GROVER: Self-supervised Message Passing Transformer on Large-scale Molecular Data

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Abstract

How to obtain informative representations of molecules is a crucial prerequisite in AI-driven drug design and discovery. Recent researches abstract molecules as graphs and employ Graph Neural Networks (GNNs) for task-specific and data-driven molecular representation learning. Nevertheless, two “dark clouds” impede the usage of GNNs in real scenarios: (1) insufficient labeled molecules for supervised training; (2) poor generalization capabilities to new-synthesized molecules. To address them both, we propose a novel molecular representation framework, GROVER, which stands for Graph Representation frOm self-superVised mEssage passing tRansformer. With carefully designed self-supervised tasks in node, edge and graph-level, GROVER can learn rich structural and semantic information of molecules from enormous unlabelled molecular data. Rather, to encode such complex information, GROVER integrates Message Passing Networks with the Transformer-style architecture to deliver a class of more expressive encoders of molecules. The flexibility of GROVER allows it to be trained efficiently on large-scale molecular dataset without requiring any supervision, thus being immunized to the two issues mentioned above. We pre-train GROVER with 100 million parameters on 10 million unlabelled molecules—the biggest GNN and the largest training dataset that we have ever met. We then leverage the pre-trained GROVER to downstream molecular property prediction tasks followed by task-specific fine-tuning, where we observe a huge improvement (more than 6% on average) over current state-of-the-art methods on 11 challenging benchmarks. The insights we gained are that well-designed self-supervision losses and largely-expressive pre-trained models enjoy the significant potential on performance boosting.

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1 Introduction

Inspired by the remarkable achievements of deep learning in many scientific domains, such as computer vision [19, 55], natural language processing [49, 51], and social networks [3, 30], researchers are exploiting deep learning approaches to accelerate the process of drug discovery and reduce costs by facilitating the rapid identification of molecules [5]. Molecules can be naturally represented by molecular graphs which preserve rich structural information. Therefore, supervised deep learning of graphs, especially with Graph Neural Networks (GNNs) [24, 45] have shown promising results in many tasks, such as molecular property prediction [13, 22] and virtual screening [54, 62].

Despite the fruitful progress, two “dark clouds” still impede the usage of deep learning in real scenarios: (1) insufficient labeled data for molecular tasks; (2) poor generalization capabilities of models for the enormous chemical spaces. First, the deep learning models are prone to overfitting with insufficient labeled data. What’s worse, it is hard to increase the labels for most molecular task since getting molecular labels usually requires wet-lab experiments which are costly and time-consuming. Consequently, insufficient labeled data further leads to the poor generalization capabilities of models, which is hard to handle the out-of-distribution molecules.

In Natural Language Processing (NLP), the deep learning methods used to face similar challenges. Researchers in NLP adopt the pre-training strategy to enforce the model to learn implicit information from the large language space with some low-cost self-supervised targets. The pre-training language models achieve a huge success in boosting the performance of language tasks, such as BERT [9], GPT [37], etc. In this vein, [36] tries to pre-train a BERT-style model on the sequential representation—SMILES [57] of molecules. Liu et.al. [28] exploit the idea from N-gram approach in NLP and embeds a sequence of $n$ vertices to self-predict the attributes of the vertices. However, these representations failed to explicitly encode the structural information of molecules.

To consider the graph structure of molecules, several works aim to establish a pre-trained graph model for molecules. Hu et.al. [18] investigate the strategies to construct the pre-training task on molecular graphs and propose three tasks, i.e., context prediction, node making and graph-level prediction for molecular pre-training. We argue that current models and pre-train tasks restrict the power of pre-trained representations. First, in the masking task, they treat the atom type as the label. Compared with the NLP tasks, the number of atom types in molecules is much smaller than that of a language vocabulary. Therefore, it suffers serious ambiguity problems on atom type and the model is hard to encode meaningful information, especially for the high frequent atoms. Second, the graph-level pre-training task in [18] depends on the supervised labels. This limits the expressive power of the model on graph-level since most of molecules are completely unlabelled and it also introduces the risk of negative transfer for the downstream tasks.

In this paper, we improve the pre-training model for molecular graph by introducing a novel molecular representation framework, GROVER, namely, Graph Representation frOm self-supeRVised mEssage passing tRansformer. GROVER constructs two types of self-supervised tasks. For the node/edge-level tasks, instead of predicting the node/edge type alone, GROVER randomly masks a local subgraph of the target node/edge and predicts this contextual property from node/edge embedding. In this vein, GROVER can alleviate the ambiguity problem by considering both the target node/edge being masked and its context. For the graph-level tasks, by incorporating the domain knowledge, GROVER extracts the semantic motifs existing in molecular graphs and predicts the occurrence of these motifs for a molecule from graph-embedding. Since the semantic motifs can be obtained by a low-cost pattern matching method, GROVER can make use of any molecules to optimize the graph-level embedding. With self-supervised tasks in node, edge and graph-levels, GROVER can learn rich structural and semantic information of molecules from enormous unlabelled molecular data. Rather, to encode such complex information, GROVER integrates Message Passing Networks with the Transformer-style architecture to deliver a class of highly expressive encoders of molecules. The flexibility of GROVER allows it to be trained efficiently on large-scale molecule data without requiring any supervision. We pre-train GROVER with 100 million parameters on 10 million of unlabelled molecules—the biggest GNN and the largest training dataset that we have ever met. We then leverage the pre-trained GROVER models to downstream molecular property prediction followed by task-specific fine-tuning. On the downstream tasks, GROVER achieve 22.4% relative improvement compared with [28] and 7.4% relative improvement compared with [18] on classification tasks. Furthermore, even compared with current state-of-the-art methods, we observe a huge relative improvement of GROVER (more than 6% on average) over 11 popular benchmarks.
2 Related Work

