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# Cost-aware Generalized $\alpha$-investing for Multiple Hypothesis Testing

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## Abstract

We consider the problem of sequential multiple hypothesis testing with nontrivial data collection cost. This problem appears, for example, when conducting biological experiments to identify differentially expressed genes in a disease process. This work builds on the generalized $\alpha$-investing framework that enables control of the false discovery rate in a sequential testing setting. We make a theoretical analysis of the long term asymptotic behavior of $\alpha$-wealth which motivates a consideration of sample size in the $\alpha$-investing decision rule. Using the game theoretic principle of indifference, we construct a decision rule that optimizes the expected return (ERO) of $\alpha$-wealth and provides an optimal sample size for the test. We show empirical results that a cost-aware ERO decision rule correctly rejects more false null hypotheses than other methods. We extend cost-aware ERO investing to finite-horizon testing which enables the decision rule to hedge against the risk of unproductive tests. Finally, empirical tests on a real data set from a biological experiment show that cost-aware ERO produces actionable decisions as to which tests to conduct and if so at what sample size.

## 1 INTRODUCTION

Machine learning systems are increasingly used to make decisions in uncertain environments. Decision-making can be viewed in the framework of hypothesis testing in that a decision is made as the result of a rejection of the null hypothesis (Arrow et al., 1949; Dickey and Lientz, 1970; Blackwell and Girshick, 1979; Verdinelli and Wasserman, 1995; Parmigiani and Inoue, 2009; Berger, 2013). When multiple hypotheses are under consideration, a false discovery rate (FDR) control procedure provides a way to control the rate of erroneous rejections in a batch of hypotheses for small-scale data sets (Benjamini and Hochberg, 1995; Storey, 2002; Storey et al., 2004; Benjamini et al., 2006; Zeisel et al., 2011; Liang and Nettleton, 2012). However, these procedures typically require the test statistics of *all* of the hypotheses under consideration so that the p-values may be sorted and a set of hypotheses may be selected for rejection. In many modern problems the test statistics for all the hypotheses may not be known simultaneously and standard FDR procedures do not work.

Online FDR methods have recently been developed to address the need for FDR control procedures that maintain control for a sequence of tests when the test statistics are not all known at one time. (Tukey and Braun, 1994) proposed the idea that one starts with a fixed amount "$\alpha$-wealth" and for each hypothesis under consideration, the researcher may choose to spend some of that wealth until it is all gone. (Foster and Stine, 2008) extended $\alpha$-spending by allowing some return on the expenditure of $\alpha$-wealth if the hypothesis is successfully rejected. (Aharoni and Rosset, 2014) introduced generalized $\alpha$-investing and provided a deterministic decision rule to optimally set the $\alpha$-level for each test given the history of test outcomes. A full review of related work is in Section 1.1.

**Contributions.** We extend generalized $\alpha$-investing to address the problem of online FDR control where the cost of data is not negligible. Our specific contributions are:

- a theoretical analysis of the long term asymptotic behavior of $\alpha$-wealth in an $\alpha$-investing procedure,
- a generalized $\alpha$-investing procedure for sequential testing that simultaneously optimizes sample size and $\alpha$-level using the game-theoretic indifference principle,
- a non-myopic $\alpha$-investing procedure that maximizes the expected reward over a finite horizon of tests.

### 1.1 Related Work

Tukey proposed the notion of $\alpha$-wealth to control the family-wise error rate for a sequence of tests (Tukey, 1991; Tukey and Braun, 1994). The Foster (Foster and Stine, 2008) $\alpha$-investing procedure controls the marginal FDR for any stopping time in the testing sequence. (Aharoni and Rosset, 2014) introduced generalized $\alpha$-investing and provided a deterministic decision rule to maximize the expected reward for the next test in the sequence. Recently, there has been much work on online FDR control in the context of A/B testing, directed acyclic graphs and quality-preserving databases (Yang et al., 2017; Ramdas et al., 2019). (Javanmard and Montanari, 2018) first proved that generalized $\alpha$-investing controls FDR, not only mFDR under an online setting with an algorithm called LORD. (Ramdas et al., 2017) proposed the LORD++ to improve the existing LORD. Recent work leverages contextual information in the data to improve the statistical power while controlling FDR offline (Xia et al., 2017) and online (Chen and Kasiviswanathan, 2020). (Ramdas et al., 2018) proposed SAFFRON, which also belongs to the $\alpha$-investing framework but adaptively estimate the proportion of the true nulls. All the aforementioned methods are synchronous, which means that each test can only start once the previous test has finished. (Zrnic et al., 2021) extended $\alpha$-investing methods to an asynchronous testing where tests are allowed to overlap in time. These state-of-the-art online FDR control $\alpha$-investing methods do not address the needs for testing when the cost of data is not negligible. So, we propose a novel $\alpha$-investing method for a setting that takes into account the cost of data sample collection, the sample size choice, and prior beliefs about the probability of rejection.

Section 2 is a technical background of generalized $\alpha$-investing. Section 3 contains a theoretical analysis of the long term asymptotic behavior of the $\alpha$-wealth. Section 4 presents a cost-aware generalized $\alpha$-investing decision rule based on the game-theoretic principle of indifference. Section 5 presents empirical experiments that show that the cost-aware optimal decision rule improves upon existing procedures when data collection costs are nontrivial. Section 6 presents an analysis of a real data set from a gene expression study that shows cost-aware $\alpha$-investing aligns with the overall objectives of the application setting. Finally, Section 7 describes limitations and future work.

## 2 BACKGROUND ON GENERALIZED $\alpha$-INVESTING

Following (Foster and Stine, 2008), we have available $m$ null hypotheses, $H_1, \ldots, H_m$ where $H_j \subset \Theta_j$. The random variable $R_j \in \{0, 1\}$ is an indicator of whether $H_j$ is rejected regardless of whether the null is true or not. The random variable $V_j \in \{0, 1\}$ indicates whether the test $H_j$ is both true and rejected. These variables are aggregated as $R(m) = \sum_{j=1}^{m} R_j$ and $V(m) = \sum_{j=1}^{m} V_j$. With these definitions, the FDR (Benjamini and Hochberg, 1995) is

$$\text{FDR}(m) = P_\theta(R(m) > 0)\, \mathbb{E}_\theta \left[ \frac{V(m)}{R(m)} \mid R(m) > 0 \right],$$

and the marginal false discovery rate is

$$\text{mFDR}_\eta(m) = \frac{\mathbb{E}_\theta \left[ V(m) \right]}{\mathbb{E}_\theta \left[ R(m) + \eta \right]}.$$

Setting $\eta = 1 - \alpha$ provides weak control over the family-wise error rate at level $\alpha$.

(Aharoni and Rosset, 2014) makes two assumptions in their development of generalized $\alpha$-investing:

$$\forall \theta_j \in H_j : P_{\theta_j}(R_j | R_{j-1}, \ldots, R_1) \leq \alpha_j, \quad (1)$$
$$\forall \theta_j \notin H_j : P_{\theta_j}(R_j | R_{j-1}, \ldots, R_1) \leq \rho_j, \quad (2)$$

where

$$\rho_j = \sup_{\theta_j \in \Theta_j - H_j} P_{\theta_j}(R_j = 1). \quad (3)$$

Assumption 1 constrains the false positive rate to the level of the test and Assumption 2 puts an upper bound of $\rho_j$ on the power of the test. A pool of $\alpha$-wealth, $W_\alpha(j)$, is available to spend on the $j$-th hypothesis. The $\alpha$-wealth is updated according to the following equations:

$$W_\alpha(0) = \alpha\eta, \quad (4)$$
$$W_\alpha(j) = W_\alpha(j-1) - \varphi_j + R_j \psi_j. \quad (5)$$

A deterministic function $\mathcal{I}_{W_\alpha(0)}$ is an $\alpha$-investing rule that determines: the cost of conducting the $j$-th hypothesis test, $\varphi_j$; the reward for a successful rejection, $\psi_j$; and the level of the test, $\alpha_j$:

$$(\varphi_j, \alpha_j, \psi_j) = \mathcal{I}_{W_\alpha(0)}(\{R_1, \ldots, R_{j-1}\}). \quad (6)$$

The $\alpha$-investing rule depends only on the outcomes of the previous hypothesis tests. The Foster-Stine ante depends hyperbolically on the level of the test $\varphi_j = \alpha_j/(1 - \alpha_j)$.

Generalized $\alpha$-investing can be viewed in a game-theoretic framework where the outcome of the test (reject or fail-to-reject) is random and the procedure provides the optimal amount of "ante" to offer to play and "payoff" to demand should the test successfully reject. We make use of this game theoretic interpretation in our contributions in Section 4.

(Aharoni and Rosset, 2014) derives a linear constraint on the reward $\psi_j$ to ensure that, for a given $(\varphi_j, \alpha_j)$, the marginal FDR is controlled at a level $\alpha$ by ensuring the sequence $A(j) = \alpha R_j - V_j + \alpha\eta - W_\alpha(j)$ is a submartingale with respect to $R_j$,

$$\psi_j \leq \min\left(\frac{\varphi_j}{\rho_j} + \alpha, \frac{\varphi_j}{\alpha_j} + \alpha - 1\right). \tag{7}$$

Maximizing the expected reward of the next hypothesis test, $\mathbb{E}(R_j)\psi_j$, leads to the following equality

$$\frac{\varphi_j}{\rho_j} = \frac{\varphi_j}{\alpha_j} - 1. \tag{8}$$

Note that this equality selects the point of intersection of the two parts of the constraint in (7). Expected Reward Optimum (ERO) $\alpha$-investing provides two equations for three unknowns in the deterministic decision rule. (Aharoni and Rosset, 2014) addresses this indeterminacy by considering three allocation schemes for $\varphi_j$: constant, relative, and relative200 and suggest that the investigator can explore various options and set $\varphi_j$ on their own. Further details on these schemes are given in Section 5.

