Fast semi-supervised discriminant analysis for binary classification of large data-sets

Joris Tavernier\textsuperscript{a,b,}, Jaak Simm\textsuperscript{b}, Karl Meerbergen\textsuperscript{a}, Joerg Kurt Wegner\textsuperscript{c}, Hugo Ceulemans\textsuperscript{c}, Yves Moreau\textsuperscript{b}

\textsuperscript{a}Department of Computer Science, KU Leuven, Celestijnenlaan 200A, B-3001 Heverlee - Belgium
\textsuperscript{b}ESAT-STADIUS, KU Leuven, Kasteelpark Arenberg 10, bus 2446, B-3001 Heverlee - Belgium
\textsuperscript{c}Janssen Pharmaceutica, Turnhoutseweg 30, B-2340 Beerse - Belgium

Abstract

High-dimensional data requires scalable algorithms. We propose and analyze three scalable and related algorithms for semi-supervised discriminant analysis (SDA). These methods are based on Krylov subspace methods which exploit the data sparsity and the shift-invariance of Krylov subspaces. In addition, the problem definition was improved by adding centralization to the semi-supervised setting. The proposed methods are evaluated on an industry-scale data set from a pharmaceutical company to predict compound activity on target proteins. The results show that SDA achieves good predictive performance and our methods only require a few seconds, significantly improving computation time on previous state of the art.

Keywords: Semi-supervised learning, Semi-supervised discriminant analysis, large-scale

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1. Introduction

In fields such as data mining, information retrieval or pattern recognition, dimensionality reduction of high-dimensional data is often used for classification. This method assumes that data can be accurately represented in a lower dimensional manifold. For instance, principal component analysis (PCA) is a widely used unsupervised feature extraction method. In addition, linear discriminant analysis (LDA) is a supervised method using dimensionality reduction to classify data.

For certain data sets, only some sample labels are known. For certain applications, verifying data point labels is extremely expensive. These applications can benefit from models that incorporate both labeled and unlabeled data in a semi-supervised setting \cite{1,2}. Semi-supervised learning is built on the assumption that taking advantage of the inherent structure of unlabeled and labeled data aids in a classification task.

Target prediction in chemogenomics is an example for which the semi-supervised setting could prove beneficial. Chemical compounds are modeled by combinations of molecules. Depending on the specific target protein, the compound can be active or inactive\footnote{In general, the chemical compound or one of the molecules the compound exists of can be active on the protein or not.}. However, due to existing drugs and research, only a few activity pairs are known. Labeling these activity pairs in vitro is expensive. Predicting which molecule affects a protein aids in the development of new drugs \cite{3,4}. This is a binary classification task. A possible feature set of a compound are the binary substructure fingerprints, which are the substructures occurring in a compound \cite{5}. The resulting data matrix is a high-dimensional binary matrix.

Scalable algorithms and high performance computing are required for high-dimensional data. Algorithms based on QR-decomposition or singu-
lar value decomposition have cubic computational complexity and are unfeasible. This eliminates several state of the art semi-supervised learning methods due to computational workload. LDA has been studied for large-scale data and scalable methods are available in the literature [6, 7]. LDA is extended to the semi-supervised setting using manifold regularization, leading to semi-supervised discriminant analysis (SDA) [8, 9].

Here, we present data centralization to improve the problem definition of SDA and how to efficiently implement the centralization. Then, we use the shift-invariance property of Krylov subspace methods to find solutions for different regularization parameters in a computationally feasible manner. We suggest three scalable algorithms for SDA and compare predictive performance and execution time. These algorithms are applied on real-life large-scale data from the database of Janssen Pharmaceutica.

Section 2.1 presents a brief review of LDA and its properties and Section 2.2 builds on the properties of LDA to introduce SDA. In Section 3 the necessary tools are explained to apply SDA on large data sets and our scalable algorithms are defined in Section 4. Finally SDA is applied on two data sets from chemogenomics in Section 5 and related semi-supervised learning algorithms and their applicability for large scale data are discussed in Section 6.

2. Discriminant analysis

In this section, we first review LDA and SDA. Then, we will look into the properties of the resulting eigenvalue problem and finally we will present state of the art algorithms for large-scale data for LDA and SDA.

2.1. Linear discriminant analysis

LDA [10, 11] is a supervised dimensionality reducing method and finds the directions that maximally separates the different classes while minimizing the spread within one class. Suppose we have $C$ classes and $N$ samples $x_i$ of dimension $D$. The data matrix $X \in \mathbb{R}^{N \times D}$ is defined as

$$X = [x_1, \ldots, x_i, \ldots, x_N]^T$$

where each row corresponds to a sample. Defining $S_B$ as the between-class-scatter matrix and $S_W$ as the within-class-scatter matrix, the LDA objective function is

$$\max_{w \in \mathbb{R}^N} w^T S_B w$$

Using the total scatter matrix $S_T$ leads to an equivalent optimization problem

$$\max_{w \in \mathbb{R}^N} \frac{w^T S_B w}{w^T S_T w}$$

Since $S_B$ and $S_T$ are positive semi-definite, the optimization problem can be reformulated as finding the large eigenvalues of

$$S_B w_i = \lambda_i (S_T + \beta I) w_i$$

which we call the LDA eigenvalue problem. The regularization parameter $\beta$ is introduced due to possibility of singularity of the total scatter matrix and as a countermeasure against overfitting. Suppose the data matrix $X$ is sorted according to the class of the data points.

$$X = [X_1; X_2; \ldots; X_C]$$

where $X_i$ are the data samples of class $i$. The between-class covariance matrix can then be simplified to

$$S_B = X^T W X$$

with $W$ an $N \times N$ block diagonal matrix with $C$ matrices $(W_1, \ldots, W_C)$ on its diagonal and each value of matrix $W_c \in \mathbb{R}^{N_c \times N_c}$ is equal to $1/N_c$ and $N_c$ is the number of samples in class $c$. The total scatter matrix can be written as $S_T = X^T X$.

