Deep Learning Model of Dock by Dock Process Significantly Accelerate the Process of Docking-Based Virtual Screening

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Abstract

Docking-based virtual screening (VS process) selects ligands with potential pharmacological activities from millions of molecules using computational docking methods, which greatly could reduce the number of compounds for experimental screening, shorten the research period and save the research cost. However, a majority of compounds with low docking scores could waste most of the computational resources. Herein, we report a novel and practical docking-based machine learning method called MLDDM (**M**achine **L**earning **D**ocking-by-**D**ocking **M**odels). It is composed of a regression model and a classification model that simulates a classical docking by docking protocol usually applied in many virtual screening projects. MLDDM could quickly eliminate compounds with low docking scores and the retained compounds with potential high docking scores would be examined for further real docking program. We demonstrated that MLDDM has a good ability to identify active compounds in the case studies for 10 specific protein targets. Compared to pure docking by docking based VS protocol, the VS process with MLDDM can achieve an over 120 times speed increment on average and the consistency rate with corresponding docking by docking VS protocol is above 0.8. Therefore, it would be promising to be used for examining ultra-large compound libraries in the current big data era.

1. Introduction

Drug discovery is a costly, complex, and time-consuming process. According to relevant statistics, the cost for development of drugs approved from 2009 to 2018 raised from \$300 million to \$2.8 billion, depending on different diseases and methods.¹ Computer-aided drug design (CADD) can significantly accelerate the process of drug discovery. Virtual Screening (VS process) as a typical CADD technique has been widely applied in the early stage of drug discovery for accelerating lead discovery.² Docking-based virtual screening aims to computationally place and evaluate small molecule compounds one by one at the binding site of a target protein with three dimensional structure. After continuously optimizing the poses of the compounds, molecular docking explicitly recommend possible potential compounds with high docking scores.

Currently, there are many protein-small molecule docking programs available. A summary of them is listed in Supplementary (**Supp Table S1**), including their release years, release organizations, descriptions, and licenses.^{3–19} Since the forms of scoring functions and the sampling methods they used are quite divergent, for certain system different docking program would yield variant docking results. Applying multiple docking programs sequentially in VS process is quite usual in many publications which is drawn as a well-known funnel like workflow.^{20–31} In such docking by docking protocol, the first docking process used in this workflow could be the one with very fast screening speed and the second could be more accurate by somehow slowly. Therefore, the balance between speed and quality of the final result are achieved.

Recently, it has been reported that docking based VS process on ultra-large databases can significantly increase the success rate of finding active hits.³² Meanwhile the sizes of compound databases also

increased significantly. For example, the widely used ZINC database, has exceeded 1.3 billion in 2019 from 700 thousand in 2005.^{33–35} Marco Capuccini et al³⁶ carried out VS process on a large-scale compounds library by running existing docking programs on parallel distributed cloud computational resources. This parallel strategy was based on the Apache Spark engine and achieved an overall efficiency of 87%.

However, only a small proportion of the compounds will have high docking scores, and most of the computational time was wasted on the vast majority of 'low-scoring' compounds. Even the improvement of computational resources make it possible to perform VS process on an ultra-large compound library, it is desirable to identify high-score compounds using reliable machine learning filters in advance as the computational time and resources on docking could be significantly reduced.

P. B. Jayaraj et al³⁷ developed a classification model based on random forest and applied this model to VS process. It can realize accelerated calculations on GPU, which significantly reduce the running time of the entire process of VS process. Francesco Gentile et al³⁸ reported the application of a deep learning framework to train classification models on the docking scores of a subset of compounds, then the model was used to predict compounds that have not been docked. Their method realized rapid VS process on a billion compounds library—ZINC-15, which greatly reduced the computational cost of VS on an ultra-large compounds library with an acceptable recall rate.

