms passes over the entire DAG, and the number of such iterations is the number of ultimately non-rejected hypotheses. Specifically, the Focus-level algorithm is prohibitively slow to repeat hundreds of times for each parameter setting in simulations, so we compare to it only in the real-data example in Section 5, but the other FWER algorithms are as fast as DAGGER. The fastest algorithms are BH, which has the highest power because it completely ignores structure, and structured-Holm which typically has the lowest power.

Across simulations, the FDR methods usually have greater power than the FWER methods. While it might be expected that BH will have more power than DAGGER because it is unconstrained, it turns out that this is not always the case, and we provide a simple counterexample. Lastly, we attempt to provide intuition about how the power of DAGGER changes with the shapes of the graphs.

DAGGER versus LORD. Since these are the only two algorithms that we are aware of that provide FDR control under setting (M1), it is instructive to compare their strengths and weaknesses. Both algorithms have the property that past rejections allow future hypotheses to be tested at larger levels. Recalling its description in Section 1, the main advantage of LORD is that it does not waste any alpha-wealth on testing hypotheses whose parents were not rejected, but it faces three significant disadvantages compared to DAGGER. Firstly, DAGGER tests each node at a different threshold that depends on the number of its descendants. As an example, if there are two nodes at the same depth, one being a leaf, and the other having thousands of descendants, then DAGGER will assign a larger test threshold to the latter node because of the number of future tests that depend on it, while LORD cannot adjust threshold levels for each test to take advantage of the DAG structure. Secondly, DAGGER can also test all the levels at a particular depth as a single batch, possibly gaining power by treating the p-values together using the generalized step-up procedure, as opposed to LORD, which cannot take other p-values into account when making each of its decisions. Lastly, unlike LORD, DAGGER does not need to conservatively reshape thresholds when dealing with positive dependence among p-values on general DAGs, and for intersection DAGs, it can handle positive dependence between the base p-values when Simes’ p-values are used at other nodes. Of course, not much can be said in general to compare the power of the two algorithms, since it is affected by the choice of graph structure, positions of the non-nulls and the density of the non-null p-values.

https://github.com/Jianbo-Lab/DAGGER/

Technically, LORD is a specific instance of monotone generalized alpha-investing rules for which FDR control is known [14, 26, 18].
4.1 Comparing various methods for FWER and FDR control

Graph structure. We follow the simulations by Meijer and Goeman [22] and choose the Gene Ontology (GO) and one of its subgraphs as the underlying graph structure. The Gene Ontology is a directed acyclic graph where each node represents a GO term and the relationships between the terms are represented by edges between the nodes. The child nodes represent more specialized terms than parent nodes. The GO graph has 4952 nodes in total. We also used the subgraph of the GO with cell proliferation as its top node with 494 nodes.

Distribution of null and alternative hypotheses. For each replication of our experiments, we distributed the null hypotheses and the alternative hypotheses randomly. The leaves are randomly chosen with probability $\pi_{L0}$ to be true and with probability $1 - \pi_{L0}$ to be false. The rest of the hypotheses are assigned true if and only if all of its children are true. We generate p-values in the following two different manners:

- **Independent p-values.** In the first setting, each p-value is independently generated as

  \[ X \sim \mu + \mathcal{N}(0, 1); \quad \text{p-value} = 1 - \Phi(X), \]  

  where $\Phi$ is the standard Gaussian CDF, with $\mu = 0$ for nulls and $\mu > 0$ for alternatives. Larger values of $\mu$ indicate stronger signals. We decrease the signal of alternatives linearly with increasing depth. Concretely, we set $\mu = 1$ at the nodes of the largest depth and increase the signal by 0.3 as depth decreases.

- **Simes’ p-values.** In the second setting, p-values in leaves are independently generated from the previous model, with $\mu = 2$ at alternatives. Each of the rest of the p-values is calculated as the p-value of all of the leaves one of whose ancestors is the corresponding node.

Parameters. For each setting, we increase the proportion of nulls on leaves $\pi_{L0}$ over the entire DAG from 0.15 to 0.95 by 0.05 and plot the power for each algorithm. We repeat each experiment 100 times. We set $\alpha = 0.2$, which refers to the target FWER for MG-b1, MG-b2 and structured-Holm and the target FDR for BH, SCR-DAG, BH-DAG and DAGGER. As SCR-DAG and BH-DAG don’t work in the case of arbitrary dependence, we only run these algorithms in the independent setting. LORD requires specification of an infinite sequence of constants, we stick to the same choice used in prior work [14, 26] for mixtures of Gaussians, since the first paper justifies its heuristic optimality by deriving a lower bound on power in unstructured settings.

