On the Unreported-Profile-is-Negative Assumption for Predictive Cheminformatics

Chao Lan, Sai Nivedita Chandrasekaran and Jun Huan

Abstract—The study of compound-target binding profiles has been a central theme in cheminformatics. For data repositories that only provide positive binding profiles, a popular assumption is that all unreported profiles are negative. In this paper, we caution audience not to take such assumptions for granted. Under a problem setting where binding profiles are used as features to train predictive models, we present empirical evidence that (1) predictive performance degrades when the assumption fails and (2) explicit recovery of unreported profiles improves predictive performance. In particular, we propose a joint framework of profile recovery and supervised learning, which shows further performance improvement. Our study not only calls for more careful treatment of unreported profiles in cheminformatics, but also initiates a new machine learning problem which we called Learning with Positive and Unknown Features.

Index Terms—Chemical-Target Interaction, GCPRs, Missing Data, Collaborative Filtering, Matrix Factorization

1 INTRODUCTION

In cheminformatics research, the study of compound-target binding profiles has been a central theme. In that, the binding profile between a compound and a target is usually presented as binary information indicating whether the two substances have positive interaction (i.e. they interact) or negative interaction (i.e. they do not interact). When working with data repositories that only report positive binding profiles, a common assumption is all unreported profiles are negative. In a recent study [1], authors pointed out the assumption may be ‘potentially wrong’ but still argued (without verification) for its appropriateness as ‘the number of unreported binding substances can be expected to be low and thus the effect should not be important’.

We caution audience not to take the ‘unreported-is-negative’ assumption for granted in cheminformatics research. As we inspected through the literature, what truly surprised us is the very rare evidence on its appropriateness. One may argue a direct evidence is difficult to collect – indeed, verifying all unreported profiles through chemical experiments can be expensive and somewhat unnecessary the evidence (as one no longer needs that assumption). However, we believe indirect evidence is still practical and worthy to collect, such as how the assumption may affect predictive performance in cheminformatics. This is a major motivation of our study.

In this paper, we empirically examine the appropriateness of the ‘unreported-is-negative’ assumption, under a problem setting where binding profiles are directly treated as features of training data to learn predictive models. Our empirical evaluations on real-world cheminformatics data set suggest that (1) predictive performance degrades when the ‘unreported-is-negative’ assumption fails and (2) explicit recovery of unreported profiles improves predictive performance. In addition, we propose a framework of joint profile recovery and predictive learning, which shows further performance improvement. Interestingly, in certain synthetic task we observe this framework outperforms the predictive model trained with no unreported profiles, suggesting it may provide a more effective way of biasing the search of hypotheses to alleviate over-fitting.

1.1 The Technical Narrative

From a technical perspective, a major contribution of this paper is the introduction of a new machine learning problem which we called Learning with Positive and Unknown Features. The problem considers supervised learning with binary-featured data, and assumes one feature value is completely missing in the training sample, while the other feature value is partly missing. This setting corresponds to the scenario in cheminformatics where binding profiles are treated as binary features of drugs to train predictive models while only positive profiles are reported. A hypothetical example is illustrated in Figure 1.

Fig. 1. A training sample matrix with binary features. Each row \(s_i\) is a feature vector of an example (e.g. a drug), each column \(f_j\) corresponds to one feature (e.g. interaction with a compound), and the last column \(\ell\) corresponds to label (e.g. any event one wishes to predict); notation ? indicates missing value. In this training sample, feature value 0 is completely missing, whereas value 1 is partly missing.
Learning with missing data is a very aged topic (e.g. [2]), which refers to the general problem of learning with missing features. However, most solutions assume all feature values are partly missing, while we assume one feature value is completely missing. This difference could completely fail the previous solutions, especially in the binary feature setting. As an example, consider the popular nearest-neighbor based imputation approach, which replaces a missing value with the mean of its neighboring observed values. When only one feature value is observed, the approach will simply replace all missing values with the observed value – in Figure 1, this means replacing all ? with value 1 and thus ‘squeezing’ all data points to a single point!

Positive and unlabeled learning (e.g. [3], [4]) refers to the problem of learning with binary label where negative examples are completely missing in the training sample. Their problem assumes the same missing pattern as our problem but on different sets, that is, they assume labels are missing while we assume features are missing. This hinders direct application of their solutions to address our problem.

Perhaps the most related topic is is one-class collaborative filtering (o.c.c.f.) (e.g. [5], [6]), which refers to the problem of recovering missing values of an one-class matrix – an incomplete matrix whose observed entries all take the same value. The o.c.c.f. solutions can be directly to address our problem, since our incomplete feature matrix is a one-class matrix. However, the goals of the two problems are different: o.c.c.f. only aims to recover missing features, while we aim to learn the predictive model given missing features. This seemingly subtle difference may lead to fundamentally different technical developments: first, in our problem the part of predictive learning may provide additional information to assist the recovery of missing features, and this is generally not considered in o.c.c.f.; second, while accurate feature recovery suffices for learning accurate predictive model, whether it is necessary remains a very open question – it is not hard to imagine different sample distributions may still admit very similar decision boundaries. This is, in fact, the very thinking that motivated us to propose a ‘bold’ framework of joint feature recovery and predictive learning, without worrying too much about the potential introduction of additional bias, and the framework seems supported by experiments. We consider the proposed joint framework another contribution of this work.

The literatures on these related topics are huge, but for interested readers we strive to develop surveys on both the topic of positive and unknown learning and the topic of one-class collaborative filtering. They are presented at the end of this paper. Since (to our knowledge) no notable survey on either topic has been published, we consider the presented survey an ‘auxiliary’ contribution of the work.

1.2 Organization

The remaining of this paper is organized as follows: in section 2, we introduce notations and the basic problem setting; a set of solutions are introduced in section 3, including our proposed joint feature recovery and predictive learning approach; experimental studies and results are presented in section 4, which serve as proof of concept; discussions are presented in section 5 and conclusions in section 6.

