A Survey of Pre-training on Graphs: Taxonomy, Methods and Applications

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Abstract

Pre-trained Language Models (PLMs) such as BERT have revolutionized the landscape of natural language processing (NLP). Inspired by their proliferation, tremendous efforts have been devoted to pre-trained graph models (PGMs) recently. Owing to its huge model parameters, PGMs can capture abundant knowledge from massive labeled and unlabeled graph data. The knowledge implicitly encoded in model parameters can benefit various downstream tasks and help to alleviate several fundamental issues of learning on graphs. In this paper, we provide a comprehensive survey for PGMs. We first briefly present the limitations of graph representation learning and thus introduce the motivation for graph pre-training. Next, we systematically categorize existing PGMs based on a taxonomy from five different perspectives including the history, model architectures, pre-training strategies, tuning strategies and applications. Finally, we outline several promising research directions that can serve as a guideline for future studies.

1 Backgrounds

The developments of Deep Neural Networks (DNNs) have revolutionized many machine learning tasks in recent years, ranging from image recognition to natural language processing. However, there are still many non-Euclidean graph datasets in real-world applications such as social networks and biochemical graphs which existing neural networks can not handle with. Recent years have witnessed the prosperity of Graph Neural Networks (GNNs) [Wu et al., 2020] that extend deep learning approaches for such graph-structured data. However, two fundamental challenges impede the wider usage of existing supervised learning on graph datasets: (1) Scarcity of Labeled Data: Task-specific labeled data can be extremely scarce especially for biochemical domains where high-quality data labeling often requires time-consuming and resource-costly wet-lab experiments. (2) Out-of-distribution Generalization: Existing GNNs lack out-of-distribution generalization abilities so that their performance substantially degrades when there exist distribution shifts between training and testing graph data. Indeed, nearly all of the deep learning domains are confronted with these challenges. To overcome these challenges, certain progress has been made. For example, the paradigm of PLMs is thriving in NLP community. Specifically, they first pre-train the models on large-scale corpus and then fine-tune these models in various downstream tasks. It is widely recognized that this paradigm can provide a better initial point across downstream tasks and leads to wider optima with better generalization than training from scratch [Hao et al., 2019]. With the emergence of Transformer architecture [Vaswani et al., 2017], PLMs such as BERT [Devlin et al., 2019] have emerged as an dominative role for NLP, which have established state-of-the-arts results for a large variety of NLP tasks.

Inspired by the proliferation of PLMs, tremendous efforts have been devoted to pre-trained graph models (PGMs) recently. In this paper, we present a survey to provide researchers a synthesis and pointer to related research on PGMs. Existing surveys related to this area have only partially focused on self-supervised learning on graphs [Liu et al., 2021; Xie et al., 2021], but did not go broader to the other important ingredients of PGMs such as supervised pre-training, tuning strategies, various extensions, their applications and etc. Overall, the contributions can be summarized as follows:

- **Comprehensive review.** To the best of our knowledge, our survey is the first work that presents a comprehensive review of PGMs.
- **New taxonomy.**
  We propose a new taxonomy, which categorizes existing PGMs from three five perspectives: (1) Brief history; (2) Model architectures; (3) Pre-training strategies; (4) Tuning Strategies; (5) Applications in social recommendation and drug discovery.
- **Abundant resources.** We collect abundant resources on PGMs, including open-sourced implementations of PGMs and paper lists.

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1https://github.com/junxia97/awesome-pre-training-on-graphs
• **Future directions.** We discuss and analyze the limitations of existing PGMs. Also, we suggest possible future research directions.

## 2 Notions

Let \( G = (\mathcal{V}, \mathcal{E}) \) be the graph, where \( \mathcal{V} = \{v_1, v_2, \cdots, v_N\} \), \( \mathcal{E} \subseteq \mathcal{V} \times \mathcal{V} \) denote the node set and edge set respectively. Besides, \( X \in \mathbb{R}^{N \times F} \) and \( A \in \{0, 1\}^{N \times N} \) are the feature matrix and the adjacency matrix. \( f_i \in \mathbb{R}^F \) is the feature of \( v_i \), and \( A_{ij} = 1 \) iiff \( (v_i, v_j) \in \mathcal{E} \). The objective of pre-training is to learn a generic GNN encoder \( f(A, X) \) that can deal with various downstream tasks.

