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Multi-Descriptor Read Across (MuDRA): a simple and transparent approach for developing accurate QSAR models

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Abstract

Multiple approaches to QSAR modeling using various statistical or machine learning techniques and different types of chemical descriptors have been developed over the years. Oftentimes models are used in consensus to make more accurate predictions at the expense of model interpretation. We propose a simple, fast, and reliable method termed Multi-Descriptor Read-Across (MuDRA) for developing both accurate and interpretable models. The method is conceptually related to the well-known kNN approach, but uses different types of chemical descriptors simultaneously for similarity assessment. To benchmark the new method, we have built MuDRA models for six different endpoints (Ames mutagenicity, aquatic toxicity, hepatotoxicity, hERG liability, skin sensitization, and endocrine disruption) and compared the results with those generated with conventional consensus QSAR modeling. We find that models built with MuDRA show consistently high external accuracy similar to that of conventional QSAR models. However, MuDRA models excel in terms of transparency, interpretability, and computational efficiency. We posit that due to its methodological simplicity and reliable predictive accuracy, MuDRA provides a powerful alternative to a much more complex consensus QSAR modeling. MuDRA is implemented and freely available at the Chembench web portal (<https://chembench.mml.unc.edu/mudra>).

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Supporting information includes curated chemical datasets for all endpoints along with predictions from QSAR models and MuDRA. These materials are available free of charge via the Internet at <http://pubs.acs.org>.

Conflict of interests

The authors declare no actual or potential conflict of interests.

Introduction

The Occam's razor principle states, in its most popular version, that "Entities are not to be multiplied without necessity".¹ Many industries have followed this rule. A great example is provided by consumer electronics, where the iPhone's simplistic design using one button to control all of its functions is widely considered innovative and effective (especially now with version X, which does not even have a home button!).² Unfortunately, one cannot say that this approach has been closely followed by the Quantitative-Structure-Activity Relationship (QSAR) modeling field. Just the opposite - the field has progressed from relatively simple use of linear or multi-linear correlation methods in the original publications by Hansch et al.³⁻⁵ to the progressive use of increasingly more sophisticated multivariate machine learning approaches and different descriptor types (reviewed in Cherkasov et al.⁶).

Several important procedures have been developed to increase the reliability and predictive power of models, such as chemical and biological data curation,⁷⁻⁹ best practices for model development and validation,^{10,11} and calculation of the modelability index (MODI)¹². The addition of these protocols has made the modeling process more complex but also, more robust, leading to the improved reliability and external predictive power of models built with any types of descriptors and model development algorithms. However, in the pursuit of higher statistical accuracy and predictive power of models, many scientists, including our group, have also begun to advocate for consensus (or ensemble/combinatorial) QSAR modeling.^{13,14} This approach relies on building many parallel QSAR models using different descriptor sets, several machine learning or statistical modeling techniques, and the integration of multiple models for consensus prediction of external compounds.

It has been established that the consensus QSAR approach has, on average, higher reliability than any of the contributing models.¹³⁻²² In addition, this approach was shown to be helpful for chemogenomics data curation.^{8,9} However, needless to say, the consensus approach requires multiple parallel efforts for developing different and diverse QSAR models, often accomplished by multiple modeling groups. For instance, the recent CERAPP project²³ led by EPA has combined contributions from 17 research groups, with the respective paper co-authored by 41 scientists who have developed dozens of models for a single endpoint. While this project has demonstrated the power of teamwork and collegial approach to model development, it cannot be regarded as sustainable and applicable to any endpoint of interest. This consideration calls for the development of no less robust but implementation-wise simpler approaches.

In addition to the complexity and expense of execution, statistical QSAR models, and especially, consensus models, have been criticized for being a "black box", *i.e.*, not interpretable, which led to limited use of statistical QSAR models in regulatory decision support.^{24,25} At the same time, methods relying on structural alerts and read-across have found much greater acceptance.²⁶ However, despite their perceived benefit, qualitative approaches such as structural alerts, chemical grouping, and read-across have been shown to be extremely over sensitive if used alone to predict biological activity.²⁷ Indeed, it has been argued that to understand the underlying toxicity mechanisms, these qualitative approaches should be used only after proper statistical validation by QSAR.²⁷

As discussed above, both qualitative and quantitative SAR modeling approaches have respective advantages as well as deficiencies. Although ensemble QSAR models represent a great advance in the field, the complexity of this approach, which requires the knowledge and integration of various QSAR approaches, is a serious barrier to their broad use. Conversely, mechanistic and alert-based approaches have been criticized for limited statistical accuracy. Recently, in an effort to establish both transparent and statistically accurate QSAR approach, we have developed a chemical-biological read-across (CBRA) approach for chemical toxicity assessment.²⁸ This approach was later adopted by several groups.^{29–31}

Using a similar methodology, herein we propose a simple approach for developing high quality QSAR models that relies on a single k -Nearest Neighbors (kNN) algorithm and multiple types of chemical descriptors used for consensus chemical similarity calculations. The latter approach - intrinsic to a single model development protocol - is in contrast with the much more complex and laborious consensus QSAR modeling approach discussed above. The proposed method is termed Multi-Descriptors Read Across (MuDRA). In benchmarking studies using several experimental datasets, we have built predictive QSAR models that were fully compliant with the OECD principles of model validation³² and demonstrated that these models offer several advantages over conventional ensemble QSAR models.

