Efficient online learning for large-scale peptide identification

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Abstract

Motivation: Post-database searching is a key procedure in peptide identification with tandem mass spectrometry (MS/MS) strategies for refining peptide-spectrum matches (PSMs) generated by database search engines. Although many statistical and machine learning-based methods have been developed to improve the accuracy of peptide identification, the challenge remains on large-scale datasets and datasets with an extremely large proportion of false positives (hard datasets). A more efficient learning strategy is required for improving the performance of peptide identification on challenging datasets.

Results: In this work, we present an online learning method to conquer the challenges remained for exiting peptide identification algorithms. We propose a cost-sensitive learning model by using different loss functions for decoy and target PSMs respectively. A larger penalty for wrongly selecting decoy PSMs than that for target PSMs, and thus the new model can reduce its false discovery rate on hard datasets. Also, we design an online learning algorithm, OLCS-Ranker, to solve the proposed learning model. Rather than taking all training data samples all at once, OLCS-Ranker iteratively feeds in only one training sample into the learning model at each round. As a result, the memory requirement is significantly reduced for large-scale problems. Experimental studies show that OLCS-Ranker outperforms benchmark methods, such as CRanker and Batch-CS-Ranker, in terms of accuracy and stability. Furthermore, OLCS-Ranker is 15–85 times faster than CRanker method on large datasets.

Availability and implementation: OLCS-Ranker software is available at no charge for non-commercial use at https://github.com/Isaac-QiXing/CRanker.

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1 Introduction

Tandem mass spectrometry (MS/MS)-based strategies are presently the method of choice for large-scale protein identification due to its high-throughput analysis of biological samples. With database sequence searching method, a huge number of peptide spectra generated from MS/MS
experiments are routinely searched by using a search engine, such as SEQUEST, Mascot or X!TANDEM, against theoretical fragmentation spectra derived from target databases or experimentally observed spectra for peptide-spectrum match (PSM).

A number of computational methods and error rate estimation procedures [15] have been proposed to improve the accuracy of target PSMs. In the early trials, empirical filters [12] were developed to choose the target PSMs, in which those above the specified thresholds are accepted as correct and those below the thresholds are assumed to be incorrect. With the absence of robust statistical and computational methods, these filtering methods could not achieve satisfactory identification results, especially on the datasets containing significant numbers of false positives.

Advanced statistical and machine learning approaches have been studied for improving the accuracy of discrimination of correct and incorrect PSMs. Among those machine learning-based tools, PeptideProphet [9] and Percolator [8] are two popular ones using semi-supervised learning. PeptideProphet employs the expectation maximization method to compute the probabilities of correct and incorrect PSM, based on the assumption that the PSM data are drawn from a mixture of two Gaussian distributions which generate samples of the correct and incorrect PSMs. The learning model of PeptideProphet was extended in [5] by incorporating decoy PSMs into a mixture probabilistic model at the estimation step of the expectation maximization. Percolator starts the learning process with a small set of trusted correct PSMs and incorrect PSMs selecting from a decoy database, and it iteratively adjusts its learning model to fit the dataset and ranks the PSMs according to confidence on the PSM.

Another category of machine learning-based methods uses supervised learning and formulates peptide identification as an optimization problem. In [17], a fully supervised method is proposed to improve the performance of Percolator. Two types of discriminant functions, linear functions and two-layer neural networks, are compared. The two-layer neural networks is a nonlinear discriminant function which adds lots parameters of hidden units. As expected, it achieves better identification performance than the model with linear discriminant function [17]. CRanker [11] is a method that employs kernel-based SVM to formulate the peptide identification problem as an optimization problem. Although CRanker has shown efficiency compared with benchmark approaches, PeptideProphet and Percolator, it could not efficiently deal with the large-scale PSM datasets because of the storage of large kernel matrix and computation complexity.

Although these advanced post-database searching approaches have dramatically improved the accuracy of peptide identification, two big challenges remain in practical implementation:

1. the performance of the algorithms degrades on the PSM datasets having an extremely large proportion of false positives (called “hard dataset”);
2. a huge amount of computational time and resources are required for large-scale datasets, resulting in a heavy burden on computation.

A number of works have attempted to conquer the two challenges. Authors in [18] integrate auxiliary information to improve the identification performance for the “hard datasets” challenge. Moreover, MSFragger [10] empowers the open database search concept and includes all the modified forms of the peptides to improve the matching quality. For the other challenge, cloud computing platform is used in [16] to tackle the intense memory requirement.