It would be promising to examine whether a workflow by two tandem models could mimic the above docking by docking protocol and applied for the scenario when the absolute number of compounds to be examined increased in one or two orders. In this paper, we setup such a machine learning model: MLDDM (**M**achine **L**earning **D**ocking-by-**D**ocking **M**odels), by training on two docking programs' results. With comprehensive evaluation of the method, MLDDM was proved to have a good ability to identify known active compounds on 10 specific protein targets. Further evaluation on protein target BRAF showed that the speed of the protocol could gain 120 times increment on average. These results show that MLDDM can quickly filter out compounds with low docking scores with high confidence. It is believed to be a good and practical filter in daily docking based virtual screening protocols with ultra large libraries.

2. Methods And Dataset

2.1 Model Construction and Usage

The framework of the MLDDM model construction and usage is illustrated in Figure 1. For certain protein Target, two supervised training processes are implemented. For the first training process, the compounds from the training library (N compounds) were docked into given target. Dock-1 was used as the first docking program, all the docking results are preserved as the first training set (**Training Set1**) for this target. The compounds with docking score ranking in the top 20% from first docking were selected for second docking process and the docking results from this setup are used as the second training set for this target (**Training Set2**). We then labeled these training sets according to the docking results. For the

second regression task, the rank percentage values of the compounds in **Training Set1** are calculated were used as labels. For the classification task, the top 20% ranked compounds within the Training Set2 were selected as the positive samples and the rest compounds were used as the negative samples. The regression model and the classification model were trained separately. After evaluation of the models, they could be used for ultra-large library filtering. When doing ultra-large library filtering, the regression model are used first which mimics the first step of docking by docking protocol and the high ranking score compounds are selected for the second prediction. The compounds with a positive sign suggested by the classification model could be used for further examination.

2.2 Programs and Parameter Settings for Molecular Docking

Two open-source and freely available docking programs, namely *vina*³⁹ as well as *vinalc*⁴⁰ implementation for large datasets and rDock¹⁶, were selected for multiple docking VS process in this research. *vina* is a molecular docking program based on an experience scoring function developed by the MGL Tools laboratory. Compare with AutoDock 4.0, *vina* improves the average accuracy of combined mode prediction, greatly accelerates the search speed by using a simpler scoring function and can still provide reproducibility when dealing with a system with about 20 rotatable bonds. rDock is a fast and versatile Open Source docking program that can be used to dock small molecules against proteins and nucleic acids. Both of the programs can be installed on a computation cluster server and deployed on an almost unlimited number of CPUs, allowing HTVS process campaigns to be carried out in a matter of days.

In our cases, the protein structures were pre-processed using ADTools, and the small molecules were prepared using openbabel.⁴¹ For parameters used in *vina*, the grid center was defined as the native ligand center in the crystal structure, a cubic grid was used with dimension (20,20,20). For rDock, the *rbcavity* program are used to determine a grid parameter from the native ligand with default parameters. *vina* was selected as the first docking program (**Docking-1**) and rDock was selected as the second docking program (**Docking-2**). Both docking scores of Docking-1 and Docking-2 were saved as csv files (**Additional file 3**).

2.3 Deep Learning Models

A open source toolkit, Chemprop (<http://github.com/chemprop/chemprop>), which is a deep learning based molecular property modeling and prediction toolkit,⁴² was used to develop our docking-based machine learning models. The architecture of Chemprop is based on graph convolutional networks, termed as the Directed Message Passing Neural Network (D-MPNN), which treats molecules as an attributed graph with node features (atom) and edge features (bond) for processing. D-MPNN was used to train regression and classification models with basic RDkit molecular descriptors. The default hyperparameters of Chemprop were used for model training. Besides, the setting parameters of `rdkit_2d_normalized` and `no_features_scaling` are added to the training process to improve the stability of the models.

Both the regression and the classification models were trained on 80% of the random split set and then validated and tested on the remaining 20% of the datasets. The hyperparameters of the D-MPNN, such as hidden_size, depth, dropout, and ffn_num_layers were optimized by 10-fold cross validation. The optimal hyperparameters were used to construct the VS-based models. The construction of these models were implemented with Pytorch and RDkit packages.