2 Notations and Problem Setting

For a number \( t > 0 \), let \( [t] := \{1, 2, ..., t\} \). For a vector \( V \), let \( V_i \) be its \( i\)th element and \( ||V||\) be its \( l_2 \) norm. For a matrix \( M \), let \( M_{ij} \) be its entry at row \( i \) and column \( j \), \( M_i \) be its \( i\)th row vector and \( M_j \) be its \( j\)th column vector; let \( ||M|| \) be its Frobenius norm, \( M^* \) be its transpose and \( \text{tr}(M) \) be its trace; let \( M_b := [M, 1] \) be an augmented matrix of \( M \), where \( 1 \) is a vector of all ones and its dimension equals the row dimension of \( M \). More generally, we use \( 1_b \) to denote a vector of all value \( b \) and \( I \) to denote an identity matrix, whose dimensions are properly defined by the context.

Consider the task of supervised learning with a labeled training sample. Suppose the sample contains \( n \) examples described by \( p \) binary features. The sample is represented as \((X, Y) \in \mathbb{R}^{n \times p} \times \mathbb{R}^n\), where \( X \) is the feature matrix with \( X_i \) being the feature vector of example \( i \), and \( Y \) is the label vector with \( Y_i \) being the label of example \( i \). Assume the label set is binary for simplicity, and assume the binary features are defined on \( \{0, 1\} \) without loss of generality.

In the problem of learning with positive and unknown features, we assume feature value \( 0 \) is completely missing in \( X \), while value \( 1 \) is (probably) partly missing. This is the same scenario as illustrated in Figure 1. We do not make statistical assumption on the missing pattern (as traditional learning with missing data study does e.g. [2]), instead, we adopt the common matrix recovery assumption that the feature matrix has low rank (which could happen when e.g. features are correlated) – this assumption is only needed in theory to justify the application of matrix recovery techniques (as we will do later), but in practice these techniques work just fine without strictly verifying the assumption [7]. Finally, recall our goal is to estimate the predictive function based on this incomplete training sample \((X, Y)\).

3 Methods

In this section, we present several methods for examining the effect of the ‘unreported-is-negative’ assumption on the predictive performance. These include the baseline method that assumes all unreported profiles are negative (i.e. all missing features are replaced with \( 0 \)), two pre-processing methods that first recover unreported profiles by mean imputation and o.c.c.f., techniques respectively, and one proposed method that jointly recover unreported profiles and learn predictive models. In all methods, ridge regression will be used as the base predictive model for its popularity and stability.

3.1 Direct Supervised Learning (DSL)

This is the baseline method adopting the ‘unreported-is-negative’ assumption. The method assumes all unreported profiles are negative, thus replacing all missing values in sample \( X \) with value \( 0 \). (Recall in \( X \) value \( 0 \) is completely missing, whereas value \( 1 \) is partly missing.) Then, the method uses the updated labeled sample \((X, Y)\) to learn the predictive model, that is, to estimate a ridge regression vector \( \beta \in \mathbb{R}^{p+1} \) which minimizes

\[
L_1(\beta) = ||X_+\beta - Y||^2 + \lambda_1||\beta||^2, \tag{1}
\]
where $\lambda_1 > 0$ is a regularization coefficient. It is well-known the learning problem admits a closed form solution

$$\beta = (X_+X_+ + \lambda_1 I)^{-1} X_+ Y,$$

(2)

Note the last element of $\beta$ is the bias term.

### 3.2 Imputation + Supervised Learning (ISL)

This method aims to first recover unreported profiles by applying statistical imputation, and then perform standard predictive learning. In this study, we employ the classic mean/mode imputation approach [2], which replaces the missing feature value of an example with the mean/mode of observed feature values of the same-class examples. In our context, this means replacing a missing value $X_{ij}$ with

$$\hat{X}_{ij} = \sigma \left( \frac{1}{N_{ij}} \sum_{a:(a,j) \in O, Y_a = Y_i} X_{a,j} \right),$$

(3)

where $O$ is the index set of observed values in $X$, $\sigma(\cdot)$ is a function rounding its input to $\{0, 1\}$ and

$$N_{ij} = \{|a \in [n]; (a,j) \in O, Y_a = Y_i\}$$

(4)

is the number of observed values at feature $j$ of examples that belong to the same class as example $i$.

Now we see an aforementioned problem: if one directly applies the above imputation approach, one obtains an updated matrix $X$ of all ones which makes it impossible to learn any useful decision boundary. This limitation is embedded in most traditional imputation approaches, mainly due to their implicit assumptions that both feature values 0 and 1 are partly observed in $X$. To lift the limitation, in practice we first assume a fraction $\delta_0$ of randomly selected missing values are 0, and then apply the above approach. Similar treatments could be found in the literature e.g. [8] but for different techniques or under different contexts.

### 3.3 OCCF + Supervised Learning (OCSL)

This method also aims to first recover unreported profiles but by applying modern matrix recovery techniques, and then perform standard predictive learning. In this study, we employ the one-class collaborative filtering (o.c.c.f.) approaches, which were particularly designed for recovering incomplete matrices like $X$. More specifically, we employ the weighted alternating least square (wALS) approach with uniform scheme [5], which recovers missing values based on a weighted low-rank factorization of $X$. This means seeking for two rank-$r$ factors $U \in \mathbb{R}^{n \times r}$ and $V \in \mathbb{R}^{p \times r}$ which minimize

$$\mathcal{L}_2(U, V) = W \circ ||X - UV'||^2 + \lambda_2 \cdot \text{tr}(U'DU + V'D'V),$$

(5)

where $\circ$ is the Hadamard product, $\lambda_2$ is the regularization coefficient and $W \in \mathbb{R}^{n \times p}$ is a mask matrix defined as

$$W_{ij} = \begin{cases} 1, & \text{if } X_{ij} \text{ is observed} \\ \delta_w, & \text{if } X_{ij} \text{ is missing} \end{cases},$$