Interestingly, *mudra* is a word in Sanskrit, and one of its meanings is “an energetic seal of authenticity employed... in Indian religions”.³³ We expect that MuDRA will become recognized as the most authentic, single universal QSAR modeling approach that can be relied upon for building models for most, if not all, target properties of interest.

Materials and Methods

Datasets

We have employed five different datasets previously used to build QSAR models for aquatic toxicity¹³, Ames mutagenicity³⁴, hepatotoxicity³⁵, hERG³⁶, skin sensitization³⁷, and endocrine receptor activity²³. The datasets were thoroughly curated following the practices developed by our group earlier.^{7–9} Information regarding dataset size including compound distribution between modeling and external validation sets along with corresponding references is available in Table 1. To make the comparison fair, we have used the same external set both for QSAR and MuDRA. For aquatic toxicity, Ames mutagenicity, and hepatotoxicity we used the same external set available in the original publication. Since hERG and skin sensitization datasets were modeled following a 5-fold external cross validation procedure using the entire datasets in the original publications, we randomly selected 20% of the dataset as external set using stratified sampling to standardize the analysis within this study. In the recent Collaborative Estrogen Receptor Activity Prediction Project (CERAPP)²³ more than 40 QSAR models for endocrine receptor activity were reported using either agonist, antagonist or binding activity data. For this endpoint only, we retrieved the external set the authors compiled from the literature containing 6,319 compounds with agonist activity, 6,539 compounds with antagonist activity, and 7,283 compounds with binding activity. We employed MuDRA to predict activity for these

compounds and benchmarked our models against those reported in the CERAPP publication.

Calculation of Modelability Index (MODI) and model accuracy

The concept of “data set modelability”¹² implies an *a priori* estimate of the feasibility to obtain predictive QSAR models for a given set of chemicals. MODI was calculated as follows (Eq. 1):

$$MODI = \frac{1}{K} \sum_{i=1}^k \frac{N_i^{same}}{N_i^{total}} \quad \text{Equation 1}$$

where K is the number of classes (in all the studied cases, $K = 2$), N_i^{same} is the number of compounds of i -th activity class that have their first nearest neighbors (NN) belonging to the same activity class i ; N_i^{total} is the total number of compounds belonging to the class i . Models were evaluated by the Correct Classification Rate (CCR, computed as the average of sensitivity and specificity of the model), sensitivity, specificity, positive predictive value (PPV), and negative predictive value (NPV).

Molecular descriptors

We calculated four different types of molecular descriptors: ECFP4-like circular fingerprints (Morgan), PaDEL, Simplex Representation of Molecular Structure (SiRMS)³⁸, and DRAGON. Morgan fingerprints with 2048 bits and atom radius of 2 were calculated using RDKit (<http://www.rdkit.org>). PaDEL descriptors³⁹ were calculated using the PaDEL-Descriptor software freely available from <http://www.yapcwsoft.com/dd/padeldescriptor/>. SiRMS descriptors (number of tetratomic fragments with fixed composition and topological structure) were generated by the HiT QSAR software⁴⁰. Finally, DRAGON descriptors were generated using DRAGON software (v.5.5, Talet SRL, Milan, Italy). All chemical descriptors, with the exception of Morgan fingerprints, were normalized to take values between 0 and 1. Constant and near constant variables were removed; and, if two or more variables were highly correlated (correlation coefficient above 0.9), only one of them was chosen randomly.

Traditional consensus QSAR modeling

Binary QSAR models were developed and rigorously validated according to the best practices of QSAR modeling.¹¹ For each dataset, all four types of descriptors in combination with random forest were used.⁴¹ The consensus model was built by averaging the predicted values from each individual model. Consensus model considered majority of votes (at least three out of four) for the final classification. Cases when two models disagreed with the other two models were considered inconclusive. The consensus AD (Consensus with Applicability Domain) model was developed in a similar way; however, only predictions from individual models when the queried compound was inside the applicability domain (z -cutoff method¹⁶) were considered. In every case, only the modeling set was used to develop the models, while the external sets were used for evaluation and for comparison of model's accuracy with the MuDRA method (see next section).

Multi-Descriptors Read-Across (MuDRA)

The MuDRA approach is based on the chemical-biology read-across (CBRA) method developed by us previously²⁸. The CBRA approach relies on both structural similarity and comparisons of biological responses to chemicals in multiple short-term assays (“biological” similarity). Likewise, the MuDRA approach infers the target property of the queried compound from those of their structural analogs identified within each of the multiple chemical spaces defined by the respective descriptor sets (see Figure 1). In each chemical space, a predetermined number of nearest neighbors (NN) is selected based on their similarity to the query compound.