2.2. Semi-supervised discriminant analysis

Since the class of each data point is not always known, we will refer to the data points where the class is known as labeled data and unlabeled data otherwise. For both the unlabeled and labeled data, their structure in the feature space, $x_i$, is known. Semi-supervised learning combines both the class information of the labeled data and the structure in the feature space of labeled and unlabeled data. SDA [8] uses manifold regularization to extend LDA to the semi-supervised setting. Information of the geometric proximity of the data points in the feature space is contained in the regularizer.

Using a binary similarity matrix $S \in \mathbb{R}^{N \times N}$, where $s_{ij} = 1 = s_{ji}$ if two samples are similar and 0
otherwise, a natural regularizer \( R(w) \) for LDA can be defined as

\[
R(w) = \sum_{i=1}^{n} \sum_{j=1}^{n} s_{ij} (w^T x_i - w^T x_j)^2
\]

where \( d_i \) is the sum of the \( i \)th row of \( S \) and \( D \in \mathbb{R}^{n \times n} \) the diagonal matrix with \( d_i \) on its diagonal. The matrix \( L = D - S \) is the Laplacian matrix of \( S \). Suppose the number of labeled data is \( \ell \), the SDA eigenvalue problem is then

\[
X^T \begin{pmatrix} W & 0 \\ 0 & 0 \end{pmatrix} X \w_i = \\
\text{Between-labeled-class-scatter} \\
\lambda_i \begin{pmatrix} X^T (1 - \alpha) & I_n \\ I_n & 0 \end{pmatrix} X + \\
\text{Total-labeled-scatter} \\
\lambda_i X^T \alpha L X + \\
\text{Manifold regularization} \\
\frac{\beta I}{2} \\
\text{Regularization}
\]

(2)

where the first \( \ell \) rows of \( X \) are the labeled data points and \( W \in \mathbb{R}^{\ell \times \ell} \) the same matrix as for LDA. The regularization parameter \( \alpha \) is limited to the interval \([0, 1]\) and resembles how much weight is given to the unsupervised information. Note that the information of the unlabeled data is only used in the Laplacian matrix \( L \).

2.3. Similarity matrix

Semi-supervised learning is based on the assumption that similar data points in the feature space are more likely to have the same class. Defining the similarity between data points is an important part of the semi-supervised setting. SDA uses a binary similarity matrix, the first approach we considered is to create a \( k \)-nearest neighbor graph \([8]\).

The value of \( s_{ij} \in S \) is 1 if there exists an undirected edge in the \( k \)-nearest neighbor graph from data point \( i \) to data point \( j \). The \( k \)-nearest neighbor graph is built using a distance measure in the feature space. The distance for each data point is calculated to all the other data points. The data point is then connected by an undirected edge to all the other points maximally separated by the distance of the \( k \)-nearest neighbor.

The second approach is to create a binary similarity matrix by thresholding. Using a distance measure a threshold is defined for all data points and if the distance from data point \( i \) to data point \( j \) is smaller than the threshold, the data points are similar and \( s_{ij} = s_{ji} = 1 \). Note that using a threshold instead of the \( k \)-nearest neighbors graph may lead to samples having no neighbors at all.

2.4. Centralization

Centralization, as for PCA, plays an important role in LDA. We will first look into the details of the influence of centralization for LDA and extend the same idea to SDA.

2.4.1. Centralization for LDA

The LDA eigenvalue problem (1) is a projection of the eigenvalue problem

\[
W z_i = \lambda_i z_i
\]

called the spectral LDA eigenvalue problem on the range of \( X \). This eigenvalue problem is quite simple due to the block diagonal structure of \( W \) where values in one block are identical. In order to gain some insight in the LDA eigenvalue problem, we will consider the binary case. If we only have two classes then the matrix \( W \) has rank 2. The two eigenvectors of the spectral LDA eigenvalue problem with eigenvalue 1 are linear combinations of

\[
\begin{pmatrix} 1 \\ \vdots \\ 1 \end{pmatrix}, \quad \begin{pmatrix} 1 \\ \vdots \\ -1 \end{pmatrix}
\]

where \( z_2 \) has value 1 for the samples of class 1 and value \(-1\) for the samples of class 2. It is obvious that eigenvector \( z_1 = 1 \in \mathbb{R}^{N \times 1} \) (all values equal to 1) has no discriminative information. The non-discriminative eigenvector \( z_1 \) can be avoided in the LDA eigenvalue problem \([1]\) by centralization of the data. If \( z_1 \in \text{Range}(X) \), then the corresponding
vector $w_1$, with $Xw_1 = z_1$, is an eigenvector of the LDA eigenvalue problem
\[ X^TWXw_1 = \lambda_1(X^TXw_1 + \beta w_1). \]

Note that due to the structure of $W$,
\[ X^TWXw_1 = X^TZ_1 \]
\[ = X^Tz_1 \]
\[ = N\mu \]

with $\mu = X^Tz_1/N$ the mean sample in the feature space. If the data is centralized the non-discriminative eigenvector $w_1$ is moved to the common null space of $S_B$ and $S_W$ of the LDA eigenvalue problem.

