Estimating the Optimal Linear Combination of Biomarkers using Spherically Constrained Optimization

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Abstract
In the context of a binary classification problem, the optimal linear combination of biomarkers is estimated by maximizing an empirical estimate of the area under the receiver operating characteristic curve. For multi-category outcomes, the optimal biomarker combination can similarly be obtained by maximization of the empirical hypervolume under the manifold (HUM). Since the empirical HUM is discontinuous, non-differentiable, and possibly multi-modal, solving this maximization problem requires a global optimization technique. The recently proposed smoothed approximation of the empirical HUM partially addresses this issue, as it is differentiable over the domain, but the objective function still remains non-concave and possibly multi-modal. Estimation of the optimal coefficient vector using existing global optimization techniques is computationally expensive, becoming prohibitive as the number of biomarkers and the number of outcome categories increases. We propose an efficient derivative-free black-box optimization technique based on pattern search to solve this problem. In both simulation studies and a benchmark real data application, the proposed method achieves better performance and greatly reduced computational time as compared to existing methods.

Keywords: Receiver operating characteristic curve, area under the curve, global optimization, pattern search, classification
1 Introduction

In the field of precision medicine, there is great interest in utilizing multiple biomarkers or diagnostic tests to better stratify patients based on disease subgroup or anticipated treatment response. To address this challenge, a number of classification methods have been proposed. Existing model-based approaches to the classification problem include logistic regression and linear discriminant analysis. As an alternative to model-based methods, several articles (e.g., Pepe & Thompson 2000, Pepe et al. 2006) have focused on classifying different subgroups based on maximization of the area under the receiver operating characteristic (ROC) curve (AUC), which typically requires fewer distributional assumptions. In its simplest form, the ROC curve can be interpreted as the probability of detection as a function of the false alarm rate. So, higher values of the AUC signify higher average hit rates over different possible values of the false alarm rate. The AUC is widely used to combine multiple diagnostic test results in the field of medical science (Dorfman et al. 1997, Metz et al. 1998, Zhou et al. 2002). The ROC curve has been used for classification problems in fields such as meteorology (Harvey et al. 1992, Mason & Graham 1999) and economics (Mylne 1999, Richardson 2000). However, the ROC curve does not have an exact analytical expression, so estimating the AUC and finding optimal biomarker combinations to maximize its value remains challenging.

In the case of a binary outcome, various non-parametric estimates of the AUC have been proposed. For example, Pepe et al. (2006) estimated the AUC using Mann-Whitney U statistics, while Ma & Huang (2007) proposed a smooth estimate obtained using a sigmoid function. However, with increasing sample size, these objective functions become challenging to maximize. In order to handle this problem for large datasets, Liu et al. (2011) proposed the min-max method, which only considers the linear combination of two extreme biomarkers in estimating the AUC, and therefore maintains the same computation time for any given sample size. For multi-categorical outcomes, the hypervolume under the manifold (HUM), also known as the volume under the ROC surface, has been proposed as an analogue to the AUC (Li & Fine 2008). For the three-category outcome scenario, various estimates of the HUM have been proposed (Scurfield 1996, Mossman 1999, Nakas 2000).
In the multi-category setting, Yanyu (2010) proposed a method to estimate the optimal combination vector when the outcomes of the biomarkers follow a normal distribution. However, their proposed method does not perform well when the biomarker values are non-normal (Hsu & Chen 2016, Maiti et al. 2019). In the presence of multiple biomarkers, to avoid the computational burden of simultaneous estimation of the combination vector, Pepe et al. (2006) proposed the step-down algorithm. However, this strategy of maximizing the HUM estimate by estimating one coordinate at a time can work poorly in higher dimensional settings. More recently, Zhang & Li (2011) proposed an empirical estimate of HUM (EHUM) for the three-category outcome scenario, but because of the lack of concavity of most of the proposed estimates, maximization of the objective functions remained challenging. To overcome this computational burden, under the assumption of normality, Kang et al. (2013) proposed a penalized and scaled stochastic distance based method. Finally, Hsu & Chen (2016) proposed an efficient approach which relies on upper and lower bounds (ULBA).

To alleviate the computational burden of maximizing EHUM, which is non-differentiable and discontinuous, Maiti et al. (2019) proposed a class of smoothed estimates of EHUM (SHUM) and extended it for any given number of outcome categories. They showed that better classification results can be obtained by maximizing SHUM compared to EHUM. Maiti et al. (2019) argued that due to the continuity of the proposed objective function, derivative-based methods can be used to maximize SHUM, yielding an improved solution. However, the objective function of SHUM still remains non-concave, therefore multiple maximums can exist. Despite the (possibly) multi-modal nature of SHUM, Maiti et al. (2019) did not attempt to apply global optimization tools, which are specifically designed to minimize non-concave or multi-modal functions.

As discussed above, most of the proposed estimates of the HUM are discontinuous and non-differentiable functions of the combination coefficients, and potentially have multiple maximums. Therefore, one of the most vital aspects regarding their performance remains the maximization step. This problem becomes more challenging with increasing sample size, number of biomarkers, and the number of outcome categories. For simple cases,
even in the presence of multiple local maximums, most of the optimization algorithms used in practice can still find the best solution. But, as the maximization problem gets harder, it becomes more difficult to find the global maximum out of all local maximums. Thus, performance becomes highly dependent on the optimization algorithm used for the maximization. When maximizing discontinuous, non-differentiable, multi-modal objective functions, derivative-free non-convex optimization techniques are critical to ensure a good solution (Horst 2002). However, to the best of our knowledge, none of the previous articles proposing HUM estimates considered using global optimization techniques for maximizing the corresponding objective function.

**Global optimization using pattern search**

Suppose $\beta$ denotes the $d$-dimensional linear combination vector to be estimated, and $f(\beta)$ denotes the value of the HUM based on either EHUM or SHUM. The way this objective functions is defined, if $f(\beta)$ is optimized over the unconstrained space $\beta \in \mathbb{R}^d$, $f(\beta)$ is not identifiable as $f(\beta) = f(a\beta)$ holds true for any given $a > 0$ (Liu et al. 2011). In order to address this non-identifiability, instead of maximizing $f(\beta)$ over $\mathbb{R}^d$, we add an extra constraint $||\beta|| = 1$ where $|| \cdot ||$ denotes the Euclidean norm. So the problem can be re-defined as

$$\maximize : f(\beta), \text{ where } \beta = (\beta_1, \ldots, \beta_d)$$

$$\text{subject to : } \sum_{i=1}^{d} \beta_i^2 = 1, \beta \in \mathbb{R}^d,$$

where $f(\beta)$ can be discontinuous (as is the case for EHUM), non-differentiable, and multi-modal. Note that here the coordinates $\beta$ must lie on the surface of a unit sphere. Due to the possibly multi-modal nature of $f(\beta)$, global optimization tools are preferred over convex optimization methods.

We now provide a brief summary of existing optimization methods. For maximizing any multi-modal function, global optimization techniques such as the genetic algorithm (Fraser 1957) and simulated annealing (Kirkpatrick et al. 1983) have been shown to yield better
results as compared to convex optimization methods such as the interior-point algorithm (Karmakar 1984) or sequential quadratic programming (Boggs & Tolle 1996). Torczon (1997) proposed pattern search (PS), where possible solution points around the current solution are found using an adaptive step-size vector. Importantly, none of these algorithms were designed to handle global optimization over a spherical parameter space.

To minimize a non-convex function (or, equivalently, maximize a non-concave function) globally over a hyper-rectangular parameter space, Das (2016a) proposed a modified version of global pattern search called Recursive Modified Pattern Search (RMPS). This approach, which is discussed in detail in Section 3.1, has desirable properties in terms of computational scalability and the fact that many of the operations can be performed in parallel. Subsequently, Das (2016b) and Das (2019) extended RMPS to problems where the parameter space is given by a collection of simplexes.

In this article we develop an algorithm called ‘Spherically Constrained Optimization Routine’ (SCOR) which utilizes the basic principle of the RMPS algorithm but accommodates the constraint of a spherical parameter space. Based on experimental studies using challenging benchmark problems, the computational efficiency of the proposed algorithm is established and its performance is compared with existing optimization techniques. We show that using SCOR to maximize EHUM or SHUM results in noticeable improvement over the step-down and min-max algorithms.

The rest of the article is organized as follows. Section 2 summarizes various measures of the HUM and existing techniques for finding the optimal combination coefficients. Section 3 describes the proposed SCOR algorithm, and its theoretical properties are discussed in Section 4. In Section 5, the performance of the proposed algorithm algorithm is compared to that of existing methods in a simulation study. In Section 6, the SCOR algorithm is used to find the optimal combination coefficient vector to distinguish different stages of Alzheimer’s Disease. Finally, we conclude with a discussion in Section 7.
2 Background on estimating and optimizing the HUM

In this section, we describe existing methods of estimating the optimal coefficient vector for combining biomarkers. Consider a study with $M$ possible outcome categories. Let $X_1, \ldots, X_M$ denote the $d$-dimensional observed biomarker values for the $M$ outcome categories. Each coordinate of $X_j$ denotes the value of a biomarker, $j = 1, \ldots, M$, where $d$ is the number of biomarkers. Suppose $X_j \sim F_j$ for $j = 1, \ldots, M$ where $F_j$ denotes a multivariate continuous distribution. Now the linear combination of the biomarkers corresponding to the $j$-th outcome category is given by $\beta^T X_j = \sum_{k=1}^{d} \beta_j X_{jk}$, where $\beta = (\beta_1, \ldots, \beta_d)$ denotes the combining coefficient vector. Without loss of generality, assuming that the higher value of the combination value corresponds to the higher outcome category, the HUM (Li & Fine 2008), which measures the diagnostic accuracy, is given by $D(\beta) = P(\beta^T X_M > \cdots > \beta^T X_2 > \beta^T X_1)$. In order to distinguish the outcome categories, our goal is to find the optimal combination coefficient vector $\beta_0$ for which $D(\beta)$ is maximized. So, $\beta_0 = \arg \max_{\|\beta\| = 1} D(\beta)$. Note that $D(\beta)$ should be maximized over all possible coefficient vectors of norm 1 to avoid the issue of non-identifiability. When $X_1, \ldots, X_M$ follow multivariate normal distributions, under a few regularity conditions, the value of $\beta_0$ can be derived (Su & Liu 1993). However, without any distributional assumption on $X_1, \ldots, X_M$, the value of $\beta_0$ cannot be analytically obtained.

2.1 Estimates of the HUM

We now review estimates of the HUM proposed in the literature. Essentially, these approaches provide different options for how to formulate the objective function.