In this work, we aim at tackling the two challenges by using efficient optimization techniques. For the challenge of “hard dataset”, we first extend CRanker [11] model to a cost-sensitive CRanker (CS-Ranker) by using different loss functions for decoy and target PSMs respectively.
The CS-Ranker model gives a larger penalty for wrongly selecting decoy PSMs than that for target PSMs, which reduces the model’s false discovery rate while increases its true positive rate. Second, we designed an online algorithm randomly selecting the PSM samples and add them into the training process. As a result, the training model is less prone to converging to poor local minima, avoiding extremely bad identification results.

The challenge of the requirement of computational resource comes from the large-sized PSM datasets. CRanker and other kernel-based batch learning algorithms need to load the entire kernel matrix into memory, and thus the memory requirement can be very intense during the training process. Also, parameter selection for CRanker and most machine learning-based models is very time-consuming. For choosing a set of appropriate parameters, it usually takes CRanker dozens of hours to determine the discriminant function on large-sized datasets.

In order to reduce the high demand on computer memory, we construct a new classification model, CS-Ranker, by incorporating the C-SVM model into an online algorithm for CS-Ranker (OLCS-Ranker) which trains PSM data samples one by one and uses an active set to keep only those PSMs effective to the discriminant function. In this way, memory requirement and total training time can be dramatically reduced.

Experimental studies have shown that OLCS-Ranker outperforms CRanker on the tested datasets in terms of accuracy and stability while it reports a list of target PSMs comparable to PeptideProphet and Percolator. More importantly, OLCS-Ranker is $15 \sim 85$ times faster on large datasets than CRanker.

2 Methods

2.1 Cost-Sensitive Ranker model

In this section, we present a cost-sensitive classification model which extends CRanker \cite{11} model by using different loss functions for decoy and target PSMs respectively.

Identification of correct target PSM can be formulated as a classification problem. Let $\Omega = \{x_i, y_i\}_{i=1}^n \subseteq R^q \times \{-1, 1\}$ be a set of $n$ PSMs, where $x_i \in R^q$ represents its $i$-th PSM record with $q$ attributes, and $y_i = 1$ or $-1$ is the corresponding label indicating a target or decoy PSM. The identification task is to train a discriminant function for filtering out the correct PSMs from the target PSMs (ones with labels “+1”).

Let $\Omega_+ = \{j \mid y_j = 1\}$, $\Omega_- = \{j \mid y_j = -1\}$. A commonly used Support Vector Machine (SVM) \cite{4}, C-SVM, assigns the PSM labels according to a discriminant function $f$ given by the following optimization model:

$$\min_{w,b} \frac{1}{2} \|w\|^2 + C \sum_i h(y_i, f(x_i))$$ (1)

where $C > 0$ is the weight of the experiential loss, $h(t) = \max(0, 1 - t)$ is the hinge loss function, and $f(x_i) = \langle w, \phi(x_i) \rangle + b$ is the value of discriminant function at $x_i$. $\phi(\cdot)$ is a feature mapping.

Here, we set offset $b \equiv 0$.

While class labels in a standard classification problem are trustworthy, a large number of “+1” labels in PSM identification are not correct. CRanker \cite{11} introduces weight $\theta_i \in [0, 1]$, for each PSM sample $(x_i, y_i)$ to indicate the degree of the reliability of the label $y_i$. Particularly, $\theta_i = 1$ indicates that label $y_i$ is definitely correct, $\theta_i = 0$ indicates that it is definitely incorrect, and $\theta_i \in (0, 1)$ indicates that label $y_i$ is probably correct. In fact, all “−1” labels (decoy PSMs)
are correct, and thus $\theta_i = 1$ for all $i \in \Omega_-$. Following the idea of CRanker we propose to solve the following optimization problem

$$\min_{w, \theta} \frac{1}{2} \|w\|^2 + C_1 \sum_{i \in \Omega_-} \theta_i h(y_i f(x_i)) + C_2 \sum_{i \in \Omega_+} \theta_i h(y_i f(x_i)) - \lambda \sum_{i=1}^n \theta_i$$

s.t. $\theta_i = 1$, $i \in \Omega_-$,

$$0 \leq \theta_i \leq 1$, $i \in \Omega_+$,

(2)

where $\lambda > 0$ is the weight to encourage the model to identify more correct PSMs. As shown in [19, 14], a larger value of parameter $\lambda$ selects more PSMs into training process.