Results. From Figure 2, the BH method, which controls FDR and doesn’t take logical constraints into consideration, has the largest power as expected. Our algorithm is more powerful than Lynch’s algorithm in the case where there are a large number of nulls, which is a relatively more common and practical setting. SCR-DAG has larger power when there are a smaller proportion of nulls, but it is both non-sequential, does not work with positive or arbitrary dependence and has a much bigger time complexity, as discussed below. LORD is less powerful than SCR-DAG, BH-DAG and DAGGER on the subgraph, but achieves larger power on the full GO graph. Finally, all the algorithms controlling FDR have larger power than the algorithms that control FWER when there are relatively large number of nulls. We refer the reader to Figure 4 for the achieved FDR of various algorithms.

Time complexity. Figure 3 shows the clock-time of various algorithms on a log scale. As the two top-down procedures of Lynch are too time-consuming to run over the whole GO graph, we only report their results on subgraphs of GO. In summary, structured-Holm and BH are the fastest, followed by LORD, DAGGER, MG-b1 and MG-b2. Lynch’s SCR-DAG and BH-DAG are the slowest, as is the Focus-level algorithm tested in the real data subsection. Those algorithms are not practical on large DAGs.
Figure 2. This figure shows the power of various algorithms on the entire GO graph (left) and the subgraph rooted at cell proliferation (right), under the setting of independent p-values (top) and Simes’ p-values (bottom).

Figure 3: The clock-time of various algorithms on the subgraph of the GO graph for independent p-values.
Figure 4. This figure shows the achieved FDP of various algorithms on the entire GO graph (left) and the subgraph rooted at cell proliferation (right), under the setting of independent p-values (top) and Simes’ p-values (bottom).

4.2 A case where DAGGER is more powerful than BH

In this and the next subsection, we generate random DAGs by first determining the number of nodes at each layer, then starting from the bottom layer, we randomly assign \( k \) distinct parents at depth \( d - 1 \) for each node at depth \( d \). Given a DAG, the leaves are randomly chosen with probability \( \pi_0 \) to be true and with probability \( 1 - \pi_0 \) to be false. The rest of the hypotheses are assigned true if and only if all of its children are true. Each p-value is independently generated from the following model:

\[
X \sim \mu + \mathcal{N}(0, 1); \quad \text{p-value} = 1 - \Phi(X),
\]

where \( \Phi \) is the standard Gaussian CDF, with \( \mu = 0 \) for nulls and \( \mu > 0 \) for alternatives. Larger values of \( \mu \) indicate stronger signals. We fix the target FDR to be \( \alpha = 0.2 \) for all experiments.

BH versus DAGGER. Unlike the BH algorithm, the rejections made by DAGGER respect the graph structure, and so we might expect BH to always have higher power. Here we describe a setting where DAGGER actually achieves higher power than Benjamini-Hochberg. It is when the non-nulls in the layers of smaller depth have stronger signal strength than the non-nulls in the deeper layers. Concretely, we generate a DAG of depth 2 with each node in the bottom layer randomly assigned to 2 nodes in the top layer. The signal strengths of non-nulls are \( \mu = 5 \) and \( \mu = 1 \) in the top and the bottom layer respectively. We control the target FDR to be \( \alpha = 0.2 \), number of nodes to be \( n = 200 \) and each experiment is repeated 100 times.
Figure 5. Plots of the achieved FDR and power versus the proportion of nulls in the case where signals are stronger at the top layer, controlling the target FDR $\alpha = 0.2$, number of nodes $n = 200$ and with 100 repetitions.

Figure 5 shows how the achieved FDR and the power vary with the proportion of nulls in the entire DAG. The error bars indicate in-sample standard deviations. The achieved power of DAGGER is larger than the achieved power of the Benjamini-Hochberg, indicating DAGGER fits specially to this setting. We also observe that both BH and DAGGER achieve a much lower FDR than the targeted FDR, opening up the possibility for using null proportion estimates [32, 25] if independence can be assumed.