The definition of similarity depends on the types of descriptors and similarity metrics that control the outcome of the MuDRA prediction. For quantitative read-across, the predicted activity of a compound (A_{pred}) is calculated using the following equation (Eq. 2) from the similarity (S_j) weighted aggregate of the activities A_i of k nearest neighbors.

$$A_{pred, RA} = \frac{\sum_{i=1}^k S_i \cdot A_i}{\sum_{i=1}^k S_i} \quad \text{Equation 2}$$

The pairwise Tanimoto similarity S_i between the molecule of interest (A) and its i^{th} neighbor (B) is calculated from the Jaccard distance d_{Jac} (see Eq. 3)⁴², where there are D descriptor spaces with the p_1, p_2, \dots, p_D descriptors $x_1^j, \dots, x_{p_j}^j$ and $j=1, \dots, D$. For each i^{th} compound of a dataset, the similarity $S_{i, B}^j$ with compound B in space j is calculated.

$$S_{i, B}^j = 1 - d_{Jac} = \frac{\sum_{j=1}^{p_j} x_i^j x_{i, B}^j}{\sum_{j=1}^{p_j} (x_i^j)^2 + \sum_{j=1}^{p_j} (x_{i, B}^j)^2 - \sum_{j=1}^{p_j} x_i^j x_{i, B}^j} \quad \text{Equation 3}$$

For a set of range-scaled continuous descriptors, Tanimoto similarity is normalized between 0 and 1, with 1 corresponding to identical pairs. The similarity-weighted aggregate in Eq. 2 ensures that the activities of more similar neighbors are given higher weights when calculating the predicted activity. This step can be enhanced by considering different descriptor scaling schemes such as range scaling or mean absolute deviation scaling. Compound activity (*i.e.*, the activity predicted by MuDRA) is defined by the similarity with activities of NN (A_{i, B_j}^j) in j space, where $B_j=1, \dots, n_j$ (Eq. 4, MuDRA model). In this study, we analyzed 1, 3, 5, and 7 neighbors. Initially, we employed four sets of descriptors ($D=4$). Activities of nontoxic compounds are assigned “0” while those of toxic compounds are assigned “1”.

$$A_i^{pred, MuDRA} = \frac{\sum_{j=1}^D \sum_{B_j=1}^{n_j} S_{i, B_j}^j A_{i, B_j}^j}{\sum_{j=1}^D \sum_{B_j=1}^{n_j} S_{i, B_j}^j} \quad \text{Equation 4}$$

Results

MODI

All datasets used in this study are well known and have been previously modeled (cf. Table 1). To ensure that datasets are modelable, we calculated MODI (cf. Eq. 1) for all sets of descriptors. All datasets, except for hepatotoxicity, had MODIs of at least 70% (Table 2).

Consensus QSAR vs. MuDRA models for chemical toxicity prediction

The statistical characteristics of consensus QSAR and MuDRA predictions for chosen toxicity endpoints are summarized in Table 3. QSAR models were built using Morgan, PaDEL, SiRMS, and DRAGON descriptors and the random forest algorithm. Statistical characteristics for all individual QSAR models can be found in the Supporting Information. All QSAR models, except for hepatotoxicity, were robust and predictive, with CCR for external sets being in the 66–93% range. The external set for the hepatotoxicity datasets was small (25 compounds), and most of the toxic compounds were mispredicted. For this particular dataset, Low et al.³⁵ were able to produce predictive models by combining both chemical descriptors and toxicogenomics data in a hybrid QSAR model.

The MuDRA models showed predictive power similar to that of traditional QSAR models. We also found that the accuracy of MuDRA did not vary considerably with the increase of the number of NNs. This is mainly due the fact that the closest NNs have higher influence, regardless of the chemical space and the number of compounds selected to be included. With the exception of hepatotoxicity, all the MuDRA models were predictive, with CCRs ranging from 62% to 88%. For the Ames mutagenicity data, the MuDRA approach presented a CCR 3–6% higher than the consensus model. Consensus AD showed the highest CCR, but at the expense of somewhat limited coverage (91%). For aquatic toxicity, the Consensus and Consensus AD model presented a CCR of 86% and 93%, respectively. The MuDRA approach produced a CCR as high as 86–88%. QSAR models for hepatotoxicity did not satisfy the standards for external validation. For this endpoint, 10 of the 25 external set compounds were toxic, but only one compound was correctly predicted as toxic by our models. Conversely, the MuDRA approach showed similar behavior, predicting only two compounds correctly. QSAR models for hERG outperformed MuDRA by 2–5% in CCR. Finally, skin sensitization QSAR models showed a CCR of 69% and 71% for consensus and consensus rigor models, respectively. The MuDRA approach for skin sensitization showed the highest variability of predictive accuracy for different numbers of NN used (9%), which may be related to the high structural diversity of skin sensitizers.^{43–46} In addition, both the QSAR models and the MuDRA approach presented a low NPV (28–31%) due to the low number of non-sensitizers ($n = 37$) in comparison to the non-sensitizers ($n = 180$) in the external set.

As a final exercise, we retrieved the literature data compiled for the CERAPP²³ project and compared the predictions from MuDRA and those obtained with different models reported in CERAPP publication. This dataset is comprised of 6,319 compounds with agonist activity, 6,539 compounds with antagonist activity, and 7,283 compounds with binding activity compounds. Since not all of the models reported in the CERAPP paper predicted all

of the compounds in the external set, we only compared our predictions obtained with MuDRA with those generated by previous models developed in CERAPP for 100% of compounds. The latter subset included five models for agonist activity, four models for antagonist activity, and nine models for binding affinity. In the CERAPP paper, sensitivity, specificity, and CCR (named “balanced accuracy” in the publication) were reported, and thus only these metrics were compared. The comparisons between predictions obtained with QSAR models reported in the CERAPP publication and those generated by MuDRA are summarized in Table 4. As one can see, MuDRA had similar performance as compared to the QSAR models reported in the CERAPP study in terms of CCR, sensitivity, and specificity for all the three endpoints (agonist, antagonist, and binding).

