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Original Paper

Drug Clearance Pathway Prediction Based on Semi-supervised Learning

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Abstract: It is necessary to confirm that a new drug can be appropriately cleared from the human body. However, checking the clearance pathway of a drug in the human body requires clinical trials, and therefore requires large cost. Thus, computational methods for drug clearance pathway prediction have been studied. The proposed prediction methods developed previously were based on a supervised learning algorithm, which requires clearance pathway information for all drugs in a training set as input labels. However, these data are often insufficient in its numbers because of the high cost of their acquisition. In this paper, we propose a new drug clearance pathway prediction method based on semi-supervised learning, which can use not only labeled data but also unlabeled data. We evaluated the effectiveness of our method, focusing on the cytochrome P_{450} 2C19 enzyme, which is involved in one of the major clearance pathways.

Keywords: drug clearance pathway prediction, drug discovery support, machine learning, semi-supervised learning

1. Introduction

Drug development is a time-consuming and expensive process. More than 10 years and tens of billion dollars are required for approval of a new drug [1]. One of the reasons for this time lag and large cost is that many candidate drug compounds are retracted in the later stage of development because of safety issues, including side effects, insufficient clearance, and so on. Thus, to reduce the cost of drug development, appropriate selection of compounds based on the safety of a drug in the early stage of development is a very effective strategy, especially if determined before the compound synthesis stage.

Drug clearance pathway prediction is one of the main computational methods used to determine a drug's safety. In general, the method predicts whether a chemical compound is cleared from the human body by a target clearance pathway. Common clearance pathways include metabolism and excretion pathways such as those involving cytochrome P_{450} (CYP), organic anion transporting polypeptide (OATP), and others. Several drug clearance pathway prediction methods have been established to date. For example, Sorich et al. proposed a prediction method for UDP-glucuronosyl transferase (UGT) excretion pathway [2], and Hammann et al. proposed a prediction method for 3 types of CYP metabolism pathways [3]. Furthermore, Hotta et al. proposed a prediction method for multiple pathway categories, including the CYP, OATP, and renal excretion (Renal) pathways, simultaneously [4].

These drug clearance pathway prediction methods are based on supervised learning techniques, which are currently the most popular method for drug clearance pathway prediction. In supervised machine learning, the algorithm constructs a prediction model using labeled data, for which correct values are already known, and then predicts labels of unknown data using the prediction model. Various algorithms have been applied for clearance pathway prediction, such as the rectangular boundary method [5], support vector machine (SVM) [6], [7], and Boosting [8] algorithms. According to previous studies, the SVM appears to be the best algorithm for this prediction problem [6]. However, the prediction accuracies are still insufficient for several pathways. One of the clear reasons for this insufficient prediction accuracy is insufficiency in the training data. It is difficult to increase the amount of labeled data because expensive wet experiments and clinical trials are required for determining the clearance pathways of a drug.

The semi-supervised learning method can be used for both labeled, and unlabeled data for which correct values are unknown in the training process. The effectiveness of the semi-supervised learning method has been confirmed in several fields, such as network traffic classification [9] and video annotation [10]. However, the semi-supervised learning method has not been applied for drug clearance pathway prediction though many prediction methods based on supervised learning method have been proposed. In clearance pathway prediction, unlabeled data are easily obtained because information for a vast amount of compounds can be gathered from public databases such as ZINC [11], PubChem [12], and DrugBank [13]. Therefore, the semi-supervised learning method would be suitable for drug clearance pathway prediction.

Here, we propose a novel drug clearance pathway prediction method based on the semi-supervised learning algorithm. We focus on CYP2C19, one of the major clearance pathways, as a prediction target. Prediction of CYP2C19 clearance pathway is

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technically difficult because of insufficient number of compounds that are known to be metabolized by CYP2C19 or not. In fact, the number of known compounds metabolized by CYP2C19 is currently only 10. Thus the supervised learning is not suitable for this prediction. Additionally, CYP2C19 has genotypes of two mutations, and approximately 25% of the Japanese population are genotypically identified as poor metabolizers [14]. This means that if these individuals take a drug that is metabolized by CYP2C19, the drug will not be appropriately cleared. Therefore, prediction of this clearance pathway is important.