Molecular Representation Learning. To represent molecules in the vector space, the traditional chemical fingerprints, such as ECFP [41], try to encode the neighbors of atoms in the molecule into a fix-length vector. To improve the expressive power of chemical fingerprints, some studies [7, 10] introduce convolutional layers to learn the neural fingerprints of molecules, and apply the neural fingerprints to the downstream tasks, such as property prediction. Following these works, [20, 60] take the SMILES representation [57] as input and use RNN-based models to encode molecular representations. Recently, many works [22, 44, 45] explore the graph convolutional network to encode molecular graphs into neural fingerprints. A slot of work [43, 59] propose to learn the aggregation weights by extending the Graph Attention Network (GAT) [52]. To better capture the interactions among atoms, [13] proposes to use a message passing framework and [24, 61] extend this framework to model bond interactions. Furthermore, [29] builds a hierarchical GNN to capture multilevel interactions.

Self-supervised Learning on Graphs. Self-supervised learning has a long history in machine learning and has achieved fruitful progresses in many areas, such as computer vision [34] and language modeling [9]. The traditional graph embedding methods [14, 36] define different kinds of graph proximity, i.e., the vertex proximity relationship, as the self-supervised objective to learn vertex embeddings. GraphSAGE [15] proposes to use a random-walk based proximity objective to train GNN in an unsupervised fashion. [35, 48, 53] exploit the mutual information maximization scheme to construct objective for GNNs. Recently, two works are proposed to construct unsupervised representations for molecular graphs. Liu et al. [28] employs an N-gram model to extract the context of vertices and construct the graph representation by assembling the vertex embeddings in short walks in the graph. Hu et al. [18] investigate various strategies to pre-train the GNNs and propose three self-supervised tasks to learn molecular representations. However, [18] isolates the highly correlated tasks of context prediction and node/edge type prediction, which makes it difficult to preserve domain knowledge between the local structure and the node attributes. Besides, the graph-level task in [18] is constructed by the supervised property labels, which is impeded by the limited number of supervised labels of molecules and has demonstrated the negative transfer in the downstream tasks. Contrast with [18], the molecular representations derived by our method are more appropriate in terms of persevering the domain knowledge, which has demonstrated remarkable effectiveness in downstream tasks without negative transfer.

3 Preliminaries of Transformer-style Models and Graph Neural Networks

GROVER is built upon the Transformer architecture [51] and GNNs, so we briefly formalize them and the supervised learning task in this section.

Supervised learning tasks of graphs. Downstream tasks of molecules are often supervised learning tasks. A molecule can be abstracted as a topological graph \( G = (\mathcal{V}, \mathcal{E}) \), where \( |\mathcal{V}| = n \) refers to a set of \( n \) nodes (atoms) in the molecule and \( |\mathcal{E}| = m \) refers to a set of \( m \) edges (bonds). \( \mathcal{N}_v \) is used to denote the set of neighbors of node \( v \) in the graph. We use \( x_v \) to represent the initial features of node \( v \), and \( e_{uv} \) as the initial features of edge \((u, v)\). For graph data, there are usually two categories of supervised learning tasks: i) Node classification/regression, where each node \( v \) has a label/target \( y_v \), and the task is to learn to predict the labels of unlabelled nodes; ii) Graph classification/regression, where a set of graphs \( \{G_1, ... , G_N\} \) and their labels/targets \( \{y_1, ..., y_N\} \) are given, and the task is to predict the label/target of a new graph.

Attention mechanism and the Transformer-style architectures. The attention mechanism is the main building block of various Transformer-style models. We focus on multi-head attention, which stacks several scaled dot-product attention layers together and allows parallel running. One scaled dot-product attention layer takes a set of queries, keys, values \((q, k, v)\) as inputs. Then it computes the dot products of the query with all keys, and applies a softmax function to obtain the weights on the values. By stacking the set of \((q, k, v)\)s into matrices \((Q, K, V)\), it admits highly optimized matrix multiplication operations. Specifically, the outputs can be arranged as a matrix:

\[
\text{Attention}(Q, K, V) = \text{softmax}(QK^\top / \sqrt{d})V, \tag{1}
\]
where \( d \) is the dimension of \( q \) and \( k \). Suppose we arrange \( k \) attention layers into the multi-head attention, then its output matrix can be written as,

\[
\text{MultiHead}(Q, K, V) = \text{Concat}(\text{head}_1, \ldots, \text{head}_k)W^O, \quad \text{head}_i = \text{Attention}(QW^Q_i, KW^K_i, VW^V_i),
\]

where \( W^Q_i, W^K_i, W^V_i \) are the projection matrices of head \( i \).

