Quantitative Evaluation of Explainable Graph Neural Networks for Molecular Property Prediction

Jiahua Rao *12 Shuangjia Zheng *12 Yuedong Yang 1

Abstract
Advances in machine learning have led to graph neural network-based methods for drug discovery, yielding promising results in molecular design, chemical synthesis planning, and molecular property prediction. However, current graph neural networks (GNNs) remain of limited acceptance in drug discovery due to their lack of interpretability. Although this major weakness has been mitigated by the development of explainable artificial intelligence (XAI) techniques, the “ground truth” assignment in most explainable tasks ultimately rests with subjective judgments by humans so that the quality of model interpretation is hard to evaluate in quantity. In this work, we first build three levels of benchmark datasets to quantitatively assess the interpretability of the state-of-the-art GNN models. Then we implemented recent XAI methods in combination with different GNN algorithms to highlight the benefits, limitations, and future opportunities for drug discovery. As a result, GradInput and IG generally provide the best model interpretability for GNNs, especially when combined with GraphNet and CMPNN. The integrated and developed XAI package is fully open-sourced and can be used by practitioners to train new models on other drug discovery tasks.

1. Introduction
Various concepts of Graph Neural Network (GNN) have been successfully adopted for drug discovery tasks in the past few years (Gilmer et al., 2017; Yang et al., 2019; Liu et al., 2018; Jin et al., 2018; Yan et al., 2020) such as molecular property prediction and de novo molecular generation. Several graph neural network models have been shown to yield more promising results than the existing machine learning and quantitative structure-activity relationship (QSAR) methods for drug discovery (Xiong et al., 2019; Song et al., 2020). This advance is mostly owed to the ability of graph neural networks to effectively model molecular graph data. With the increasing high-quality labeled data, graph neural networks are promising to learn better molecular representations that finally replace decades-old hand-crafted molecular fingerprint representations.

Despite their promise, graph neural networks remain of limited acceptance in drug discovery partly due to their lack of interpretability, and these models are often considered as “black-box” (Jiménez-Luna et al., 2020; 2021). While there have been efforts to model interpretability based on simplifications of models, feature sub-selection, or attention (Ribeiro et al., 2016; Sundararajan et al., 2017; Shrikumar et al., 2017; Vaswani et al., 2017), this problem is further exacerbated by the fact that these models often produce the correct answers for wrong reasons (Lapuschkin et al., 2019). Given the current pace of AI in drug discovery, there will be an increased demand for interpretability methods that help us understand and interpret the GNN models. Thus, a highly accurate and mechanically interpretable model may be the key to accelerated drug discovery with graph neural networks.

Explainable artificial intelligence (XAI) aims to help scientists to know how the model reached a particular answer and explain why the answer provided by the model is acceptable (Guidotti et al., 2018; Ying et al., 2019; Lundberg et al., 2020). In drug discovery-related applications, in particular for property prediction tasks, XAI methods could help the development of graph neural networks by quantifying the molecular substructures that are critical for a given prediction and explaining how reliable a prediction is (Jiménez-Luna et al., 2021; Yu et al., 2021). Feature attribution is one approach to interpretability, which measures how important the feature is to the model’s prediction of a target property. Attribution methods have been studied in the domains of drug discovery,
for example, McCloskey et al. (2019) developed an attribution method to verify whether each model trained on protein–ligand binding data learns its corresponding binding logic correctly. Jiménez-Luna et al. (2021) established an Integrated Gradients (IG) feature attribution technique to examine the interpretability of GNN models in molecular property predictions. Furthermore, with the development of graph neural networks, it does not come as surprise in the fields of drug discovery to explore the interpretability of models trained with graph convolution architecture. For instance, Jin et al. (2020) employed Monte Carlo tree search to extract molecular substructures with the help of a property predictor, which are likely responsible for each property of interest. Yu et al. (2021) proposed a framework of Graph Information Bottleneck (GIB) for the subgraph recognition, which could recognize a compressed subgraph with minimum information loss in terms of predicting the molecular properties. These methods, which can be considered as subgraph recognition methods, are interested in directly identifying the substructures that mostly represent certain properties of molecules.