**Empirical hypervolume under the manifold (EHUM)**

In order to estimate the optimal coefficient vector, Zhang & Li (2011) proposed maximizing the empirical estimate of the HUM from the given sample. Suppose the sample is denoted by $\{X_{ji} : j = 1, \ldots, M, i_j = 1, \ldots, n_j\}$, so the total sample size is $n = \sum_{j=1}^{M} n_j$. Then the
empirical estimate of HUM is given by

\[
D_E(\beta) = \frac{1}{n_1 n_2 \cdots n_M} \sum_{i_1=1}^{n_1} \sum_{i_2=1}^{n_2} \cdots \sum_{i_M=1}^{n_M} I(\beta^T X_{i_M} > \beta^T X_{i_{M-1}} > \cdots > \beta^T X_{i_1}).
\]

Here \(I(\cdot)\) denotes the indicator function. The optimal combination coefficient vector obtained by maximizing \(D_E(\beta)\) is given by \(\hat{\beta}_E = \arg \max_{||\beta||=1} D_E(\beta)\). Note that \(D_E(\beta)\) can be multi-modal. The discontinuity and non-differentiability of \(D_E(\beta)\) pose additional challenges in maximizing it using existing optimization methods.

**Upper and lower bound approach (ULBA)**

In order to alleviate the computational burden of maximizing \(D_E(\beta)\), [Hsu & Chen, 2016] proposed alternative objective functions which can be maximized more easily. [Hsu & Chen, 2016] showed that

\[
\max\{0, (M - 1)P_A(\beta) - (M - 2)\} \leq D(\beta) \leq P_M(\beta),
\]

where \(P_A(\beta)\) and \(P_M(\beta)\) are defined by

\[
P_A(\beta) = \frac{1}{M - 1} \sum_{j=1}^{M-1} P(\beta^T X_{j+1} > \beta^T X_j),
\]

\[
P_M(\beta) = \min_{1 \leq j \leq M-1} P(\beta^T X_{j+1} > \beta^T X_j).
\]

[Hsu & Chen, 2016] proposed that instead of maximizing \(D_E(\beta)\), we can either maximize \(P_A(\beta)\) or \(P_M(\beta)\), as they are much easier to solve. Since they showed that the solution obtained by maximizing \(P_A(\beta)\) yields better results than that obtained using \(P_M(\beta)\), in this paper we consider the optimal coefficient combination vector using ULBA as given by \(\hat{\beta}_{ULBA} = \arg \max_{||\beta||=1} P_A(\beta)\). Despite the simpler form of \(P_A(\beta)\) compared to \(D_E(\beta)\), this function is still discontinuous with possibly multiple modes.

**Smooth approximation of empirical HUM (SHUM)**

Because \(D_E(\beta)\) is discontinuous and non-differentiable, it is hard to maximize it using efficient derivative-based algorithms. To ease the challenge in maximizing \(D_E(\beta)\) directly,
Maiti et al. (2019) proposed a smoothed approximation of $D_E(\beta)$. Their proposed objective function is given by

$$D_g(\beta) = \frac{1}{n_1 n_2 \cdots n_M} \sum_{i_1=1}^{n_1} \sum_{i_2=1}^{n_2} \cdots \sum_{i_M=1}^{n_M} g_n(\beta^T(X_{M_{iM}} - X_{(M-1)(i_{(M-1)}),\cdot})) \cdots g_n(\beta^T(X_{2i2} - X_{1i1})), $$

where $g(x)$ is any any continuous function on $(-\infty, \infty)$ such that $g(x) + g(-x) = 1$ and $g''(x)$ is continuous. Maiti et al. (2019) took $g(\cdot)$ as a function of the total sample size $n$, given by $g_n(\cdot)$. They proposed two possible choices of $g_n(\cdot)$ using either a sigmoid curve or normal cumulative distribution function (CDF) which are given by $s_n(x) = \frac{1}{1+\exp(-\sqrt{n}x)}$ and $\Phi_n(x) = \Phi(\sqrt{n}x)$, respectively, where $\Phi(\cdot)$ denotes the normal CDF. Since they found that maximizing $D_{s_n}(\beta)$ and $D_{\Phi_n}(\beta)$ yielded similar estimates, here we only consider maximizing $D_{s_n}(\beta)$ as it is computationally less time consuming than maximizing $D_{\Phi_n}(\beta)$. Hence the SHUM estimator is given by $\hat{\beta}_{SHUM} = \arg\max_{||\beta||=1} D_{s_n}(\beta)$.

2.2 Existing techniques for estimating the optimal value of $\beta$

Due to the multi-modal nature of the objective functions discussed above, it is challenging to optimize the combination coefficient vector $\beta$ simultaneously. In Supplementary Material Section A, we provide background on general-purpose global optimization techniques including the genetic algorithm (GA), simulated annealing (SA), and pattern search (PS) which can be applied here. In the current section, we focus on approaches designed specifically for estimation of the combination vector developed in the past few decades.

Pepe et al. (2006) proposed the step-down algorithm for combining multiple biomarkers. Although the method was first proposed for the binary categorical outcome case, this principle can also be used in scenarios with more than two categorical outcomes (Kang et al. 2013). In the step-down approach, the biomarkers are first ordered based on their individual EHUM value. Then the coefficient of the biomarker with highest EHUM value is taken to be 1. Then at each step one additional biomarker is included and its coefficient is estimated. Thus, the coefficients of the biomarkers are estimated one at a time. A detailed description of the step-down algorithm is provided in Supplementary Material Section B.1.
Hsu & Chen (2016) used this algorithm to maximize the upper or lower bound of HUM, namely $P_M$ or $P_A$. Liu et al. (2011) proposed the min-max (MM) principle in the context of a binary outcome, where, corresponding to each vector of biomarkers of length $d$, only the maximum and the minimum values of those $d$ values are used to estimate the combination coefficient vector. The estimation procedure using the MM principle is provided in detail in Supplementary Material Section B.2.

3 Spherically Constrained Optimization Routine

We now describe the algorithm for our proposed optimization approach, Spherically Constrained Optimization Routine (SCOR).

3.1 Basic Principle

The basic principle of the search for the optimal value is as follows. Within an iteration, at first a step size $s > 0$ is fixed. Then, two new points in the neighborhood are obtained by adding and subtracting $s$ from each coordinate keeping all other coordinates fixed. Thus, at any given iteration, $2d$ possible new solution points are generated. For example, if $(\beta_1, \beta_2, \beta_3)$ denotes the current solution (taking $d = 3$), then the new set of possible solutions are $(\beta_1 + s, \beta_2, \beta_3), (\beta_1 - s, \beta_2, \beta_3), (\beta_1, \beta_2 + s, \beta_3), (\beta_1, \beta_2 - s, \beta_3), (\beta_1, \beta_2, \beta_3 + s)$ and $(\beta_1, \beta_2, \beta_3 - s)$. This strategy is related to the approach used in Fermi & Metropolis (1952) to solve an unconstrained optimization problem. This specific principle has two desirable properties: firstly, at each iteration the size of the search space (i.e., the set of newly generated points) is of $O(d)$ (i.e., $2d$), unlike GA, where the search space increases exponentially with the dimension (Geris 2012). Secondly, after the step-size $s$ is fixed, the operations for finding the $2d$ new points and evaluating the objective function at those points are independent, so they can be performed in parallel. However, due to the spherical constraint on $\beta$, this simple search strategy cannot be directly applied here.

We now summarize the proposed optimization scheme designed to address this issue. The algorithm can be broken into a sequence of runs where within each run, a number of
iterations are performed. At the beginning of each iteration, the step-size \( s > 0 \) is fixed. The location of the new set of points to be evaluated in the iteration depends on this step size \( s \). The exact relationship between the step size and the new set of possible solutions is described in the following subsections. The first iteration in the first run starts from a starting point provided by the user. At each iteration, a new set of \( 2d \) points around the current solution is generated. As mentioned above, the location of these new points is directly related to the value of step-size \( s \). In general, larger values of \( s \) result in more distant points from the current solution. Then, the objective function is evaluated at all \( 2d + 1 \) points. At the end of an iteration, the point with the maximum objective function value is taken as the updated solution. Thus, at each iteration the objective function value either increases or stays the same. At the beginning of a run, the step size is taken to be large. Depending on the improvement of the objective function across iterations, the step size is reduced. Once the step size within a run becomes sufficiently small (determined by a threshold \( \phi \) which is a tuning parameter of the algorithm), the run ends, and the current solution is passed to the next run, which uses this solution as its starting point. Once two consecutive runs yield the same solution, the algorithm stops execution and returns the final solution. A brief overview of the SCOR algorithm is given in Figure 1.

Figure 1: Flowchart of the SCOR algorithm where \( s \) denotes the step size, \( \phi \) denotes the step size threshold, and \( \text{SOL}(k) \) denotes the solution returned by the \( k \)-th run.
3.2 Derivation of adjustment step-size

The RMPS method (Das 2016a) incorporates adjustments to the step size to ensure that the proposed points remain within a restricting hyper-rectangle. In that approach, once the step size $s$ is added to (or subtracted from) any of the coordinates, the other coordinates are kept unchanged. However, over a spherically constrained parameter space, adding the step size $s$ to a coordinate of the current solution while keeping the other coordinates fixed would yield a point outside the unit sphere surface, assuming the current solution is on the unit sphere. To handle a spherically constrained parameter space, a critical challenge is devising an adjustment strategy such that when $s$ is added to (or subtracted from) the $i$-th coordinate, the adjustment of other coordinates ensures that the proposed solution point is still on the unit sphere. We derive an appropriate adjustment step size $t_i$ which depends on $s$ and is chosen so that when $t_i$ is added to the remaining coordinates, the point obtained is still on the unit-sphere. In Figure 2(a) an exemplary plot is provided giving an idea why adjustment step-size should be a function of $s$.