The eigenvector $w_2$, with $Xw_2 = z_2$, is the direction that maximizes the LDA objective function when $z_2 \in \text{Range}(X)$. In general, the eigenvalue associated with $w_2$ is smaller but close to 1 since it is the projection onto the range of $X$ of the eigenvector $z_2$ with eigenvalue 1. For $C$ classes, the eigenvectors belonging to the $C - 1$ largest eigenvalues of the LDA eigenvalue problem are the separators if the data is centralized.

2.4.2. Centralization for SDA

The centralization trick from LDA to avoid the non-discriminative eigenvector can be applied for SDA as well. Consider the vector $z_1 \in \mathbb{R}^{N \times 1}$ with all values equal to 1. From the definition of the Laplacian matrix $L$, we know that $Lz_1 = 0$ and $z_1$ is an eigenvector of the spectral SDA eigenvalue problem
\[ \begin{pmatrix} W & 0 \\ 0 & 0 \end{pmatrix} z_1 = \lambda_1 \begin{pmatrix} (1 - \alpha) & 0 \\ 0 & 0 \end{pmatrix} z_1 + \alpha Lz_1 \]
\[ (4) \]
with $\lambda_1 = 1/(1 - \alpha)$. The SDA eigenvalue problem is a projection of this eigenvalue problem onto the range of $X$. As in LDA, we have
\[ X^T \begin{pmatrix} W \\ 0 \\ 0 \end{pmatrix} z_1 = \ell \mu_\ell \]

with $\mu_\ell$ the mean of the labeled data in the feature space. To avoid the non-discriminative eigenvector, we need to centralize the data around the mean of the labeled data since the Laplacian does not influence the eigenvector $w_1$, found by solving the system $Xw_1 = z_1$. In the original formulation of SDA \cite{2} the non-discriminative eigenvector is also calculated.

2.5. State of the art algorithms

LDA has been investigated for large-scale data. Here we present one state of the art algorithms for LDA and one for SDA.

2.5.1. Spectral regression discriminant analysis

Spectral regression discriminant analysis (SRDA) \cite{6} uses the eigenvectors $Z$ of the spectral LDA eigenvalue problem and solves the system $Xw = z$ in a regularized least-squares (RLS) manner where $Z = [z_2, \ldots, z_C]$ are the $C - 1$ eigenvectors orthogonal to the non-discriminative eigenvector $z_1$ of the spectral LDA eigenvalue problem. The eigenvectors are determined by the class of the samples and are easily determined.

2.5.2. Spectral regression

Using the spectral regression framework \cite{12} the $C$ eigenvectors of the spectral SDA eigenvalue problem
\[ \begin{pmatrix} W & 0 \\ 0 & 0 \end{pmatrix} z_i = \lambda_i \begin{pmatrix} (1 - \alpha) & 0 \\ 0 & 0 \end{pmatrix} z_1 + \alpha Lz_i \]
\[ (5) \]
are calculated and next a linear system $Xw = z$ is solved in a regularized least squares manner
\[ (X^TX + \beta I)w = X^Tz. \]

Due to the addition of the Laplacian, the eigenvectors of the spectral SDA eigenvalue problem are more difficult to calculate than for SRDA. The Lanczos method applied to \cite{5} converges in $C$ iterations \cite{13}. One of the $C$ eigenvectors of the spectral SDA eigenvalue problem \cite{5} is the non-discriminative vector $z_1$ and spectral regression in its original formulation does not avoid this eigenvector.

3. Large-scale data

Exact solutions for high dimensional data are costly to calculate and are no longer feasible. First we look at an iterative method to solve a large generalized singular eigenvalue problem in Section 3.1 and next we look at Krylov subspace methods to solve linear systems in Section 3.2.

3.1. Subspace iteration

For the SDA eigenvalue problem, we have to solve a singular generalized eigenvalue problem
\[ Aw = \lambda Bw \]
where $A$ is of low rank $(C - 1)$. It is known that subspace iteration has geometric asymptotic convergence for eigenvalue $\lambda_i$ with ratio $\lambda_{i+1}/\lambda_i$ for $i = 1, \ldots, j$ with $j$ the dimension of the subspace. Choosing $j = C - 1$ leads to instant convergence for the SDA eigenvalue problem. The subspace iteration algorithm for SDA, assuming centralized data, is given in Algorithm 1 with random meaning generated from a uniform distribution between $-1$ and $1$.