As mentioned above, many efforts have been made to mitigate the major weakness of deep learning approaches, that is the lack of causal understanding. Unfortunately, the quality and evaluation of model interpretations is hard to examine because acquiring ground truth sub-structures or attributions requires expensive wet experiment and subjective expert judgment. Although Sanchez-Lengeling et al. (2020) have built an open-source synthetic benchmarking suite for attribution methods on GNNs, the synthetic tasks were designed for recognize simple subgraphs such as benzene from molecules. In fact, effective XAI should reveal more complex information to scientists and render the decision-making process. For example, in toxicity prediction, there are often dozens of fragments that cause a particular toxicity, and some even have to be considered many-to-one scenarios. Moreover, there is a kind of molecular pairs with similar structures but completely different properties, which is known as property cliffs (Stumpfe et al., 2014). Such realistic and sophisticated scenarios will bring more challenges and opportunities to XAI.

In this work, we established three levels of benchmarks, from easy to hard, for quantitatively and comprehensively assessing the interpretability of current graph neural networks and XAI modules, highlighting theirs benefits, limitations and future opportunities for drug discovery. In addition, we provide a uniform and rigorous framework to evaluate the performance of commonly-used XAI methods on several GNN model types. We examine the quality of those XAI methods through accuracy and consistency, which evaluate the ability of XAI methods in identifying the subgraphs that mostly represent certain properties of the molecules and perturbations that are most likely to cause property cliffs. We offer three main contributions:

- We build three levels of benchmark datasets to quantitatively assess the interpretability of the state-of-the-art GNN models.
- We provide a uniform and rigorous framework to evaluate the performance of commonly-used XAI methods on several GNN model types.
- We provide a comprehensive overview of recent XAI methods, highlighting their benefits, limitations and future opportunities for drug discovery.
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Table 1. Statistics of the datasets

| Tasks                   | Type            | Dataset Name | Compounds | Train | Test | Subgraph ground truth         |
|-------------------------|-----------------|--------------|-----------|-------|-----|--------------------------------|
| Single-rationale Graph classification | 3MR             | 3152         | 2521      | 631   | Three-membered ring          |
|                         | Benzene         | 12000        | 9600      | 2400  | Benzene ring                 |
| Multiple-rationales     | Mutagenicity    | 6506         | 5204      | 1302  | Mutagenicity alerts          |
|                         | Liver           | 587          | 469       | 118   | Hepatotoxic alerts           |
| Property cliff          | hERG            | 6993         | 6483      | 510   | Structural motifs            |
|                         | CYP450          | 9122         | 9025      | 97    | Structural motifs            |

2. Method

In this section, we will first define the tasks and datasets used in DrugXAI and provide necessary information analyzing its effectiveness in evaluating the model interpretations. For the model interpretations, we will introduce commonly-used XAI methods on several GNN model types. Finally, detailed information about training and evaluating the XAI methods in drug discovery applications will be presented in the end.

2.1. Tasks and Benchmark Datasets

Our goal is to evaluate whether current XAI methods allow GNNs to perform graph classification or regression tasks while identifying task-relevant molecular substructures (i.e., rationales). The substructures can be a particular subgraph, the conjunction of multiple subgraphs or a local transformation between two molecular graphs (i.e., property cliff).

Correspondingly, we design three levels (single rationale, multiple rationales, and property cliff) of benchmark datasets to quantitatively assess the interpretability of the state-of-the-art GNN models. We summarized the statistics of the datasets in Table 1.

2.1.1. Single-rationale Tasks

Following the strategy of McCloskey et al. (2019), we first established two single rationale benchmarks, whose goal is to identify if a molecular graph contains particular subgraphs of interest. We defined two synthetic subgraph logics: Benzene and 3MR, aiming to verify whether each model is able to capture the corresponding subgraphs correctly. In particular, we collected 50K unlabeled molecules from ZINC15 lead-like subset (Sterling & Irwin, 2015) and used substructure matching (Benzene and 3MR) to identify positive molecules that matched, and then randomly selected the same amount of unmatched molecules as negative samples. Both datasets are graph classification tasks, 1 for those containing a specific substructure, 0 otherwise.