Figure 2: Exploratory moves on the surface of unit sphere by SCOR. Figure (a) shows an initial point $(\beta_1, \beta_2, \beta_3)$ (green) on the surface of the unit sphere and a point explored $(\beta_1 + t_2, \beta_2 + s, \beta_3 + t_2)$ (red) after making exploratory move with step-size $s$ for the 2$^{nd}$ coordinate, where $t_2$ denotes the adjustment step-size. Figure (b) shows exploratory moves in a typical iteration of SCOR: starting from the current solution point $(0.289, -0.816, 0.5)$ (green), the points explored after making exploratory moves with step-size $s = 0.03$ (blue) and $s = 0.06$ (red).
For example, suppose within any given run, at the $j$-th iteration, the current solution is given by $\mathbf{\beta}^{(j)} = (\beta_1^{(j)}, \ldots, \beta_d^{(j)})$. Note that $\sum_{k=1}^d (\beta_k^{(j)})^2 = 1$. Suppose we update the $i$-th coordinate as $\beta_i^{(j+1)} = \beta_i^{(j)} + s$. Then the corresponding adjustment step size $t_i$ is added to the rest of the coordinates, $\beta_k^{(j+1)} = \beta_k^{(j)} + t_i$, $k \in \{1, \ldots, d\} \setminus \{i\}$. By the definition of the adjustment step size, $\mathbf{\beta}^{(j+1)}$ is on the unit sphere as long as such a $t_i$ exists. Since $\mathbf{\beta}^{(j)}$ is also on the unit-sphere, we have,

$$
\sum_{k=1}^d (\beta_k^{(j)})^2 = \sum_{k=1}^d (\beta_k^{(j+1)})^2 = \sum_{k=1, k \neq i}^d (\beta_k^{(j)} + t_i)^2 + (\beta_i^{(j)} + s)^2 = 1,
$$

which implies,

$$
(d - 1)t_i^2 + 2t_i \sum_{k=1, k \neq i}^d \beta_k^{(j)} + (2s\beta_i^{(j)} + s^2) = 0.
$$

The value of $t_i$ can be obtained by solving (3) to obtain $t_i = T_1(s)$ or $T_2(s)$ where

$$
T_1(s) = \frac{-2 \sum_{k=1, k \neq i}^d \beta_k^{(j)} + \sqrt{D_i(s)}}{2(d - 1)}, \quad T_2(s) = \frac{-2 \sum_{k=1, k \neq i}^d \beta_k^{(j)} - \sqrt{D_i(s)}}{2(d - 1)},
$$

$$
D_i(s) = \left(2 \sum_{k=1, k \neq i}^d \beta_k^{(j)}\right)^2 - 4(d - 1)(2s\beta_i^{(j)} + s^2).
$$

In order for the proposed algorithm to converge to the true solution, the value of $t_i$ needs to be chosen such that the distance of the new possible solution $\mathbf{\beta}^{(j+1)}$ from the current solution $\mathbf{\beta}^{(j)}$ should go to 0 as $s$ goes to 0, which only holds true for $t_i = T_1(s)$. So for a given step size $s$, the adjustment step size is taken to be $T_1(s)$. It should be noted that $T_1(s)$ may come out to be complex implying that for the given step size $s$ and coordinates of the current solution, no appropriate adjustment step size $t_i$ exists. In those cases, we adopt alternative strategies, as discussed in the Section 3.4. In Figure 2(b), starting with a current solution on the surface of unit sphere, the new set of explored points are plotted on the unit-sphere corresponding to two different exemplary step sizes. In order to make the algorithm more efficient, further minor modification is considered which is described in Section C of the Supplementary Material.
3.3 Tuning parameters

In SCOR, the tuning parameters and their roles are similar to those considered in RMPS and RMPSS \cite{Das2016, Das2019}. Since the solution update strategy is consistent across runs, explaining the roles of the tuning parameters within a single run is sufficient to illustrate their effect. Within each run, iterations are initialized with a starting point which is either the initial guess provided by the user (for the first run) or the solution returned by the previous run (for all runs after the first run). At the beginning, the step size is set to \( s_{\text{initial}} \), which is preferably taken to be large in order to promote selection of distant candidate solutions w.r.t. the current solution. Suppose \( \beta^{(j)} = (\beta^{(j)}_1, \ldots, \beta^{(j)}_d) \) denotes the solution at the end of \( j \)-th iteration. At the beginning of \((j + 1)\)-th iteration, suppose the current step-size is \( s = s^{(j+1)}(>0) \). Then the set of \( d \) new candidate solutions is given by \( \{\beta^{(j+1)}_{(i,+)}\}_{i=1}^d \) where

\[
\beta^{(j+1)}_{(i,+)} = (\beta^{(j)}_1 + t_i, \beta^{(j)}_2 + t_i, \ldots, \beta^{(j)}_{i-1} + t_i, \beta^{(j)}_i + s, \beta^{(j)}_{i+1} + t_i, \ldots, \beta^{(j)}_d + t_i).
\]

for \( s > 0, i = 1, \ldots, d \). Similarly, taking \( s = -s^{(j+1)} \), another \( d \) candidate solutions are generated given by \( \{\beta^{(j+1)}_{(i,-)}\}_{i=1}^d \) where

\[
\beta^{(j+1)}_{(i,-)} = (\beta^{(j)}_1 + t'_i, \beta^{(j)}_2 + t'_i, \ldots, \beta^{(j)}_{i-1} + t'_i, \beta^{(j)}_i + s, \beta^{(j)}_{i+1} + t'_i, \ldots, \beta^{(j)}_d + t'_i), s < 0.
\]

Thus, within any given iteration, based on the step size \( s \), \( 2d \) new candidate solutions are generated. The objective function is evaluated at these \( 2d + 1 \) points (\( 2d \) candidate solutions and the current solution \( \beta^{(j)} \)), and the point with the lowest value of the objective function value is taken as the updated solution \( \beta^{(j+1)} \). As discussed in Section 3.2, in some scenarios, the adjustment step sizes \( t_i \) or \( t'_i \) might be complex. In those settings, we propose alternative update strategies which is discussed in Section 3.4.

Within a run, at the end of any given iteration, if the improvement of the objective function value is less than a user-specified tolerance \textit{tol.fun}, the step size is divided by a factor \( \rho > 1 \) denoted as the \textit{step decay rate}. So, at each iteration, the step size is either kept the same or reduced by dividing it by the \textit{step decay rate}. For example, \( s^{(j+1)} \) will be
either $s^{(j)}$ or $\frac{s^{(j)}}{\rho}$ depending on the improvement to the solution obtained in the $(j + 1)$-th iteration. The step size is reduced to enable finer search close to the current solution if no better solution is found in the set of candidate solutions using a larger value of $s$. The idea of reducing the step size is a well-known strategy used in existing derivative-free optimization algorithms on unconstrained parameter spaces [Fermi & Metropolis 1952, Kerr et al. 2018].

We consider the step size as sufficiently close to 0 once its value gets smaller than the step size threshold $\phi$. Once the step size becomes less than $\phi$, no further iterations are performed within that particular run. If two consecutive runs yield the same solution, the algorithm terminates after returning the solution obtained in the last run.

To handle cases where the solution is known to be sparse a priori, we consider the sparsity threshold $\lambda$ as another tuning parameter. Once the step size for the $j$-th iteration $s^{(j)}$ is determined, before calculating the adjustment step size $t_i$, all the coefficients (except the $i$-th coordinate) with absolute values less than $\lambda$ are set equal to zero. Suppose at the $j$-th iteration, while updating $i$-th coordinate, out of the remaining $d - 1$ coordinates, $h$ of them have absolute values less than $\lambda$. Then those $h$ coordinates are set equal to 0. The adjusted step size $t_i$ is calculated based on rest of the remaining $d - h$ coordinates. In case a sparse solution is not expected, the user can set the value of $\lambda$ to 0.

### 3.4 Local step sizes

At the beginning of the $j$-th iteration, we initialize $2d$ local step sizes such that $s_i^+ = s^{(j)}$ and $s_i^- = -s^{(j)}$ for $i = 1, \ldots, d$. When adding $s_i^+$ (or $s_i^-$) to the $i$-th coordinate, if the corresponding adjustment step size $t_i$ (or $t'_i$) exists, update movements are performed without modifying $s_i^+$ (or $s_i^-$). However, in case no such real $t_i$ (or $t'_i$) exists for the given local step size $s_i^+$ (or $s_i^-$), it is subsequently divided by the step decay rate $\rho$ until the solution $t_i$ (or $t'_i$) becomes real. Note that in equation (4), $D_i(s) \rightarrow (2 \sum_{k=1,k\neq i}^d \beta_k^{(j)})^2 > 0$ as $s \rightarrow 0$. Therefore, a real $t_i$ (or $t'_i$) will exist given a local step size $s_i^+$ (or $s_i^-$) sufficiently close to 0 (see Theorem 1). Since at the beginning of the iteration, the values of these local step-sizes are set equal to the step size for that iteration, the values of the local step sizes in the current iteration do not depend on the values from the previous iteration.
3.5 Overview of algorithm

Pseudocode for the proposed procedure is given in Algorithm 1. There we let $\hat{\beta}^{(R)}$ denote the solution obtained at the end of $R$-th run, and $\beta^{(j)}$ denotes the solution obtained after the $j$-th iteration within a particular run. We set an upper limit $\text{max \_runs}$ on the maximum number of runs to be executed. Within each run, there is an upper limit $\text{max \_iters}$ on the number of iterations. The roles of the tuning parameters along with their default values are provided in Supplementary Material Table S1.

4 Theoretical properties

In this section we show that when the objective function is continuous, convex, and differentiable, then starting from any initial point, the global minimum can be found by executing only one run of SCOR with step size threshold $\phi$ sufficiently close to zero.

**Theorem 1** Suppose $S = \{(x_1, \ldots, x_n) \in \mathbb{R}^n : \sum_{i=1}^{n} x_i^2 = 1, i = 1, \ldots, n\}$. Consider a sequence of step-sizes $\delta_k = \frac{s}{\rho^k}$ for $k \in \mathbb{N}$ and $s \neq 0, \rho > 1$. Then there exists a $K$ such that for $k \geq K$, all adjustment step sizes $\{t_i\}_{i=1}^d$ are real.

**Theorem 2** Suppose $f$ is convex, continuous and differentiable on $S$. Consider a sequence $\delta_k = \frac{s}{\rho^k}$ for $k \in \mathbb{N}$ and $s > 0, \rho > 1$. Suppose $u$ is a point in $S$ such that all its coordinates are positive. Define $u^{(i+)}_k = (u_1 + t_i(\delta_k), \ldots, u_{i-1} + t_i(\delta_k), u_i + \delta_k, u_{i+1} + t_i(\delta_k), \ldots, u_n + t_i(\delta_k))$ and $u^{(i-)}_k = (u_1 + t_i(-\delta_k), \ldots, u_{i-1} + t_i(-\delta_k), u_i - \delta_k, u_{i+1} + t_i(-\delta_k), \ldots, u_n + t_i(-\delta_k))$ for $i = 1, \ldots, n$, where $t_i(s)$ denotes the adjustment step size corresponding to step size $s$. Given conditions detailed in Supplementary Material Section D, the global minimum of $f$ over $S$ occurs at $u$.