Such a scenario could arise naturally in applications. For example, in the problem of supervised feature selection, one is interested in testing whether $X_1, X_2, \ldots, X_k$ are associated with $Y$. Similar features can be grouped into a node of a DAG, which takes the form of an intersection DAG. Every child corresponds to features which are a subset of the features in its parent node. Then nodes near the top contain more features and are expected to contain stronger signals than their children.

4.3 Additional experiments to study the effects of graph structure

We study how the structure of DAGs affect the achieved FDR and power of DAGGER. We focus on three scenarios:

In the first scenario, we make a comparison between shallow and deep networks. In the second scenario, we compare DAGs of two shapes: the diamond and the hourglass DAGs. In the third scenario, we compare DAGs in the shape of a mountain with DAGs in the shape of a valley.

**Shallow versus deep.** We define shallow DAGs to be DAGS composed of two layers with the same number of nodes in each layer. Deep DAGs are composed of four layers with the same number of nodes on each layer. For both cases, each node in a lower layer is randomly assigned to two parents in its upper layer. The target FDR is fixed to be $\alpha = 0.2$, the number of nodes are fixed to be 500 and the signal strength of non-nulls is $\mu = 2$.

Figure 6 shows the plots of the achieved FDR and power of DAGGER versus the proportion of nulls on shallow and deep graphs. DAGGER achieves larger power with a higher false discovery proportion on shallow DAGs. In fact, an incorrect acceptance of a non-null in the first layer has a worse effect when the DAG is deeper, because non-nulls in its descendants have no chance to be discovered at all.

**Diamond versus hourglass.** We define diamond DAGs to have the largest number of nodes in middle layers and fewer nodes at the top and the bottom layers, while hourglass DAGs have the smallest number of nodes in middle layers with more nodes at the top and bottom. In this experiment, we consider diamond and hourglass DAGs with three layers and 500 nodes in total. For diamond DAGs, there are 125, 250, 125 nodes on the three subsequent layers. Each node in the last layer is randomly assigned to two parents in its middle layer. Each node in the middle layer is randomly assigned to one parent in the top layer. For hourglass DAGs, there are 200, 100 and 200 nodes.
on the three subsequent layers. Each node in the last layer is randomly assigned to one parent in its middle layer. Each node in the middle layer is randomly assigned to two parents in the top layer.

Figure 7 shows plots of the achieved FDR and power of DAGGER versus the proportion of nulls on diamond and hourglass graphs. We set the target FDR $\alpha = 0.2$ and the signal strength of non-nulls to be $\mu = 2$. DAGGER achieves a higher power on hourglass DAGs. Intuitively, for each non-null in the top layer incorrectly accepted, there are a larger number of non-nulls ignored by DAGGER among its descendants when the DAG is of diamond shape. For each non-null in the second layer incorrectly accepted, there are a larger number of non-nulls ignored by DAGGER among its descendants when the DAG is of hourglass shape. Due to the structure of DAGs, the first case has a stronger negative effect on the power of DAGs, resulting in less power in diamond DAGs.

Mountain versus valley. Mountain DAGs have the smallest number of nodes in the top layers and increasing numbers of nodes in subsequent layers, while valley DAGs have the largest number of nodes in the first layers with increasing numbers of nodes in subsequent layers.

In this experiment, we consider mountain and valley DAGs with three layers and 498 nodes in total. For mountain DAGs, there are 83, 166, 249 nodes on the three subsequent layers. Each node in a layer is randomly assigned to one parent in its higher neighborhood layer. For valley DAGs, there are 249, 166, 83 nodes on the three subsequent layers. Each node in a layer is randomly assigned to two parents in its higher neighborhood layer.

Figure 8 shows plots of the achieved FDR and power of DAGGER versus the proportion of nulls on mountain and valley graphs. We set the target FDR $\alpha = 0.2$ and the signal strength of non-nulls to be $\mu = 2$. DAGGER achieves a higher power on valley DAGs. Intuitively, there are smaller number of descendants for each incorrectly accepted non-nulls in valley DAGs, among which all non-nulls are ignored.
Figure 7. Plots of the achieved FDR and power of DAGGER versus the proportion of nulls on diamond and hourglass graphs, controlling the target FDR $\alpha = 0.2$, number of nodes $n = 500$, signal strength $\mu = 2$ and with 100 repetitions.

