Improving Molecular Contrastive Learning via Faulty Negative Mitigation and Decomposed Fragment Contrast

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Abstract

Deep learning has been a prevalence in computational chemistry and widely implemented in molecule property predictions. Recently, self-supervised learning (SSL), especially contrastive learning (CL), gathers growing attention for the potential to learn molecular representations that generalize to the gigantic chemical space. Unlike supervised learning, SSL can directly leverage large unlabeled data, which greatly reduces the effort to acquire molecular property labels through costly and time-consuming simulations or experiments. However, most molecular SSL methods borrow the insights from the machine learning community but neglect the unique cheminformatics (e.g., molecular fingerprints) and multi-level graphical structures (e.g., functional groups) of molecules. In this work, we propose iMolCLR: improvement of Molecular Contrastive Learning of Representations with graph neural networks (GNNs) in two aspects, (1) mitigating faulty negative contrastive instances via considering cheminformatics similarities between molecule pairs; (2) fragment-level contrasting between intra- and inter-molecule substructures decomposed from molecules. Experiments have shown

that the proposed strategies significantly improve the performance of GNN models on various challenging molecular property predictions. In comparison to the previous CL framework, iMolCLR demonstrates an averaged 1.3% improvement of ROC-AUC on 7 classification benchmarks and an averaged 4.8% decrease of the error on 5 regression benchmarks. On most benchmarks, the generic GNN pre-trained by iMolCLR rivals or even surpasses supervised learning models with sophisticated architecture designs and engineered features. Further investigations demonstrate that representations learned through iMolCLR intrinsically embed scaffolds and functional groups that can reason molecule similarities.

1 Introduction

Recent years have witnessed the development of computational molecule design and property prediction driven by deep learning (DL), 1,2 owing to the ability to perform fast and accurate computation.³⁻⁶ Several works build deep neural networks on top of cheminformatics fingerprints to predict molecular properties. 7-9 DL methods have been also implemented on string-based molecular embeddings, like SMILES¹⁰ and SELFIES,¹¹ for molecule design. 12,13 However, both fingerprints and string embeddings can neglect important structural information of molecules. Recently, graph neural networks (GNNs) 14,15 are developed to learn representations from non-Euclidean graphs of chemical structures, where each node in molecule graphs are defined as an atom and each edge represent chemical bond or adjacency of atoms. 16 Modern GNNs rely on message-passing to aggregate neighboring node information within the graph and have been introduced to predict various properties from molecule graphs. 17,18 Aggregation based upon a continuous filter is also developed for GNNs to model quantum interactions within molecules. 19,20 Attention mechanism 21 has also been leveraged in node aggregation for better prediction accuracy and model interpretability. ^{22,23} Instead of only considering molecules as two-dimensional (2D) graphs, several works have built GNNs in use of 3D molecular conformations with equivariant aggregation. ^{24–27}

Despite the success of DL in computational chemistry, the potential is greatly limited by the availability of labeled data, as the collection of molecule properties usually requires time-consuming and costly lab experiments or simulations. ²⁸ Moreover, it is challenging for DL models trained on such limited data to generalize among the gigantic chemical space, ²⁹ which significantly restricts real-world applications like drug discovery and material design. To address this, self-supervised learning (SSL)^{30,31} have been investigated to utilize the large unlabelled molecule data and learn representations generalizable to various downstream applications. Motivated by the success of SSL in language models, transformer-based models. 21 like BERT, 32 have been implemented to learn representations from large SMILES database. ^{33–37} Apart from language models, SSL has also been developed for representation learning from molecule graphs. Liu et al. 38 embed molecules to N-gram representations by assembling the vertex embedding in short walks. Hu et al. ³⁹ propose both node-level and graphlevel GNN pre-training strategies. The former includes self-supervised context prediction and attribute masking, while the latter is based on supervised property prediction, which is still limited by label availability. Following the insights, Rong et al. 40 propose contextual property and graph-level motif predictions as SSL tasks combined with a transformer-based model. Besides node-level pre-training, Zhang et al. 41 introduce a motif-level SSL strategy, which builds motif trees from molecules and performs motif generative pre-training. Additionally, contrastive learning (CL), 42-46 which learns representation through contrasting positive pairs against negative pairs, has been a prevalence in representation learning 47 and implemented to graphical data. 48 Wang et al. 49 propose MolCLR, a CL framework for molecular representation learning, as well as three augmentation strategies to generate contrastive pairs. Zhang et al. ⁵⁰ further leverage frequently-occurring subgraph patterns and perform CL on subgraph level. Liu et al.⁵¹ and Stärk et al.⁵² perform contrastive training between 2D topological structures and 3D geometric views to learn molecular representations with 3D information embedded. Also, Zhu et al. 53 develop multi-view CL between SMILES strings and molecule graphs, encoded by transformer and GNN, respectively. Although CL has demonstrated

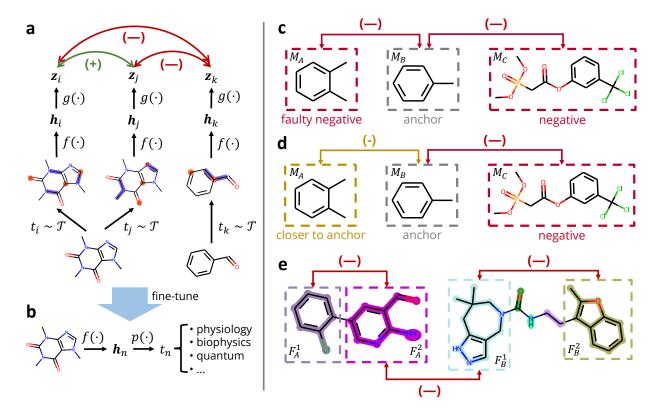


Figure 1: Overview of the proposed iMolCLR framework. (a) CL pre-training pipeline for molecular representation learning. (b) Fine-tuning of pre-trained model for various property predictions. (c) An example of faulty negative introduced by ordinary CL methods due to treating all negative instances equivalently. (d) In iMolCLR, latent vectors of molecules are repelled based upon the similarities between different molecule pairs to mitigate faulty negatives. (e) Fragment-level contrast on decomposed molecular substructures in iMolCLR.

the effectiveness in molecular representation learning, these methods assume all the other molecules are equal negative pairs in contrast with a given anchor, which introduces faulty negatives. Faulty negatives are instances that are supposed to be similar with the anchor while considered as negative instances in CL.⁵⁴ Such faulty negative instances harm the robustness and performance of CL pre-trained model on downstream property prediction tasks. Additionally, the previous motif-level CL learns a motif dictionary and trains a sampler to sample subgraphs within each molecule, ⁵⁰ which may ignore unique chemical substructure patterns. Chemical substructures of molecules contain functional groups that are critical to various molecular properties, which can provide multi-level information for representation learning.

In this work, we propose iMolCLR: improvement of molecular contrastive learning through mitigating faulty negative instances and contrasting decomposed chemical fragments as shown in Figure 1. A GNN encoder is first trained on large unlabeled data to learn expressive molecular representations via contrasting positive pairs against negative pairs in a self-supervised manner (Figure 1a). The pre-trained GNN is fine-tuned on downstream datasets to predict a wide variety of molecular properties (Figure 1b). Unlike ordinary CL framework that introduces faulty negatives (Figure 1c), iMolCLR does not treat all negative pairs equivalently. On the contrary, similar molecules are encouraged to have closer representations than dissimilar ones (Figure 1d). Apart from molecule-level contrast, different substructures decomposed via breaking retrosynthetically interesting chemical substructures (BRICS)⁵⁵ are also considered as contrastive negative pairs (Figure 1e). Such a decomposition strategy maintains major structural features of compounds and molecular representations are forced to distinguish important functional groups within molecules. Experiments show that iMolCLR pre-training significantly improves the performance of GNN models on challenging molecular property prediction benchmarks. Through fine-tuning, iMolCLR rivals and even surpasses strong supervised learning baselines on multiple classification and regression tasks. Additionally, it shows an overall advantage over other SSL baselines. In particular, iMolCLR outperforms the original CL framework by an average 1.3% improvement of ROC-AUC on 7 classification benchmarks and an average 4.8% reduction of the error on 5 regression benchmarks. Additional investigations demonstrate that the proposed CL framework effectively learns intrinsic relations between atoms without meticulously engineered input descriptors. The representations learned through iMolCLR also show an advantage to reason molecule similarities in consideration of scaffold and functional groups in comparison to previous SSL methods.