2. Drug Clearance Pathway Prediction Based on Semi-supervised Learning

2.1 Semi-supervised Learning

Semi-supervised learning is a machine learning method originated from the self-training algorithm proposed by Scudder [15]. The supervised learning method uses only labeled data for the training stage, and cannot use unlabeled data. By contrast, the unsupervised learning method uses only unlabeled data for the training stage. Some semi-supervised learning algorithms make clusters based on the unlabeled data and simultaneously make predictions based on the labeled data. Thus, better prediction can be obtained by using both labeled and unlabeled data. There are various semi-supervised learning algorithms, such as co-training [16], transductive framework [17], and Universum SVM [18].

In this study, we used a transductive SVM (TSVM) algorithm, which is an extension of the SVM algorithm based on a transductive framework. The TSVM algorithm was proposed by Joachims [19], and this algorithm has been already applied in some fields. For instance, the effectiveness of TSVM was confirmed in text-classification problem by Joachims [19]. In addition, Röttig et al. showed the algorithm was also useful for substrate specificity prediction, which is one of the bioinformatics problems [20]. Therefore, we considered that TSVM would also be effective in clearance pathway prediction. Details of the training algorithm are described below:

(1) The support vectors are constructed from only labeled data, as in the conventional SVM model.
(2) Based on the constracted SVM model, unlabeled data are classified into positive or negative. The number of positively classified unlabeled data is given as a parameter num+.
(3) The labeled and unlabeled data are given a penalty parameter, which is a weight for misclassification. The penalty for unlabeled data is smaller than that for labeled data.
(4) The support vectors are constructed again from both the labeled and unlabeled data.
(5) The unlabeled data are re-classified based on the new support vectors in the same manner as step (2).
(6) Step (4) and (5) are repeated until there is no change in any of the classified results.
(7) The penalty for unlabeled data is strengthened.
(8) Step (4) to step (7) are repeated.
(9) When the penalty for unlabeled data is equal to the penalty for labeled data, the training process is ended and the last support vectors are outputted.

As this algorithm suggests, if the number of unlabeled data entries is equal to 0, the TSVM algorithm works in the same way as the conventional SVM algorithm. Therefore, the comparison between the SVM and TSVM algorithms is easier than among other semi-supervised learning algorithms.

In this experiment, we used SVM^{light} v6.02 for implementation of both the SVM and TSVM algorithms [21].

2.2 Dataset

We adopted the dataset used in Toshimoto et al. [7] as the labeled data of this work. This dataset contains 240 compounds, which have the information whether the main clearance pathway is CYP2C19 or not. Notice that the label of each compound is decided by the main clearance pathway and is not decided by the metabolization by CYP2C19. This is because the main clearance pathway of a compound can be the other clearance pathway even if the compound is metabolized by CYP2C19. For instance, if a compound is metabolized by CYP2C19 but also metabolized by CYP3A4 and the CYP3A4 metabolization is dominant, then the main clearance pathway of the compound becomes CYP3A4. Thus, the dataset was labeled based on all possible clearance pathway information by investigation of published data. Therefore, the prediction based on this dataset is more worth than that based on raw metabolism information. In this dataset, 10 of the compounds are positively labeled and 230 of the compounds are negatively labeled.

In the TSVM algorithm, both unlabeled and labeled data are used in the training process. Ideally, both the labeled and unlabeled data should be sampled from the same population. However, the labeled data are often biased because the clearance pathways are generally determined only for drug candidates, and the distribution of labeled compounds might be different from that of whole chemical compounds. Thus, to reduce the influence of sampling from different populations, all of the unlabeled data were selected only from already approved drug compounds. We constructed an unlabeled dataset using the ZINC database, which is a popular public compounds database, and includes data for more than 35 million compounds. There are also data subsets in the ZINC database, and we used the ZINC drug database (zdd) subset, which consists of 2,924 FDA-approved drug compounds, including chiral compounds and duplicated compounds to the labeled data. We omitted these compounds because the chiral compounds cannot be distinguished using our method, and finally obtained 1,390 compounds as the unlabeled dataset.