2.4 Datasets and Their Usages

In this study, several datasets were used for different purposes. Firstly, for the compound library to be docked into each target, a ChemDiv (ChemDiv Inc) library with 1.25 million purchasable compounds were clustered with a tanimoto similarity threshold 0.4 to obtain a clustered subset of 287,216 compounds (named as ChemDiv subset, and the SMILES file of the compounds are available in **Additional file 2**). Secondly, the description of target proteins used to build the MLDDMs are listed in **Table 1**. The number of their experimentally validated active compounds as well as decoy compounds selected from the DUD-E database⁴³ are also listed here. They are used to act as validation sets for MLDDM's validity. All these compounds were docked with two programs to corresponding targets and not used in the training process. (Their SMILES strings are list in **Additional file 4**). Thirdly, we tested MLDDM's performance in Expanded prediction stage by constructing two datasets. For evaluation of those regression models, a relative small dataset are constructed by a subset of 500,000 compounds randomly selected from the ChEMBL database to alleviate the actual docking load while keeping the generality of the result. (Their SMILES strings are listed in **Additional file 5**) The consistency of the regression model will be evaluated. For evaluation of those classification modes, for each targets, the compounds from the ChEMBL database are labeled as active or inactive depends on whether their IC₅₀s are less than 50μM or not. (Their SMILES are provided in **Additional file 6**). The whole ChEMBL database (about 19M molecules) were predicted by the regression model, and those passed this filter will be used as the input to the classification model. The number of active compounds are evaluated. Finally, ZINC-15 dataset was used to illustrate the speed of MLDDM on a large dataset for target BARF as example.

Table1 Detailed information of the selected targets (from DUD-E) and their active/decoy compounds numbers

Num	Target	PDB-ID	Type	Actives	Decoys
1	ACE	3BKL	Protease	808	17144
2	ADRB1	4BVN	GPCR	458	15958
3	BRAF	3D4Q	Kinase	251	10098
4	CDK2	1H00	Kinase	798	28328
5	DRD3	3PBL	GPCR	877	34188
6	DPP4	2I78	Protease	1079	41373
7	EGFR	2RGP	Kinase	832	35442
8	JAK2	3LPB	Kinase	153	6590
9	LCK	2OF2	Kinase	683	27856
10	VGFR2	2P2I	Kinase	620	25280

3. Results And Discussion

3.1 Model Construction of MLDDM

To reflect the consistency of the model's performance and its generalizability, we summarized the the training statistical metrics of those models for the 10 selected targets in **Figure S1**. The AUC and RMSE on the internal test sets of the D-MPNN models for each target are presented in Table 2. For those regression models, the RMSE values ranges from 0.14 to 0.11, illustrating an acceptable error in ranking percentage prediction. For those classification models, the AUC values ranges from 0.89 to 0.96, indicating a good ability to distinguish between positive data (top 20% ranked compounds by Dock-2) and negative data (the rest compounds by Dock-2).

Table 2
Performance on of D-MPNN regression and classification models based on the ChemDIV subset against 10 protein targets.

Target	Regression RMSE	Classification AUC
ACE	0.1237+/-0.0008	0.9601+/-0.0030
ADRB1	0.1210+/-0.0008	0.9478+/-0.0043
BRAF	0.1323+/-0.0007	0.9473+/-0.0047
CDK2	0.1177±0.0009	0.9448+/-0.0028
DRD3	0.1118+/-0.0010	0.9478+/-0.0037
DPP4	0.1210+/-0.0006	0.9257+/-0.0027
EGFR	0.1235+/-0.0006	0.9611+/-0.0035
JAK2	0.1340+/-0.0007	0.9124+/-0.0039
LCK	0.1220+/-0.0008	0.9604+/-0.0014
VGFR2	0.1425+/-0.0005	0.9556+/-0.0071

3.2 Evaluations of Regression Models

3.2.1 Regression Model Evaluation on DUD-E dataset

Considering there may be some topology bias in DUD-E, we do not intentionally incorporate compounds into training set and use it as one-time validation only.⁴⁴ Since the DUD-E dataset also used in success classification model We labeled these as follows: DUD-E actives/decoys were docked by *vina* and compounds with docking score above the top 20% percentile of the Training-Set-1 were selected. The number of compounds selected were compared with the number of compounds that selected by the regression model. Next, these dock selected compounds were used for the classification model in 3.3.1. The results are listed in Table 3. It is shown that among the 10 targets, except for those of ACE, the consistency rates between the docking regression and MLVS classification were 75.0%, with the highest consistency rate of 98% for the CDK2. This suggests that the regression model from MLDDM achieved an acceptable performance as corresponding docking methods.