## 3 Overview of PGMs

### 3.1 A Brief History of PGMs for Graph

As early as 2006, the breakthrough of deep learning came with greedy layer-wise unsupervised pre-training followed by supervised fine-tuning [Hinton and Salakhutdinov, 2006]. With the development of computational power, the emergence of the deep models including GNNs and Transformer, and the constant enhancement of training skills, PGMs has scored remarkable progress. The development of PGMs broadly fall into two generations according to their different usage, which we will elaborate below.

### 3.2 First-Generation PGMs: Pre-trained Graph Embeddings

The first-generation PGMs aim to learn good graph embeddings for various tasks such as node clustering, link prediction and visualization while these models themselves are no longer needed by downstream tasks. Initially, inspired by Skip-Gram [Mikolov et al., 2013] model for word embedding, DeepWalk [Perozzi et al., 2014] pioneers graph embedding by considering the node paths traversed by random walks over graphs as the sentences and leveraging Skip-Gram for learning latent node representations. LINE [Tang et al., 2015b] defines loss functions to preserve the first-order or second-order proximity separately. After optimizing the loss functions, it concatenates these representations. Following DeepWalk, Node2vec [Grover and Leskovec, 2016] defines a flexible notion of a node’s network neighborhood and designs a
biased random walk procedure, which efficiently explores diverse neighborhoods. Besides, some researchers also try to learn embeddings for heterogeneous graphs, sub-graphs and molecular graph such as PTE [Tang et al., 2015a], sub2vec [B. Adhikari and Prakash, 2018], sub-graph2vec [Narayanan et al., 2016] and N-gram Graph [Liu et al., 2019]. Although pre-trained graph embeddings have been shown effective in graph tasks, the learned embeddings cannot be used to initialize other models for fine-tuning over other tasks and thus impede wider applications.

3.3 Second-Generation PGMs: Pre-trained Encoders

With the emergence of expressive GNNs and Transformer, recent PGMs have embraced a transfer learning setting where the goal is to pre-train a generic encoder that can deal with different tasks. Apart from learning universal graph embeddings for downstream tasks as the first-generation PGMs, the second-generation PGMs can also provide a better model initialization, which usually leads to a better generalization performance and speeds up convergence on the target tasks. For example, Hu et al. [Hu et al., 2020a] initialize a 5-layer Graph Isomorphism Network (GIN) [Xu et al., 2019] with the pre-trained model obtained with both graph-level and node-level pre-training tasks. Also, GCC [Qiu et al., 2020] utilizes a 5-layer GIN to extract representations for subgraphs and adopts subgraph discrimination in and across networks as the pre-training task to learn the intrinsic and transferable structural representations. Since these precursor PGMs, the modern PGMs are usually trained with larger scale database, more powerful or deeper architectures (e.g., Transformer), and new pre-training tasks. For example, the huge PGMs with ten millions of parameters have shown their powerful ability in learning universal molecular graph representations, such as GROVER [Rong et al., 2020] and MPG [Li et al., 2021b]. Besides, various advanced pre-training tasks are proposed to capture more knowledge from database of larger scale.

4 Model Architectures

The model architectures of modern PGMs broadly fall into two categories: Graph Neural Networks (GNNs), hybrid of GNNs and Transformer. We introduce them in details below.

4.1 Graph Neural Networks (GNNs)

Recent years have witnessed the proliferation of GNNs. The structure of graph data guides the aggregation of local neighborhood information and lead to a more contextual representation for each node. Also, we can adopt a graph pooling operation [Mesquita et al., 2020] to get the representation for the whole graph. For PGMs, GIN [Xu et al., 2019] is the most popular encoder for its high expressive power [Hu et al., 2020a]. Besides, Heterogeneous Attention Network (HAN) [Wang et al., 2019] is a more suitable alternative for pre-training on heterogeneous graphs [W. et al., 2021; Zhu et al., 2022].

