Pre-Training Graph Neural Networks on Molecules by Using Subgraph-Conditioned Graph Information Bottleneck

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Abstract

This study aims to build a pre-trained Graph Neural Network (GNN) model on molecules without human annotations or prior knowledge. Although various attempts have been proposed to overcome limitations in acquiring labeled molecules, the previous pre-training methods still rely on semantic subgraphs, i.e., functional groups. Only focusing on the functional groups could overlook the graph-level distinctions. The key challenge to build a pre-trained GNN on molecules is how to (1) generate well-distinguished graph-level representations and (2) automatically discover the functional groups without prior knowledge. To solve it, we propose a novel Subgraph-conditioned Graph Information Bottleneck, named S-CGIB, for pre-training GNNs to recognize core subgraphs (graph cores) and significant subgraphs. The main idea is that the graph cores contain compressed and sufficient information that could generate well-distinguished graph-level representations and reconstruct the input graph conditioned on significant subgraphs across molecules under the S-CGIB principle. To discover significant subgraphs without prior knowledge about functional groups, we propose generating a set of functional group candidates, i.e., ego networks, and using an attention-based interaction between the graph core and the candidates. Despite being identified from self-supervised learning, our learned subgraphs match the real-world functional groups. Extensive experiments on molecule datasets across various domains demonstrate the superiority of S-CGIB.

Introduction

Graph Neural Networks (GNNs) have recently emerged in computational chemistry, offering powerful tools for predicting molecular properties (Gilmer et al. 2017; Kearnes et al. 2016). While GNNs have shown remarkable performance in molecular property prediction, their effectiveness depends on the availability of abundant labeled molecules for model training (Hao et al. 2020; Hoang et al. 2023).

Recently, pre-training strategies have offered considerable potential in overcoming the challenges of the scarcity of labeled molecular data (Rong et al. 2020; Luong and Singh 2023). The existing pre-training strategies can be categorized into three primary groups: node-level pre-training, contrastive learning, and subgraph-level pre-training. Node-level pre-training mainly focuses on node-level prediction, e.g., node attribute reconstruction or edge prediction, which may not fully leverage the high-order structure of molecules, i.e., functional groups (Rong et al. 2020). The second strategy is contrastive learning, which focuses on learning representations by contrasting multiple views of molecules based on random or heuristic augmentations (You et al. 2021; Xu et al. 2021). More recently, subgraph-level strategies focus on semantic subgraphs, which can capture both local and global structural patterns by identifying functional groups (Subramonian 2021; Zhang et al. 2021; Rong et al. 2020; Liu et al. 2023; Inae, Liu, and Jiang 2023). The main idea is to use human annotations or prior knowledge to extract the semantic subgraphs, e.g., frequent subgraphs across molecules, to enhance recognizing significant substructures and molecular property prediction (Luong and Singh 2023; Degen et al. 2008). To sum up, most recent pre-training strategies aggregate information from node-level or subgraph-level to generate graph-level representations.

However, two challenges limit the existing pre-training strategies on molecules. ***First***, the existing strategies lack the ability to generate well-distinguished graph-level representations. Most node-level strategies mainly focus on the local structure and then adopt a pooling function, e.g., mean, max, or sum, to aggregate information, resulting in poor-distinguished graph-level representations as information from noisy and redundant nodes can be aggregated to form graph-level representations (Hu et al. 2020a). Besides, while subgraph-level strategies (Subramonian 2021; Zhang et al. 2021) can capture specific subgraphs at multiple scales, they could overlook the entire graph-level distinctions (Rong et al. 2020; Inae, Liu, and Jiang 2023). That is, subgraph-level representations based on discrete pre-defined patterns, e.g., frequent subgraphs, ignore global interactions between important nodes that derive the molecule's entire structure. For contrastive learning strategies, applying augmentation schemes, e.g., edge perturbation, could potentially disrupt the structures and properties of molecules (Lee, Lee, and Park 2022). ***Second***, it is challenging for subgraph-based strategies to cover all possible functional groups given in diverse molecule datasets. To capture functional groups, recent subgraph-level strategies create dictionaries based on pre-defined rules, e.g., counting the discrete occurrences of

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subgraphs across molecules to decompose molecules into a bag of subgraphs, commonly prioritizing subgraphs with larger sizes and frequent occurrences (Luong and Singh 2023; Kong et al. 2022). The prioritization and static dictionaries could limit the model's ability to capture new and uncommon functional groups.

In this paper, we overcome the above challenge of pre-training strategies by considering how to (1) generate well-separated graph-level representations and (2) automatically capture significant subgraphs without explicit annotations or prior knowledge. The fundamental idea behind our strategy is that, across the chemical domain, molecules share universal core subgraphs that can combine with specific significant subgraphs to robust representations of molecules.

To generate well-distinguished graph-level representations, this initiates a problem in recognizing a set of important nodes (graph cores) that can allow robust and well-separated representations (Hu et al. 2020a). We interpret this problem as the Graph Information Bottleneck (GIB) principle, which aims to compress an input graph into a core subgraph that keeps sufficient and compressed information about the input graph (Yu et al. 2021). However, current GIB methods learn compressed subgraphs by minimizing information loss in predicting the graph labels, which still require the label information. To solve it, we propose a Subgraph-conditioned Graph Information Bottleneck (S-CGIB) for self-supervised pre-training to compress an input graph into a graph core conditioned on specific significant subgraphs without using label information. First, the graph cores contain important nodes, which could generate robust representations under the S-CGIB principle. Second, toward capturing functional groups without prior knowledge, we suppose that graph cores then could reconstruct input graphs conditioned on specific significant subgraphs across molecules.

To discover the significant subgraphs, as we intentionally ignore using prior knowledge about functional groups, we propose to generate a set of functional group candidates, i.e., ego networks rooted at each node. The reason is that the graph core of molecules typically consists of central substructures composing important nodes only for generating well-separated representations. In other words, the compression process ignored unimportant nodes, which can be a part of functional groups in terms of molecular properties. Then, we propose an attention-based interaction between the graph core and candidates to recognize significant subgraphs as functional groups. The attention coefficients can highlight significant subgraphs, which benefit from recognizing functional groups across molecules.

