

Using Attribution to Decode Binding Mechanism in Neural Network Models for Chemistry

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1 **Deep neural networks have achieved state of the art accuracy at clas-**
2 **sifying molecules with respect to whether they bind to specific pro-**
3 **tein targets. A key breakthrough would occur if these models could**
4 **reveal the fragment pharmacophores that are causally involved in**
5 **binding. Extracting chemical details of binding from the networks**
6 **could enable scientific discoveries about the mechanisms of drug**
7 **actions. But doing so requires shining light into the black box that**
8 **is the trained neural network model, a task that has proved difficult**
9 **across many domains. Here we show how the binding mechanism**
10 **learned by deep neural network models can be interrogated, using**
11 **a recently described attribution method. We first work with carefully**
12 **constructed synthetic datasets, in which the molecular features re-**
13 **sponsible for 'binding' are fully known. We find that networks that**
14 **achieve perfect accuracy on held out test datasets still learn spu-**
15 **rious correlations, and we are able to exploit this non-robustness**
16 **to construct adversarial examples that fool the model. This makes**
17 **these models unreliable for accurately revealing information about**
18 **the mechanisms of protein-ligand binding. In light of our findings,**
19 **we prescribe a test that checks whether a hypothesized mechanism**
20 **can be learned. If the test fails, it indicates that either the model must**
21 **be simplified or regularized and/or that the training dataset requires**
22 **augmentation.**

Virtual screening | Deep learning | Attribution for molecules | Overfitting

1 **A** major stumbling block to modern drug discovery is to
2 discover small molecules that bind selectively to a given
3 protein target, while avoiding off-target interactions that are
4 detrimental or toxic. The size of the small molecule search
5 space is enormous, making it impossible to sort through all
6 the possibilities, either experimentally or computationally (1).
7 The promise of *in silico* screening is tantalizing, as it would
8 allow compounds to be screened at greatly reduced cost (2).
9 However, despite decades of computational effort to develop
10 high resolution simulations and other approaches, we are still
11 not able to rely solely upon virtual screening to explore the
12 vast space of possible protein-ligand binding interactions (3).

13 The development of high throughput methods for empiri-
14 cally screening large libraries of small molecules against pro-
15 teins has opened up an approach where machine learning
16 methods correlate the binding activity of small molecules with
17 their molecular structure (4). Among machine learning ap-
18 proaches, neural networks have demonstrated consistent gains
19 relative to baseline models such as random forest and logistic
20 regression (5–9). In addition to protein-ligand binding, such
21 models have been trained to predict physical properties that
22 are calculated using density functional theory, such as polar-
23 izable and electron density (10–12). The ultimate promise
24 of data-driven methods is to guide molecular design: models
25 learned from ligands that bind to particular proteins will eluci-

26 date mechanism and generate new hypotheses of ligands that
27 bind the required target in addition to improved understanding
28 of the non-covalent interactions responsible.

29 The motivating question for this work is: *Why do virtual*
30 *screening models make the predictions they do?* Despite their
31 high accuracy, the major weakness of such data-driven ap-
32 proaches is the lack of causal understanding. While the model
33 might correctly predict that a given molecule binds to a partic-
34 ular protein, it typically gives no indication of which molecular
35 features were used to make this decision. Without this, it is
36 not clear if the model learns the mechanism of binding, or
37 spurious molecular features that correlate with binding in the
38 dataset being studied (13–15). Such model weaknesses are
39 not captured by traditional evaluations that measure model
40 accuracy on held out test sets because these held out sets suffer
41 from experimental selection bias and do not contain random
42 samples drawn at uniform from the space of *all* molecules.

43 The key issue is to assess whether state-of-the-art neural
44 network models trained on protein-ligand binding data learn
45 the correct binding mechanisms, despite the presence of dataset
46 bias. To unravel this, we define a synthetic "binding logic" as a
47 combination of molecular fragments that must be present (or
48 absent) for binding to occur, e.g. "naphthalene and no primary
49 amine". We construct 16 binding logics and use each to label
50 molecules from the Zinc12 database (16). We randomly split
51 the dataset for each logic into test and train splits, and train
52 models. Model attribution is used to assess whether each
53 trained model has learned the correct binding logic.