(6)

where $\delta_w$ is a small constant weighting one’s confidence in guessing missing values being 0’s; matrices $D^c \in \mathbb{R}^{n \times n}$ and $D^e \in \mathbb{R}^{p \times p}$ are both diagonal and defined as

$$D^c_{ii} = \sum_{j \in [p]} W_{ij} \quad \text{and} \quad D^e_{jj} = \sum_{i \in [n]} W_{ij},$$

(7)

Minimizing (5) was solved by alternately updating

$$U_i = X_i \tilde{W}^i V \left( V' \tilde{W}^i V + \lambda_2 \sum_j W_{ij} I \right)^{-1},$$

(8)

and

$$V_j = X'_j \tilde{W}^j U \left( U' \tilde{W}^j U + \lambda_2 \sum_i W_{ij} I \right)^{-1},$$

(9)

where $\tilde{W}^i : \in \mathbb{R}^{p \times p}$ and $\tilde{W}^j : \in \mathbb{R}^{n \times n}$ are diagonal matrices defined by

$$\tilde{W}_{ik}^i = W_{ik} \quad \text{and} \quad \tilde{W}_{kk}^j = W_{kj}.$$

(10)

Finally, it should be mentioned formula (5) is a new matrix representation of the proposed method in [5], which we derived here for the ease of discussion.

### 3.4 Joint OCCF and Supervised Learning (JOCSL)

The previous two methods ISL and OCSL aim to recover unreported profiles, but perform profile recovery and predictive learning separately. In this section, we push their initiatives further and propose a framework which jointly performs profile recovery and predictive learning.

The arguments behind the joint framework are tri-facet. First, the predictive learning task may bias the profile recovery task in a ‘good’ way that improves recovery accuracy, which would reversely improve learning accuracy. Second, if the bias does not lead to more accurate recovery, the framework could at least reduce the estimation variance of both tasks (by letting them further constrain each other’s search space). Finally, even if the bias may mislead profile recovery, we had found no evidence suggesting one must accurately recover missing features in order to learn an accurate predictive model – it could be that two distant samples (distributions) admit similar decision boundaries.

With the above thoughts in mind, we integrate the objective function $\mathcal{L}_1$ of predictive learning and the objective function $\mathcal{L}_2$ of feature recovery, and propose to minimize

$$\mathcal{L}_3(U, V, \beta) = W \circ ||X - UV'||^2 + \lambda_2 \cdot \text{tr}(U'DU + V'D'V) + \alpha ||(UV')_+ \beta - Y||^2 + \lambda_1 ||\beta||^2,$$

(11)

The objective function $\mathcal{L}_3$ is interpreted as follows: the first term aims to recover unreported profiles, the third term aims to learning predictive model based on the recovered feature matrix $UV$ (not $X$), and $\alpha$ is a constant weighting the roles of these two parts; the second and fourth terms are standard regularizations.

Our goal of learning is to find $(U, V, \beta)$ which minimizes formula (11). Similar to prior work, we solve this by alternately updating each variable – to update a variable, we set its derivative in formula (11). Similar to prior work, we solve this by alternately updating each variable – to update a variable, we set its derivative in formula (11).
coefficients of the model, and $\beta_{p+1}$ corresponds to the bias term of the model. Write

$$h := ||(UV')^+_+\beta - Y||^2. \tag{12}$$

It is easy to verify that

$$h = \sum_{i\in[n]} \left( \sum_{j\in[p]} (U_i;V_j')\beta_k + \beta_{p+1} - Y_i \right)^2. \tag{13}$$

Taking derivatives of $h$, we have

$$\frac{\partial h}{\partial U_i} = 2 \left( (U_i;V')^+_+\beta - Y_i \right) \beta^+_p V, \tag{14}$$

$$\frac{\partial h}{\partial V_j} = 2 \beta_j U' \left( (UV')^+_+\beta - Y \right), \tag{15}$$

and

$$\frac{\partial h}{\partial \beta} = 2 (UV')^+_+ (UV')^+_+ - Y. \tag{16}$$

Based on (14, 15, 16), we take derivatives of $\mathcal{L}_\beta$ with respect to different variables and set them to zero. Solving for each variable gives the following update rules

$$U_i = \left( \bar{X}_i \tilde{W}^i V + \alpha (Y_i - \beta_{p+1}) \beta^+_p V \right), \tag{17}$$

$$V_j = \left( \bar{X}_j \tilde{W}^j U + 2 \beta_j (Y - \bar{Y}^i \beta_{i+1} U - \tilde{\beta}_j VU'U) \right), \tag{18}$$

$$\beta = ( (UV')^+_+ \lambda_1 I)^{-1} (UV')^+_+. \tag{19}$$

Based on (17), (18) and (19), we alternately update $U, V$ and $\beta$ until certain termination criterion is met.

4 Experiments

In the previous section, we have introduced several solutions to the problem of learning with positive and unknown features. In this section, we evaluate and compare the performance of these solutions, as indirect evidence on the appropriateness of the ‘unreported-is-negative’ assumption. To better interpret the experimental results, recall the DSL protocol assured a general separability of two classes, as illustrated in the left of Figure 2.

![Fig. 2. Distributions of feature-complete sample $X$ (left) and feature-incomplete sample $\tilde{X}$ (right). In both figures, the two axes are projections of samples on their two leading principal directions.](image)

Fig. 2. Distributions of feature-complete sample $X$ (left) and feature-incomplete sample $\tilde{X}$ (right). In both figures, the two axes are projections of samples on their two leading principal directions.

4.1 A Toy Dataset

In reality it is difficult (if not impossible) to collect ground truth on the missing features. To better understand our new problem and the introduced approaches, we first perform experiments on a synthetic data set.