Table 3
Performance of MLDDM regression models and docking results on DUD-E compounds

Model	Compounds	Number of compounds Selected by Dock-1 top20%	Number of compounds Selected by MLDDM Regression ¹	Consistency rate ³
ACE	actives	55	31	56.4%
	decoys	745	643	86.3%
ADRB1	Actives	60	51	85.0%
	decoys	679	575	84.7%
BRAF	actives	98	88	89.8%
	decoys	949	779	82.1%
CDK2	actives	245	240	98.0%
	decoys	1341	1091	81.4%
DRD3	actives	170	136	80.0%
	decoys	1437	1214	84.5%
DPP4	actives	84	66	78.6%
	decoys	1500	1190	79.3%
EGFR	actives	225	216	96.0%
	decoys	2788	2308	82.8%
JAK2	actives	34	26	76.5%
	decoys	395	302	76.5%
LCK	actives	291	253	86.9%
	decoys	2096	1737	82.9%
VGFR2	actives	158	120	76.0%
	decoys	1312	1086	82.8%
1. Consistency rate equals the Number of compounds Selected by MLDDM Regression over Number of compounds Selected by Dock-1 top20%				

3.2.2 Regression Model Evaluation on the ChEMBL subset

We used regression models in MLDDM to predict the ranking percentage of the compounds in the ChEMBL subset. The compounds with top 20% percentage ranking prediction were further docked to their targets using *vina* to test their real distribution.

Figure 3 shows the superposition of the *vina* docking score distributions from four representative targets as examples. The figures for other 6 targets are shown in **Figure S2**. The *vina* docking score from those selected compounds from ChEMBL subset, the whole ChemDiv dataset and the top 20% scored ChemDiv compounds are illustrated as follows:

In Figure 3, we can see that most of the selected ChEMBL compounds were located in the top20% docked ChemDiv compounds region. This suggests that the our regression models have a strong ability to enrich compounds with a high docking score, therefore, the models can distinguish compounds with potentially high docking scores for specific targets in a quickly manner without docking.

3.3 Evaluation of Classification Models on the DUD-E sets

In section 3.2.1, previously docked DUD-E actives/decoys by *vina* and selected compounds with docking score above the top20% percentile of the Training Set1. These compounds were then docked by rDock. The compounds whose rDock docking score is above the top20% percentile of the Training Set2 was labeled as positive while the bottom 20% of them were labeled as negative. These compounds were further predicted by the classification model from MLDDM.

Table 4 shows the statistical results of the various metrics of the classification model on the DUD-E external data set. The statistical results show that, except for the target DPP4, the accuracies of the other 9 targets on the DUD-E external data set are above 70%. Except for the targets DPP4 and BRAF, the specificity values of the other 8 targets on the DUD-E external data set are above 72%. The false-positive rates of the targets EGFR, DPP4, and BRAF are overall higher than other targets, 24.8%, 46.9%, and 37.9%, respectively, for the rest targets, the false-positive rates are all less than 20%. As for the true positive rate, the maximum and minimum values were 89.5% of BRAF and 27.5% of JAK2. Obviously, for different targets, the performances of the MLDDM are different here. In general, on the external test sets, the models showed a good performance of accuracy and specificity.