**Algorithm 1** Subspace iteration

1. Initialize $R \in \mathbb{R}^{D \times C-1}$ randomly
2. Solve $W$ from $BW = AR$
3. return $W$

The computational bottleneck is solving the linear system with $B$. When $B$ is high-dimensional this can no longer be done exactly in a feasible manner and iterative methods are used. The convergence of subspace iteration is no longer guaranteed in one iteration. In general, many applications such as SDA require only an approximate solution and for these applications it is not necessary to solve the problem to machine precision.

### 3.2. Linear systems

Subspace iteration contains a step where a large-scale symmetric linear system has to be solved. We use Krylov subspace based methods to solve linear system $Bw = b$. A Krylov base $K$ is an orthogonal basis determined by the space of a sequence of matrix-vector multiplications $K = \text{span}\{b, Bb, \ldots, B^{k-1}b\}$. A nice property of these methods is that if the matrix $B$ is sparse the cost of a matrix-vector multiplication is linear with the number of nonzero entries in the matrix $B$. For the SDA eigenvalue problem (2), the matrix $B$ is a product of sparse matrices, which we do not compute explicitly since this generally leads to a dense matrix.

#### 3.2.1. Solving the symmetric linear system

For symmetric matrices (which is the case in SDA) the idea is to find a Krylov base $K$ such that

$$K^*BK = T$$

with

$$T = \begin{bmatrix}
\alpha_1 & \gamma_1 & & \\
\gamma_1 & \ddots & \ddots & \\
& \ddots & \ddots & \gamma_{k-1} \\
& & \gamma_{k-1} & \alpha_k
\end{bmatrix}$$

a tridiagonal matrix. The approximate solution of the linear system $Bw = b$ is found by searching the space spanned by the vectors of the Krylov space $K$. One way to find an approximate solution is to make the residual orthogonal to the Krylov base $((B + \beta I)w_k - b \perp K)$. This is true when $w_k = Kz_k$ where $z_k$ is the solution of the linear system

$$(T + \beta I)z_k = ||b||e_1$$

of dimension $k$. If the matrix is positive-definite, the solution minimizes the error under the $B$-norm. This method is the Lanczos algorithm to solve a linear system and is related to the conjugate gradient method (CG, Algorithm 2) for which they use a Cholesky factorization of $T$ to define an recursive process.

#### 3.2.2. Regularization

Singular eigenvalue problems are well understood for small scale matrices. However, these algorithms are unfeasible for large scale problems, since singular subspace deflation from both matrices is required. In contrast, adding a regularization parameter in matrix $B$ is computationally cost-effective, equally well-defined and offers a countermeasure against overfitting.

Replacing $B$ by $B + \beta I$ makes the eigenvalue problem well defined for which we can use a standard method, such as subspace iteration. If $\beta$ is small, the eigenvalues and eigenvectors of interest do not change significantly. In addition, the singularity of $B$ is inexact, namely, the singular values quickly decay, but they do not reach zero. These singular values are the result of ‘noise’ in the data or a mismatch in the imposed classification. The effect of this ‘noise’ is reduced by adding the regularization parameter $\beta$.

In general, the best solution is chosen from a range of $\beta$ values in the terms of a performance measure. Furthermore, using the shift-invariance property of Krylov bases is very efficient. In the previous discussion, the Krylov vectors are independent of the value of $\beta$ and the tridiagonal matrix $T$ is not influenced by $\beta$. This means that the computationally expensive part, i.e. building
the Krylov base, can be reused for several $\beta$ values instead of restarting the process for each $\beta$ value. The parameter $\beta$ only plays a role in solving the small linear system in $[0]$. The conjugate gradient method for the shifted linear systems of the form 

$$(B + \beta I)w = b$$

is given in Algorithms 3 [18, 19]. Superscript $\beta$ means that the variable is stored for all different regularization parameters $\beta$ in such a way that scalars ($\gamma$) become vectors ($\gamma^\beta$) and vectors ($w$) change into matrices ($W^\beta$).

3.2.3. Implementation

In Section 2.4 it was shown that centralization avoids calculating the non-discriminative eigenvector. Note that if we apply centralization directly on the matrix $X$, we will lose the sparsity of the data matrix and one of the advantages of Krylov subspace methods. In order to avoid creating a dense matrix filled with real values, the centralization is applied in the matrix-vector product. Using $z_1 = 1 \in \mathbb{R}^{N \times 1}$ as the vector of all ones and defining $z_\ell = 1_\ell \in \mathbb{R}^{N \times 1}$ as the vector with value $1$ for the labeled samples and $0$ otherwise, the mean labeled sample in the feature space $\mu_\ell = X^T 1_\ell / \ell$ can then be derived. The centralized multiplication with $X$ can be written as

$$
(I_N - \frac{11^T}{\ell}) X v = (X - 1 \mu_\ell^T) v
$$

$$
= X v - 1(X^T, v)
$$

and the centralized multiplication with $X^T$ as

$$
(I_N - \frac{11^T}{\ell}) X^T w = (X - 1 \mu_\ell^T)^T w
$$

$$
= X^T w - \mu_\ell^T (1^T, w)
$$

were the last inner product is the sum of the elements of $w$.