2.3 Features

Kusama et al. used four features for the prediction: molecular weight (MW), octanol-water distribution coefficient (logD), protein unbound fraction in plasma (fup), and category of charge at neutral pH [5]. In this study, we essentially used the same features as those used in Kusama et al.: MW, logD, fup and charge. About charge, we used the difference between the number of positively charged atoms at neutral pH and the number of negatively charged atoms at neutral pH (charge) instead of the category of charge at neutral pH. These features were calculated by using PreADMET v2.0 software (Bioinformatics & Molecular Design

Research Center, South Korea).

3. Results

We constructed a prediction model using the SVM and TSVM algorithms, and performed evaluation experiments to check the performance of our proposed method.

3.1 Evaluation Measure

In this study, the number of positive and negative labels were imbalanced, and therefore accuracy, which is the ratio of correctly classified data, is an inappropriate measure for this evaluation. Thus, we employed the f-measure as the evaluation measure. The f-measure is the harmonic mean of precision and recall, and is useful for evaluating the performance of prediction based on an imbalanced dataset. Previous related studies also used the f-measure [4], [7], therefore making it suitable for comparison to previous work.

To calculate the f-measure, precision and recall values are required:

$$\text{Precision} = \frac{\#\text{TP}}{\#\text{TP} + \#\text{FP}} \tag{1}$$

$$\text{Recall} = \frac{\#\text{TP}}{\#\text{TP} + \#\text{FN}} \tag{2}$$

TP, FN, and FP represent the number of true positives, false negatives, and false positives, respectively. Thus, precision is the ratio of the number of positives that correctly predict to the number of predicted positives, and recall is the ratio of the number of positives that correctly predict to the number of all positives, which are predicted as both positives and negatives.

$$\text{F} = 2 \cdot \frac{\text{recall} \cdot \text{precision}}{\text{recall} + \text{precision}} = \frac{2 \cdot \#\text{TP}}{\#\text{FN} + \#\text{FP} + 2 \cdot \#\text{TP}} \tag{3}$$

Because it is based on the harmonic mean, a better f-measure is obtained when both the recall and precision are relatively high.

To calculate the evaluation measure, we used leave-one-out cross validation. If the number of labeled data entries is N, $N-1$ data entries are used as a training data and the remaining data entry is predicted. This training and prediction are repeated N times, and the results of each prediction are cumulated. The cumulated result is then used to calculate the evaluation measure.

3.2 Kernel Selection and Hyper-parameter Optimization

The selection of a kernel function and hyper-parameter optimization highly influence the performance of prediction in an SVM-based algorithm. In this study, we employed the Gaussian kernel shown below.

$$K(\boldsymbol{x}, \boldsymbol{z}) = \exp\left(-\gamma \| \boldsymbol{x} - \boldsymbol{z} \|^2\right) \tag{4}$$

$\boldsymbol{x}$ and $\boldsymbol{z}$ indicate the vectors of features. If these features are similar, the output of $K(\boldsymbol{x}, \boldsymbol{z})$ is higher; therefore, $K(\boldsymbol{x}, \boldsymbol{z})$ indicates the similarity of the two vectors.

When employing the Gaussian kernel, there are two hyper-parameters that need to be optimized: cost of the soft-margin parameter C, and the width parameter of the Gaussian kernel γ. The larger the cost parameter C and the width parameter γ, there is an increased likelihood of obtaining a more complicated hyperplane. For hyper-parameter optimization, we employed the following two steps.

global optimization First, we trained the TSVM and SVM for each combination of 20 patterns of parameter C and 20 patterns of parameter γ as follows:

$$\gamma = \{2^{-15}, 2^{-14}, \cdots, 2^3, 2^4\} \tag{5}$$

$$C = \{2^{-15}, 2^{-14}, \cdots, 2^3, 2^4\} \tag{6}$$

The best global parameters C_0 and γ_0 were obtained on the basis of the evaluation measure.

local optimization Second, we determined the best parameter using the results of global optimization. As for global optimization, we trained the TSVM and SVM for each combination of 24 patterns of parameters C and γ as follows:

$$\gamma = \{\gamma_0 \cdot 2^{-3}, \gamma_0 \cdot 2^{-2.75}, \cdots, \gamma_0 \cdot 2^{2.5}, \gamma_0 \cdot 2^{2.75}\} \tag{7}$$

$$C = \{C_0 \cdot 2^{-3}, C_0 \cdot 2^{-2.75}, \cdots, C_0 \cdot 2^{2.5}, C_0 \cdot 2^{2.75}\} \tag{8}$$

We obtained the best parameters C_{best} and γ_{best} from these combinations.

