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Data Set Modelability by QSAR

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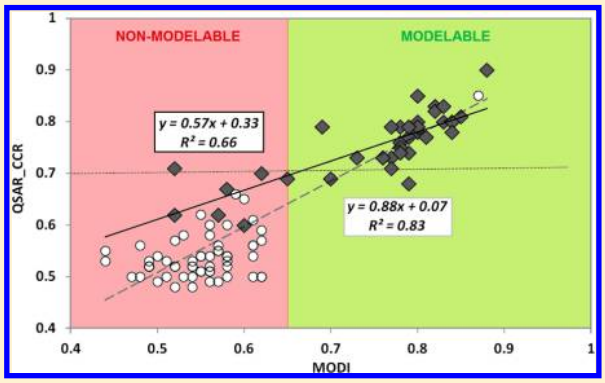
Supporting Information



ABSTRACT: We introduce a simple MODelability Index (MODI) that estimates the feasibility of obtaining predictive QSAR models (correct classification rate above 0.7) for a binary data set of bioactive compounds. MODI is defined as an activity class-weighted ratio of the number of nearest-neighbor pairs of compounds with the same activity class versus the total number of pairs. The MODI values were calculated for more than 100 data sets, and the threshold of 0.65 was found to separate the nonmodelable and modelable data sets.

Cheminformatics approaches such as QSAR modeling are applied widely for the analysis of growing collections of bioactive compounds in private and publicly available online repositories such as ChEMBL[1] and PubChem.[2] The resulting models are used for designing new bioactive molecules or identifying those by virtual screening; thus, it is imperative that such models have reliable external predictive power.

We[3,4] and others[5] have shown previously that the predictivity of QSAR models is directly influenced by various data set characteristics (e.g., size, chemical diversity, activity distribution, presence of activity cliffs, etc.) as well as the modeling workflow (e.g., data set curation, variable selection, external validation, consensus modeling, use of applicability domain, etc.) utilized to build, select, and validate the models.[6] It is not uncommon for cheminformaticians to employ many different descriptor types, machine-learning techniques, validation workflows, etc., in a combinatorial manner in order to maximize the prediction performance of QSAR models.[7] Such attempts are time and resource consuming, especially when the data sets contain more than a few thousands compounds (which becomes more and more common). However, extensive investigations of large collections of data sets suggests that it is often impossible to build models with appreciable external predictive power even when the most sophisticated algorithms and rigorous modeling workflows are employed.[8]

Herein, we introduce a concept of "data set modelability", i.e., an a priori estimate of the feasibility to obtain externally predictive QSAR models for a data set of bioactive compounds. This concept has emerged from analyzing the effect of so-called "activity cliffs" on the overall performance of QSAR models. Indeed, in a seminal observation, Maggiora[9] suggested that the presence of activity cliffs, i.e., very similar compounds with very different activities, present significant challenges for QSAR modeling. Thus, SALI[10] and ISAC[11] scores were developed for identifying activity cliffs based on ligand- and structure-based approaches, respectively. A recent excellent review from the Bajorath group[12] discusses many issues posed by the activity cliffs for cheminformatics investigations.

The effect of activity cliffs in a data set on the process and outcome of the QSAR modeling can be illustrated by the case of stereoisomers. Indeed, the nature and the actual number of activity cliffs not only depends on the end point and overall data quality but also on the choice of descriptors used to characterize chemical structures. When stereoisomers (as well as some other types of isomers) are present in a data set, it is important to explore whether descriptors used to characterize compounds are sensitive to chirality. Obviously, when using two-dimensional (2D) descriptors, any pair of stereoisomers appears as duplicates. In this case, prior to the actual modeling of the chemical data set, one should carefully check the experimental properties reported for all the pairs of stereoisomers present in the set. If the target property values for stereoisomers are significantly different, we have an extreme case of activity cliffs when two formally identical compounds have different activities and we have no ground to chose one over another; therefore such pairs should be removed from the data set prior to model building (or 3D descriptors should be employed). On the other hand, if stereoisomers have similar activities, one of them could be kept for model development.