54 To measure model performance on heldout sets we report
55 the Area Under the Curve ("AUC") of the Receiver Operating
56 Characteristic ("ROC") curve (17), and refer to this as the

Significance Statement

Advances in machine learning have led to neural networks for virtual screening, which sift through trillions of small molecules to find those that are pharmacologically important. Such methods have the potential to make chemical discoveries, but only if it is possible to untangle why models make the predictions that they do. Here we use attribution methods to investigate neural networks models for small molecule binding, and show that while it is possible to identify pharmacophores, there is also the real possibility that a model which seems to perform perfectly instead learns spurious correlations in the underlying dataset. We propose an attribution based test for determining whether a model can learn a hypothesized binding mechanism.

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57 *Model AUC.* We then use a recently developed attribution
58 method (18) to verify if each model learns its corresponding
59 binding logic correctly. The method assigns an attribution
60 score to each atom that reports how important the atom is to
61 the model's ultimate prediction. We develop a novel metric
62 called the *Attribution AUC* that measures how well the per-
63 atom attribution scores reflect the ground truth binding logic.
64 The atoms within each molecule are ranked by their attribution
65 scores, and these rankings compared with the ground truth
66 binary label for each atom indicating whether that atom is
67 part of the binding logic.

68 The synthetic labels perfectly obey each binding logic, re-
69 moving issues of experimental noise, so it is perhaps not sur-
70 prising that neural network models obtain Model AUC ≈ 1.0
71 in all cases on heldout sets filtered from Zinc. Nonetheless,
72 the Attribution AUC is often much lower than 1.0, likely due
73 to biases in the original dataset. Zinc12 does not contain all
74 possible molecules, so there are molecular fragments that cor-
75 relate with the binding logic but are not themselves involved in
76 binding. This dataset bias implies that there exist "adversarial
77 molecules" that do not satisfy the defined binding logic, for
78 which the model makes incorrect predictions. Indeed, exam-
79 ining the model attributions allows us to identify adversarial
80 molecules. Hence, even in this controlled setting, the network
81 fails to learn the binding logic. Real-world protein-binding
82 tasks are even more complex, due to noise in the binding assay,
83 as well as underlying binding logics that are potentially more
84 complex.

85 To illustrate the practical utility of this approach, we apply
86 this framework to ligands from the DUD-E dataset (19) that
87 bind ADRB2. We create a hypothesized logic for the binding
88 mechanism, and create synthetic labels for the DUD-E dataset
89 based on this logic. Although a graph convolutional neural
90 network makes perfect predictions on a held out dataset, biases
91 in the dataset lead us to discover molecules which the model
92 predicts bind to ADRB2, despite not satisfying the logic. The
93 pattern used by the model to decide binding is different from
94 the logic we imposed. Thus, despite its seemingly perfect
95 performance, the model is fundamentally not able to predict
96 that molecules bind for the right reason.

97 Analysis Framework

98 To generate data with ground truth knowledge of the bind-
99 ing mechanism, we construct 16 synthetic binary label sets
100 in which binding is *defined* to correspond to the presence
101 and/or absence of particular logical combinations of molecular
102 fragments. For example, ligands could be labeled positive
103 (i.e. bind to the target protein) if they obey the binding logic
104 "carbonyl **and no** phenyl." Each binding logic is used to filter
105 the Zinc database of molecules to yield sets of positive and
106 negative labeled molecules. In our implementation we specify
107 molecular fragments using the SMARTS format (20) and we
108 use RDKit (21) to match them against candidate molecules,
109 with a custom implementation of the logical operators **and**,
110 **or**, and **not**. The 16 logics used in this paper are made up
111 of elements sampled from 10 functional groups (Table S1),
112 with up to four elements per logic joined by randomly selected
113 operators (Tables 1, S2).