Related Work

We now discuss how the existing pre-training strategies can learn the molecular structure and chemical properties in the context of Self-Supervised Learning compared to our method. Early pre-training strategies focus on learning node representations, which are then aggregated into a single graph-level representation through pooling mechanisms, e.g., min, max, or sum, (Hu et al. 2020b,a). The node-level strategies can be mainly grouped into node-level structure reconstruction, e.g., neighborhood prediction (Hu et al. 2020b; Hoang and Lee 2024), or node feature reconstruction (Devlin et al. 2019). However, these methods focus on learning to distinguish individual node representations, which do not directly handle the challenge of incorporating node embeddings into a single graph-level representation. Furthermore, node-level pre-training strategies could be limited to capture the high-order structures, i.e., functional groups.

Another line is contrastive learning, which is generally grouped into two categories: node-level contrastive methods and graph-level contrastive methods (Liu et al. 2022; Stärk et al. 2022; Qiu et al. 2020). The node-level contrastive learning strategies seek to generate multiple node views by applying augmentation schemes, e.g., edge perturbation, which modifies the graph connectivity while preserving the node's identity. For example, GraphCL (You et al. 2020) adopts multiple augmentation schemes to generate multiple views of the input graph and uses contrastive loss to obtain embeddings of these views closer. The idea of JOAO (You et al. 2021) is to automatically search schemes to find the most effective augmentations. In contrast, graph-level methods generate multi-views of an input graph and guarantee similar representations while discriminating them from the other graph-level representations (Xu et al. 2021). Such augmentations often change the molecular connectivity and structure, failing to preserve the molecule's properties.

Recent pre-training approaches on molecules emphasize recognizing and learning semantic patterns, such as functional groups, across molecule data (Zhang et al. 2021; Liu et al. 2023; Inae, Liu, and Jiang 2023). The semantic subgraphs can be discovered under pre-defined rules with the use of prior knowledge or human annotation. For example, GROVER (Rong et al. 2020) extracts 85 frequent functional groups and employs a Self-supervised Learning (SSL) task to predict the presence of the functional groups. MGSSL (Zhang et al. 2021) employs depth-first or breadth-first search to discover the semantic subgraphs at multiple scales. Recently, GraphFP (Luong and Singh 2023) decomposes molecules into bags of functional groups by composing a dictionary via frequent subgraph mining, i.e., common and large frequent subgraphs across molecules. Such strategies rely on pre-defined vocabulary with discrete counting frequent subgraphs in molecules, making it challenging to build a complete dictionary to cover new or less common functional groups. In contrast, we automatically discover functional groups via attention-based interaction between the molecular core and a set of functional group candidates.

Problem Descriptions

We study the problem of pre-trained GNNs on molecules, which recognize graph cores conditioned on significant subgraphs (functional group candidates) under the S-CGIB principle. Thus, we first present notations and then the definition of S-CGIB, which is a modification of GIB and CGIB.

A molecule can be represented as a graph $G = (V, E)$, where $V = \{v_1, v_2, \cdots, v_N\}$ represents the set of atoms and E denotes the set of bonds. G is associated with its adjacency matrix A and feature matrix X. Let $N_k(v)$ be a set of neighboring nodes within a k-hop distance from the root

node v. The set of functional group candidates in G is defined as: $S = \{G[N_k(v)] \mid v \in V\}$, where $G[N_k(v)]$ is the k-hop ego network rooted at node v.

Recently, the Information Bottleneck (IB) principle (Tishby, Pereira, and Bialek 2000) has been used on graphs, called GIB, to discover a core subgraph from an input graph.

Definition 1 (GIB) *The GIB principle was originally introduced by Yu et al. (2021) to recognize a compressed and informative subgraph from an input graph. Given an input graph G and its label Y, the compressed graph, as graph core G_c, is discovered as:*

$$\min_{G_c} -I(Y; G_c) + \beta I(G; G_c), \tag{1}$$

where β is a Lagrange multiplier used to balance the two terms. The first term encourages G_c to be informative to the graph label Y, and the second term is the compression term, which minimizes the mutual information of G and G_c.

In the context of the presence of side information T, several studies have accounted for the conditional information T, named CIB (Chechik and Tishby 2002; Gondek and Hofmann 2003). We then apply CIB on graphs as Conditional Graph Information Bottleneck (CGIB).

Definition 2 (CGIB) *Given an input graph G and its label Y, the graph core G_c is discovered given the side information T, as:*

$$\min_{G_c} -I(Y; G_c|T) + \beta I(G; G_c). \tag{2}$$

The first term quantifies how much information the graph core G_c retains about Y, given the side information T. The variable T is supposed to be known as prior knowledge.

To employ the CGIB principle under an SSL task without prior knowledge, we propose to minimize the first term of Eq. 2 by replacing the prediction with a reconstruction task. As the compression process ignored unimportant nodes, which can be a part of functional groups, we suppose they can be side information for a graph reconstruction task. The key idea is that molecules share universal graph cores, which can reconstruct the molecule structure conditioned on specific significant subgraphs. Specifically, we suppose that G is formed by combining a graph core G_c and a set of functional group candidates S, such that $G = G_c \cup S$. Then, the Subgraph-conditioned Graph Information Bottleneck can be defined below:

Definition 3 (S-CGIB) *Given an input graph G and a set of functional group candidates S, we define the S-CGIB principle conditioned on the subgraph S as:*

$$\min_{G_c} - \underbrace{I\left(G; G_c|S\right)}_{\textit{Conditional Reconstruction}} + \underbrace{\beta I\left(G; G_c\right)}_{\textit{Compression}}, \tag{3}$$

By conditioning on S, the first term encourages the graph core G_c to capture sufficient information for reconstructing input graph G (*conditional reconstruction*), while the graph core also needs to be compressed from the input graph (*compression*). Overall, jointly optimizing the two terms allows G_c to be compressed and preserve the input graph structure conditioned on S. Since S consists of all ego networks rooted at each node, to discover important ego networks, i.e., functional groups, we propose an attention-based strategy detailed in the following Section.