Note that if the discriminant function assigns “+1” label to a decoy PSM, then we know for sure that the label assignment is wrong. In this case, the learning error is more likely caused by the model itself rather than the quality of data sample, and hence we should give the loss function a large penalty. On the other hand, if a target is classified as negative and assigned label “−1”, we are not even sure whether the label assignment is correct, and thus we consider a small penalty for the loss function. Based on these observations, we incorporate the new penalty policy into model (2) and the new model is described as follows:

$$\min_{w, \theta} \frac{1}{2} \|w\|^2 + C_1 \sum_{i \in \Omega_-} \theta_i h(y_i f(x_i)) + C_2 \sum_{i \in \Omega_+} \theta_i h(y_i f(x_i)) - \lambda \sum_{i=1}^n \theta_i$$

s.t. $\theta_i = 1$, $i \in \Omega_-$,

$$0 \leq \theta_i \leq 1$, $i \in \Omega_+$,

(3)

where $C_1 > 0$, $C_2 > 0$ are cost weights for the losses of the decoys and targets, respectively. Model (3) is named cost-sensitive ranker model and denoted by CS-Ranker. As we choose a larger penalty for decoy losses, $C_1 \geq C_2$ always holds.

### 2.2 The batch convex-concave procedure for solving CS-Ranker

In this section, we present a batch algorithm to solve the CS-Ranker model by leveraging the DC (difference of two convex functions) structure of (3).

It can be shown by [14] that if a pair of $w^* \in \mathbb{R}^n$ and $\theta^* \in \mathbb{R}^n$ is an optimal solution to CS-Ranker model (3), then $w^*$ is also an optimal solution of the following model,

$$\min_w \frac{1}{2} \|w\|^2 + C_1 \sum_{i \in \Omega_-} h(y_i f(x_i)) + C_2 \sum_{i \in \Omega_+} R_s(y_i f(x_i))$$

(4)

with $R_s(t) = \min(1 - s, \max(0, 1 - t))$, $s = 1 - \frac{\lambda}{C_2}$, and vice versa.

Since $R_s(t) = H_1(t) - H_s(t)$, with $H_s(t) = \max(0, s - t)$, then model (4) can be recast as programming:

$$\min J(w) = J_{\text{vex}}(w) + J_{\text{cav}}(w),$$

(5)

where

$$J_{\text{vex}}(w) = \frac{1}{2} \|w\|^2 + C_1 \sum_{i \in \Omega_-} H_1(y_i f(x_i)) + C_2 \sum_{i \in \Omega_+} H_1(y_i f(x_i))$$

$$J_{\text{cav}}(w) = -C_2 \sum_{i \in \Omega_+} H_s(y_i f(x_i)).$$

(6)

$J_{\text{vex}}(\cdot)$ and $J_{\text{cav}}(\cdot)$ are convex and concave functions respectively. Model (5) can be solved by a standard Concave-Convex Procedure (CCCP) [20], which iteratively solves subproblems

$$w^{k+1} = \arg\min_w J_{\text{vex}}(w) + J'_{\text{cav}}(w^k) \cdot w$$

(7)
with initial $w^0$. The Lagrange dual of (7) can be deduced as follows:

$$
\begin{align*}
\max_{\alpha} & \quad G(\alpha) = -\frac{1}{2} \sum_{i,j} \alpha_i \alpha_j k(x_i, x_j) + \langle \alpha, y \rangle + \sum_{i \in \Omega_+} C_2 \eta_i^k \\
\text{s.t.} & \quad A_i \leq \alpha_i \leq B_i, \quad i = 1, \ldots, n \\
& \quad A_i = \min(0, C_1 y_i), \quad i \in \Omega_- \\
& \quad B_i = \max(0, C_1 y_i), \quad i \in \Omega_- \\
& \quad A_i = \min(0, C_2 y_i) - C_2 \eta_i y_i, \quad i \in \Omega_+ \\
& \quad B_i = \max(0, C_2 y_i) - C_2 \eta_i y_i, \quad i \in \Omega_+ 
\end{align*}
$$

(8)

where $\eta_i = \begin{cases} 
1, & \text{if } y_i f(x_i) < s, \\
0, & \text{otherwise}. 
\end{cases}$

Based on the CCCP framework, we solve CS-Ranker with Algorithm 1 as follows.