Table 4
Statistics of various indicators of the model on external data sets

Num	Target	Accuracy	Precision	Specificity	FPR	TPR	F1-score	Prevalence
1	ACE	73.9%	52.0%	84.0%	15.9%	46.3%	49.0%	27.1%
2	ADRB1	79.9%	66.5%	85.5%	14.5%	54.6%	60.0%	30.1%
3	BRAF	82.8%	87.9%	62.1%	37.9%	89.5%	88.7%	67.6%
4	CDK2	73.3%	59.3%	82.2%	17.8%	53.8%	56.4%	32.2%
5	DRD3	76.0%	60.2%	89.7%	10.3%	40.4%	48.3%	27.8%
6	DPP4	60.4%	41.8%	53.1%	46.9%	77.2%	54.3%	32.5%
7	EGFR	72.9%	49.7%	75.2%	24.8%	66.3%	56.8%	27.0%
8	JAK2	74.3%	46.3%	89.5%	10.5%	27.5%	34.5%	24.7%
9	LCK	77.5%	63.4%	90.3%	9.7%	44.1%	52.0%	27.6%
10	VGFR2	72.9%	62.2%	90.7%	9.3%	33.8%	43.8%	31.2%

3.4 Overall Performance of MLDDM to Retrieve all active compounds

To further verify whether the model can identify active compounds for specific targets after the whole MLDDM process, the active compounds of the 10 targets were selected from ChEMBL for verification. The active compounds for 10 targets were filtered and considering a relative loose threshold. If a compound has an activity of IC_{50} less than $50\mu M$, it would be kept as a positive sample.

To explore the models' ability of recalling actives, the whole 19 million molecules from the ChEMBL database were predicted with the regression model from the corresponding MLDDM and the compounds which passed the top20% percentile of the training set were selected to make the second prediction. After using the classification model, we count the number of actives recalled.

In Table 5, it shows the percentage of recalled compounds in the total positive sample with the different activity cutoff. The statistical results showed that most of the models can identify over 50% of active compounds for specific targets, for example, the proportions of ADRB1, BRAF, EGFR, JAK2, LCK, and VGFR2 were 65.78%, 79.30%, 68.63%, 51.88%, 74.61%, 52.72%, respectively. That is to say, for most targets, the potential active compounds could be recalled by our models.

Table 5
Active compounds prediction statistics of the model

Target	Threshold of active compounds from ChEMBL (IC ₅₀)							
	<50nM	<100nM	<200nM	<500nM	<1μM	<10μM	<20μM	<50μM
ACE	30.00%	31.56%	32.73%	34.46%	33.42%	32.35%	31.83%	31.10%
ADRB1	44.62%	55.81%	60.68%	62.89%	64.44%	66.81%	65.34%	65.78%
BRAF	79.01%	79.18%	79.37%	79.26%	79.14%	79.23%	79.32%	79.30%
CDK2	23.29%	23.08%	23.34%	24.22%	24.35%	29.41%	29.41%	28.80%
DPP4	34.81%	34.64%	34.24%	33.12%	32.55%	32.18%	32.34%	32.34%
DRD3	28.97%	29.45%	33.51%	35.68%	38.91%	42.17%	42.04%	42.43%
EGFR	74.45%	74.30%	73.17%	72.46%	69.84%	68.88%	68.96%	68.63%
JAK2	55.95%	55.03%	53.59%	52.39%	51.97%	51.78%	51.82%	51.88%
LCK	77.97%	78.19%	78.94%	78.31%	77.74%	74.77%	74.66%	74.61%
VGFR2	36.53%	40.93%	43.62%	46.96%	48.65%	52.58%	52.59%	52.72%

To test the generalization of our framework, we used the MLDDM trained from current chemDiv training set and calculated $EF_{0.04}$ on ChEMBL. As the current MLDDM would retrieve top4% ($0.2 \times 0.2 = 0.04$) of the training set, the enrichment factor $EF_{0.04}$ could be calculated and evaluated.

The summarized results of the enrichment factors for 10 targets are listed in Table 6. From this table, the enrichment factors against 10 targets range from the lowest 5.86 (CDK2) to the highest 17.03 (ADRB1). However, the predictive ability of the model does not show a strong correlation with activity, which may be related to the way our training datasets were acquired.