Since the dominant paradigm in testing of biological hypotheses is a bounded finite range for $\Theta_j$, for the remainder we assume $\Theta_j = [0, \bar{\theta}_j]$ for some upper bound, $\bar{\theta}_j$, and $H_j = \{0\}$. This scenario may be viewed as a test that the expression for gene $j$ is differentially increased in an experimental condition compared to a control. We consider a simple z-test here for concreteness. The power of a one-sided z-test is $(1-\beta) := 1 - \Phi\left(z_{1-\alpha} + \frac{(\mu_0 - \mu_1)}{\sigma/\sqrt{n}}\right)$ where $z_{1-\alpha} = \Phi^{-1}(1-\alpha)$ is the z-score corresponding to level $\alpha$, $\mu_0$ is the expected value of the simple null hypothesis, $\mu_1$ is the expected value of the simple alternative hypothesis, $\sigma$ is the standard deviation of the measurements, and $n$ is the sample size.

Using Equation (3), the best power under the previously defined $\Theta_j$ is

$$\rho_j = 1 - \Phi\left(z_{1-\alpha_j} - \frac{\bar{\theta}_j}{\sigma_j/\sqrt{n_j}}\right). \tag{9}$$

The best power depends on: (1) the level of the test, $\alpha_j$, (2) the scale of the bound on the alternative, $\bar{\theta}_j$, (3) the sample size, $n_j$, and the measurement standard deviation, $\sigma_j$. One may compare multiple measurement technologies based on their precision by exploring the effect of changing $\sigma_j$ — for example, for a fixed budget and all other things equal, a trade-off can be computed between more samples with a higher variance technology, versus fewer samples with a lower variance technology. For the remainder, we assume $\sigma_j$ is fixed and known. We implemented an exact form of ERO $\alpha$-investing for Neyman-Pearson testing problems by solving the following nonlinear optimization problem:

$$\max_{\alpha_j, \psi_j} \quad \mathbb{E}_\theta(R_j)\psi_j \tag{10a}$$

$$\text{s.t.} \quad \psi_j \leq \frac{\varphi_j}{\rho_j} + \alpha, \tag{10b}$$

$$\psi_j \leq \frac{\varphi_j}{\alpha_j} + \alpha - 1, \tag{10c}$$

$$\frac{\varphi_j}{\rho_j} = \frac{\varphi_j}{\alpha_j} - 1, \tag{10d}$$

$$\rho_j = 1 - \Phi\left(z_{1-\alpha_j} - \frac{\bar{\theta}_j}{\sigma_j/\sqrt{n_j}}\right) \tag{10e}$$

Constraints 10b and 10c correspond to (7) which controls the mFDR level, and constraint 10d ensures the maximal expected reward for the $j$-th test. The optimal ERO still depends on an external choice of the sample size $n_j$, and the cost of the test $\varphi_j$.

## 3 LONG-TERM $\alpha$-WEALTH

Since the levels of future tests depend on the amount of $\alpha$-wealth available at the time of the tests, a theoretical consideration in generalized $\alpha$-investing is whether the long-term $\alpha$-wealth is submartingale or supermartingale (stochastically non-decreasing or stochastically non-increasing) for a given decision-rule. Here we outline two scenarios where the long-term $\alpha$-wealth can be either submartingale or supermartingale.

In order to state the theorems regarding the $\alpha$-wealth sequence, we require a lemma bounding $\alpha$-wealth as a function of the prior probability of the null hypothesis.

**Lemma 1.** *Given an $\alpha_j$-level for the $j$-th hypothesis test from rule $\mathcal{I}(R_1, \ldots R_{j-1})$, the expected value of $\alpha$-wealth for Foster-Stine $\alpha$-investing is*

$$\mathbb{E}^{j-1}[W_j] \leq -\frac{\alpha_j}{1-\alpha_j} + [\rho_j - (\rho_j - \alpha_j)q_j]\left(\alpha + \frac{\alpha_j}{1-\alpha_j}\right), \tag{11}$$

*where $\mathbb{E}^{j-1}[W_j] = \mathbb{E}[W(j) - W(j-1) | W(j-1)]$, and $q_j = \Pr[\theta_j \in H_j]$, the prior probability (belief) that the $j$-th null hypothesis is true. In the case of a simple null and alternative $\Theta_j = \{0, \bar{\theta}_j\}$, the bound is tight.*

It is important to note that while $\alpha_j$ is marginally random because it depends on the sequence of rejections up until $j$, conditional on $W_\alpha(j-1)$, it is deterministic and given by the decision rule $\mathcal{I}$.

**Theorem 1** (Submartingale)**.** *Given a simple null and alternative* $\Theta_j = \{0, \bar{\theta}_j\}$, $\{W(j) : j \in \mathbb{N}\}$ *is submartingale (stochastically non-decreasing) if*

$$\rho_j \geq \frac{\alpha_j/(1-\alpha_j)}{\alpha + \alpha_j/(1-\alpha_j)} \frac{1}{1-q_j}. \tag{12}$$

Theorem 1 shows that one will be able to conduct an infinite number of tests in the long-term if the power is close to one or the prior probability of the null is close to zero. This scenario may occur when the hypothesis stream contains a large proportion of true alternative hypotheses, or if the sample sizes of the individual tests are large.

**Theorem 2** (Supermartingale)**.** *For any null and alternative hypothesis,* $\{W(j) : j \in \mathbb{N}\}$ *is supermartingale (stochastically non-increasing) if*

$$\rho_j \leq \left( \frac{\alpha_j/(1-\alpha_j)}{\alpha + \alpha_j/(1-\alpha_j)} - q_j \right) \frac{1}{1-q_j}. \tag{13}$$

Theorem 2 shows that the generalized $\alpha$-investing testing procedure will end in a finite number of steps if the power of the test is close to zero or the prior probability of the null hypothesis is close to one. This scenario may occur when the hypothesis stream is made up of a large proportion of true null hypotheses, or if the sample sizes used for each test results in an under powered test.

These theorems provide general insights for understanding when the $\alpha$-wealth can be expected to be (stochastically) non-decreasing or non-increasing. The non-decreasing sequences require that $\rho_j \uparrow 1$ for a fixed $\bar{\theta}_j$ which, in the case of a Gaussian, would require $\sigma_j/\sqrt{n} \to 0$ or $n \to \infty$. So, the $\alpha$-wealth grows unbounded if the sample size is unbounded. This theory in combination with the premise of non-trivial experiment costs motivates the need for methods for cost-aware $\alpha$-investing when the sample size is not fixed. We formally state the proofs of these lemmas and theorems in Appendix A.

# 4 COST-AWARE GENERALIZED $\alpha$-INVESTING

Our development in this section derives from two key differences in assumptions compared to previous work. Here we make the following assumptions: (1) the per sample monetary cost to conduct hypothesis tests is not trivial, and (2) the $\alpha$-cost of a hypothesis test, $\varphi_j$, should account for the a-priori probability that the null hypothesis is true as well as the pattern of previous rejections.

**Cost-aware ERO $\alpha$-investing.** The generalized $\alpha$-investing decision rule, (6), is augmented to include a notion of dollar-wealth $W_\$(j)$ available for expenditure to collect data to test the $j$-th hypothesis

$$(\varphi_j, \alpha_j, \psi_j, n_j) = \mathcal{I}(W_\alpha(0), W_\$(0))(\{R_1, \ldots, R_{j-1}\}), \tag{14}$$

where $n_j$ is the sample size allocated for testing of the $j$-th hypothesis. A natural update plan for the dollar-wealth is

$$W_\$(0) = B \tag{15}$$
$$W_\$(j) = W_\$(j-1) - c_j n_j, \tag{16}$$

where $c_j$ is the per-sample cost for data to test the $j$-th hypothesis, and $B$ is the initial dollar-wealth. Allowing the cost to vary with the hypothesis test enables one to model different experimental methods and cost inflation for long-term experimental plans. The augmented optimization problem is identical to Problem 10 with objective $\max_{\varphi_j,\alpha_j,\psi_j,n_j} \mathbb{E}_\theta(R_j)\psi_j$ and constraint $n_j c_j \leq W_\$(j)$.