Number of descriptors vs. model predictivity

To test how the number of descriptor types affects the model quality, we calculated the average CCR for one, two, three, and four descriptor space components for each studied dataset. As one can see from Figure 2, CCR for Ames, aquatic toxicity, hERG, and skin sensitization increases gradually, stabilizing at 3-NN. The only endpoint the CCR is higher at one and two NN is hepatotoxicity, but as one can see from Table 3 this dataset is not modelable. As Bender⁴⁷ have shown, the use of different types of descriptors leads to different chemical similarity assessment for the same pairs of compounds. Therefore, a compound may not preserve the same NNs in another chemical space. By using four chemical spaces, the error in predictions given by a particular nearest neighbor is minimized and the predictivity of the method is on par with conventional ensemble QSAR.

Discussion

QSAR models vs. MuDRA for chemical toxicity prediction

In chemical toxicity prediction, the expected outcome is a reliable, computationally efficient, and transparent prediction for every queried compound. Developing an ensemble of models requires access to diverse modeling approaches (or software), which is hard to achieve within a single research group, or consolidation of results generated in multiple research groups. For instance, in the CERAPP project²³, more than 30 diverse models generated by several research groups using different tools to predict estrogen receptor activity of environmental compounds were integrated. Therefore, we sought to develop a simple, fast, and reliable approach that would produce the same quality predictions of current QSAR models while also providing 100% coverage of the chemical space.

As one can see from Table 3 and Table 4, the use of the MuDRA approach resulted in models with similar accuracy to those built individually with Random Forest. The nearest neighbor aggregation employed by MuDRA ensures that most similar neighbors have higher weights, regardless of the descriptor type. Thus, this feature ensures that the most similar neighbors will drive the outcome of the prediction.

The final prediction of MuDRA differs from qualitative approaches such as structural alerts, chemical grouping, and chemical read-across. Structural alerts are used to flag potential hazards and to group compounds into categories for read-across.⁴⁸ Chemical read-across is a

data gap filling procedure to assess certain endpoint effect of a chemical by using data for the same endpoint from another chemical (or a group of chemicals), which is (are) considered structurally similar.⁴⁹ These methods have earned acceptance among toxicologists due to their simplicity and ease of interpretation.⁵⁰ However, as we have shown,²⁷ structural alerts are extremely over-sensitive if used alone to predict biological activity. Moreover, the use of structural alerts may be detrimental in the drug discovery pipeline as well as for the safety assessment due to high false-positive rate.⁵¹ If the MuDRA model is built for a high quality and properly curated dataset⁷⁻⁹ following the best practices for model development and validation,^{6,11} its accuracy is expected to be similar to that of conventional QSAR models. In contrast with the current chemical read-across procedure, the newly-developed MuDRA approach consists of an instance-based learner, *i.e.*, it compares new instances with instances seen in training set, instead of performing explicit generalization.⁵² We posit that the MuDRA method provides an alternative to the ensemble modeling approach due to the easier implementation and decreased computational cost.

Another important benefit of MuDRA is its transparency, which can aid in the design of new compounds with improved characteristics. We illustrate this approach in Figure 3. As one can see, the predicted compound preserves toxicity if a nitro group is inserted in *meta* position relative to the bromomethyl group, as observed in Morgan and SiRMS spaces. However, as shown in PADEL space, if bromine is substituted by a bulkier group, as well as the change substitution of a isoquinoline heterocycle by a quinoxaline leads to a non-toxic compound. Moreover, Dragon descriptors demonstrate that, although NN in the chemical space of the integral (whole-molecule) descriptors may be unexpected and substantially different from others, it still may contribute to final correct prediction.

We also envision that the MuDRA approach will be useful for the prediction of activity cliffs based on the Matched Molecular Pair (MMP) methodology.⁵³ It should be noted, however, that since MuDRA is based on the activity profiles of structurally similar compounds, the efficiency of this approach would depend entirely on the diversity of MMP network-space and the consistency of the SAR within this network. This observation is also reflected in Figure 3.

In summary, MuDRA was shown to be as reliable as QSAR models, but easier and faster to develop, as well as more transparent while providing 100% coverage. The workflow for MuDRA model generation includes the following steps: (i) calculation of various chemical descriptors for the training set, (ii) calculation of Tanimoto similarity for the query compound against all chemicals in the training set in all descriptor spaces; (iii) activity prediction for the query compound based on the weighted similarity to the nearest neighbors of the query in each chemical space. Since the increase in the number of NNs is not followed by the increase in the accuracy of MuDRA models, we strongly suggest using only one NN per descriptor type. We also emphasize that similar to any QSAR method, the MuDRA model accuracy is estimated for an external set not used to build and/or select the models.

Dissemination

To enable the use of this approach, we have added a MuDRA module to Chembench, our integrated cheminformatics web portal⁵⁴. More details about Chembench could be found

elsewhere⁵⁴. Similar to other cheminformatics services at Chembench⁵⁴, MuDRA module is freely accessible at <https://chembench.mml.unc.edu/mudra>.