Figure 8. Plots of the achieved FDR and power of DAGGER versus the proportion of nulls on mountain and valley graphs respectively over 100 repetitions, with target FDR $\alpha = 0.2$, number of nodes $n = 498$, signal strength $\mu = 2$. 
5 An application to the Gene Ontology (GO) DAG

In this section we present an experiment which compares DAGGER with Focus-level methods \(^{[9]}\), Benjamini-Yekutieli \(^{[5]}\) and all the other algorithms used in the simulation section on a subset of the Golub dataset \(^{[11]},^{[10]}\). This dataset contains 72 tumor mRNA samples in which the expression of 7129 genes is recorded. Specifically, the Golub data set is from the leukemia microarray study, recording the gene expression of 47 patients with acute lymphoblastic leukemia and 25 patients with acute myeloid leukemia. We focus on the biological process “cell cycle” (GO:0007049) and its descendants in the Gene Ontology (GO) graph, a DAG of 307 nodes in total.

The GO graph represents a partial order of the GO terms, and the set of genes annotated to a certain term (node) is a subset of those annotated to its parent node \(^{[2]}\). We test for differential biological process activity between the two kinds of patients. Concretely, the null hypothesis at each node is

\[
H_0: \text{ No gene in the node’s gene set is associated with the type of diseases.} \tag{10}
\]

Multiple testing procedures on the GO graph are expected to preserve the graph structure of Gene Ontology \(^{[9]}\), meaning that a child node is rejected only if all of its parents are rejected, which holds true for DAGGER.

Construction of p-values. Individual (raw) \(p\)-values on each node are obtained by Global Ancova \(^{[12]}\), which are calculated using the GlobalAncova package in R \(^{[13]}\). The test is carried out by comparison between the linear model containing all covariates and the reduced model containing the covariates of interest, which are the genes in the corresponding node here, via the extra sum of squares principle. The test statistic involves residual sums of squares from both the full model (FM) and the reduced model (RM):

\[
F_{GA} = \text{Const} \cdot \frac{\text{RSS}_\text{RM} - \text{RSS}_\text{FM}}{\text{RSS}_\text{FM}}, \tag{11}
\]

and the \(p\)-values are computed with a permutation-based approximation \(^{[12]}\). Note that the \(p\)-values obtained by are arbitrarily dependent, and we consequently adopt the Benjamini-Yekutieli reshaping function in DAGGER and LORD, which we call reshaped DAGGER and reshaped LORD.

Compared algorithms. Figure 9 shows the number of rejections at various critical levels \(\alpha\), where \(\alpha\) refers to the target FDR levels for DAGGER, LORD, reshaped DAGGER, reshaped LORD, SCR-DAG, BH-DAG, BH and BY (the reshaped BH procedure by Benjamini and Yekutieli \(^{[5]}\)), whereas \(\alpha\) refers to the target FWERs for structured-Holm, MG-b1, MG-b2 and Focus-level. \(P\)-values do not have the assumption of independence or positive dependence, but we include algorithms with these assumptions for comparison. Algorithms that only control FDR under an independence assumption are shown with a dotted line, namely LORD and SCR-DAG. Algorithms that control FDR under an assumption of positive dependence are followed by a (+) symbol in the legend, namely DAGGER, BH-DAG and BH. All other methods control FDR/FWER without dependence assumptions.

Time. We apply the Focus-level method with the default focus level in the GlobalAncova package \(^{[13]}\), which takes about four minutes to run. We note that the Short-Focus-Level procedure, recently proposed as a more computationally efficient algorithm to control FWER on the GO graph by \(^{[30]}\), takes about 1 second. The rest of the algorithms are much faster in clock time and in particular, DAGGER takes about 0.02 seconds.

Power. Among the algorithms that control FDR under no dependence assumptions while respecting the strong hierarchical principle (SHP), namely reshaped DAGGER, reshaped LORD and all the FWER algorithms, we see that reshaped DAGGER is the most powerful. Similarly, among algorithms that control FDR under the assumption of positive dependence and also respect SHP, namely the aforementioned algorithms as well as DAGGER and BH-DAG, we find that DAGGER again consistently yields the largest number of rejections.

It is worth noting that DAGGER performs only slightly worse than BH, while the reshaped DAGGER performs almost as well as BY.

