Geometry-aware Transformer for molecular property prediction

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Abstract

Recently, graph neural networks (GNNs) have achieved remarkable performances for quantum mechanical problems. However, a graph convolution can only cover a localized region, and cannot capture long-range interactions of atoms. This behavior is contrary to theoretical interatomic potentials, which is a fundamental limitation of the spatial based GNNs. In this work, we propose a novel attention-based framework for molecular property prediction tasks. We represent a molecular conformation as a discrete atomic sequence combined by atom-atom distance attributes, named Geometry-aware Transformer (GeoT). In particular, we adopt a Transformer architecture, which has been widely used for sequential data. Our proposed model trains sequential representations of molecular graphs based on globally constructed attentions, maintaining all spatial arrangements of atom pairs. Our method does not suffer from cost intensive computations, such as angle calculations. The experimental results on several public benchmarks and visualization maps verified that keeping the long-range interatomic attributes can significantly improve the model predictability.

1 Introduction

Quantum mechanical (QM) calculations have been used for development of chemicals in various fields, such as drugs, catalysts, or novel industrial materials. Density functional theory (DFT) is the most widely used computational modelling method used for modern QM research. However, DFT requires tremendous computations to predict properties for a small molecule.

For this reason, several machine learning-based methods have been developed to replace DFT calculation with more cost-effective alternatives [1, 2, 3, 4]. Motivated by recent advances in deep
learning, many recent models adopted deep learning-based methods to predict various molecular properties including energy and forces.

However, the exact QM modelling is still challenging because most of the QM properties are determined by complex intramolecular interactions of various factors. Moreover, subtle local variations may cause significant changes in QM properties of the whole molecule. It means that QM based models should predict subsequent effects from a slight perturbation of molecular structures. Therefore, training accurate and precise prediction models for molecular properties without DFT is not trivial.

Message passing neural network (MPNN) [5] is one of the most widely used frameworks for graph neural networks (GNNs) in recent days. In these kinds of works, a molecule is described as a graph, and its atoms are represented as discrete nodes scattered in Euclidean space. These models do not consider any bond type information. Instead, they construct edges between all node pairs located within the fixed cutoff distance from each other. Then, the message passing layers do a graph convolution with each atom and its local substructures (messages) which are controlled by radial basis filters. Many atomistic models based on MPNN showed competitive performances in various QM tasks.

Although promising performances on existing MPNNs, there are several fundamental limitations in the localization-based approaches. In theory, every atom pair in a molecule has their own quantum mechanical interaction defined by their charges and distance. In other words, atom-atom interactions ranges far from the source. Therefore, all atom-atom interactions should be considered properly in molecular property prediction models regardless of their distances.

However, the localized convolution-based approaches conflict with the conformational behavior of molecules. Basically, MPNN assumes that messages are transferred within a restricted region. As a result, these models need a fixed cutoff value, which limits the receptive field of the model. It means that an MPNN with a finite cutoff value cannot identify any interatomic relationship between atom pairs located outside the cutoff distance from each other. Consequently, MPNNs fail to capture long-range interatomic relationships, which is not a desired property in the tasks on molecules.

Furthermore, the MPNN models are vulnerable to over-smoothing problem, which is caused by over-mixing of localized features especially in a deep architecture. The atom features cannot be distinguished from each other, because the message-passing updates an atom feature with its neighboring features in every step.

To address these issues, we developed an attention-based model to predict molecular properties based on molecular conformation. In particular, we adopted the Transformer [6] architecture, which comprises successive self-attention layers for sequential data. To represent a molecular graph as a sequence without losing geometric attributes, we replaced an original distance encoding in the Transformer by trainable radial basis embeddings in the initial step. We removed the positional encoding of the original Transformer, and implemented a novel distance encoding with radial basis. The self-attention is calculated from atom sequences of each molecule in each encoding layer during the training.