**Algorithm 1** Batch algorithm for solving CS-Ranker (Batch-CS-Ranker)

1. Initialize $\eta_i = 0, i \in \Omega_+, k = 0$.
2. repeat
3. Solve the quadratic programming (8), and the optimal solution is set as $\alpha^{k+1}$.
4. update $\eta^{k+1}$: $\eta^{k+1}_i = \begin{cases} 
1, & \text{if } y_i f^{k+1}(x_i) < s, \\
0, & \text{otherwise}, 
\end{cases}$ $i \in \Omega_+$, $f^{k+1}(x_i) = \sum_{j=1}^n \alpha^{k+1}_j k(x_j, x_i)$.
5. Update $A_i$ and $B_i$: $A_i = \min(0, C_2 y_i) - C_2 \eta^k_i y_i, B_i = \max(0, C_2 y_i) - C_2 \eta^k_i y_i, i \in \Omega_+$.
6. set $k \leftarrow k + 1$.
7. until convergence of $\alpha_k$

Algorithm 2 iteratively executes two main steps: 1) Solve the SVM quadratic programming (8) (Line 3). 2) Updates the bounds $A_i$ and $B_i$ with $i \in \Omega_+$ (Line 4–Line 5). As the training set is fed into the algorithm once at the beginning, we name Algorithm 2 Batch-CS-Ranker.

### 2.3 The online learning algorithm for CS-Ranker model

Inspired by the work in [2, 6], we present an online CS-Ranker algorithm for overcoming the two challenges remaining in the Batch-CS-Ranker algorithm, and name it OLCS-Ranker. It is actually an online version of the Batch-CS-Ranker algorithm, and both algorithms solve CS-Ranker model (4) to train the discriminant function. Different with the Batch-CS-Ranker algorithm taking the PSM samples all at once, OLCS-Ranker train the discrimination function in an iterative manner and adds only one PSM sample into the training process at each iteration. The PSM sample is randomly selected to help the solution of discrimination function not trap at a local minimum, and the effectiveness has been observed in approaches such as stochastic gradient descent [3]. Moreover, OLCS-Ranker maintains an active set to only keep indices of PSMs that determine the discriminant function in model training, and the PSMs that do not affect the discriminant function are discarded. As a result, the cost of memory and computation is minimized.

#### 2.3.1 Online Algorithm for Solving CS-Ranker

The implementation of OLCS-Ranker is depicted in Algorithm 2. Particularly, given a chosen PSM sample (Line 3), OLCS-Ranker updates bounds $A_j, B_j$, for all $j \in \Omega_+ \cap S$ (Line 4 – Line 7), and call subroutines PROCESS and REPROCESS to solve dual programming (8) with training.
samples in active set $S$ (Line 8–Line 12). Periodically, the algorithm calls subroutine CLEAN to remove part of redundant instances from the kernel expansion (Line 13). The iteration terminates when all the training PSMs has been chosen for training.

Algorithm 2 Online CS-Ranker algorithm for solving model (4)

**Input:** PSM samples $\{x_i, y_i\}_{i=1}^n$.

**Output:** solution $\alpha \in \mathbb{R}^n$.

**Parameters:**
- $M$: minimum number of PSMs in the active set $S$;
- $\tau > 0$: the tolerance to solve the dual programming (8);
- $\mu_{s_{afe}}, \mu_{s_{afe-target}}$: thresholds to select candidate PSMs.

1: Set $\eta \leftarrow 0$, $\alpha \leftarrow 0$, $S \leftarrow \emptyset$.
2: for $i_0 \in \{1, 2, \ldots, n\}$ do
3: Randomly select a training PSM sample $(x_{i_0}, y_{i_0})$.
4: Update bounds $A_j, B_j, \forall j \in \Omega_+ \cap S$: $\eta_j = \begin{cases} 1, & \text{if } y_j f(x_j) < s \text{ and } |S| > M, \\ 0, & \text{otherwise} \end{cases}$, $j \in \Omega_+ \cap S$, $f(x_j) = \sum_{s \in S} \alpha_s k(x_s, x_j)$;
5: Update bounds $A_j = \min(0, C_2 y_j) - C_2 \eta_j^2 y_j$, $B_j = \max(0, C_2 y_j) - C_2 \eta_j^2 y_j$, $j \in \Omega_+ \cap S$.
6: Call PROCESS().
9: exitFlag $\leftarrow 0$;
10: while (exitFlag == 0) do
11: exitFlag $\leftarrow$ REPRECESS()
12: end while
13: Periodically call CLEAN().
14: end for

2.3.2 Subroutines

Subroutine PROCESS ensures that all the coordinates of $\alpha_j$ satisfy the bound constraint conditions in CS-Ranker model (8). It initializes $\alpha_{i_0}$ with $i_0$ the index of the chosen PSM and updates the coordinates $\alpha_j$ with bounds $A_j$ or $B_j$ changed (Line 1-2). Then it updates gradient vector $g_j$, $j \in S$ (Line 3), where $g$ is defined by

$$g_i = \frac{\partial G(\alpha)}{\partial \alpha_i} = y_i - \sum_{j \in S} \alpha_j k(x_i, x_j). \quad (9)$$

Algorithm 3 PROCESS

1: $\alpha_{i_0} \leftarrow 0$ for new chosen PSM indexing $i_0$.
2: For all $j \in S$ that bounds $A_j$ or $B_j$ has been changed, update $\alpha_j$: $\alpha_j \leftarrow 0$.
3: For all $j \in S$, calculate $g_j$: $g_j \leftarrow y_j - \sum_{s \in S} \alpha_s k(x_j, x_s)$.
Subroutine REPROCESS aims to find a better solution of model (8). It selects the instances with the maximal gradient in active set $S$ (Line 1 – Line 12). Once an instance is selected, it computes a stepsize (Line 13 – Line 17) and performs a direction search (Line 18 – Line 19).