**Game Theoretic Formulation.** The resulting optimization problem has an infinite number of solutions because $\varphi_j$ is not constrained. Thus the problem does not yet constitute a self-contained decision rule for (14). Indeed, (Aharoni and Rosset, 2014), throughout, suggest a scenario where $\varphi_j$ is chosen by the investigator and the level and reward are given by the decision rule. To develop a self-contained decision rule, we cast the objective function in a Bayesian framework by allowing for the specification of the prior probability of the null hypothesis,

$$\mathbb{E}_\theta[R_j]\psi_j = [\alpha_j q_j + \rho_j(1-q_j)]\,\psi_j,$$

where $q_j = \Pr[\theta_j \in H_j]$. Suppose that we have a zero-sum game involving two players: the investigator (Player I) and nature (Player II). Nature, independent of the investigator, chooses to hide $\theta_j \in H_j$ with probability $q_j$ and $\theta_j \notin H_j$ otherwise. The investigator has the choice between two pure strategies: to conduct a test or to not conduct a test. If the investigator chooses not to conduct a test, there is no cost ($\varphi_j = 0$) and there is no reward ($\psi_j = 0$) regardless of what nature has chosen. So, the $\alpha$-value of not conducting a test is zero. If the investigator chooses to conduct a test, the value of the game is $-\varphi_j + \psi_j$ with probability $\alpha_j q_j + \rho_j(1-q_j)$ (the investigator rejects), and $-\varphi_j$ with probability $(1-\alpha_j)q_j + (1-\rho_j)(1-q_j)$ (the investigator fails to reject). The investigator selects as the amount they are willing to pay to conduct the experiment, $\varphi_j$, an amount such that they are indifferent as to whether or not to conduct the experiment,

$$\begin{aligned}(-\varphi_j + \psi_j) \cdot [\alpha_j q_j + \rho_j(1-q_j)] + \\ (-\varphi_j) \cdot [(1-\alpha_j)q_j + (1-\rho_j)(1-q_j)] = 0\end{aligned} \tag{17}$$

The value of this two-player game is in fact the change in $\alpha$-wealth, analyzed in section 3. The principle of indifference selects a rule that strikes a balance between the settings proposed in Theorem 1 and Theorem 2.

**Cost-aware ERO Decision Rule.** Incorporating this indifference constraint and the cost of the experiment into the ERO problem yields a self-contained decision rule in the form of (14),

$$\max_{\varphi_j, \alpha_j, \psi_j, n_j} \quad \mathbb{E}_\theta(R_j)\psi_j \tag{18a}$$

$$\text{s.t.} \quad \psi_j \le \frac{\varphi_j}{\rho_j} + \alpha, \tag{18b}$$

$$\psi_j \le \frac{\varphi_j}{\alpha_j} + \alpha - 1, \tag{18c}$$

$$\frac{\varphi_j}{\rho_j} = \frac{\varphi_j}{\alpha_j} - 1, \tag{18d}$$

$$\rho_j = 1 - \Phi\left(z_{1-\alpha_j} - \frac{\bar{\theta}_j}{\sigma_j/\sqrt{n_j}}\right), \tag{18e}$$

$$\varphi_j \le W_\alpha(j-1), \tag{18f}$$

$$n_j c_j \le W_\$(j), \tag{18g}$$

$$0 = \mathbb{E}\left[\Delta W_\alpha\right], \tag{18h}$$

Constraints (18b) and (18c) ensure control over the mFDR. Constraint (18e) connects the level, power, and sample size of the test. Constraints (18f) and (18g) ensure the existing $(\alpha, \$)$-wealth is not exceeded. Constraint (18h) ensures the minimax solution to the game. Written out explicitly,

$$\mathbb{E}\left[\Delta W_\alpha\right] = (-\varphi_j + \psi_j)\Pr[R_j = 1] + (-\varphi_j)\Pr[R_j = 0],$$

$$\Pr[R_j = 1] = \alpha_j q_j + \rho_j(1 - q_j),$$

$$\Pr[R_j = 0] = (1 - \alpha_j)q_j + (1 - \rho_j)(1 - q_j).$$

A pseudo-code algorithm of the full cost-aware ERO method and further extensions to cost-aware ERO are described in Appendix C.

Constraint (18h) sets the expected change in $\alpha$-wealth equal to zero. This enforces that $W_\alpha(j)$ is martingale. Allowing $W_\alpha(j)$ to be submartingale, as per Theorem 1, can lead to a situation where hypotheses are tested at high $\alpha$-levels due to the accumulated $W_\alpha$ from previous rejections. This is referred to as piggybacking in the literature when such accumulated wealth leads to poor decisions (Ramdas et al., 2017). On the other hand, allowing $W_\alpha(j)$ to be supermartingale, as per Theorem 2, causes the testing to end, and is referred to as $\alpha$-death in the literature. Using a game-theoretic formulation allows us to propose an expected-reward optimal procedure which considers preventing $\alpha$-death and piggybacking.

**Finite horizon cost-aware ERO $\alpha$-investing.** The standard ERO framework optimizes only the one-step expected return, $\mathbb{E}_\theta(R_j)\psi_j$. But, when tests are expensive, it is logical to consider the expected return after two (or more) tests. We consider $q_j$ to be known, and extend the game theoretic framework to a finite horizon of decisions. The extensive form of the game between Nature, who hides $\theta_j$ in the null or alternative hypothesis region, and the investigator, who seeks to find $\theta_j$ and gain the reward for doing so, is shown in Appendix G. We note that sequential two-step cost-aware ERO investing is a different problem than batch ERO investing because two-step investing accounts for the change in $(\alpha, \$)$-wealth after each step while batch cost-aware ERO only received the payoff at the conclusion of all of the tests in the batch.

The two-step objective function is

$$\begin{aligned}\mathbb{E}(R_j\psi_j + R_{j+1}\psi_{j+1}) = \mathbb{E}(R_j)\psi_j + \\ \psi_{j+1}[P(R_j = 0)\mathbb{E}(R_{j+1}|R_j = 0) + \\ P(R_j = 1)\mathbb{E}(R_{j+1}|R_j = 1)]\end{aligned} \tag{19}$$

with constraints a-f from Problem 18 remaining for steps $j$ and $j+1$. Applying the principle of indifference to this game results in a system of equations (Appendix G) that form constraints in the ERO optimization problem.

## 5 SYNTHETIC DATA EXPERIMENTS

**Experimental Settings** To compare our method with state-of-the-art related methods, we generate synthetic data as described in (Aharoni and Rosset, 2014). The synthetic data is composed of $m = 1000$ possible hypothesis tests. For the $j$-th test, the true state of $\theta_j$ is set to the null value of 0 with probability 0.9 and otherwise set to 2. A set of $n_j = 1000$ potential samples $(x_{ji})_{i=1}^{n_j}$ were generated i.i.d from a $\mathcal{N}(\theta_j, 1)$ distribution. For each hypothesis test, the z-score was computed as $z_j = \sqrt{n_j^*}\sum_{i=1}^{n_j^*} x_{ji}$, where $n_j^*$ is described in the table and the one-sided p-value is computed. The methods were tested on $10,000$ realizations of this simulation data generation mechanism. Pseudo-code, as well as other implementation details, for this simulation up can be found in Appendix B.

### 5.1 Comparison to state-of-the-art methods

Table 1 compares our method, cost-aware ERO, with related state-of-the-art $\alpha$-investing methods including: $\alpha$-spending (Tukey and Braun, 1994), $\alpha$-investing (Foster and Stine, 2008), $\alpha$-rewards (Aharoni and Rosset, 2014), ERO-investing (Aharoni and Rosset, 2014), LORD (Javanmard and Montanari, 2018; Ramdas et al., 2017), and SAFFRON (Ramdas et al., 2018). The table is indexed by the allocation scheme (Scheme), and the reward method (Method). The allocation scheme determines the value of $\varphi_j$ at each step. The constant scheme simply allocates,

$$\varphi_j = \min\left\{\frac{1}{10}W_\alpha(0), W_\alpha(j-1)\right\},$$

| Scheme | Method | Tests | True Rejects | False Rejects | mFDR |
|---|---|---|---|---|---|
| constant | $\alpha$-spending | 10.0 | 0.28 | 0.04 | 0.032 |
| | $\alpha$-investing | 16.0 | 0.44 | 0.06 | 0.044 |
| | $\alpha$-rewards $k = 1$ | 14.7 | 0.41 | 0.06 | 0.043 |
| | $\alpha$-rewards $k = 1.1$ | 16.4 | 0.44 | 0.06 | 0.043 |
| | ERO investing | 18.3 | 0.50 | 0.07 | 0.048 |
| relative | $\alpha$-spending | 66.0 | 0.55 | 0.04 | 0.026 |
| | $\alpha$-investing | 81.5 | 0.87 | 0.08 | 0.044 |
| | $\alpha$-rewards $k = 1$ | 80.7 | 0.85 | 0.08 | 0.042 |
| | $\alpha$-rewards $k = 1.1$ | 80.4 | 0.81 | 0.07 | 0.039 |
| | ERO investing | 82.7 | 0.92 | 0.10 | 0.050 |
| other | LORD++ | 934.9 | 2.59 | 0.06 | 0.015 |
| | LORD1 | 1000.0 | 1.45 | 0.03 | 0.014 |
| | LORD2 | 1000.0 | 2.00 | 0.06 | 0.020 |
| | LORD3 | 1000.0 | 2.72 | 0.07 | 0.020 |
| | SAFFRON | 1000.0 | 1.64 | 0.09 | 0.035 |
| cost-aware | ERO $n_j = 1$ | **365.6** | **4.16** | **0.22** | **0.041** |
| cost-aware | ERO $n_j \leq 10$ | 39.8 | 3.99 | 0.21 | 0.040 |
| cost-aware | ERO $n_j \leq 100$ | 34.3 | 3.43 | 0.17 | 0.038 |
| cost-aware | ERO $n_j^*$ | 34.2 | 3.42 | 0.17 | 0.038 |

Table 1: Comparison of cost-aware $\alpha$-investing with state-of-the-art sequential hypothesis testing methods. Values for Tests, True Rejects and False Rejects are the average across 10,000 iterations, and these estimates are used for mFDR.

for each test, the relative scheme allocates an amount that is proportional to the remaining $\alpha$-wealth,

$$\varphi_j = \frac{1}{10} W_\alpha(j-1)$$

and continues until $W_\alpha(j) < (1/1000)W_\alpha(0)$. The relative 200 scheme follows the same proportional steps as the relative, but always performs 200 tests (Aharoni and Rosset, 2014). The results from our implementation of these methods matches or exceeds previously reported results.