Note that we do not use either message passing framework or graph convolution in our method. Therefore, our proposed model can capture the global perspective of a molecular conformation without any local restriction. In addition, our method is free from over-smoothing problems regardless of the model depth, because our model does not aggregate features in the training process. Finally, our model does not need explicit angle values obtained by intensive computations in several existing works. Our model showed comparable performances with recent MPNN models on the several public benchmarks. We also validate that our model can identify long-range interatomic relationships with attention maps.

To the best of our knowledge, it is the first model to predict molecular properties from the molecular conformation with Transformer architectures incorporating radial basis embeddings for rich representation of geometric measurements. Our model is more scalable than previous MPNN models, because it does not need extra attributes, or cost-intensive computations to represent Euclidean geometries. Finally, the performances are comparable to most recent MPNN models on the various benchmarks. The visualized attention maps validated that the visual fields of our model are globally distributed, and not restricted to local regions.
2 Related Works

2.1 Graph neural networks for molecules

The molecular representation as a graph has been widely used from early stages. These methods regard a molecule as a graph consisting of discrete atom nodes with bonds as edges. BPNN [3] is the first neural network model which calculates energy from molecular graphs. The first work using graph convolution on molecules [7] trained each atom representation with localized filters. GDML [8, 9, 10] used conservative force fields of each atom, and MPNN [5] proposed message passing framework for local update of each atom representation in the network.

SchNet [11], PhysNet [12] and several MPNN-based models constructed localized messages centered on atoms with continuous filters based on interatomic distances. More recent works as DimeNet [13, 14] compute angles to describe molecular conformations more concretely. Some works like TFN [15], Cormorant [16], and SE(3)-Transformer [17] adopt group equivariances in their models to preserve roto-translational symmetry. These previous models need a cutoff value in common, which restricts the receptive field of an atom-wise convolution.

2.2 Self-attention and Transformer on molecules

The self-attention has been widely adopted for training sequential data, because it can capture similarities between two component from the sequence. Transformer [6] is the architecture with a stack of self-attention layers, to efficiently learn sequential data such as sentences regardless of their lengths.

For molecular property prediction tasks, self-attention or Transformer are mostly adopted for sequential representation of molecules such as SMILES [18], MAT [19] and GRAT [20] used a self-attention on molecular graphs, whereas the distance representations between atom pairs of their model were incomplete to capture long-range interactions.

3 Preliminary

3.1 Notation

We denote atoms charges \( \{z_i\} \in \mathbb{R} \) and its coordinates \( \{r_i\} \in \mathbb{R}^3 \) of \( i \)th atom (1 \( \leq i \leq |V| \)) of a molecule consisting of \( |V| \) atoms. We calculated the Euclidean distance \( d_{ij} = \|r_i - r_j\|_2 \) between atom \( i \) and \( j \). We represent an embedding vector of \( z_i \) as \( x_i^0 \in \mathbb{R}^{d_e} \).

3.2 Transformer encoder

For given set of \( N \) sequences \( x \in \mathbb{R}^{N \times d_e} \), self-attention calculates output \( \tilde{x}_i \) by aggregating other vectors using weight called attention, which represents cosine similarity between target vector \( x_j \) and reference vector \( x_i \).

The standard Transformer encoder [6] is a stack of multiple self-attention layers. Each layer updates sequence representations based on their similarities. In particular, they first calculate multi head self-attention for each vectors, then applied layer normalization [21] to output with residual connection [22].

3.2.1 Self-attention

In this layer, the input representations are represented as three components: query \( q \), key \( k \), and vector \( v \). For given set of vectors \( \{x_i\} \in \mathbb{R}^{d_e} \), \( q \), \( k \), and \( v \) are obtained by multiplication of trainable weight matrices \( (W_Q, W_K, W_V \in \mathbb{R}^{d_e \times d_m}) \).

\[
\begin{align*}
    v_i &= W_V x_i, \\
    q_i &= W_Q x_i, \\
    k_i &= W_K x_i
\end{align*}
\]
The self-attention of $x$ is obtained by dot product of corresponding $q$ and $k$.