For the SDA eigenvalue problem, we only have to implement one centralized multiplication. For example, using the centralized multiplication with $X^T$, the matrix-vector product in SDA for the non-discriminative eigenvector becomes

$$
\left( (I_N - \frac{11^T}{\ell}) X \right)^T \left( (1 - \alpha) \begin{pmatrix} I_\ell & 0 \\ 0 & 0 \end{pmatrix} + \alpha L \right) X w_1
$$

$$
= \left( (I_N - \frac{11^T}{\ell}) X \right)^T \left( (1 - \alpha) \begin{pmatrix} I_\ell & 0 \\ 0 & 0 \end{pmatrix} + \alpha L \right) z_1
$$

$$
= \left( (I_N - \frac{11^T}{\ell}) X \right)^T (1 - \alpha) z_\ell
$$

$$
= X^T (I_N - \frac{11^T}{\ell}) (1 - \alpha) z_\ell
$$

$$
= (1 - \alpha) X^T (z_\ell - \frac{\ell z_\ell}{\ell})
$$

$$
= 0.
$$

Using the centralized multiplication with $X^T$ avoids the non-discriminative eigenvector. This holds for the centralized multiplication with $X$ as well and the derivation is similar.

4. Four algorithms for SDA

Here we present four methods for solving the SDA eigenvalue problem for binary classification. First we present spectral regression, then our improved variations of spectral regression and finally our method.

For binary classification, there is only one discriminative eigenvector. To perform the classification using this eigenvector, the data is projected along this vector, namely $Xw = s \in \mathbb{R}^{N \times 1}$, and results in the sample rating or score. Here we use the rating directly to calculate the area under the curve of the receiver operating characteristic (AUC-ROC), but other classification methods like support vector machines, nearest neighbor or centroid can be used to classify the data based on the projection.

4.1. Spectral regression

For the spectral regression (SR) framework, we need to solve the spectral SDA eigenvalue problem. The original framework finds all the eigenvectors of the spectral SDA eigenvalue problem and then finds the corresponding feature vectors by solving a linear system in a regularized least squares manner. Here we used subspace iteration with the block conjugate gradient method [20] to find the eigenvectors. Subspace iteration will actually find the eigenspace $V \in \mathbb{R}^{N \times 2}$ and the discriminative eigenvector can be found by Rayleigh-Ritz subspace projection. Using the eigenspace $V$, the spectral SDA eigenvalue
Algorithm 2 Conjugate gradient

1: Initialize:
   • \( r_0 = p_0 = b \)
   • \( w = 0 \)

2: for \( i = 0, \ldots, k \) do
   3: \( q_i = Bp_i \)
   4: \( \gamma_i = -\frac{\langle r_i, r_i \rangle}{\langle p_i, q_i \rangle} \)
   5: \( w_{i+1} = w_i + \gamma_i q_i \)
   6: if \( ||r_{i+1}|| < tol \) then
      7: Break
   8: end if
   9: \( \alpha_{i+1} = \frac{\langle r_{i+1}, r_{i+1} \rangle}{\langle r_i, r_i \rangle} \)
   10: \( p_{i+1} = r_{i+1} + \alpha_{i+1} p_i \)
11: end for

Algorithm 3 Shifted conjugate gradient

1: Initialize:
   • \( \alpha_0 = 0, W_0^\beta = 0, \alpha_0^\beta = 0 \)
   • \( r_0 = b, p_0 = b, P_0^\beta = b \)
   • \( \gamma_{-1} = 1, \zeta_{-1}^\beta = 1, \xi_0^\beta = 1 \)

2: for \( i = 0, \ldots, k \) do
   3: \( q_i = Bp_i \)
   4: \( \gamma_i = -\frac{\langle r_i, r_i \rangle}{\langle p_i, q_i \rangle} \)
   5: \( \frac{\xi_{i+1}^\beta}{\xi_i^\beta} = \frac{\xi_{i-1}^\beta \xi_i^\beta \gamma_{i-1}}{\gamma_i \alpha_i (\xi_{i-1}^\beta - \xi_i^\beta) + \xi_{i-1}^\beta \gamma_{i-1} (1 - \beta \gamma_i)} \)
   6: \( \gamma_i^\beta = \frac{\zeta_{i+1}^\beta}{\zeta_i^\beta} \)
   7: \( W_{i+1}^\beta = W_i^\beta - \gamma_i^\beta P_i^\beta \)
   8: \( r_{i+1} = r_i + \gamma_i q_i \)
   9: if \( ||r_{i+1}|| < tol \) then
      10: Break
   11: end if
   12: \( \alpha_{i+1} = \frac{\langle r_{i+1}, r_{i+1} \rangle}{\langle r_i, r_i \rangle} \)
   13: \( p_{i+1} = r_{i+1} + \alpha_{i+1} p_i \)
   14: \( \alpha_{i+1}^\beta = \frac{\xi_{i+1}^\beta}{\xi_i^\beta} \)
   15: \( P_{i+1}^\beta = \xi_{i+1}^\beta r_{i+1} + \alpha_{i+1}^\beta P_i^\beta \)
   16: for \( s = 0, \ldots, \text{size}(\beta) \) do
      17: if \( ||\xi_{i+1}^\beta(s) r_{i+1}|| < tol \) then
         18: Stop updates for \( \beta(s) \)
      19: end if
   20: end for
   21: end for

Figure 1: The Conjugate Gradient algorithm in Algorithm 2 and the Conjugate Gradient algorithm for various shifted linear systems in Algorithm 3.
problem is transformed to a two-by-two eigenvalue problem \( V^T A V q_i = \lambda_i V^T B V q_i \), and the discriminative eigenvector is the projection of the second largest eigenvector \( z_2 = V q_2 \). Next we solve the linear system \((X^T X + \beta I)w_2 = X^T z_2\) using CG to find the discriminative eigenvector in the feature space.