The obvious attention given to the problem of activity cliffs notwithstanding, to the best of our knowledge there has not been any exhaustive study to explore (i) how the number of activity cliffs in a given data set correlates with the overall prediction performance of QSAR models for this data set, (ii) whether such correlation is conserved across different data sets,

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and (iii) whether one could use the fraction of activity cliffs in a data set to assess the overall possibility of success or failure for QSAR modeling. To this end, we propose a "MODelability Index" (MODI) as a quantitative means to quickly assess whether predictive QSAR model(s) can be obtained for a given chemical data set. The current version of MODI is only applicable to binary end points, but its extension to data sets of compounds with real activity values is also possible.

MODI is computed based on the following considerations. For every compound in a data set, we determine whether its first nearest neighbor, i.e., a compound with the smallest Euclidean distance from a given compound estimated in the entire descriptor space, belongs to the same or different activity class. In the latter case, the pair can be formally designated as an activity cliff. The number of nearest neighbor pairs that are not activity cliffs is counted for each class of compounds and is used to calculate MODI as follows:

$$\mathrm{MODI} = \frac{1}{K}\sum_{i=1}^{K}\frac{N_i^{\mathrm{same}}}{N_i^{\mathrm{total}}} \quad (1)$$

where K is the number of classes ($K = 2$ for binary data sets), N_i^{same} is the number of compounds of i-th activity class that have their first nearest neighbors belonging to the same activity class i; N_i^{total} is the total number of compounds belonging to the class i.

The predictive performance of QSAR models is expressed as the correct classification rate (or balanced accuracy)[13] calculated with 5-fold external cross-validation (QSAR_CCR). Note that QSAR_CCR could be also estimated from a formula similar to eq 1, where N_i^{same} would be the number of correctly predicted compounds belonging to ith activity class. In general, we consider the QSAR model to have an acceptable predictive power if it affords QSAR_CCR equal or higher than 0.7 (see ref 6).

The utility of MODI was assessed initially using 42 diverse data sets related to pharmaceutical targets: MDR1,[14] MDR1i,[14] six types of *C. Elegans* toxicity,[15] and 34 GPCR data sets.[16] All the details related to QSAR modeling including molecular descriptors, machine learning techniques, and the results of the modeling are given in the Supporting Information. Prior to the analysis, all data sets considered in this study were rigorously curated according to the workflow developed in our laboratory.[3] QSAR models were built using Dragon[17] and, for a few cases, MOE[18] descriptors, and one or several machine learning techniques including k-nearest neighbors (kNN), support vector machines (SVM), and random forest (RF). When examining the results, we have found a significant correlation ($R^2 = 0.66$) between MODI and a model's predictivity (i.e., QSAR_CCR) as illustrated in Figure 1. Although this correlation is not high enough to predict the exact QSAR_CCR value from MODI, it still affords a reasonable assessment whether the data set is modelable or not. Obviously, this initial collection had a bias toward modelable data sets (QSAR_CCR > 0.7) because these data sets included compounds tested in high-quality in vitro assays against specific molecular targets.

Recently, Thomas et al.[8] published the results of massive QSAR calculations for ToxCast (www.epa.gov/ncct/toxcast/) data sets with the goal of predicting 60 ToxRefDB (epa.gov/ncct/toxrefdb/) in vivo toxicity end points. They used both chemical descriptors and the results of in vitro assays considered as independent variables as well as a combination

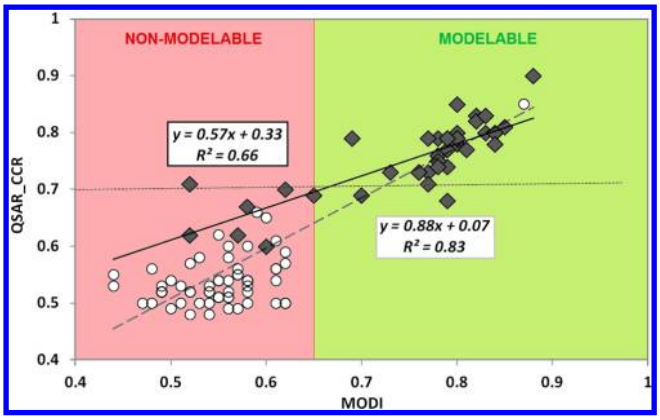

Figure 1. Correlation between QSAR_CCR (*Y*-axis) and MODI (*X*-axis) for 42 miscellaneous (*black diamonds*) and 60 ToxCast data sets (*hollow circles*). Regression lines and the corresponding equations are shown for 42 data sets (*solid line*) and all 102 data sets (*dashed line*).