Methodology

Model Architecture

Graph Compression The overall architecture of S-CGIB is shown in Figure 1. Given an input graph G with adjacency matrix A and node feature matrix X, we learn node representations in G through a GNN encoder as:

$$H = f_\phi\left(X, A\right), \tag{4}$$

where $H \in R^{N\times d}$ refers to node embeddings, $f_\phi(\cdot,\cdot)$ is a GNN encoder, e.g., GIN (Xu et al. 2019). Inspired by recent VGIB principle (Yu, Cao, and He 2022) that injects noise information into an input graph to obtain important nodes, we compress G by injecting noise into H to obtain a graph core G_c with new node representations Z, which is a bottleneck to distill the important nodes, thereby generating well-distinguished graph-level representations. The key idea is that the important nodes will be injected with less noise information compared to unimportant nodes. Specifically, given the embedding matrix H, for each node v_i, S-CGIB learns a probability p_i with a multi-layer perceptron (MLP) followed by a $\mathrm{Sigmoid}(\cdot)$ function. We then replace the node representation h_i by ϵ with probability p_i, as:

$$p_i = \mathrm{Sigmoid}\left(\mathrm{MLP}(H_i)\right), \tag{5}$$

$$\varepsilon \sim N\left(\mu_H, \sigma_H^2\right),\ \lambda_i \sim \mathrm{Bernoulli}\left(p_i\right), \tag{6}$$

$$z_i = \lambda_i h_i + (1-\lambda_i)\varepsilon, \tag{7}$$

where λ is obtained by sampling from Bernoulli distribution parameterized with the probability p_i, μ_H and σ_H are the mean and variance of H, ϵ is sampled from H based on Gaussian distribution. Therefore, the information of the input graph is compressed into Z with the probability of p_i by masking unimportant nodes with noisy information. That is, the compression process ensures that Z focuses on the important nodes (graph core) while discarding irrelevant and unimportant nodes. To allow the differentiable sampling, we adopt the Gumbel sigmoid method (Jang, Gu, and Poole 2017; Maddison, Mnih, and Teh 2017), i.e., $\lambda_i = \mathrm{Sigmoid}(1/\tau \log[p_i/(1-p_i)]) + \log\left[q/(1-q)\right]$ where $q \sim \mathrm{Uniform}(0,1)$ and τ is the temperature parameter. For the detailed compression optimization process, we refer readers to the Model Optimization Section.

Subgraph Learning The next problem is to extract functional group candidates and encode them to obtain vector representations. Let $G[N_k(v)]$ denotes the k-hop ego network rooted at the node v. We first apply a GNN encoder on nodes within the $G[N_k(v)]$. Then, the subgraph-level representation rooted at node v is obtained via a pooling function $\mathrm{POOL}(\cdot)$. Formally, the representations of ego networks in the input graph G can be computed as:

$$h_v^{(l+1)} = g_\theta^{(l)}\left(G\left[N_k\left(v\right)\right]\right), l = 0, \cdots, L-1, \tag{8}$$

$$h_v = \mathrm{POOL}\left(h_u^{(L)} | u \in N_k\left(v\right)\right), \tag{9}$$

$$H_S = [h_v | v \in V], \tag{10}$$

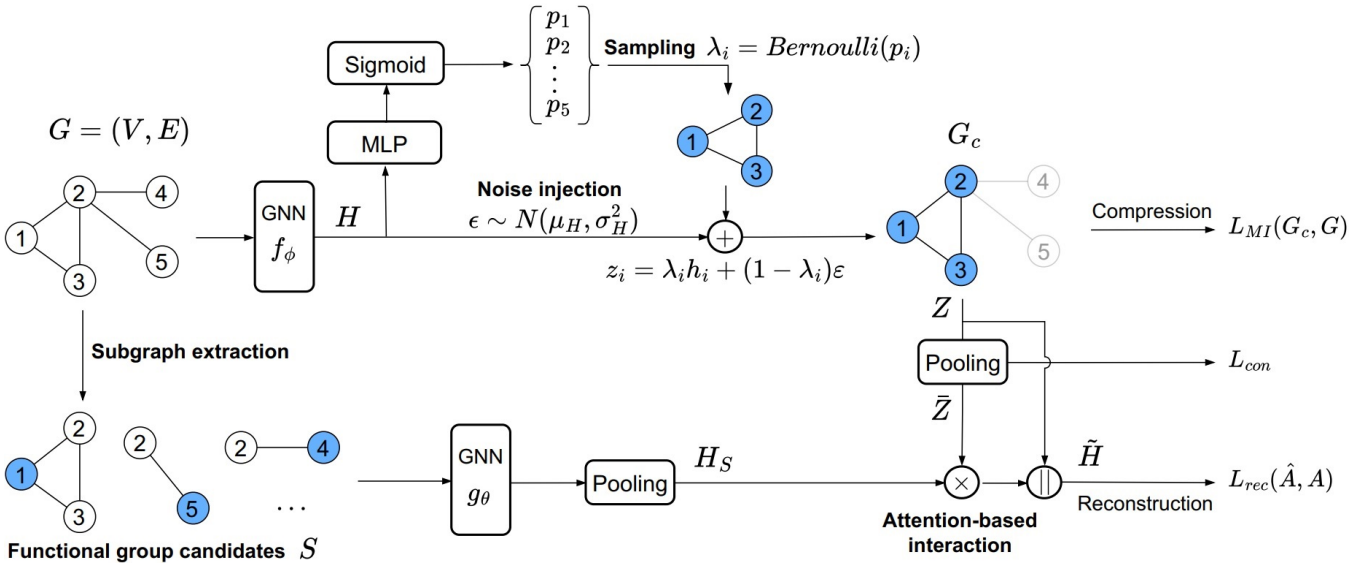

Figure 1: The overall architecture of S-CGIB.

where $g_\theta^{(l)}(\cdot)$ denotes a GNN encoder, e.g., GIN, for the subgraph $G[N_k(v)]$, POOL$(\cdot)$ refers to a subgraph pooling, e.g., sum. Therefore, the local surrounding structures rooted at each node are captured via GNNs.