2 Methods

2.1 Contrastive Learning Framework

CL aims at learning representations through contrasting positive pairs against negative pairs. We develop the CL framework ^{43,49} containing four components: molecule graph augmentation, GNN-based encoder, non-linear projection head, and contrastive loss, as shown in Figure 1a. Given a batch of N molecules $\{m_1, \ldots, m_N\}$, each molecule m_n is augmented into two graphs G_i and G_j through augmentations, t_i and t_j , sampled from \mathcal{T} , where i = 2n - 1 and j = 2n. We implement \mathcal{T} as random atom masking of 25% and random bond deletion of 25% following widely-used graph augmentation strategies. 49,56 The masked atoms are colored by orange and deleted bonds are colored by dark blue in Figure 1a. Two graphs augmented from the same molecule compose a positive pair while those from different molecules are negative pairs. The GNN-based encoder $f(\cdot)$ takes in an augmented graph G_i and encodes it to the representation h_i , followed by the non-linear projection head $g(\cdot)$ which maps h_i into a latent vector z_i . Contrastive loss is applied on the 2N latent vectors from the projection head to maximize the agreement between positive pair vectors (e.g., z_i and z_j) while minimizing the agreement between negative ones (e.g., z_i and z_k , z_j and z_k). After pre-training, the model $f(\cdot)$ is fine-tuned to predict various molecular properties of interest as shown in Figure 1b. During fine-tuning, only the GNN encoder $f(\cdot)$ is preserved followed by a randomly initialized prediction head $p(\cdot)$ to map the representation to the target property.

2.2 Graph Neural Network

A molecule graph G is defined as G = (V, E), where each node $v \in V$ represents an atom and each edge $e_{uv} \in E$ represents a chemical bond between atoms u and v.⁵⁷ Each node is featurized as \boldsymbol{x}_v and each edge is featurized as $\boldsymbol{\epsilon}_{uv}$, which contain unambiguous input vectors to denote each node and edge like atomic number and covalent bond type. Modern GNNs¹⁴

updates the feature of each node layer-wise through iterative combination and aggregation operations. The update rule for the feature of node v at k-th graph convolutional layer, $\boldsymbol{h}_{v}^{(k)}$, is given in Equation 1:

$$\boldsymbol{a}_{v}^{(k)} = \text{AGGREGATE}^{(k)} \left(\left\{ \boldsymbol{h}_{u}^{(k-1)} : u \in \mathcal{N}(v) \right\} \right), \ \boldsymbol{h}_{v}^{(k)} = \text{COMBINE}^{(k)} \left(\boldsymbol{h}_{v}^{(k-1)}, \boldsymbol{a}_{v}^{(k)} \right), \quad (1)$$

where $\mathcal{N}(v)$ denotes the set of all the neighbors of node v. Aggregation passes the information of neighboring nodes to v and combination updates the aggregated feature. Each $\boldsymbol{h}_{v}^{(0)}$ is initialized by the node feature \boldsymbol{x}_{v} . After K layers of node updates, readout operation integrates all the node features within the graph G to a graph-level feature \boldsymbol{h} as shown in Equation 2:

$$\mathbf{h}_G = \text{READOUT}\Big(\Big\{\mathbf{h}_u^{(k)} : v \in G\Big\}\Big).$$
 (2)

In this work, we develop our GNN encoder based on Graph Isomorphism Network (GIN), ¹⁵ a widely-used generic model. To consider edge features, we follow Hu et al. ³⁹ to extend node aggregation as $\boldsymbol{a}_{v}^{(k)} = \sum_{u \in \mathcal{N}(v)} \sigma(\boldsymbol{h}_{u}^{(k-1)} + \boldsymbol{\epsilon}_{uv})$ where $\sigma(\cdot)$ is a non-linear activation function. Combination operation is modeled by summation followed by an MLP as $\boldsymbol{h}_{v}^{(k)} = \text{MLP}(\boldsymbol{h}_{v}^{(k-1)} + \boldsymbol{a}_{v}^{(k)})$. Readout operation is implemented as an average pooling over all nodes to obtain a graph-level representation for each molecule.

2.3 Mitigating Faulty Negatives

Contrastive loss,⁵⁸ like the Normalized Temperature-scaled Cross-Entropy (NT-Xent) loss,⁴³ aims at representation learning through maximizing the agreement between positive pairs while minimizing the agreement between negative pairs. Given 2N latent vectors $\{z_1, \ldots, z_{2N}\}$ from a batch of N molecules, NT-Xent for a positive pair (z_i, z_j) is given in Equation 3:

$$\mathcal{L}_{i,j} = -\log \frac{\exp(\cos(\boldsymbol{z}_i, \boldsymbol{z}_j)/\tau)}{\sum_{k=1}^{2N} \mathbb{1}_{k \neq i} \exp(\cos(\boldsymbol{z}_i, \boldsymbol{z}_k)/\tau)},$$
(3)

where τ is the temperature parameter and $\cos(\mathbf{z}_i, \mathbf{z}_j) = \frac{\langle \mathbf{z}_i, \mathbf{z}_j \rangle}{\|\mathbf{z}_i\| \|\mathbf{z}_j\|}$ measures the cosine similarity between two latent vectors. However, such a contrastive loss assumes all negative pairs are equally negative against the anchor \mathbf{z}_i , which leads to faulty negatives. Faulty negatives are instances that are similar with the anchor yet are treated as negative instances in contrastive training. An example of faulty negatives introduced in original molecular CL framework is illustrated in Figure 1c. When NT-Xent loss is applied, both the molecule M_A (o-xylene, CID 7237) and molecule M_C (CID 89970782) are trained as equivalent negative instances against the anchor molecule M_B (toluene, CID 1140). However, M_B has much more similar molecular properties to M_A than M_C , since M_A and M_B share a similar structure and functional groups. In this case, M_A is a "faulty negative" as it should not be far away from the anchor in the representation domain as other negative samples like M_C . Faulty negatives strongly repel the anchor and the negative sample, even though they should preferably be close in representation domain. 59,60

To mitigate the effect of faulty negatives in CL, M_A and M_B should be "less negative" comparing to M_B and M_C as illustrated in Figure 1d. Namely, the latent vector of M_A is not pushed too far away from M_B , while the agreement of M_B and M_C is still minimized during training. In particular, we propose a weighted NT-Xent loss $\mathcal{L}_{i,j}^{w}$ which penalizes each negative instance against the anchor via molecular similarities. The similarity measurement between two latent vectors $(\mathbf{z}_i, \mathbf{z}_k)$ from a negative molecule pair (M_i, M_k) is penalized by a weight coefficient w_{ik} , as given in Equation 4:

$$\mathcal{L}_{i,j}^{w} = -\log \frac{\exp(\cos(\boldsymbol{z}_{i}, \boldsymbol{z}_{j})/\tau)}{\sum_{k=1}^{2N} \mathbb{1}_{k \neq i} \exp(w_{ik} \cos(\boldsymbol{z}_{i}, \boldsymbol{z}_{k})/\tau)},$$
(4)

where $w_{ik} \in [0, 1]$. To identify the faulty negative instances, cheminformatic fingerprint is leveraged to evaluate the similarity between molecule pairs, as shown in Equation 5:

$$w_{ik} = 1 - \lambda_1 FPSim(M_i, M_k), \tag{5}$$

where $FPSim(M_i, M_k)$ evaluates the fingerprint similarity of the given two molecules (M_i, M_k) and λ_1 is the hyperparameter that determines the scale of penalty for faulty negatives. In this work, we model $FPSim(\cdot, \cdot)$ as the Tanimoto similarity of extended-connectivity fingerprint (ECFP), 62 since it has been demonstrated to be efficient and effective measurement of molecule similarities in multiple domains. Through the weighted NT-Xent loss, faulty negative molecule pairs, i.e., those with high fingerprint similarities, are forced to be closer in representation domain, this greatly mitigates faulty negatives and benefits the prediction of molecular properties.