of chemical and biological descriptors to predict in vivo toxicities but for this study we only used QSAR models built with conventional chemical descriptors (see the Supporting Information for details). The authors[8] employed all possible combinations (as many as 84) of descriptors, modeling techniques, and rigorous validation workflows. However, no models with significant predictive power (much greater than 50% for binary classification models) were obtained with only one exception. Thus, we enriched our initial pool of data sets with those taken directly from ref 8. Similarly to the initial pool of 42 sets, we chose models with the highest QSAR_CCR values among the 84 models obtained by Thomas et al.[8] for each of the 60 in vivo end points (see Figure 1).

As Thomas et al.[8] have already established that no good models have been generated for those data sets, we should have expected low MODI values. Indeed, we have found that 59 out of 60 data sets (represented as a cluster of white circles in the lower left part of Figure 1) were characterized by low MODI values, in full agreement with the failure of Thomas et al.[8] to develop QSAR models with significant predictive power. The only exception was the rat cholinesterase inhibition data set for which MODI = 0.83 and QSAR_CCR = 0.82 (white circle in upper-right part of Figure 1). Similar results have been generated using models built with biological descriptors (data not shown). Interestingly, the authors commented on their findings by positing that in vitro assays have "limited applicability for predicting in vivo chemical hazards using standard statistical classification methods", i.e., questioning the in vitro to in vivo extrapolation paradigm as applied to the Toxcast data sets. On the contrary, our studies suggest that the data sets employed in that study, with one exception, were merely not amenable to the development of predictive models because of a large fraction of activity cliffs.

In order to study how the choice of chemical descriptors influences the MODI values, we computed different types of descriptors (SiRMS,[19] Dragon,[17] ISIDA,[20] MACCS,[21] and MOE[18]) for six different data sets: DEV[8] (n = 241 compounds), CHR[8] (n = 238), 212.ind[15] and 212.scor[15] (the same 212 compounds but different end points), D_3[16] (n = 1509), and $5HT_5$[16] (n = 195). As shown in Figure 2, the types of chemical descriptors had rather weak influence on MODI. Additional details about these data sets can be found in Supporting Information.

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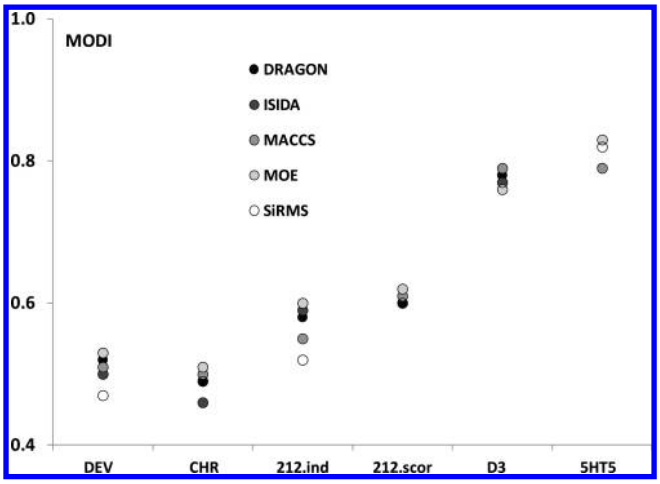

Figure 2. Low variability of MODI when different types of chemical descriptors are used.

Overall, for all 102 data sets (42 pharmaceutical targets plus 60 Toxcast data sets), the correlation between QSAR_CCR and MODI values was high (R^2 = 0.83) demonstrating the validity of MODI as a reliable simple metric to evaluate the data set modelability a priori. The correlation shown in Figure 1 affords a simple means to estimate the highest QSAR_CCR value from that of MODI. However, as a possible pitfall, this correlation may have limited generality: for instance, only a small number of data sets had MODI values ranging between 0.65 and 0.75. Thus, additional studies with more data sets are needed to validate the quantitative relationship between MODI and the best QSAR_CCR.