Graph Core and Subgraph Interaction Note that each functional group has distinct chemical characteristics that contribute differently to the overall molecule behavior. To capture significant subgraphs across molecules, we then propose an attention-based interaction between the graph core and subgraph candidates to highlight specific significant subgraphs. Specifically, we first employ a pooling function to aggregate important node features Z into $\bar{Z}$, i.e., $\bar{Z} = \text{POOL}(Z)$, to obtain a single vector representation of the graph core. We then calculate the normalized attention coefficients for each functional group candidate. Formally, the coefficient of a subgraph candidate rooted at a node v_i can be computed as:

$$\alpha_i = \frac{\exp\left(\left(\bar{Z}||H_{S_i}\right) W_a^T\right)}{\sum_{k=1}^{N} \exp\left(\left(\bar{Z}||H_{S_k}\right) W_a^T\right)}, \tag{11}$$

where $W_a \in R^{1\times 2d}$ refers to learnable projection and H_{S_i} is the representations of the ego network rooted at node v_i. Thus, the interaction could capture the correlation between the graph core and functional group candidates. The final representations are then concatenated along with the coefficients as:

$$\tilde{H}_i = Z_i || \left(\alpha_i H_{S_i}\right). \tag{12}$$

In a nutshell, given an input graph G, our model jointly learns the graph core and the significant subgraphs under the S-CGIB principle. We first inject noisy information into H to obtain the graph core Z under the compression process. Meanwhile, we capture the significant specific subgraphs from the subgraph candidates (ego networks rooted at each node) through the attention-based interaction between the graph core and the ego networks under the graph reconstruction.

Model Optimization

To train the model while optimizing the graph core conditioned on S, we optimize the objective function:

$$G_c^* = \arg\min_{G_c} \; -I(G; G_c|S) + \beta I(G; G_c), \tag{13}$$

where each term denotes the conditional graph reconstruction and compression, respectively. Then, we present upper bounds for each term to guide the optimization.

Minimizing $-I(G; G_c|S)$ The first term of Eq. 13 denotes a reconstruction of the input graph G, given G_c conditioned on S. Thus, we utilize the chain rule for mutual information on the Conditional Graph Reconstruction term as follows:

$$\min -I(G; G_c|S) = \min -I(G; G_c, S) + I(G; S). \tag{14}$$

We observed that including the second term, i.e., $I(G; S)$, into our objectives severely degrades the overall model performance (Appendix D.1). The appendices can be found in our paper repository[1]. That is, the model performs worse as we push the input graph G and its functional group candidates S far apart. Therefore, we only minimize the first term of Eq. 14.

The first term of Eq. 14 can be bounded as follows:

$$-I(G; G_c, S) \leq \mathbb{E}_{G;G_c,S}[-\log p_\varsigma(G|G_c, S)], \tag{15}$$

where $p_\varsigma(G|G_c, S)$ is a variational approximation of $p(G|G_c, S)$, which outputs the input graph G (see Appendix A.1). Thus, we model $p_\varsigma(G|G_c, S)$ as a graph structure reconstruction parametrized by ς, which outputs the graph G based on the G_c and S. Therefore, we can minimize the

[1]https://arxiv.org/abs/2412.15589

upper bound of $-I(G; G_c, S)$ by minimizing the graph reconstruction loss $L_{rec}(G; G_c, S)$, which can be modeled as graph structure recovery. Specifically, given the output representation $\tilde{H}$, to minimize the graph structure loss, we first capture the similarity between any two nodes v_i and v_j in $\tilde{H}$ by employing cosine similarity, i.e., $\hat{A}_{i,j} = \frac{\tilde{H}_i^\top \tilde{H}_j}{\|\tilde{H}_i\| \|\tilde{H}_j\|}$, (Zhang et al. 2020). The reconstruction loss then can be defined as follows:

$$L_{rec} = \frac{1}{|V|^2} \|A - \hat{A}\|_F^2 \,, \tag{16}$$

where A refers to the original adjacency matrix of G and $||\cdot||_F$ is the Frobenius norm.

Minimizing $I(G; G_c)$ To minimize the second term of Eq. 13, we employ the sufficient encoder assumption that the latent representation Z is lossless in the encoding process, i.e., $I(Z|H) \approx I(G_c|G)$. To optimize the graph core G_c, we can employ a variational upper bound that is tractable and can be minimized during training (Yu, Cao, and He 2022). Formally, given the mutual information $I(G; G_c)$, the variational upper bound of $I(G; G_c)$ is:

$$L_{MI}\left(G, G_c\right) \leq \mathbb{E}\left(-\tfrac{1}{2}\log P + \tfrac{1}{2N}\log P + \tfrac{1}{2N}\log Q^2\right), \tag{17}$$

where $P = \sum_{j=1}^{N} \left(1 - \lambda_j\right)^2$, $Q = \frac{\sum_{j=1}^{N} \lambda_j (H_j - \mu_H)}{\sigma_H}$, and λ is computed from Eq. 6. For the proof of the upper bound, we refer readers to Appendix A.2.

Contrastive Learning We note that minimizing the upper bound of $I(G, G_c)$ from Eq. 17 could lead to over-compression with sufficient information on S. That is, the graph core G_c can be too distinguished from its input graph G compared to other graphs. We argue that the ideal core should at least satisfy the high mutual information with its input graph compared to others during the compression process, as $I\left(G_c, G\right) \geq I\left(G_c, \backslash G\right)$, where $\backslash G$ refers to remaining graphs, excluding G. Thus, we propose to use a contrastive learning-based method to maximize the agreement between the graph core and its input graph. Specifically, the contrastive objective is computed as:

$$L_{con} = -\frac{1}{B}\sum_{i=1}^{B} \log \frac{\exp\left(s\left(\bar{Z}^i, \bar{H}^i\right)\right)}{\sum_{j=1, j\neq i}^{B} \exp\left(s\left(\bar{Z}^i, \bar{H}^j\right)\right)}, \tag{18}$$

where B denotes the number of graphs in a mini-batch, $s(\cdot, \cdot)$ is the cosine similarity between graph core and input graph, $\bar{Z} = \text{POOL}(Z)$, and $\bar{H} = \text{POOL}(H)$.