$$a_{ij} = q_j \cdot k_i / \sqrt{d_k}$$
$$Attn(x_i, x_j) = \text{softmax}(a_{ij})$$ (2)

The output vector of $i$th atom’s representation from self-attention $\bar{x}_i$ is given by sum all multiplications between attention and value vectors.

$$f_{attn}(x_i) = \sum_{j=1}^{C} Attn(x_i, x_j) \cdot v_j$$ (3)

### 3.2.2 Multi head attention

Multi head attention (MHA) [6] was proposed to build more rich representations instead of using single self-attention only. For MHA, original query, key and value vectors are split into $h$ vectors
We utilized radial basis functions
\[
\text{concat}(v_{i,1}, v_{i,2}, \ldots, v_{i,h}) = W_V x_i \\
\text{concat}(q_{i,1}, q_{i,2}, \ldots, q_{i,h}) = W_Q x_i \\
\text{concat}(k_{i,1}, k_{i,2}, \ldots, k_{i,h}) = W_K x_i
\] (4)
with dimension \(d_k/h\).

\[
\alpha_{ij,m} = q_{i,m} \cdot k_{i,m}/\sqrt{d_k/h}
\]
\[
\text{Attn}_{MHA}(x_{i,m}, x_{j,m}) = \text{softmax}(\alpha_{ij,m})
\] (5)
Then attentions for each vectors are calculated individually and reshaped back into \(d_k\) dimension after calculation.

\[
f_{MHA}(x_i) = \text{concat}(\sum_{j=1}^{h} \text{Attn}_{MHA}(x_{i,m}, x_{j,m}) \cdot v_{j,m})_{m=1,2,...,h}
\] (6)

### 3.2.3 Transformer encoder layer
The Transformer encoder of our model consists of \(N\) consecutive blocks for inputs. Each transformer encoder layer repeatedly executes self-attention followed by layer normalization.

Each \(n\)th Transformer encoder layer’s output for \(i\)th atom \(x_i^n\) with dimension \(d_e\) fed into next layer, especially for first layer \(x_i^0\) is given from embedding.

In the Transformer encoder layer, the output from multi head self-attention \(f_{MHA}(x_i^{n-1})\) added to original input \(x_i^{n-1}\) by residual connection accompanied by layer normalization. After that, the last output \(\tilde{x}_i^n\) fed into feed forward network \((FFN)\), consisting of two linear transformations with a ELU \([23]\) activation, connected with hidden dimension \(d_h\).

\[
\tilde{x}_i^n = \text{LayerNorm}(f_{MHA}(x_i^n) + x_i^n)
\]
\[
x_i^{n+1} = \text{LayerNorm}(FFN(\tilde{x}_i^n) + \tilde{x}_i^n)
\] (7)

### 4 Geometry-aware Transformer
We introduced the Geometry-aware Transformer architecture to solve chemical property prediction problem with capturing long range interaction. Geometry-aware Transformer is built based on Transformer encoder, which modified to capture distance information in every layer.

Geometry-aware Transformers adopt distance information expanded by multiple RBFs. The expanded vectors from RBFs are aggregated with query and key vector in self-attention block. Therefore, attention is the cosine similarities between query and key, multiplied by the expanded vectors. The final readout layer produces predicted labels.

#### 4.1 Radial basis function
We utilized radial basis functions \(rbf(d_{ij}) : \mathbb{R} \rightarrow \mathbb{R}^{d_m}\) for training representations of the distances between atom pairs. Many previous studies suggested different types of radial basis functions for these distances \([11, 12, 14, 16]\). We selected \(n_{basis}\) type of different Gaussian basis functions for RBF, proposed in SchNet \([11]\). The formula are denoted as below, where \(\gamma_k = 10\) adjust the scales of distance representations.