**Graph Neural Networks (GNNs).** Recently, GNNs have received a surge of interest in various domains, such as knowledge graph, social networks and drug discovery. The key operation of GNNs can be abstracted to a message passing process, which involves message passing (also called neighborhood aggregation) between the nodes in the graph. The message passing operation iteratively updates a node \( v \)’s hidden state, \( h_v \), by aggregating the hidden states of \( v \)’s neighboring nodes and edges. In general, the message passing process involves several iterations, each iteration can be further partitioned into several hops. Suppose there are \( L \) iterations, and iteration \( l \) contains \( K_l \) hops. Formally, in iteration \( l \), the \( k \)-th hop can be formulated as,

\[
m_v^{[(l,k)]} = \text{AGGREGATE}^{(l)}(\{(h_v^{[(l,k-1)]}, h_u^{[(l,k-1)]}, e_{uv}) \mid u \in N_v\}),
\]

\[
h_v^{[(l,k)]} = \sigma(W^{(l)}m_v^{[(l,k)]} + b^{(l)}),
\]

where \( m_v^{[(l,k)]} \) is the aggregated message, and \( \sigma() \) is some activation function. We make the convention that \( h_v^{[(1,0)]} := h_v^{[(l-1,K_{l-1})]} \). There are several popular ways of choosing \( \text{AGGREGATE}^{(l)}(\cdot) \), such as mean, max pooling and graph attention mechanism [15, 52]. For one iteration of message passing, there are a layer of trainable parameters (i.e., parameters inside \( \text{AGGREGATE}^{(l)}(\cdot), W^{(l)} \) and \( b^{(l)} \)). These parameters are shared across the \( K_l \) hops within iteration \( l \). After \( L \) iterations of message passing, the hidden states of the last hop in the last iteration are used as the embeddings of the nodes, i.e., \( h_v^{(L,K)} \), \( v \in V \). Lastly, a READOUT operation is applied to get the graph-level representation,

\[
h_G = \text{READOUT}([h_v^{(0,K_0)}, \ldots, h_v^{(L,K)} \mid v \in V]).
\]

### 4 The GROVER Pre-training Framework

This section contains details of our pre-training architecture together with the well-designed self-supervision tasks. On a high level, the model is a Transformer-based neural network with tailored GNNs as the self-attention building blocks. The GNNs therein enable capturing structural information in the graph data and information flow on both the node and edge message passing paths. Furthermore, we introduce a dynamic message passing scheme in the tailored GNN, which is proved to boost the generalization performance of GROVER models.

#### 4.1 Details of Model Architecture

GROVER consists of two submodules: the node GNN transformer and edge GNN transformer. In order to ease the exposition, we will only explain details of the node GNN transformer (abbreviated as node GTransformer in the sequel), and ignore the edge GNN transformer since it has a similar structure. The overall architecture of GROVER is deferred in Appendix A.

**GNN Transformer** (GTransformer). The key component of the node GTransformer is our proposed graph multi-head attention component, which is the attention blocks tailored to structural input data. A vanilla attention block, such as that in Equation (1), requires vectorized inputs. However, graph inputs are naturally structural data that are not vectorized. So we use our designed dynamic GNNs (dyMPN, see the following sections for details) to extract vectors as queries, keys and values from nodes of the graph, then feed them into the attention block.

This strategy is simple yet powerful, because it enables utilizing the highly expressive dyMPN, in order to better model the structural information in molecular data. The

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**Figure 1:** Overview of GTransformer.
high expressiveness of GTransformer can be attributed to its bi-level information extraction framework. It is well-known that the message passing process captures local structural information of the graph, therefore using the outputs of dyMPN as queries, keys and values would get the local subgraph structure involved, thus constituting the first level of information extraction. Meanwhile, the Transformer encoder can be viewed as a variant of the GAT [21, 52] on a fully connected graph constructed by \( \mathcal{V} \). Hence, using Transformer encoder on top of these dyMPN queries, keys and values makes it possible to extract global relations between nodes, which enables the second level of information extraction. This bi-level information extraction largely enhances the representational power of GROVER models.

The second feature of GTransformer is that we use a single long-range residual connection, while the Transformer encoder uses several short-range residual connections within each attention layer. The long-range residual connection conveys the initial node/edge feature information directly to the last layers of GTransformer. Two benefits could be obtained from this single long-range residual connection: i) like ordinary residual connections, it improves the training process by alleviating the vanishing gradient problem [17], ii) compared to the various short-range residual connections in the Transformer encoder, our long-range residual connection can alleviate the over-smoothing [33, 42] problem in the message passing process.

**Dynamic Message Passing Network (dyMPN).** The general message passing process (see Equation (2)) has two hyperparameters: number of iterations/layers \( L \) and number of hops \( K_l, l = 1, \ldots, L \) within each iteration. The number of hops is closely related to the size of the receptor field of the graph convolution operation, which would affect generalizability of the message passing model.

Given a fixed number of layers \( L \), we find out that the pre-specified number of hops might not work well for different kinds of dataset. Instead of pre-specifying the number of hops, we develop a randomized strategy for choosing the number of hops during training process: at each epoch, we choose \( K_l \) from some random distribution for layer \( l \). Two choices of randomization work well: i) \( K_l \sim U(a, b) \), drawn from a uniform distribution; ii) \( K_l \) is drawn from a truncated normal distribution, which is derived from that of a normally distributed random variable by bounding the random variable from both below and above.

The above randomized message passing scheme enables random receptor field for each node in graph convolution operation. We call the induced network Dynamic Message Passing networks (abbreviated as dyMPN). Extensive experimental verification demonstrates that dyMPN enjoys better generalization performance than vanilla message passing networks without the randomization strategy.

**4.2 Self-supervised Task Construction for Pre-training**

The success of the pre-training model crucially depends on the design of self-supervision tasks. Different from Hu et.al. [18], to avoid negative transfer on downstream tasks, we do not use the supervised labels in pre-training and propose new self-supervision tasks on both of these two levels: contextual property prediction and graph-level motif prediction, which are sketched in Figure 2.

