MOLECULAR GEOMETRY PRETRAINING WITH SE(3)-INVARIANT DENOISING DISTANCE MATCHING

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ABSTRACT

Pretraining molecular representations is critical in a variety of applications for drug and material discovery due to the limited number of labeled molecules, yet most existing work focuses on pretraining on 2D molecular graphs. The power of pretraining on 3D geometric structures, however, has been less explored. This is owning to the difficulty of finding a sufficient proxy task that can empower the pretraining to effectively extract essential features from the geometric structures. Motivated by the dynamic nature of 3D molecules, where the continuous motion of a molecule in the 3D Euclidean space forms a smooth potential energy surface, we propose a 3D coordinate denoising pretraining framework to model such an energy landscape. Leveraging an SE(3)-invariant score matching method, we propose GeoSSL in which the coordinate denoising proxy task is effectively boiled down to denoising the pairwise atomic distances in a molecule. Our comprehensive experiments confirm the effectiveness and robustness of our proposed method.

1 INTRODUCTION

Learning effective molecular representations is critical in a variety of tasks in drug and material discovery, such as molecular property prediction [13, 19, 70], *de novo* molecular design and optimization [6, 49, 72], and retrosynthesis and reaction planning [21, 48, 60]. Recent work based on graph neural networks (GNNs) [19] has shown superior performance thanks to the simplicity and effectiveness of GNNs in modeling graph-structured data. However, the problem remains challenging due to the limited number of labeled molecules as it is in general expensive and time-consuming to label molecules, which usually requires expensive physics simulations or wet-lab experiments.

As a result, recently, there is growing interest in developing pretraining or self-supervised learning methods for learning molecular representations by leveraging the huge amount of unlabeled molecule data [27, 34, 59, 71]. These methods have shown superior performance on many tasks, especially when the number of labeled molecules is insufficient. One limitation of these approaches is, however, that they represent molecules as topological graphs and molecular representations are learned through pretraining 2D topological structures (*i.e.*, based on the covalent bonds). But intrinsically, for molecules, a more natural representation is based on their 3D geometric structures, which largely determine the corresponding physical and chemical properties. Indeed, recent work [19, 35] has empirically verified the importance of applying 3D geometric information for molecular property prediction tasks. Therefore, a more promising direction is to pretrain molecular representations based on their 3D geometric structures, which is the main focus of this paper.

The main challenge for molecule geometric pretraining arises from discovering an effective proxy task to empower the pretraining to extract essential features from the 3D geometric structures. Our proxy task is motivated by the following observations. Studies [44] have shown that molecules are not static but in a continuous motion in the 3D Euclidean space, forming a potential energy surface (PES). As shown in Figure 1, it is desirable to study the molecule in the local minima of the PES, called *conformer*. However, such stable state conformer often comes with different noises for the following reasons. First, the statistical and systematic errors on conformation estimation are unavoidable [10]. Second, it has been well-acknowledged that a conformer can have vibrations around the local minima in PES. Such characteristics of the molecular geometry motivate us to attempt to denoise the molecular coordinates around the local minima, to mimic the computation errors and conformation vibration within the corresponding local region. The denoising goal is to

learn molecular representations which are robust to such noises and effectively capture the energy surface around the local minima.

To achieve the aforementioned goal, we propose GeoSSL, an SE(3)-invariant denoising distance matching pretraining algorithm. In a nutshell, to capture the smooth energy surface around the local minima, we aim to maximize the mutual information (MI) between a given *stable geometry* and its *perturbed version* (*i.e.*, $\boldsymbol{g}_1$ and $\boldsymbol{g}_2$ in Figure 1). In practice, it is difficult to directly maximize the mutual information between two random variables. Thus, we propose to maximize a lower-bound of the above mutual information, which in turn amounts to denoising a geometric structure. Moreover, directly denoising such noisy coordinates, nevertheless, remains challenging because one may need to effectively constrain the pairwise atomic distances while changing the atomic coordinates. To cope with this obstacle, we further leverage an SE(3)-invariant score matching method to successfully transform the coordinate denoising desire to the denoising of pairwise atomic distances, which then can be effectively computed. In other words, our pretraining proxy task, namely mutual information maximization, effectively boils down to achieving an intuitive learning objective: denoising a molecule's pairwise atomic distances. We empirically verify, using 22 downstream geometric molecular prediction tasks, that our method outperforms nine pretraining baselines.

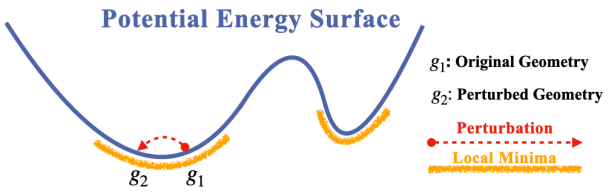

Figure 1: Illustration on coordinate geometry of molecules. The molecule is in a continuous motion, forming a potential energy surface (PES), where each 3D coordinate (x-axis) corresponds to an energy value (y-axis). The provided molecules, *i.e.*, conformers, are in the local minima ($\boldsymbol{g}_1$). It often comes with noises around the minima (*e.g.*, statistical and systematic errors or vibrations), which can be captured using the perturbed geometry ($\boldsymbol{g}_2$).

Our main contributions are summarized as follows. (1) We propose a novel coordinate denoising method for molecular geometry pretraining, which to the best of our knowledge is the first to only utilize 3D molecular data for pretraining. (2) To overcome the challenge of attaining the coordinate denoising objective, we introduce an SE(3)-invariant score matching strategy to successfully transform such objective into the denoising of pairwise atomic distances, which can be effectively computed. (3) We empirically demonstrate the effectiveness and robustness of our proposed method, GeoSSL.