4.2 Hybrid of GNNs and Transformer

To leverage the high expressiveness of Transformer, several recent works try to integrate GNNs into Transformer-style models. For PGMs, GROVER [Rong et al., 2020] first utilize GNNs to capture local structural information of the graph data and then the outputs of the GNNs as queries, keys and values for Transformer encoder. They claim that this bi-level information extraction strategy largely enhances the representational power of the proposed models. Analogously, MPG [Li et al., 2021b] devises a neighbor attention module to get produce a message representation for each node and feed it to a fully connected feed-forward network. With the proper message representation obtained, they adopt a GRU network [Cho et al., 2014] to update node representation. For heterogeneous graphs pre-training [Hu et al., 2020b; Jiang et al., 2021], Heterogeneous Graph Transformer (HGT) [Hu et al., 2020c] is usually adopted as the encoder.

5 Pre-training Strategies

In this section, we will elaborate on the supervised, unsupervised pre-training strategies and the extensions of PGMs.

5.1 Supervised Strategies

Although the supervised labels are often time-consuming and expensive to collect, some cheaper annotations that may be less related to downstream tasks can also help pre-training on graphs, especially in biochemical domains. For example, Hu et al. [Hu et al., 2020a] propose to pre-train GNNs to predict essentially all the properties of molecules that have been experimentally measured so far. Analogously, for protein function prediction, they pre-train GNNs to predict the existence of diverse protein functions that have been validated so far. Also, they leave a future work to take the structural similarities between two graphs as supervision. Inspired by this, MoCL [Sun et al., 2021] first calculates the Tanimoto coefficient [Bajusz et al., 2015] between two molecules as the measure of structural similarity, which serves as the supervisions for the pre-training. For molecular graphs, one important class of motifs in molecules are functional groups that encodes rich domain knowledge of molecules and can be easily detected by the professional software such as RDkit2 or developed algorithms [Ertl, 2017]. In light of this, GROVER [Rong et al., 2020] and MGSSL [Zhang et al., 2021b] propose to predict the presence of the motifs or generate the motifs respectively. Although the supervised pre-trainings brings remarkable improvements, they often require domain-specific knowledge which significantly limits their wider application. More importantly, some supervised pre-training tasks might be unrelated to the downstream task of interest and can even hurt the downstream performance.

5.2 Unsupervised Strategies

Graph AutoEncoders (GAEs)

Graph reconstruction serves as a natural self-supervision for learning discriminative representations. The predic-

2https://www.rdkit.org/
tion targets in graph reconstruction are certain parts of the given graphs such as the attribute of a subset of nodes or the existence of edge between a pair of nodes. Inspired by the success of AutoEncoders in CV and NLP, various GAEs have been proposed recently. Among many, GAE [Kipf and Welling, 2016] is the simplest version of the graph autoencoders, which reconstructs adjacency matrix $\hat{A}$ with,

$$\hat{A} = \sigma(HH^T), \quad H = f(A, X),$$

(1)

and is optimized by the binary cross-entropy loss between $\hat{A}$ and $A$. $\sigma(\cdot)$ is the sigmoid function. Also, there exist multiple variants of GAEs that utilize graph reconstruction to pre-train the GNNs. Representative examples include VGAE [Kipf and Welling, 2016], MGAE [Wang et al., 2017], ARVGA [Pan et al., 2018], SIG-VAE [Hasanzadeh et al., 2019] and so on.

**Graph Autoregressive Modeling (GAM)**

Following the idea of GPT that conducts generative language model pre-training, GPT-GNN [Hu et al., 2020b] proposes an autoregressive framework to perform reconstruction on given graphs iteratively, which is different from graph autoencoders that reconstruct the graph all at once. In particular, given a graph with its nodes and edges randomly masked, GPT-GNN generates one masked node and its edges at a time and optimizes the parameterized models via maximizing the likelihood of the node and edges generated in the current iteration. Then, it iteratively generates nodes and edges until all masked nodes are generated. Analogously, MGSSL [Zhang et al., 2021b] generates molecular graph motifs in an autoregressive way based on existing motifs and connections.