2.1.2. Multiple-rationales Tasks

In real-world scenario, there are often dozens of rationales that cause a particular property. To this end, we construct two multiple-rationales benchmarks in which ground truths are the hand-crafted structural alerts that raise the problems of hepatotoxicity and ames mutagenicity. In particular, for hepatotoxicity, we collected the data from Liu et al. (2015), which contains 174 hepatotoxic, 230 possible hepatotoxic and 183 non-hepatotoxic compounds, and 12 molecular rationales have been identified as structural alerts for human liver injuries. For ames mutagenicity, we used a well-established dataset compiled by Hansen et al. (2009), including 6506 compounds and corresponding ames mutagenicity results. Sushko et al. (2012) summarizes 46 structural toxic alerts that raise the mutagenicity, which have been computed as ground truth subgraphs.

2.1.3. Property Cliff Tasks

To further explore the interpretability of the commonly-used XAI methods in extreme cases, we compiled two publicly available datasets, hERG inhibition and Cytochrome P450 Inhibition, for property cliff tasks. We use the dataset constructed by Jiménez-Luna et al. (2021), which collected by a literature survey and publicly available data. Specifically, hERG inhibition is an important anti-target that must be avoided during drug development. For this endpoint, 6993 compounds with reported activity (IC50 values) in the nanomolar range were collected and IC50 values were transformed into the pIC50 scale during model training (Sato et al., 2018). Inhibition of cytochrome P450 (CYP450) enzymes is the most common mechanism leading to drug–drug interactions. For this endpoint, 9120 CYP3A4 inhibitors and substrates with binary activity information (active/inactive) were determined by Veith et al. (2009).

Previously, Jiménez-Luna et al. (2021) established these endpoint datasets but missed ground truths for interpretations. The “ground truth” in their experiments ultimately rests with subjective human judgment. Differently, we have constructed a quantitatively assessable scheme based on the
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Table 2. Prediction Performance on benchmarks

| Dataset | 3MR | Benzene | Liver | Mutagenicity | hERG | CYP450 |
|---------|-----|---------|-------|--------------|------|--------|
| Metric  | AUROC | AUROC | ACC   | AUROC | RMSE | AUROC |
| GNN Model | CMPNN | 0.998 | 0.999 | 0.432 | 0.866 | 1.328 |
|          | GraphSAGE | 0.989 | 0.999 | 0.415 | 0.843 | 1.230 |
|          | GraphNet | 0.995 | 0.998 | 0.423 | 0.823 | 1.304 |
|          | GAT | 0.995 | 0.989 | 0.381 | 0.852 | 1.361 |

Figure 2. XAI method accuracy across Single-ratiocle tasks and model architectures. Colors are used to distinguish two metric types — Attribution AUROC and Attribution ACC. With the perfect predictive performances, the existing popular XAI methods on the trained GNN models are consistently superior to the random baseline and the improvements are significant.
characteristics of the property cliff. Particularly, we first split these datasets into training and testing, forcing those eligible property cliff molecular pairs to appear only in the test set. Then, the property cliff pairs of molecules with similar structure but completely different properties were captured by MMPA technique (Hussain & Rea, 2010) in the RDKit package and the ground truth attributions were computed according to the local differences between the molecular pairs. For the property cliff dataset which is the graph regression task, we define a local transformation to create a pair of active cliff pairs when it causes more than a 100-fold change (Δ pIC50 > 2) in properties.

2.2. Graph Neural Network

When viewing molecules as graphs with atoms as nodes and chemical bonds as edges, Graph Neural Network (GNN) (Kipf & Welling, 2017; Gilmer et al., 2017) is a neural network that takes as input and outputs a graph with the same topology, but with updated node, edge and/or graph-level information. One key feature of the GNNs we study is the message passing function, which allows nodes to update their states by aggregating feature information from neighboring nodes and edges. Depending on the message passing strategy, the message can contain information about the node, edge, or the global information.