The overall loss for the pre-training task is as follows:

$$L_{total} = L_{con} + L_{rec} + \beta L_{MI}, \tag{19}$$

where β is a hyperparameter to balance the compression and structure preservation trade-off.

Domain Adaptation We note that our pre-trained model can learn significant subgraphs only on the domains of pre-training datasets. However, generalizing toward varied downstream tasks can be challenging due to the node attribute distinctions in specific downstream datasets. That is, while pre-training primarily focuses on structural molecular features, node feature reconstruction is also essential and helps our model adapt to learn node feature characteristics in downstream datasets. Therefore, we employ an unsupervised domain adaptation after pre-training, which acts as a domain-oriented generalization for downstream datasets. Then, we utilize a loss function to reconstruct node feature information for each graph as:

$$L_{att} = \frac{1}{|V|}\sum_{v_i \in V} \|x_i - \hat{x}_i\|_2, \tag{20}$$

where x_i is the initial feature of node v_i and $\hat{x}_i = \text{MLP}(\tilde{H}_i)$.

Evaluation

Experimental Settings

Datasets We conducted experiments across various molecular domains to evaluate the effectiveness of our proposed model, including Biophysics (mol-HIV, mol-PCBA, and BACE (Wu et al. 2018)), Physiology (BBBP, Tox21, ToxCast, SIDER, ClinTox, and MUV), Physical Chemistry (ESOL, FreeSolv, and Lipophilicity) (Wu et al. 2018), Bioinformatics (Mutagenicity, NCI1, and NCI109 (Morris et al. 2020)), Quantum Mechanics (PCQ4Mv2 and QM9 (Hu et al. 2021)). For pre-training datasets, we considered 300k unlabeled molecules sampled from three datasets, i.e., PCQ4Mv2, QM9, and mol-PCBA. The remaining datasets are used as fine-tuning datasets. Furthermore, we also evaluated the model's performance on large molecular graphs using two peptide molecules: peptide-func and peptide-struct (Dwivedi et al. 2022). For the model explainability, we utilized four datasets with the availability of ground truth, i.e., Mutagenicity, Benzene, Alkane Carbonyl, and Fluoride Carbonyl (Agarwal et al. 2023). We randomly split the datasets into training/validation/test sets with a ratio of 6:2:2. The datasets are given in Appendix B.

Baselines and Implementation Details We considered three groups of baselines. (i) The node-level pretraining methods are ContextPred and AttrMasking (Hu et al. 2020a), and EdgePred (Hamilton, Ying, and Leskovec 2017). (ii) The contrastive learning methods are Infomax (Velickovic et al. 2019), JOAO and JOAOv2 (You et al. 2021), GraphCL (You et al. 2020), and GraphLoG (Xu et al. 2021). (iii) The subgraph-based methods are MICRO-Graph (Subramonian 2021), MGSSL (Zhang et al. 2021), GraphFP (Luong and Singh 2023), GROVE (Rong et al. 2020), SimSGT (Liu et al. 2023), and MoAMa (Inae, Liu, and Jiang 2023). We adopted a 5-layer GIN (Xu et al. 2019) as graph encoders. The hyperparameters and experimental setups are given in Appendix C. The open-source implementation of S-CGIB is available for reproducibility[2].

Performance Analysis

Tables 1 and 2 present the performance of our proposed model and the baselines on the graph classification task. We observed that: (i) S-CGIB consistently outperformed other baselines, obtaining the best performance in 10 out of 11 downstream datasets in the graph classification tasks. For

[2]https://github.com/NSLab-CUK/S-CGIB

Methods	BBBP	Tox21	ToxCast	SIDER	ClinTox	MUV	HIV	BACE
ContextPred	69.10±0.29	73.26±0.59	63.28±0.68	61.83±0.60	55.63±1.35	71.43±0.79	72.04±0.48	78.39±0.58
AttrMasking	67.12±0.45	73.37±0.55	61.66±1.20	61.21±0.65	60.11±1.19	67.93±0.56	72.71±0.70	75.95±0.50
EdgePred	64.73±1.10	70.32±1.62	60.04±0.81	60.18±0.76	61.62±1.25	70.81±1.58	70.55±1.68	74.29±1.37
Infomax	68.39±0.64	72.66±0.16	62.76±0.54	59.02±0.56	58.62±0.83	72.14±1.25	73.55±0.47	77.80±0.46
JOAO	71.63±1.11	73.67±1.06	63.30±0.27	63.55±0.81	77.02±1.64	69.81±0.26	77.55±1.94	74.94±1.35
JOAOv2	71.98±0.18	73.95±1.88	63.12±1.90	59.88±1.72	65.22±0.75	68.50±1.58	77.13±1.51	74.38±1.71
GraphCL	68.39±0.64	73.26±0.59	62.76±0.54	61.83±0.60	61.62±1.25	72.14±1.25	73.55±0.47	77.80±0.46
GraphLoG	66.75±0.32	71.64±0.49	61.53±0.35	59.09±0.53	53.76±0.95	72.52±2.02	73.76±0.29	76.60±1.04
GraphFP	72.05±1.17	77.35±1.40	69.15±1.92	**65.93±3.09**	76.80±1.83	71.82±1.33	75.71±1.39	80.28±3.06
MICRO-Graph	67.21±1.85	71.79±1.70	60.80±1.15	60.34±0.96	77.56±1.56	70.46±1.62	76.73±1.07	63.57±1.55
MGSSL	79.52±1.98	74.82±1.60	63.86±1.57	57.46±1.45	75.84±1.82	73.44±3.47	77.45±2.94	82.03±3.79
GROVE	87.15±0.06	68.59±0.24	64.45±0.14	57.53±0.23	72.53±0.14	67.67±0.12	75.04±0.13	81.13±0.14
SimSGT	71.51±1.75	76.23±1.27	65.83±0.79	59.74±1.32	74.11±1.05	72.79±1.52	78.13±1.07	79.75±1.28
MoAMa	85.89±0.61	78.29±0.55	68.01±1.07	62.69±0.37	77.11±1.67	72.41±1.76	78.11±0.64	81.32±1.06
S-CGIB w/o D.A.	86.71±0.74	79.52±0.71	68.93±0.45	62.76±1.83	74.69±1.28	74.12±1.85	77.41±1.63	86.51±1.49
S-CGIB	**88.75±0.49**	**80.94±0.17**	**70.95±0.27**	64.03±1.04	**78.58±2.01**	**77.71±1.19**	**78.33±1.34**	**86.46±0.81**

Table 1: A performance comparison on graph classification tasks in terms of ROC-AUC. (D.A.: Domain Adaptation).