**Masked Components Modeling (MCM)**

Similar to masked language modeling (MLM) that masks out some tokens from the input sentences and then trains the model to predict the masked tokens by the rest of the tokens, MCM first mask out some component from the graphs and then trains the model to predict them. For example, Hu et.al [Hu* et al., 2020a] propose attribute masking where the input node/edge attributes are randomly masked, and the GNN is asked to predict them. Also, GROVER [Rong et al., 2020] tries to predict the masked subgraphs to capture the contextual information in molecular graphs. These masking methods are especially beneficial for richly-annotated graphs from scientific domains. For example, masking nodes attributes (atom type) enables GNNs to learn simple chemistry rules such as valency, as well as potentially more complex chemistry phenomenon such as the electronic or steric properties of functional groups.

**Graph Context Prediction (GCP)**

GCP is proposed to explore the distribution of graph structure in graph data. For example, Hu et al. [Hu* et al., 2020a] use subgraphs to predict their surrounding graph structures. They pre-train a GNN so that it maps nodes appearing in similar structural contexts to nearby embeddings. GROVER tries to predict the context-aware properties of the target node/edge within some local subgraph. Here, the properties refer to some node-edge counts terms around the target node/edge.

**Graph Contrastive Learning (GCL)**

**Deep InfoMax (DIM)**

Deep InfoMax is originally proposed for images, which improves the quality of the representation by maximizing the mutual information between an image representation and local regions of the image. For graphs, initially, DGI [Velickovic et al., 2019] and InfoGraph [Sun, 2020] are proposed to obtain expressive representations for graphs or nodes via maximizing the mutual information between graph-level representations and substructure-level representations of different granularity. Similarly, GMI [Peng et al., 2020] adopts two discriminators to directly measure mutual information between input and representations of both nodes and edges. Besides, MV-GRL [Hassani and Khasahmadi, 2020] performs node diffusion to generate augmented view and then maximizes the mutual information between original and augmented views by contrasting node representations of one view with graph representation of the other view and vice versa.

**Instance Discrimination (IND)**

IND is one of the most popular pre-training tasks which embeds augmented versions of the anchor close to each other (positive samples) and pushes the embeddings of other samples (negatives) apart. For node-level representations, GRACE [Zhu et al., 2020] and its variants [Zhu et al., 2021c; Jin et al., 2021; Xia et al., 2021b] maximize the agreement of node embeddings across two corrupted views of the

| Task | Loss Function | Description |
|------|--------------|-------------|
| GAEs | $L_{GAE} = -\log p(X, E | G)$ | Graph construction. |
| GAM | $L_{GAM} = -\sum_{i=1}^{\vert V \vert} \log p(X_i, E_i | X_{<i}, E_{<i})$ | $X_{<i}, E_{<i}$ are the attributes and edges generated before node $i$ respectively. |
| MCM | $L_{MCM} = -\sum_{G \in \mathcal{G}} \log p(G | G_{\setminus(m(G)})$ | $m(G)$ are the masked components from $G$ and $G_{\setminus(m(G)}$ are the rest. |
| GCP | $L_{GCP} = -\log p(t | G_1, G_2)$ | $t = 1$ if neighborhood graph $G_1$ and contexts $G_2$ belong to the same node. |
| IND | $L_{IND} = -s(G, G^+) + \log \sum_{G^{-}} s(G, G^-)$ | $N$ is a set of negatives; $G^+$ is a positive sample. |
| DIM | $L_{IND} = -s(G, C) + \log \sum_{G^{-}} s(G, C^-)$ | $N$ is a set of negatives; $C$ is a substructure of $G$. |
| RCD | $L_{RCD} = -\log p(t | G_1, G_2)$ | $t = 1$ if two half graphs $G_1$ and $G_2$ are homologous couples. |
graph. Besides, GraphCL [You et al., 2020] and its variants [You et al., 2021; Sun et al., 2021; Suresh et al., 2021] propose various advanced augmentation strategies for graph-level pre-training. More recently, some works such as BGRL [T. et al., 2021], CCA-SSG [Zhang et al., 2021a], LP-Info [You et al., 2022] and SimGRACE [Xia et al., 2022a] try to simplify graph contrastive learning via discarding the negatives, parameterized mutual information estimator or even data augmentations respectively. We develop an open-source graph contrastive learning (GCL) library\(^3\) for PyTorch [Zhu et al., 2021b].