114 Dataset bias in chemistry is a well known issue that has
115 previously been described (13). Essentially molecules that
116 have been used in protein-ligand binding assays are not drawn

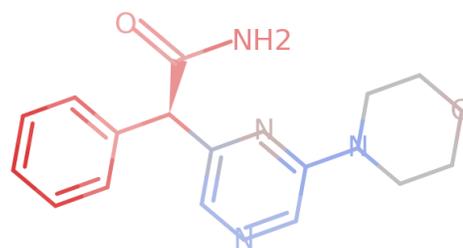


Fig. 1. An example of per-atom model attributions visualized for a molecule. Each atom is colored on scale from red to blue in proportion to its attribution score with red being the most positive and blue being the most negative.

uniformly at random from chemical space, but instead their se-
lection for inclusion in a binding assay reflects the knowledge of
expert chemists. These biases mean that large neural network
models are at risk of overfitting to the training data. To reduce
this risk, we carefully construct each dataset to be balanced,
by sampling equally from all combinations of negations of the
functional groups that make up each logic. In the case of just
one functional group (A), this means that dataset contains
equal numbers of molecules that match "A" and "~A". When
there are two functional groups, say A and B, we have equal
numbers matching "A&B", "A&~B", "~A&B", and "~A&~B".
Similarly, all combinations are considered for logics with 3 and
4 functional groups. Each negation combination is represented
by 1200 molecules in the dataset, with approximately 10% of
each reserved for held out model evaluation.

Model Training. We use two models: the molecular graph
convolution (GC) model from Kearnes et al (22) and the
message passing neural network (MPNN) from Gilmer et al
(10). Both featurize each molecule using atoms and pairs of
atoms. We use the same hyperparameters reported, with the
exception of a minibatch size of 99 and training each to 10,000
steps, taking ≈ 1 hour on one GPU for each dataset. The
model returns a binding probability for each molecule in the
heldout test set, which is used to rank the molecules. Each
molecule has a binary label indicating whether it binds. The
ROC curve is generated by plotting the true positive rate
against the false positive rate for ranking score thresholds
in $[0, 1]$. The AUC is the area under the ROC curve: 1.0
is a perfect classifier with 100% true positives and 0% false
positives, while a random classifier would receive 0.5.

Attribution Technique: Integrated Gradients. We
next seek to determine whether these models have learned the
binding logic used to generate the synthetic labels. Given a
trained model and an input, an attribution method assigns
scores to each input feature that reflect the contribution of
that feature to the model prediction. Inspecting or visualizing
the attribution scores reveals what features, in our case atoms
and atom-pairs, were most relevant to the model's decision;
see Figure 1. Formally, suppose a function $F : \mathbb{R}^n \rightarrow [0, 1]$
represents a deep network.

Definition 1 The attribution at input $x = (x_1, \dots, x_n) \in \mathbb{R}^n$ is a vector $A_F(x) = (a_1, \dots, a_n) \in \mathbb{R}^n$ where a_i is the contribution of x_i to the prediction $F(x)$.

In our case, the input x is a molecule featurized into atoms
and atom pairs, and $F(x)$ denotes the probability of binding

162 to a protein target. To compute attributions to individual
 163 molecular features we use the *Integrated Gradients* method(18).
 164 This method is justified by an axiomatic result showing that
 165 it is essentially the unique method satisfying certain desirable
 166 properties of an attribution method. Formal definitions, re-
 167 sults, and comparisons to alternate attribution methods are
 168 available in (18).

169 In this approach, attributions are defined relative to a
 170 baseline input, which serves as the counterfactual in assessing
 171 the importance of each feature. Such counterfactuals are
 172 fundamental to causal explanations (23). For attribution on
 173 images, the baseline is typically an image made of all black
 174 pixels. Here, we use an input where all atom and atom-pair
 175 features are set to zero (details in Supplementary Information).