2 Related Work

2.1 Equivariant Geometric Molecule Representation Learning

Geometric representation learning. Recently, 3D geometric representation learning has been widely explored in the machine learning community, including but not limited to 3D point clouds [7, 40, 51, 63], N-body particle [41, 43], and 3D molecular conformation [5, 30, 31, 37, 46, 47, 52], amongst many others. The learned representation should satisfy the physical constraints, *e.g.*, it should be equivariant to the transition on the Euclidean space. Such constraints can be depicted with the group symmetry as introduced below.

SE(3)-invariant energy. Constrained by the physical nature of 3D data, a key principle we need to follow is to learn an SE(3)-equivariant representation function. The SE(3) is the special Euclidean group consisting of rigid transformations in the 3D Cartesian space, where the transformations include all the combinations of translations and rotations. Namely, the learned representation should be equivariant to translations and rotations for molecule geometries. We also note that for some specific tasks like molecular chirality [1], the representation needlessly satisfy the reflection equivariance. For more rigorous discussion, please check [16, 18, 61]. In this work, we will design an SE(3)-invariant energy function based on an SE(3)-equivariant representation backbone model.

2.2 Self-Supervised Learning for Molecule Representation Learning

In general, there are two categories of self-supervised learning (SSL) [36, 38, 67, 68]: contrastive and generative, and the main difference is if the supervised signals are constructed in an inter-data or intra-data manner. Contrastive SSL extracts two views from the data and designs the supervised

signals by detecting if the sampled view pairs are from the same data, and generative SSL learns structural information by reconstructing partial information from the data itself.

2D molecular graph (topology) self-supervised learning. One of the mainstream research lines for molecule pretraining is on the 2D molecular graph. It treats the molecules as 2D graphs, where atoms and bonds are nodes and edges respectively. It then carries out a pretraining task by either detecting if the two augmentations (*e.g.*, neighborhood extraction, node dropping, edge dropping, etc) correspond to the same molecular graph [27, 59, 71] or if the representation can successfully reconstruct certain substructures of the molecular graphs [27, 28, 34].

3D molecular graph (geometry) self-supervised learning. As the increasing interest on the 3D geometric representation learning, there have been certain initial explorations [15, 35] involving the geometric SSL for molecules. GraphMVP [35] introduces an extra 2D topology and employs detection and reconstruction tasks simultaneously between 2D and 3D graphs, yet it focuses on 2D downstream tasks. ChemRL-GEM [15] designs a novel model using both the 2D and 3D molecular graphs. In terms of SSL, it utilizes the geometry information by taking the distance prediction and angle prediction as the generative pretraining tasks. Some of their geometric SSL tasks will be used as baselines in our work, yet we want to highlight that our work is focusing on the pure 3D geometric data without the covalent bonds (2D topology). To the best of our knowledge, our work is the first to explicitly do SSL on pure 3D geometry along the molecule representation learning research line.

3 PRELIMINARIES

Molecular geometry graph. Molecules can be naturally featured in a geometric formulation, *i.e.*, all the atoms are spatially located in 3D Euclidean space. Note that the covalent bonds are added heuristically by expert rules, so they are only applicable in 2D topology graph not 3D geometry graph. Besides, atoms are not static, but in a continual motion along a potential energy surface [2]. The 3D structures at the local minima on this surface are named *conformer*, as shown in Figure 1. Conformers at such equilibrium state possess nice properties and we would like to model them during pretraining.

Geometric neural network. We denote each conformer as $\boldsymbol{g} = (X, R)$. Here $X \in \mathbb{R}^{n\times d}$ is the atom attribute matrix and $R \in \mathbb{R}^{n\times 3}$ is the atom 3D-coordinate matrix, where n is the number of atoms and d is the feature dimension. The representations for the i-th node and whole molecule are:

$$h_i = \text{GNN-3D}(T(\boldsymbol{g}))_i = \text{GNN-3D}(T(X, R))_i, \qquad h = \text{READOUT}\big(h_0, \ldots, h_{n-1}\big), \tag{1}$$

where T is the transformation function like atom masking, and READOUT is the readout function. In this work, we take the mean over all the node representations as the readout function.

Energy-based model and denoising score matching. Energy-based model (EBM) is a flexible tool for modeling the underlying data distribution in the form of Gibbs distribution as $p_\theta(\boldsymbol{x}) = \exp(-E(\boldsymbol{x}))/A$, where $p_\theta(\boldsymbol{x})$ is the model distribution, A is the normalization constant and it is intractable due to the high cardinality of the data space. Recently, there has been various progress in solving this intractable function, including contrastive divergence [11], noise contrastive estimation [24], and score matching (SM) [29, 56, 57]. Specifically, SM solves this by introducing a concept called score: it is the gradient of the log-likelihood with respect to the data. SM then matches the model score and data score using Fisher divergence. Further along this research line, denoising score matching (DSM) [65] combines SM with denoising auto-encoding. The main advantage of DSM is that its solution is equivalent to SM yet with a computationally feasible and efficient solver. In this work, we will explore how DSM can be applied for molecule geometry representation learning by utilizing the distance information, one of the most fundamental factors in the geometric data.

Problem setup. Our goal here is to apply a self-supervised pretraining algorithm on a large molecular geometric dataset, and adapt the pretrained representation for fine-tuning on geometric downstream tasks. For both the pretraining and downstream tasks, only the 3D geometric information is available, and our solution is agnostic in terms of the backbone geometric neural network.