**Algorithm 4** exitFlag = REPROCESS()

1: $i \leftarrow \arg\min_{s \in S} g_s$ with $\alpha_s > A_s$;
2: $j \leftarrow \arg\max_{s \in S} g_s$ with $\alpha_s < B_s$.
3: if $\max(g_j, -g_i) \leq \tau$ then
4:   exitFlag = 1; Return;
5: else
6:   exitFlag = 0;
7: end if
8: if $(-g_i > \tau, g_j < \tau)$ Or $(-g_i > \tau, g_j > \tau$ and $-g_i > g_j)$ then
9:   $g \leftarrow g_j, t \leftarrow j$;
10: else
11:   $g \leftarrow g_i, t \leftarrow i$;
12: end if
13: if $g < 0$ then
14:   $\lambda = \max(A_t - \alpha_t, \frac{g}{K_{tt}})$
15: else
16:   $\lambda = \min(B_t - \alpha_t, \frac{g}{K_{tt}})$
17: end if
18: $\alpha_t \leftarrow \alpha_t + \lambda$,
19: $g_s \leftarrow g_s - \lambda K_{ts}, \forall s \in S$.

Subroutine CLEAN removes PSMs that are not effective to the discriminant function from the active set $S$ to minimize the requirement of memory and computation. The subroutine selects non-support vectors as a set $V$ (Line[1] – Line[4]), and then remove $m$ PSMs among $V$ with largest gradients (Line[5] – Line[9]).

**Algorithm 5** CLEAN

**parameter:**

$m$: maximum number of removed non-support vectors;

1: $V \leftarrow \emptyset$
2: for $i$: $i \in S, \alpha_i = 0$ do
3:   $V \leftarrow V \cup \{i\}$.
4: end for
5: if $|V| \leq m$ then
6:   remove $i$ from $S, \forall i \in V$
7: else
8:   select $m$ indices from $V$ with largest gradients $g_i$ and remove from $S$.
9: end if
2.3.3 Calculate PSM scores

After discriminant function \( \hat{f} \): \( \hat{f}(x) = \sum_{j \in S} \alpha_j k(x_j, x) \), where \( k(\cdot) \) is the selected kernel function, is trained, we calculate the scores of all PSMs on both training and test sets. The score of PSM \((x_i, y_i)\) is defined in [11]:

\[
score(i) = \frac{2}{\pi} \arctan(\hat{f}(x_i)).
\]

The larger the score value is, the more likely a PSM is correct. The PSMs are ordered according to their scores, and a certain number of PSMs are reported according to a pre-selected FDR.

3 Results and discussion

3.1 Experimental Setup

To evaluate the performance of OLCS-Ranker, we compare its performance against other algorithms on eight MS/MS datasets: universal proteomics standard set (Ups1), the \textit{S. cerevisiae} Gcn4 affinity-purified complex (Yeast), \textit{S. cerevisiae} transcription complexes using the Tal08 minichromosome (Tal08 and Tal08-large) and Human Peripheral Blood Mononuclear Cells (PBMC datasets: Orbit-mips, Orbit-nomips, Velos-mips and Velos-nomips). The MS/MS spectra were extracted from the mzXML file using the program MzXML2Search and all data was processed using the SEQUEST software. Refer to [7] for the details of the sample preparation and LC/MS/MS analysis. For analysis of SEQUEST output with PeptideProphet, we used the Trans Proteomic Pipeline V.4.0.2 (TPP). For analysis of SEQUEST output with Percolator, we converted the SEQUEST outputs to a merged file in SQT format [13, 1]. OLCS-Ranker was implemented with Matlab R2015b and ran on a PC with Intel Core E5-2640 CPU 2.40GHz and 24Gb RAM.