\[
g_k(d_{ij}) = \exp(-\gamma_k |d_{ij} - \mu_k|^2), \quad 1 \leq k \leq n_{basis}
\] (8)
After that, we combined multiple types of these Gaussian functions by concatenation. We applied two multilayer perceptron (MLP) layers, with the hidden dimension and output dimension of \(d_{rbf}\) and \(d_m\), respectively. The RBFs were created in each layer, and trained individually.

\[
rbf_n(d_{ij}) = f_{MLP,2}(f_{MLP,1}([g_1(d_{ij})||g_2(d_{ij})||\ldots||g_{n_{basis}}(d_{ij})])) \in \mathbb{R}^{d_m}
\] (9)
4.2 Geometry-aware self-attention

Note that, we did not use the standard self-attention in our model. Our Geometry-aware self-attention is different from the standard self-attention in two points: 1) inserting distance representations and 2) the absence of softmax operation. In details, we replaced attention in Eq. 5 with geometry-aware attention, by introducing RBF from Eq. 9 to capture interactions between atoms.

\[
\text{Attn}_{geo,m}(x^n_i, x^n_j) = q^n_{i,m} \cdot (k^n_{i,m} \odot rbf_n(d_{ij}))/\sqrt{d_k}
\]  \hspace{1cm} (10)

4.3 Readout layer

We introduced a pooling layer at the final step, to obtain molecular properties by aggregating atom features. We applied sum-pooling and a linear layer to get the final scalar-valued predictions.

\[
\hat{y} = W_{pool} \sum_{i=1}^{n} v^n_i + b, \quad W_{pool} \in \mathbb{R}^{d_m \cdot 1}
\]  \hspace{1cm} (11)

5 Dataset

We evaluated our model on two benchmark datasets QM9 [24, 25] and MD17 [8, 9, 10]. QM9 consists of 134k small organic molecules made up of carbon, hydrogen, nitrogen, oxygen, and fluorine in equilibrium state. All molecular conformations and their corresponding properties were created by computational simulation based on DFT calculation. Dataset contains each molecule’s stable three-dimensional coordinate and 12 scalar quantum chemical properties consist of geometric, energetic, electronic, and thermodynamic properties of given molecular structure. The task of the datasets are predicting properties from molecular conformation. Because the dataset contains comprehensive chemicals with high consistence [25], many molecular property prediction tasks were evaluated on this dataset.

The original MD17 dataset [8] consists of 10 small molecules. For each molecule, dataset contains energy and forces for different geometry with more than 10k structures, based on DFT calculation. Instead of using original dataset we used dataset consist of 1,000 training sample [10] with more
precise calculation than original MD17 dataset. The task of the datasets are predicting forces and energy of given conformation, from other conformations of specific molecule.

6 Implementation

In this paper, we stacked up eight Geometry-aware Transformer layers \( N = 8 \) for QM9 prediction. We used 300 \( (n_{\text{basis}} = 300) \) different Gaussian functions with \( \mu = 0.1 \cdot k \) to embed atom-atom distances. For MLPs in RBF, We set the hidden dimension to 64 \( (d_{\text{rbf}} = 64) \). All embedded representations \( (d_e) \), model dimensions \( (d_m) \) and all hidden dimensions \( (d_h) \) of the DT layers were set as 1,024. For multi head attention, we used 16 heads \( (h = 16) \) which results separation of embedding vector with dimension of 1,024 into 64 vectors of 16 dimensions for DHMA. We used swish activation function \[26\] for RBF and ELU activation function \[23\] for feed forward network and readout phase.

7 Training

For QM9 training, we removed 3k data which reported as structures are unstable following previous works for fair comparison \[11, 12, 14, 16, 20\]. Each label was trained individually. Mean absolute error (MAE) was used for evaluation according to the guidelines. Adam \[27\] was used as the optimizer with MAE loss and the batch size was 32 in all experiments. The learning rate was set to 0.0002 with linear warmup 3,000 steps. The learning rate decreased at 0.95 for every 200k step. We applied the early stopping method by evaluating every 10k step of training. The number of training epochs was up to 300.