The LSQR method is advocated for linear systems arising from regularized least squares [21]. However, to the best of our knowledge, there is no specific LSQR variant exploiting the shift-invariance property of Krylov subspaces [22].

### 4.2. Centralized spectral regression

The spectral SDA eigenvalue problem is actually an SDA eigenvalue problem where the data matrix \( X \) is the identity matrix \( I_N \). In order to avoid the non-discriminative eigenvector \( z_1 \) in the spectral SDA eigenvalue problem, we can centralize the identity matrix. Now we only require one eigenvector and therefore we propose to use the power method, which is subspace iteration with one right-hand side. The full algorithm for centralized spectral regression (CSR) is given is Algorithm 4.

### 4.3. Spectral analysis

For CSR, first the eigenvalues of the spectral eigenvalue problem are found and next the corresponding feature vectors are found by solving the system \( X_{\text{data}} w = z \) in a regularized least squares manner (line 5 Algorithm 3). To perform the classification, the feature vectors are used to project the samples to a low-dimensional space \( s = X_{\text{pred}} w \). If \( X_{\text{pred}} \subseteq X_{\text{data}} \), then the regularized least squares step can be avoided and the rating of the wanted samples can be approximated by their corresponding value in the eigenvector \( z \). If \( X_{\text{pred}} = X_{\text{data}} \), the rating of all the samples is close to the eigenvector \( s \approx z \). Spectral analysis (SA) only works when the samples to be classified are present in \( X_{\text{data}} \). If \( \alpha = 0 \), the Laplacian is neutralized and the unlabeled data receive a rating of zero. Therefore this approach only works if \( \alpha \neq 0 \).

### 4.4. Fast semi-supervised discriminant analysis

Since we are working with sparse data and Krylov subspace methods, the complexity of the algorithm is proportional to the number of nonzeros. Hence, we can solve the SDA eigenvalue problem directly by using the power method. The full algorithm for Fast semi-supervised discriminant analysis (FSDA) is given in Algorithm 5.

### 5. Experimental results

For evaluating the different methods, we present the AUC-ROC in function of the execution time for the data sets. Since these methods solve the same underlying problem, we are interested in convergence speed and difference in the algorithms predictive performances.

This work is performed with drug-protein activity prediction in mind. We have tested our methods on different targets for two different data sets. The first data set is described in section 5.1 and is publicly available. The implementation for this data set was compiled with gcc 5.3.1 and OPENMP 4.0 with compile option -O3 and executed on a machine with an Intel(R) Core(TM) i7-6560U (2.20GHz) processor with an L3 cache memory of 4096 Kb and 16 GB of DRAM where all 4 cores were used [3]. The second industry-scale data set is described in section 5.2 and stronger hardware was required. These experiments were run using a computing node with dual Intel(R) Xeon(R) E5-2699 v3 (2.30GHz) processors with a L3 cache memory of 46080 Kb and 264 gb of DRAM. For these experiments we used 12 cores.

#### 5.1. ChEMBL data

For drug-protein activity prediction, one of the possible indicators is the IC50 value. IC50 or the half maximal inhibitory concentration measures the
Algorithm 4 CSR-SDA

1: Given $\alpha, \beta$
2: Initialize $r \in \mathbb{R}^{N \times 1}$ randomly
3: Orthogonalize: $r = r - \frac{1}{\ell} r^T r$
4: Solve $z$ with CG from
$$
\left( (I_N - \frac{1}{\ell} I) \right)^T \left( (1 - \alpha) \left( I_{\ell} \ 0 \right) + \alpha L \right) I_N \right) z = \left( W \ 0 \right) r
$$
5: Solve $w$ with CG from
$$(X^T X + \beta I)w = X^T z$$
6: return Rating: $s = Xw$

Algorithm 5 FSDA

1: Given $\alpha, \beta$
2: Initialize $r \in \mathbb{R}^{D \times 1}$ randomly
3: Calculate mean labeled sample: $\mu^T \ell = X^T 1_{\ell}$
4: Solve $w$ with CG from
$$
\left( (X - 1 \mu^T \ell) \right)^T \left( (1 - \alpha) \left( I_{\ell} \ 0 \right) + \alpha L \right) X + \beta I_D \right) w = \left( (X - 1 \mu^T \ell) \right)^T \left( W \ 0 \right) X r
$$
5: return Rating: $s = Xw$

The substance concentration required to inhibit the activity of a protein by 50%. Using the bioactivity database ChEMBL version 19 [22], we selected protein targets that had at least 200 or more IC50 values for the compounds. A compound was considered active with an IC50 value less than 1000 nM. We then kept the protein targets that had at least 30 actives and inactives, resulting in 330 targets with enough labels to perform 5-fold nested cross-validation.