2.4 Fragment Contrast

Most CL frameworks for molecular representation learning perform contrastive training on the whole molecule graph level. 49,51-53 Few works have investigated motif-level CL for molecules, which learns a table of frequently-occurring motif embeddings and trains a sampler to generate informative subgraphs for CL.⁵⁰ Though such a method shows performance enhancement on various benchmarks, the learned sampler may not cover all the unique substructures in the large molecule dataset. Additionally, the previous work performs contrast across molecule graphs and motif subgraphs, which can lead to the ignorance of unsampled substructures while each molecule relies on a combination of different motifs to function. Driven by the insight, we leverage a widely used systematic fragmentation method, BRICS decomposition, 55 to break each molecule into fragments, which preserves major structural features of chemical compounds, ⁶⁴ and perform CL on substructures individually from molecule-level contrast. Figure 1e illustrates the proposed fragment contrast, where different colors indicate fragments obtained from BRICS. Instead of pooling over the entire graph, we conduct pooling on the decomposed subgraphs to obtain fragment representations. Different fragments, either from the same molecule or different molecules, are treated as negative pairs, like chlorobenzene (colored by purple) and benzofuran (colored by dark yellow). Notably, some fragments may share similar structures, however, they are still considered as negative instances. This

is because different fragments have different neighbors to aggregate from. By this means, representations of fragments are forced to embed their unique neighboring information through layer-wise aggregation in GNNs. Such neighboring information can benefit molecular property prediction as molecules function differently due to the categorical and positional combination of various functional groups.

Assume 2M fragments are created given a batch of 2N augmented molecule graphs. Notice that when conducting augmentations, fragments within molecules are also randomly transformed (i.e., atom masking and bond deletion). Thus, no extra augmentation is required to generate positive fragment pairs. A positive fragment pair (F_i, F_j) is mapped to latent vectors $(\boldsymbol{z}_i^{\text{frag}}, \boldsymbol{z}_j^{\text{frag}})$ through the same GNN encoder $f(\cdot)$ except the readout is conducted on the fragment subgraph instead of the whole molecule graph. The contrastive loss on the fragment level is given in Equation 6:

$$\mathcal{L}_{i,j}^{\text{frag}} = -\log \frac{\exp(\cos(\boldsymbol{z}_i^{\text{frag}}, \boldsymbol{z}_j^{\text{frag}})/\tau)}{\sum_{k=1}^{2M} \mathbb{1}_{k \neq i} \exp(\cos(\boldsymbol{z}_i^{\text{frag}}, \boldsymbol{z}_k^{\text{frag}})/\tau)}.$$
 (6)

Eventually, the total loss given in Equation 7 is a combination of the weighted contrastive loss on the whole molecule graph level shown in Equation 4, and fragment level constrastive loss shown in 6:

$$\mathcal{L}_{i,j}^{total} = \mathcal{L}_{i,j}^{w} + \lambda_2 \mathcal{L}_{i,j}^{frag}, \tag{7}$$

where $\lambda_2 \in (0, 1]$ is a hyperparameter that controls the scale of fragment-level contrast during pre-training.

2.5 Datasets

The model is pre-trained on approximately 10 million unique unlabeled molecules from PubChem⁶⁵ collected and cleaned by Chithrananda et al.³⁴ The pre-training dataset is randomly split into training and validation sets by the ratio of 95/5. The GNN model is pre-trained on the training set and tested on the validation set to select the best-performing

model.

To evaluate the performance of iMolCLR framework, we fine-tune the pre-trained GNN model on 12 benchmarks from MoleculeNet, ²⁸ including 7 classification and 5 regression benchmarks. These benchmarks contain a wide variety of molecular properties covering physiology, biophysics, physical chemistry, and quantum mechanics. During fine-tuning, each dataset is split into train/validation/test sets through scaffold split by the ratio of 80/10/10 following previous molecule SSL works. ^{39,40,49,53} Comparing to random split, scaffold split provides a more challenging yet more realistic setting to benchmark molecular property predictions. ²⁸ During fine-tuning, the model is only trained on the train set and leverages the validation set to select the best-performing model. The performance of the selected model on the test set is reported in this work. More details of molecular property benchmarks can be found in Supplementary Table 1.

2.6 Training Details

In iMolCLR pre-training, the GNN encoder embeds each molecule graph into a 512-dimension representation \boldsymbol{h} . The projection head is modeled by an MLP with one hidden layer maps \boldsymbol{h} into 256-dimensional latent vector \boldsymbol{z} . ReLU⁶⁶ is implemented as the non-linear activation function. The whole model is pre-trained for 50 epochs with batch size 512. We use Adam optimizer⁶⁷ with an initial learning rate 5×10^{-4} and the weight decay 1×10^{-5} . Additionally. cosine learning rate decay⁶⁸ is performed during pre-training.

During fine-tuning, we replace the projection head with a randomly initialized MLP which maps the representation h into the desired property prediction while keeping the pre-trained GNN encoder. The pre-trained model is trained individually for 100 epochs on each task from the benchmarks. We perform a random search of hyperparameters on validation sets and report the results on test sets. For each benchmark, we run three individual runs and report the average and standard deviation of three trials. The whole model is implemented on PyTorch Geometric. ⁶⁹ More details of fine-tuning hyperparameters can be

found in Supplementary Table 2.

2.7 Baselines

To demonstrate the effectiveness of iMolCLR, we compare its performance with various supervised GNN models. GCN¹⁴ and GIN, ^{15,39} as prevalent GNN models for general graphical tasks, are implemented for performance comparison. Additionally, GNN models that are designed for molecular property prediction and have achieved state-of-the-art (SOTA) performance on certain benchmarks are included. D-MPNN¹⁸ leverages a message-passing architecture that is invariant to molecule graph. SchNet¹⁹ and MGCN²⁰ model the quantum interactions within molecules in the graph aggregation. Additionally, attention-based model, AttentiveFP, ²² is included in baselines.

We further compare our proposed method with other pre-training and SSL models. N-gram ³⁸ obtains molecular representation through assembling the vertex embedding in short walks. Hu et al. ³⁹ is included, which contains both a self-supervised node-level and a supervised graph-level pre-training. MolCLR ⁴⁹ proposes a general CL framework for molecular representation learning. Notably, Hu et al., MolCLR, and our proposed iMolCLR are all implemented based on the GIN encoder. Thus, a comparison of these models, as well as supervised-learning GIN, well reflects the effectiveness of different SSL methods on various molecular property predictions.