To calculate forces, we assumed that the predicted energy as a function of positions \( E(\{r_i\}) \). Based on the relation between force and potential energy of atoms, we calculated forces by differentiating energies with atom positions as previous works \[9,11\].

\[
F_j = \frac{\partial}{\partial r_j} E(\{r_i\}) 
\]

(12)

In the MD17 dataset, both the energy and forces of molecular conformations are provided. To utilize both features with Eq. 12, we trained our model with the modified loss function with additional force terms as Eq. 13 \[9,11\].

\[
L(E, \hat{E}) = |E - \hat{E}| + c \times \sum_{j=1}^{n} |F_j - \frac{\partial}{\partial r_j} \hat{E}(\{r_i\})| 
\]

(13)

Where \( c \) is a weight coefficient for the loss on forces. We set \( c \) as 1,000 in our experiments.

8 Result

8.1 Mean absolute error

We compared our result with five previous studies. Note that \[11,16,12,14\] are MPNN-based studies, and \[20\] is the only Transformer-based study. Our model outperformed previous models which are only used distance between atoms. However, the performances from our model did not exceed those of DimeNet++ \[14\], which adopted angular information. We achieved comparable performances with DimeNet++ among six targets and outperformed for one. We achieved better performances than those from GRAT, which also adopted the Transformer architecture for QM9, except three targets.

We also compared our MAE with two previous models. Our model achieved the best performances on benzene and ethanol.

We executed ablation studies on various types of radial basis functions. We used Bessel basis functions, adopted in DimeNet++ and simple linear basis functions. We also examined for linear basis function, which is most simple case of RBF. As shown in Table 4 we found that Gaussian basis functions used in our model significantly improved the model performances.
Table 1: Mean absolute error on QM9

| Target | Unit | SchNet | PhysNet | GRAT | Cormorant | DimeNet++ | GeoT |
|--------|------|--------|---------|------|-----------|-----------|------|
| $\mu$  | D    | 0.033  | 0.0529  | 0.03898 | 0.038     | **0.0297** | **0.0297** |
| $\alpha$ | $a_0^3$ | 0.235  | 0.0615  | 0.07219 | 0.085     | **0.0435** | 0.05269 |
| $\epsilon_{\text{HOMO}}$ | eV    | 0.041  | 0.0329  | **0.0228** | 0.034     | 0.0246     | 0.0250* |
| $\epsilon_{\text{LUMO}}$ | eV    | 0.034  | 0.0247  | 0.02053 | 0.038     | **0.0195** | 0.0202* |
| $\Delta_e$ | eV    | 0.063  | 0.0425  | 0.035  | 0.061     | **0.0326** | 0.04392 |
| $<R^2>$ | $a_0^2$ | **0.073** | 0.765   | 0.76681 | 0.961     | 0.331      | 0.3008 |
| $z_{\text{pve}}$ | eV    | 0.0017 | 0.0014  | 0.00208 | 0.0020    | **0.00121** | 0.00173* |
| $U_0$ | eV    | 0.014  | 0.0082  | 0.0705 | 0.022     | **0.00632** | 0.0111 |
| $U$   | eV    | 0.019  | 0.0083  | 0.02825 | 0.021     | **0.0062** | 0.0117 |
| $H$   | eV    | 0.014  | 0.0084  | 0.02549 | 0.023     | **0.0065** | 0.0113 |
| $G$   | eV    | 0.014  | 0.0094  | 0.02505 | 0.020     | **0.0075** | 0.0117 |
| $C_v$ | cal/mol K | 0.033  | 0.028   | 0.0326 | 0.026     | **0.023**  | 0.0276 |

* $\mu$, $\epsilon_{\text{HOMO}}$, $\epsilon_{\text{LUMO}}$, and $z_{\text{pve}}$ were evaluated on $N = 16$, which is different from other targets ($N = 8$).