For the compounds the extended-connectivity fingerprints (ECFP [5]) were computed using rdkit [23] with 3 layers. In summary, ECFP generates the features for a compound in layers. In the first layer each individual atom receives an initial identifier based on its atomic symbol. In the following layer this value is concatenated with the bound and the identifiers of the neighboring atoms and then hashed to a new identifier for this atom. This process is repeated for a fixed number of layers. These generated substructures represented by their hash value are the features for this compound. Duplicate identifiers or duplicate substructures are removed from the feature list. Figure 2 depicts the creation of the ECFP features for a small chemical compound. The characteristics of the resulting ECFP data matrix $X$ are given in Table 1.

The similarity matrix was made using a 5-nearest neighbor graph and the Tanimoto similarity. The cross-validated mean and standard deviation for AUC-ROC of FSDA over the 330 protein targets is $89 \pm 4\%$. In addition, to evaluate the convergence and execution time for the different methods, we have randomly selected 6 targets with 2000 or more labeled compounds. The number of active and inactive compounds for each target is given in Table 2.

For all methods, we varied the number of CG iterations which increases the complexity, but also the accuracy of CG. Note that the spectral regression methods require two linear solves and the best pair (execution time, AUC-ROC) is reported. The different number of iterations for the linear solvers are given in Table 3. 5-Fold nested cross-validation was used for the experiments, with the inner-folds used to pick the best value of the regularization parameter $\beta$. We report the average execution time for the outer cross-validation using only one optimal
(a) Compound structure
(b) Resulting features

Figure 2: Example of the ECFP feature generation.

| Parameter | Value   |
|-----------|---------|
| Compounds | 167 668 |
| Features  | 291 714 |
| Nonzeros  | 12 246 376 |
| Density   | 0.025038% |

Table 1: The characteristics of the ChEMBL data matrix.

The reported AUC-ROC is the average along with the standard deviation for all outer folds and 5 different seed initializations of the random number generator.

Figure 5 shows the AUC-ROC in function of the execution time for the different methods. Solving SDA directly in the feature space (FSDA) gives higher or equal average AUC-ROC for all 6 targets in comparison with the spectral regression methods. Only SA-SDA converges faster than FSDA but is slightly worse in predictive performance for most targets.

5.2. Janssen data

Next, we investigate the performance of the proposed methods on a industrial-scale data set containing a few million of compounds. This large-scale data set was provided by Janssen Pharmaceutica. Out of more than 1000 protein targets, we chose 6 with a large number of IC50 measurements, see Table 3 for an overview of these targets. For these targets, a compound was considered active with an IC50 value below 1.0 µM. Using ECFP over 10 million compound features were generated and the SDA similarity matrix was created using the Tanimoto similarity with a threshold of 0.4.

Figure 4 shows the AUC-ROC in function of the execution time for the targets. The number of iterations for the linear solves was set to 70. As can be seen from the figure, the centralization improves the execution time by a factor 2 in comparison with previous state of the art. SA-SDA even gains a factor 7-8. All methods reach the same predictive performance with a small advantage for FSDA.

The relatively large assays for the Janssen data allows us to subsample the labeled data. Figure 5 gives the AUC-ROC in function of randomly subsampled labeled data for different values of the parameter α. Using only 0.1 to 1% labels, SDA outperforms LDA for all the targets.

6. Related methods and further research

The difficulty and cost of labeling samples for certain applications stimulated surging interest in semi-supervised learning. This interest has led to several different methods of incorporating information of the unlabeled samples to aid the supervised classification task. Here, we present several methods, discuss their computational bottleneck and argue why our setup of SDA has most likely the smallest execution time.

Semi-supervised Orthogonal Discriminant Analysis via label propagation (SODA) operates in two stages [21]. First estimates of the unknown labels are computed via label propagation. In the second stage these label estimates are used in their semi-supervised version of orthogonal discriminant analysis. SODA however, requires the full eigenvalue decomposition of the within class scatter ma-
Figure 3: Comparison of spectral regression methods and FSDA for the 6 chosen targets of the ChEMBL data set. The AUC-ROC is given in function on the execution time in seconds.
Table 2: The characteristics of the chosen targets for the 167668 chemical compounds of the ChEMBL data set.

| Name           | Active | Inactive | Known labels | % labeled |
|----------------|--------|----------|--------------|-----------|
| CHEMBL100503  | 2225   | 1729     | 3954         | 2.36      |
| CHEMBL10062   | 1365   | 1275     | 2640         | 1.57      |
| CHEMBL100670  | 1621   | 491      | 2112         | 1.26      |
| CHEMBL1007    | 1409   | 1170     | 2579         | 1.54      |
| CHEMBL100763  | 817    | 3144     | 3961         | 2.36      |
| CHEMBL100875  | 2514   | 516      | 3030         | 1.81      |

Table 3: The different parameters used in the experiments for each method.

| Method   | Description                                      | Iterations          |
|----------|--------------------------------------------------|---------------------|
| FSDA     | Iterations linear solve for SDA                  | [2, 3, 5, 10, 20, 40, 60, 80] |
| CSR-SDA  | Iterations linear solve for spectral SDA         | [2, 3, 5, 10, 20, 40, 60, 80] |
| SA-SDA   | Iterations linear solve for spectral SDA         | [3, 5, 10, 20, 40, 60, 80] |
| SR-SDA   | Iterations linear solve for spectral SDA         | [2, 3, 5, 10, 20, 40, 60, 80] |

metric. The optimal projection matrix $W$ is then chosen from these eigenvectors using trace optimization. The within class scatter matrix is almost full rank and computing all eigenvectors is unfeasible for high dimensional data. SODA additionally needs a few iterations to converge, requiring the solution of more than one eigenvalue problem.