3 Results and Discussion

3.1 Molecular Property Predictions

Molecular SSL methods are commonly evaluated by their predictive performance on various molecular properties. It is expected that good molecular representations learned through SSL greatly boost the prediction performance. ^{39,40,49} Table 1 demonstrate the test compute area

Table 1: Mean and standard deviation of test ROC-AUC (%) of iMolCLR in comparison to different supervised and self-supervised learning models on classification benchmarks.

Dataset	BBBP	Tox21	ClinTox	HIV	BACE	SIDER	MUV	Avg.
$ m GCN^{14}$	71.8±0.9	70.9 ± 2.6	$62.5{\pm}2.8$	74.0 ± 3.0	71.6 ± 2.0	53.6 ± 3.2	71.6 ± 4.0	68.0
$ m GIN^{15}$	65.8 ± 4.5	$74.0 {\pm} 0.8$	$68.2 {\pm} 3.7$	$75.3 {\pm} 1.9$	$70.1 {\pm} 5.4$	57.3 ± 1.6	71.8 ± 2.5	68.9
$SchNet^{19}$	84.8 ± 2.2	77.2 ± 2.3	71.5 ± 3.7	70.2 ± 3.4	$76.6 {\pm} 1.1$	53.9 ± 3.7	71.3 ± 3.0	72.2
$\rm MGCN^{20}$	85.0 ± 6.4	$70.7 {\pm} 1.6$	$63.4 {\pm} 4.2$	$73.8 {\pm} 1.6$	73.4 ± 3.0	$55.2 {\pm} 1.8$	70.2 ± 3.4	70.2
D -MPNN 18	81.2 ± 3.8	$78.9 {\pm} 1.3$	90.5 ± 5.3	75.0 ± 2.1	85.3 ± 5.3	$63.2 {\pm} 2.3$	76.2 ± 2.8	78.7
AttentiveFP ²²	$90.8{\pm}5.0$	$\textbf{80.7} {\pm} \textbf{2.0}$	$93.3 {\pm} 2.0$	$\textbf{82.9} {\pm} \textbf{2.2}$	$\textbf{86.3} {\pm} \textbf{1.5}$	60.5 ± 6.0	$77.6{\pm}3.1$	81.7
$N-Gram^{38}$	$91.2{\pm}3.0$	76.9 ± 2.7	85.5 ± 3.7	$83.0 {\pm} 1.3$	87.6 ± 3.5	$63.2 {\pm} 0.5$	81.6 ± 1.9	81.3
Hu et al. 39	70.8 ± 1.5	$78.7 {\pm} 0.4$	$78.9 {\pm} 2.4$	80.2 ± 0.9	85.9 ± 0.8	$65.2 {\pm} 0.9$	81.4 ± 2.0	77.3
$MolCLR^{49}$	73.6 ± 0.5	$\textbf{79.8} {\pm} \textbf{0.7}$	$93.2 {\pm} 1.7$	80.6 ± 1.1	$89.0 \!\pm\! 0.3$	68.0 ± 1.1	$88.6 {\pm} 2.2$	81.8
iMolCLR	76.4 ± 0.7	$\textbf{79.9} {\pm} \textbf{0.6}$	$95.4 {\pm} 1.1$	80.8 ± 0.1	$88.5 {\pm} 0.5$	$69.9 {\pm} 1.5$	$90.8 {\pm} 1.7$	83.1

under the receiver operating characteristic curve (ROC-AUC) on classification benchmarks of our CL pre-training model in comparison to a wide variety of supervised (the first 6 models) and self-supervised (the last 4 models) baselines. Both best performing supervised and self-supervised models for each benchmark are highlighted in bold. The last column lists the averaged performance over all the classification benchmarks for each model. As shown in Table 1, iMolCLR pre-training significantly boosts the performance of the GIN model by 14.2% comparing to mere supervised learning. Built upon GIN, a generic GNN architecture, iMolCLR rivals strong supervised learning models and even exceeds them on 4 out of 7 classification benchmarks, where the latter develop sophisticated graph convolutional operations or engineered descriptors. For example, on SIDER and MUV, iMolCLR prevails over the best-performing supervised models by 6.7% and 13.2%, respectively. Furthermore, iMolCLR demonstrates an overall preferable performance of 83.1% ROC-AUC on average for all the datasets that we considered. Particularly, in comparison to MolCLR, the original CL framework with neither faulty negative mitigation nor fragment contrast, iMolCLR outperforms by 1.3% ROC-AUC which demonstrates the effectiveness of improvement for CL in these challenging benchmarks.

Additionally, we test the performance of our CL pre-training model and baselines on 5 regression benchmarks as demonstrated in Table 2. The last column of the table shows

Table 2: Mean and standard deviation of test RMSE (for FreeSolv, ESOL, Lipo) or MAE (for QM7, QM8) of iMolCLR in comparison to different supervised and self-supervised learning models on regression benchmarks. The scaled error is calculated by dividing RMSE/MAE by the range of each benchmark labels.

Dataset	FreeSolv	ESOL	Lipo	QM7	QM8	Scaled avg.
$\rm GCN^{14}$	2.87 ± 0.14	1.43 ± 0.05	$0.85 {\pm} 0.08$	122.9 ± 2.2	0.0366 ± 0.0011	0.1002
$ m GIN^{15}$	2.76 ± 0.18	$1.45{\pm}0.02$	$0.85 {\pm} 0.07$	$124.8 {\pm} 0.7$	0.0371 ± 0.0009	0.1002
SchNet^{19}	3.22 ± 0.76	1.05 ± 0.06	0.91 ± 0.10	$\textbf{74.2} {\pm} \textbf{6.0}$	0.0204 ± 0.0021	0.0861
$MGCN^{20}$	3.35 ± 0.01	$1.27{\pm}0.15$	1.11 ± 0.04	$77.6 {\pm} 4.7$	$0.0223 {\pm} 0.0021$	0.0982
$D-MPNN^{18}$	2.18 ± 0.91	$0.98 {\pm} 0.26$	$\boldsymbol{0.65 {\pm} 0.05}$	105.8 ± 13.2	$0.0143 \!\pm\! 0.0022$	0.0699
AttentiveFP ²²	$2.03{\pm}0.42$	$\boldsymbol{0.85 {\pm} 0.06}$	$\boldsymbol{0.65 {\pm} 0.03}$	126.7 ± 4.0	0.0282 ± 0.0010	0.0755
N-Gram ³⁸	2.51 ± 0.19	$1.10{\pm}0.03$	0.88 ± 0.12	125.6 ± 1.5	0.0320 ± 0.0032	0.0919
Hu et al. 39	2.83 ± 0.12	$1.22 {\pm} 0.02$	0.74 ± 0.00	110.2 ± 6.4	0.0191 ± 0.0003	0.0837
$MolCLR^{49}$	2.20 ± 0.20	$\boldsymbol{1.11 {\pm} 0.01}$	$\boldsymbol{0.65 {\pm} 0.08}$	87.2 ± 2.0	0.0174 ± 0.0013	0.0714
iMolCLR	$2.09{\pm}0.03$	1.13 ± 0.02	$\boldsymbol{0.64} {\pm} \boldsymbol{0.00}$	$66.3 {\pm} 2.0$	$0.0170 \!\pm\! 0.0002$	0.0680

the average of scaled error over all the regression benchmarks for each model, which is calculated by dividing the error by the range of each database label. We report root mean square error (RMSE) for FreeSolv, ESOL, and Lipo and mean absolute error (MAE) for QM7 and QM8 following MoleculeNet. Similar to the performance on classification benchmarks, iMolCLR also demonstrates a rival or even superior prediction accuracy over supervised baseline models on challenging regression benchmarks. In terms of the averaged scaled error, iMolCLR outperforms the best-supervised model, D-MPNN, by 0.0019, which is a nontrivial improvement as regression tasks are more challenging than classifications. In comparison with the original CL pre-training, iMolCLR decreases the prediction errors on 4 out of 5 benchmarks and shows competitive performance on the remaining ESOL dataset. Other SSL baselines also cannot emulate iMolCLR on most datasets. In particular, iMolCLR shows an advantage of 0.0157 and 0.0239 on scaled error over N-Gram and Hu et al., see provided the result of the result of the result of the result of the remaining expectively.