Figure 10 shows the rejections made by DAGGER and by reshaped DAGGER at \(\alpha = 0.001\) respectively. By construction, the set of rejections by DAGGER always contains all of the rejections made by reshaped DAGGER, but interestingly, in this example, one does not lose much power by removing the assumption of positive dependence.
Figure 9. Plots of the number of rejections with various levels of $\alpha$: \{0.001, 0.002, 0.005, 0.01, 0.02, 0.05, 0.1, 0.2\}, where $\alpha$ refers to the target FDR or FWER. The algorithms that work under an independence assumption (unrealistic for this dataset) are shown with a dotted line. The algorithms that work with the assumption of positive dependence (plausible, but not provable) are followed by (+) in the legend. Other algorithms make no dependence assumptions.

Figure 10. Green nodes (size 177) are rejections made by reshaped DAGGER, while red nodes (size 18) are the additional rejections made by DAGGER if positive dependence is assumed, both at a target FDR of $\alpha = 0.001$. 
6 The proof of Theorem \( \mathbf{I} \) (FDR control for DAGGER)

Below, we will prove that FDR(\( \mathcal{H}_{1:d} \)) = FDR ≤ \( \alpha \), from which it must necessarily follow that FDR(\( \mathcal{H}_{1:d} \)) ≤ \( \alpha \) for all \( d \). The latter implication is true because DAGGER must control FDR regardless of null p-values, and when it has completed \( d \) rounds (for any \( d \)), it must automatically guard against the hypothetical possibility that all remaining hypotheses are nulls, and all those null p-values equal 1, in which case DAGGER will make no more rejections, resulting in FDR(\( \mathcal{H}_{1:d} \)) equaling FDR(\( \mathcal{H}_{1:d} \)) and hence being at most \( \alpha \).

To proceed, we first define random variables that we need in the proofs, namely the effective number of discoveries and false discoveries in the subgraph below a node. Recalling that \( \mathcal{R} \) and \( \mathcal{V} \) are the set of discoveries and false discoveries, we define \( R(\text{Sub}(a)) \) and \( V(\text{Sub}(a)) \) in a bottom-up fashion. They are set for leaves \( a \in \mathcal{L} \) as

\[
V(\text{Sub}(a)) := 1 \{ a \in \mathcal{V} \}, \\
R(\text{Sub}(a)) := 1 \{ a \in \mathcal{R} \}.
\]

We then calculate their effective values for non-leaf nodes \( a \) recursively up the DAG as

\[
V(\text{Sub}(a)) := 1 \{ a \in \mathcal{V} \} + \sum_{b \in \text{Child}(a)} V(\text{Sub}(b)) \left( \frac{1}{|\text{Par}(b)|} \right), \tag{12}
\]

\[
R(\text{Sub}(a)) := 1 \{ a \in \mathcal{R} \} + \sum_{b \in \text{Child}(a)} R(\text{Sub}(b)) \left( \frac{1}{|\text{Par}(b)|} \right).
\]

They satisfy the following identities at the roots:

\[
V = \sum_{a \in \mathcal{H}_1} V(\text{Sub}(a)) \quad \text{and} \quad R = \sum_{a \in \mathcal{H}_1} R(\text{Sub}(a)). \tag{13}
\]

Before proceeding, we summarize the notation used in this paper, much of which is needed for the proof.

| Notation | Meaning |
|----------|---------|
| \( N \) | the number of nodes in the DAG, each one representing a null |
| \( D \) | the maximum depth of any node in the DAG |
| \( \mathcal{H}_{d} \) | the set of hypotheses at depth \( d \) |
| \( \mathcal{H}_{1:d} \) | the set of hypotheses with depth less than or equal to \( d \) |
| \( \mathcal{H}_{d,i} \) | the \( N \) null hypotheses, one at each node |
| \( \mathcal{H}_0 \) | the set of all null hypotheses |
| \( P_{d,i} \) | the \( N \) p-values, one at each node |
| \( \mathcal{L} \) | the set of all leaves in the DAG |
| \( L = |\mathcal{L}| \) | the total number of leaves in the DAG |
| \( \alpha_{d,i} \) | the level at which \( H_{d,i} \) is tested |
| \( R_{d,i} \) | the indicator of whether the \( i \)-th hypothesis was rejected |
| \( \mathcal{R} \) | the set of all rejected hypotheses |
| \( R = \sum_{d,i} R_{d,i} \) | the total number of rejections |
| \( \mathcal{R}(\mathcal{H}_{1:d}) \) | the set of all rejections up until, and including depth \( d \) |
| \( R(\mathcal{H}_{1:d}) \) | the total number of rejections up until, and including depth \( d \) |
| \( \mathcal{V} = \mathcal{H}_0 \cap \mathcal{R} \) | the set of all false discoveries |
| \( V \) | the total number of false discoveries |
| \( \text{Depth}(a) \) | the depth of node \( a \) |
| \( \text{Par}(a) \) | the set of all parents of node \( a \) |
| \( \text{Child}(a) \) | the set of all children of node \( a \) |
| \( \text{Sub}(a) \) | the set of all descendents of node \( a \), including node \( a \) |
| \( m_a \leq |\text{Sub}(a)| \) | the effective number of nodes in \( \text{Sub}(a) \) |
| \( \ell_a \leq |\text{Sub}(a)| \) | the effective number of leaves in \( \text{Sub}(a) \) |
| \( R(\text{Sub}(a)) \leq m_a \) | the effective number of discoveries made in \( \text{Sub}(a) \) |
| \( V(\text{Sub}(a)) \) | the effective number of false discoveries made in \( \text{Sub}(a) \) |
The key enabler of the proof of Theorem 1 is the following lemma.