ERO investing yields more true rejects than $\alpha$-spending, $\alpha$-investing, and both $\alpha$-rewards methods. The LORD variants and SAFFRON perform nearly the maximum number of tests while maintaining control of the mFDR. For the use scenarios considered in the LORD and SAFFRON papers (large-scale A/B testing), this is optimal — tests are nearly free and the goal is to be able to keep testing while maintaining mFDR control. The cost-aware ERO setting is different and more applicable to biological experiments where one aims to maximize a limited budget of tests to achieve as many true rejects as possible while controlling the mFDR. Increasing the sample size capacity for each test to $n_j^* \leq 10$ enables cost-aware ERO to achieve the same power with fewer tests. Releasing the restriction on sample size enables cost-aware ERO to allocate the optimal number of samples based on the prior of the null as well as the available budget and the method returns an optimal $n_j^*$. Appendix D shows the comparisons for $q = 0.1$ and Appendix F shows comparisons with all of the other methods set to $n_j = 10$. We note, that the difference between restricting $n_j \leq 100$ and not restricting $n_j$ is rather small. For most of the tests, the sample sizes chosen are quite similar, but differences appear when $\alpha$-wealth becomes small, and the optimal sample size without restriction is above 100.

It is worth noting that ERO and cost-aware ERO with $n_j = 1$ are still quite different despite the restriction of sample size. We can view the difference in performance between these two methods as the benefit of allocating $\varphi_j$ using the principle of indifference. The principle of indifference incorporates our prior knowledge of the probability of the null hypothesis being true and aims to maintain $\alpha$-wealth (as a martingale). The experimental set up of (Aharoni and Rosset, 2014) implicitly leverages similar prior knowledge in the spending schemes proposed. All spending schemes proposed in (Aharoni and Rosset, 2014) allow us to test at least one true alternative, in expectation, at which point the $\alpha$-wealth should increase. This increase in $\alpha$-wealth should then sustain testing until another true alternative appears. However, in the cost-aware ERO optimization problem, this information is explicitly accounted for, and helps us avoid situations described in 1 and 2. By restricting $n_j = 1$, we have effectively limited our ability to inflate $\rho_j$ with a large sample size, and influence $W_\alpha(j)$ towards being submartingale. On the other hand, the principle of indifference

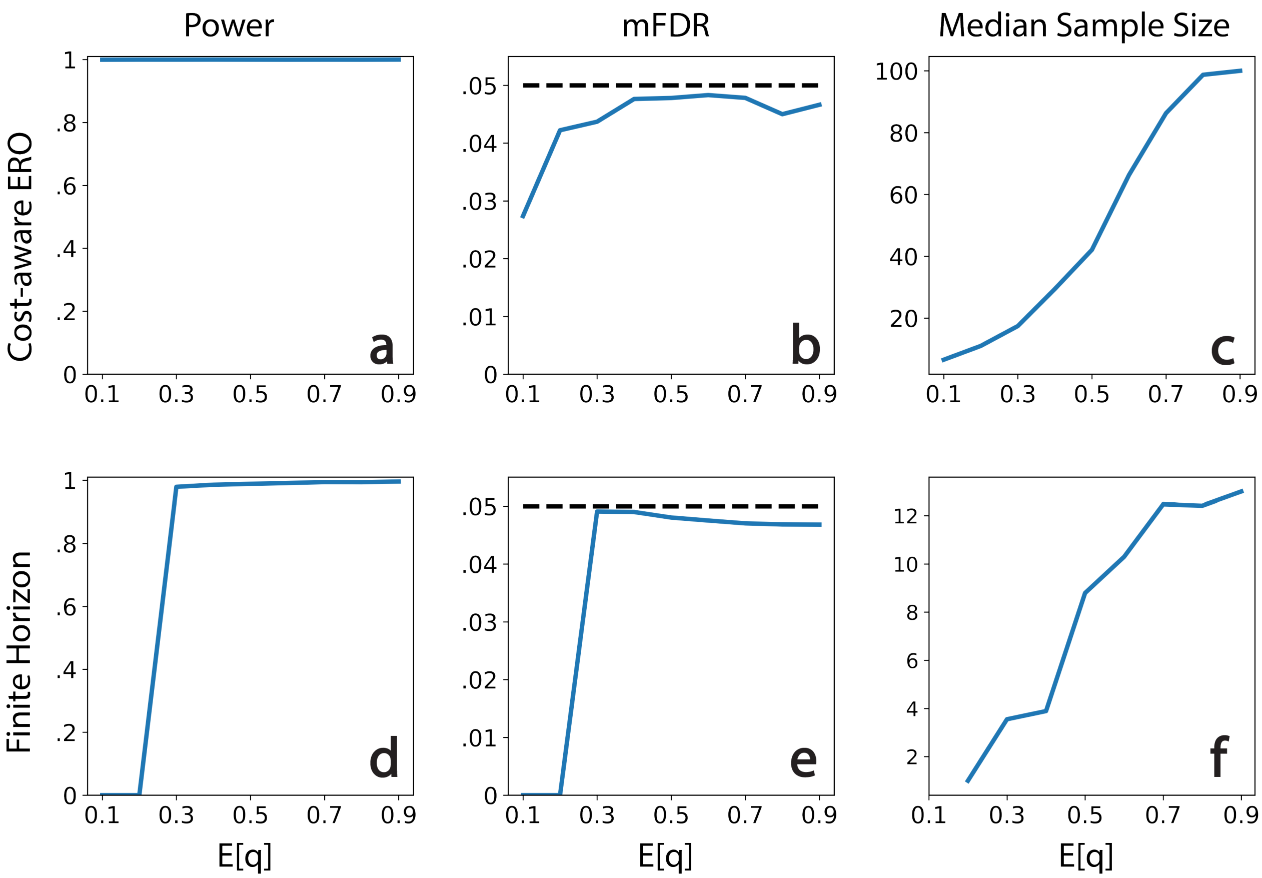


Figure 1: Empirical results for cost-aware ERO with random $q_j$ (a-c) and finite-horizon cost-aware ERO (d-f). Power, mFDR, and median number of samples per test are shown in columns.

optimizes the two-player game to have a value of zero, by limiting the size of $\varphi_j$, preventing the experimenter from experiencing $\alpha$-death quickly, as seen in the constant spending scheme.

**Computation and Implementation** In our experiments, for one set of $1,000$ potential hypothesis tests ERO investing, cost-aware, and finite-horizon cost-aware ERO all take $\sim$ 30 seconds on a single 2.5GHz core and 16Gb RAM. The nonlinear optimization problem was solved using CONOPT (Drud, 1994). Because the solver depends on initial values and heuristics to identify an initial feasible point, infrequently the solver was not able to find a local optimal solution; in these instances, the solver was restarted 10 times and if it failed on all restarts the iteration was discarded. Out of $10,000$ data sets at most 27 iterations were discarded (for $n_j = 1$). Code to replicate these experiments is available at `https://github.com/anonymous`.

### 5.2 Random Prior of the Null Hypothesis

One of the benefits of incorporating a notion of sampling cost into the hypothesis testing problem is the ability to allocate resources based on the prior probability of the null, $q$. We generated simulation data as previously described except the prior probability of the null hypothesis is selected at random from $q_j \sim \text{Beta}(a, b)$ where $a + b = 100$ and with $2,500$ independent realizations of the data. An upper limit of 100 samples was set to all individual tests. Appendix B contains pseudo-code and further implementation details. Figure 1(a-c) shows the power, mFDR, and median number of samples per test as a function of $\mathbb{E}[q_j]$. The results show that cost-aware ERO $\alpha$-investing achieves high power while maintaining control of the mFDR. A key result of this experiment is that should it not be possible to collect as many samples as the principle of indifference yields, the investigator may choose to not perform the test at all and instead wait for a test (with associated prior) that does yield an optimal sample size within the budget or may choose to allow the $\alpha$-wealth ante to adjust to the bound on the sample size. This often occurs for large values of $q_j$, which we know by Theorem 2 will influence $W_\alpha(j)$ towards behaving as a supermartingale. Cost-aware ERO will compensate by increasing $\rho_j$ through the sample size, $n_j$, and will expend the $W_\$$ available, as the optimization only considers a single step.

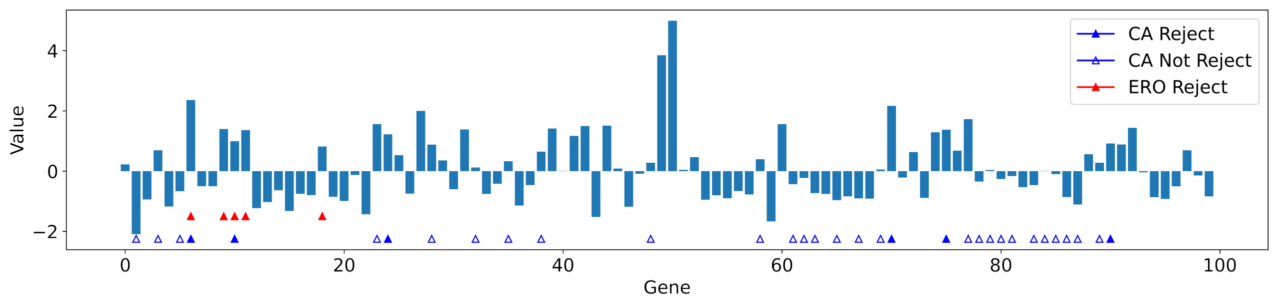


Figure 2: Cost-aware ERO investing and ERO investing for real gene expression data. Cost-aware ERO distributes the finite allocation of samples across the set of genes while ERO expends the sample allocation within the first 20 tests.