176 The Integrated Gradient is defined as the path integral
 177 of the gradient along the linear path from the baseline x' to
 178 the input x . The intuition is as follows. As we interpolate
 179 between the baseline and the input, the prediction moves
 180 along a trajectory, from uncertainty to certainty (the final
 181 probability). At each point on this trajectory, the gradient
 182 of the function F with respect to the input can be used to
 183 attribute the change in probability back to the input variables.
 184 A path integral is used to aggregate the gradient along this
 185 trajectory.

186 **Definition 2** Given an input x and baseline x' , the integrated
 187 gradient along the i^{th} dimension is defined as follows.

$$188 \quad a_i ::= (x_i - x'_i) \times \int_{\alpha=0}^1 \frac{\partial F(x' + \alpha \times (x - x'))}{\partial x_i} d\alpha \quad [1]$$

189 where $\frac{\partial F(x)}{\partial x_i}$ is the gradient of F along the i^{th} dimension at x .

190 Attribution scores are assigned to both atom and atom-pair
 191 features. To simplify the analysis, we distribute the atom
 192 pair scores evenly between the atoms present in each pair. If
 193 $v_i \in A_F$ is the attribution for atom i , and $e_{ij} \in A_F$ is the
 194 attribution for atom pair i, j , then our aggregated attribution
 195 vector (indexed over k atoms) $\tilde{A}_F = (\tilde{a}_1, \dots, \tilde{a}_k) \in \mathbb{R}^k$ where:

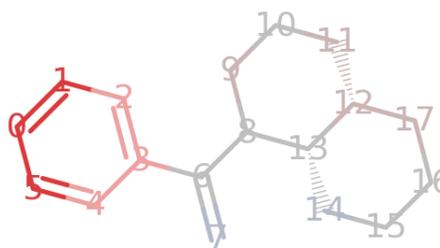
$$196 \quad \tilde{a}_i = v_i + \sum_{(i,j) \in E_i} \frac{e_{ij}}{2} \quad [2]$$

197 and E_i is the set of all featurized pairs that include atom i .
 198 Henceforth we study these aggregated per-atom attributions
 199 for each molecule.

200 **Attribution AUC.** Ideally, we would like the attribution
 201 scores to isolate the synthetic binding logic used to label the
 202 dataset, since this would translate to the ability to identify
 203 pharmacophores in real data. Attribution scores are typically
 204 studied by visualization using heatmaps; figure 1 provides a
 205 visualization of the per-atom attribution scores for a molecule.
 206 If a model learns the correct binding logic, we would expect
 207 the attribution scores to be larger in magnitude for atoms
 208 involved in the binding logic and small elsewhere.

209 Figure 2 illustrates the attributions calculated for a
 210 molecule using the model trained on logic 1, which requires
 211 a phenyl group. A positive attribution score (red) indicates
 212 that this atom increases "protein binding" ability, according to
 213 the trained model, whereas a negative attribution score (blue)
 214 indicates that the model thinks that this atom hurts binding.

215 Our goal is to evaluate how faithfully these scores reflect
 216 the binding logic used to label the dataset. To that end,



Atom index	Attribution scores ranked in decreasing order	Involved in ground truth binding logic
1	0.29	1
5	0.29	1
0	0.28	1
2	0.09	1
4	0.09	1
3	0.07	1
9	0.03	0
11	0.02	0
...

Fig. 2. Top, visualization of Integrated Gradients on a "binding" molecule for Logic 1 (must contain a phenyl group). Bottom, the top 8 atoms ranked by attribution score in descending order. This molecule would receive an Attribution AUC of 1.0 for these attributions, because all atoms involved the binding logic (indicated by 1 in the second column) have larger scores than all other atoms (marked 0 in second column).