Semi-supervised Local Fisher discriminant analysis (SELF) is the semi-supervised extension of local fisher discriminant analysis which localizes the within class scatter matrix $\Sigma$ [25, 26]. This approach involves again a full generalized eigenvalue decomposition of the order $N-1$. The advantage of SELF over SODA is that the reduced dimension restricts the number of required eigenvectors. However, SDA requires a low rank decomposition with the rank equal to $C-1$. This is a clear advantage over SELF in terms of convergence for the eigenvalue solver as explained in Section 3, resulting in several magnitudes less computation time for our methods.

Trace Ratio based Flexible Semi-supervised Discriminant Analysis (TR-FSDA) adjusts SDA to fit the trace ratio form [27, 28]. In addition to reformulating the original formulation, the constraint that the low-dimensional data representation should lie in the linear subspace ($S = XW$) is relaxed. This is accomplished by adding the flexible regularizer $\|S - XW\|^2$ to the objective function. The main computational step in the algorithm is the eigenvalue decomposition of an adjusted total scatter matrix. An advantage is that only the $d$ largest eigenvectors are required with $d$ the reduced dimension. Since the matrix is nearly full rank, an Krylov subspace method will converge slowly. TR-SDA is an iterative method, with each iteration requiring an eigenvalue decomposition, resulting in a significant increase of execution time.

Flexible Manifold Embedding (FME) [29] incorporates unsupervised information for the unknown labels in the form of a smooth manifold. Using this manifold, the optimal labels are estimated and then used to determine the optimal projection matrix $W$. These two steps both involve a linear system solve with the total scatter matrix $S_T$ for $C$ right hand sides. Applying the same techniques described here, we expect a an increase of a factor 4 execution time for FME binary classification since SDA only requires one linear system solve with $C-1$ right hand sides.

More recently, the method Semi-supervised Linear Discriminant Analysis (SLDA) was proposed, consisting of an iterative process computing the labels of the training data in the projected dimension and using these computed labels for updating the projection matrix [30]. Unfortunately, this method involves a step that calculates the full singular value
Table 4: The characteristics of the Janssen targets.

| Name | Active | Inactive | Total labels | % labeled |
|------|--------|----------|--------------|-----------|
| 389  | 20000  | 275000   | 295000       | 15        |
| 685  | 10000  | 475000   | 485000       | 25        |
| 739  | 5000   | 750000   | 755000       | 40        |
| 1448 | 2500   | 300000   | 302500       | 15        |
| 1736 | 5000   | 500000   | 505000       | 25        |
| 1833 | 2500   | 300000   | 302500       | 15        |

(a) Target 389  
(b) Target 685  
(c) Target 739  
(d) Target 1448  
(e) Target 1736  
(f) Target 1833

Figure 4: Comparison of spectral regression methods and FSDA for the 6 Janssen targets. The AUC-ROC is given in function of the execution time in seconds with a fixed number of iterations equal to 70. Our methods improve the execution time by a factor 2 in comparison with SR-SDA or more for SA-SDA.

decomposition of the total scatter matrix which is not feasible for high-dimensional data. Wang et al. [30] showed in their work that the performance of SDA is of the same order of SODA, FME and TR-SDA for different data sets, while being outperformed by SLDA. It is left for further research to see how FME and TR-SDA actually scale for our application and if the increase in computational work results in significant improvement in predictive accuracy.

Semi-supervised learning has mainly been developed for cases where there is a small number of labels. In our application, there is a medium number of labels and an abundance of unlabeled data samples. Further research is required specifically for this kind of large-scale data sets in the semi-supervised setting. For the chemogenomics application, even the smallest speed-up for an algorithm is multiplied by the number of specific targets, resulting in a significant reduction of the total execution time.

In the semi-supervised setting, information of the unlabeled data is incorporated in the classification task. To include this information, SDA uses geometric distance in the feature space to define similarity between samples. Defining similarity in the feature space is sensitive to noise and redundant information of the defined features. For our application, the features are exact but do contain redundant information. The sample similarity could be further improved by removing non-informative features as suggested in [30].
Figure 5: The AUC-ROC for the Janssen data in function of number of used labels (randomly subsampled) for 6 different targets. Using only 0.1 to 1% labels, SDA outperforms LDA for all the targets.
7. Conclusion

We have presented semi-supervised discriminant analysis for large-scale data. We have shown how to use the centralization to avoid the calculation of the non-discriminative eigenvector and an efficient way to implement the centralization. We used the shift-invariance property of Krylov subspaces to our advantage to solve SDA efficiently for different regularization parameters $\beta$. Using our proposed methods it was possible to apply SDA on real-life large-scale data from the pharmaceutical industry in seconds, improving on previous state of the art by a factor 2 or more. Solving the problem directly in the feature space had for almost all targets better or equal predictive performance than the spectral regression methods.

Conflict of interest

No conflict of interest.

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