4 METHOD

This section introduces our proposed GeoSSL. We start with exploring the coordinate perturbation for molecular data in Section 4.1. Then we propose a coordinate-aware MI maximization formula

and turn it into a coordinate denoising problem in Section 4.2. Nevertheless, the coordinate denoising is non-trivial, since it requires the geometric data reconstruction, and we adopt the score matching for estimation, as introduced in Section 4.3. The ultimate training objective is discussed in Section 4.4.

4.1 Coordinate Perturbation for Geometric Data

The mainstream self-supervised learning community designs the pretraining task by defining multiple views from the data, and these views share common information to some degree. Thus, by designing generative or contrastive task to maximize the mutual information (MI) between these views, the pretrained representation can encode certain key information. This will make the representation more robust and can be more generalizable to downstream tasks. In our work, we propose GeoSSL, an SE(3)-invariant self-supervised learning (SSL) method for molecule geometric representation learning.

The 3D geometric information, or the atomic coordinates are critical to molecular properties. We carry out an additional ablation study to verify this in Appendix B. Then based on this acknowledgement, we propose a geometry perturbation, which adds small noises to the atom coordinates. For notation, following Section 3, we define the original geometry graph and an augmented geometry graph as two views, denoted as $\boldsymbol{g}_1 = (X_1, R_1)$ and $\boldsymbol{g}_2 = (X_2, R_2)$ respectively. The augmented geometry graph can be seen as a coordinate perturbation to the original graph with the same atom types, *i.e.*, $X_2 = X_1$ and $R_2 = R_1 + \epsilon$, where ϵ is drawn from a normal distribution.

4.2 Coordinate Denoising with Mutual Information Maximization

The two views defined above share certain common information. By maximizing the mutual information (MI) between them, we expect that the learned representation can better capture the geometric information and is robust to noises and thus can generalize well to the target downstream tasks. To maximize the MI, we turn to maximizing the following lower bound on the two geometry views:

$$I(G_1; G_2) = \mathbb{E}_{p(\boldsymbol{g}_1,\boldsymbol{g}_2)}\Big[\log \frac{p(\boldsymbol{g}_1,\boldsymbol{g}_2)}{p(\boldsymbol{g}_1)p(\boldsymbol{g}_2)}\Big] \geq \frac{1}{2}\mathbb{E}_{p(\boldsymbol{g}_1,\boldsymbol{g}_2)}\Big[\log p(\boldsymbol{g}_1|\boldsymbol{g}_2) + \log p(\boldsymbol{g}_2|\boldsymbol{g}_1)\Big] \triangleq \mathcal{L}_{\text{MI}}. \tag{2}$$

In Equation (2), we transform the MI maximization problem into maximizing the summation of two conditional log-likelihoods. In addition, these two conditional log-likelihoods are in the mirroring direction, and such symmetry can reveal certain nice properties, *e.g.*, it highlights the equal importance and uncertainty of the two views and can lead to a more robust representation of the geometry.

To solve Equation (2), we introduce the energy-based model (EBM) for estimation. EBM has been acknowledged as a flexible framework for its powerful usage in modeling distribution over highly-structured data, like molecules [26, 33]. To adapt it for MI maximization in our setting, the lower bound can be turned into:

$$\begin{aligned}\mathcal{L}_{\text{Coor-MI}} &= \frac{1}{2}\mathbb{E}_{p(\boldsymbol{g}_1,\boldsymbol{g}_2)}\Big[\log p(R_1|\boldsymbol{g}_2)\Big] + \frac{1}{2}\mathbb{E}_{p(\boldsymbol{g}_1,\boldsymbol{g}_2)}\Big[\log p(R_2|\boldsymbol{g}_1)\Big] \\ &= \frac{1}{2}\mathbb{E}_{p(\boldsymbol{g}_1,\boldsymbol{g}_2)}\Big[\log \frac{\exp(f(R_1,\boldsymbol{g}_2))}{A_{R_1|\boldsymbol{g}_2}}\Big] + \frac{1}{2}\mathbb{E}_{p(\boldsymbol{g}_2,\boldsymbol{g}_1)}\Big[\log \frac{\exp(f(R_2,\boldsymbol{g}_1))}{A_{R_2|\boldsymbol{g}_1}}\Big],\end{aligned} \tag{3}$$

where the $f(\cdot)$ are the negative of energy functions, and $A_{R_1|\boldsymbol{g}_2}$ and $A_{R_2|\boldsymbol{g}_1}$ are the intractable partition functions. The first equation in Equation (3) results from that the two views share the same atom types. This equation can be treated as denoising the atom coordinates of one view from the geometry of the other view. In the following, we will explore how to use the score matching for solving the above EBM, and further to transform the coordinate-aware mutual information maximization to the denoising distance matching as the final objective.