Table 6
Enrichment factor statistics of 10 targets

Target	Actives	Total	Recall Comps	True positive	EF _{4%}
ACE	553	1941964	72638	172	8.32
ADRB1	529	1941940	74995	348	17.03
BRAF	5222	1946633	94479	4141	16.34
CDK2	1684	1943095	95447	485	5.86
DPP4	3779	1945190	87247	1222	7.21
DRD3	337	1941748	85286	143	9.66
EGFR	8232	1949643	134286	5650	9.96
LCK	1713	1943124	93253	1278	15.55
JAK2	5181	1946592	108679	2688	9.29
VGFR2	9329	1950740	71504	4918	14.38

3.3 Computation Speed Comparison

To demonstrate the advantage of our MLDDM models in speed, the target BRAF was selected as an example of the prediction test. The drug-like molecules (containing 981,247,974 compounds) from the ZINC-15 were selected in this case.

Table 7
Comparison of running time

Num Compounds (k)	Time Cost-Calculate Descriptors (h)	Time Cost-Prediction (h)	Estimated Time of Docking(h) ¹	Recall Compounds	Recall Rate (%)	Times ²
5	0.065	0.005	8.20	—	—	117
10	0.111	0.009	16.41	—	—	137
20	0.202	0.018	32.82	—	—	149
50	0.509	0.041	82.04	5	0.001	149
100	1.101	0.079	164.08	11	0.001	139
200	2.393	0.157	328.16	19	0.001	129
500	6.009	0.391	820.40	446	0.009	128
1,000	12.111	0.779	1640.80	1143	0.011	127
2,000	24.323	1.557	3281.60	2364	0.012	127
5,000	59.319	3.891	8204.00	8979	0.018	129
10,000	122.851	7.779	16408.00	33305	0.033	125
20,000	254.803	15.557	32816.00	111281	0.056	121
50,000,	638.009	38.891	82040.25	686365	0.130	121
98,124	1249.044	77.586	161002.35	6213291	0.633	121

Notes:

Model prediction computing resource: 10 * CPUs (Xeon Gold 5118) +1 * GPU(Tesla V100);

Molecular docking computing resources: 20 * CPUs (Xeon E5-2670 V2);

1. The docking time is linearly predicted according to the docking speed of 300,000 ChemDiv compounds;
2. Speed improvement based on the above resource allocation;

The statistical results in Table 7 show that based on the above available computing resources, the prediction speed of the machine learning VS model is greatly improved compared to traditional dock by dock process with an average speed increament of >120 times. A large amount of time was used to calculate the descriptors with single-core CPU are included in case every time a unique compound library is used. It means that the MLDDM we built here could greatly increase the speed of dock-by-dock process. This framework could quickly filter out low-scoring compounds against the specific targets, at the same

time, the compounds with high docking score were recalled quickly. Therefore, the calculation time and resources of VS on ultra-large compounds library can be greatly reduced.

4. Discussion

Recently, several active learning based protocols have been proposed.^{38, 45–47} Yang et. al., use DOCK3.7 and Glide SP to do an active learning process. They used a random chosen subset which is 0.1% of the total library and then iteratively updated the ML models with an active learning strategy. For the same target, the two programs' performance varied. Most top-ranking compounds by both DOCK3.7 and Glide SP could be recovered by the ML models. It was necessary to increase the recall rate where 5% of the compounds were redocked with corresponding programs. This process obtained a 20-fold speed increment for virtual screening. Therefore, it would be greatly valuable to explore and design a practical dock by dock framework for decreasing computational workload of real docking.

Due to the availability and accessibility of the docking software, we only tested the combination of *vina* (*vinalc*) and rDock, which tends to be orthogonal to each other. Conceptionally, this framework is believed to be general to other combinations of docking programs, and flexible to accommodate different requirements in variant projects.