**Replaced Component Detection (RCD)**

To capture the global information of graphs, RCD is proposed as a graph-level pre-training task on a random permutation of input graphs. For example, PHD [Li et al., 2021a] first decomposes each molecular graph in the database into two half-graphs and replace one of them with a half-graph from other graph randomly. The GNN encoder is pre-trained to detect whether two half-graphs are homologous couples.

5.3 Extensions

**Knowledge-Enriched Pre-training**

PGMs usually learn universal graph representation from general-purpose graphs database. However, they often lack domain-specific knowledge. To enhance their performance, several recent works try to inject external knowledge during pre-training. For example, GraphCL [You et al., 2020] first pointed out that edge perturbation is conceptually incompatible with domain knowledge and empirically unhelpful for down-stream performance for chemical compounds. And then, they avoid adopting edge perturbation for molecular graphs augmentation. To incorporate the domain knowledge into pre-training more explicitly, MoCL [Sun et al., 2021] proposed a new augmentation operator called substructure substitution, in which a valid substructure in a molecule is replaced by a bioisostere [Meanwell, 2011] which produces a new molecule with similar physical or chemical properties as the original one. They compile 230 substitution rules from domain resource in total and empirically validate their effectiveness. More recently, to capture the correlations between atoms that have common attributes but are not directly connected by bonds, KCL [Fang et al., 2022] construct a Chemical Element Knowledge Graph (KG) to summarize microscopic associations between elements and propose a novel Knowledge-enhanced Contrastive Learning (KCL) framework for molecular representation learning. Considering that 3D geometric information of molecule also plays a vital role in predicting molecular functionalities, 3DInfoMax [Stäck et al., 2021] proposes pre-training a model to reason about the geometry of molecules given only their 2D molecular graphs while GraphMVP [Liu et al., 2022] performs self-supervised pre-training via maximizing the correspondence and consistency between 2D topological structures and 3D geometric views.

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\(^3\)https://github.com/GraphCL/PyGCL

**Learn to Pre-train**

Due to the divergence of the optimization objectives between pre-training and fine-tuning steps, there exists a gap between them which will significantly hurt the generalization ability of PGMs. To narrow this gap, L2P-GNN [Lu et al., 2021] simulate the fine-tuning via creating new tasks during pre-training. This setup enables PGMs to adapt to new tasks quickly and lead to better generalization on downstream tasks.

6 Tuning Strategies

Although PGMs can capture abundant knowledge that is useful for downstream tasks, the process of vanilla fine-tuning is still brittle. For example, Xia et al. [Xia et al., 2022b] observe that PGMs are prone to overfit insufficient labeled data for downstream tasks due to PGMs’ high complexity. In particular, unlike image or text data, getting labels for biochemical graph data often requires wet-lab experiments which often lead to inaccurate annotations [Xia et al., 2021a]. To enrich the labeled data of downstream tasks, they propose to augment molecular graph data with chemical enantiomers and homologies, which share the similar physical (permeability, solubility and etc) or chemical (toxicity, side effect and etc) properties with original molecules. To control the complexity of PGMs, they introduce a new regularization built on dropout which encourages the output of PGMs not to change much when injecting a small perturbation and thus effectively controls PGMs’ capacity. Besides, catastrophic forgetting often happens when adapting PGMs to downstream tasks. In other words, PGMs often forget their learned general knowledge when fine-tuning. To alleviate this issue, Han et al. [Han et al., 2021] utilize meta learning to adaptively select and combine various auxiliary tasks with the target task in fine-tuning stage to achieve a better adaptation. This preserves sufficient knowledge captured by self-supervised auxiliary tasks while improving the effectiveness of transfer learning on GNNs. However, it takes the auxiliary tasks of pre-training as a prerequisite, which impedes the usage of their methods in practice where the auxiliary tasks are often unknown.