The data set consisted of 200 examples described by 50 binary features defined on $\{0, 1\}$, and the examples were equally divided into a positive class and a negative class. The examples were generated by the following random protocol: the first 10 features of positive data and the last 10 features of negative data were i.i.d. drawn from a Bernoulli distribution with probability 0.4, and all remaining features were i.i.d. drawn from Bernoulli with probability 0.2. This protocol assured a general separability of two classes, as illustrated in the left of Figure 2.

To simulate the scenario of learning positive and unknown features, in sample matrix $X$ we hid all value 0’s and a fraction $\delta$ of value 1’s, resulting in a feature-incomplete matrix $\tilde{X}$. The locations of hided values were assumed unknown. Now, by adopting the ‘unreported-is-negative’ assumption, we replaced all unknown (hidden) values with 0, and the resulted new sample distribution with $\delta = 25\%$ was shown in the right of Figure 2.

Comparing the two distributions in Figure 2, we see the ‘unreported-is-negative’ assumption is likely to mislead learning by pushing data from two classes towards each other and hence reducing class separability. This would increase the difficulty of learning and, in a worst case,
significantly bias the decision boundary\(^1\). This was further confirmed in Figure 3, where we reported performance of the DSL approach on sample \((X, Y)\) under different settings of \(\delta\). We saw the performance degraded as \(\delta\) increased, i.e. as more missing features of value 1 were mis-assumed as 0.

Finally, we benchmarked the performance of all approaches on \(\hat{X}\). The hyper-parameters were grid-searched by the following protocol: the regularization coefficients \(\lambda_1, \lambda_2\) were searched over \(\{0.01, 0.1, 1, 10, 50\}\); the rank \(r\) of the factorization model was searched over \(\{10, 20, 30, 40, 50\}\); the constant \(\delta_w\) used in wALS was searched over \(\{0.2, 0.5, 0.8\}\); the sampling rate \(\delta_s\) of negative examples used in mean imputation was searched over \(\{0.1, 0.3, 0.5, 0.7\}\). For each approach, its best performance over searched hyper-parameters was reported. For evaluation, we randomly selected 75\% labeled examples for training and used the rest for testing. All approaches were performed over 10 random choices of training samples and the averaged performance was shown in Table 1. The FULL approach is an ‘ideal’ baseline which assumes no missing feature and performs standard predictive learning – it is also equivalent to performing DSL on \((\hat{X}, Y)\) with \(\delta = 0\).

From Table 1 we observed the performance of all approaches degraded, as more features were missing (i.e. as \(\delta\) increased). The performance of OCSL and JOCSL were slightly better than DSL, suggesting their efforts in recovering missing features had positive impacts. We did, however, notice the performance improvements were marginal and conjectured this may be largely due to the fact that features were generated independently, hence the feature matrix did not have low rank as assumed by the o.c.c.f. recovery technique used in OCSL and JOCSL. In addition, JOCSL performed slightly better than OCSL, suggesting the joint framework had positive impact on prediction performance. Again, the improvements appeared marginal, probably due to the feature independency. Finally, the ISL approach performed poorly on this data set, and we conjectured this was partly due to the random missing pattern.

The experiment on synthetic data set had revealed some trends: that one could indeed suffer performance loss by the ‘unreported-is-negative’ assumption, and one could indeed gain performance improvement by explicit recovery of un-reported profiles, in particular, by the joint profile recovery and predictive learning framework\(^2\).

What this experiment did not revealed was whether the performance improvement could be significant – it showed the improvements were marginal, and we believed this was mainly due to the dependency between features and completely random missing pattern. As we experimented on real-world data sets where these conditions were less likely to hold, we observed more significant performance improvement. This will be clear in the next two sections.

### 4.2 Real-World Data Set: Experiment One

In this section, we evaluated the prediction performance of all approaches on a real-world cheminformatics data set.

We collected the data set from the popular Laboratory of Molecular Modeling and Design (LMMD) repository [9]. Our data set contained interaction information between 203 drugs and two sets of proteins, namely, 95 Enzyme proteins and 240 GCPR proteins. We treated each drug as an instance, its interactions with Enzyme proteins as features, and its interactions with GCPR proteins as labels. In other words, our task is to predict a drug’s interaction with GCPR proteins based on its interactions with Enzyme proteins.

Now, the problem is that LMMD repository only provides positive interaction information, and a common assumption is that unreported interactions are negative (i.e. the drug and the protein does not interact). For better understanding the issue, we took a snapshot of the data repository and showed in Table 2. It can be seen drug 10161 interacts with protein D00528, and thus their interaction information will be encoded as 1 in the feature matrix. However, as the interaction between drug 10800 and protein D00528 is not reported, they are commonly assumed not to interact and their interaction information will be encoded as 0. This is the ‘unreported-is-negative’ assumption. Our following experimental results suggests its inappropriateness.

For evaluation, we selected 10 GPCR proteins to formalize 10 separate learning tasks. Since the data set is highly imbalance with most labels being negative, we selected 10 tasks having the most positive examples, and then randomly down-sampled the negative examples until the two classes had equal number of examples.

In each task, we evaluated the performance of all approaches. Their hyper-parameters were grid-searched as

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1. Of course, in Figure 2 the distribution was not terribly distorted, partly because the missing pattern was completely random.

2. An interesting observation was JOCSL even outperformed FULL when the missing features were few (\(\delta = 25\%\)), suggesting it may provide a better way to control model complexity to avoid over-fitting.