The proofs of Theorems 1 and 2 are provided in Supplementary Material Section D. As is the case for other existing black-box optimization methods, SCOR is not theoretically guaranteed to find the global minimum of any arbitrary function. However, it incorporates strategies to avoid getting stuck at local minima. Moreover, as discussed in the next section, SCOR outperforms competing methods in terms of identifying better solutions for benchmark functions.
Algorithm 1 SCOR

1: \( R \leftarrow 1 \)
2: \( top \)
3: \( j \leftarrow 1 \)
4: \( s^{(0)} \leftarrow s_{\text{initial}} \)
5: if \( R = 1 \) then
6: \( \beta^{(0)} \leftarrow \text{Initial guess} \)
else
7: \( \beta^{(0)} \leftarrow \hat{\beta}^{(R-1)} \)
8: while \( (j \leq \text{max\_iter} \text{ and } s^{(j)} > \phi) \) do
9: \( F \leftarrow f(\beta^{(j-1)}) \)
10: \( s \leftarrow s^{(j-1)} \)
11: for \( h = 1 : 2d \) do
12: \( \beta_h \leftarrow \beta^{(j-1)} \)
13: \( \Lambda \leftarrow \text{which}(|\beta_h^{(j-1)}| < \lambda), k \in \{1, \ldots, d\} \setminus \{i\} \)
14: \( \Gamma \leftarrow \text{which}(|\beta_h^{(j-1)}| \geq \lambda), k \in \{1, \ldots, d\} \setminus \{i\} \)
15: \( s_h \leftarrow (-1)^h s_h^{(j)} \)
16: \( D \leftarrow (2 \ast \text{sum}(|\beta_h(\Gamma)|)^2 - 4 \ast \text{length}(\Gamma) \ast (2s_h\beta_h(i) + s_h^2) - \text{sumsquare}(\beta_h(\Lambda))) \).
17: while \( (D < 0 \text{ and } |s_h| > \phi) \) do
18: \( s_h \leftarrow s_h^\rho \)
19: \( D \leftarrow (2 \ast \text{sum}(|\beta_h(\Gamma)|)^2 - 4 \ast \text{length}(\Gamma) \ast (2s_h\beta_h(i) + s_h^2) - \text{sumsquare}(\beta_h(\Lambda))) \).
20: if \( (D \geq 0) \) then
21: \( t \leftarrow -2 \ast \text{sum}(|\beta_h(\Gamma)|) + \sqrt{7} \)
22: \( \beta_h(i) \leftarrow \beta_h(i) + s_h \)
23: \( \beta_h(\Gamma) \leftarrow \beta_h(\Gamma) + t \)
24: \( \beta_h(\Lambda) \leftarrow 0 \)
25: \( f_h \leftarrow f(\beta_h) \)
26: else
27: \( f_h \leftarrow F \)
28: \( B \leftarrow \arg \min_{\beta_h} f_h \)
29: \( FF \leftarrow \min\{f_h\}_{h=1}^{2d} \)
30: if \( (FF < F) \) then
31: \( \beta^{(j)} \leftarrow B \)
32: else
33: \( \beta^{(j)} \leftarrow \beta^{(j-1)} \)
34: if \( (j > 1) \) then
35: if \( (|F - \min(F, FF)| < \text{tol\_fun} \text{ and } s > \phi) \) then
36: \( s \leftarrow s^\rho \)
37: \( j \leftarrow j + 1 \)
38: \( \hat{\beta}^{(R)} \leftarrow \beta^{(j)} \)
39: if \( ||\hat{\beta}^{(R)} - \hat{\beta}^{(R-1)}|| < \text{tol\_fun} \times 2 \) then
40: return \( \hat{\beta} = \hat{\beta}^{(R)} \) as final solution
41: exit
42: else
43: \( R \leftarrow R + 1 \)
44: goto \( top \).
5 Simulation study

In this section, we compare the performance of SCOR with the step-down and min-max methods in the context of simulated data. Under different simulation scenarios, we estimate the optimal combination vector by maximizing the the EHUM, SHUM, or ULBA objective functions using each of these three approaches. We measure performance in terms of the EHUM objective function value \( D_E(\cdot) \) at the estimated optimal solution. The SCOR algorithm is implemented in MATLAB 2016b. For the step-down and min-max algorithms, we use the \texttt{fminsearch} function in MATLAB 2016b.

We consider two simulation scenarios based on the normal distribution and the Weibull distribution (to illustrate performance in the context of non-normal data). For each simulation scenario, we consider settings with \( M = 2 \) and \( M = 3 \) ordinal outcomes. The number of biomarkers is taken to be \( d = 5, 10, 20 \). For each case, only the first 5 biomarkers are generated from the corresponding five-dimensional normal or Weibull distribution. For \( d = 10, 20 \), the remaining biomarker values are generated from \( U(0, 1) \). For the case of \( M = 2 \) categories, we consider the sample sizes for each category to be 15, 30, and 60. For the \( M = 3 \) category case, we take the sample sizes of each category to be 15 and 30.

**Scenario 1:** For the two category outcome case, for the \( i \)-th disease category, the values of the biomarkers are simulated from the 5-variate normal distribution with mean \( \mu_i \), and variance covariance matrix \( \Sigma_i = I \), where \( i = 0, 1 \), where \( \mu_0 = (0, 0, 0, 0, 0)^T \), \( \mu_1 = (1.0, 1.1, 1.2, 1.3, 1.4)^T \). For the three category outcome case, we take \( \Sigma_i = I \), where \( i = 0, 1, 2 \), \( \mu_0 = (0, 0, 0, 0, 0)^T \), \( \mu_1 = (1.0, 1.1, 1.2, 1.3, 1.4)^T \) and \( \mu_2 = (2.0, 2.2, 2.4, 2.6, 2.8)^T \), respectively.

**Scenario 2:** Here the values of the biomarkers are generated from the multivariate Weibull distribution. For \( i \)-th disease category, the \( j \)-th biomarker follows a univariate Weibull distribution with scale parameter \( \lambda_i \) and shape parameter \( k_j \). For two category case, corresponding to \( i = 0, 1 \), we take \( \lambda_0 = 1, \lambda_1 = 2 \) and \( k_1 = 0.5, k_2 = 1, k_3 = 1.5, k_4 = 2, k_5 = 2.5 \). For three category case, corresponding to \( i = 0, 1, 2 \), we take \( \lambda_0 = 1, \lambda_1 = 2, \lambda_2 = 3 \) and \( k_1 = 0.5, k_2 = 1, k_3 = 1.5, k_4 = 2, k_5 = 2.5 \).
In Table 1, we provide the results for two and three category outcome problems where the sample size of each category is 15. The results for sample size 30 (for two and three category outcomes) and 60 (for two category outcomes) are provided in Table S3 and S4 of the Supplementary Material. We report the EHUM objective function value $D_E(\cdot)$ at the estimated optimal solutions obtained by the SCOR, step-down and min-max algorithms under different simulation scenarios. The results reported are the means over 100 replications. SCOR outperforms both step-down and min-max for all the scenarios considered. As the dimension $d$ of the biomarker vector increases, estimates by SCOR tend to improve, while the estimates from step-down and min-max under-perform. For non-normal (Weibull) simulation scenarios, SCOR outperforms other methods by a larger margin compared to that for the simulation study where the true biomarkers are generated from a normal distribution. SCOR estimates have in general lower standard errors compared to other methods. Finally, maximizing the SHUM objective function yields better estimates compared to those

Table 1: Performance comparison for two and three ordinal outcomes, where each class has sample size 15. The empirical hypervolume under manifolds (EHUM), smoothed approximated hypervolume under manifolds (SHUM) and upper and lower bound approach (ULBA) objective functions are maximized by the proposed Spherically Constrained Optimization Routine (SCOR) algorithm and the existing step-down and min-max algorithms. The mean EHUM objective function values at the obtained solutions are reported based on 100 simulations, with the standard error in the parentheses.
obtained by maximizing the ULBA or EHUM objective functions.

In Supplementary Material Section E, we compare the performance of SCOR with general-purpose global optimization algorithms based on optimization of five benchmark functions on the unit-spherical parameter space with dimensions $d = 5, 20, 50, 100, 500$, and show that in general SCOR outperforms existing optimization algorithms, with greatly reduced computation time. Specifically, using SCOR, we obtain an improvement in computation time up to 67 fold over pattern search, up to 43 fold over simulated annealing, and up to 38 fold over the genetic algorithm.

6 Application to Alzheimer’s disease data

Alzheimer’s is a form of dementia which causes problems with thinking, memory and behaviour. The greatest known risk factor for Alzheimer’s is increasing age, and it is more prevalent in people 65 years old or older. In 2010, 4.7 million Americans over the age of 65 years had Alzheimer’s, and researchers predict that by 2050, it will increase to 13.8 million (Hebert et al. 2013). Early detection of Alzheimer’s is crucial to slow down the worsening of dementia symptoms and to improve quality of life. We consider a dataset (Luo & Xiong 2012) consisting of measures on 14 neuropsychometric markers for 118 individuals. This dataset is available in the R package DiagTest3Grp. These 118 individuals can be divided into three diagnostic categories: healthy, mild cognitive impairment (MCI), and Alzheimers disease (AD). We disregard data on 10 individuals with missing observations. Out of the remaining 108 patients, the number of subjects in the healthy, MCI, and AD groups are 44, 43, and 2,1 respectively. The 14 markers correspond to numeric measurements on the following neuropsychometric tests: global (factor1), temporal (ktemp), parietal (kpar), frontal (kfront), logical memory (zpsy004), digital span forward (zpsy005), digital span backward (zpsy006), information (zinfo), two measures of visual retention (zbentc, zbentd), Boston naming (zboston), mental control (zmentcon), word fluency (zworflu), and associate learning (zassc). Since factor1, ktemp and zpsy004 are highly correlated (Luo & Xiong 2012), we only consider the ktemp biomarker out of these three markers, as it has the highest individual EHUM value. So, in total, 12 biomarkers are included in the analysis.
To illustrate the relative performance of the SCOR, step-down and min-max techniques, we compute the estimated combination coefficients maximizing the EHUM, ULBA, and SHUM criteria using each techniques. Then EHUM value at those solutions are evaluated. We also compute the optimal cut-points to categorize the combination scores (obtained by multiplying the optimal coefficient vector with the biomarker values) using Youden’s index \cite{Youden1950}. Youden’s index is defined as the maximum possible value of (sensitivity + specificity − 1) over all possible decision thresholds, and provides a summary measure combining sensitivity and specificity \cite{Luo2012}. Note that before obtaining the combination scores, all the solution combination vectors obtained in the step-down and min-max techniques are divided by their corresponding norms so that each solution vector has norm 1.

In Figure 3 shows that using SCOR we obtain both higher values of EHUM and Youden’s Index across all three objective functions (ULBA, EHUM, or SHUM). In addition, the cut-points obtained distinguish the three outcome categories more clearly for SCOR than step-down or min-max. In Table 2 we provide the values of the optimal combination coefficients using SCOR and step-down. Note that the signs of the estimated coefficients of the biomarkers are more consistent across the objective functions SHUM, EHUM and ULBA for SCOR compared to the step-down approach. Since we obtain the highest value of $D_E(\hat{\beta})$ using the estimate obtained by maximizing SHUM with the SCOR algorithm, the coefficients obtained using this approach (i.e., those given in the first column) represent the preferred solution.