4.3 From Coordinate Denoising to Distance Denoising: GeoSSL

Before going into details, first we would like to briefly discuss the denoising score matching (DSM). DSM has three main advantages that inspire us to apply it for solving the coordinate-aware MI. (1) The DSM solution has a nice formulation, such that the final objective function can be simplified with an intuitive explanation: GeoSSL can be seen as solving the denoising pairwise distance at multiple noise levels. (2) The score defined in geometric data can be viewed as a coordinate-based pseudo-force. Such pseudo-force can play an important role for the corresponding geometric representation learning. (3) In terms of the MI maximization, existing methods like InfoNCE [64], EBM-NCE and Representation Reconstruction [35] map the data to the *representation* space for either inter-data

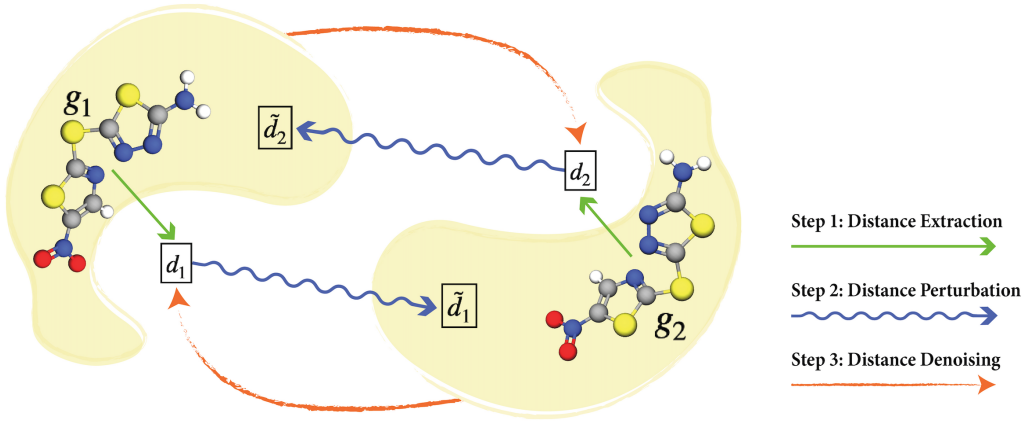

Figure 2: Pipeline for GeoSSL (GeoSSL). The $\boldsymbol{g}_1$ and $\boldsymbol{g}_2$ are around the same local minima, yet with coordinate noises perturbation. Originally we want to conduct coordinate denoising between these two views. Then as proposed in GeoSSL, we transform it to an equivalent problem, *i.e.*, distance denoising. This figure shows the three key steps: extract the distances from the two geometric views, then perform distance perturbation, and finally denoise the perturbed distances. Notice that the covalent bonds are added for illustration only.

contrastive learning or intra-data reconstruction. This operation can avoid the decoding design issue for highly-structured data [12], yet the trade-off is losing the data-inherent information by certain degree. In other words, the data-level reconstruction task (*e.g.*, DSM) is expected to lead to a more robust representation. Thus, by combining the above three points, we adopt DSM to our problem and propose GeoSSL. We expect that it is able to learn an expressive geometric representation function by solving coordinate-aware SSL task. In addition, the two terms in Equation (3) are in the mirroring direction. Thus in what follows, we may as well adopt a proxy task that these two directions can be calculated separately, and we take one direction for illustration, *e.g.*, $\log \frac{\exp(f(R_1,\boldsymbol{g}_2))}{A_{R_1|\boldsymbol{g}_2}}$.

4.3.1 Denoising Distance Matching

Score. The score is defined as the gradient of the log-likelihood w.r.t. the data, *i.e.*, the atom coordinates in our case. Because the normalization function is a constant w.r.t. the data, it will disappear during the score calculation. To adapt it into our setting, the score is obtained as the gradient of the negative energy function w.r.t. the atom coordinates, as:

$$s(R_1, \boldsymbol{g}_2) \triangleq \nabla_{R_1} \log p(R_1|\boldsymbol{g}_2) = \nabla_{R_1} f(R_1, \boldsymbol{g}_2). \tag{4}$$

If we assume that the learned optimal energy function, *i.e.*, $f(\cdot)$, possesses certain physical or chemical information, then the score in Equation (4) can be viewed as a special form of the pseudo-force. This may require more domain-specific knowledge, and we leave this for future exploration.

Score decomposition: from coordinates to distances. Through back-propagation [50], the score on atom coordinates can be further decomposed into the scores attached to pairwise distances:

$$s(R_1, \boldsymbol{g}_2)_i = \sum_{j \neq i} \frac{\partial f(R_1, \boldsymbol{g}_2)}{\partial d_{1,ij}} \cdot \frac{\partial d_{1,ij}}{\partial r_{1,i}} = \sum_{j \neq i} \frac{1}{d_{1,ij}} \cdot s(\boldsymbol{d}_1, \boldsymbol{g}_2)_{ij} \cdot (r_{1,i} - r_{1,j}), \tag{5}$$

where $s(\boldsymbol{d}_1, \boldsymbol{g}_2)_{ij} \triangleq \frac{\partial f(R_1, \boldsymbol{g}_2)}{\partial d_{1,ij}}$. Such decomposition has a nice underlying intuition from the pseudo-force perspective: the pseudo-force on each atom can be further decomposed as the summation of pseudo-forces attached to the pairwise distances between this atom and all its neighbors. Note that here the pairwise atoms are connected in the 3D Euclidean space, not by the covalent bonds.

Denoising distance matching (DDM). Then we adopt the denoising score matching (DSM) [65] to our task. To be more concrete, we take the Gaussian kernel as the perturbed noise distribution on each pairwise distance, *i.e.*, $q_\sigma(\tilde{\boldsymbol{d}}_1|\boldsymbol{g}_2) = \mathbb{E}_{p_{\text{data}}(\boldsymbol{d}_1|\boldsymbol{g}_2)}[q_\sigma(\tilde{\boldsymbol{d}}_1|\boldsymbol{d}_1)]$, where σ is the deviation in Gaussian perturbation. One main advantage of using the Gaussian kernel is that the following gradient of conditional log-likelihood has a closed-form formulation: $\nabla_{\tilde{\boldsymbol{d}}_1} \log q_\sigma(\tilde{\boldsymbol{d}}_1|\boldsymbol{d}_1, \boldsymbol{g}_2) = (\boldsymbol{d}_1 - \tilde{\boldsymbol{d}}_1)/\sigma^2$, and the objective function of DSM is to train a score network to match it. This trick was first introduced in [65], and has been widely utilized in the deep generative modeling tasks [54, 55].