### Table 1

Classification Accuracy on Synthetic Data Set

<table>
<thead>
<tr>
<th>Method</th>
<th>(\delta = 25%)</th>
<th>(\delta = 50%)</th>
<th>(\delta = 75%)</th>
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<tbody>
<tr>
<td>FULL</td>
<td>0.810 ± 0.055</td>
<td>0.810 ± 0.055</td>
<td>0.810 ± 0.055</td>
</tr>
<tr>
<td>DSL</td>
<td>0.800 ± 0.059</td>
<td>0.742 ± 0.042</td>
<td>0.714 ± 0.047</td>
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<tr>
<td>ISL</td>
<td>0.548 ± 0.071</td>
<td>0.540 ± 0.072</td>
<td>0.556 ± 0.075</td>
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<tr>
<td>OCSL</td>
<td>0.812 ± 0.068</td>
<td>0.744 ± 0.043</td>
<td>0.720 ± 0.074</td>
</tr>
<tr>
<td>JOCSL</td>
<td>0.826 ± 0.068</td>
<td>0.756 ± 0.038</td>
<td>0.726 ± 0.050</td>
</tr>
</tbody>
</table>

### Table 2

Drug Interaction with Enzyme Proteins

<table>
<thead>
<tr>
<th>Drug ID</th>
<th>Protein ID</th>
<th>Interaction</th>
</tr>
</thead>
<tbody>
<tr>
<td>hsa:10161</td>
<td>D00528</td>
<td>positive</td>
</tr>
<tr>
<td>hsa:10800</td>
<td>D00411</td>
<td>positive</td>
</tr>
<tr>
<td>hsa:10800</td>
<td>D01828</td>
<td>positive</td>
</tr>
<tr>
<td>hsa:10800</td>
<td>D05129</td>
<td>positive</td>
</tr>
</tbody>
</table>
equals the number of reported positive interactions; and so that the number of (assumed) negative interactions form on a data set with no missing features. To examine this problem of learning with positive and unknown features, we were left wondering how the JOCSL approach may perform in addressing the issue of learning with positive and unknown features. This may be because many unreported profiles were indeed negative, largely validating the ISL assumption that its random selection of unreported profiles were negative. Finally, the deficiency of the ‘unreported-is-negative’ assumption. Second, the ISL and OCSL approaches performed better than DSL, suggesting the effectiveness of explicit profile recovery. What turned out surprising was ISL gave much more descent performance on the real-world data set, as compared with its performance on the synthetic data set. This may be because many unreported profiles were indeed negative, largely validating the ISL assumption that its randomly selected unreported profiles were negative. Finally, our proposed JOCSL approach consistently achieved the best performance, suggesting the effectiveness of such joint profile recovery and predictive learning framework.

4.3 Real-World Data Set: Experiment Two

In the previous two experiments, we had demonstrated the deficiency of the ‘unreported-is-negative’ assumption, and the effectiveness of the JOCSL approach in addressing the problem of learning with positive and unknown features. We were left wondering how the JOCSL approach may perform on a data set with no missing features. To examine this issue, we continued the previous experiment setting, except this time using the drug descriptors as complete features for predicting the drug interactions with the 10 GPCR proteins. The drug descriptors were the MACCS and EFP fingerprints of the drugs in the GPCR data set, which we extracted from their sdf structures collected from Drugbank by using the PaDel descriptor software [10].

The experimental protocol remained the same as before, and the new results were reported in Table 4. A similar trend was observed here, that DSL gave the worst performance, ISL and OCSL effectively improved performance, and JOCSL consistently achieved the best performance. The result showed JOCSL could perform well even on complete features – this should make sense, if one re-interprets the feature recovery component as a low-dimensional feature learning component which could remove noise; this may also suggest the joint framework provide a more effective way of controlling model complexity to avoid over-fitting.

4.4 On the Performance of JOCSL

In this section, we took more careful examination on the behavior of the JOCSL approach, and reported its sensitivity to various hyper-parameters in Figure 4 and Figure 5. The experiments were performed on the LMMD data set constructed in section 4.2, but only on the task which had most positive examples. All performance were obtained by averaging results of 4-fold cross validation on the data set.

Figure 4 shows the performance of JOCSL under different combinations of two regularization coefficients – recall $\lambda_1$ is for controlling the predictive model complexity, and $\lambda_2$ is for controlling the profile recovery model complexity. We see JOCSL performs well across a broad range of

### Classification Accuracy on Real-World Data Set

<table>
<thead>
<tr>
<th>Method</th>
<th>Task</th>
</tr>
</thead>
<tbody>
<tr>
<td>ISL</td>
<td>1</td>
</tr>
<tr>
<td>DSL</td>
<td>2</td>
</tr>
<tr>
<td>OCSL</td>
<td>3</td>
</tr>
<tr>
<td>JOCSL</td>
<td>4</td>
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</table>

<table>
<thead>
<tr>
<th>Task</th>
<th>1</th>
<th>2</th>
<th>3</th>
<th>4</th>
<th>5</th>
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<th>7</th>
<th>8</th>
<th>9</th>
<th>10</th>
</tr>
</thead>
<tbody>
<tr>
<td>ISL</td>
<td>0.564 ± 0.12</td>
<td>0.513 ± 0.12</td>
<td>0.523 ± 0.13</td>
<td>0.479 ± 0.16</td>
<td>0.592 ± 0.15</td>
<td>0.513 ± 0.13</td>
<td>0.483 ± 0.26</td>
<td>0.525 ± 0.15</td>
<td>0.491 ± 0.18</td>
<td>0.553 ± 0.10</td>
</tr>
<tr>
<td>DSL</td>
<td>0.509 ± 0.11</td>
<td>0.380 ± 0.11</td>
<td>0.454 ± 0.11</td>
<td>0.521 ± 0.09</td>
<td>0.454 ± 0.09</td>
<td>0.487 ± 0.11</td>
<td>0.417 ± 0.17</td>
<td>0.550 ± 0.13</td>
<td>0.591 ± 0.12</td>
<td>0.465 ± 0.17</td>
</tr>
<tr>
<td>OCSL</td>
<td>0.500 ± 0.13</td>
<td>0.440 ± 0.11</td>
<td>0.531 ± 0.11</td>
<td>0.550 ± 0.11</td>
<td>0.492 ± 0.17</td>
<td>0.587 ± 0.13</td>
<td>0.467 ± 0.15</td>
<td>0.575 ± 0.12</td>
<td>0.646 ± 0.14</td>
<td>0.477 ± 0.17</td>
</tr>
<tr>
<td>JOCSL</td>
<td>0.564 ± 0.13</td>
<td>0.517 ± 0.09</td>
<td>0.562 ± 0.12</td>
<td>0.543 ± 0.12</td>
<td>0.615 ± 0.10</td>
<td>0.600 ± 0.10</td>
<td>0.508 ± 0.14</td>
<td>0.592 ± 0.08</td>
<td>0.700 ± 0.14</td>
<td>0.529 ± 0.12</td>
</tr>
</tbody>
</table>