Overall, experiments on a wide variety of challenging molecular property benchmarks demonstrate that our proposed iMolCLR is an effective SSL strategy that greatly improves the performance of pre-trained GNN models. Further, iMolCLR shows superiority over the original CL framework on both classification and regression tasks, which validates the

effectiveness of faulty negative mitigation and fragment contrast. The following section investigates how the two techniques impact the molecular CL methods in detail.

3.2 Influence of Faulty Negative Mitigation and Fragment Contrast in Molecular CL

We further probe the impact of the two improvement strategies: faulty negative mitigation and fragment contrast on molecular CL. Specifically, whether contrastive training benefits from each method solely or the combination of both strategies. To this end, we consider four pre-training strategies: original CL pre-training, CL with only weighted NT-Xent for faulty negative mitigation, CL with only fragment contrast, and CL with both improvement methods, as shown in Figure 2. The four strategies are illustrated by green, blue, orange, and purple bars, respectively. Figure 2a shows ROC-AUC on classification tasks and Figure 2b shows scaled error on regression tasks. The height of each bar denotes the averaged performance while the length of each error bar represents the standard deviation over three individual runs. It is illustrated that the integration of weighted NT-Xent and fragment contrast demonstrates the best performance on 6 out 7 classification benchmarks and 3 out of 5 regression benchmarks. On average, iMolCLR with both improvement strategies applied surpasses weighted NT-Xent and fragment contrast solely by 0.9% and 1.5% on classifications, respectively. Similarly, iMolCLR shows a decrease of the averaged scaled error by 0.0003 and 0.0025 over each strategy alone on regressions. Also, weighted NT-Xent solely improves the property prediction over original CL on most benchmarks except for Tox21, BACE, and ESOL. Interestingly, fragment contrast alone shows a limited advantage over original CL pre-training. This could be because when applying only fragment contrast, decomposed substructures are considered as negative pairs, this may exacerbate the faulty negatives in contrastive training. On the other hand, with faulty negative mitigated through weighted NT-Xent loss, through fragment contrast the backbone model can easily identify the functional groups or motifs within each molecule. Thus, the weighted NT-Xent mitigates the faulty negative instances

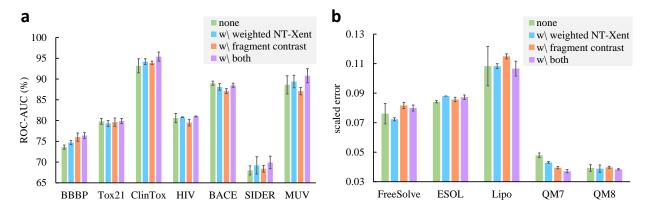


Figure 2: Investigation of the impact of weighted NT-Xent and fragment contrast on molecular CL pre-training. (a) Mean and standard deviation of test ROC-AUC (\uparrow) for different CL strategies on classification benchmarks. (b) Mean and standard deviation of scaled error (\downarrow) for different CL strategies on regression benchmarks.

not only on the molecule level, but also on the decomposed fragment level. Overall, the combination of faulty negative mitigation together with fragment contrast greatly improves the molecular CL for property prediction and it demonstrates an advantage over applying each strategy solely. More test results of different pre-training strategies can be found in Supplementary Tables 3 and 4.

3.3 Empirical Study of Hyperparameters

To better investigate the proposed strategies for molecular CL, we conduct empirical study of hyperparameters of contrastive loss given in Equation 4, 5, 6, and 7. Different combinations of λ_1 , λ_2 , and τ are tested on molecular property prediction benchmarks. λ_1 controls the scale of penalty on faulty negative instances and λ_2 weighs the magnitude of fragment-level contrast. Besides, the selection of the appropriate τ benefits learning from hard negative samples. ⁴³ Table 3 shows the performance of iMolCLR pre-trained GNNs with different combinations of the three hyperparameters on both classification and regression benchmarks. λ_1 and λ_2 are selected from $\{0.3, 0.5, 0.7\}$, and τ is selected from $\{0.05, 0.1, 0.5\}$. iMolCLR achieves the best overall performance on classifications under $\lambda_1 = 0.5, \lambda_2 = 0.5, \tau = 0.1$, while on regressions, using $\lambda_1 = 0.5, \lambda_2 = 0.5, \tau = 0.5$ obtains the best results. Tuning each hyperparameter may

Table 3: Evaluation for iMolCLR pre-trained GNNs with different combinations of λ_1 , λ_2 , and τ . Both averaged ROC-AUC over classification benchmarks and averaged error over regression benchmarks are reported.

$egin{array}{c} \lambda_1 \ \lambda_2 \ au \end{array}$	0.5 0.5 0.1	0.5	0.5	0.3	0.7	0.5	0.5
Avg. ROC-AUC (%) (\uparrow) Avg. scaled error (\downarrow)	82.8 0.0733	82.0 0.0725	81.6 0.0730	82.3 0.0726	82.0 0.0723	81.0 0.0736	81.4 0.0712

have an opposite impact on different benchmarks. For instance, decreasing λ_1 from 0.5 to 0.3 causes a drop of 0.8% ROC-AUC on classifications, while a gain of 0.0008 is observed on regressions. It indicates that the best combination of hyperparameters is task-dependent on the target property and data distribution. However, it should be pointed out that though the selection of hyperparameters affects the performance on downstream molecular property predictions as demonstrated in Table 3, all the listed hyperparameter combinations still significantly boost GNNs in comparison to supervised learning. This reflects the robustness of our proposed molecular CL framework in learning expressive representations. Detailed test results of property prediction on each benchmark can be found in Supplementary Tables 3 and 4.

3.4 Does Extra Features Benefit Molecular CL Pre-training?

We implement simple yet distinguishable node and edge features via RDKit⁷⁰ to model 2D molecule graphs following previous pre-training frameworks. ^{39,49} In particular, node features include atomic number and chirality type, and edge features consist of covalent bond type and direction. However, extra features can also be considered in molecule graphs. ²² In supervised learning, rich input features are expected to benefit molecular property predictions as more information is provided. This leads to the question: whether enriched input benefits molecular CL pre-training for property predictions? To this end, we introduce more node and edge features to iMolCLR pre-training as shown in Table 4. Besides the original features, degree,

Table 4: List of extended node and edge features for molecule graphs.

Type	Name	Description	Range
Node	atomic chirality degree charge hybrization aromatic hydrogen	Atomic number Chirality type Number of bonded neighbors Formal charge of the atom Hybrization type Whether on a aromatic ring Number of bonded hydrogens	$ \{x: 1 \le x \le 119, x \in \mathbb{Z}\} $ {unspecified, CW, CCW, other} $ \{x: 0 \le x \le 10, x \in \mathbb{Z}\} $ { $x: -5 \le x \le 5, x \in \mathbb{Z}$ } { $sp, sp^2, sp^3, sp^3d, sp^3d^2, other}$ { $0, 1$ } { $x: 0 \le x \le 5, x \in \mathbb{Z}$ }
Edge	bond_type bond_dir stereo	Type of covalent bonds Direction of covalent bonds Stereotype	{single, double, triple, aromatic} {none, end-upright, end-downright} {None, Any, Z, E, Cis, Trans}

charge, hybridization, aromatic, and number of hydrogens are included in the node feature, meanwhile, the stereotype of bond is added to edge features. The extra features are fed into embedding layers and added to the embedding from original features before being sent to graph convolutional layers. During augmentation, each feature of masked nodes is set to a unique code. For example, atomic is set to 0 when masked. Through adding richer features, more molecular information is provided during pre-training as well as downstream fine-tuning.