### 5.3 Finite-Horizon Cost-aware ERO Investing

To test whether extending the horizon of the reward to be maximized would enable better decisions as to $(\alpha, \$)$-wealth allocation, we compared one-step and two-step ERO investing decision rules. Figure 1(d-f) shows two-step ERO has high power for most values of $\mathbb{E}(q_j)$; for low values of $\mathbb{E}(q_j)$ the prior of all of the alternatives is so high that the method chooses not to test. The finite horizon method uses a much smaller sample size when it does test as evidenced by panels (c) and (f) in Figure 1. Incorporating knowledge of the prior probability of future tests into the decision rule enables it to avoid a myopic optimization of the next reward and instead allocate samples to a test that is likely to be more productive. We expect that this hedging effect will continue as the finite horizon is extended beyond two-steps of the hypothesis sequence.

## 6 REAL DATA EXPERIMENTS

Gene expression data was collected to investigate the molecular determinant of prostate cancer (Dettling, 2004). The data set contains 50 normal samples and 52 tumor samples and each sample is a $m = 6033$ vector of gene expression levels. The data set has been normalized and log-transformed so that the data for each gene is roughly Gaussian. Let the empirical mean and standard deviation of the normal samples be denoted $\hat{\mu}_j$ and $\hat{\sigma}_j$ respectively. The goal is to test whether the tumor gene expression is increased relative to the normal samples.

A logistic function using only the first two samples for each gene was used to compute the prior probability of the null hypothesis $q_j = 1 - (1 + \exp(-\beta([\bar{x_j}]_{1:2} - x_0)))^{-1}$, where $x_0 = \log_{10}(4)/\sigma$ and $\beta = 2$; these first two samples were then removed from the data set. The set of genes was permuted randomly and the cost-aware decision function was computed for each gene in sequence with $q_j$ as described and $\bar{\theta}_j = \log_{10}(2)/\hat{\sigma}_j$. If the optimal sample size was greater than the number of available samples ($\bar{n}_j = 50$), the test was skipped, otherwise the one-sided Gaussian test was performed with the optimal number of samples. This procedure is compared to ERO investing with the maximum number of samples for all tests that were selected to be performed by that procedure. For both procedures $c_j = 1, \forall j$, and $W_\$[0] = 1000$. Pseudo-code and implementation details for this experiment can be found in Appendix B.

Figure 2 shows a single iteration of the cost-aware and ERO decision rules on the gene expression data set. The ERO method selects many tests, but rapidly expends $W_\$$, as it does not optimize the sample size. In contrast, cost-aware ERO is more conservative and tests when the benefits outweigh the risks for a given dual-currency wealth state $(W_\alpha, W_\$)$. Across 1000 permutations of the data cost-aware ERO performed, on average, 32.9 tests and skipped 44.6 tests. For the tests that were performed, the average optimal sample size was 26.9.

## 7 DISCUSSION

We have introduced an ERO generalized $\alpha$-investing procedure that has a self contained decision rule. This rule removes the need for a user-specified allocation scheme and optimally selects the sample size for each test. We have shown empirical results in support of the benefits of optimizing these testing parameters rather than being left to user choice. An experiment with gene expression data shows that we can conduct more tests than with previous methods. The societal impact and ethical concerns of this work are limited, as this work proposes a principled method to control for multiple testing. These concerns are influenced more by the hypotheses and motivation by the experiment rather than the multiple testing correction.

There are some limitations of the current work. First, the cost-aware ERO method may be sensitive to misspecification in $q_j$. Simulations with an increasing distance between the true $q_j$ and that used by the cost-aware ERO method show that cost-aware ERO performance degrades for misspecified values of $q_j$ (Appendix E), however, mFDR control is not affected.

Second, the finite horizon method requires known values $q_j$. In a streaming situation this information may not be available. Finally, cost-aware ERO does not have a mechanism to hedge the risk of dollar wealth or $\alpha$-wealth expenditure. In our simulations we observed that cost-aware ERO can choose to ante ($\varphi_j$) the entire pool of $\alpha$-wealth on the first promising test in the hopes of maximizing the expected reward. While this strategy is certainly one that maximizes the expected reward, it may be too risky in practice. One solution is to constrain $\varphi_j$ for any single test or to include $\varphi_j$ in the objective function. Preliminary experiments on including $\varphi_j$ in the objective (Appendix F) are encouraging for this direction. For future work, it would be interesting to investigate a principled risk-hedging approach to conserve some wealth for future tests with the hope that a test with a more favorable reward structure is over the horizon.

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# A THEORETICAL ANALYSIS OF LONG-TERM ALPHA-WEALTH

## A.1 Proof of Lemma 1

*Proof of Lemma 1.* The expected increment in $\alpha$-wealth is

$$\mathbb{E}[W_\alpha(j) - W_\alpha(j-1)] = \mathbb{E}[R_j]\alpha - \mathbb{E}[1 - R_j]\frac{\alpha_j}{1-\alpha_j}.$$

This equation requires the probability of rejection, which can be written in factorized form as

$$\Pr(R_j = 1) = \Pr(R_j = 1 | \theta_j \in H_j) \Pr(\theta_j \in H_j) + \Pr(R_j = 1 | \theta_j \notin H_j) \Pr(\theta_j \notin H_j).$$

Now, $\Pr(R_j = 1 | \theta_j \in H_j) \leq \alpha_j$ by Assumption 1 and $\Pr(R_j = 1 | \theta_j \notin H_j) \leq \rho_j$ by Assumption 2. Defining $\Pr(\theta_j \in H_j) = q_j$ gives the result. □

## A.2 Proof of Theorem 1

*Proof.* Since $\Theta_j = \{0, \bar{\theta}_j\}$, by lemma 1 we have

$$\mathbb{E}\left[W_\alpha(j) - W_\alpha(j-1) \mid W_\alpha(j-1)\right] = -\frac{\alpha_j}{1-\alpha_j} + \left[\rho_j - (\rho_j - \alpha_j)\, q_j\right]\left(\alpha + \frac{\alpha_j}{1-\alpha_j}\right)$$

We define $M_j := \rho_j - (\rho_j - \alpha_j)q_j$, then $\{W_\alpha(j) : j \in \mathbb{N}\}$ is submartingale, if and only if

$$M_j \geq \frac{\alpha_j/(1-\alpha_j)}{\alpha + \alpha_j/(1-\alpha_j)}.$$

Since $M_j = \rho_j - (\rho_j - \alpha_j)q_j > \rho_j(1 - q_j)$, thus $\{W_\alpha(j)\}$ is submartingale if

$$\rho_j \geq \frac{\alpha_j/(1-\alpha_j)}{\alpha + \alpha_j/(1-\alpha_j)} \frac{1}{1-q_j}.$$

□

## A.3 Proof of Theorem 2

*Proof.* Let $M_j := \rho_j - (\rho_j - \alpha_j)q_j$, by Lemma 1, $\{W_\alpha(j) : j \in \mathbb{N}\}$ is supermartingale, if

$$M_j \leq \frac{\alpha_j/(1-\alpha_j)}{\alpha + \alpha_j/(1-\alpha_j)}. \tag{20}$$

Next we define $s_j \in [0, (1-\alpha_j)/\alpha_j]$, a positive number to control how large the power is for the $j$th test, such that

$$\rho_j = s_j \alpha_j / (1 - \alpha_j)$$

And we have

$$\rho_j - \alpha_j = [(s_j - 1)\alpha_j + \alpha_j^2]/(1-\alpha_j) \geq (s_j - 1)\alpha_j/(1-\alpha_j).$$

Thus,

$$M_j \leq \frac{s_j \alpha_j}{1-\alpha_j} - \frac{(s_j - 1)\alpha_j}{1-\alpha_j} q_j.$$

The condition in (20) becomes

$$\frac{1-\alpha_j}{\alpha_j} M_j \leq s_j - (s_j - 1)q_j = s_j(1-q_j) + q_j \leq \frac{1}{\alpha + \alpha_j/(1-\alpha_j)}.$$

Thus, for a given $q_j$, the condition on $s_j$ for stochastically non-increasing wealth is

$$s_j \leq \left(\frac{1}{\alpha + \alpha_j/(1-\alpha_j)} - q_j\right) / (1 - q_j). \tag{21}$$

The upper-bound in condition (21) is valid if it is positive. For $j$ large enough, if $\alpha_j/(1-\alpha_j) < \alpha$, then

$$\frac{1}{\alpha + \alpha_j/(1-\alpha_j)} - q_j > \frac{1}{2\alpha} - q_j.$$

If $\alpha_j < 1/2$, this term is positive and the upper-bound for $s_j$ is positive. □

## B SIMULATION DETAILS

In this section we describe simulations in greater detail so that our work can be fully reproduced. We briefly present the cost-aware ERO $\alpha$-investing method in algorithmic form.