To execute the MuDRA approach on Chembench, the user must first upload chemical structures and associated activities (either continuous or binary values) as a modeling dataset in the Datasets module. Then, MODI¹² and the descriptors required for MuDRA are calculated. The descriptors available for building MuDRA models include DragonH⁵⁵, MOE2D⁵⁶, MACCS keys⁵⁷, and ISIDA⁵⁸. These descriptors were selected because they are different in nature and available for QSAR model development on our publicly accessible Chembench portal. It should be noted that several publicly available datasets such as Tox21 stress response and nuclear receptor signaling toxicity assay datasets⁵⁹ have been included with the MuDRA module.

Once the modeling dataset is uploaded successfully, the user must access the MuDRA module within Chembench and select the dataset. This module facilitates predictions of single compounds, batches of multiple compounds, and virtual chemical libraries. A single compound can be sketched directly using JSME⁶⁰ or its SMILES can be input. A specific library of interest or a batch of compounds can be uploaded within the Datasets module and used for virtual screening. Chembench has several publicly available chemical libraries, such as the DrugBank⁶¹ and the ZINC lead-like library⁶², that can be also used for virtual screening. Next, the predicted activity of the compound(s) is calculated according to MuDRA equations 2–4.

For a single compound predictions, the outputs are the compound SMILES, the predicted activity, the number of k nearest neighbors (default is to set $k = 1$), as well as the average Tanimoto similarity, average activity, and k nearest neighbor IDs for all four descriptor types used (Figure 4). For predictions of multiple compounds, the outputs are the ID of the screened compound, the average prediction value, the rounded prediction value (for binary data), the number of k nearest neighbors (default is to set $k = 1$), as well as the average activity, average similarity, and IDs of the k nearest neighbor IDs for all four descriptor types used (Figure 5). Multiple compound prediction results can be downloaded as a CSV-delimited file.

Conclusions

We have developed a simple, fast, and reliable approach that yields models of high accuracy with 100% coverage of the prediction set. We posit that because of its simplicity and high accuracy, MuDRA can be successfully used as a computationally efficient but no less reliable, in terms of statistical accuracy and predictive power, alternative to ensemble QSAR. The results obtained on several diverse datasets demonstrated that MuDRA has similar predictive performance to traditional QSAR approaches. At the same time, due to its conceptual simplicity and transparency, MuDRA affords non-experts in the field an alternative to structural alerts and read-across. We have made an implementation of MuDRA freely available on the Chembench web-portal (<https://chembench.mml.unc.edu/mudra>).

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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Abbreviations

AD	applicability domain
CBRA	Chemical-Biology Read-Across
CCR	correct classification rate
MuDRA	Multi-Descriptors Read-Across
MODI	Modelability Index
NN	nearest neighbor
NPV	negative predictive value
PPV	positive predictive value
QSAR	quantitative structure-activity relationship
SiRMS	Simplex Representation of Molecular Structure

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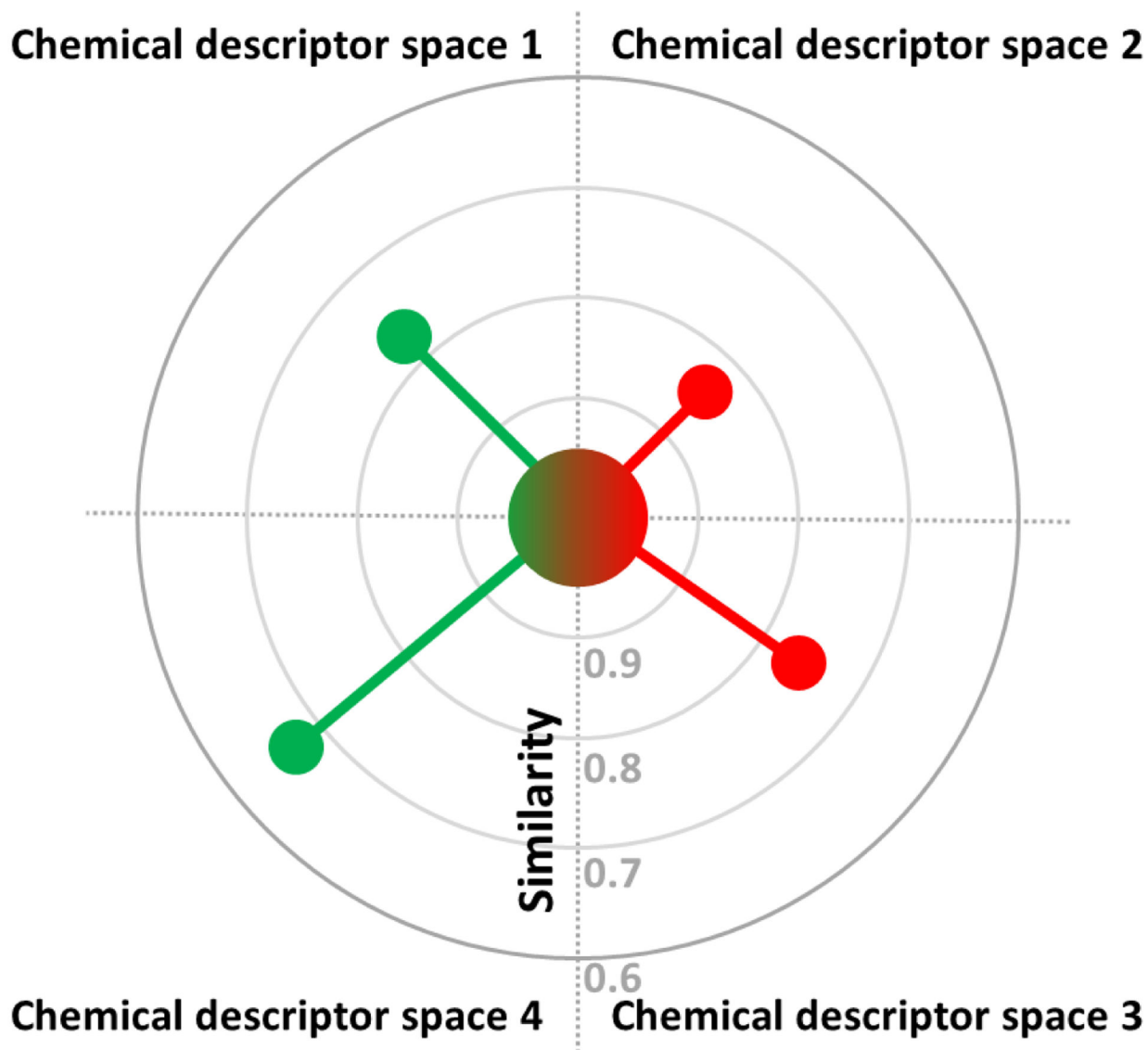