We compare the results of GNN models pre-trained and fine-tuned with original and enriched features. As shown in Figure 3, we implement molecular CL pre-training with weighted NT-Xent loss, where green bars represent training using original input features while purple bars represent enriched features. Both the mean and standard deviation of performance on each benchmark are illustrated in Figure 3. On most benchmarks, adding extra input features benefits the downstream molecular property prediction. For instance, enriched features improve ROC-AUC by 1.6% on SIDER and reduce MAE by 3.9 on QM7. Although adding extra features demonstrates better performances on several benchmarks, the improvements are limited comparing to the various categories of extra features included. In few benchmarks, CL with enriched features even slightly falls behind the original model like on HIV and Tox21. This reveals that our molecular CL framework effectively learns

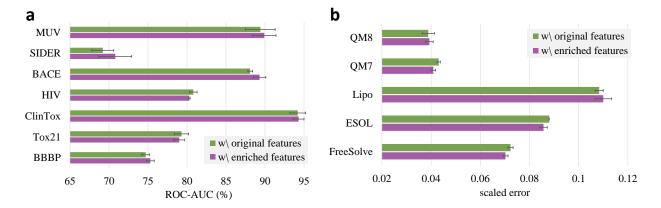


Figure 3: Comparison of molecular CL pre-training with original and enriched input features. (a) Test ROC-AUC (\uparrow) of pre-trained GNNs on classification benchmarks. (b) Test scaled error (\downarrow) of pre-trained GNNs on regression benchmarks.

the intrinsic relationships between atoms without heavily relying on engineered features. Extra node features, like degree (i.e., number of neighbors) and hydrogen (i.e., number of neighboring hydrogen atoms), can be inherently learned by pre-trained graph aggregations without explicit provided. Other features such as hybrization and charge are strongly related with the atomic feature, providing a redundant input for CL. The major takeaway is that our proposed molecular CL, as a self-supervised pre-training strategy, learns expressive representations from graphs even, which does not require engineered and enriched features to achieve better performance.

3.5 Case Study of iMolCLR Representations

To further evaluate iMolCLR, we compare the molecular representations learned by iMolCLR with those learned by original CL together with cheminformatics fingerprints. Given the query molecule (CID: 132820209) shown in Figure 4a, we compute the Tanimoto similarities ⁶¹ of cheminformatics fingerprints between the query and all the molecules in the ~10M pre-training dataset. Figure 4b and 4c exhibit the distribution of similarities on extended-connectivity fingerprint (ECFP) ⁶² and RDKit-specific fingerprint (RDKFP), ⁷⁰ respectively. ECFP is a topological fingerprint for structure-activity modeling while RDKFP identifies subgraphs of

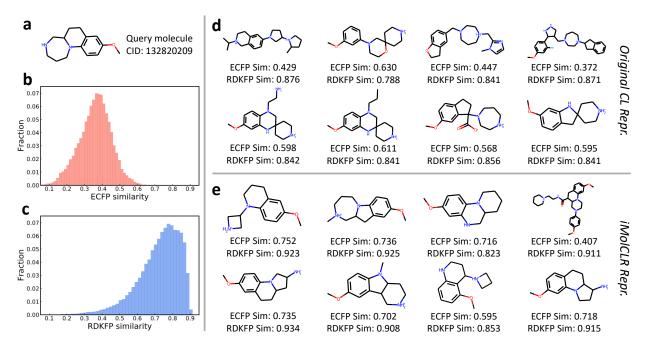


Figure 4: Case study of CL learned molecular representations. (a) Query molecule of CID 132820209. (b) Distribution of Tanimoto similarities on ECFP between molecules from the pre-training dataset and the query. (c) Distribution of Tanimoto similarities on RDKFP between molecules from the pre-training dataset and the query. (d) 8 molecules that are closest to the query on the original CL learned representation domain with Tanimoto similarities on ECFP and RDKFP denoted. (e) 8 molecules that are closest to the query on the iMolCLR learned representation domain with Tanimoto similarities on ECFP and RDKFP denoted.

different sizes. Overall, ECFP leads to lower similarity scores than RDKFP due to the different features and algorithms implemented. Within the database, molecules are considered very similar to the query with respect to ECFP if their similarity is greater than 0.6 (Figure 4b). While with regard to RDKFP, similar molecules are expected to have similarities greater than 0.9 (Figure 4c). We then select 8 molecules that are closest to the query in the representation domain learned by either original CL (Figure 4d) or iMolCLR (Figure 4e). Cosine similarity is used to measure the distances between learned representations. The 8 molecules selected by original CL have averaged ECFP similarity of 0.540 and RDKFP of 0.839, while those selected by iMolCLR have remarkably higher averaged ECFP similarity of 0.655 and RDKFP of 0.893. It is indicated that through faulty negative mitigation with weighted NT-Xent, iMolCLR embeds molecular cheminformatics in the learned representations, which can reason

molecular similarities. Additionally, benefiting from the fragment contrast, substructure-level topology is also embedded in iMolCLR representations. For instance, almost all the closest molecules found by iMolCLR share the phenanthroline-like substructure of three fused rings with the query molecule, whereas the original CL retrieves molecules with the substructure of only two rings fused. Besides, the C-O-C substructure of the query is captured by iMolCLR and shared among all the selected molecules. Through the case study, iMolCLR demonstrates the improvement over original CL on the learned representations, which better embed cheminformatics and substructure topology. More examples of molecule retrieval through iMolCLR can be found in Supplementary Figures 1, 2, and 3.

4 Conclusions

In this work, we propose iMolCLR, an improvement of molecular contrastive learning of representations with GNNs. Specifically, two strategies are introduced in iMolCLR: (1) the weighted NT-Xent loss to mitigate faulty negative instances during contrastive pre-training, (2) fragment-level contrast on substructures from BRICS decomposition. The former considers cheminformatics such that learned representations are related to molecular similarities, which are neglected by previous molecular CL methods. The latter, on the other hand, encourages the pre-trained GNNs to embed functional groups and motif information which are vital to molecular properties. Benefiting from the two strategies, iMolCLR outperforms other SSL baseline models, including the original molecular CL, on a wide variety of molecular property prediction benchmarks. Further investigation demonstrates that iMolCLR is an effective and robust pre-training framework, which learns expressive representations from limited input features. iMolCLR, an SSL method that can leverage large unlabeled data, bears a promise for accurate molecular property prediction, which can greatly benefit applications like drug and material discovery.