To adapt to our setting, this is essentially saying that we want to train a "distance network", *i.e.*, $s_\theta(\tilde{\boldsymbol{d}}_1|\boldsymbol{g}_2)$, to match the distance perturbation, or we can say it aims at matching the pseudo-force with the pairwise distances from the pseudo-force aspect. By taking the Fisher divergence as the discrepancy metric and the trick mentioned above, the estimation objective can be simplified to

$$D_F(q_\sigma(\tilde{\boldsymbol{d}}_1|\boldsymbol{g}_2)||p_\theta(\tilde{\boldsymbol{d}}_1|\boldsymbol{g}_2)) = \frac{1}{2}\mathbb{E}_{p_{\text{data}}(\boldsymbol{d}_1|\boldsymbol{g}_2)}\mathbb{E}_{q_\sigma(\tilde{\boldsymbol{d}}_1|\boldsymbol{d}_1,\boldsymbol{g}_2)}\big[\|s_\theta(\tilde{\boldsymbol{d}}_1,\boldsymbol{g}_2) - \frac{\boldsymbol{d}_1-\tilde{\boldsymbol{d}}_1}{\sigma^2}\|^2\big] + C. \tag{6}$$

For more detailed derivations, please refer to Appendix C. In this section, we turn the coordinate-aware MI maximization problem into distance perturbation matching problem, which is equivalent to denoising distance matching. The corresponding pipeline is illustrated in Figure 2. This can also be explained intuitively. That is, we add the distance noise from $\boldsymbol{d}_1$ to $\tilde{\boldsymbol{d}}_1$ to mimic the coordinate noise between $\boldsymbol{g}_2$ and $\boldsymbol{g}_1$, and conduct the denoising distance matching from $\boldsymbol{g}_2$ and $\tilde{\boldsymbol{d}}_1$ to denoise $\boldsymbol{d}_1$.

4.3.2 SE(3)-Invariant Distance Network Modeling

To solve Equation (6), the key step is to design an SE(3)-invariant distance network. For modeling, we take an SE(3)-equivariant 3D geometric graph neural network as the geometric representation backbone model, *i.e.*, the $h(\cdot)$. Following the notations in Section 3 and $\boldsymbol{g}_2$ modeling, we can have

$$h(\boldsymbol{g}_2)_i = \text{3D-GNN}(T(\boldsymbol{g}_2)), \qquad h(\boldsymbol{g}_2)_{ij} = h(\boldsymbol{g}_2)_i + h(\boldsymbol{g}_2)_j, \tag{7}$$

for the atom-level and atom pairwise-level representation respectively. Based on the pairwise representation, we define the distance network as:

$$s_\theta(\tilde{\boldsymbol{d}}_1,\boldsymbol{g}_2)_{ij} = \text{MLP}\big(\text{MLP}(\tilde{\boldsymbol{d}}_{1,ij}) \oplus h(\boldsymbol{g}_2)_{ij}\big), \tag{8}$$

where $\oplus$ is the concatenation and MLP is the multi-layer perceptron. Because the backbone model satisfies SE(3)-equivariance and the distance network in Equation (8) is based on the pairwise distance and SE(3)-equivariant representation, our proposed GeoSSL pretraining is SE(3)-invariant [18].

4.4 Ultimate Objective

With the above distance network modeling, we can formulate the ultimate objective function. We further adopt the following four training tricks from [35, 54, 55] to stabilize the score matching training process. (1) We carry out the distance denoising at L-level of noises. (2) We add a weighting coefficient $\lambda(\sigma) = \sigma^\beta$ for each noise level, where β acts as the annealing factor. (3) We scale the score network by a factor of $1/\sigma$. (4) We sample the exactly same atoms from the two geometry views with a masking ratio r. Finally, by considering the two directions and all the above tricks, the objective function for GeoSSL is as follows:

$$\begin{aligned}\mathcal{L}_{\text{GeoSSL}} =& \frac{1}{2L}\sum_{l=1}^{L}\sigma_l^\beta \mathbb{E}_{p_{\text{data}}(\boldsymbol{d}_1|\boldsymbol{g}_2)}\mathbb{E}_{q(\tilde{\boldsymbol{d}}_1|\boldsymbol{d}_1,\boldsymbol{g}_2)}\left[\left\|\frac{s_\theta(\tilde{\boldsymbol{d}}_1,\boldsymbol{g}_2)}{\sigma_l} - \frac{\boldsymbol{d}_1-\tilde{\boldsymbol{d}}_1}{\sigma_l^2}\right\|_2^2\right] \\ &+ \frac{1}{2L}\sum_{l=1}^{L}\sigma_l^\beta \mathbb{E}_{p_{\text{data}}(\boldsymbol{d}_2|\boldsymbol{g}_1)}\mathbb{E}_{q(\tilde{\boldsymbol{d}}_2|\boldsymbol{d}_2,\boldsymbol{g}_1)}\left[\left\|\frac{s_\theta(\tilde{\boldsymbol{d}}_2,\boldsymbol{g}_1)}{\sigma_l} - \frac{\boldsymbol{d}_2-\tilde{\boldsymbol{d}}_2}{\sigma_l^2}\right\|_2^2\right].\end{aligned} \tag{9}$$

The algorithm is in Algorithm 1.