Figure 1.

Radial plot representation of the MuDRA method. Activity (toxicity) prediction for a query compound (in the center) is accomplished based on the identification of the nearest neighbor compounds of the query compound in each chemical space (for simplicity of illustration, only one nearest neighbor is shown, but multiple such neighbors are identified typically). Red color circles represent active (or toxic) compounds and green circles represents inactive (or non-toxic) compounds. The activity (or toxicity) of a query compound is predicted as a weighted average of those of the similar compounds where the weight is inversely proportional to the distance from the query (see Eqs. 2 and 3).

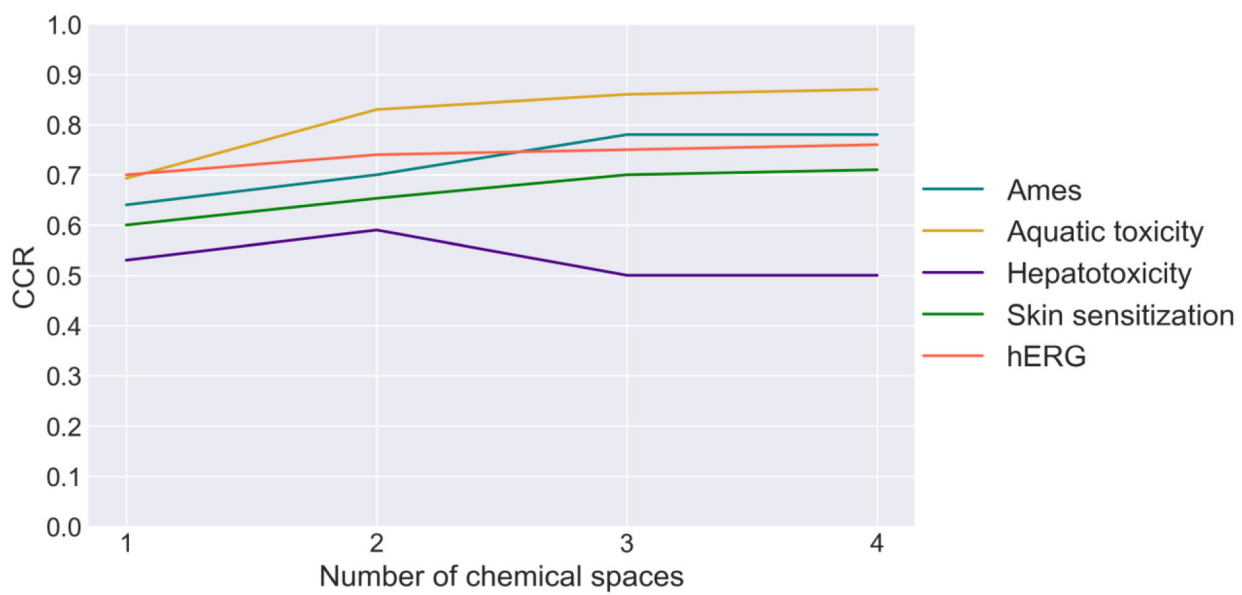


Figure 2.
Correct classification rate variation for 1, 2, 3, and 4 chemical spaces.