References

- (1) LeCun, Y.; Bengio, Y.; Hinton, G. Deep learning. nature **2015**, 521, 436–444.
- (2) Schmidhuber, J. Deep learning in neural networks: An overview. Neural networks 2015, 61, 85–117.
- (3) Duvenaud, D.; Maclaurin, D.; Aguilera-Iparraguirre, J.; Gómez-Bombarelli, R.; Hirzel, T.; Aspuru-Guzik, A.; Adams, R. P. Convolutional Networks on Graphs for Learning Molecular Fingerprints. Proceedings of the 28th International Conference on Neural Information Processing Systems. 2015.
- (4) Butler, K. T.; Davies, D. W.; Cartwright, H.; Isayev, O.; Walsh, A. Machine learning for molecular and materials science. *Nature* **2018**, *559*, 547–555.
- (5) Wang, Y.; Cao, Z.; Barati Farimani, A. Efficient water desalination with graphene nanopores obtained using artificial intelligence. npj 2D Materials and Applications 2021, 5, 1–9.
- (6) AlQuraishi, M.; Sorger, P. K. Differentiable biology: using deep learning for biophysics-based and data-driven modeling of molecular mechanisms. *Nature Methods* 2021, 18, 1169–1180.
- (7) Unterthiner, T.; Mayr, A.; Klambauer, G.; Steijaert, M.; Wegner, J. K.; Ceulemans, H.; Hochreiter, S. Deep learning as an opportunity in virtual screening. Proceedings of the deep learning workshop at NeurIPS. 2014; pp 1–9.
- (8) Ma, J.; Sheridan, R. P.; Liaw, A.; Dahl, G. E.; Svetnik, V. Deep neural nets as a method for quantitative structure–activity relationships. *Journal of chemical information and modeling* **2015**, *55*, 263–274.
- (9) Vamathevan, J.; Clark, D.; Czodrowski, P.; Dunham, I.; Ferran, E.; Lee, G.; Li, B.;

- Madabhushi, A.; Shah, P.; Spitzer, M., et al. Applications of machine learning in drug discovery and development. *Nature Reviews Drug Discovery* **2019**, *18*, 463–477.
- (10) Weininger, D. SMILES, a chemical language and information system. 1. Introduction to methodology and encoding rules. *Journal of chemical information and computer sciences* **1988**, *28*, 31–36.
- (11) Krenn, M.; Häse, F.; Nigam, A.; Friederich, P.; Aspuru-Guzik, A. Self-Referencing Embedded Strings (SELFIES): A 100% robust molecular string representation. *Machine Learning: Science and Technology* **2020**, *1*, 045024.
- (12) Xu, Z.; Wang, S.; Zhu, F.; Huang, J. Seq2seq fingerprint: An unsupervised deep molecular embedding for drug discovery. Proceedings of the 8th ACM international conference on bioinformatics, computational biology, and health informatics. 2017; pp 285–294.
- (13) Gómez-Bombarelli, R.; Wei, J. N.; Duvenaud, D.; Hernández-Lobato, J. M.; Sánchez-Lengeling, B.; Sheberla, D.; Aguilera-Iparraguirre, J.; Hirzel, T. D.; Adams, R. P.; Aspuru-Guzik, A. Automatic chemical design using a data-driven continuous representation of molecules. ACS central science 2018, 4, 268–276.
- (14) Kipf, T. N.; Welling, M. Semi-supervised classification with graph convolutional networks. arXiv preprint arXiv:1609.02907 2016,
- (15) Xu, K.; Hu, W.; Leskovec, J.; Jegelka, S. How Powerful are Graph Neural Networks? International Conference on Learning Representations. 2019.
- (16) Jiang, D.; Wu, Z.; Hsieh, C.-Y.; Chen, G.; Liao, B.; Wang, Z.; Shen, C.; Cao, D.; Wu, J.; Hou, T. Could graph neural networks learn better molecular representation for drug discovery? A comparison study of descriptor-based and graph-based models. *Journal of cheminformatics* 2021, 13, 1–23.

- (17) Gilmer, J.; Schoenholz, S. S.; Riley, P. F.; Vinyals, O.; Dahl, G. E. Neural message passing for quantum chemistry. International conference on machine learning. 2017; pp 1263–1272.
- (18) Yang, K.; Swanson, K.; Jin, W.; Coley, C.; Eiden, P.; Gao, H.; Guzman-Perez, A.; Hopper, T.; Kelley, B.; Mathea, M., et al. Analyzing learned molecular representations for property prediction. *Journal of chemical information and modeling* 2019, 59, 3370–3388.
- (19) Schütt, K. T.; Sauceda, H. E.; Kindermans, P.-J.; Tkatchenko, A.; Müller, K.-R. SchNet– A deep learning architecture for molecules and materials. The Journal of Chemical Physics 2018, 148, 241722.
- (20) Lu, C.; Liu, Q.; Wang, C.; Huang, Z.; Lin, P.; He, L. Molecular property prediction:
 A multilevel quantum interactions modeling perspective. Proceedings of the AAAI
 Conference on Artificial Intelligence. 2019; pp 1052–1060.
- (21) Vaswani, A.; Shazeer, N.; Parmar, N.; Uszkoreit, J.; Jones, L.; Gomez, A. N.; Kaiser, Ł.; Polosukhin, I. Attention is all you need. Advances in neural information processing systems. 2017; pp 5998–6008.
- (22) Xiong, Z.; Wang, D.; Liu, X.; Zhong, F.; Wan, X.; Li, X.; Li, Z.; Luo, X.; Chen, K.; Jiang, H., et al. Pushing the boundaries of molecular representation for drug discovery with the graph attention mechanism. *Journal of medicinal chemistry* **2019**, *63*, 8749–8760.
- (23) Ying, C.; Cai, T.; Luo, S.; Zheng, S.; Ke, G.; He, D.; Shen, Y.; Liu, T.-Y. Do Transformers Really Perform Badly for Graph Representation? Advances in Neural Information Processing Systems. 2021.
- (24) Klicpera, J.; Groß, J.; Günnemann, S. Directional Message Passing for Molecular Graphs.

 International Conference on Learning Representations. 2020.

- (25) Fuchs, F.; Worrall, D.; Fischer, V.; Welling, M. SE(3)-Transformers: 3D Roto-Translation Equivariant Attention Networks. Advances in Neural Information Processing Systems. 2020; pp 1970–1981.
- (26) Liu, Y.; Wang, L.; Liu, M.; Zhang, X.; Oztekin, B.; Ji, S. Spherical Message Passing for 3D Graph Networks. 2021.
- (27) Jing, B.; Eismann, S.; Suriana, P.; Townshend, R. J. L.; Dror, R. Learning from Protein Structure with Geometric Vector Perceptrons. International Conference on Learning Representations. 2021.
- (28) Wu, Z.; Ramsundar, B.; Feinberg, E. N.; Gomes, J.; Geniesse, C.; Pappu, A. S.; Leswing, K.; Pande, V. MoleculeNet: a benchmark for molecular machine learning. *Chemical science* **2018**, *9*, 513–530.
- (29) Oprea, T. I.; Gottfries, J. Chemography: the art of navigating in chemical space. *Journal of combinatorial chemistry* **2001**, *3*, 157–166.
- (30) Hadsell, R.; Chopra, S.; LeCun, Y. Dimensionality reduction by learning an invariant mapping. 2006 IEEE Computer Society Conference on Computer Vision and Pattern Recognition (CVPR'06). 2006; pp 1735–1742.
- (31) Doersch, C.; Zisserman, A. Multi-task self-supervised visual learning. Proceedings of the IEEE International Conference on Computer Vision. 2017; pp 2051–2060.
- (32) Devlin, J.; Chang, M.-W.; Lee, K.; Toutanova, K. Bert: Pre-training of deep bidirectional transformers for language understanding. arXiv preprint arXiv:1810.04805 2018,
- (33) Wang, S.; Guo, Y.; Wang, Y.; Sun, H.; Huang, J. SMILES-BERT: large scale unsupervised pre-training for molecular property prediction. Proceedings of the 10th ACM international conference on bioinformatics, computational biology and health informatics. 2019; pp 429–436.