Statistics of the SEQUEST search results of the eight datasets are listed in Table 1, where “Full”, “Half” and “None” indicates the three types of tryptic peptides: full-digested, half-digested and none-digested peptides generated by Trypsin digestion of the protein samples.

| Dataset     | Total | Target     | Decoy     |
|-------------|-------|------------|-----------|
|             |       | Full | Half | None | Full | Half | None |
| Ups1        | 17335 | 645 | 2013 | 6316 | 236 | 2588 | 5537 |
| Yeast       | 14892 | 1453 | 1210 | 4040 | 106 | 1465 | 6618 |
| Tal08       | 18653 | 1081 | 2133 | 6693 | 164 | 1923 | 6659 |
| Tal08-large | 69560 | 14893 | 6809 | 20520 | 419 | 5877 | 21042 |
| Orbit-mips  | 103679 | 26760 | 15647 | 25927 | 737 | 8583 | 26025 |
| Orbit-nomips| 117751 | 28561 | 17490 | 30344 | 948 | 10333 | 30075 |
| Velos-mips  | 301879 | 110404 | 35915 | 62446 | 2520 | 24682 | 65912 |
| Velos-nomips| 447350 | 134117 | 77052 | 96380 | 3414 | 34985 | 101402 |

Following CRanker [11], a PSM record is represented by a vector of nine attributes: xcorr, deltacn, sprank, ions, hit mass, enzN, enzC, numProt, deltacnR. PSMs have randomly divided into a training set and a test set according to the ratio 2:1. The numbers of PSMs identified on the training set and on the test set are calculated. Weight 1.0 was assigned for xcorr and deltacn,
and 0.5 for all others. We used the Gaussian kernel \( k(x_i, x_j) = \exp \left( \frac{\|x_i - x_j\|^2}{2\sigma^2} \right) \) for OLCS-Ranker with kernel parameter \( \sigma = 1 \).

We choose the values of parameters of OLCS-Ranker by 3-fold cross-validation in terms of the number of identified PSMs and test/total ratio.

### 3.2 Comparison with benchmark methods

We compared OLCS-Ranker, PeptideProphet and Percolator on the seven datasets, and Table 2 shows the numbers of validated PSMs at FDR \( \approx 0.05 \). The performance of a validation approach is better if it validates more target PSMs compared to another approach with the same FDR. As we can see, OLCS-Ranker identifies more PSMs than PeptideProphet and Percolator over all the eight datasets. Particularly, 5% more PSMs were identified by OLCS-Ranker on Tal08 and Tal08-large, and the improvement on the other datasets were about 2% or more.

Table 2: Target PSMs output by PeptideProphet, Percolator, and OLCS-Ranker. #TP: number of true positive PSMs. #FP: number of false positive PSMs. #(total targets): number of the total targets in the PSM dataset (refer to Table 1 for detailed quantities.)

| Data set   | Method       | Total | #TP  | #FP  | #TP/#(total targets) |
|------------|--------------|-------|------|------|----------------------|
| ups1       | PepProphet   | 582   | 566  | 16   | 6.3%                 |
|            | Percolator   | 450   | 438  | 12   | 4.9%                 |
|            | OLCS-Ranker  | 597   | 582  | 15   | 6.5%                 |
| yeast      | PepProphet   | 1481  | 1443 | 38   | 21.5%                |
|            | Percolator   | 1429  | 1394 | 35   | 20.8%                |
|            | OLCS-Ranker  | 1516  | 1479 | 37   | 22.1%                |
| tal08      | PepProphet   | 982   | 957  | 25   | 9.7%                 |
|            | Percolator   | 978   | 953  | 25   | 9.6%                 |
|            | OLCS-Ranker  | 1145  | 1118 | 27   | 11.3%                |
| tal08-large| PepProphet   | 16025 | 15638| 387  | 37.0%                |
|            | Percolator   | 14725 | 14371| 354  | 34.0%                |
|            | OLCS-Ranker  | 16792 | 16373| 419  | 38.8%                |
| Orbit-mips | PepProphet   | 34035 | 33233| 802  | 48.6%                |
|            | Percolator   | 34118 | 33270| 848  | 48.7%                |
|            | OLCS-Ranker  | 35095 | 34257| 838  | 50.1%                |
| Orbit-nomips| PepProphet | 36542 | 35673| 869  | 46.7%                |
|            | Percolator   | 36962 | 36096| 866  | 47.2%                |
|            | OLCS-Ranker  | 37387 | 36454| 933  | 47.7%                |
| Velos-mips | PepProphet   | 123908| 120961|2947 | 57.9%                |
|            | Percolator   | 125701| 122568|3133 | 58.7%                |
|            | OLCS-Ranker  | 126015| 122866|3149 | 58.9%                |
| Velos-nomips| PepProphet | 180182| 175789|4393 | 57.2%                |
|            | Percolator   | 178280| 173917|4363 | 56.5%                |
|            | OLCS-Ranker  | 183573| 178985|4588 | 58.2%                |