Table 2: Mean absolute error on MD17

| Target      | SchNet | DimeNet | GeoT |
|-------------|--------|---------|------|
| Benzene     | 0.31   | 0.187   | **0.135** |
| Aspirin     | 1.35   | **0.499** | 0.85 |
| Malonaldehyde | 0.66  | **0.383** | 0.402 |
| Ethanol     | 0.39   | 0.23    | **0.225** |
| Toluene     | 0.57   | **0.216** | 0.328 |

Table 3: Basis functions for ablation study

| Type          | Basis function                                                                 |
|---------------|-------------------------------------------------------------------------------|
| Linear basis  | $a + b \cdot d_{ij}$                                                         |
| Gaussian basis| $\exp(-\gamma ||d_{ij} - d_k||^2)$                                          |
| Bessel basis  | $\sqrt{\frac{\sin(n\pi c d)}{d}}$                                           |

Table 4: Ablation study for basis set in QM9

| Target | Unit   | Gaussian basis | Linear basis | Bessel basis |
|--------|--------|----------------|--------------|--------------|
| $\mu$  | D      | **0.0299**     | 0.664        | 0.0876       |
| $\alpha$ | $a_0^3$ | **0.05269**    | 0.752        | 0.15         |
| $\epsilon_{\text{HOMO}}$ | eV    | **0.02675**    | 0.0659       | 0.056        |
| $\epsilon_{\text{LUMO}}$ | eV    | **0.02145**    | 0.122        | 0.0326       |
| $\Delta_e$ | eV    | **0.04392**    | 0.158        | 0.0575       |
| $<R^2>$ | $a_0^2$ | **0.3008**     | 55.4         | 0.3262       |
| $z_{\text{pve}}$ | eV    | **0.00174**    | 0.00845      | 0.00255      |
| $U_0$ | eV    | **0.0111**     | 0.2026       | 0.0147       |
| $U$   | eV    | **0.0117**     | 51.99        | 0.0275       |
| $H$   | eV    | **0.0113**     | 0.952        | 0.06         |
| $G$   | eV    | **0.0117**     | 0.574        | 0.013        |
| $C_v$ | cal/mol K | **0.0276**   | 0.195        | 0.06         |
8.2 Attention map visualization

We calculated attention weight norms from the trained model, to prove our model’s ability on capturing long-range interactions. Attention weights are usually used to visualize Transformer based models [28]. In Transformer, each atom’s information can refer information of other atoms in attention block only. Specifically, each atom representations updates its value with scale of attention, given by Eq. 10. In consequence, we can interpret attention $\text{Attn}_{\text{geo,} \text{m}}(x_i, x_j)$ as indicator that how much given atom $i$ attend $j$. Because we are interested in total attention among all head instead of specific head, we calculated L2 norm of attentions, rather than specific attention weight that other works [28] uses.

$$\text{AttnWeight}_{i,j} = \sqrt{\sum_{h=1}^{m} \text{Attn}_{\text{geo,} \text{m}}(x_i^n, x_j^n)^2} \quad (14)$$

To see interaction between atoms, we visualized attention weight norm for large molecules in Figure 3. We marked query atom $i$ as red dot, and visualized attention weight norm by color and dispersion which is proportional to its attention weight. The more blue and the more vivid color map is, the more attention was given to atom marked as red dot. We can find that some attention weights further than 4-hop, which usually further than cutoff values in the previous models [12][14].

9 Conclusion

In this study, we introduced geometry-aware attention which can capture interactions regardless of distances. We added geometric information by adopting self-attentions of the distance representations between atoms with the RBF. We evaluated our model on QM9 and MD17. Our model outperformed previous works based on distances and comparable with state-of-the-art models which utilized additional angular information. We also studied on the candidates of the RBF, and showed Gaussian basis function performed significantly better than other functions. We also displayed attention weights, which supported our assumption that model can attend atom pairs located far from each other. We argue that our model achieved that long-range interactions between any intramolecular atom pairs, which cannot be available for previous methods using the restricted convolutional filters. We will explore additional geometric features to improve our model performance.

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