**Algorithm 1** Cost-aware ERO Algorithm

```
Input α, W_α(0), W_$(0)
j ← 0
while W_α(j) > ϵ and W_$(j) > ϵ do
    Define q_j, c_j for hypothesis j
    Solve Problem 18 to obtain φ_j, α_j, ψ_j, and n_j
    Collect data (x_{j1}, ..., x_{jn_j}) and compute p-value p_j.
    if p_j ≤ α_j then
        R_j ← 1
    else
        R_j ← 0
    end if
    Update W_$(j+1) ← W_$(j) − c_j n_j
    Update W_α(j+1) ← W_α(j) − φ_j + R_j ψ_j
    j ← j + 1
end while
```

**Experiment for Table 1** For cost-aware ERO, the initial value of $\alpha_j$ was set $0.001$, and the initial value of $\rho_j$ was set to $0.9$. These initial values tended to give more conservative allocations of sample size as the optimal value of $\rho_j$ often approached a value of 1. In our simulation we define $\alpha = 0.05$, $W_\alpha(0) = 0.0475$, $W_\$(0) = 1000$, $n_{iter} = 10000$ (number of iterations), $m = 1000$ (maximum number of tests per iteration), and $c = 1$ (cost per sample). $W_\alpha(0)$ for implementations of LORD and SAFFRON follow suggestions from (Javanmard and Montanari, 2018) and (Ramdas et al., 2018). An explicit algorithm is given in Algorithm 2. A similar experimental set up is used for Table 2 and Table 4 where $q_j$ and $n_j$ are adjusted respectively.

**Experiment for Figure 1** We next discuss the experimental details for producing Figure 1. The initial value for $\rho_j$ (and for $\rho_{j+1}$) was set to 1. Contrary to the previous experiment, we desire to demonstrate that myopic allocation of samples is avoided in finite-horizon ERO regardless of initial values. In our simulation we define $\alpha = 0.05$, $W_\alpha(0) = 0.0475$, $W_\$(0) = 1e8$, $n_{iter} = 2500$, $m = 1000$, and $c = 1$. An additional $q$, specifically $q_{1001}$ is drawn for solving the finite-horizon optimization problem when we reach the final test. We sample $q_j$ from a Beta$(a, 100 - a)$ distribution, and then sample whether $\theta_j$ is null or not based on the realization of $q_j$. This sampling scheme and relevant parameter values are given in Algorithm 3.

**Experiment for Figure 2** The real data experiment shown in Figure 2 and detailed in Section 6 can be broken down into two steps: preprocessing and testing.

In preprocessing, we load in two dataframes, one containing gene expression data for 50 normal (non-cancerous) samples ($6033 \times 50$), and a second containing similar data for 52 tumor samples ($6033 \times 52$). We take then mean across the normal samples to obtain a ($6033 \times 1$) vector containing the mean gene expression for normal patients. We calculate the standard deviation in a similar manner and use these vectors to standardize the $(6033 \times 52)$ dataframe containing tumor samples. Next, the first two columns of the tumor samples dataframe is separated from the remaining 50 columns to provide an informed estimate of $q_j$ for each test. It is important to note that we are allowing the potential for misspecification of $q_j$ by using an estimate of only two samples. Using these two samples:

$$q_j = 1 - \left(1 + \exp(-\beta([\bar{x_j}]_{1:2} - x_0))\right)^{-1},$$

where $x_0 = \log_{10}(4)/\hat{\sigma}$, $\beta = 2$, $[\bar{x_j}]_{1:2}$ denotes the sample mean of the two tumor samples separated from the remaining 50 tumor samples for the $j^{th}$ gene, and $\hat{\sigma}$ is the estimated standard deviation from the normal samples.

During the testing process, we perform a random shuffle of the genes and then run testing. This process is shown in Algorithm 4. In this scenario, we set $\alpha = 0.05$, $W_\alpha(0) = 0.0475$, $W_\$(0) = 1000$, $n_{iter} = 1000$ (number of permutations),

**Algorithm 2** Simulation run in Table 1

```
Input α, W_α(0), W_$(0), n_iter, m, c
for i = 0 to i = n_iter do
    Set seed to i
    X = [ ]
    for j = 0 to m do
        Sample θ_j, with Pr(θ_j = 0) = q_j = 0.9, and Pr(θ_j = 2) = 1 − q_j = 0.1.
        X[j] = 1000 realizations from N(θ_j, 1).
    end for
    for each testing method (unique row in Table 1) do
        j ← 0
        while W_α(j) > ε and W_$(j) > ε do
            n_j = 1                                   ▷ Sample size to use if method not cost-aware.
            if Spending and Investing rule separate then
                Obtain φ_j from spending scheme.
                Obtain α_j, ψ_j from investing rule I
            else
                Obtain φ_j, α_j, ψ_j from self-contained investing rule I. (If using cost-aware, obtain and update n_j).
            end if
            Perform 1-sided Z-test on X[j][0 : n_j], and obtain p-value, p_j.
            if p_j ≤ α_j then
                R_j ← 1
            else
                R_j ← 0
            end if
            Update W_$(j + 1) ← W_$(j) − c n_j
            Update W_α(j + 1) ← W_α(j) − φ_j + R_j ψ_j
            j ← j + 1
        end while
    end for
end for
Aggregate results
```

**Algorithm 3** Simulation run in Figure 1

```
Input α, W_α(0), W_$(0), n_iter, m, c
for i = 0 to i = n_iter do
    Set seed to i
    for a ∈ {10, 20, 30, 40, 50, 60, 70, 80, 90} do
        X = [ ]
        for j = 0 to m do
            Sample q_j ∼ Beta(a, 100 − a)
            Sample θ_j, with Pr(θ_j = 0) = q_j, and Pr(θ_j = 2) = 1 − q_j.
            X[j] = 1000 realizations from N(θ_j, 1).
        end for
        for each testing method (unique row in Figure 1) do
            while W_α(j) > ε and W_$(j) > ε do
                Perform while loop in Algorithm 2.
            end while
        end for
    end for
end for
Aggregate results
```

$m = 6033$, and $c = 1$. We set ERO investing to always use a sample size of $n_j = 50$. For cost-aware ERO, we set the initial value of $\rho_j = 0.9$ and do not set a restriction on the upper value of $n_j$. However, if the optimized value is greater than 50, we choose to skip the test. Lastly, we set the constraint of $\varphi_j \leq (1 - q_j)W_\alpha(j)$ to avoid quick $\alpha$-death in some permutations. This idea is supported by results seen in Table 5, where we do not allow all $\alpha$-wealth to be myopically allocated to the next test. We note that this does not affect tests with large $q_j$ very much, as one might expect, since those tests require small bets in order to remain indifferent.

**Algorithm 4** Simulation run in Figure 2

```
Input α, W_α(0), W_$(0), n_iter, m, c
for i = 0 to i = n_iter do
    Set seed to i
    Randomly shuffle data
    for Method ∈ { ERO, cost-aware ERO} do
        while W_α(j) > ϵ and W_$(j) > ϵ do
            if Method is cost-aware ERO then
                Set constraint φ_j ≤ (1 − q_j)W_α(j)
                Solve Problem 18 to obtain φ_j, α_j, ψ_j, and n_j
                if 0 < n_j ≤ 50 then
                    Perform test and update as per other simulations.
                else
                    Skip test
                end if
            else
                Perform test with sample size n_j = 50 and update as per other simulations.
            end if
        end while
    end for
end for
Aggregate results.
```

# C EXTENSIONS OF COST-AWARE $\alpha$-INVESTING

In this section, we explore extensions of cost-aware ERO $\alpha$-investing.

**Cost tradeoffs.** In Problem 18 the monetary cost does not factor in to the objective except through the constraints. In many practical applications, it may be useful to simultaneously maximize the $\alpha$-reward and minimize the \$-cost. In those applications, the objective function can be augmented to $\mathbb{E}(R_j)\psi_j - \gamma c_j n_j$, where $\gamma$ controls the trade-off between improving $\alpha$-wealth and minimizing \$-cost.

**Variable utility.** Not all hypotheses may have equal value to the investigator and their value assessment may be independent of their assessment of the prior probability of the null hypothesis (Ramdas et al., 2017). For example, an investigator may be confident that a gene is differentially expressed in a particular tissue based on prior literature. Then the prior probability that $\theta_j = 0$ is low, $p_j \approx 0$, and the utility of testing that hypothesis is also low. There may be a different gene that has not been reported to be differentially expressed in the tissue, but if it is it would be a major scientific discovery. Then, the investigator may assign a high prior probability to the null $\theta_j = 0$, but also a high utility to the event that the null is rejected. A generalized form of the cost-aware decision rule can be constructed to account for varying utility levels for each hypothesis in the batch by making the objective function $\sum_{j=1}^{K} \mathbb{E}_\theta(R_j)U(R_j)\psi_j$, where $U(R_j)$ is the utility of the rejection of the $j$-th null hypothesis.

**Batch testing.** Many biological experiments are conducted in batches. This scenario leads to a need for a decision rule that provides $(\alpha_j, \psi_j, n_j)_{j=1}^K$ for a batch of $K$ tests. To address this need, the objective function in Problem 18 can be modified to $\sum_{j=1}^{K} \mathbb{E}_\theta(R_j)\psi_j$. It seems reasonable to expend all of the $\alpha$-wealth for each batch and then collect the reward at the completion of the batch so that a next batch of hypotheses can be tested. Therefore, we have constraints $\sum_{j=1}^{K} \varphi_j \leq W_\alpha(0)$ and $\sum_{j=1}^{K} c_j n_j \leq W_\$(0)$. The other constraint remain and apply for each test in the batch.