7 Applications

7.1 Social Recommendations

Owing to the outstanding performance in graph data learning, GNNs have been widely applied to recommender systems. Despite their proliferation, GNNs based recommender systems are still fraught with issues. For example, cold-start problem impedes their wider applications because GNNs fail to learn high-quality embeddings for the cold-start users/items with sparse interactions. To alleviate this critical issue, Hao et al. [Hao et al., 2021] propose to pre-train the GNN model via predicting the ground-truth embeddings of users/item. In this way, they can enhance the embeddings of the cold-start users or items with the PGMs. For Heterogeneous Information Network (HIN)-based recommendation [Hu et al., 2018; Jin et al., 2020], Wang et al. [Wang et al., 2021a] capture the rich semantics in the
subgraph extracted from HIN via a heterogeneous subgraph Transformer and devise a curriculum pre-training strategy to provide an elementary-to-advanced learning process. This strategy can smoothly transfer basic semantics in HIN for modeling user-item interaction relation and effectively utilize the rich information in HIN for recommendation task.

### 7.2 Drug Discovery

A molecule is naturally treated as a graph, where nodes refer to atoms and edges correspond to chemical bonds. Recently, the advancements in graph pre-training provide opportunities to expedite drug discovery and development pipeline. For example, the oral bioavailability of a drug is related to many properties, such as solubility in gastrointestinal tract, intestinal membrane permeability and intestinal/hepatic first-pass metabolism [Hou et al., 2007]. However, it is often time-consuming and unsafe to conduct such experiments on human bodies. In molecular property prediction tasks, PGMs can be directly applied as a drug encoder to obtain expressive representations [Wang et al., 2021b; Rong et al., 2020]. Besides, drug-drug interaction (DDI) prediction is also of vital importance in drug discovery because DDIs may lead to adverse drug reactions which will damage the health or even cause death. DDI prediction tasks can be regarded as a task that classify the influence of combining drugs into three categories: synergistic, additive and antagonistic. Works on molecular graph pre-training, such as MPG [Li et al., 2021b] and WordReg & MolAug [Xia et al., 2022b], have applied DDI prediction as a downstream task to reveal the effectiveness of the PGMs. Also, drug-target interaction (DTI) prediction is important in drug discovery. When a new indication occurs, the best choice for coping is to recycle approved drugs because of their availability and known safety profiles. In this case, PGMs can be directly applied as a drug encoder. Thus, the well pre-trained model weights can be regarded as the initial weights of drug encoder. The drug encoder and target encoder are then trained with the DTI prediction task. Related works include MPG and WordReg & MolAug have followed this idea to achieve DTI prediction. For molecule generation, MGM [Mahmood et al., 2021] introduces a masked graph model, which learns a distribution over graphs by capturing conditional distributions over unobserved nodes (atoms) and edges (bonds) given observed ones.

### 8 Conclusion and Future Outlooks

Despite the fruitful progress of PGMs, challenges still exist due to the complexity of graph data. In this section, we suggest several promising research directions for future.

#### 8.1 Better Knowledge Transfer

Currently, tremendous efforts are focusing on pre-training strategies. However, how to leverage these huge PGMs is still under-explored compared to PLMs. Fine-tuning is an dominant technique to adapt the knowledge to various downstream tasks, but there are several nonnegligible deficiencies to be solved. The first one is poor generalization of PGMs especially for various molecular tasks where collecting labeled data is laborious. The second issue is parameter inefficiency. The fine-tuned parameters vary across both datasets and tasks, which are often huge in scale and thus being inconvenient in special scenarios such as low-capacity devices. Furthermore, there are some promising alternatives to mine the knowledge from PGMs. For example, PGMs can serve as the feature extractor to extract expressive representations as adopted in graph self-supervised learning. Also, distilling the knowledge from PGMs as adopted in NLP is expected [Yang et al., 2020].

#### 8.2 Interpretability of PGMs

Despite their proliferation, a major limitation of PGMs is that they are not amenable to interpretability. Worse still, unlike CNNs for images, interpreting PGMs is more difficult due to the complexities of both the Transformer-style architecture and graph data. However, for some specific scenarios like molecular toxicity prediction, it is of vital importance.