PepProphet: PeptideProphet.
We also compared the overlapping of target PSMs identified by OLCS-Ranker, PeptideProphet and Percolator, as a PSM reported by multiple methods is more likely to be correct. As we can see in Figure 1, the majority of validated PSMs by the three approaches overlaps. For example, on Tal08, the three algorithms have 870 PSMs in common, covers more than 77.8% of the total target PSMs identified by each of the algorithms. This ratio of common PSMs is 86.2% and 81.9% on Yeast and Tal08-large, respectively, and more than 90% on the four PBMC datasets. Moreover, on each dataset, OLCS-Ranker identified a certain part of PSMs that identified by PeptideProphet but not by Percolator, or identified by Percolator but not by PeptideProphet. The above overlap results indicate that the identified PSMs output by OLCS-Ranker are reasonable.

**Hard datasets and normal datasets**

As shown in Table 2, PeptideProphet, Percolator and OLCS-Ranker reported similar ratios of the number of identified target PSMs to the total target PSMs over eight datasets. Note that the ratios on two datasets Ups1 and Tal08 are relatively lower than the other six datasets. Particularly, the ratios on Ups1 and Tal08 are 4.9%~6.5%, 9.6%~11.3% respectively while the ratios are more than 20% on the other six datasets. As a large proportion of incorrect PSMs in
Table 3: FDR of OLCS-Ranker on test set. \( \frac{\text{test}}{\text{total}} \) test/toal ratio, the ratio of PSMs identified on the test set to that on the total dataset. FDR: false discovery rate.

|           | #TP | #FP | FDR  | \( \frac{\text{test}}{\text{total}} \) |
|-----------|-----|-----|------|----------------------------------|
| Ups1      | 180 | 5   | 5.41%| 30.99%                           |
| Yeast     | 491 | 12  | 4.77%| 33.18%                           |
| Tal08     | 348 | 8   | 4.49%| 31.10%                           |
| Tal08-large| 5546| 139 | 4.98%| 33.26%                           |
| Orbit-mips| 11384| 281 | 4.99%| 33.24%                           |
| Orbit-nomips| 12048| 308 | 4.99%| 33.05%                           |
| Velos-mips| 40905| 1048| 5.00%| 33.29%                           |
| Velos-nomips| 59777| 1532| 5.00%| 33.39%                           |

A dataset usually reduces the accuracy of PSM identification, we named two datasets Ups1 and Tal08 “hard datasets”. In contrast, the other six datasets have much lower ratios of incorrect matches than those of Ups1 and Tal08, and we named them “normal datasets”.

3.3 Model evaluation

We use a separate test dataset to examine whether the OLCS-Ranker model overfits the training datasets. The ratio of identified PSMs to the total PSMs (test/total ratio) is calculated. As the test datasets are randomly chosen from the whole datasets according to the ratio of 1:3, a value of 33.3% is an expected test/total ratio. The test/total ratios of all datasets under FDR \( \approx 0.05 \) are listed in the last column of Table 3.

On all the six “normal datasets”, the test/total ratios are extremely close to the ideal ratio, indicating that no overfitting problem occurs on OLCS-Ranker classifiers. On the remaining two “hard datasets”, Ups1 and Tal08, the test/total ratio is near 31%, which is 2.3% lower than the ideal ratio. The relatively low test/total ratios on “hard datasets” is mainly induced by extremely unbalanced PSM datasets, in which there are few correct target PSMs.

We have also evaluated the performance of OLCS-Ranker, PeptideProphet and Percolator by using receiver operating characteristic (ROC). As shown in Figure 2, OLCS-Ranker reaches highest TPRs among the three methods at most values of FPRs on the eight datasets, except the FPR at 0.003 on Ups1, the FPR in the range from 0.001 to 0.003 on Yeast, and the FPR in the range from 0.05 to 0.1 on Velos-mips. Particularly, CS-CRANKER reaches significantly higher TPR levels than that of PeptideProphet and Percolator on Tal08 and Tal08-large dataset.

3.4 The algorithm efficiency

To evaluate the efficiency of OLCS-Ranker, we compare its algorithmic performance with those of Batch-CS-Ranker and C-Ranker. Batch-CS-Ranker solves model (4) by using Algorithm 1 which transforms subproblem (7) to its dual programming and then solved it with Matlab built-in solver while OLCS-Ranker solves model (4) by using Algorithm 2 which is our designed online algorithm. As the Batch-CS-Ranker algorithm and C-Ranker require the whole training data for construction of kernel matrix, it is difficult to implement the two algorithms on large-scale
datasets. Instead, we divided the whole training dataset into five subsets by randomly selecting 16000 PSMs for each subset. The final score of a PSM is the average of the scores on the five subsets.