# D METHOD COMPARISON WITH $q = 0.1$

In Table 2 we explore the comparison of cost-aware ERO investing with other methods for $q_j = 0.1$. The results presented in the main body of the paper are for $q_j = 0.9$ to align with previous work. When true alternatives are abundant, the principle of indifference requires a large ante to remain indifferent. This causes cost-aware ERO to rapidly deplete the $\alpha$-wealth. In contrast, other methods do not increase the ante as severely as cost-aware ERO. However, it should be noted that the fraction of the tests that are true rejects among those that are performed is very high. For example, in constant ERO investing the proportion of true rejects is 24% and the proportion of true rejects for cost-aware ERO ($n_j \leq 10$) is $90\%$. This is a highly desirable result for the setting of biological experiments and other settings where sample cost is nontrivial.

| Scheme | Method | Tests | True Rejects | False Rejects | mFDR |
|---|---|---|---|---|---|
| constant | $\alpha$-spending | 10.0 | 2.49 | 0.00 | 0.001 |
| | $\alpha$-investing | 932.4 | 231.55 | 0.46 | 0.002 |
| | $\alpha$-rewards $k = 1$ | 925.0 | 230.13 | 0.46 | 0.002 |
| | $\alpha$-rewards $k = 1.1$ | 926.5 | 221.54 | 0.42 | 0.002 |
| | ERO investing | 934.3 | 230.87 | 0.45 | 0.002 |
| relative | $\alpha$-spending | 66.0 | 4.95 | 0.00 | 0.001 |
| | $\alpha$-investing | 994.0 | 661.55 | 10.19 | 0.015 |
| | $\alpha$-rewards $k = 1$ | 989.2 | 416.37 | 2.00 | 0.005 |
| | $\alpha$-rewards $k = 1.1$ | 991.4 | 626.93 | 7.47 | 0.012 |
| | ERO investing | 994.8 | 820.57 | 34.14 | 0.040 |
| other | LORD++ | 885.8 | 197.07 | 0.39 | 0.002 |
| | LORD1 | 1000.0 | 93.81 | 0.07 | 0.001 |
| | LORD2 | 1000.0 | 301.45 | 0.94 | 0.004 |
| | LORD3 | 1000.0 | 271.22 | 0.68 | 0.003 |
| | SAFFRON | 1000.0 | 779.92 | 23.92 | 0.030 |
| cost-aware | ERO $n_j = 1$ | 11.1 | 9.94 | 0.15 | 0.013 |
| cost-aware | ERO $n_j \leq 10$ | 12.8 | 11.48 | 0.21 | 0.017 |
| cost-aware | ERO $n_j^*$ | 10.6 | 9.48 | 0.13 | 0.012 |

Table 2: Comparison of cost-aware $\alpha$-investing with state-of-the-art sequential hypothesis testing methods with a prior probability of the null, $q = 0.1$ using 2,500 iterations. Cost-aware uses an initial $\rho_j$ for each iteration of 1.

# E SENSITIVITY ANALYSIS WITH RESPECT TO $q_j$

Since the cost-aware ERO method makes use of the prior probability of the null hypothesis, $q_j$, we investigate the sensitivity of the method to misspecification of that parameter. Table 3 shows the number of tests, mean true rejects, mean false rejects, and mFDR for simulation where the $q_j$ provided for optimization is misspecified. Specifically, we vary the specified $q_j$, when holding the true $q_j$ fixed at $0.9$. We performed $10,000$ iterations where cost-aware $\alpha$-investing is restricted to a single sample.

| Specified q | Tests | True Rejects | False Rejects | mFDR |
|---|---|---|---|---|
| 0.50 | 2.7 | 0.13 | 0.06 | 0.049 |
| 0.70 | 10.6 | 0.33 | 0.06 | 0.047 |
| 0.80 | 32.9 | 0.72 | 0.08 | 0.047 |
| 0.85 | 92.4 | 1.58 | 0.13 | 0.049 |
| 0.89 | 282.4 | 3.54 | 0.20 | 0.044 |
| 0.90 | 365.0 | 4.15 | 0.22 | 0.041 |

Table 3: Varying the magnitude of misspecification of $q_j$ shows that small deviations from the true value do not dramatically change performance, however, larger misspecifications result in fewer tests performed and fewer rejections. However, mFDR is still controlled.

When $q_j$ is fixed, the optimal sample size displays a peak. Empirically, it seems that when the probability of the null is large, but not too large, cost-aware ERO finds it advantageous to commit a large amount of samples because the $\alpha$-reward is high if rejection is successful.

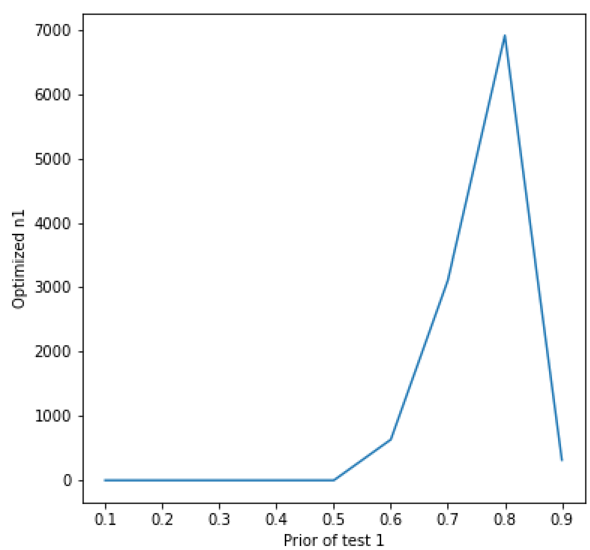


Figure 3: Optimal Sample size for varying levels of the prior of the null hypothesis. Here we initialize $rho_j = 1$, set $W_\alpha = 0.0475$, and do not set an upper bound for $n_j$.

# F COMPARISON WITH OTHER METHODS WITH $n_j = 10$

The simulation study used in Table 1 was repeated with setting $n = 10$ for the existing methods and $n_j \leq 10$ for cost-aware ERO. The cost per sample was set to $c_j = 1$, and the total budget was $W_\$[0] = 1000$. Hence, for methods that do not optimize sample size, the number of tests was limited to 100.

Cost-aware ERO investing expends the pool to $\alpha$-wealth more rapidly than other methods. The reason for this is that the principle of indifference forces the ante for each experiment to be higher than it would otherwise be in ERO investing. The overall power for cost-aware ERO is roughly the same as ERO investing and $\alpha$-investing at 10% and the mFDR is controlled at 0.05 for all methods.

| Scheme | Method | Tests | True Rejects | False Rejects | mFDR |
|---|---|---|---|---|---|
| constant | spending | 10.0 | 1.00 | 0.05 | 0.02 |
| | investing | 54.0 | 5.40 | 0.23 | 0.035 |
| | rewards k = 1 | 47.8 | 4.79 | 0.20 | 0.034 |
| | rewards k = 1.1 | 49.1 | 4.91 | 0.19 | 0.031 |
| | ERO investing | 54.0 | 5.40 | 0.23 | 0.035 |
| relative | spending | 66.0 | 6.55 | 0.05 | 0.006 |
| | investing | 99.9 | 10.00 | 0.52 | 0.045 |
| | rewards k = 1 | 99.9 | 10.00 | 0.45 | 0.039 |
| | rewards k = 1.1 | 99.9 | 10.00 | 0.40 | 0.036 |
| | ERO investing | 99.9 | 10.00 | 0.52 | 0.045 |
| cost-aware | ERO investing | 39.8 | 3.99 | 0.21 | 0.040 |
| other | LORD++ | 98.0 | 9.80 | 0.12 | 0.011 |
| | LORD1 | 100.0 | 9.99 | 0.07 | 0.006 |
| | LORD2 | 100.0 | 10.00 | 0.16 | 0.014 |
| | LORD3 | 100.0 | 10.00 | 0.16 | 0.014 |
| | saffron | 100.0 | 10.00 | 0.44 | 0.038 |

Table 4: Using a non-optimized pure strategy of setting n=10 (max n permissible in cost-aware simulations in Table 1). Although using a larger number of samples for each test gives more powerful tests, the number of samples used by cost-aware ERO investing is lower than all methods other than a constant spending scheme for $\alpha$-spending, which only gives a single true rejection.

In Table 4 it appears that cost-aware ERO performs fewer tests than standard ERO investing and has a lower number of true rejects. However, the power is roughly the same and the mFDR is controlled in both methods. The reason for this discrepancy is that cost-aware ERO expends the $\alpha$-wealth via the ante while ERO maintains a pool of $\alpha$-wealth because it employs a relative ante allocation. We explored whether including the ante $\varphi_j$ in the cost-aware objective would improve the number of tests and true rejects. While this modification would not technically be an ERO method, it would be expected to improve the conservation of $\alpha$-wealth. Indeed, it does. Table 5 shows the comparisons with this additional term in the objective.

| Scheme | Method | Tests | True Rejects | False Rejects | mFDR |
|---|---|---|---|---|---|
| relative | ERO investing | 139.3 | 13.15 | 0.24 | 0.016 |
| cost-aware | ERO investing | 176.1 | 16.20 | 0.16 | 0.009 |

Table 5: Using a strategy of setting $n \leq 10$ (max $n$ permissible in cost-aware simulations in Table 1). The addition of $-\varphi_j$ into the cost-aware objective enables cost-aware ERO to conserve $\alpha$-wealth and perform more tests than relative ERO investing. These mean value metrics were calculated with 10,000 data sets.

## G TWO-STEP COST AWARE ERO INVESTING

In order to include the principle of indifference as a constraint in the two-step optimal procedure, the expected change in $\alpha$-wealth must be equal no matter what strategy the experimenter uses. It follows that the expected change in $\alpha$-wealth must be found for each strategy, and the system of equations solved.