217 we develop a novel metric called the *Attribution AUC* that
 218 measures how well the per-atom attribution scores reflect the
 219 ground truth binding logic. We handle fragments required to
 220 present for binding to occur separately from those required
 221 to be absent. If a binding logic contains fragments required
 222 to be present, we assign each fragment atom the label 1, and
 223 all other atoms the label 0. We then use these labels and the
 224 attribution scores to compute the Present-Attribution-AUC.
 225 If a logic contains fragments required to be absent, the process
 226 is analogous, except that we first multiply all attribution
 227 scores by -1.0 to reverse their ranking before calculating the
 228 Absent-Attribution-AUC. The final Attribution AUC for the
 229 molecule is simply the average of its Present-Attribution-AUC
 230 and its Absent-Attribution-AUC. This same process is applied
 231 regardless of which synthetic "binding" label the molecule
 232 carries. We report the average Attribution AUC across all
 233 molecules in the heldout set for each dataset. The Attribution
 234 AUC is entirely distinct from the Model AUC, which measures
 235 model performance on heldout data.

236 For some molecules and binding logics, there is more than
 237 one correct set of ground truth labels. Consider disjunctive
 238 binding logics (that contain an "or" operator), e.g. "phenyl or
 239 alkyne or alcohol." The model can satisfy the binding logic by
 240 detecting phenyl alone or alkyne alone, or alcohol alone, or any
 241 pair of the fragments, or all three together. Each case results
 242 in different sets of ground truth labels. A similar multiplicity
 243 of possible ground truth labels arises when a molecule exhibits
 244 multiple occurrences of a fragment in the binding logic (e.g.
 245 if a molecule has two phenyl groups). Because all these label
 246 sets are correct, we enumerate them and report the maximum
 247 Attribution AUC found among them. Formally, for a set S of
 248 molecular fragments in a disjunctive binding logic or present
 249 multiple times in the molecule, we enumerate the set of all
 k -combinations $\binom{S}{k}$ ($1 \leq k \leq |S|$) of molecular fragments.

Each k -combination has a ground truth labeling where atoms in its molecular fragment(s) receive a 1 label while others are labelled 0. We report the maximum Attribution AUC found.

Zinc+2 test set. We also report the Model AUC for a "Zinc+2" holdout set, generated from the Zinc holdout set by iterating through molecules and adding or removing an atom or bond to each in nearly every valence-valid way as in (24). This process is then repeated, resulting in a set of molecules each a molecular graph edit distance ≤ 2 from the Zinc holdout set, and about 5000 times larger, for each logic.

Results

Table 1 lists the results obtained for networks trained using data with synthetic labels that reflect the binding logics listed. The Zinc Model AUC is near perfect (1.0) for each of the binding logics indicating that the trained models can correctly classify the molecules in the held-out test sets. Furthermore the Attribution AUC is significantly lower than 1.0 for several logics. For instance, for binding logic 9 the GC Attribution AUC is only 0.7 while the Zinc Model AUC is 0.995. We note that the Attribution AUC declines as the logics become more complicated and include larger numbers of functional groups. The MPNN models exhibit a similar pattern. We now discuss further implications of these findings.

Attacks guided by attributions. The combination of near-perfect model performance and low Attribution AUCs indicates either: (1) a weakness of the attribution technique, or (2) failure of the model to learn the ground truth binding logics. We distinguish these cases by investigating individual molecules that were correctly classified but have low Attribution AUCs. Guided by patterns across multiple molecules where the attributions were misplaced with respect to the ground truth binding logic, we discovered small perturbations of each molecule which caused the class predicted by the model to be incorrect. By manually inspecting a few perturbations for a few mis-attributed molecules, we found at least one perturbation attack for every logic that did not have a high Attribution AUC, leading us to conclude that the model did not learn the correct binding logic. These results clarify that the Zinc heldout sets are still under-representative, despite their careful balancing, discussed above.