**Contextual Property Prediction.** A good self-supervision task on the node level should satisfy the following properties: i) The prediction target is reliable and easy to get; ii) The prediction target should reflect contextual information of the node/edge. Guided by these criteria, we present the tasks on both nodes and edges. They both try to predict the context-aware properties of the target node/edge within some local subgraph. What kinds of context-aware properties shall one use? We define recurrent statistical properties of local subgraph in the following two-step manner (let us take the node subgraph in Figure 3 as the example): i) Given a target node (e.g.,
the Carbon atom in red color), we extract its local subgraph as its $k$-hop neighboring nodes and edges. When $k=1$, it involves the Nitrogen atom, Oxygen atom, the double bond and single bond. ii) We extract statistical properties of this subgraph, specifically, we count the number of occurrence of (node, edge) pairs around the center node, which makes the term of node-edge-counts. Then we list all the node-edge counts terms in alphabetical order, which constitutes the final property: e.g., \texttt{C\_N\_DOUBLE1\_O\_SINGLE1} in the example. This step can be viewed as a clustering process: the subgraphs are clustered according to the extracted properties, one property corresponds to a cluster of subgraphs with the same statistical property.

With the context-aware property defined, the contextual property prediction task works as follows: given a molecular graph, after feeding it into the GROVER encoder, we obtain embeddings of its atoms and bonds. Suppose randomly choose the atom $v$ and its embedding is $h_v$. Instead of predicting the atom type of $v$, we would like $h_v$ to encode some contextual information around node $v$. The way to achieve this target is to feed $h_v$ into a very simple model (such as a fully connected layer), then use the output to predict the contextual properties of node $v$. This prediction is a multi-class prediction problem (one class corresponds to one contextual property).

**Graph-level Motif Prediction.** Graph-level self-supervision task also needs reliable and cheap labels. Motifs are recurrent sub-graphs among the input graph data, which are prevalent in molecular graph data. One important class of motifs in molecules are functional groups, which encodes the rich domain knowledge of molecules and can be easily detected by the professional software, such as RDKit [26]. Formally, the motif prediction task can be formulated as a multi-label classification problem, where each motif corresponds to one label. Suppose we are considering the presence of $p$ motifs \{$m_1, \ldots, m_p$\} in the molecular data. For one specific molecule (abstracted as a graph $G$), we use professional software to detect whether each of the motif shows up in $G$, then use it as the target of the motif prediction task.

**4.3 Fine-tuning for Downstream Tasks**

After pre-training GROVER models on massive unlabelled data with the designed self-supervised tasks, one should obtain a high-quality molecular encoder which is able to output embeddings for both nodes and edges. These embeddings can be used for downstream tasks through the fine-tuning process. Various downstream tasks could benefit from the pre-trained GROVER models. They can be roughly divided into three categories: node level tasks, e.g., node classification; edge level tasks, e.g., link prediction; and graph level tasks, such as the property prediction for molecules. Take the graph level task for instance. Given node/edge embeddings output by the GROVER encoder, we can apply some READOUT function Equation (3) to get the graph embedding firstly, then use additional multiple layer perceptron (MLP) to predict the property of the molecular graph. One would use part of the supervised data to fine-tune both the encoder and additional parameters (READOUT and MLP). After several epochs of fine-tuning, one can expect a well-performed model for property prediction.

**5 Experiments**

**Pre-training Data Collection.** We collect 11 million (M) unlabelled molecules sampled from ZINC15 [46] and Chembl [11] datasets to pre-train GROVER. We randomly split 10\% percent of unlabelled molecules as the validation sets for model selection.

**Fine-tuning Tasks and Datasets.** To thoroughly evaluate GROVER on downstream tasks, we conduct experiments on 11 benchmark datasets from the MoleculeNet [58] with various targets, such as quantum mechanics, physical chemistry, biophysics and physiology.\footnote{All datasets can be downloaded from http://moleculenet.ai/datasets-1} Details are deferred to the Appendix B.1. In machine learning tasks, random splitting is a common process to split the dataset. However, for molecular property prediction, scaffold splitting [2] offers a more challenging yet realistic way of splitting. We adopt the scaffold splitting method with a ratio for train/validation/test
Table 1: The performance comparison. The numbers in brackets are the standard deviation. The methods in green are pre-trained methods.

| Dataset  | Classification (Higher is better) | Regression (Lower is better) |
|----------|-----------------------------------|------------------------------|
|          | BBP                              | SIDR                         | ChnTox | BACE | Tox21 | ToxCast |
| # Molecules | 2039 | 1427 | 1478 | 1513 | 7831 | 8575 |
| TF_Roubust [39] | 0.860(0.087) | 0.607(0.033) | 0.705(0.065) | 0.824(0.022) | 0.698(0.012) | 0.585(0.031) |
| GraphConv [23] | 0.877(0.036) | 0.593(0.035) | 0.815(0.051) | 0.854(0.011) | 0.772(0.041) | 0.650(0.025) |
| Weave [22] | 0.837(0.065) | 0.548(0.034) | 0.823(0.023) | 0.791(0.008) | 0.741(0.044) | 0.678(0.024) |
| SchNet [44] | 0.849(0.024) | 0.545(0.036) | 0.717(0.042) | 0.758(0.033) | 0.767(0.025) | 0.879(0.021) |
| MPNN [13] | 0.913(0.041) | 0.597(0.030) | 0.879(0.054) | 0.815(0.044) | 0.808(0.034) | 0.691(0.013) |
| DMPNN [61] | 0.919(0.030) | 0.632(0.023) | 0.807(0.040) | 0.852(0.053) | 0.826(0.023) | 0.718(0.011) |
| MGCN [29] | 0.850(0.064) | 0.552(0.018) | 0.634(0.042) | 0.734(0.030) | 0.707(0.016) | 0.663(0.009) |
| AttentiveFP [59] | 0.908(0.050) | 0.605(0.030) | 0.933(0.020) | 0.863(0.015) | 0.807(0.020) | 0.579(0.001) |
| N-GRAM [28] | 0.912(0.013) | 0.632(0.005) | 0.859(0.037) | 0.576(0.035) | 0.769(0.027) | * |
| HU et.al [18] | 0.915(0.040) | 0.614(0.006) | 0.762(0.056) | 0.851(0.027) | 0.811(0.015) | 0.714(0.019) |
| GROVER_base | 0.954(0.006) | 0.651(0.008) | 0.967(0.013) | 0.578(0.016) | 0.819(0.020) | 0.724(0.010) |
| GROVER_large | **0.940 (0.019)** | **0.658 (0.023)** | **0.944 (0.023)** | **0.894 (0.029)** | **0.831 (0.025)** | **0.737 (0.010)** |