Methods	Mutagenicity	NCI1	NCI109
ContextPred	57.95±1.42	49.47±1.12	50.32±1.05
AttrMasking	58.03±1.16	49.51±1.21	46.25±1.73
EdgePred	48.58±1.02	49.88±1.12	49.19±1.36
Infomax	56.64±1.77	49.55±1.14	53.03±1.48
JOAO	62.33±1.13	49.03±1.21	58.23±1.49
JOAOv2	63.36±1.74	50.73±1.74	53.75±1.32
GraphCL	66.32±3.62	49.11±1.31	56.62±1.59
GraphLoG	66.47±1.47	60.94±1.93	57.52±1.61
GraphFP	68.43±1.32	53.77±1.13	58.14±1.45
MICRO-Graph	80.64±1.28	74.45±1.51	76.15±3.53
MGSSL	66.47±1.47	60.94±1.93	57.52±1.61
GROVE	80.49±0.94	75.79±0.91	76.01±0.73
SimSGT	68.27±0.53	56.93±0.43	60.48±0.31
MoAMa	80.37±0.87	78.59±0.81	76.82±1.05
S-CGIB w/o D.A.	80.26±0.71	78.51±1.06	77.08±1.55
S-CGIB (Ours)	**81.12±0.90**	**79.75±0.82**	**77.54±1.51**

Table 2: A performance comparison on graph classification tasks in terms of accuracy.

Methods	FreeSolv	ESOL	Lipophilicity
ContextPred	3.195±0.058	2.190±0.026	1.053±0.048
AttrMasking	4.023±0.039	2.954±0.087	0.982±0.052
EdgePred	3.192±0.023	2.368±0.070	1.085±0.061
Infomax	3.033±0.026	2.953±0.049	0.970±0.023
JOAO	3.282±0.002	1.978±0.029	1.093±0.097
JOAOv2	3.842±0.012	2.144±0.009	1.116±0.024
GraphCL	3.166±0.027	1.390±0.363	1.014±0.018
GraphLoG	2.335±0.052	1.542±0.026	0.932±0.052
GraphFP	2.528±0.016	2.136±0.096	1.371±0.058
MICRO-Graph	1.865±0.061	0.842±0.055	0.851±0.073
MGSSL	2.940±0.051	2.936±0.071	1.106±0.077
GROVE	2.712±0.327	1.237±0.403	0.823±0.027
SimSGT	1.953±0.038	0.932±0.026	0.771±0.041
MoAMa	2.072±0.053	1.125±0.029	1.085±0.024
S-CGIB w/o D.A.	1.832±0.095	0.894±0.052	0.803±0.067
S-CGIB (Ours)	**1.648±0.074**	**0.816±0.019**	**0.762±0.042**

Table 3: A performance comparison on regression tasks in terms of RMSE.

the graph regression tasks, we can observe that S-CGIB consistently outperformed other methods on three regression benchmarks, as shown in Table 3. We attribute the superior performance of S-CGIB to its ability to generate well-distinguished representations and effectively capture significant substructures, i.e., functional groups. For example, in the BBBP dataset, the task is to predict the barrier permeability, where molecular structures with different sizes, skeletal ring structures, and functional groups will decide the penetrating properties. Capturing such structural information to generate graph-level molecular representations can enhance the prediction of molecular properties. (ii) Subgraph-level strategies, e.g., GraphFP and MGSSL, outperformed node-level and contrastive learning methods. This implies that subgraph-level methods could capture well global molecular structure and functional groups, which benefits molecular property prediction in downstream tasks. In contrast, S-CGIB not only learns well-separated representations but also automatically captures functional groups.

Performance on Large Molecular Graphs. To validate the model's ability on large molecules, we conducted experiments on two large molecular graphs, i.e., Peptides-func and Peptides-struct, as shown in Table 5. The results demonstrated that S-CGIB outperformed other baselines, including subgraph-based strategies. For example, on the Peptides-func dataset, our proposed model gained a 12.3% improvement compared to the GraphFP method. It indicates that S-CGIB could capture long-range dependencies by generating well-separated representations and then capturing significant subgraphs, thanks to the attention-based interaction between graph core and significant subgraphs. The results verified the effectiveness of our strategy for capturing well-separated representations and significant subgraphs.

Efficiency Analysis. Beyond performance improvement, we also validated the impacts of the pre-trained model's con-