Here, we describe a few of the perturbation attacks that we found. Binding logic 9 requires the presence of "a primary amine and an ether and a phenyl." One example from Zinc that satisfies this logic is shown in Figure 3A. This molecule is correctly classified as positive (i.e. binding) by the model with a probability of 0.97, however as seen in the figure it has misplaced attributions on several atoms in the ring structures on the left. We perturb those atoms and separate the primary amine from them with an additional carbon, resulting in the molecule shown in Figure 3B. The model gives this perturbed molecule a predicted score of 0.20, a negative class prediction, despite the fact that the molecule still fully satisfies the same binding logic that the model was trained against.

Binding logic 12 requires that a molecule satisfy the "absence of an alcohol or presence of a primary amine, along with an unbranching alkane and a fluoride group." One example from Zinc that satisfies this logic is shown in Figure 3C. It is correctly classified as positive by the model with a prediction of 0.97, however it has misplaced attributions on the carbon

atom in the carbonyl group on the left. Guided by these attributions we perturb that carbonyl, converting it to a single bond, resulting in the molecule in Figure 3D. The model gives this perturbed molecule a predicted score of 0.018, a negative class prediction, despite the fact that the molecule still satisfies the ground truth binding logic.

Zinc+2 holdout set. To further probe the ability of the model to generalize, and the role played by dataset bias we also report Model AUCs for each logic measured on the "Zinc+2" holdout sets described above. These sets are a factor of 5000 larger than the Zinc holdout sets, and contain many of the perturbations that led to adversarial attacks. The Zinc+2 Model AUCs are almost uniformly lower than the Zinc Model AUCs, reflecting the more stringent nature of this test. In some logics (e.g. number 13) the Zinc+2 Model AUC is substantially lower, indicating dataset bias in the Zinc holdout for these models. In most logics, the Zinc+2 Model AUC is slightly lower, and we interpret this as evidence for some degree of bias in the Zinc datasets. We conclude that even when adversarial examples are rare, finding them is easy by following mis-attributions. Furthermore, if only the Model AUC on the Zinc holdout set is considered - as in common practice - the MPNN and GC models perform similarly on 15 of the 16 datasets. However, our Zinc+2 sets reveal that they do not generalize with the same fidelity.

A pharmacological hypothesis. These results indicate that the attribution can be more trustworthy than the model: even if the model achieves a high Model AUC, a low Attribution AUC appears to indicate that there exist molecules that do not satisfy the binding logic but are predicted to bind by the model. This occurs because of biases in the underlying dataset learned by the model.

The same concern applies to real protein binding datasets. Our results suggest a simple test that can be performed to test an existing hypothesis about the pharmacophore(s) that control binding. First, the hypothesis is codified as a "binding logic", which is used to create a set of synthetic labels. Next, these synthetic labels are used to train a neural network and analyze its attributions and Attribution AUC. A good Attribution AUC, with attribution to the correct functional groups suggests that the combination of dataset and trained neural network is able to generalize. However, a poor Attribution AUC or consistent unexpected attribution artifacts would suggest a need for model simplification and regularization, and/or dataset augmentation.

We follow this protocol using data for binding to the protein ADRB2 from the DUD-E dataset (19). One hypothesis for a pharmacophore is a benzene ring with a two-carbon chain connected to an ionized secondary amine. This results in a dataset with 934 positives and 14290 negatives, of which $\sim 10\%$ are reserved as a heldout set by ID hash. We trained a graph convolution model (see details in SI text), and achieved a Model AUC on the heldout set of 1.0. However its Attribution AUC is extremely low, at only 0.11. Visualizations of the attributions show the attribution only consistently highlights the NH₂⁺ group. This means that attacks (e.g. Figure 4) are easily discovered using this insight.