**Lemma 1.** For every node $a$ in the DAG, the DAGGER method guarantees that
\[ E\left[ \frac{V(\text{Sub}(a))}{R}\right] \leq \alpha \frac{\ell_a}{L}. \]

Before proving this lemma under the assumptions of the various theorem statements (a,b,c,d), we first demonstrate that it easily implies the statement of the theorem. This follows by noting that
\[ \text{FDR} = E\left[ \frac{V}{R}\right] = \sum_{a \in H_1} E\left[ \frac{V(\text{Sub}(a))}{R}\right] \leq \sum_{a \in H_1} \alpha \frac{\ell_a}{L} = \alpha, \]
where the equalities follow by identities (13) and (4), and the sole inequality follows by Lemma 1.

Hence, to conclude the proof of Theorem 1 we only need to prove Lemma 1 under the different dependence assumptions. With this aim in mind, we utilize variants of the super-uniformity lemma proved by Ramdas et al. [25], generalizing work by Blanchard and Roquain [6]. In particular, first note that our super-uniformity assumption (1) on null p-values can be reformulated as follows:
\[ \text{For any } i \in H^0, \quad E\left[ \frac{1}{t} \{ P_i \leq f(P) \}\right] \leq 1 \text{ for any non-random } t \in [0, 1]. \quad (14) \]

Of course, if $P_i$ is uniform then the above inequality holds with equality. The following lemma, which combines parts of Lemmas 1 and 3 from Ramdas et al. [25], guarantees that property (14) continues to hold for certain random thresholds $f(P)$. Recall that the term “nonincreasing” is interpreted coordinatewise, with respect to the orthant ordering (Def. [1]).

**Lemma 2** (Super-uniformity lemmas (Ramdas et al. [25])). Let $f : [0, 1]^n \mapsto [0, \infty)$ be an arbitrary function, let index $i \in H^0$ refer to some null hypothesis, and let $g \subseteq H^0$ refer to some null group with Simes’ p-value $P_g$.

(a) If $f$ is nonincreasing, then under independence or positive dependence, we have
\[ E\left[ \frac{1}{c} \{ P_i \leq f(P) \}\right] \leq 1. \]

(b) For any constant $c > 0$, and any $\beta \in \beta(T)$, then under arbitrary dependence we have
\[ E\left[ \frac{1}{c \beta(f(P))} \{ P_i \leq c \beta(f(P)) \}\right] \leq 1. \]

(c) If $f$ is nonincreasing, and the base p-values are positively dependent, we have
\[ E\left[ \frac{1}{c f(P)} \{ P_g \leq f(P) \}\right] \leq 1. \]

We will apply the above super-uniformity lemma to prove Lemma 1 where cases (a,b,c) above will correspond exactly to cases (a,b,c) in the statement of Theorem 1. Theorem statement (d) actually follows directly from theorem statement (b)—independence at leaf p-values is only required so that p-value combination methods like Fisher’s and Rosenthal’s can produce valid p-values; however, since different Fisher combinations can be arbitrarily dependent, we may utilize reshaping to protect against this scenario.

We now have the tools in place to prove Lemma 1, concluding the proof of Theorem 1. At a high level, Lemma 1 is proved using a bottom-up induction.
Proof of Lemma \[\text{[7]}\] We divide the proof into two cases, depending on whether \( H_d \equiv H_{d,i} \) is true or not.