### Classification Accuracy on Real-World Data Set

<table>
<thead>
<tr>
<th>Method</th>
<th>Task</th>
</tr>
</thead>
<tbody>
<tr>
<td>ISL</td>
<td>1</td>
</tr>
<tr>
<td>DSL</td>
<td>2</td>
</tr>
<tr>
<td>OCSL</td>
<td>3</td>
</tr>
<tr>
<td>JOCSL</td>
<td>4</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Task</th>
<th>1</th>
<th>2</th>
<th>3</th>
<th>4</th>
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<th>7</th>
<th>8</th>
<th>9</th>
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</thead>
<tbody>
<tr>
<td>ISL</td>
<td>0.473 ± 0.19</td>
<td>0.567 ± 0.10</td>
<td>0.515 ± 0.08</td>
<td>0.521 ± 0.19</td>
<td>0.485 ± 0.08</td>
<td>0.520 ± 0.12</td>
<td>0.492 ± 0.18</td>
<td>0.542 ± 0.14</td>
<td>0.518 ± 0.11</td>
<td>0.488 ± 0.10</td>
</tr>
<tr>
<td>DSL</td>
<td>0.536 ± 0.13</td>
<td>0.533 ± 0.17</td>
<td>0.539 ± 0.19</td>
<td>0.371 ± 0.12</td>
<td>0.439 ± 0.12</td>
<td>0.513 ± 0.08</td>
<td>0.408 ± 0.09</td>
<td>0.408 ± 0.12</td>
<td>0.455 ± 0.13</td>
<td>0.441 ± 0.11</td>
</tr>
<tr>
<td>OCSL</td>
<td>0.636 ± 0.11</td>
<td>0.493 ± 0.16</td>
<td>0.577 ± 0.16</td>
<td>0.514 ± 0.13</td>
<td>0.546 ± 0.10</td>
<td>0.540 ± 0.14</td>
<td>0.492 ± 0.09</td>
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<td>0.535 ± 0.07</td>
</tr>
<tr>
<td>JOCSL</td>
<td>0.636 ± 0.12</td>
<td>0.527 ± 0.09</td>
<td>0.592 ± 0.17</td>
<td>0.507 ± 0.15</td>
<td>0.554 ± 0.11</td>
<td>0.553 ± 0.12</td>
<td>0.575 ± 0.14</td>
<td>0.600 ± 0.19</td>
<td>0.555 ± 0.14</td>
<td>0.571 ± 0.12</td>
</tr>
</tbody>
</table>
5 DISCUSSIONS

This paper aims to caution cheminformatics practitioners not to take the popular ‘unreported-is-negative’ assumption for granted. From a machine learning perspective, we presented empirical evidence on how it may degrade predictive performance on real-world cheminformatics data set, and instead how proper and explicit recoveries of unreported profiles may improve the predictive performance.

This work was actually inspired by our earlier study on social network analysis [11]. When clustering nodes on social graphs, we noticed a sparse graph might be interpreted as having missing edges but had no idea which edges were missing. If one models the graph by a binary adjacent matrix of its nodes, with value ‘1’ indicating an edge between two nodes and ‘0’ otherwise, then the adjacent matrix is the same as the incomplete feature matrix considered in this paper (with the same missing pattern). In [12], we were investigating the impact of such missing pattern on the clustering task, and became curious how it might affect the supervised learning task, which motivated the problem setting considered in this paper.

This work considered a supervised learning setting, where binding profiles of one compound family were directly used as features to train models that predict binding profiles of another compound family. This choice is largely inherited from the previous study on social network analysis, and to some extent simplifies analysis. A similar but more complicated setting has been studied in the cheminformatics literature (e.g. [13], [14], [15]), where binding profiles were indirectly used as features to train models that predict unknown binding profiles. (For instance, profiles were used to construct a kernel matrix based on which standard supervised learning was performed.) We conjecture similar conclusions would be found under more complicated settings, but leave investigations for future study.

The technical developments of this work were based on the regularized linear regression model not only due to its popularity in machine learning but also for convenience (e.g. the proposed joint approach admits close-form update formula). However, our key point is not that linear regression is a best supervised learning model for predicting binding profiles, but (1) assuming all unreported profiles are negative is dangerous, (2) proper recoveries of unreported profiles improve performance and (3) it would be better to perform recovery and supervised learning jointly instead of separately. More practically, our study suggested one at least perform OCCF first to recover unreported profiles before using them to construct kernel matrices in [13], [14], [15]. It further suggested unify the processes of profile recovery and supervised learning in the methodology development.

We should also mention the presented study assumed unreported profiles in both training and testing data, and focused on profile recovery in training data only. It remains an open question on how to effectively recover unreported profiles in testing data, and whether that could bring significant improvement on the classification accuracy.

Finally, the optimization of JOCSL was not investigated in detail in this paper. For hyper-parameters, we used grid-search to find best candidate combinations, but in practice one could use cross-validation to find combinations configurations, suggesting its stability in performance. In addition, JOCSL performs well when \( \lambda_1 \leq 1 \) but \( \lambda_2 \leq 0.01 \), which seems to suggest for JOCSL controlling predictive model complexity is relatively more important than controlling recovery model complexity. This partly support our earlier suspect that accurate feature recovery may not be as important as one thinks for accurate predictive learning.