Logic number	Synthetic binding logic	GC Zinc AUC	GC Zinc+2 AUC	GC Attribution AUC	MPNN Zinc AUC	MPNN Zinc+2 AUC	MPNN Attribution AUC
1.		1.000	0.987	0.980	0.990	0.981	0.990
2.		0.995	0.997	0.980	1.000	1.000	0.990
3.		1.000	0.998	1.000	1.000	0.998	1.000
4.	no 	1.000	0.995	0.970	1.000	0.944	1.000
5.	 or (no )	0.992	0.974	0.910	1.000	0.997	0.900
6.	 and (no )	0.999	0.993	0.890	1.000	0.978	0.770
7.	 and 	1.000	0.995	0.770	1.000	0.999	0.610
8.	 and 	1.000	0.994	0.790	1.000	0.921	0.830
9.	 and  and (no )	1.000	0.983	0.930	0.990	0.975	0.900
10.	 and  and 	0.995	0.992	0.700	0.990	0.915	0.600
11.	( or no ) and (no )	0.999	0.994	0.860	1.000	0.972	0.830
12.	 and (no ) and (no )	1.000	0.994	0.880	1.000	0.999	0.850
13.	 and  and ( or no )	0.999	0.947	0.670	0.940	0.869	0.660
14.	( and no ) or ( and no )	1.000	0.981	0.700	1.000	0.995	0.670
15.	( or no ) and  and (no )	1.000	0.991	0.750	1.000	0.982	0.710
16.	 and (no ) and  and 	0.996	0.975	0.760	0.980	0.812	0.620

Table 1. This table shows the Attribution AUC and the Model AUCs for two heldout sets for Graph Convolution networks and MPNNs trained against synthetic data labels generated according to the binding logics listed in column 1. See the Supplementary Information for more details on the binding logics and their component molecular fragments.

Discussion

There is growing concern about the non-robustness of machine learning models, and much recent research has been devoted to finding ways to assess and improve model robustness (13–15, 25–30). A common source of non-robustness is bias in the training dataset (13, 25, 27, 30). An approach to identifying such bias is to examine attributions of the model’s predictions, and determine if too much attribution falls on non-causal features or too little falls on causal features (25); both are undesirable and indicate bias in the training dataset that the model erroneously learned.

The central challenge in applying this approach to virtual screening models is that *a priori*, we know neither the internal logic of the model, nor the logic of protein binding. Thus we have no reference for assessing the attributions. To resolve this, we introduce the idea of evaluating hypotheses for binding logics by setting up a synthetic machine learning task. We use the hypothesized logic to relabel molecules used in the original study, and train a model to predict these labels. If attributions fail to isolate the hypothesized logic on this synthetic problem, it signals that there exist biases in the training data set that fool the model into learning the wrong logic. Such bias would also likely affect the model’s behavior on the original task.

To quantitatively assess attributions, we introduce the Attribution AUC metric, measuring how well the attributions isolate a given binding logic. It is not a measure of the “correctness” of the attributions. The mandate for an attribution method is to be faithful to the model’s behavior, and not the

behavior expected by the human analyst (18). In this work, we take the faithfulness of the attributions obtained using Integrated Gradients as a given. For our synthetic task, we find the attributions to be very useful in identifying biases in the model’s behavior, and we were able to successfully translate such biases into perturbation attacks against the model. These attacks perturb those bonds and atoms with unexpected attributions, and their success confirms the faithfulness of the attributions. The attacks expose flaws in the model’s behavior despite the model having perfect accuracy on a held out test set. This reiterates the risk of solely relying on held out test sets to assess model behavior.

Finally, we acknowledge that attributions as a tool offer a very reductive view of the internal logic of the model. They are analogous to a first-order approximation of a complex non-linear function. They fail to capture higher order effects such as how various input features interact during the computation of the model’s prediction. Such interactions between atom and bond features are certainly at play in virtual screening models. Further research must be carried out to reveal such feature interactions.