7 Discussion

In this paper, we propose a novel derivative-free black-box optimization technique to minimize any non-convex function where the parameters are constrained to the surface of a unit sphere. Our algorithm is highly efficient, as it allows parallelization using up to $2n$ parallel threads when maximizing a function whose parameters belong to the surface of an $n$-dimensional unit sphere. Our simulations demonstrate that SCOR outperforms existing methods for biomarker combination, as well as other black-box optimization techniques, in
Figure 3: Boxplots of the optimal combination vector scores are shown across the outcome categories healthy, MCI, and AD. The methods compared are SCOR ((a) ULBA, (b) EHUM (c) SHUM), Step-down ((d) ULBA, (e) EHUM (f) SHUM) and Min-max ((g) ULBA, (h) EHUM (i) SHUM). The horizontal dotted lines denote the corresponding cut-points for classification obtained by maximizing Youden’s Index.
We show that using SCOR, we obtain better estimates of the empirical hypervolume under the manifold (EHUM) compared to the estimates obtained using the step-down and min-max algorithms. Irrespective of the objective function considered, the EHUM value at the solution obtained by SCOR is always better than that obtained using the step-down or min-max algorithms. SCOR is used to find the optimal combination coefficients of neuropsychometric markers to distinguish individuals belonging to three severity categories of Alzheimer’s disease. We observe two key benefits of using SCOR over existing methods for this particular dataset. First, higher EHUM values are obtained using SCOR. Secondly, the signs of the estimated coefficients obtained by maximizing different objective functions are more similar under SCOR vs. step-down, suggesting the results are more robust.

Here the proposed SCOR algorithm is used mainly in the context of a classification problem with hypervolume under manifolds criteria. However, this algorithm can be used in various other statistical problems such as directional statistics or single-index models where fixing the norm of the coefficient vector is need to avoid the issue of non-identifiability. In the future, the SCOR algorithms can be extended to the variable selection problem over

| Markers | ULBA (SCOR) | EHUM (SCOR) | SHUM (SCOR) | ULBA (ST) | EHUM (ST) | SHUM (ST) |
|---------|-------------|-------------|-------------|-----------|-----------|-----------|
| ktemp   | -0.360      | -0.360      | -0.399      | -0.640    | -0.622    | -0.465    |
| kpar    | -0.084      | -0.084      | -0.155      | 0.160     | 0.160     | -0.014    |
| kfront  | -0.367      | -0.367      | -0.265      | -0.228    | -0.221    | -0.170    |
| zpsy005 | 0.206       | 0.206       | 0.184       | -0.347    | -0.436    | -0.188    |
| zpsy006 | -0.204      | -0.204      | -0.267      | 0.223     | 0.215     | -0.690    |
| zinfo   | 0.694       | 0.694       | 0.666       | 0         | 0         | 0         |
| zbentc  | -0.160      | -0.160      | -0.187      | 0.114     | 0.128     | -0.045    |
| zbentd  | 0.251       | 0.251       | 0.273       | -0.223    | -0.170    | 0.242     |
| zboston | -0.047      | -0.047      | 0.0463      | 0.095     | 0.091     | -0.019    |
| zmentcon| 0.228       | 0.228       | 0.167       | 0.256     | 0.253     | 0.405     |
| zworflu | 0.108       | 0.108       | 0.163       | 0.060     | 0.057     | 0.077     |
| zassc   | -0.095      | -0.095      | 0.178       | 0.441     | 0.426     | 0.109     |

| $D_E(\hat{\beta})$ | 0.849 | 0.849 | **0.859** | 0.750 | 0.747 | 0.824 |

Table 2: Optimal coefficients obtained by maximizing the ULBA, EHUM and SHUM objective functions using the SCOR and step-down algorithms. The EHUM objective function values at all the obtained solutions are reported in the last row.
the coefficients belonging to the surface of a unit sphere.

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SUPPLEMENTARY MATERIAL

Supplementary material: The supplementary material file is provided in pdf format.

R package: The R-package SCOR (available at https://github.com/synx21/SCOR) contains code to maximize the ULBA, EHUM and SHUM objective functions for multi-category classification using the proposed method described in this article. This optimization method can also be used to maximize or minimize any black-box function on a spherically constrained parameter space. The package also contains the Alzheimer’s dataset which is used as example in the article (GNU zipped tar file). The MATLAB code is made available at https://github.com/priyamdas2/SCOR.

Alzheimer’s data set: Data set used in the illustration of SCOR method in Section 6 is provided within the R package by the name test_biomarker.rda.

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A Global optimization

In this section, we provide additional background on global optimization procedures. For maximizing any multi-modal function, global optimization techniques such as the genetic algorithm (GA; Fraser 1957, Bethke 1980) and simulated annealing (SA; Kirkpatrick et al. 1983, Granville et al. 1994) have been shown to yield better results compared to regular convex optimization methods such as the interior-point algorithm (IP; Karmakar 1984, Potra & Wright 2000) or the sequential quadratic programming algorithm (SQP; Wright 2005, Boggs & Tolle 1996). In most global optimization techniques, unlike convex optimization algorithms, once a local maximum is reached, based on some heuristic principles, attempts are made to look for a possible better solution in a different neighbourhood. Global optimization techniques provide better results compared to convex optimization methods when dealing with multi-modal objective functions. However, for our problem of interest, with an increasing number of biomarkers, most existing global optimization techniques become computationally too expensive. Specifically for GA, there is an exponential increase in the search space with the dimension of the parameter space (Geris 2012). Due to the excessive time consumption of existing global optimization techniques, to maximize the estimates of HUM, only convex optimization techniques are generally used, with or without using the step-down principle.

In addition to GA and SA, over the last few decades, several deterministic and stochastic global search algorithms have been proposed over unconstrained and constrained parameter spaces (Nelder & Mead 1965, Steihaug & Suleiman 2013). In the direct search algorithm for unconstrained optimization, first introduced by Hooke & Jeeves (1961), in each iteration a set of possible solution points are chosen around the current solution without using gradient-based techniques. Then, the best solution point is chosen out of the combined set of possible solutions including the current solution and the new set of possible solutions. Extending the idea of direct search, Torczon (1997) proposed generalized pattern search (GPS), where the possible solution points around the current solution are found by moving along the coordinates with a step-size vector, derived using an algorithm of exploratory moves. Later, Kolda et al. (2003) and Audet & Dennis (2006) further generalized GPS
into the generating set search (GSS) and mesh adaptive direct search (MADS) algorithms, respectively. Although other global optimization tools have been proposed (see for example Audet et al. [2008], Conn et al. [2009], Digabel [2011]), most of them deal with unconstrained optimization problems.

B Existing techniques for estimating the optimal $\beta$

In this section, we review the most popular algorithms for estimating the optimal value of the combination vector $\beta$.

B.1 The step-down algorithm

When maximizing a non-concave function, as the dimension of the parameter space increases, it becomes harder for any given algorithm to reach the true solution. In the step-down approach (Pepe et al. [2006]), all the biomarkers are first ranked according to their importance. The coefficient of the first (i.e., the most important) biomarker is taken to be 1. Then at each step, one new biomarker is included and its coefficient is calculated without changing the coefficients of the other already included biomarkers. Thus, the problem of maximizing an objective function of an $m$-dimensional parameter is broken down into $d - 1$ univariate maximization problems. As step-down is a strategy for maximizing any given objective function, any HUM estimate can be solved using this strategy. Because the performance of most optimization algorithms declines with the increasing dimension of the parameter space, the step-down strategy is commonly used (e.g., Maiti et al. [2019]) when combining more than 2 biomarkers.

The step-down algorithm to maximize any given objective function $D(\cdot)$, for example, EHUM or SHUM, goes as follows:

**Step 1.** EHUM values are computed for the individual biomarkers, which are arranged in decreasing order by their EHUM values. $X_{(1)}$ and $X_{(d)}$ would therefore have the highest and the lowest individual EHUM values, respectively.
Step 2. The first two biomarkers with the highest EHUM values are taken and combined as $V_2 = X_{(1)} + \lambda_2 X_{(2)}$, where $\lambda_2$ is a parameter that needs to be estimated.

Step 3. $D(\cdot)$ for the combined marker $V_2$ is maximized with respect to $\lambda_2$. Let $\hat{V}_2 = X_{(1)} + \hat{\lambda}_2 X_{(2)}$ denote the updated combination vector.

Step 4. For $i = 3, \ldots, d$ define $V_i = \hat{V}_{i-1} + \lambda_i X_i$ and maximize $D(\cdot)$ with respect to $\lambda_i$. The combination vector obtained at $i$-th step is given by $\hat{\lambda}_i$.

The estimated optimal marker $\hat{V}_d = X_{(1)} + \hat{\lambda}_2 X_{(2)} + \cdots + \hat{\lambda}_d X_{(d)}$ is obtained at the end of Step 4.

B.2 The min-max technique

Liu et al. (2011) proposed the min-max (MM) method in the context of binary outcome, where, corresponding to each vector of biomarkers of length $d$, only the maximum and the minimum values of those $d$ values are used to estimate the combination coefficient vector. Suppose $X_{ij,\text{max}} = \max_{1 \leq k \leq d} X_{ij,k}$ and $X_{ij,\text{min}} = \min_{1 \leq k \leq d} X_{ij,k}$. Consider the linear combination of these two quantities as $V_{ij} = \beta_{\text{max}} X_{ij,\text{max}} + \beta_{\text{min}} X_{ij,\text{min}}, \ i = 1, 2, \cdots, n_j, \ j = 1, 2, \cdots, M$. Then the objective function to be maximized using the EHUM, ULBA and SHUM approaches are given by:

$$D_E^{(MM)}(\beta_{\text{max}}, \beta_{\text{min}}) = \frac{1}{\prod_{j=1}^M n_j} \sum_{i_1=1}^{n_1} \sum_{i_2=1}^{n_2} \cdots \sum_{i_M=1}^{n_M} I(V_{i_M} > V_{i_{M-1}} > \cdots > V_{i_1}),$$

$$P_A^{(MM)}(\beta_{\text{max}}, \beta_{\text{min}}) = \frac{1}{M-1} \sum_{j=1}^{M-1} P(V_{j+1} > V_j),$$

$$D_s^{(MM)}(\beta_{\text{max}}, \beta_{\text{min}}) = \frac{1}{\prod_{j=1}^M n_j} \sum_{i_1=1}^{n_1} \sum_{i_2=1}^{n_2} \cdots \sum_{i_M=1}^{n_M} g_n(V_{i_M} - V_{i_{M-1}}) \cdots g_n(V_{i_2} - V_{i_1}).$$