The number of positively classified unlabeled data num+ was decided by default manner. The default value of num+ is the number of unlabeled data multiplied by the ratio of positive examples in the labeled data.

3.3 Unlabeled Dataset

In the evaluation, we generated subsets of sizes 100, 200, 400, and 800 by randomly selecting from the unlabeled dataset including 1,390 compounds, and used these subsets in the training to confirm the influence of the number of unlabeled data entries and how many unlabeled data entries are needed for this prediction problem. In addition, we performed the random sampling ten times and checked the performance for each sample.

3.4 Results of the Evaluation Test

Table 1 and **Fig. 1** show the results of the evaluation test. Numbers in parentheses represent the numbers of unlabeled data entries. For the results of the TSVM, the averages and standard errors (S.E.) are shown for checking the influence of sampling bias of the unlabeled data. The best parameters of SVM and TSVM are also shown in Table 1. Because of the random sampling of unlabeled data, there are ten best parameters for each TSVM result. Therefore, the parameter when f-measure is the best in ten trials is shown as the best parameter of each TSVM. The results showed that the TSVM always performed much better than the SVM. The average f-measure was improved until reaching a size of 200 unlabeled data entries, and then appeared to be saturated. On the other hand, as the number of unlabeled data entries was increased, the S.E. of the f-measure was likely to decrease.

Table 1 Prediction result of pathway CYP2C19.

CYP2C19	f-measure		best parameter	
	average	S.E.	gamma γ	cost C
SVM	0.2941	—	$2^{1.25}$	$2^{-0.25}$
TSVM (100)	0.3506	0.0118	$2^{3.75}$	$2^{-4.5}$
TSVM (200)	0.3742	0.0140	2^{4}	2^{-2}
TSVM (400)	0.3586	0.0109	$2^{2.5}$	$2^{-0.5}$
TSVM (800)	0.3668	0.0072	2^{2}	$2^{-0.75}$

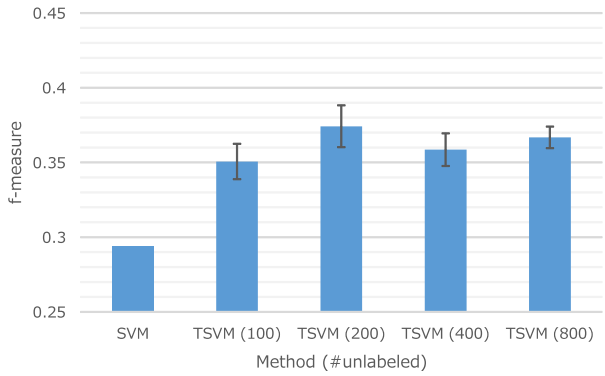

Fig. 1 Average and standard error of f-measure: CYP2C19.

Table 2 The result of the Student's *t*-test.

p-value	SVM	TSVM (100)	TSVM (200)	TSVM (400)
TSVM (100)	**0.0010**			
TSVM (200)	**2.9e-4**	0.2430		
TSVM (400)	**2.2e-4**	0.5003	0.3934	
TSVM (800)	**3.5e-6**	0.2281	0.6916	0.5456

To assess the statistical significance of the improvement in prediction given by the TSVM and the effectiveness of the increase of the unlabeled dataset, we analyzed the f-measures using the Welch's *t*-test and calculated p-values for all combinations. **Table 2** shows the results, and the values indicated in bold represent the values that are statistically significant ($p < 0.05$). The results showed that all p-values for differences between the SVM and TSVM were less than 0.05. This indicates that the improvement conferred by the TSVM was statistically significant regardless of the number of unlabeled data entries. In contrast, the p-values for differences among TSVMs with different sizes of the unlabeled dataset were not less than 0.05. These results indicate 100 is sufficient for the number of unlabeled data. According to Joachims [19], there is a limitation of improvement in prediction even when using a vast amount of unlabeled data, which suggests that this small unlabeled dataset is sufficient for the improvement of the prediction, and increasing the number of unlabeled data entries is not effective for this prediction problem.