**Case 1.** Suppose \( H_{d,i} \) is true. Note that \( V(\text{Sub}(a)) \) is nonzero only if \( H_{d,i} \) was rejected. Since \( V(\text{Sub}(a)) \leq R(\text{Sub}(a)) \leq m_a \), we have

\[
\mathbb{E} \left[ \frac{V(\text{Sub}(a))}{R} \right] \leq \mathbb{E} \left[ \frac{V(\text{Sub}(a))}{V(\text{Sub}(a)) + R - R(\text{Sub}(a))} \right] \\
\leq \mathbb{E} \left[ \frac{m_a}{m_a + R - R(\text{Sub}(a))} 1 \{ H_{d,i} \text{ is rejected} \} \right] \\
\leq \mathbb{E} \left[ \frac{m_a}{m_a + R(H_{1:d}) - 1} 1 \{ H_{d,i} \text{ is rejected} \} \right],
\]

where the last inequality follows because \( R = R(H_{1:D}) \geq R(H_{1:d}) + R(\text{Sub}(a)) - 1 \). By definition of our procedure, we may then infer that

\[
\mathbb{E} \left[ \frac{V(\text{Sub}(a))}{R} \right] \leq \alpha \frac{\ell_a}{L} \mathbb{E} \left[ \frac{1}{\alpha \ell_a} \frac{1}{m_a + R(H_{1:d}) - 1} 1 \{ P_{d,i} \leq \alpha \frac{\ell_a}{L} m_a R(H_{1:d}) - 1 \} \right] \\
\leq \alpha \frac{\ell_a}{L},
\]

where the last inequality follows by applying Lemma \[\text{[3]}\] (a, b, c) to the function \( f : P \mapsto \alpha \frac{\ell_a}{L} m_a + R(H_{1:d}) - 1 \), which is easily seen to be nonincreasing in \( P \); indeed, decreasing any of the p-values can only possibly increase the total number of rejections.

**Case 2.** We handle the case when \( H_a \) is false by induction, leaves upwards. If \( H_a \) is a leaf, the lemma is trivially true. Now assume for the purpose of induction that the lemma is true for every false child of \( H_a \), which along with case 1 means that the lemma would then be true for every child of \( H_a \). Hence,

\[
\mathbb{E} \left[ \frac{V(\text{Sub}(a))}{R} \right] = \sum_{b \in \text{Child}(a)} \frac{1}{|\text{Par}(b)|} \mathbb{E} \left[ \frac{V(\text{Sub}(b))}{R} \right] \\
\leq \sum_{b \in \text{Child}(a)} \frac{1}{|\text{Par}(b)|} \alpha \frac{\ell_b}{L} \\
= \alpha \frac{\ell_a}{L},
\]

where the first equality follows by the identity \[\text{(12)}\], the inequality follows by the induction hypothesis, and the last equality follows by the identity \[\text{(3)}\].

This concludes the proof of Theorem \[\text{[1]}\].

7 Summary

We have presented a sequential algorithm that can be applied when the structure of a general DAG is known in advance, that selectively carries out tests as needed, ultimately rejecting a sub-DAG that satisfies the strong hierarchy principle, whose FDR is controlled at a prespecified level under the settings of independence, positive or arbitrary dependence between the p-values. We have demonstrated the utility of our procedure on both simulations as well as real data.

There are many promising theoretical as well as practical directions for future work, including designing procedures for other error metrics as well as other types of logical constraints. For example, it may also be of importance
to consider logical constraints beyond the SHP, by changing (C2) to other natural options, for example by changing
the “all” to “any” (for WHP), or to other pre-defined Boolean operators, with special consideration to the subclass
of two-way constraints. Also note that we have assumed that the DAG is finite and known in advance to the scient-
ist. An important direction for future work under motivation (M1) is to design sequentially rejective algorithms,
that work on DAGs whose size and structure is not known in advance, but are revealed as the algorithm proceeds
down the DAG.

There are other plausible applications that fall under the umbrella of motivation (M2) beyond the GO example
that we considered. For example, the nodes can represent possible splits that a regression tree might make, with
upper nodes representing coarser splits and lower ones representing finer splits; we would then like to return a
regression tree with at most a small proportion of statistically insignificant splits. As another example consider de-
noising images using a tree-structured wavelet basis, going from lower to higher frequency as we proceed down the
hierarchy, with the aim of retaining only those members of the basis that have a statistically significant coefficient;
then, the rejected subset of nodes can be reasonably expected to form a tree.

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