Algorithm 1 GeoSSL pretraining

Input: A 3D geometry dataset and L levels of Gaussian noise.
Output: A pre-trained 3D representation function $h(\cdot)$.
for each 3D geometry graph $\boldsymbol{g}_1$ **do**
  Obtain its perturbed geometry graph $\boldsymbol{g}_2$.
  for each noise level $l \in \{1, ..., L\}$ **do**
    Add noise to the pairwise distance with $\tilde{\boldsymbol{d}}_1 = \boldsymbol{d}_1 + \sigma_l, \tilde{\boldsymbol{d}}_2 = \boldsymbol{d}_2 + \sigma_l$.
    Get the score $s_\theta(\tilde{\boldsymbol{d}}_1, \boldsymbol{g}_2), s_\theta(\tilde{\boldsymbol{d}}_2, \boldsymbol{g}_1)$ with Equation (8) accordingly.
  end for
  Update 3D GNN representation function $h(\cdot)$ using Equation (9).
end for

Comparison with score matching in generative modeling. We note that score matching has been widely used for generative modeling task. One of the main drawbacks in the generative setting is the long mixing time for MCMC sampling. However, our work aims at representation learning, so the sampling issue won't affect our task. We further note that there also exists a series of work exploring the score matching for conformation generation [50]. However, their scores or pseudo-forces are attached to the 2D topology (the covalent bonds), while our work is based on the pairwise distances from the geometric coordinates only.

5 EXPERIMENTS

In this section, we compare our method with nine 3D geometric pretraining baselines, including one randomly-initialized, one supervised, and seven self-supervised approaches. For the downstream tasks, we adopt 22 tasks covering quantum mechanics prediction, force prediction, and binding affinity prediction. We provide all the experiment details and ablation studies in Appendix D.

5.1 BACKBONE MODELS

Our proposed GeoSSL is model-agnostic, and here we evaluate our method using one of the state-of-the-art geometric graph neural networks, PaiNN [47]. We carry out the exactly same experiments on another backbone model, SchNet [45], and results are in in Appendix D due to space limit.

PaiNN [47] is a follow-up work of SchNet [45]. It addresses the limitation of rotational equivariance in SchNet by embracing rotational invariance, attaining a more expressive 3D geometric model.

Other backbone models. First we want to highlight that what we propose is a general solution and is agnostic to the backbone 3D geometric models. And in addition to the PaiNN, we want to acknowledge that there are more recent progress in this research line, including but not limited to [5, 16, 16, 31, 37, 43, 52]. Yet, they may require large computation resources and may be infeasible (*e.g.*, out of GPU memory) in our setting. The decision is made by considering the model performance, computation efficiency, and memory cost. For more benchmark results and detailed comparisons of the 3D geometric models, please check Appendix A.

5.2 BASELINES AND PRETRAINING DATASET

Pretraining dataset. The PubChemQC database is a large-scale database with around 4M molecules with 3D geometries, and it calculates both the ground-state and excited-state 3D geometries using DFT (density functional theory). Due to the high computational cost, only several thousand molecules can be processed every day, and this dataset takes years of efforts in total. Following this, Molecule3D [69] takes the ground-state geometries and transforms the data formats into a deep learning-friendly way. It also parses essential quantum properties for each molecule, including energies of the highest occupied molecular orbital (HOMO) and the lowest occupied molecular orbital (LUMO), the energy gap between HOMO-LUMO, and the total energy. For our molecular geometry pretraining, we take a subset of 1M molecules with 3D geometries from Molecule3D.

Self-supervised learning pretraining baselines. We first consider the four coordinate-MI-unaware SSL methods: (1) *Type Prediction* is to predict the atom type of masked atoms; (2) *Distance Prediction* aims to predict the pairwise distances among atoms; (3) *Angle Prediction* is to predict the angle among triplet atoms, *i.e.*, the bond angle prediction; (4) *3D InfoGraph* adopts the contrastive learning paradigm by taking the node-graph pair from the same molecule geometry as positive and negative otherwise. Next, following the coordinate-aware MI maximization framework introduced in Equation (2), we include two contrastive and one generative SSL baselines. (5) InfoNCE [64] and (6) EBM-NCE [35] are the two widely-used contrastive learning loss functions, where the goal is to simultaneously align the positive views and contrast the negative views. Finally, (7) Representation Reconstruction (RR) [35] is a generative SSL that is proxy to maximize the MI. It is a more general form of non-contrastive SSL methods like BOYL [22] and SimSiam [8], and the goal is to reconstruct each view from its counterpart in the representation space. Following this, our proposed GeoSSL can be classified as generative SSL, yet it aims at denoising the pairwise distances instead.

Supervised pretraining baseline. We also compare our method with a supervised pretraining baseline. As aforementioned, the large-scale pretraining dataset uses the DFT to calculate the energy, and extracts the most stable conformers with the lowest energies, which reveal the most fundamental properties of molecules in the 3D Euclidean space. Thus, such energies can be naturally adopted as the supervised signals, and we take this as a supervised pretraining baseline.