Table 1: The performance comparison. The numbers in brackets are the standard deviation. The methods in green are pre-trained methods.

Experimental Configurations. We use Adam optimizer for both pre-train and fine-tuning. The Noam learning rate scheduler [9] is adopted to adjust the learning rate during training. Specific configurations are: GROVER Pre-training. For the contextual property prediction task, we set the context radius \( k = 1 \) to extract the contextual property dictionary, and obtain 2518 and 2686 distinct node and edge contextual properties as the node and edge label, respectively. For each molecular graph, we randomly mask 15% of node and edge labels for prediction. For the graph-level motif prediction task, we use RDKit [26] to extract 85 functional groups as the motifs of molecules. We represent the label of motifs as the one-hot vector. To evaluate the effect of model size, we pre-train two GROVER models, GROVER_base and GROVER_large with different hidden sizes, while keeping all other hyper-parameters the same. Specifically, GROVER_base contains \( \sim48M \) parameters and GROVER_large contains \( \sim100M \) parameters. Fine-tuning Procedure. We use the validation loss to select the best model. For each training process, we train models for 100 epochs. For hyper-parameters, we perform the random search on the validation set for each dataset and report the best results. More pre-training and fine-tuning details are deferred to Appendix C and Appendix D.

Note: The result is not presented since N-Gram on ToxCast is too time consuming to be finished in time.

as 8:1:1. For each dataset, as suggested by [58], we apply three independent runs on random-seeded scaffold splitting and report the mean and standard deviations.

Baselines. We comprehensively evaluate GROVER against 10 popular baselines from MoleculeNet [58] and several state-of-the-arts (STOAs) approaches. Among them, the TF_Roubust [39] is a DNN-based multitask framework taking the molecular fingerprints as the input. GraphConv [23], Weave [22] and SchNet [44] are three graph convolutional models. MPNN [13] and its variants DMPNN [61] and MGCN [29] are models considering the edge features during message passing. AttentiveFP [59] is an extension of the graph attention network. Specifically, to demonstrate the power of our self-supervised strategy, we also compare GROVER with two pre-trained model: N-Gram [28] and Hu et.al [18]. We only report classification results for [18] since the original implementation do not admit regression task without non-trivial modifications.
5.1 Results on Downstream Tasks

Table 1 documents the overall results of all models on all datasets, where the cells in gray indicate the previous STOAs, and the cells in blue indicates the best result achieved by GROVER. Table 1 offers the following observations: (1) GROVER models consistently achieve the best performance on all datasets with large margin on almost of them. The overall relative improvement is 6.1% on all datasets (2.2% on classification tasks and 10.8% on regression tasks). This remarkable boosting validates the effectiveness of the pre-training model GROVER for molecular property prediction tasks. (2) Specifically, GROVER\textsubscript{base} outperforms the STOAs on 8/11 datasets, while GROVER\textsubscript{large} surpasses the STOAs on all datasets. This improvement can be attributed to the high expressive power of the large model, which can encode more information from the self-supervised tasks. (3) In the small dataset FreeSolv with only 642 labeled molecules, GROVER gains a 23.9% relative improvement over existing STOAs. This confirms the strength of GROVER since it can significantly help with the tasks with very few label information.

5.2 Ablation Studies on Design Choices of the GROVER Framework

How Useful is the Self-supervised Pre-training? To investigate the contribution of the self-supervision strategies, we compare the performances of pre-trained GROVER and GROVER without pre-training on classification datasets, both of which follow the same hyper-parameter setting. We report the comparison of classification task in Table 5.2, it is not supervising that the performance of GROVER becomes worse without pre-training. The self-supervised pre-training leads to a performance boost with an average AUC increase of 3.8% over the model without pre-training. This confirms that the self-supervised pre-training strategy can learn the implicit domain knowledge and enhance the prediction performance of downstream tasks. Notably, the datasets with fewer samples, such as SIDER, ClinTox and BACE gain a larger improvement through the self-supervised pre-training. It re-confirms the effectiveness of the self-supervised pre-training for the task with insufficient labeled molecules.