Figure 5 shows the performance of JOCSL under different combinations of two weights – recall weight \( \alpha \) is for balancing predictive learning and feature recovery, and weight \( \delta_w \) for setting the confidence of assuming unreported profiles are negative. Again, we see JOCSL performs well on a broad range of configurations. Second, the best performance were achieved when \( \delta_w \) was relatively high, implying many unreported profiles might be negative. (Note this does not unnecessarily profile recovery, as evidenced in Table 3 and Table 4.) It was noted the best performance was not achieved at the largest \( \alpha \), partly implying the importance of feature recovery. An interesting observation was that when \( \alpha \) was large, JOCSL performed better with larger \( \delta_w \). This seemed to be suggesting that, if one wishes to focus on predictive learning, one should place more confidence on assuming unreported profiles were negative (even though this may not be resulting in the globally optimum performance).
with probably better generalization abilities. One may also consider adding some hyper-parameters to the automatic optimization process (e.g. [16], [17]) by developing more sophisticated algorithms. For optimizing parameters, we alternately updated $U$, $V$ and $\beta$, but one may also first focus on updating $U$ and $V$ (recovering unreported profiles first) and then add the update of $\beta$ in the loop.

6 Conclusion

In this paper, we present empirical evidence on the deficiency of a popular cheminformatics assumption that unreported binding profiles are negative. Under a problem setting where incomplete profiles were used as features to train predictive models, we showed explicit recovery of unreported profiles improved predictive performance. We then proposed an approach that jointly recover profiles and learn predictive models, which showed further performance improvement. Our problem setting turned out novel as we survey related topics in the literature, and we called it learning with positive and unknown features.

Appendix A

Review: One-Class Collaborative Filtering

The one-class collaborative filtering (o.c.c.f.) problem was arguably first coined by Pan [5]. It aimed to predict users' binary feedbacks on products (e.g. 'like' or 'dislike') based on their known feedbacks on other products, but faced the challenge that only positive feedbacks were known – for instance, the system only showed which users 'like' which products, but not who 'dislike' which products. Unlike traditional solutions that confidently assumed all unknown feedbacks were negative, Pan proposed to weight this confidence and incorporated the weight into the matrix-factorization based prediction method. In the same year, a similar problem was considered by Hu [18] under slightly different context. It seemed both Pan's and Hu's works were considered to pioneer the o.c.c.f. problem in the literature.

A main line of research cast o.c.c.f. as a matrix completion problem (i.e. completing the missing feedbacks in user-product feedback matrix), and adopted the matrix factorization technique for completion. The technique factorizes an incomplete feedback matrix into a user-specific factor and a product-specific factor under proper constraints, and treated the product of these factors as the completed feedback matrix. Representative works include both Pan and Hu's approaches, where unknown feedbacks were treated as negative but with weighted confidence; Pan [19] also proposed a low-rank approximation method to improve the scalability of the matrix factorization technique; Sindhwani [20] proposed to jointly estimate the factors and predict the unknown feedbacks based on the non-negative matrix factorization technique; Vinagre [8] proposed to sample for each possible feedback a set of unknown feedbacks and treat them as negative; Zhao [21] replaced the user-specific factors with one projection matrix per user, which embodies the user's personal item preference; Liu [22] introduced a boosting framework which builds each factorization model based on a permuted feedback matrix.

For enhancing the performance of matrix factorization techniques, several researchers proposed to incorporate side information, such as users' search query history, purchasing and browsing activities as proposed by Li [23], the user and item profiles as proposed by Fang [24], and the user-user and item-item graphs as proposed by Yao [25].

Another line of research cast o.c.c.f. as a problem of ranking products under proper constraints induced from known feedbacks, and adopted the Bayesian method for ranking. The idea was first proposed by Rendle [26], who made the pair-wise assumption that each user's unobserved products should rank no higher than his observed products; Pan [27] extended this assumption from a single user to a group of users for injecting richer user interactions, and Xu [28] replaced this assumption with one that biases ranking by user-generated content; Yao [29] proposed to incorporate meta-data on products to improve the ranking performance on sparse feedback matrix. The scalability of this set of approaches was addressed by Paquet [30] based on a distributed learning framework.

In addition to the above two lines of research, other feedback predictions approached included nearest neighbor as proposed by Pappas [31] and Verstegen [32], and LRece proposed by Sedhain [6]. Recently, a theoretical study was presented by Hsieh [33], where he proved upper error bounds for recovering such incomplete feedback matrix.

It is also noted o.c.c.f has found broad applications in recommending scientific articles [34], Top-N product recommendation [35], predicting drug-target interaction [36], location recommendation [37] and job recommendation [38].

While the literature of o.c.c.f. continues to grow rich, we did not notice its interplay with feature-based classification problems, although many incomplete feature matrices may inherit the one-class nature. It would be helpful to understand if o.c.c.f. would suffice to address these problems, and what improvements could be made. Our study in this paper is an attempt to advance the research in this direction.

Appendix B

Review: Positive and Unlabeled Learning

B.1 Studies in General Contexts

The research on positive and unlabeled learning (p.u.l.) problem has a long history. The problem considers learning to classify data into a positive class and a negative class, but faces the challenge that training sample only contains positive data and (usually) unlabeled data.

We traced the p.u.l. research back to Muggleton’s work in 1997 [39], where he proved the error bound of learning from positive data alone. Under the p.u.l. setting, Denis proved DNF and decision tree were PAC learnable [40] and had the respective algorithms developed in [41], [42].