5.3 DOWNSTREAM TASKS ON QUANTUM MECHANICS AND FORCE PREDICTION

QM9 [42] is a dataset of 134K molecules consisting of 9 heavy atoms. It includes 12 tasks that are related to the quantum properties. For example, U0 and U298 are the internal energies at 0K at 0K and 298.15K respectively, and U298 and G298 are the other two energies that can be transferred from

Table 1: Downstream results on 12 quantum mechanics prediction tasks from QM9. We take 110K for training, 10K for validation, and 11K for test. The evaluation is mean absolute error, and the best results are in **bold**.

Pretraining	Alpha ↓	Gap ↓	HOMO↓	LUMO ↓	Mu ↓	Cv ↓	G298 ↓	H298 ↓	R2 ↓	U298 ↓	U0 ↓	Zpve ↓
–	0.048	44.50	26.00	21.11	0.016	0.025	8.31	7.67	0.132	7.77	7.89	1.322
Supervised	0.049	45.33	26.61	21.77	0.016	0.026	8.97	8.59	0.170	8.35	8.19	1.346
Type Prediction	0.050	47.28	30.56	23.18	0.016	**0.024**	9.32	9.10	0.163	8.94	8.60	1.357
Distance Prediction	0.063	47.62	29.18	22.40	0.019	0.045	12.02	12.31	0.636	11.76	12.22	1.840
Angle Prediction	0.056	47.36	29.53	22.61	0.018	0.027	10.23	10.13	0.143	9.95	9.70	1.643
3D InfoGraph	0.053	44.79	27.09	21.66	0.016	0.027	9.22	8.78	0.143	8.94	9.11	1.465
RR	0.048	44.85	25.42	20.82	**0.015**	0.025	8.56	8.20	0.133	7.89	7.62	1.329
InfoNCE	0.052	45.65	26.70	21.87	0.016	0.027	9.17	9.62	0.130	8.77	8.63	1.519
EBM-NCE	0.049	44.18	26.29	21.46	**0.015**	0.026	8.56	8.13	0.126	8.01	7.96	1.447
GeoSSL (ours)	**0.046**	**40.22**	**23.48**	**19.42**	**0.015**	**0.024**	**7.65**	**7.09**	**0.122**	**6.99**	**6.92**	**1.307**

Table 2: Downstream results on 8 force prediction tasks from MD17. We take 1K for training, 1K for validation, and the number of molecules for test are varied among different tasks, ranging from 48K to 991K. The evaluation is mean absolute error, and the best results are in **bold**.

Pretraining	Aspirin ↓	Benzene ↓	Ethanol ↓	Malonaldehyde ↓	Naphthalene ↓	Salicylic ↓	Toluene ↓	Uracil ↓
–	0.556	0.052	0.213	0.338	0.138	0.288	0.155	0.194
Supervised	0.478	0.145	0.318	0.434	0.460	0.527	0.251	0.404
Type Prediction	1.656	0.349	0.414	0.886	1.684	1.807	0.660	1.020
Distance Prediction	1.434	0.090	0.378	1.017	0.631	1.569	0.350	0.415
Angle Prediction	0.839	0.105	0.337	0.517	0.772	0.931	0.274	0.676
3D InfoGraph	0.844	0.114	0.344	0.741	1.062	0.945	0.373	0.812
RR	0.502	0.052	0.219	0.334	0.130	0.312	0.152	0.192
InfoNCE	0.881	0.066	0.275	0.550	0.356	0.607	0.186	0.559
EBM-NCE	0.598	0.073	0.237	0.518	0.246	0.416	0.178	0.475
GeoSSL (ours)	**0.453**	**0.051**	**0.166**	**0.288**	**0.129**	**0.266**	**0.122**	**0.183**

H298 respectively. The other 8 tasks are quantum mechanics related to the DFT process. MD17 [9] is a dataset on molecular dynamics simulation. It includes eight tasks, corresponding to eight organic molecules, and each task includes the molecule positions along the potential energy surface (PES), as shown in Figure 1. The goal is to predict the energy-conserving interatomic forces for each atom in each molecule position. We follow the literature [30, 37, 46, 47] of using 1K for training and 1K for validation, while the test set (from 48K to 991K) is much larger.

The results on QM9 and MD17 are displayed in Tables 1 and 2 respectively. From Tables 1 and 2, we can observe that most the pretraining baselines tested perform on par with or even worse than the randomly-initialized baseline. The top performing baseline is the representation reconstruction method (RR), which optimizes the coordinate-aware MI; it outperforms the other baselines on 5 out of 12 tasks in QM9 and 6 out of 8 tasks in MD17. This implies the potential of applying generative SSL for maximizing this coordinate-aware MI. Promisingly, our proposed GeoSSL achieves consistently improved performance on all the 12 tasks in QM9 and 8 tasks in MD17. All these observations empirically verify the effectiveness of the distance denoising in GeoSSL, which models the most determinant factor in molecule geometric data.

5.4 Downstream Tasks on Binding Affinity Prediction

Atom3D [62] is a recently published dataset. It gathers several core tasks for 3D molecules, including binding affinity. The binding affinity prediction is to measure the strength of binding interaction between a small molecule to the target protein. Here we will model both the small molecule and protein with their 3D atom coordinates provided. We follow Atom3D in data preprocessing and data splitting. For more detailed discussions and statistics, please check Appendix D.

During the binding process, there is a cavity in a protein that can potentially possess suitable properties for binding a small molecule (ligand), and it is termed a pocking [58]. Because of the large volume of the protein, we follow [62] by only taking the binding pocket, where there are no more than 600 atoms for each molecule and protein pair. To be more concrete, we consider two binding affinity tasks. (1) The first task is ligand binding affinity (LBA). It is gathered from [66] and the task is to predict the binding affinity strength between a small molecule and a protein pocket. (2) The second task is ligand efficacy prediction (LEP). The input is a ligand and both the active and inactive conformers of a protein, and the goal is to predict whether or not the ligand can activate the protein's function.