Our experiments use four existing popular GNN architectures distinguished by their message-passing strategies. The first is a framework for inductive representation learning (GraphSAGE) (Hamilton et al., 2017), which is used to generate low-dimensional vector representations for nodes. The second model is the Communicative Message Passing Neural Network (CMPNN) (Song et al., 2020) which improve the molecular embedding by strengthening the message interactions between nodes and edges through a communicative kernel. Another model is the Graph Attention Network (GAT) (Veličković et al., 2018) which aggregates node information via an attention mechanism. The fourth is Graph Nets (Battaglia et al., 2018) in which the message mechanism utilizes a global features vector in addition to node and edge features.

2.3. XAI methods

An XAI method $A$ takes a model $M$ and a molecular graph $G$ as inputs to generate an attribution score $G_A = (v_A, e_A)$ where $v_A$ and $e_A$ are node and edge weightings relevant for predicting property $y$. These weightings can be visualized as a heatmap superimposed on a graph. Our ground-truths for attributions are node-level, so we redistribute edge attributions equally onto their endpoint nodes’ attributions. In our framework, we utilize the following methods for molecular graphs: GradInput ($Shrikumar et al.$ et al., 2017), GradCAM ($Selvaraju et al.$ et al., 2017), Integrated Gradients ($Sundararajan et al.$ et al., 2017), CAM ($Zhou et al.$ et al., 2016), MCTS ($Jin et al.$ et al., 2020) and Attention weights ($Vaswani et al.$ et al., 2017).

Class Activation Map (CAM) is a feature attribution method, which uses a global average pooling (GAP) layer prior to class outputs to obtain attributions. CAM attributions could be derived by multiplying the final convolutional layer’s feature map activations with the output weights at the last message passing layer. GradInput attributions are calculated by the element-wise product of the input graph with the gradient of property with respect to the input node and edge features while GradCAM extends GradInput by using intermediate activations in which corresponds to the element-wise product of the activations of intermediate message-passing layer with the gradient of property. Integrated Gradients (IG) integrates the element-wise product of an interpolated input with the gradient of property. Attention mechanism method is specific to the GAT model, which will produce attention scores on edges to adjacent nodes. We can use these attention scores as a measure of importance for propagating information relevant to the predictive task. Monte Carlo Tree Search (MCTS), a subgraph recognition method, is also used to extract candidate rationales from molecules with the help of a property predictor.

3. Experiments

In this section, we first present the predictive performance evaluation for graph classification and regression tasks on different benchmarks. It’s necessary as the interpretations generated by the model with poor predictive capability bear little trust. Next, we evaluate the attribution performance of commonly-used XAI methods on the trained GNN models. Finally, we analyze the performances on the three levels of benchmarks, from easy to hard, from recognizing particular subgraphs of interest to identifying property cliffs. All the GNN models and XAI methods were implemented based on $Rao et al.$ (2021) and $Sanchez-Lengeling et al.$ (2020). Particularly, no explicit hyper-parameter optimization is performed on any model training to avoid unnecessary model selection bias. All the implementation details can be found in https://github.com/biomed-AI/MolRep.
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Figure 3. XAI method accuracy across Multiple-rationales tasks and model architectures. Colors are used to distinguish two metric types — Attribution AUROC and Attribution ACC. GradInput and IG consistently well across these tasks and GNN models. The attribution performances, for example, the Attribution-ACC on Liver datasets ranging between 0.835 and 0.938, have shown that the GNN models with XAI methods were able to detect the implicit relationships compared to the random baselines.

els showed perfect predictive capabilities on the single-rationale datasets, with AUROC ranging between 0.989 and 0.999, as shown in Table 2. These values suggested that the meaningful molecular graph features were identified by all trained models in the learning process. On the multiple-rationales benchmarks, the results obtained were also markedly better than random, with ACC ranging between 0.381 and 0.432 for the three-classification dataset, and AUROC ranging between 0.823 and 0.866 for the binary classification model. Finally, on the most difficult datasets, the poorest performances of the existing GNN models were obtained, suggesting that current GNN models have difficulties to capture the property-relevant features during the learning process.