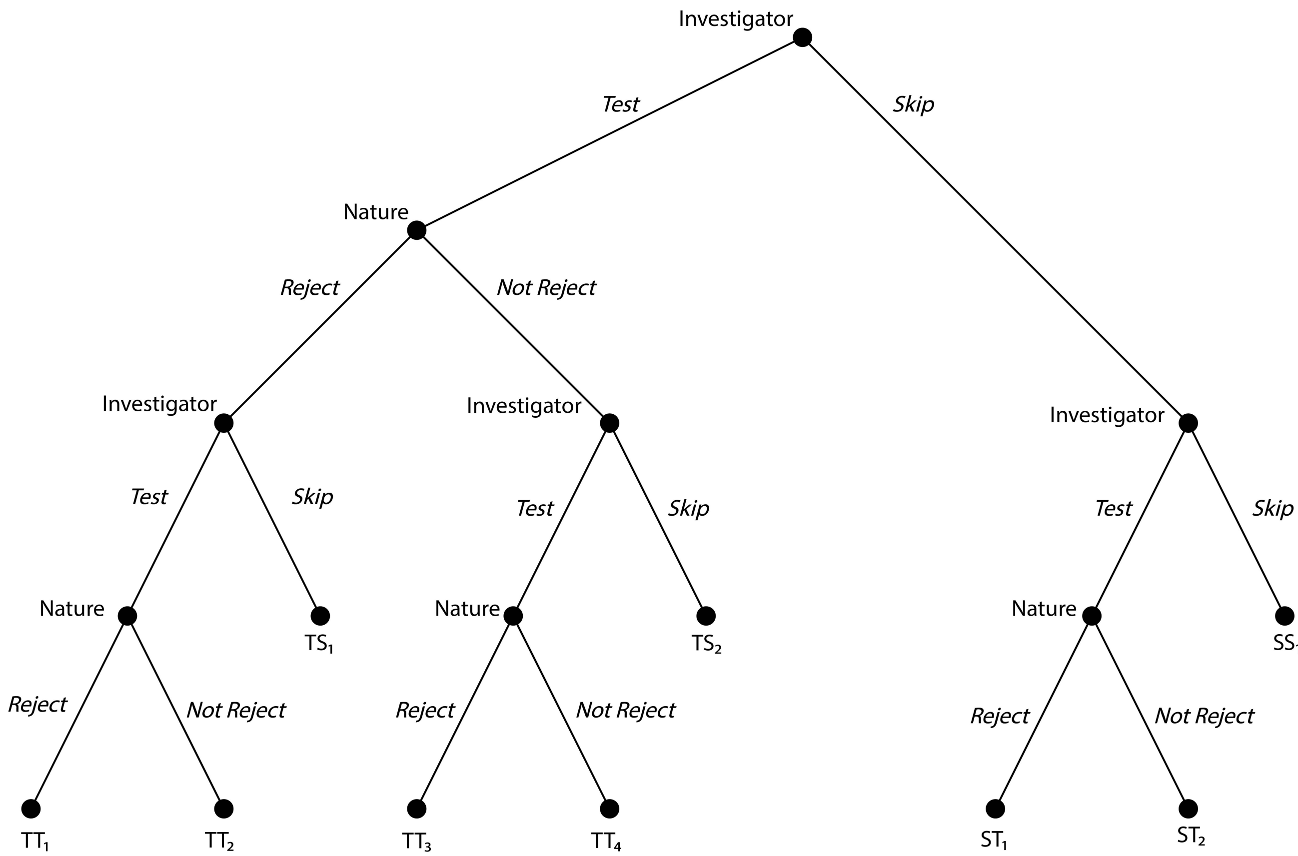


Figure 4: Extensive form of two-step game between Investigator (Player I) and the Nature (Player II). Strategies for each player are italicized. The leaves are labeled to denote the strategy taken by the investigator and are enumerated for indifference equations.

In order for the minimax solution for the two-step game to hold, the following equations must hold.

$$0 = P(TT_1)(-\varphi_1 - \varphi_2 + \psi_1 + \psi_2) + P(TT_2)(-\varphi_1 - \varphi_2 + \psi_1) + P(TT_3)(-\varphi_1 - \varphi_2 + \psi_2) + P(TT_4)(-\varphi_1 - \varphi_2) \quad (22)$$

$$0 = P(TS_1)(-\varphi_1 + \psi_1) + P(TS_2)(-\varphi_1) \quad (23)$$

$$0 = P(ST_1)(-\varphi_2 + \psi_2) + P(ST_2)(-\varphi_2), \quad (24)$$

where

$$P(TT_1) = (q_1\alpha_1 + (1-q_1)\rho_1)(q_2\alpha_2 + (1-q_2)\rho_2) \quad (25)$$

$$P(TT_2) = (q_1\alpha_1 + (1-q_1)\rho_1)(q_2(1-\alpha_2) + (1-q_2)(1-\rho_2)) \quad (26)$$

$$P(TT_3) = (q_1(1-\alpha_1) + (1-q_1)(1-\rho_1))(q_2\alpha_2 + (1-q_2)\rho_2) \quad (27)$$

$$P(TT_4) = (q_1(1-\alpha_1) + (1-q_1)(1-\rho_1))(q_2(1-\alpha_2) + (1-q_2)(1-\rho_2)) \quad (28)$$

$$P(TS_1) = q_1\alpha_1 + (1 - q_1)\rho_1 \tag{29}$$

$$P(TS_2) = q_1(1 - \alpha_1) + (1 - q_1)(1 - \rho_1) \tag{30}$$

$$P(ST_1) = q_2\alpha_2 + (1 - q_2)\rho_2 \tag{31}$$

$$P(ST_2) = q_2(1 - \alpha_2) + (1 - q_2)(1 - \rho_2) \tag{32}$$

Selecting the optimal sample size of one step versus two steps reveals that knowledge of future tests inherently limits the number of samples allocated on a single test. We can see that the knowledge of the second test greatly reduces the desire to risk such high levels of alpha and dollar wealth. We do note, for certain combinations of $q_1$ and $q_2$, although rare, the optimized $n_1$ and $n_2$ seem to converge to large values and this may be due to the nonlinear solver.

| $q_1/q_2$ | 0.1 | 0.2 | 0.3 | 0.4 | 0.5 | 0.6 | 0.7 | 0.8 | 0.9 |
|---|---|---|---|---|---|---|---|---|---|
| 0.1 | 0.588 | 0.588 | 0.595 | 0.592 | 0.586 | 0.458 | 0.532 | 0.765 | 0.352 |
| 0.2 | 0.608 | 0.588 | 0.594 | 0.586 | 0.586 | 0.587 | 0.485 | 0.767 | 0.351 |
| 0.3 | 0.591 | 0.588 | 0.588 | 0.585 | 0.593 | 0.586 | 0.484 | 1.603 | 0.434 |
| 0.4 | 0.851 | 0.851 | 0.851 | 0.851 | 0.851 | 0.851 | 0.851 | 1.613 | 0.851 |
| 0.5 | 1.895 | 1.895 | 1.895 | 1.895 | 1.895 | 1.895 | 1.895 | 1.895 | 1.895 |
| 0.6 | 553.624 | 552.578 | 550.467 | 13.314 | 3264.044 | 12.280 | 12.383 | 12.107 | 12.790 |
| 0.7 | 518.789 | 514.956 | 1303.099 | 29.686 | 13.409 | 12.350 | 12.536 | 12.510 | 13.653 |
| 0.8 | 15.839 | 14.104 | 14.321 | 12.650 | 12.650 | 12.962 | 12.473 | 12.530 | 13.660 |
| 0.9 | 49.216 | 13.400 | 49.334 | 13.404 | 13.612 | 13.038 | 12.958 | 12.969 | 13.498 |

Table 6: Values for optimal sample size of test 1, for unlimited $W_\$$ and $W_\alpha$ = 0.0475

| $q_1/q_2$ | 0.1 | 0.2 | 0.3 | 0.4 | 0.5 | 0.6 | 0.7 | 0.8 | 0.9 |
|---|---|---|---|---|---|---|---|---|---|
| 0.1 | 0.473 | 0.473 | 0.434 | 0.851 | 1.895 | 522.703 | 12.334 | 14.206 | 13.456 |
| 0.2 | 0.582 | 0.473 | 0.434 | 0.851 | 1.895 | 12.704 | 13.577 | 14.201 | 13.452 |
| 0.3 | 0.595 | 0.473 | 0.474 | 0.851 | 1.895 | 13.037 | 13.584 | 20.383 | 13.386 |
| 0.4 | 0.589 | 0.591 | 0.434 | 0.851 | 1.895 | 12.225 | 12.700 | 48593.014 | 13.365 |
| 0.5 | 0.554 | 0.556 | 0.434 | 0.851 | 1.895 | 11.828 | 12.252 | 20.707 | 12.913 |
| 0.6 | 0.506 | 0.506 | 0.506 | 0.851 | 1.895 | 12.271 | 12.723 | 12.815 | 13.400 |
| 0.7 | 0.528 | 0.526 | 0.543 | 0.851 | 1.895 | 11.963 | 12.462 | 12.738 | 13.428 |
| 0.8 | 0.487 | 0.466 | 0.465 | 0.851 | 1.895 | 12.379 | 12.653 | 12.526 | 13.087 |
| 0.9 | 0.508 | 0.508 | 0.507 | 0.851 | 1.895 | 12.092 | 12.964 | 15.516 | 16.036 |

Table 7: Values for optimal sample size of test 2, for unlimited $W_\$$ and $W_\alpha$ = 0.0475