4. Discussion

4.1 The Importance of Each Feature

Although 100 unlabeled data was sufficient for CYP2C19 clearance prediction as shown in the result section, the number of required unlabeled data would be different for other analyses and the number of unlabeled data should be optimized for each analysis. However, the optimization of the number of the unlabeled data for each case needs too heavy computation. Therefore, we fixed the number of unlabeled data to 800 in this section. As shown in the result section, the smallest p-value was obtained when 800 unlabeled data was used, and thus we considered that 800 unlabeled data might not be excess for all following analyses.

As previously described, we employed 4 features used in Kusama et al. [5]: MW, logD, fup and charge. However, it is not obvious which feature is important. To check it, we tried to predict CYP2C19 clearance based on 3 features (without 1 feature) and only 1 feature of the 4 features.

Table 3 shows the results. "N/A" means that we could not obtain the f-measure because software could not work correctly. According to these results, MW is the most important to predict CYP2C19 clearance, and logD and fup are less important. Additionally, the f-measure was not improved as the number of feature decreased. Thus all features are necessary, especially for semi-supervised learning.

Table 3 Importance of each feature: f-measure.

# features		SVM	TSVM (800)
4	all features	0.2941	0.3668
3	w/o MW	0.2667	0.3263
	w/o logD	0.2941	0.3430
	w/o fup	0.2941	0.3304
	w/o charge	0.2857	0.3331
1	MW	0.1714	0.1691
	logD	0.1455	N/A
	fup	0.1707	N/A
	charge	0.1404	0.1404

Table 4 Precision & recall: CYP2C19.

	precision		recall		f-measure	
	average	S.E.	average	S.E.	average	S.E.
SVM	0.2083	—	0.5000	—	0.2941	—
SVM (th = 0.13)	0.1500	—	0.3000	—	0.2000	—
TSVM (800)	0.4088	0.0217	0.3500	0.0224	0.3668	0.0072

4.2 Balance of Precision and Recall

If f-measure values are equivalent in two prediction methods, the precision and recall may nonetheless be different. Even if the performance is improved according to the f-measure, a large decrease of recall or precision can cause problems in some applications. Thus, we checked the precision and recall of the prediction results.

Table 4 shows the precision and recall values for the TSVM (800). The precision of the TSVM was higher than that of the SVM, whereas the recall of the TSVM became lower than that of the SVM. Therefore, the TSVM can be suitable for predicting a few compounds that are more likely to metabolize. Because there are millions of candidate compounds, whereas only hundreds or thousands of compounds can reasonably be tested in wet experiments, the ability to obtain a relatively small amount of compounds that are predicted to be most likely to metabolize is a very important feature of this model. Thus, we think that this characteristic of the TSVM makes it more desirable than the SVM.

4.3 ROC Analysis

As previously discussed, positive compounds should be ranked among the top hundreds or thousands. This means that it is more important to determine the true positive rate in a couple of percent of data that are top-ranked by prediction. This determination is called early enrichment. Unfortunately, since there are only a few labeled data entries, especially for the positive data, we could not stably obtain the positive rate in the top few percent of the data. Due to this limitation, we drew a receiver operating characteristic (ROC) curve based on the positiveness of the data (in this case, the decision values of the SVM and TSVM), and calculated the area under the curve (AUC) for the overall data and the top 10%. For distinction, the overall AUC is referred to as AUC (100%) and the top 10% AUC is referred to as AUC (10%) hereafter. To

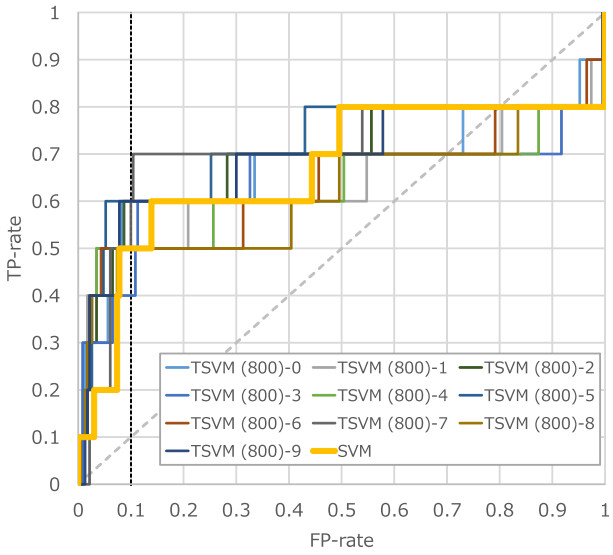

Fig. 2 ROC curve: CYP2C19.