Methods	Mutagenicity		BENZENE		Alkane Carbonyl		Fluoride Carbonyl	
	$Fidelity-\downarrow$	$Fidelity+\uparrow$	$Fidelity-\downarrow$	$Fidelity+\uparrow$	$Fidelity-\downarrow$	$Fidelity+\uparrow$	$Fidelity-\downarrow$	$Fidelity+\uparrow$
ContextPred	0.061±0.002	0.223±0.004	0.419±0.008	0.483±0.005	0.261±0.001	0.293±0.007	0.363±0.018	0.413±0.024
AttrMasking	0.078±0.005	0.230±0.004	0.448±0.002	0.543±0.016	0.260±0.011	0.310±0.009	0.276±0.007	0.384±0.005
EdgePred	0.081±0.003	0.451±0.013	0.386±0.068	0.457±0.061	0.581±0.074	0.603±0.069	0.342±0.073	0.389±0.072
Infomax	0.064±0.004	0.240±0.008	0.363±0.041	0.410±0.082	0.353±0.021	0.376±0.054	0.331±0.032	0.453±0.012
JOAO	0.103±0.004	0.424±0.013	0.047±0.005	0.481±0.007	0.263±0.005	0.568±0.008	0.183±0.007	0.295±0.004
JOAOv2	0.152±0.005	0.431±0.008	0.062±0.006	0.481±0.009	0.387±0.004	0.586±0.007	0.184±0.007	0.207±0.008
GraphCL	0.283±0.008	0.476±0.002	0.120±0.005	0.469±0.008	0.430±0.027	0.578±0.016	0.284±0.002	0.570±0.001
GraphLoG	0.117±0.001	0.439±0.003	0.137±0.000	0.459±0.007	0.355±0.002	0.695±0.007	0.358±0.004	0.475±0.006
GraphFP	0.213±0.025	0.603±0.003	0.093±0.006	0.494±0.012	0.276±0.022	0.529±0.005	0.263±0.026	0.595±0.034
MICRO-Graph	0.235±0.008	0.466±0.016	0.140±0.012	0.483±0.003	0.155±0.037	0.524±0.015	0.281±0.007	0.595±0.002
MGSSL	0.150±0.005	0.489±0.006	**0.019±0.001**	0.480±0.006	**0.049±0.001**	0.205±0.002	0.231±0.001	0.550±0.006
GROVE	0.218±0.005	0.522±0.014	0.064±0.029	0.489±0.010	0.183±0.041	0.518±0.007	0.321±0.067	0.628±0.038
MoAMa	0.228±0.020	0.585±0.012	0.076±0.006	0.483±0.002	0.274±0.021	0.514±0.005	0.220±0.007	0.451±0.008
S-CGIB (Ours)	**0.008±0.001**	**0.638±0.003**	0.049±0.001	**0.720±0.003**	0.134±0.001	**0.727±0.003**	**0.133±0.002**	**0.672±0.004**

Table 4: An interpretability comparison on functional group detection tasks in terms of $Fidelity-/+$.

Methods	Peptides-func (AP↑)	Peptides-struct (MAE↓)
ContextPred	0.311±0.013	0.587±0.001
AttrMasking	0.318±0.002	0.580±0.002
EdgePred	0.310±0.012	0.546±0.001
Infomax	0.335±0.013	0.574±0.001
JOAO	0.386±0.009	0.463±0.008
JOAOv2	0.398±0.009	0.541±0.008
GraphCL	0.380±0.002	0.973±0.014
GraphLoG	0.313±0.034	0.419±0.006
GraphFP	0.618±0.014	0.327±0.026
MICRO-Graph	0.505±0.014	0.332±0.002
MGSSL	0.541±0.006	0.322±0.008
GROVE	0.587±0.023	0.376±0.005
SimSGT	0.612±0.005	0.358±0.003
MoAMa	0.584±0.019	0.365±0.005
S-CGIB w/o D.A.	0.658±0.013	0.306±0.007
S-CGIB (Ours)	**0.694±0.002**	**0.269±0.004**

Table 5: A performance comparison on the two large molecular graph datasets.

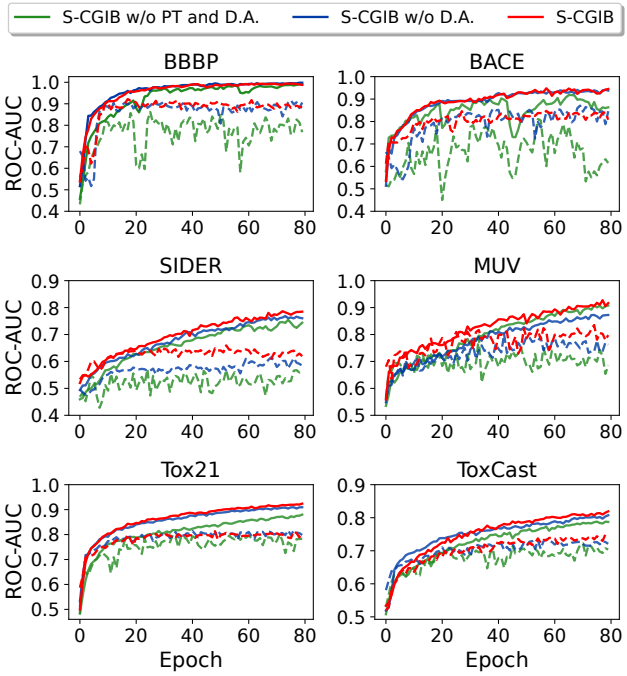

Figure 2: An efficiency analysis for variants of S-CGIB. The solid lines are training curves, and the dashed lines are validation curves (PT: Pre-training, D.A.: Domain Adaptation).

vergence and generalization. Figure 2 shows that S-CGIB almost converged faster than that without pre-training and domain adaptation. This is because S-CGIB has already captured the important patterns from the pre-training dataset well. Besides, our pre-trained model is considered a one-time effort, which can significantly reduce the training and validation time on specific downstream datasets. Moreover, S-CGIB with pre-training and domain adaptation typically exhibits stable training and validation curves.

Analysis on Distinguishability of Representations To validate the model's ability to generate well-distinguished representations, we further conducted experiments to validate the well-distinguished representations between different molecular structures. We utilized Jensen-Shannon Divergence (JSD) measurement to validate the distinction between learned embeddings, as shown in Table 6. We adopted three datasets: BENZENE, Alkane Carbonyl, and Fluoride Carbonyl datasets, with ground-truth explanations, whose classes are labeled based on structures. We observed that our proposed model learned well-distinguished and robust representations. This robustness enhances the discriminability of molecular representations, confirming the effectiveness of our proposed model in capturing different molecular structures across molecules.