Irrespective of the dimension of the biomarker vector, here the number of parameters to be estimated is only 2. In order to avoid the non-identifiability issue, in practice $\beta_{\text{max}}$ is taken to be 1 and only $\beta_{\text{min}}$ is estimated (Hsu & Chen 2016, Maiti et al. 2019, Liu et al. 2011).
The solutions obtained by maximizing the above-mentioned modified objective function for EHUM, ULBA and SHUM are denoted by:

\[
\hat{\beta}_{E}^{(MM)} = \arg \max_{(\beta_{\text{max}}, \beta_{\text{min}}) \in \mathbb{R}^2} D_{E}^{(MM)}(\beta_{\text{max}}, \beta_{\text{min}}),
\]

\[
\hat{\beta}_{ULBA}^{(MM)} = \arg \max_{(\beta_{\text{max}}, \beta_{\text{min}}) \in \mathbb{R}^2} P_{A}^{(MM)}(\beta_{\text{max}}, \beta_{\text{min}}),
\]

\[
\hat{\beta}_{SHUM}^{(MM)} = \arg \max_{(\beta_{\text{max}}, \beta_{\text{min}}) \in \mathbb{R}^2} D_{s_{n}}^{(MM)}(\beta_{\text{max}}, \beta_{\text{min}}).
\]

C Modification for better convergence of SCOR

A discussion on how to choose the adjustment step size for SCOR is provided in Section 3.2 of the main paper. After solving equation (3) of the main paper, we obtain two possible solutions for the corresponding adjusted step sizes which are \( T_{1}(s) \) and \( T_{2}(s) \) (provided in equation (4) of the main paper). As shown in Section [D] below, by considering only \( T_{1}(s) \) as the adjusted step size, theoretical properties under the regularity conditions can be derived for SCOR. Although considering \( T_{2}(s) \) as the adjustment step size along with \( T_{1}(s) \) does not offer any improvement in a theoretical sense, by extensive experimental study we have observed that considering both \( T_{1}(s) \) and \( T_{2}(s) \) as the adjustment sizes generally results in faster convergence with better results. Corresponding to the step size \( s \) for any given position of the array, using both \( T_{1}(s) \) and \( T_{2}(s) \) as adjustment step sizes, we obtain 4 candidate points (instead of 2, which occurs when we only consider \( T_{1}(s) \) as the adjusted step size). Thus, for any given step size \( s \), in total, we get \( 4n \) candidate solutions (instead of \( 2n \)). We employ this strategy for further improvement of SCOR in convergence and computation time in the simulation study (Section 5 in the main paper), application (Section 6 in the main paper) and comparative performance over benchmark functions (Section [E]). An overview of the SCOR parameters is given in Table 3 below.
| Parameter | Description | Role | Recommended values and comments |
|-----------|-------------|------|----------------------------------|
| $s_{initial}$ | initial global step size | Initial step size at the beginning of the run, higher value promotes selection of distant candidate solutions. | 2 (setting it 2 allows maximum possible coordinate-wise jump on unit-sphere space) |
| $\rho$ | step decay rate | Controls the rate of decay of global step-size, smaller value of $\rho$ results in slower decay of the global step size, thus it allows denser search in the neighborhood of the current solution at the expense of higher computation time. | 2 (must be > 1) |
| $\phi$ | lower bound of global step size | Controls precision of search, smaller value of $\phi$ results in more accurate solution in the expense of higher computation time. | $10^{-20}$ |
| $\lambda$ | sparsity threshold | (i) Controls sparsity, encourage sparse solution. (ii) Helps in the search procedure when coordinate(s) of the starting point of any iteration is(are) close to 0. | $10^{-6}$ (may consider $10^{-2}$ or $10^{-1}$ for inducing more sparsity, or can be set as small as 0) |
| $\text{tol}_\text{fun}$ | termination tolerance on the function value | The minimum amount of improvement in objective function value required so that the global step size is not reduced after the iteration. | $10^{-6}$ |
| $\text{tol}_\text{fun,2}$ | termination tolerance on the difference of solutions of two consecutive runs | The minimum euclidean distance between solutions of two consecutive runs so that next run is executed. | $10^{-20}$ |
| $\text{max}\_\text{runs}$ | max no. of runs | Put an upper limit on number of runs. | 10000 (however the algorithm converged before 1000 runs in all the cases considered in this article) |
| $\text{max}\_\text{iter}$ | max no. of iterations | Put an upper limit on number of iterations allowed within each run. | 10000 (however required number of iterations within a run never crossed 10000 in any of the considered cases) |

Table 3: Tuning parameters, their roles and default values in the SCOR algorithm.

**D Proof of theorems**

**Theorem 3** Suppose $S = \{(x_1, \ldots, x_n) \in \mathbb{R}^n : \sum_{i=1}^{n} x_i^2 = 1, i = 1, \ldots, n\}$. Consider a sequence of step sizes $\delta_k = \frac{s}{\rho^k}$ for $k \in \mathbb{N}$ and $s \neq 0, \rho > 1$. Then there exists a $K$ such that for $k \geq K$, all adjustment step sizes $\{t_i\}_{i=1}^d$ are real.

**Proof:** [Proof of Theorem 3] From Equation (4) of the main paper, the adjustment step size $t_i$ as a function of $\delta_k$ is given by

$$t_i(\delta_k) = \frac{-2 \sum_{k=1, k \neq i}^{n} \beta_k^{(j)} + \sqrt{D_i(\delta_k)}}{2(n-1)}, i = 1, \ldots, n,$$

$$D_i(\delta_k) = (2 \sum_{k=1, k \neq i}^{n} \beta_k^{(j)})^2 - 4(n-1)(2\delta_k\beta_i^{(j)} + \delta_k^2).$$
Note that $\delta_k \to 0$ as $k \to \infty$. Hence,

$$
\lim_{k \to \infty} D_i(\delta_k) = (2 \sum_{k=1,k \neq i}^{n} \beta_k^{(j)})^2
$$

Since $D_i(\delta_k)$ is a continuous function of $\delta_k$, if we take $k$ to be sufficiently large, we can make $D_i(\delta_k) \geq 0$. Suppose for $k \geq K_i$, $D_i(\delta_k) \geq 0$ holds true for $i = 1, \ldots, n$. Take $K = \max_{1 \leq i \leq n} K_i$, hence, for all $k \geq K$, $t_i$ is real for $i = 1, \ldots, n$. \hfill \Box

**Proposition 1** Consider a matrix $A = (a_{ij})_{(n-1) \times (n-1)}$ such that $a_{ii} = 1$ for $i = 1, \ldots, n-1$ and $a_{ij} = b_i$ for $i \neq j, i = 1, \ldots, n-1, j = 1, \ldots, n-1$. Then $A$ is full rank for $n \in \mathbb{N} \setminus \{1\}$ iff

1. $1 - b_i \neq 0$ for $i = 1, \ldots, n-1$.

2. $[(n - 2) + \sum_{i=1}^{n-1} \frac{1}{1-b_i}] \neq 0$.

**Proof:** We have

$$
A = \begin{bmatrix}
1 & b_1 & \cdots & b_1 \\
b_2 & 1 & \cdots & a_2 \\
\vdots & \vdots & \ddots & \vdots \\
b_{(n-1)} & b_{(n-1)} & \cdots & 1
\end{bmatrix}.
$$

By performing a series of column operations $C_i : C_i - C_{n-1}$ for $i = 1, \ldots, n-2$, we obtain $A'$ as follows:

$$
A' = \begin{bmatrix}
1 - b_1 & 0 & \cdots & b_1 \\
0 & 1 - b_2 & \cdots & b_2 \\
\vdots & \vdots & \ddots & \vdots \\
b_{(n-1)} - 1 & b_{(n-1)} - 1 & \cdots & 1
\end{bmatrix}
$$

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Now consider the following series of row and column operations

\[
\begin{pmatrix}
1 - b_1 & 0 & \cdots & b_1 \\
0 & 1 - b_2 & \cdots & b_2 \\
\vdots & \vdots & \ddots & \vdots \\
1 & 1 & \cdots & (n - 2) + \frac{1}{b_{(n-1)} - 1}
\end{pmatrix}
\]

\[
\begin{pmatrix}
1 - b_1 & 0 & \cdots & 1 \\
0 & 1 - b_2 & \cdots & 1 \\
\vdots & \vdots & \ddots & \vdots \\
1 & 1 & \cdots & (n - 2) + \frac{1}{b_{(n-1)} - 1}
\end{pmatrix}
\]

\[
\begin{pmatrix}
1 - b_1 & 0 & \cdots & 0 \\
0 & 1 - b_2 & \cdots & 0 \\
\vdots & \vdots & \ddots & \vdots \\
1 & 1 & \cdots & (n - 2) + \frac{1}{b_{(n-1)} - 1}
\end{pmatrix}
\]

\[
\begin{pmatrix}
1 - b_1 & 0 & \cdots & 0 \\
0 & 1 - b_2 & \cdots & 0 \\
\vdots & \vdots & \ddots & \vdots \\
0 & 0 & \cdots & (n - 2) + \frac{1}{b_{(n-1)} - 1}
\end{pmatrix}
\]

Since $A''$ is diagonal matrix, the determinant of $A''$ is given by

\[
det(A'') = [(n - 2) + \sum_{i=1}^{n-1} \frac{1}{b_i - 1}] \prod_{i=1}^{n-2} (1 - b_i)
\]

Clearly $r(A) = r(A'')$ where $r(B)$ denotes the rank of any given matrix $B$. Hence $A$ is full.
rank iff

1. \((1 - b_i) \neq 0\) for \(i = 1, \ldots, n - 1,\)

2. \([n - 2 + \sum_{i=1}^{n-1} \frac{1}{b_i - 1}] \neq 0.\)

\[\square\]

**Theorem 4** Suppose \(S = \{(x_1, \cdots, x_n) \in \mathbb{R}^n : \sum_{i=1}^{n} x_i^2 = 1, i = 1, \cdots, n\}\) and \(f\) is convex, continuous and differentiable on \(S\). Consider a sequence \(\delta_k = \frac{s}{\rho^k}\) for \(k \in \mathbb{N}\) and \(s > 0, \rho > 1\). Suppose \(u\) is a point in \(S\) such that all its coordinates are positive. Define \(u_{k}^{(i+)} = (u_1 + t_i(\delta_k), \ldots, u_{i-1} + t_i(\delta_k), u_i + \delta_k, u_{i+1} + t_i(\delta_k), \ldots, u_n + t_i(\delta_k))\) and \(u_{k}^{(i-)} = (u_1 + t_i(-\delta_k), \ldots, u_{i-1} + t_i(-\delta_k), u_i - \delta_k, u_{i+1} + t_i(-\delta_k), \ldots, u_n + t_i(-\delta_k))\) for \(i = 1, \cdots, n,\) where \(t_i(s)\) denotes the adjustment step size corresponding to step size \(s\). Define \(b_i = -\frac{u_i}{\sum_{k=1, k\neq i}^{n} u_k}\). If the following conditions hold true

1. \(1 - b_i \neq 0\) for \(i = 1, \ldots, n - 1,\)

2. \([n - 2 + \sum_{i=1}^{n-1} \frac{1}{b_i - 1}] \neq 0,\)

3. for all sufficiently large \(k \in \mathbb{N}\), \(f(u) \leq f(u_{k}^{(i+)})\) and \(f(u) \leq f(u_{k}^{(i-)})\) for all \(i = 1, \cdots, n,\)

then the global minimum of \(f\) over \(S\) occurs at \(u\).