To explore a reasonable threshold in the process of obtaining the training dataset, the DUD-E active compounds were selected to carry out statistical analysis on the relationships between the enrichment ratio of the active compounds and the top value of the two docking programs for 10 selected targets respectively. Representative results of 4 targets were listed in Figure 4, others are shown in **Figure S3**. The X-axis represents the top value of the compounds sorted by the docking score, and the Y-axis represents the proportion of DUD-E active compounds enrichment status for the corresponding target. The statistical results showed that there is a logarithmic growth relationship between enrichment ratio and top value, and the enrichment ratio has the maximum profit in the top20% for most of the targets. Besides, the active compounds enrichment ability of rDock is better than *vina* overall. For the target DPP4, the enrichment ratios of active compounds in the top20% compounds of the two docking programs are both >20%. It showed that the two selected docking programs have a certain ability to enrich active compounds. Thus, top20% was selected for the preparation of the training dataset.

To obtain a higher enrichment ratio, we further explored the usage ordering of two docking programs. The enrichment ratios of different-ordering combinations were summarized in Figure 4. The red curve represents the enrichment ratio of the corresponding target by the rDock program, the blue one represents that of the *vina* (*vinalc*) program, and the green one represents the re-docking of the top20% compounds using the rDock after docking with *vina* (*vinalc*), accordingly, the orange one represents the enrichment ratio in the order of rDock first and then *vina*.

The statistical results showed that for most targets, the enrichment ratio of using rDock alone is higher than the other three methods. Besides, we found it could further improve the enrichment ratio through

using the *vina* program for first docking and then using the rDock program for re-docking. It means that the strategy of combining two docking programs can get more active compounds in the training dataset compared with using *vina* (*vinalc*) alone. Moreover, considering the large amount of computing resources of the two docking programs, we choose a combination of using *vina* for the first-step quick screening and then using the rDock program to run a more precise multi-conformations search for re-docking. This strategy ensures that there are enough active compounds we obtained while reducing the time to obtain the training dataset.

5. Conclusion

In the current work, we demonstrated a framework MLDDM which mimics the dock-by-dock screening process powered by deep learning. We implemented it by utilizing the docking results of certain target on a commercially purchasable chemDiv subsets with open access docking program *vina* and rDock as well as deep learning toolkit Chemprop. Various statistical results showed that the models could have a good performance of VS process. Moreover, compared with the traditional dock by dock process, the MLDDM we constructed here could realize screening on an ultra-large compounds library with the speed improvement of 120 times. These models can quickly identify molecules with potentially high docking scores and filter out molecules with low docking scores, which greatly reducing the consumption of computing resources on the VS of ultra-large compound library. In addition, it is found that the reasonable combination of the two docking programs can further increase the enrichment ratio of the screening and make the obtained training dataset more reliable.

With the applications of compound generative models in the field of drug development in recent years, it is believed that the models of MLDDM would be used as a rapid scoring metric for generative models to efficiently produce a set of diversity compounds with high docking scores for a specific target.

Declarations

Availability of data and materials

The Python codes can be available at

<https://github.com/OpenIIPharma/mlddm> with the MIT license.

The MOL2 and CSV file of the clustered compounds from ChemDiv are available in **Additional file 2**

Docking scores of training set1 and the following training set2 for each target were saved as csv files and provided in **Additional file 3**.

The SMILES, MOL2, SDF of DUD-E compounds and PDB of receptors used for validation are provided in **Additional file 4**.

The SMILES of 500,000 compounds randomly selected from the ChEMBL database are provided in **Additional file 5**

The SMILES of compounds with activities from the ChEMBL database for each target are provided in **Additional file 6**

All these Additional files could be downloaded at:

<https://zenodo.org/record/5665378>

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Contributions

W.Z, Y.X and X.D designed the major strategy of this work. W.M and Q.X. made the implementations and major analysis on this work. J.Z made input for D-MPNN and supported the deep learning model implementation; S.L. make helpful discussions and guidances on this work. W.M, Q.X, S.L., Y.X and W.Z wrote the manuscript. All authors read and approved the final manuscript.

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Competing interests

The authors declare that they have no competing interests.

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Figures

Figure 1

The workflow of MLDDM construction and usage.

Figure 2

vina docking score distribution for D-MPNN regression model. ChEMBL compounds and ChemDiv compounds for a) BRAF b) LCK c) VGFR2 and d) DPP4.

Figure 3

Enrichment ratio of DUD-E active compound for two docking programs

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