Effect of the Proposed dyMPN and GTransformer. In this section, we use a toy data set with 600K unlabelled molecules to pre-train GROVER with 38M parameters. Besides, to justify the rationale behind the proposed GTransformer and dyMPN, we implement two variants: GROVER w/o dyMPN and GROVER w/o GTrans. GROVER w/o dyMPN fix the number of message passing hops $K_1$, while GROVER w/o GTrans replace the GTransformer with the original Transformer. Figure 4 displays the curve of training and validation loss for three models. First, GROVER w/o GTrans is the worst one in both training and validation. It implies that trivially combining the GNN and Transformer cannot enhance the expressive power of GNN. Second, dyMPN slightly harms the training loss by introducing randomness in the training process. However, the validation loss becomes better. Therefore, dyMPN brings a better generalization ability to GROVER by randomizing the receptor field for every message passing step. Overall, with new Transformer-style architecture and the dynamic message passing mechanism, GROVER enjoys high expressive power and can well capture the structural information in molecules, thus helping with various tasks.

|                      | GROVER | GROVER w/o DyMPN | GROVER w/o GTrans |
|----------------------|--------|------------------|-------------------|
| BBBP (2019)          | 0.940  | 0.911            | +0.029            |
| SIDER (1427)         | 0.658  | 0.624            | +0.034            |
| ClinTox (1478)       | 0.964  | 0.884            | +0.080            |
| BACE (1513)          | 0.894  | 0.858            | +0.036            |
| Tox21 (7831)         | 0.851  | 0.803            | +0.028            |
| ToxCast (8575)       | 0.737  | 0.721            | +0.016            |
| **Average**          | 0.854  | 0.801            | +0.053            |

Table 2: Comparison between GROVER with and without pre-training.

6 Conclusion and Future Works

We explore the potential of the large-scale pre-trained GNN models in this work. With well-designed self-supervised tasks and largely-expressive architecture, our model GROVER can learn rich implicit information from the enormous unlabelled graphs. More importantly, by fine-tuning on GROVER,
we achieve huge improvements (more than 6% on average) over current STOAs on 11 challenging molecular property prediction benchmarks, which first verifies the power of self-supervised pre-trained approaches in the graph learning area.

Despite the successes, there is still room to improve GNN pre-training in the following aspects: **More self-supervised tasks.** Well designed self-supervision tasks are the key of success for GNN pre-training. Except for the tasks presented in this paper, other meaningful tasks would also boost the pre-training performance, such as distance-preserving tasks and tasks that getting 3D input information involved. **More downstream tasks.** It is desirable to explore a larger category of downstream tasks, such as node prediction and link prediction tasks on different kinds of graphs. Different categories of downstream tasks might prefer different pre-training strategies/self-supervision tasks, which is worthwhile to study in the future. **Wider and deeper models.** Larger models are capable of capturing richer semantic information for more complicated tasks, as verified by several studies in the NLP area. It is also interesting to employ even larger models and data than GROVER. However, one might need to alleviate potential problems when training super large models of GNN, such as gradient vanishing and oversmoothing.

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Figure 5: Overview of the whole GROVER architecture with both node-view GTransformer (in pink background) and edge-view GTransformer (in green background)

Figure 5 illustrates the complete architecture of GROVER models, which contains a node-view GTransformer (in pink background) and an edge-view GTransformer (in green background). Brief presentations of the node-view GTransformer have been introduced in the main text, and the edge-view GTransformer is in a similar structure. Here we elaborate more details of the GROVER model and its associated four sets of output embeddings.

As shown in Figure 5, node-view GTransformer contains node dyMPN, which maintains hidden states of nodes \( h_v, v \in V \) and performs the message passing over nodes. Meanwhile, edge-view GTransformer contains edge dyMPN, that maintains hidden states of edges \( h_{vw}, h_{wv}, (v, w) \in E \) and conducts message passing over edges. The edge message passing is viewed as an ordinary message passing over the line graph of the original graph, where the line graph describes the neighboring of edges in the original graph and enables an appropriate way to define message passing over edges [6]. Note that edge hidden states have directions, i.e., \( h_{vw} \) is not identical to \( h_{wv} \) in general.

Then, after the multi-head attention, we denote the transformed node and edge hidden states by \( \bar{h}_v \) and \( \bar{h}_{vw} \), respectively.

Given the above setup, we can explain why GROVER will output four sets of embeddings in Figure 5. Let us focus on the information flow in the pink panel of Figure 5, first. Here the node hidden states \( \bar{h}_v \) encounter the two components, Aggregate2Node and Aggregate2Edge, which are used to aggregate the node hidden states to node messages and edge messages, respectively. Specifically, the Aggregate2Node and Aggregate2Edge components in node-view GTransformer is formulated as follows:

\[
\begin{align*}
    m_{\text{node-embedding-from-node-states}} &= \sum_{u \in \mathcal{N}_v} \text{CONCAT}(\bar{h}_u, x_u) \\
    m_{\text{edge-embedding-from-node-states}} &= \sum_{u \in \mathcal{N}_v \setminus w} \text{CONCAT}(\bar{h}_u, e_{uv}).
\end{align*}
\]

Then the node-view GTransformer transforms the node messages \( m_{\text{node-embedding-from-node-states}} \) and edge messages \( m_{\text{edge-embedding-from-node-states}} \) through Pointwise Feed Forward layers [51] and Add&LayerNorm to produce the final node embeddings and edge embeddings, respectively.

Similarly, for the information flow in the green panel, the edge hidden states \( \bar{h}_{vw} \) encounter the two components Aggregate2Node and Aggregate2Edge as well. Their operations are formulated as
follows,

$$\mathbf{m}_v^{\text{node-embedding-from-edge-states}} = \sum_{u \in \mathcal{N}_v} \text{CONCAT}(\bar{\mathbf{h}}_{uv}, \mathbf{x}_u),$$  \hspace{1cm} (6)$$

$$\mathbf{m}_e^{\text{edge-embedding-from-edge-states}} = \sum_{u \in \mathcal{N}_v \setminus w} \text{CONCAT}(\bar{\mathbf{h}}_{uv}, \mathbf{e}_{uv}).$$  \hspace{1cm} (7)

Then, the edge-view GTransformer transforms the node messages and edge messages through Pointwise Feed Forward layers and Add&LayerNorm to produce the final node embeddings and edge embeddings, respectively.