**Proof:** [Proof of Theorem 4] From Theorem 3 there exists a \(K_1 \in \mathbb{N}\) such that for all \(k \geq K_1, t_i(\delta_k)\) is real for \(i = 1, \ldots, n\). Similarly it can be shown that there exists a \(K_2 \in \mathbb{N}\) such that for all \(k \geq K_2, t_i(-\delta_k)\) is real for \(i = 1, \ldots, n\). Take \(K = \max(K_1, K_2)\). Hence for all \(k \geq K\), both \(t_i(\delta_k)\) and \(t_i(-\delta_k)\) are real for \(i = 1, \ldots, n\), and, therefore, for \(k \geq K\), \(u_{k}^{(i+)}\) and \(u_{k}^{(i-)} \in S\) for all \(i = 1, \ldots, n\). For the rest of the proof, we only consider the cases for \(k \geq K\). Define

\(S^+ = \{(x_1, \cdots, x_n) \in \mathbb{R}^n : \sum_{i=1}^{n} x_i^2 = 1, x_n \geq 0, i = 1, \cdots, n\}\).
\[S^- = \{(x_1, \ldots, x_n) \in \mathbb{R}^n : \sum_{i=1}^{n} x_i^2 = 1, x_n < 0, i = 1, \ldots, n\}.\]

Note that \(S = S^+ \cup S^-\). So if we can prove this theorem on both \(S^+\) and \(S^-\), that would suffice. Suppose \((u_1, \ldots, u_n) \in S^+\). The \(n\)-th coordinate \(u_n\) can be derived as a unique function of first \(n - 1\) coordinates given by \(u_n = \sqrt{1 - \sum_{i=1}^{n-1} u_i^2}\). Define

\[S^* = \{(x_1, \ldots, x_{n-1}) \in \mathbb{R}^{n-1} : \sum_{i=1}^{n-1} x_i^2 < 1, i = 1, \ldots, n - 1\},\]

\[u^* = (u_1, \ldots, u_{n-1}),\]

\[u_k^{*(i+)} = (u_1 + t_i(\delta_k), \ldots, u_{i-1} + t_i(\delta_k), u_i + \delta_k, u_{i+1} + t_i(\delta_k), \ldots, u_n - 1),\]

\[u_k^{*(i-)} = (u_1 + t_i(-\delta_k), \ldots, u_{i-1} + t_i(-\delta_k), u_i - \delta_k, u_{i+1} + t_i(-\delta_k), \ldots, u_n + t_i(-\delta_k)),\]

for \(i = 1, \ldots, n - 1\). Note that \(u^*, u_k^{*(i+)}\), and \(u_k^{*(i-)}\) are the first \((n - 1)\) coordinates of \(u, u_k^{(i+)}\), and \(u_k^{(i-)}\), respectively. Define \(f^* : S^* \mapsto \mathbb{R}\) such that

\[f^*(x_1, \ldots, x_{n-1}) = f(x_1, \ldots, x_{n-1}, \sqrt{1 - \sum_{i=1}^{n-1} x_i^2}).\]

Hence we have \(f^*(u^*) = f(u)\), \(f^*(u_k^{*(i+)}) = f(u_k^{(i+)})\) and \(f^*(u_k^{*(i-)}) = f(u_k^{(i-)})\). \(f\) is continuous and differentiable on \(S\), hence \(f\) is continuous and differentiable on \(S^+\). Therefore, \(f^*\) is continuous and differentiable on \(S^*\). Since \(f\) is convex on \(S\), \(f\) is also convex on \(S^+\).

We claim that \(f^*\) is convex on \(S^*\). Consider \(x_1^*, x_2^* \in S^*\). Suppose \(x_1, x_2 \in S^+\) are such that their first \((n - 1)\) coordinates are the same as \(x_1^*\) and \(x_2^*\), respectively. Take any \(\gamma \in (0, 1)\). Now

\[\gamma f^*(x_1^*) + (1 - \gamma)f^*(x_2^*) = \gamma f(x_1) + (1 - \gamma)f(x_2)\]

\[\geq f(\gamma x_1 + (1 - \gamma)x_2)\]

\[= f^*(\gamma x_1^* + (1 - \gamma)x_2^*).\]
Hence \( f^* \) is also convex.

Define \( h_i : U_i \mapsto \mathbb{S}^* \) such that

\[
h_i(z) = (u_1 + t_i(z), \ldots, u_{i-1} + t_i(z), u_i + z, u_{i+1} + t_i(z), \ldots, u_{n-1} + t_i(z))
\]

for \( i = 1, \ldots, n-1 \), where \( U_i = [-\delta_K, \delta_K] \). Note that \( h_i(U_i) \subset \mathbb{S}^* \). Define \( g_i : U_i \mapsto \mathbb{R} \) for \( i = 1, \ldots, n-1 \) such that \( g_i = f^* \circ h_i \). Hence,

\[
g_i(z) = f^*(u_1 + t_i(z), \ldots, u_{i-1} + t_i(z), u_i + z, u_{i+1} + t_i(z), \ldots, u_{n-1} + t_i(z))
\]

for \( i = 1, \ldots, n-1 \).

Note that \( h_i \) is continuous on \( U_i = [-\delta_K, \delta_K] \) and differentiable on \((-\delta_K, \delta_K)\) for \( i = 1, \ldots, n-1 \). Also \( f^* \) is continuous and differentiable on \( \mathbb{S}^* \). The composition of any two continuous functions is continuous. Also the composition of two differentiable functions is differentiable. Therefore, \( g_i \) is continuous on \( U_i = [-\delta_K, \delta_K] \) and differentiable on \((-\delta_K, \delta_K)\).

For any \( i \in \{1, \ldots, n-1\} \),

\[
g_i(\delta_K) = f^*(u_K^{*(i+1)}), \quad g_i(-\delta_K) = f^*(u_K^{*(i-1)}) \quad \text{and} \quad g_i(0) = f^*(u^*)
\]

From the conditions provided in the theorem, we have \( g_i(0) \leq g_i(-\delta_K) \) and \( g_i(0) \leq g_i(\delta_K) \). Without loss of generality, suppose \( f^*(u_K^{*(i-1)}) \leq f^*(u_K^{*(i+1)}) \) which implies \( g_i(0) \leq g_i(-\delta_K) \leq g_i(\delta_K) \).

Since \( g_i(0) \leq g_i(-\delta_K) \leq g_i(\delta_K) \), from the continuity of \( g_i \) it can be said that there exists a \( w \in [0, \delta_K] \) such that \( g_i(w) = g_i(-\delta_K) \geq g_i(0) \). Since \( g_i \) is continuous on \([-\delta_K, \delta_K]\) and differentiable on \((-\delta_K, \delta_K)\), \( g_i \) is also continuous on \([-\delta_K, w]\) and differentiable on \((-\delta_K, w)\).

Using the mean value theorem, there exists a point \( v \in [-\delta_K, w] \) such that \( g_i'(v) = 0 \).

We claim that \( g_i'(v) = 0 \) holds for \( v = 0 \). Suppose \( g_i'(0) \neq 0 \) and \( g_i'(v^*) = 0 \) for some \( v^* \in (-\delta_N, w) \setminus \{0\} \). Without loss of generality, take \( v^* > 0 \). Since \( h_i \) and \( f^* \) are convex on \( U_i \) and \( \mathbb{S}^* \) respectively, \( g_i \) is also convex on \((-\delta_K, w) \subset U_i \). Now \( g_i'(v^*) = 0 \) implies \( v^* \) is a local minimum. Also \( g_i'(0) \neq 0 \), implies 0 is not a local minimum (or critical point). Therefore, \( g_i(0) > g_i(v^*) \). Take \( M \in \mathbb{N} \) such that it satisfies \( 0 < \delta_M < v^* \). Clearly, \( K < M \).
since $\delta_M < v^* \leq \delta_K$. Hence there exists a $\lambda \in (0, 1)$ such that $\delta_M = (1 - \lambda)v^* + \lambda.0$. So,

$$g_i(\delta_M) = g_i((1 - \lambda)v^* + \lambda.0)$$

$$\leq (1 - \lambda)g_i(v^*) + \lambda g_i(0)$$

$$= g_i(0) - (1 - \lambda)(g_i(0) - g_i(v^*))$$

$$< g_i(0).$$

But, for all $k \geq K$, $g_i(0) \leq g_i(\delta_k)$, which implies $g_i(0) \leq g_i(\delta_M)$ (since $K < M$). It is a contradiction. Thus, $g'_i(0) = 0$. Now

$$g'_i(0) = \left[ \frac{\partial}{\partial \epsilon} g_i(\epsilon) \right]_{\epsilon=0}$$

$$= \left[ \frac{\partial}{\partial \epsilon} f^*(h_i(\epsilon)) \right]_{\epsilon=0}$$

$$= \left[ \frac{\partial}{\partial h_i(\epsilon)} f^*(h_i(\epsilon)) \right]_{\epsilon=0} \left[ \frac{\partial}{\partial \epsilon} h_i(\epsilon) \right]_{\epsilon=0}.$$

Now $h_i(0) = u^*$. Hence

$$\left[ \frac{\partial}{\partial h_i(\epsilon)} f^*(h_i(\epsilon)) \right]_{\epsilon=0} = \nabla f^*(u^*)$$

$$= \left[ \frac{\partial}{\partial x_1} f^*(u^*), \ldots, \frac{\partial}{\partial x_{n-1}} f^*(u^*) \right]$$

$$= \left[ \nabla_1, \ldots, \nabla_{n-1} \right]$$

where $\nabla_i = \frac{\partial}{\partial x_i} f^*(u^*)$ for $i = 1, \ldots, n - 1$.

$$\left[ \frac{\partial}{\partial \epsilon} h_i(\epsilon) \right]_{\epsilon=0} = [a_{i1}, \ldots, a_{i(n-1)}]^T$$

where $a_{ii} = 1$ and

$$a_{ij} = \frac{\partial t_i(s)}{\partial s} \bigg|_{s=0} = \frac{1}{2(n-1)} \frac{-8(n-1)u_i}{\sqrt{(2 \sum_{k=1,k\neq i}^n u_k)^2}} = \frac{-u_i}{\sqrt{\sum_{k=1,k\neq i}^n u_k^2}} = b_i,$$

$$38$$
for \( j \in \{1, \ldots, n - 1\} \setminus \{i\} \). Hence

\[
g'_i(0) = \left. \frac{\partial}{\partial \epsilon} g_i(\epsilon) \right|_{\epsilon=0} = \begin{bmatrix} \nabla_1, \ldots, \nabla_{n-1} \end{bmatrix} \begin{bmatrix} a_{i1}, \ldots, a_{i(n-1)} \end{bmatrix}^T
= \begin{bmatrix} a_{i1}, \ldots, a_{i(n-1)} \end{bmatrix} \begin{bmatrix} \nabla_1 \\ \vdots \\ \nabla_{n-1} \end{bmatrix}
= 0.
\]