In summary, we have introduced the QSAR MODI as a simple metric for rapidly assessing whether a given chemical data set is likely to be modelable or not. The results of this study suggest (cf. Figure 1) that a MODI value for a given data set below 0.65 indicates that one should not expect to achieve QSAR models with significant predictive power; whereas MODI > 0.65 implies that the underlying data set is modelable and will have QSAR_CCR greater than 0.7. As follows from Figure 1, there are very few outliers from this general simple rule.

This study begs a natural question as to why some data sets are modelable whereas others are not. As follows from the simple formula for MODI (see eq 1), this index depends on the fraction of activity cliffs in a data set. Activity cliffs are not uncommon and indeed there are many examples of compound pairs that are highly similar to each other and yet have significantly different or opposite (in case of binary classification) activities:[12] these cases represent true activity cliffs. However, we shall point out that eq 1 does not require that the pairs of compounds defined formally as activity cliffs should be highly similar to each other. These pairs are defined as nearest neighbors only within a given data set and they may not be highly similar to each other based on absolute similarity metric such as Tanimoto coefficient (Tc). The use of eq 1 to estimate MODI is based on a reasonable expectation (which is the foundation of the active analog principle widely used by both experimental and computational medicinal chemists) that similar compounds are expected to have similar activities; thus a "modelable" data set is expected to have a large fraction of compound pairs that follow the active analog principle. On the other hand, many modern data sets especially relatively large ones evaluated for some general biological effect such as toxicity (e.g., Toxcast data set explored by Thomas et al.[8]) may include rather diverse collections of chemicals that may exert the underlying biological effects through multiple mechanisms. In such cases, one should not have any rational expectation that two compounds with different chemical structure that appear as formal nearest neighbors should have similar end point effects, and in fact this is often not the case. It then follows that chemically diverse data sets tested for the same end point activity should contain a large fraction of activity cliffs making them nonmodelable. Indeed, the analysis of data sets explored in this study suggests that as a rule, nonmodelable data sets with relatively low MODI values also have relatively low average Tc values for all pairs of nearest neighbors and, vice versa, modelable data sets have relatively high Tc values (Figure 3). It also suggests that, although a data set with low MODI is not modelable as a whole, it may still contain subsets of compounds with high MODI for which local QSAR models can be built.

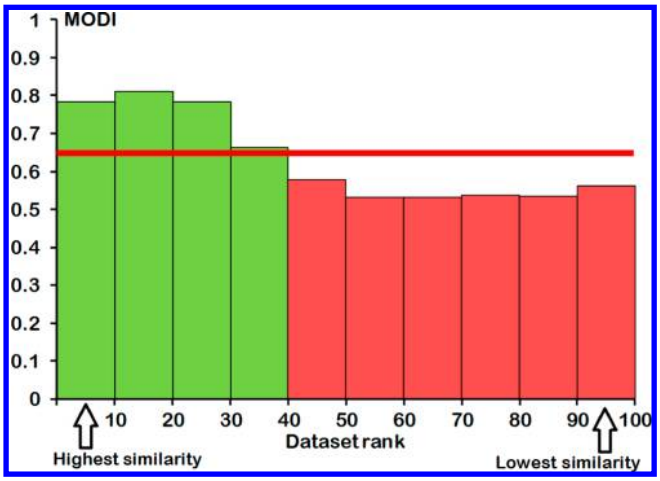

Figure 3. MODI (*Y-axis*) vs data set rank (ordered by descending average structural similarity (Tc) between all pairs of nearest neighbors within a data set; *X-axis*). The horizontal line at MODI = 0.65 is a cutoff value separating modelable (*green bars*) vs nonmodelable (*red bars*) data sets.

In conclusion, we suggest that MODI is a simple characteristic that can be easily computed for any data set at the onset of any QSAR investigation. We hope that this simplicity will prompt our colleagues to compute and report MODI for any data set they consider developing QSAR models for, which will enable further evaluation of the data set modelability concept introduced in this study. Finally, we shall point out that studies reported herein for binary data sets can be easily extended for additional data sets with multiclass and continuous value activities.

■ ASSOCIATED CONTENT

Ⓢ Supporting Information

Details about data sets, Dragon descriptors, and machine leaning techniques. Tables A–E. This material is available free of charge via the Internet at http://pubs.acs.org.

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Notes

The authors declare no competing financial interest.

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