In summary, the GROVER model outputs four sets of embeddings from two information flows. The node information flow (node GTransformer) maintains node hidden states and finally transform them into another node embeddings and edge embeddings, while the edge information flow (edge GTransformer) maintains edge hidden states and also transforms them into node and edge embeddings. The four sets of embeddings reflect structural information extracted from the two distinct views, and they are flexible to conduct downstream tasks, such as node-level prediction, edge-level prediction and graph-level prediction (via an extra READOUT component).

### A.1 Fine-tuning Model for Molecular Property Prediction

As explained above, given a molecular graph $G_i$ and the corresponding label $y_i$, GROVER produces two node embeddings, $\mathbf{H}_{i,\text{node-view}}$ and $\mathbf{H}_{i,\text{edge-view}}$, from node-view GTransformer and edge-view GTransformer, respectively. We feed these two node embeddings into a shared self-attentive READOUT function to generate the graph-level embedding [27, 52]:

$$\mathbf{S} = \text{softmax} \left( \mathbf{W}_2 \tanh \left( \mathbf{W}_1 \mathbf{H}^\top \right) \right),$$

$$\mathbf{g} = \text{Flatten}(\mathbf{S} \mathbf{H}),$$  \hspace{1cm} (8)

where $\mathbf{W}_1 \in \mathbb{R}^{d_{\text{attn-hidden}} \times d_{\text{hidden-size}}}$ and $\mathbf{W}_2 \in \mathbb{R}^{d_{\text{attn-out}} \times d_{\text{attn-hidden}}}$ are two weight matrix and $\mathbf{g}$ is the final graph embedding. After the READOUT, we employ two distinct MLPs to generate two predictions: $\mathbf{p}_{i,\text{node-view}}$ and $\mathbf{p}_{i,\text{edge-view}}$. Besides the supervised loss $\mathcal{L}(\mathbf{p}_{i,\text{node-view}}, y_i) + \mathcal{L}(\mathbf{p}_{i,\text{edge-view}}, y_i)$, the final loss function also includes a disagreement loss [27] $\mathcal{L}_{\text{dis}} = \| \mathbf{p}_{i,\text{node-view}} - \mathbf{p}_{i,\text{edge-view}} \|_2^2$ to retrain the consensus of two predictions.

### A.2 Constructing Contextual Properties for Edges

In Section 4.2 we describe an example of constructing contextual properties of nodes, here we present an instance of cooking edge contextual properties in order to complete the picture.

Similar to the process of node contextual property construction, we define recurrent statistical properties of local subgraph in a two-step manner. Let us take the graphs in Figure 6 for instance and consider the double chemical bond in red color in the left graph.

Step I: We extract its local subgraph as its $k$-hop neighboring nodes and edges. When $k=1$, it involves the Nitrogen atom, Carbon atom and the two single bonds. Step II: We extract statistical properties of this subgraph, specifically, we count the number of occurrence of (node, edge) pairs around the

![Figure 6: Examples of constructing contextual properties for edges](image-url)
center edge, which makes the term of node-edge-counts. Then we list all the node-edge counts terms in alphabetical order, which makes the final property: e.g., DOUBLE_C_SINGLE1_N-SINGLE1 in the example.

Note that there are two graphs and two double bonds in red color in Figure 6, since their subgraphs have the same statistical property, the resulted contextual properties of the two bonds would be the same. For a different point of view, this step can be viewed as a clustering process: the subgraphs are clustered according to the extracted properties, one property corresponds to a cluster of subgraphs with the same statistical property.

B Details about Experimental Setup

B.1 Dataset Description

| Type       | Category       | Dataset | # Tasks | # Compounds | Metric   |
|------------|----------------|---------|---------|-------------|----------|
| Classification | Biophysics     | BBBP    | 1       | 2039        | ROC-AUC  |
|            | Physiology     | SIDER   | 27      | 1427        | ROC-AUC  |
|            |                | ClinTox | 2       | 1478        | ROC-AUC  |
|            |                | BACE    | 1       | 1513        | ROC-AUC  |
|            |                | Tox21   | 12      | 7831        | ROC-AUC  |
|            |                | ToxCast | 617     | 8575        | ROC-AUC  |
| Regression | Physical chemistry | FreeSolv | 1       | 642         | RMSE     |
|            |                | ESOL    | 1       | 1128        | RMSE     |
|            |                | Lipophilicity | 1   | 4200        | RMSE     |
|            |                | QM7     | 1       | 6830        | MAE      |
|            |                | QM8     | 12      | 21786       | MAE      |

Table 3 summaries information of benchmark datasets, including task type, dataset size, and evaluation metrics. The details of each dataset are listed below [58]:

Molecular Classification Datasets.

- BBBP [31] involves records of whether a compound carries the permeability property of penetrating the blood-brain barrier.
- SIDER [25] records marketed drugs along with its adverse drug reactions, also known as the Side Effect Resource.
- ClinTox [12] compares drugs approved through FDA and drugs eliminated due to the toxicity during clinical trials.
- BACE [47] is collected for recording compounds which could act as the inhibitors of human β-secretase 1 (BACE-1) in the past few years.
- Tox21 [1] is a public database measuring the toxicity of compounds, which has been used in the 2014 Tox21 Data Challenge.
- ToxCast [40] contains multiple toxicity labels over thousands of compounds by running high-throughput screening tests on thousands of chemicals.

Molecular Regression Datasets.