Table 4 summaries performance comparison among OLCS-Ranker, C-Ranker and Batch-CS-Ranker in terms of the total number of identified PSMs, total/test ratio, elapsed time. We measured the execution time of each algorithm on eight datasets. As we can see in Table 4, OLCS-Ranker is about $15 \sim 85$ times faster than CRanker and $30 \sim 140$ times faster than Batch-CS-Ranker algorithm on large-scale datasets.

3.5 The algorithm stability

As the training data are randomly selected from the training dataset, the output of a model-based algorithm may slightly vary due to different training PSMs. Ideally, a good algorithm should report very similar target PSMs even with a different training set. We have run OLCS-Ranker and Batch-CS-Ranker for 30 times, each with an independent training set. Due to the excessive computation of Batch-CS-Ranker on large-sized datasets, we compared the stability on three small datasets. The numbers of identified PSMs at the 30 runs on Ups1, Yeast and Tal08 are depicted in Figure 3 (A), (B) and (C), resp. Note that Batch-CS-Ranker reported a relatively small number of identified PSMs at the 8-th trial on Ups1 (Figure 3 (A)) and the 21-th trial on Tal08 (Figure 3 (C)), which indicates the optimization solver used in Batch-CS-Ranker
| Dataset     | Method      | #Total PSMs | \( \text{test}\) \(\text{total}\) | time (s) |
|-------------|-------------|-------------|-----------------|---------|
| Ups1        | C-Ranker    | 614.3       | 27.24%          | 1507.0  |
|            | Batch-CS-Ranker | 597.7     | 31.73%          | 255.4   |
|            | OLCS-Ranker  | 590.6       | 30.77%          | 19.3    |
| Yeast       | C-Ranker    | 1462.3      | 33.90%          | 667.8   |
|            | Batch-CS-Ranker | 1489.3    | 31.81%          | 642.5   |
|            | OLCS-Ranker  | 1507.9      | 31.89%          | 16.9    |
| Tal08       | C-Ranker    | 1118.7      | 30.61%          | 1579.6  |
|            | Batch-CS-Ranker | 1116.7    | 30.85%          | 345.3   |
|            | OLCS-Ranker  | 1146.5      | 30.28%          | 26.0    |
| Tal08-large | C-Ranker    | 16659.3     | 33.39%          | 10090.1 |
|            | Batch-CS-Ranker | 16366.0  | 33.28%          | 8088.3  |
|            | OLCS-Ranker  | 16725.7     | 33.07%          | 116.7   |
| Orbit-mips  | C-Ranker    | 34720.3     | 32.99%          | 10207.5 |
|            | Batch-CS-Ranker | 34557.7  | 33.29%          | 18264.0 |
|            | OLCS-Ranker  | 35222.3     | 33.07%          | 146.2   |
| Orbit-nomips| C-Ranker    | 37147.3     | 33.25%          | 9630.1  |
|            | Batch-CS-Ranker | 36738.0  | 33.30%          | 22428.1 |
|            | OLCS-Ranker  | 37321.7     | 33.21%          | 155.8   |
| Velos-mips  | C-Ranker    | 125435.0    | 33.40%          | 9052.9  |
|            | Batch-CS-Ranker | 124233.0 | 33.34%          | 21107.0 |
|            | OLCS-Ranker  | 125328.7    | 33.33%          | 495.5   |
| Velos-nomips| C-Ranker    | 182665.7    | 33.18%          | 11478.5 |
|            | Batch-CS-Ranker | 179811.7 | 33.31%          | 23849.7 |
|            | OLCS-Ranker  | 182276.3    | 33.32%          | 754.3   |
Figure 3: Numbers of PSMs identified by OLCS-CRanker and Batch-CS-Ranker algorithm in 30 times

is trapped in bad local minima. In contrast, OLCS-Ranker, with online iteration technique, can escape from the bad local minima.
4 Conclusion

We have presented a cost-effective post-database search approach for peptide identification using an SVM-based learning model, which introduces different penalties for learning errors on decoy and target PSMs. An efficient online learning algorithm, OLCS-Ranker, is designed for tackling the challenge of identification on hard datasets and large-scale datasets. Experimental studies show that OLCS-Ranker based on the cost-effective learning model has improved the learning algorithmic performance and increased identified PSMs, compared with other kernel-based batch algorithms, CRanker and Batch-CS-Ranker.

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Notes

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