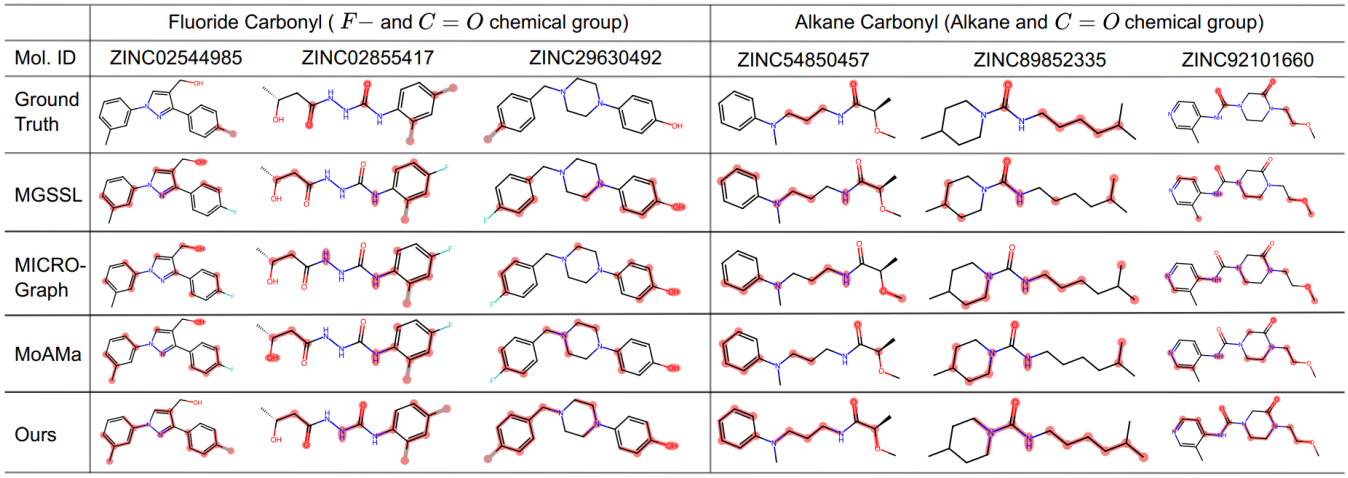

Figure 3: Visualizations of model interpretability in functional group detection tasks.

Methods	BENZENE	Alkane Carbonyl	Fluoride Carbonyl
MGSSL	0.201±0.008	0.253±0.012	0.218±0.011
SimSGT	0.173±0.010	0.124±0.014	0.137±0.007
MoAMa	0.215±0.016	0.209±0.013	0.153±0.015
S-CGIB	**0.381±0.009**	**0.362±0.005**	**0.295±0.006**

Table 6: A distinguishability comparison in terms of JSD.

G_c	α	BBBP	Tox21	ToxCast
–	–	81.15±0.75	78.68±0.63	68.39±0.48
✓	–	86.26±0.63	79.48±0.49	69.04±0.38
–	✓	83.41±0.71	78.85±0.16	69.77±0.67
✓	✓	**88.75±0.49**	**80.94±0.17**	**70.95±0.27**

Table 7: An ablation analysis on graph core (G_c) and attention coefficients (α).

Interpretability Analysis

There have been increasing concerns about the explainability of pre-trained GNNs, as GNNs can be seen as black boxes. Thus, we employed S-CGIB to explain the molecule prediction compared to ground-truth explanations on four downstream datasets, i.e., Mutagenicity, BENZENE, Alkane Carbonyl, and Fluoride Carbony (Agarwal et al. 2023). We used the *Fidelity* score (Amara et al. 2022) to assess how well the explanation aligns with S-CGIB, as shown in Table 4. The lower value of the $Fidelity-$ score shows a more reliable explanation, while the higher $Fidelity+$ score implies that more important nodes are recognized. For S-CGIB, we considered the top 50% of nodes with the highest attention score as explainable nodes. For the baseline methods, we identified the top 50% of nodes with the highest positive saliency values as explainable nodes, following the work Pope et al. (2019). We observed that S-CGIB achieved the highest fidelity scores on almost datasets in terms of the two metrics. This implies that S-CGIB generates a reliable explanation that is aligned with the model prediction. Moreover, we conducted the qualitative validation on graph interpretation via visualization on two datasets, i.e., Alkane Carbonyl and Fluoride Carbonyl datasets, as shown in Figure 3. We observed that S-CGIB provided a more accurate interpretation of molecules than the baselines.

Model Analysis

Ablation Analysis We further validate the contribution of graph core G_c and subgraph learning in S-CGIB, as shown in Table 7. To validate the importance of G_c, we considered the presence when using compression or not. For the subgraph learning, we evaluated the presence of attention coefficients to explore the significant subgraphs. We observed that: (i) S-CGIB with both modules performs best in all the downstream datasets. This result indicates that exploring graph core and significant subgraphs is crucial to fully generating a pre-trained model as well as the property prediction in downstream datasets. (ii) While considering the graph core is important, exploring significant subgraphs is more beneficial for molecular property prediction. For example, the use of graph core can achieve a second ahead in the BBBP dataset, while the model performance for only exploring significant subgraphs remains a close second ahead of other datasets. We argue that for molecular property prediction, while both graph core and significant subgraphs are important, capturing only significant subgraphs is slightly more beneficial than considering graph core for molecular prediction in specific downstream tasks. Furthermore, we also investigated the use of decoders (see Appendix D.2).

Sensitivity Analysis We further conducted sensitivity analyses on the choice of graph encoders (Appendix D.3), the subgraph sizes (Appendix D.4), and the number of GIN layers (Appendix D.5). We observed that the GIN encoder showed the best performance among graph encoders, e.g., GCN, GraphSage, and GT (Dwivedi and Bresson 2021), which matches the previous findings (Luong and Singh 2023). For the subgraph size, S-CGIB gained the best perfor-

mance when the subgraph size was small ($k \leq 3$). This indicates that the subgraph size should be large enough to capture sufficient information but not larger, which can obtain noisy information. For the number of GIN layers, the model performance remained stable at $l \geq 3$ in most datasets, which helps S-CGIB capture the global graph structures.

Conclusion

In this paper, we present a novel pre-training strategy for molecules, named S-CGIB, which can discover graph core and significant subgraphs to generate well-distinguished representations. The main idea is to explore the graph cores of molecules that contain compressed and sufficient information regarding the reconstruction task conditioned on significant subgraphs under the S-CGIB principle. By doing so, S-CGIB can generate robust representations, improving performance in molecular property prediction tasks. The experiments over numerous domains showed that S-CGIB consistently outperforms baselines in various downstream tasks. Furthermore, S-CGIB also delivers model interpretability regarding the functional group detection task despite being learned from self-supervised learning.

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