- QM7 [4] is a subset of GDB-13, which records the computed atomization energies of stable and synthetically accessible organic molecules, such as HOMO/LUMO, atomization energy, etc. It contains various molecular structures such as triple bonds, cycles, amide, epoxy, etc.
- QM8 [38] contains computer-generated quantum mechanical properties, e.g., electronic spectra and excited state energy of small molecules.
- ESOL is a small dataset documenting the solubility of compounds [8].
- Lipophilicity [11] is selected from the ChEMBL database, which is an important property that affects the molecular membrane permeability and solubility. The data is obtained via octanol/water distribution coefficient experiments.
- FreeSolv [32] is selected from the Free Solvation Database, which contains the hydration free energy of small molecules in water from both experiments and alchemical free energy calculations.

**Dataset Splitting.** We apply the scaffold splitting [2] for all tasks on all datasets. It splits the molecules with distinct two-dimensional structural frameworks into different subsets. It is a more challenging but practical setting since the test molecular can be structurally different from training set. Here we apply the scaffold splitting to construct the train/validation/test sets.

**B.2 Feature Extraction Processes for Molecules**

The feature extraction contains two parts: 1) Node / edge feature extraction. We use RDKit to extract the atom and bond features as the input of dyMPN. Table 4 and Table 5 show the atom and bond feature we used in GROVER. 2) Molecule-level feature extraction. Following the same protocol of [58, 61], we extract additional 200 molecule-level features by RDKit for each molecule and concatenate these features to the output of self-attentive READOUT, to go through MLP for the final prediction.

| Table 4: Atom features. |
|--------------------------|
| features | size | description |
| atom type | 100 | type of atom (e.g., C, N, O), by atomic number |
| formal charge | 5 | integer electronic charge assigned to atom |
| number of bonds | 6 | number of bonds the atom is involved in |
| chirality | 5 | number of bonded hydrogen atoms |
| number of H | 5 | number of bonded hydrogen atoms |
| atomic mass | 1 | mass of the atom, divided by 100 |
| aromaticity | 1 | whether this atom is part of an aromatic system |
| hybridization | 5 | sp, sp2, sp3, sp3d, or sp3d2 |

| Table 5: Bond features. |
|--------------------------|
| features | size | description |
| bond type | 4 | single, double, triple, or aromatic |
| stereo | 6 | none, any, E/Z or cis/trans |
| in ring | 1 | whether the bond is part of a ring |
| conjugated | 1 | whether the bond is conjugated |

**C Implementation and Pre-training Details**

We use Pytorch to implement GROVER and horovod for the distributed training. We use the Adam optimizer with learning rate 0.00015 and L2 weight decay for $10^{-7}$. We train the model for 500 epochs. The learning rate warmup over the first two epochs and decreases exponentially from 0.00015 to 0.00001. We use PReLU [16] as the activation function and the dropout rate is 0.1 for all layers. Both GROVER_base and GROVER_large contain 4 heads. We set the iteration $L = 1$ and sample $K_t \sim \phi(\mu = 6, \sigma = 1, a = 3, b = 9)$ for the embedded dyMPN in GROVER. $\psi(\mu, \sigma, a, b)$ is a truncated normal distribution with a truncation range $(a, b)$. For the The hidden size for GROVER_base and GROVER_large are 800 and 1200 respectively.

We use 250 Nvidia V100 GPUs to pre-train GROVER_base and GROVER_large. Pre-training GROVER_base and GROVER_large took 2.5 days and 4 days respectively. For the models depicted in Figure 4 in the ablation study, we use 32 Nvidia V100 GPUs to pre-train the GROVER model and its variants. We will release the pre-trained models and the training code in the future.
D Fine-tuning Details

For each task, we try 300 different hyper-parameter combinations via random search to find the best results. Table 6 demonstrates all the hyper-parameters of fine-tuning model. All fine-tuning tasks are run on a single P40 GPU.

Table 6: The fine-tuning hyper-parameters

| hyper-parameter | Description                                                                 | Range          |
|-----------------|------------------------------------------------------------------------------|----------------|
| batch_size      | the input batch_size.                                                       | 32             |
| init_lr         | initial learning rate ratio of Noam learning rate scheduler.                | 10             |
| max_lr          | maximum learning rate of Noam learning rate scheduler.                     | 0.0001 ~ 0.001 |
| final_lr        | final learning rate ratio of Noam learning rate scheduler.                 | 0.05, 0.1, 0.2 |
| dropout         | dropout ratio.                                                             | 0.0, 0.05, 0.1, 0.2 |
| attn_hidden     | hidden size for the self-attentive readout.                               | 0, 0.05, 0.1, 0.2 |
| attn_out        | the number of output heads for the self-attentive readout.                 | 0, 0.05, 0.1, 0.2 |
| dist_coff       | coefficient of the disagreement loss                                        | 0.05, 0.1, 0.15 |
| bond_drop_rate  | drop edge ratio [42]                                                       | 0, 0.2, 0.4, 0.6 |
| ffn_num_layer   | the number of MLP layers.                                                  | 2, 3           |
| ffn_hidden_size | the hidden size of MLP layers.                                             | 4, 8           |

E Additional Experimental Results

Table 7 depicts the additional results of the comparison of the performance of pre-trained GROVER and GROVER without pre-training on regression tasks.

Table 7: Comparison between GROVER with and without pre-training on regression tasks

|        | GROVER | No Pre-training | Absolute Improvement |
|--------|--------|-----------------|----------------------|
| RMSE   |        |                 |                      |
| FreeSolv | 1.544  | 1.987           | 0.443                |
| ESOL   | 0.831  | 0.911           | 0.080                |
| Lipo   | 0.560  | 0.643           | 0.083                |
| MAE    |        |                 |                      |
| QM7    | 72.600 | 89.408          | 16.808               |
| QM8    | 0.013  | 0.017           | 0.004                |