Thoughts for practitioners. The recent machine learning revolution has led to great excitement regarding the use of neural networks in chemistry. Given a large dataset of molecules and quantitative measurements of their properties, a neural network can learn/regress the relationship between features of the molecules and their measured properties. The resulting model can have the power to predict properties of

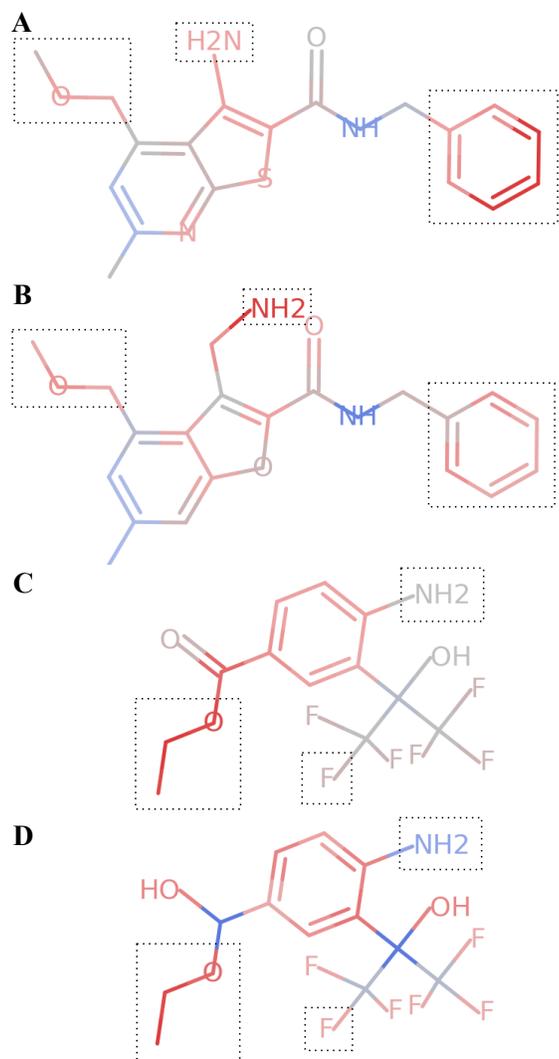


Fig. 3. Visualizations of attribution scores, calculated using Integrated Gradients. A) Attribution scores for a molecule from the logic 9 heldout set that obeys the binding logic. B) A minor perturbation of the above molecule, guided by errors in the attributions shown in (A), which gets misclassified by the model. C) Attribution scores for a molecules from the logic 12 heldout set that obeys the binding logic. D) A minor perturbation of the above molecule which still obeys the logic, but is misclassified by the model. Dotted boxes are added around the fragments whose presence defines the molecules as members of the positive class.

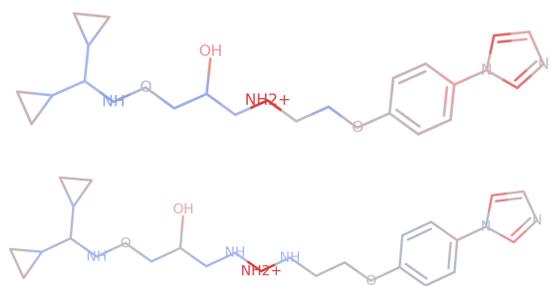


Fig. 4. Visualizations of Integrated Gradients attributions. Top, on an example "binder" from the synthetic ADRB2 dataset, correctly predicted as a positive with prediction 0.999. Bottom, a minor perturbation of the above molecule which should be a negative but gets misclassified as still a positive with prediction 0.995.

molecules in a held out test set, and indeed can be used to find other molecules with these properties. Despite this promise, an abundance of caution is warranted: it is dangerous to trust a model whose predictions one does not understand. A serious issue with neural networks is that although a held out test set may suggest that the model has learned to predict perfectly, there is no guarantee that the predictions are made for the right reason. Biases in the training set can easily cause errors in the model's logic. The solution to this conundrum is to take the model seriously: analyze it, ask it why it makes the predictions that it does, and avoid relying solely on aggregate accuracy metrics. The attribution-guided approach described in this paper for evaluating learning of hypothesized binding logics may provide a useful starting point.

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