A notable line of p.u.l. research focused on developing two-step solutions – in the first step, an identifier selected a subset of ‘reliable’ unlabeled data and confidently assumed they were negative data; in the second step, a classifier was trained (iteratively) with both positive data and the identified negative data. For instance, Liu [43] used naive Bayes model as both the identifier and the classifier, and proved the sample complexity of the developed learner; Yu [44] used 1-DNF as the identifier and SVM as the classifier,
and speeded up his approach in [45] and addressed its over-iteration problem in [46]; Li [47] used Ricchio method as the identifier for its robustness and SVM as the classifier; while previous studies largely ignored unreliable negative data, Xiao [48] added them into learning by carefully weighting these data based on their similarities.

A more recent line of research assumed all unlabeled data were negative but with weighted confidence. For instance, Lee [49] proposed a weighted logistic regression that treated all unlabeled data as negative data with label noise; Liu [50] proposed a SVM-style learner which treats all unlabeled data as negative but suffers weighted loss (the learner was showed equivalent to a two-step method with naive bayes as the identifier and SVM as the classifier); a generative version of both above approaches was proposed by Zhang [51], who also improved the SVM-style learner in [52]; Elkan [53] proposed a principled scheme to weight the unlabeled data under proper assumptions.

A group of studies focused on addressing the challenge that positive data could be scarce. In the context of text classification, Denis [54] addressed this problem by first mapping the documents to a layer of words and then to the class labels, provided that the positive class prior was known. He later extended this method to a multi-view version in [55], and Calvo [56] also refined this method on its classifier and prior probability estimation. Liu [57] proposed a framework similar to [54], but instead carefully selected those key words that were manually associated with class labels; he later relaxed the manual labeling in this method to automatic labeling in [58]; Fung [59] tackled the scarce positive data challenge by additionally labeling reliable positive data from the unlabeled data set.

We noted p.u.l. had been cast and addressed from an outlier detection point of view. A popular solution was the one-class SVM proposed by Scholkopf [60], which finds a decision boundary that separates the positive data from the origin; Manevitz [61] refined this idea by replacing the origin with a neighborhood of the origin that consists of unlabeled ones, and Vert [62] proved its consistency as a density level set estimator. Another popular method was proposed by Tax [63], who used support vectors to construct a spherical decision boundary that covers the positive data; he later refined its error estimation by generating negative data [64]; this idea was also adopted by Manevitz [65] who developed a one-class neural network which restricts the search space for covering positive data.

The p.u.l. problem has also been studied jointly with other machine learning topics. For instance, He [66] studied p.u.l. with uncertain data; Pelckmans studied p.u.l. in a transductive setting [67]; Li studied p.u.l. in the online setting [68], [69]; Ghasemi proposed active solution for p.u.l. [70]; Mordelet proposed ensemble learning solution for p.u.l. [71]; Li [72] addressed the problem that distributions of positive data may be different in the observed training sample and the unlabeled data set; more recently, Plessis [73] suggested that in p.u.l., non-convex loss function is better than convex loss function since the latter may mislead the classification boundary; (we were all relieved) he later corrected this argument by finding a convex formula which does not mislead the boundary [74].

Finally, there has been an increasing application of p.u.l., ranging from image retrieval [75], remote sensing [76], blog classification [77], graph classification [78], deceptive review detection [79], [80], [81], name entity recognition [82], entity-attribute query [3], cross-modal retrieval [83], activity recognition [84], computer security event extraction [85] to bioinformatics [4], [86], [87].

While extensive research has been done on the p.u.l., to our knowledge they all focused on positive and unknown labels, but no work considered positive and unknown features (which is the focus on this paper). Under different settings, these once ‘labels’ could be used as ‘features’ for other tasks, and it would be helpful to understand their impact on learning. Our study in this paper is an attempt to advance the research in this direction.

B.2 Studies in the Context of Cheminformatics

Studies of PUL learning in cheminformatics can be broadly categorized into (i) drug-drug, protein-protein or drug-target interactions [88] [89](ii) disease-gene identification [90] [87]

In the first category, drug-drug interactions (DDI) or drug-target (DTI) studies are vital when more than one drug is administered together or each drug has the potential to modulate more than one target. Known interactions are utilized in a PUL setting to infer new associations since verified negative interactions are very few. Hameed et al., proposed a PUL method to identify P450 cytochrome dependent and P450 cytochrome independent DDIs by integrating GSOM (growing self organizing maps) and SVM [91]. The GSOM is used to cluster drugs to identify potential negative DDIs and then use an SVM classifier to build a model using positive DDIs and the identified negative DDIs. Cheng et al., used biased-SVM to predict compound-protein pairs in which the strategy is to use a pair of spherical hyperplanes such that the inner sphere tries to accomodate as many positive interactions as possible and the outer plane tries to push the negative samples out of the sphere [92]. Tsai et al., adopted a similar data level preprocessing to identify likely positive samples from U and use SVM to identify protein-protein interactions [93]. The second category of work that utilizes PUL is to identify disease genes. Yang et al., [94] proposed an ensemble PU method that first identifies reliable negative and positive samples from U and estimates the weight of the rest of the samples in U by a random walk approach. They exploit multiple biological spaces (gene expression, GO similarity and PPI) by building a network on each one of them to estimate the gene weights. The gene weights obtained from each network is then used to learn a classifier using positive and weighted unlabeled samples. They use weighted KNN, weighted Naive Bayes and SVM and combine the outputs from these classifiers for final predictions. ProDiGe is a state of the art algorithm that ranks genes for disease in a multi-task PUL setting. This model enforced similar diseases to share gene information not just across a single source but across multiple sources where each source characterizes a gene [95]. The gene information was shared in a weighted manner across diseases where the weights are proportional to the the similarity of diseases.

References


[36] H. Yu, J. Han, and K. C.-C. Chang, “Pebbl: positive example based learning for web page classification using svm,” in *Conferences on Knowledge Discovery and Data Mining (KDD)*, 2002.