Results in Table 3 illustrate that, for the LBA task, two pretraining baseline methods fail to generalize to LBA (the loss gets too large), and all the other pretraining baselines cannot beat the randomly-initialized baseline. For the LEP task, the supervised and two contrastive learning pretraining

Table 3: Downstream results on 2 binding affinity tasks. We select three evaluation metrics for LBA: the root mean squared error (RMSD), the Pearson correlation (R_p) and the Spearman correlation (R_S). LEP is a binary classification task, and we use the area under the curve for receiver operating characteristics (ROC) and precision-recall (PR) for evaluation. We run cross validation with 5 seeds, and the best results are in **bold**.

Pretraining	LBA			LEP	
	RMSD ↓	R_P ↑	R_C ↑	ROC ↑	PR ↑
–	1.463 ± 0.06	0.572 ± 0.02	0.568 ± 0.02	0.675 ± 0.04	0.549 ± 0.05
Supervised	1.551 ± 0.08	0.539 ± 0.03	0.533 ± 0.03	0.696 ± 0.03	0.554 ± 0.03
Charge Prediction	2.316 ± 0.80	0.387 ± 0.11	0.400 ± 0.11	0.630 ± 0.05	0.557 ± 0.07
Distance Prediction	1.542 ± 0.08	0.545 ± 0.03	0.540 ± 0.03	0.521 ± 0.07	0.479 ± 0.07
Angle Prediction	–	–	–	0.545 ± 0.07	0.504 ± 0.07
3D InfoGraph	–	–	–	0.540 ± 0.03	0.469 ± 0.03
RR	1.515 ± 0.07	0.545 ± 0.03	0.539 ± 0.03	0.654 ± 0.05	0.518 ± 0.06
InfoNCE	1.564 ± 0.05	0.508 ± 0.03	0.497 ± 0.05	0.693 ± 0.06	0.571 ± 0.08
EBM-NCE	1.499 ± 0.06	0.547 ± 0.03	0.534 ± 0.03	0.691 ± 0.05	0.603 ± 0.07
GeoSSL (ours)	**1.451 ± 0.03**	**0.577 ± 0.02**	**0.572 ± 0.01**	**0.776 ± 0.03**	**0.694 ± 0.06**

baselines stand out for both ROC and PR metrics. Meaningfully, for both tasks, GeoSSL is able to achieve promising improvement, revealing that modeling the local region around conformer with distance denoising can also benefit for binding affinity downstream tasks.

5.5 Discussion: Connection with Multi-task Pretraining

In the above experiments, we test multiple self-supervised and supervised pretraining tasks separately. Yet, all these pretraining methods are not contradict, but could be complementary instead. Existing work has successfully shown the effect of combining them in various ways. For example, [27] shows that jointly doing supervised and self-supervised pretraining can augment the pretrained representation. [35, 53] prove that contrastive and generative SSL pretraining methods can be learned simultaneously as a multi-task pretraining. In addition, in terms of the molecule-specific pretraining, [35] empirically verifies that 2D topology and 3D geometry views can share certain information, and maximizing their mutual information together with 2D topology SSL for pretraining is beneficial.

With these insights, we would like to claim that all of these points are worth exploration in the future, especially in the line of pretraining for molecular geometry. Because pretraining datasets often come with multiple quantum properties and the 2D molecular topology can be obtained heuristically. Yet as the first step to explore the self-supervised learning using only the 3D geometric data (*i.e.*, without covalent bonds), our study here would like to leave multi-task pretraining for future exploration.

6 Conclusions and Future Directions

We proposed a novel coordinate denoising method, coined GeoSSL, for molecular geometry pretraining. GeoSSL leverages an SE(3)-invariant score matching strategy, under the energy-based model (EBM) framework, to successfully decompose its coordinate denoising objective into the denoising of pairwise atomic distances in a molecule, which then can be effectively computed and directly target the determinant factors in molecular geometric data. We empirically verified the effectiveness and robustness of our method, showing its superior performance to nine state-of-the-art pretraining baselines on 22 benchmarking geometric molecular property prediction and binding affinity tasks.

Our work here opens up venues for multiple promising directions. First from the machine learning perspective, we propose a general pipeline on using EBM for MI maximization on geometric data pretraining. Yet, there are more explorations on the success of EBM, like GFlowNet [3], and it would be interesting to explore how to combine it with molecular geometric data along this systematic path. In addition, GeoSSL does not utilize the 2D structure (*i.e.*, covalent bonds for molecules), and it would be desirable to consider how to utilize the distance denoising together with the 2D topology information.

In terms of applications, our proposed GeoSSL is a general framework, and it can be naturally applied to other geometric data, such as point clouds and protein pretraining. In addition, our current goal is to perform denoising in the local region, yet it would be interesting to explore larger regions. From this aspect, the denoising can be viewed as recovering the molecular dynamics trajectory, and we would explore how generalizable this pretrained representation is to the downstream tasks.

ETHICS STATEMENT

We authors acknowledge that we have read and commit to adhering to the ICLR Code of Ethics.

REPRODUCIBILITY STATEMENT

To ensure the reproducibility of the empirical results, we provide the implementation details (hyperparameters, dataset statistics, etc.) in Section 5 and appendix D, and the source code will be released in the future. Besides, the complete derivations of equations and clear explanations are given in Section 4 and appendix C.

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