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**Table 2: List of Representative PGMs. Here KG of KCL is Chemical Element Knowledge Graph.**

| PGMs | Input | Architecture | Pre-Training Task | Pre-training Database | # Params. |
|------|-------|--------------|------------------|-----------------------|-----------|
| Hu et al. [Hu et al., 2020a] | Graph | 5-layer GIN | GCPC + MCM | ZINC15(2M) + ChEMBL(456K) | ~2M |
| Graph-BERT [Zhang et al., 2020] | Graph | Graph Transformer [Zhang et al., 2020] | GAExs | Cora + CiteSeer + PubMed | N/A |
| GPT-GNN [Hu et al., 2020b] | Graph | HGT [Hu et al., 2020c] | GAT | GAG + Amazon | N/A |
| GCC [Qiu et al., 2020] | Graph | 5-layer GIN | IND | Academia + DBLP + IMDb + <1M |
| GraphCLC [You et al., 2020] | Graph | 5-layer GIN | IND | ZINC15(2M) + ChEMBL(456K) | ~2M |
| JOAA [You et al., 2021] | Graph | 5-layer GIN | IND | ZINC15(2M) + ChEMBL(456K) | ~2M |
| AD-CCL [Sun et al., 2021] | Graph | 5-layer GIN | IND | ZINC15(2M) + ChEMBL(456K) | ~2M |
| GraphLog [Xu et al., 2021] | Graph | 5-layer GIN | IND | ZINC15(2M) + ChEMBL(456K) | ~2M |
| GROVER [Rong et al., 2020] | Graph | GT Transformer [Rong et al., 2020] | GCP + MCM | ZINC + ChEMBL(10M) | 48M~<100M |
| KGSSL [Zhang et al., 2021] | Graph | HGT [Hu et al., 2020c] | MCM + GAM | ZINC15(250K) | ~2M |
| CPT-HG [Jiang et al., 2021] | Graph | HGT [Hu et al., 2020c] | IND | DBLP + YELP + Aminer | N/A |
| PGM [Li et al., 2021b] | Graph | MolGNet [Li et al., 2021b] | RCD + MCM | ZINC + ChEMBL(11M) | 53M |
| LP-Info [You et al., 2022] | Graph | 5-layer GIN | IND | ZINC15(2M) + ChEMBL(456K) | ~2M |
| SimGRACE [Xia et al., 2022a] | Graph | 5-layer GIN | IND | ZINC15(2M) + ChEMBL(456K) | ~2M |
| MolCLR [Wang et al., 2021b] | Graph + SMILES | GCN + GIN | IND | PubChem(10M) | N/A |
| DMP [Zhu & et al., 2021a] | Graph + SMILES | DeeperGCN + Transformer | MCM + IND | PubChem(110M) | 104.1M |
| ChemRL-GEM [Fang et al., 2021] | Graph + Geometry | GeoGRF [Fang et al., 2021] | MCM+GCP | ZINC15(20M) | N/A |
| KCL [Fang et al., 2022] | Graph + KG | GCN + KMPNN [Fang et al., 2022] | IND | ZINC15(250K) | <1M |
| 3D Infomax [Stark et al., 2021] | 2D and 3D graph | PNA [Corso et al., 2020] | IND | QM9(90K) + GEOM-drugs(140K) + QMugs(620K) | N/A |
| GraphMVP [Liu et al., 2022] | 2D and 3D graph | 5-layer GIN + SchNet [Schutt et al., 2017] | IND + GAEs | GEOM (50k) | ~2M |
for the PGMs possess the ability to explain the reason why a molecule is non-toxic. Also, interpretability can accelerate some scientific findings such as identifying biomarkers. Overall, as a key component in graph-related applications, the interpretability of PGMs remains to be explored further in many respects, which helps us understand how PGMs work and provides a guide for better usage and further improvement.

8.3 Broader Scope of Applications

PGMs have been applied in various sub-tasks in drug discovery such as molecular property prediction, DDI and DTI. However, it is still underexplored how PGMs can benefit other small molecule-related tasks such as chemical reaction prediction, retrosynthesis, de novo molecule design and optimization. For macromolecules such as proteins, recent works demonstrate that GNNs can help learn expressive representations for them [Xia and Ku, 2021]. More endeavors are still expected to study whether PGMs are conducive to protein representation learning.

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