3.2. Single Rationale Recognition

On the single-rationale datasets, we used Attribution-AUC and Attribution-ACC, designed by McCloskey et al. (2019), to assess attribution accuracy and consistency in identifying the corresponding substructure correctly. If multiple attributions are valid (e.g., a subgraph is present twice in a graph), we take the maximum attribution value of all possible solutions. Particularly, the subgraph recognition methods such as MCTS could not be evaluated by Attribution-AUC since their outputs are directly subgraphs rather than a node probability.

Jointly analyzing Table 2 and figure 2, we found that with the perfect predictive performances, the existing popular XAI methods on the trained GNN models are consistently superior to the random baseline and the improvements are significant, suggesting that the trained models have identified the meaningful features that are relevant to molecular property and the current XAI approaches could effectively recognize subgraph logics corresponding. This makes sense since the graph labels of single-rationale datasets are whether the corresponding molecule contains the particular subgraphs of interest. The direct relationship between target rationales and graph labels helps the models to capture accurate information.

3.3. Multiple Rationales Recognition

Furthermore, in real-world scenario, the relationships between the molecular structures and their related properties are often implicit. Therefore, whether the current GNN model with the popular XAI methods is capable of capturing the implicit relationships is the motivation for us to conduct the attribution experiments on multiple-rationales datasets.

As shown in Figure 3 and Table 2, owing to the prediction performances have demonstrated that the useful graph features were identified during the learning process, the attribution performances, for example, the Attribution-ACC on Liver datasets ranging between 0.835 and 0.938, have shown that the GNN models with XAI methods were able to detect the implicit relationships compared to the random baselines. More specifically, we could observe that GraphNet and CMPNN with high predictive performance have better attribution performance than other baselines across
the popular XAI methods. And GradInput and IG across tasks and model architectures have better attribution performances. We attribute the improvements to the utilization of the gradients of the predicted property, which directly provide detailed insight into the relationship between the input features and the property.

### 3.4. Property Cliff Identification

Finally, to explore the interpretability of GNN models on the more complex relationships between substructures and graph properties, we evaluated the capabilities of the models to recognize property cliffs. Since the ground truths (local transformations) on these datasets have been classified to positive and negative based on the change of property, we only report Attribution-ACC and Attribution-F1 to assess the attribution accuracy and verify whether each model learns the corresponding key substructure transformations relevant for predicting property correctly.

Jointly analyzing Figure 4 and Table 2, we observed that most of the XAI methods failed to recognize property cliffs effectively under this condition, with low Attribution-F1 ranging from 0.104 to 0.294 on hERG and CYP datasets. There are two possible reasons for the results. Firstly, the poor predictive performances of the existing GNN models were obtained, suggesting that current GNN models were unable to capture the property-relevant features on the property-cliff tasks. Secondly, the relationships between property cliffs and their corresponding property are extremely diverse and complex. But considered from another perspective, on property cliff benchmarks, GNN methods are ten or even tens of times better than the random baseline, proving that although the problem is very difficult, the GNNs have captured some key features from it.

### 4. Discussion and conclusions

In this work we have established a series of XAI benchmarks in the context of drug discovery and created a framework to quantitatively evaluate attribution methods in GNNs. We expect that our benchmark and framework will aid in developing better methodology for interpretability in molecular graph tasks. Overall, our experiments show existing popular XAI methods have good performance with GNN architectures in recognizing regular subgraphs in molecules but performed poorly in identifying the property cliff on realistic datasets. As a final caveat, we find that XAI techniques that are directly related to predicted labels like GradInput and IG also tend to have better attribution performance, across many models. This also hints that current XAI methods cannot yet be used as a recipe for drug discovery, requiring significant human expertise for correct interpretation. The reasons for these phenomena remain a topic of further study.

There also remains much room for improvement in interpretation performance for GNNs. Nonetheless, further de-
Development of XAI applications would greatly benefit from this meaningful benchmarking. We hope that our quantitative benchmark and framework of interpretations in GNNs are useful for developing new XAI methods. Our framework and dataset are available for further study, broadening the development of explainable artificial intelligence in drug discovery-related applications.

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