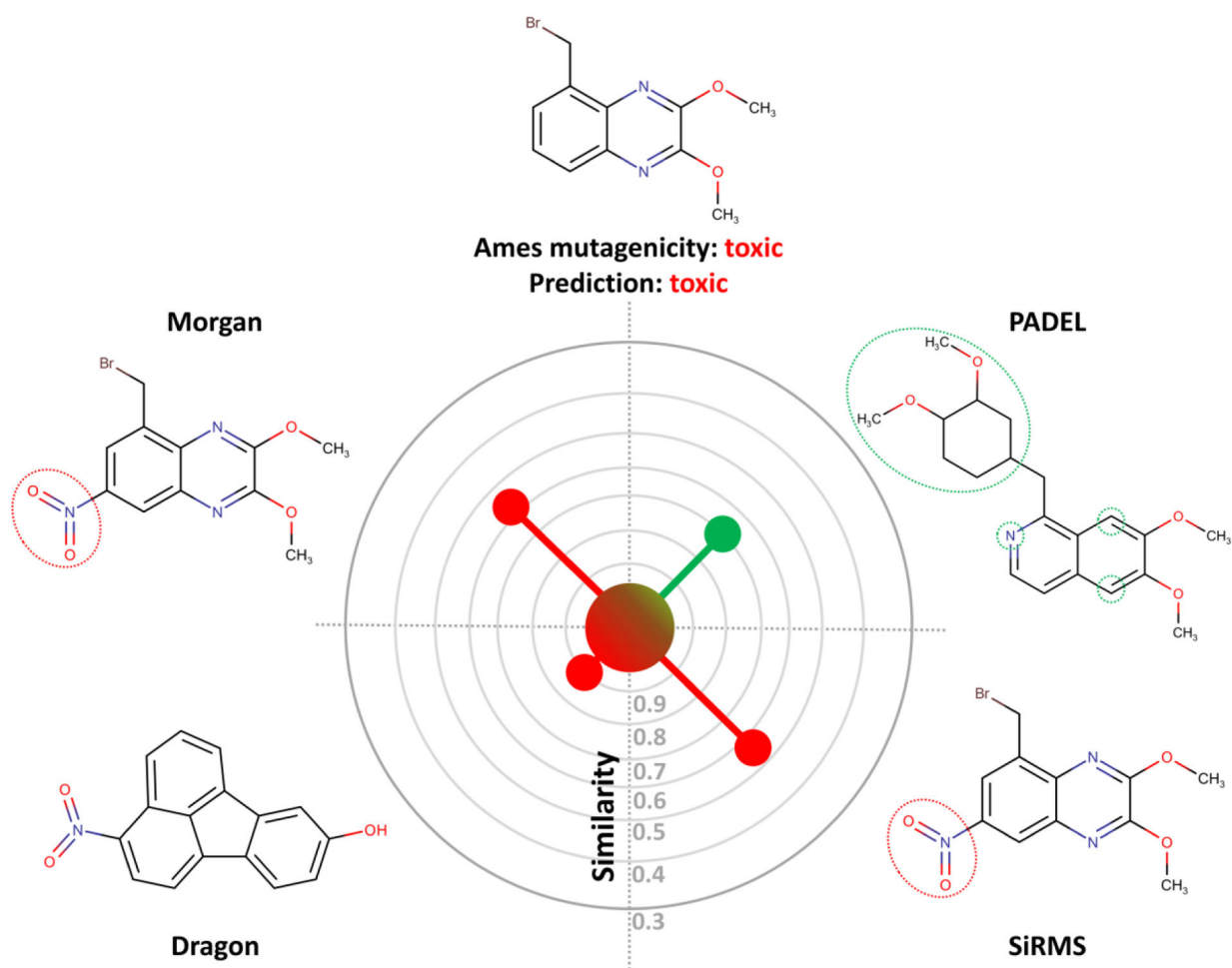


Figure 3.
Example of the analysis of NNs in different chemical spaces provided by MuDRA.

Select a Modeling Dataset

Name	Size	Type	Descriptors	MODI	Date	Public?
AURKB Download Delete	743	Modeling (category)	Dragon 7, CDK, DragonX-H, DragonX-NoH, MOE2D, MACCS, ISIDA	0.91	2017-10-22	Public

Make a Prediction

Now you can make a prediction using the modeling dataset you have selected above. You can either predict a single compound at a time, or predict an entire dataset at once. Use the tabs to change the selected prediction mode.

Predict a Single Compound | Predict a Dataset

Predict a Single Compound

Clear | Get SMILES and Predict

Enter a molecule in SMILES format, e.g. C1=CC=C(C=C1)CC(=O)N (phenylalanine). Or, use the applet on the left to draw a molecule, then click "Get SMILES and Predict".

SMILES:

Predict

Compound: COc3cc2ncnc(Nc1ccc(F)c(Cl)c1)c2cc3OC
 Predicted Activity: 0.73
 Rounded Activity: 1
 Nearest Neighbors: 1

Descriptor Type	Average Similarity	Average Activity	Neighbor Ids
DRAGONH	1	1	4489623
MOE2D	0.99	0	4365574
MACCS	0.78	1	4489599
ISIDA	0.88	1	4489296

Figure 4. MuDRA prediction for a single compound. In the MuDRA module, a modeling dataset "AURKB" was selected and the single compound to be assessed was sketched. The compound was then predicted and results of MuDRA were output.

Select a Modeling Dataset

Name	Size	Type	Descriptors	MODI	Date	Public?
AURKB Download Delete	743	Modeling (category)	Dragon 7, CDK, DragonX-H, DragonX-NoH, MOE2D, MACCS, ISIDA	0.91	2017-10-22	Public

Make a Prediction

Predict a Single Compound | Predict a Dataset

Predict a Dataset

Name	Size	Type	Descriptors	MODI	Date	Public?
Ebola_SM1 Download Delete	166	Modeling (category)	CDK, DragonX-H, DragonX-NoH, MOE2D, MACCS, ISIDA	0.65	2016-09-09	Public

Download (.csv)

Showing 166 entries

DRAGONH							
Compound	Prediction	Rounded Prediction	# Neighbors	Activity	Similarity	Neighbors	Activity
2247	0.73	1	1	1	1	4418000	0
2351	0.28	0	1	0	0.97	4472287	1
2377	0.73	1	1	0	0.91	4384276	1

Figure 5. MuDRA predictions for multiple compounds. In the MuDRA module, a modeling dataset “AURKB” was selected and a library of 166 compounds called “Ebola_SM1” was assessed. The compounds were then predicted and results of MuDRA were output. These results are downloadable as a CSV file. It should be noted that the full list of compounds and the associated outputs are not shown here.