Table 5 AUC value: CYP2C19.

	AUC (100%)	AUC (10%)
SVM	0.6665	0.0265
TSVM (800) (average)	0.6635	0.0393
(random)	(0.5000)	(0.0050)

draw the ROC curve, the FP-rate and TP-rate are required:

$$\text{FP-rate} = \frac{\#\text{FP}}{\#\text{FP} + \#\text{TN}} \tag{9}$$

$$\text{TP-rate} = \frac{\#\text{TP}}{\#\text{TP} + \#\text{FN}} \tag{10}$$

The ROC curve can be drawn once the positiveness of each tested data entry is obtained. To draw the curve, we added the data in order of their positiveness. If positive data are added, the TP-rate increases, whereas if negative data are added, the FP-rate increases. The ROC curve shows these changes as a line, and the curve describes the tradeoff between the TP-rate and FP-rate. Higher AUCs are obtained when the TP-rate is higher, even if the FP-rate is still low.

The ROC curves for the TSVM with 800 unlabeled data entries (TSVM (800)) and the SVM are shown in **Fig. 2**. There are 10 plots for the TSVM and one plot for the SVM. The diagonal dotted line shows the performance of random prediction, and the vertical dotted line shows the threshold for the top-ranked 10%. The results of the ROC analysis showed that the performance of the TSVM was comparable to that of the SVM in AUC 100% but was superior to the SVM in AUC (10%) (**Table 5**). This result suggests that the prediction improvement by the TSVM is more obvious in earlier enrichment, indicating it is effective for this type of prediction because of the importance of earlier enrichment described above.

4.4 Application of the Proposed Method to Other Clearance Pathways

Our results demonstrated that the TSVM is effective to predict the CYP2C19 clearance pathway. Thus, we also applied the method to other clearance pathways. We focused on five pathways: CYP2C9, CYP2D6, CYP3A4, Renal and OATP. These pathways were used by Kusama et al. [5]. The compounds used in this experiment were same as these used in our CYP2C19 experiment. **Table 6** shows the number of positively labeled data and negatively labeled data for five pathways. Just like Section 2.2, these labels of each compound were also decided by the main clearance pathway and were not decided by the metabolization or excretion by each pathway.

Table 6 The numbers of positives and negatives.

clearance pathway	positively labeled	negatively labeled
CYP2C9	17	223
CYP2D6	25	215
CYP3A4	79	161
Renal	69	171
OATP	18	222

Table 7 Prediction result of other pathways.

f-measure	SVM	TSVM (800) average	TSVM (800) S.E.	Kusama et al., 2010
CYP2C9	0.4151	0.4537	0.0110	0.1905
CYP2D6	0.6667	0.6940	0.0059	0.0606
CYP3A4	0.7630	0.7417	0.0018	0.5730
Renal	0.7361	0.7262	0.0021	0.7015
OATP	0.6667	0.6319	0.0110	0.6250
Average	0.6495	0.6495	—	0.4301

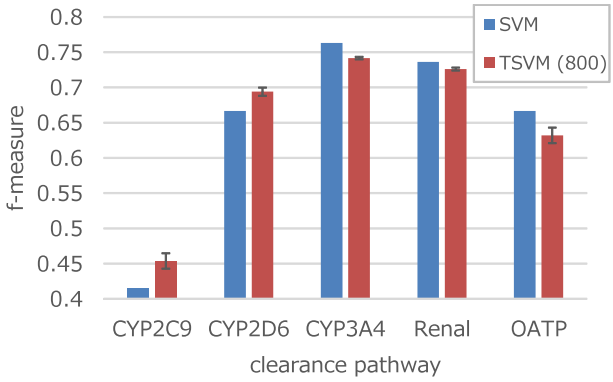

Fig. 3 Average and standard error of f-measure: other pathways.