- (34) Chithrananda, S.; Grand, G.; Ramsundar, B. ChemBERTa: Large-Scale Self-Supervised Pretraining for Molecular Property Prediction. arXiv preprint arXiv:2010.09885 2020,
- (35) Fabian, B.; Edlich, T.; Gaspar, H.; Segler, M.; Meyers, J.; Fiscato, M.; Ahmed, M. Molecular representation learning with language models and domain-relevant auxiliary tasks. arXiv preprint arXiv:2011.13230 2020,
- (36) Flam-Shepherd, D.; Zhu, K.; Aspuru-Guzik, A. Keeping it Simple: Language Models can learn Complex Molecular Distributions. arXiv preprint arXiv:2112.03041 2021,
- (37) Ross, J.; Belgodere, B.; Chenthamarakshan, V.; Padhi, I.; Mroueh, Y.; Das, P. Do Large Scale Molecular Language Representations Capture Important Structural Information? arXiv preprint arXiv:2106.09553 2021,
- (38) Liu, S.; Demirel, M. F.; Liang, Y. N-Gram Graph: Simple Unsupervised Representation for Graphs, with Applications to Molecules. NeurIPS. 2019.
- (39) Hu, W.; Liu, B.; Gomes, J.; Zitnik, M.; Liang, P.; Pande, V.; Leskovec, J. Strategies for Pre-training Graph Neural Networks. International Conference on Learning Representations. 2020.
- (40) Rong, Y.; Bian, Y.; Xu, T.; Xie, W.; WEI, Y.; Huang, W.; Huang, J. Self-Supervised Graph Transformer on Large-Scale Molecular Data. Advances in Neural Information Processing Systems. 2020; pp 12559–12571.
- (41) Zhang, Z.; Liu, Q.; Wang, H.; Lu, C.; Lee, C.-K. Motif-based Graph Self-Supervised Learning for Molecular Property Prediction. *Advances in Neural Information Processing Systems* **2021**, *34*.
- (42) He, K.; Fan, H.; Wu, Y.; Xie, S.; Girshick, R. Momentum contrast for unsupervised visual representation learning. Proceedings of the IEEE/CVF Conference on Computer Vision and Pattern Recognition. 2020; pp 9729–9738.

- (43) Chen, T.; Kornblith, S.; Norouzi, M.; Hinton, G. A simple framework for contrastive learning of visual representations. International conference on machine learning. 2020; pp 1597–1607.
- (44) Caron, M.; Misra, I.; Mairal, J.; Goyal, P.; Bojanowski, P.; Joulin, A. Unsupervised learning of visual features by contrasting cluster assignments. *Advances in Neural Information Processing Systems* **2020**, *33*, 9912–9924.
- (45) Chen, X.; He, K. Exploring simple siamese representation learning. Proceedings of the IEEE/CVF Conference on Computer Vision and Pattern Recognition. 2021; pp 15750–15758.
- (46) Zbontar, J.; Jing, L.; Misra, I.; LeCun, Y.; Deny, S. Barlow twins: Self-supervised learning via redundancy reduction. International Conference on Machine Learning. 2021; pp 12310–12320.
- (47) Bengio, Y.; Lecun, Y.; Hinton, G. Deep learning for AI. Communications of the ACM **2021**, 64, 58–65.
- (48) You, Y.; Chen, T.; Sui, Y.; Chen, T.; Wang, Z.; Shen, Y. Graph contrastive learning with augmentations. *Advances in Neural Information Processing Systems* **2020**, *33*, 5812–5823.
- (49) Wang, Y.; Wang, J.; Cao, Z.; Farimani, A. B. MolCLR: Molecular contrastive learning of representations via graph neural networks. arXiv preprint arXiv:2102.10056 2021,
- (50) Zhang, S.; Hu, Z.; Subramonian, A.; Sun, Y. Motif-driven contrastive learning of graph representations. arXiv preprint arXiv:2012.12533 2020,
- (51) Liu, S.; Wang, H.; Liu, W.; Lasenby, J.; Guo, H.; Tang, J. Pre-training Molecular Graph Representation with 3D Geometry. arXiv preprint arXiv:2110.07728 2021,

- (52) Stärk, H.; Beaini, D.; Corso, G.; Tossou, P.; Dallago, C.; Günnemann, S.; Liò, P. 3D Infomax improves GNNs for Molecular Property Prediction. arXiv preprint arXiv:2110.04126 2021,
- (53) Zhu, J.; Xia, Y.; Qin, T.; Zhou, W.; Li, H.; Liu, T.-Y. Dual-view Molecule Pre-training. arXiv preprint arXiv:2106.10234 2021,
- (54) Morgado, P.; Misra, I.; Vasconcelos, N. Robust Audio-Visual Instance Discrimination. Proceedings of the IEEE/CVF Conference on Computer Vision and Pattern Recognition. 2021; pp 12934–12945.
- (55) Degen, J.; Wegscheid-Gerlach, C.; Zaliani, A.; Rarey, M. On the art of compiling and using 'drug-like' chemical fragment spaces. *ChemMedChem* **2008**, *3*, 1503.
- (56) Magar, R.; Wang, Y.; Lorsung, C.; Liang, C.; Ramasubramanian, H.; Li, P.; Farimani, A. B. AugLiChem: Data Augmentation Library of Chemical Structures for Machine Learning. arXiv preprint arXiv:2111.15112 2021,
- (57) Bronstein, M. M.; Bruna, J.; LeCun, Y.; Szlam, A.; Vandergheynst, P. Geometric deep learning: going beyond euclidean data. *IEEE Signal Processing Magazine* **2017**, *34*, 18–42.
- (58) Oord, A. v. d.; Li, Y.; Vinyals, O. Representation learning with contrastive predictive coding. arXiv preprint arXiv:1807.03748 2018,
- (59) Robinson, J. D.; Chuang, C.-Y.; Sra, S.; Jegelka, S. Contrastive Learning with Hard Negative Samples. International Conference on Learning Representations. 2021.
- (60) Huynh, T.; Kornblith, S.; Walter, M. R.; Maire, M.; Khademi, M. Boosting contrastive self-supervised learning with false negative cancellation. arXiv preprint arXiv:2011.11765 2020,

- (61) Chen, X.; Reynolds, C. H. Performance of similarity measures in 2D fragment-based similarity searching: comparison of structural descriptors and similarity coefficients.

 Journal of chemical information and computer sciences 2002, 42, 1407–1414.
- (62) Rogers, D.; Hahn, M. Extended-connectivity fingerprints. *Journal of chemical information and modeling* **2010**, *50*, 742–754.
- (63) Bajusz, D.; Rácz, A.; Héberger, K. Why is Tanimoto index an appropriate choice for fingerprint-based similarity calculations? *Journal of cheminformatics* **2015**, *7*, 1–13.
- (64) Liu, T.; Naderi, M.; Alvin, C.; Mukhopadhyay, S.; Brylinski, M. Break down in order to build up: decomposing small molecules for fragment-based drug design with e MolFrag. Journal of chemical information and modeling 2017, 57, 627–631.
- (65) Kim, S.; Chen, J.; Cheng, T.; Gindulyte, A.; He, J.; He, S.; Li, Q.; Shoemaker, B. A.; Thiessen, P. A.; Yu, B., et al. PubChem 2019 update: improved access to chemical data. Nucleic acids research 2019, 47, D1102–D1109.
- (66) Maas, A. L.; Hannun, A. Y.; Ng, A. Y. Rectifier nonlinearities improve neural network acoustic models. Proc. icml. 2013; p 3.
- (67) Kingma, D. P.; Ba, J. Adam: A method for stochastic optimization. arXiv preprint arXiv:1412.6980 2014,
- (68) Loshchilov, I.; Hutter, F. Sgdr: Stochastic gradient descent with warm restarts. arXiv preprint arXiv:1608.03983 2016,
- (69) Fey, M.; Lenssen, J. E. Fast Graph Representation Learning with PyTorch Geometric. ICLR Workshop on Representation Learning on Graphs and Manifolds. 2019.
- (70) Landrum, G. RDKit: Open-source cheminformatics. https://www.rdkit.org/, 2006.