Table 1.

Summary of datasets employed in this study.

Endpoint	Modeling set	External set	Reference
Ames mutagenicity	4,361	2,181	34
Aquatic toxicity	644	339	13
Hepatotoxicity	102	25	35
hERG	4,787	1,197	36
Skin sensitization	294	221	37
Endocrine disruptors	Not applicable.	6,319, 6,539, and 7,283	23

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Table 2.

Calculated MODI for each set of descriptors.

Datasets	Descriptors			
	Morgan	PaDEL	SiRMS	DRAGON
Ames mutagenicity	0.70	0.71	0.72	0.70
Aquatic toxicity	0.77	0.80	0.78	0.79
Hepatotoxicity	0.58	0.67	0.68	0.57
hERG	0.70	0.71	0.72	0.71
Skin sensitization	0.75	0.72	0.72	0.72

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Table 3.

Statistical characteristics of external QSAR predictions vs. MuDRA predictions for selected toxicity endpoints.

Ames mutagenicity (<i>n</i> = 2,181)						
Models	CCR	Sensitivity	PPV	Specificity	NPV	Coverage
Consensus	0.79	0.91	0.76	0.67	0.86	1.00
Consensus AD	0.79	0.91	0.77	0.66	0.86	0.91
1-NN MuDRA	0.78	0.78	0.80	0.78	0.76	1.00
3-NN MuDRA	0.80	0.80	0.82	0.80	0.77	1.00
5-NN MuDRA	0.79	0.81	0.81	0.78	0.78	1.00
7-NN MuDRA	0.80	0.82	0.80	0.77	0.79	1.00
Aquatic toxicity (<i>n</i> = 339)						
	CCR	Sensitivity	PPV	Specificity	NPV	Coverage
Consensus	0.86	0.93	0.85	0.80	0.89	1.00
Consensus AD	0.93	0.97	0.92	0.89	0.96	0.81
1-NN MuDRA	0.87	0.90	0.88	0.85	0.87	1.00
3-NN MuDRA	0.88	0.92	0.88	0.83	0.89	1.00
5-NN MuDRA	0.86	0.88	0.88	0.84	0.85	1.00
7-NN MuDRA	0.86	0.89	0.88	0.84	0.86	1.00
Hepatotoxicity (<i>n</i> = 25)						
	CCR	Sensitivity	PPV	Specificity	NPV	Coverage
Consensus	0.48	0.11	0.33	0.86	0.60	1.00
Consensus AD	0.49	0.17	0.33	0.82	0.64	0.68
1-NN MuDRA	0.50	0.20	0.40	0.80	0.60	1.00
3-NN MuDRA	0.50	0.20	0.40	0.80	0.60	1.00
5-NN MuDRA	0.53	0.20	0.50	0.87	0.62	1.00
7-NN MuDRA	0.50	0.20	0.40	0.80	0.60	1.00
hERG (<i>n</i> = 1,197)						
	CCR	Sensitivity	PPV	Specificity	NPV	Coverage
Consensus	0.80	0.87	0.82	0.72	0.80	1.00
Consensus AD	0.80	0.87	0.82	0.73	0.80	0.93
1-NN MuDRA	0.76	0.82	0.78	0.69	0.74	1.00
3-NN MuDRA	0.77	0.87	0.79	0.68	0.79	1.00
5-NN MuDRA	0.78	0.87	0.78	0.68	0.80	1.00
7-NN MuDRA	0.75	0.87	0.76	0.64	0.78	1.00
Skin sensitization (<i>n</i> = 217)						
	CCR	Sensitivity	PPV	Specificity	NPV	Coverage
Consensus	0.66	0.64	0.90	0.68	0.28	1.00
Consensus AD	0.78	0.82	0.94	0.75	0.46	0.42
1-NN MuDRA	0.71	0.66	0.93	0.76	0.31	1.00
3-NN MuDRA	0.64	0.64	0.90	0.65	0.27	1.00

5-NN MuDRA	0.62	0.62	0.89	0.62	0.25	1.00
7-NN MuDRA	0.68	0.65	0.91	0.70	0.29	1.00

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Table 4.

Statistical characteristics of external QSAR predictions reported in CERAPP *vs.* MuDRA predictions for endocrine receptor activity.

Agonist (<i>n</i>=6,319)			
Model	CCR	Sensitivity	Specificity
CERAPP (<i>n</i> = 5)	0.73 (\pm 0.05)	0.51 (\pm 0.13)	0.95 (\pm 0.05)
MuDRA	0.74	0.65	0.83
Antagonist (<i>n</i>=6,532)			
Model	CCR	Sensitivity	Specificity
CERAPP (<i>n</i> =)	0.53 (\pm 0.02)	0.11 (\pm 0.09)	0.95 (\pm 0.05)
MuDRA	0.52	0.05	0.99
Binding (<i>n</i>=7,283)			
Model	CCR	Sensitivity	Specificity
CERAPP (<i>n</i> = 9)	0.57 (\pm 0.02)	0.27 (\pm 0.11)	0.85 (\pm 0.08)
MuDRA	0.58	0.35	0.81