The results with 800 unlabeled data entries are shown in **Table 7** and **Fig. 3**. The prediction results using Kusama et al.'s method are also shown in Table 7. The TSVM succeeded in improving the predictions for some pathways (CYP2C9, CYP2D6) compared with those of the SVM. However, the accuracy of prediction for the other pathways (CYP3A4, Renal, OATP) was equal to or worse than that of the SVM. The TSVM particularly improved the accuracy of the CYP2C9 pathway, which showed the worst f-measure among all of the tested pathways when the SVM was used. Although we cannot say for sure because of insufficient number of cases, this result indicates that the TSVM may improve the accuracy of prediction when that of the SVM is considerably insufficient.

To investigate the effect of the TSVM more deeply, we also drew an ROC curve for CYP3A4 prediction, which was worse when the TSVM was used compared to the SVM. ROC curves of CYP3A4 are shown in **Fig. 4** and the AUC values are shown in **Table 8**. According to the ROC curves and AUC values, the TSVM was worse than the SVM in terms of f-measure, whereas the TSVM was better than the SVM in terms of AUC (10%). The f-measure is calculated with respect to the points of the ROC curve lines, whereas the AUC is calculated using all or a par-

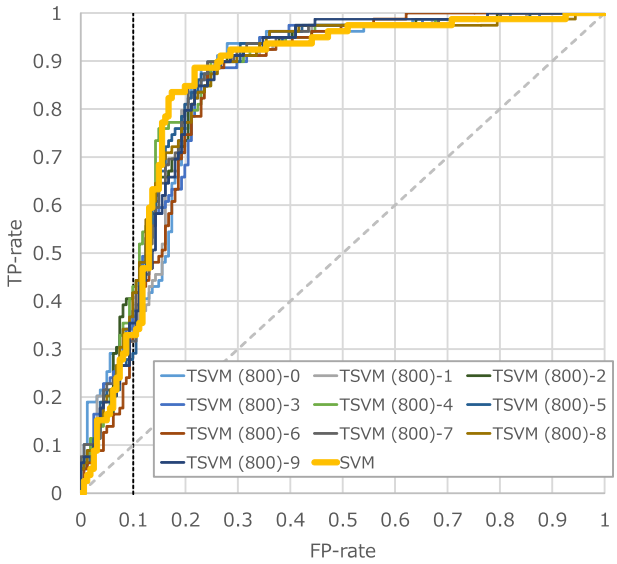

Fig. 4 ROC curve: CYP3A4.

Table 8 AUC value: CYP3A4.

	AUC (100%)	AUC (10%)
SVM	0.8499	0.0187
TSVM (800) (average)	0.8479	0.0215
(random)	(0.5000)	(0.0050)

ticular (for example 10%) area of the ROC curve. Therefore, if one method is much better on one point of the ROC curve, the f-measure would be drastically improved, while the AUC would be only slightly improved. In this case, the calculation point of the f-measure for SVM prediction of CYP3A4 is the point (FP-rate, TP-rate) = (0.2547, 0.8987). This point is slightly above the other TSVM ROC curves, which explains why the CYP3A4 f-measure based on the SVM was better than that of the TSVM. On the other hand, because the distance of the ROC curves between the SVM and TSVM is very small, their AUC (100%) values were approximately equivalent.

5. Conclusion

In this study, we proposed a new drug clearance pathway prediction based on the TSVM. The TSVM improved the clearance pathway prediction for CYP2C19 compared with the SVM, and the improvement was statistically significant. By contrast, there was no significant improvement observed by increasing the number of unlabeled data entries in the TSVM. These results suggest that a dataset with only 100 unlabeled data entries is sufficient for this clearance pathway prediction problem with a dataset containing 240 labeled data entries.

The investigation of the cases that we should use semi-supervised learning methods is one of the important future works. As previously discussed, we insisted semi-supervised learning may improve the accuracy of prediction when that of supervised learning is considerably insufficient. However, this condition was ambiguous and not clearly confirmed. Thus, we have to concrete conditions, such as the number of labeled data, the ratio of positively labeled data and so on, for judging whether semi-supervised learning should be used or not.

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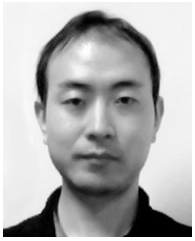

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