Since this equation holds for all \( i = 1, \cdots, n - 1 \), we have \( Ax = 0 \) where

\[
A_{(n-1)\times (n-1)} = \begin{bmatrix}
1 & b_1 & \cdots & b_1 \\
b_2 & 1 & \cdots & b_2 \\
\vdots & \vdots & \ddots & \vdots \\
b_{n-1} & b_{n-1} & \cdots & 1
\end{bmatrix},
\begin{bmatrix}
\nabla_1 \\
\vdots \\
\nabla_{n-1}
\end{bmatrix}.
\]

By Proposition 1, \( A_{(n-1)\times (n-1)} \) is full-rank. Since \( A \) is full rank for \( n \in \mathbb{N} \setminus \{1\} \), \( Ax = 0 \) implies \( x = 0 \). Hence \( \frac{\partial}{\partial x_i} f^*(u^*) = 0 \) for all \( i = 1, \ldots, n - 1 \). Hence \( u^* \) is a critical point. Since \( f^* \) is convex on \( S^* \), a local minimum occurs at \( u^* \). But for a convex function, the global minimum occurs at any local minimum. Hence the global minimum of \( f^* \) occurs at \( u^* \), which clearly implies the global minimum of \( f \) on \( S^+ \) occurs at \( u \). Now, in case \( u \in S^- \), similarly it can be shown that the global minimum of \( f \) on \( S^- \) occurs at \( u \). Hence the global minimum of \( f \) occurs at \( u \) for \( u \in S \). \( \square \)

### E Performance of SCOR on benchmark functions

We compare the performance of SCOR with existing black-box optimization algorithms, namely the genetic algorithm (GA), simulated annealing (SA), and pattern search (PS), which were introduced in Section A above. The GA, SA and PS algorithms are available in the MATLAB 2016b toolbox under the functions `ga`, `simulannealbnd`, and `patternsearch`, respectively. Note that `ga` and `patternsearch` can be used to minimize any function.
whose parameters are on a unit sphere. However, the `simulannealbnd` function in MATLAB 2016b cannot handle non-linear constraints (to the best of our knowledge). Therefore while minimizing the following functions using simulated annealing, we minimize them over the compact region $[-1,1]^d$ where $d$ denotes the number of parameter coordinates in the objective functions. We use the default function parameter options for all of these aforementioned algorithms in MATLAB. SCOR is also coded in MATLAB 2016b. We use the default parameter values as mentioned in Table S1. We consider the following benchmark functions on the parameter space $S$ where

$$
S = \{(x_1, \ldots, x_d) : \sum_{i=1}^{d} x_i^2 = 1\}.
$$

The explicit form of the following functions can be also found in Jamil & Yang (2013).

**Example 1 (Negative log of product of absolute values):**

$$
f(x_1, \ldots, x_d) = -\sum_{i=1}^{d} \log |x_i| - \frac{d}{2} \log d.
$$

The global minimum value is 0 which is attained at $(x_1, \ldots, x_d) = (\pm \frac{1}{\sqrt{d}}, \ldots, \pm \frac{1}{\sqrt{d}})$.

**Example 2 (Modified Griewank function):**

$$
f(x_1, \ldots, x_d) = \frac{1}{4000} \sum_{i=1}^{d} (x_i - \frac{1}{\sqrt{d}})^2 - \prod_{i=1}^{d} \cos \left[ \frac{x_i - \frac{1}{\sqrt{d}}}{\sqrt{i}} \right] + 1.
$$

The global minimum value is 0 which is attained at $(x_1, \ldots, x_d) = (\frac{1}{\sqrt{d}}, \ldots, \frac{1}{\sqrt{d}})$.

**Example 3 (Negative sum of squares function):**

$$
f(x_1, \ldots, x_d) = d - \sum_{i=1}^{d} ix_i^2.
$$

The global minimum value is 0 which is attained at $(x_1, \ldots, x_d) = (0, \ldots, 0, \pm 1)$. 

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Example 4 (Modified exponential function):

\[
f(x_1, \ldots, x_d) = 1 - \exp(-0.5 \sum_{i=1}^{d-1} x_i^2).
\]

The global minimum value is 0 which is attained at \((x_1, \ldots, x_d) = (0, \ldots, 0, \pm 1)\).

Example 5 (Modified Easom function):

\[
f(x_1, \ldots, x_d) = 1 - \prod_{i=1}^{2} \cos(\sqrt{2}\pi x_i) \exp[-\sum_{i=1}^{2} (x_i - \frac{1}{\sqrt{2}})^2].
\]

The global minimum value is 0 which is attained at \((x_1, \ldots, x_d) = (\frac{1}{\sqrt{2}}, \frac{1}{\sqrt{2}}, 0, \ldots, 0)\).

We minimize these functions for \(d = 5, 20, 50, 100, \) and 500 using the proposed SCOR algorithm and the existing algorithms GA, SA and PS. As shown in Table 4, SCOR generally outperforms other methods both in terms of the quality of the solution as well as computation times. Among other methods, PS performs better than GA or SA. For the high-dimensional modified Easom function, SA provides the best solution at the expense of a huge computational time. SCOR outperforms other methods in most of the scenarios. Using SCOR, we obtain up to a 67 fold improvement over PS in computation time (for the modified Griewank function for \(d = 5\)), up to a 43 fold improvement over SA (for the modified Easom function for \(d = 20\)) and up to a 38 fold improvement over GA (for the exponential function for \(d = 5\)).
Table 4: Comparison of minimum value achieved and average computation time (in seconds) for solving the transformed $d$-dimensional negative log-product function, modified Griewank's function, negative sum of squares function, modified Exponential function, and modified Easom function for $d = 5$, 20, 50, 100 and 500 using SCOR, PS, GA, SA starting from 10 randomly generated points in each case.
Additional simulation results

In Section 5 of the main paper, we show the comparative performance of SCOR and other existing algorithms (step-down and min-max) for two and three category outcome classification problems based on the existing objective functions estimating the hypervolume under manifolds (namely, ULBA, EHUM, and SHUM) with sample size 15 for each class. Here we provide an extended simulation study with sample sizes of 30 and 60 in each class for two category classification (in Table 5) and with sample size 30 in each class for three category classification (in Table 6).

| Sample sizes | Method | Scenario 1 | Scenario 2 |
|--------------|--------|------------|------------|
|              |        |    ULBA    |    EHUM    |    SHUM    |    ULBA    |    EHUM    |    SHUM    |
| (30,30)      | SCOR   | 0.984 (0.01) | 0.984 (0.01) | 0.983 (0.01) | 0.964 (0.03) | 0.964 (0.03) | 0.963 (0.03) |
|              | Step-Down | 0.966 (0.02) | 0.966 (0.02) | 0.980 (0.01) | 0.940 (0.04) | 0.940 (0.04) | 0.961 (0.03) |
|              | Min-Max | 0.947 (0.03) | 0.947 (0.03) | 0.953 (0.02) | 0.798 (0.06) | 0.798 (0.06) | 0.804 (0.06) |
|              | SCOR   | 0.990 (0.01) | 0.990 (0.01) | 0.992 (0.01) | 0.972 (0.03) | 0.972 (0.03) | 0.977 (0.02) |
|              | Step-Down | 0.957 (0.02) | 0.957 (0.02) | 0.987 (0.01) | 0.924 (0.04) | 0.924 (0.04) | 0.973 (0.02) |
|              | Min-Max | 0.927 (0.03) | 0.927 (0.03) | 0.933 (0.03) | 0.794 (0.06) | 0.794 (0.06) | 0.800 (0.06) |
| (60,60)      | SCOR   | 0.995 (0.01) | 0.995 (0.01) | 0.999 (0.004) | 0.975 (0.03) | 0.975 (0.03) | 0.992 (0.01) |
|              | Step-Down | 0.926 (0.03) | 0.926 (0.03) | 0.996 (0.01) | 0.899 (0.06) | 0.899 (0.06) | 0.988 (0.02) |
|              | Min-Max | 0.923 (0.03) | 0.923 (0.03) | 0.931 (0.03) | 0.795 (0.06) | 0.795 (0.06) | 0.798 (0.06) |
|              | SCOR   | 0.979 (0.01) | 0.979 (0.01) | 0.979 (0.01) | 0.959 (0.02) | 0.959 (0.02) | 0.958 (0.02) |
|              | Step-Down | 0.970 (0.01) | 0.970 (0.01) | 0.977 (0.01) | 0.954 (0.02) | 0.954 (0.02) | 0.958 (0.02) |
|              | Min-Max | 0.952 (0.02) | 0.952 (0.02) | 0.954 (0.02) | 0.797 (0.04) | 0.797 (0.04) | 0.799 (0.04) |
|              | SCOR   | 0.984 (0.01) | 0.984 (0.01) | 0.984 (0.01) | 0.964 (0.02) | 0.964 (0.02) | 0.967 (0.02) |
|              | Step-Down | 0.967 (0.02) | 0.967 (0.02) | 0.981 (0.01) | 0.953 (0.02) | 0.953 (0.02) | 0.965 (0.02) |
|              | Min-Max | 0.932 (0.02) | 0.932 (0.02) | 0.933 (0.02) | 0.794 (0.04) | 0.794 (0.04) | 0.797 (0.04) |
|              | SCOR   | 0.990 (0.01) | 0.990 (0.01) | 0.994 (0.01) | 0.972 (0.02) | 0.972 (0.02) | 0.982 (0.01) |
|              | Step-Down | 0.960 (0.02) | 0.960 (0.02) | 0.989 (0.01) | 0.956 (0.02) | 0.956 (0.02) | 0.976 (0.01) |
|              | Min-Max | 0.926 (0.02) | 0.926 (0.02) | 0.929 (0.02) | 0.794 (0.05) | 0.794 (0.05) | 0.796 (0.04) |

Table 5: Two outcome category case: the empirical hypervolume under manifolds (EHUM), smoothed approximated hypervolume under manifolds (SHUM) and upper and lower bound approach (ULBA) objective functions are maximized by the proposed Spherically Constrained Optimization Routine (SCOR) algorithm and the step-down and min-max algorithms. The average EHUM objective function values at the obtained solutions are provided based on 100 simulations, with the standard error in the parentheses.
Table 6: Three outcome category case: the empirical hypervolume Under manifolds (EHUM), smoothed approximated hypervolume under manifolds (SHUM), and upper and lower bound approach (ULBA) objective functions are maximized by proposed Spherically Constrained Optimization Routine (SCOR) algorithm and the step-down and min-max algorithms. The average EHUM objective function values at the obtained solutions are provided based on 100 simulations, with the standard error in the parentheses.