Three-Dimensionally Embedded Graph Convolutional Network (3DGCN) for Molecule Interpretation

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Abstract

The target scope of graph convolutional networks (GCNs) for learning the graph representation of molecules has been expanded from chemical properties to biological activities, but the incorporation of the three-dimensional topology of molecules to the deep-learning models has not been explored. Most GCNs that achieve state-of-the-art performance rely only on the node distances, limiting the spatial information of molecules. In this work, we propose an advanced derivative of GCNs, coined a 3DGCN (three-dimensionally embedded graph convolutional network), which takes molecular graphs embedded in three-dimensional Euclidean space as inputs and recursively updates the scalar and vector features based on the relative positions of nodes. We demonstrate the learning capabilities of the 3DGCN using physical and biophysical prediction tasks.
1. Introduction

Deep learning methods have revolutionized the way problems in chemistry are being solved, as they have in other domains. The latest deep-learning models outperform traditional machine-learning algorithms and nonneural networks in studies on quantitative structure–activity relationships (QSARs), computer-aided drug design, and prediction of chemical reactions, aided by the rapid progress of hardware and algorithms. The most notable advance in deep learning is the advent of the graph convolutional network (GCN), which is the derivative of the well-known convolutional neural network (CNN), for learning non-Euclidean graph structures. The GCN proves its capability of interpreting raw molecular representations, interlocked with innate graph-like structures – atoms as nodes and bonds as edges – beyond molecular fingerprints. The attempts to predict molecular properties of solubility, ab initio calculations and biological activities, with relatively small molecules, have provided the basis for the GCN-based generative models such as variational autoencoder, adversarial autoencoder, and generative adversarial network.

However, these models are based on classic graphs, focusing on the representation of the connectivity; therefore, they do not represent molecules perfectly. Molecules are intrinsically three-dimensional structures with atomic orientations and dihedral angles, having multiple conformations with a single structural formula. The inadequate representation may deteriorate the performance on tasks involving spatial topology, such as molecular dynamics simulation and protein-ligand interactions. To bridge the gap, GCN variants with Gaussian feature expansion schemes upon bond distances and angles have been suggested, but a GCN strategy to handle the complete three-dimensional molecular topology has not been explored yet.

In this work, we propose a GCN model on graphs embedded in three-dimensional Euclidean space $\mathbb{R}^3$. Our graph convolutional model, coined the 3DGCN, uses a novel convolution mechanism, which enables topography-relevant integration of vector-formed information among neighborhoods. In essence, the 3DGCN updates the node features from adjacent
neighbors in the vector form, along with node-to-node direction vectors. We expect that the 3DGCN has discriminative power on conformation-level differences on molecules.

2. Methods

Utilizing the power of graph convolution to interpret molecular structures, we built the 3DGCN based on the GCN by Kipf et al.\cite{15} We designed our model to be capable of handling a bidirected graph embedded in Euclidean space, which is how molecules are represented. Each atom is considered as a node with the Cartesian coordinate, and a bond between them is represented by two diametrical vectors with the same length. The motivation behind this representation is to embody the three-dimensional topology of molecules in a graph structure, which can take advantage of the graph convolution with some modifications.

The 3DGCN consists of three modules: convolutional layers, a feature collection layer, and a fully connected layer. As inputs, scalar features of nodes are encoded as previously described, while vector features are initialized using zeros. The convolutional layers intermingle two features from each node and sum them along neighborhoods, generating updated features. The sequence of the convolutional layers provides an effect of expanding receptive fields, integrating information from local regions. After the convolutions, the feature collection layer sums the features along the nodes to make a node-independent, molecule-level feature, as the number of nodes differ from molecule to molecule. The resulting molecule-level vector feature is fed to fully connected neural network for prediction. The mechanism will be described in detail in the following sections.

2.1 Graph Representation of Molecules

Molecular graph $G$ embedded in three-dimensional Euclidean space is represented using a set of three matrices $(X, A, R)$: a feature matrix $X \in \mathbb{R}^{N \times M}$, an adjacency matrix $A \in \{0, 1\}^{N \times N}$, and a position matrix $R \in \mathbb{R}^{N \times N \times 3}$, where $N$ and $M$ are the number of
atoms and the atom-level features in a molecule, respectively. The feature matrix $X$ contains the characteristics of individual atoms comprising a molecule. Detailed information of the atom-level information is listed in Table 1. The adjacency matrix $A$ is a symmetric matrix holding the graph topology. We assume that there are no isolated nodes and self-loops in our graph. To provide translational invariance, the position matrix $R$ is defined as a three-dimensional matrix rather than $\mathbb{R}^{N \times 3}$, by utilizing relative position vectors between atoms instead of individual positions.

Table 1: Scalar features in the initial representation of molecules.

| Feature               | Description                                                                 | Size |
|-----------------------|-----------------------------------------------------------------------------|------|
| Atom Type             | Atom type in one-hot vector of H, B, C, N, O, F, P, S, Cl, Br, I, and others.| 12   |
| Degree                | Number of heavy atom neighbors in one-hot vector of 0, 1, 2, 3, 4, 5, and 6. | 7    |
| Number of Hydrogens   | Number of neighboring hydrogens in one-hot vector of 0, 1, 2, 3, and 4.      | 5    |
| Hybridization         | Hybrid orbital of an atom in one-hot vector of $sp$, $sp^2$, $sp^3$, $sp^3d$, and $sp^3d^2$. | 5    |
| Aromaticity           | Whether an atom is the part of an aromatic system.                          | 1    |

2.2 Generation of Position Matrix

To acquire three-dimensional position for each atom in molecules, we generate conformers according to the previously published protocol using RDKIT when they are not provided on the dataset. Conformers are then optimized by Merck molecular force field (MMFF94). The lowest energy conformation is selected for generating the position matrix. Molecules that fail to generate stable conformers are excluded from the dataset.

2.3 Three-Dimensional Graph Convolution Architecture

The 3DGCN follows a neighborhood aggregation strategy, which iteratively updates the features of nodes based on the aggregated adjacent node features, while each node contains
two features: scalar and vector features. Scalar features are composed of individual numbers, and vector features are the collection of three-dimensional vectors with shapes of $X_s \in \mathbb{R}^{N \times M}$ and $X_v \in \mathbb{R}^{N \times M \times 3}$, where $N$ and $M$ are the number of atoms and atom-level features in a molecule, respectively. To transfer information between scalar and vector features, we define four operations updating each feature. The scalar and vector features could recursively update self and the other on the convolutional cycles along with neighborhood feature collection. Overall operations are depicted in Fig 1.

Figure 1: Four operations between scalar and vector features inside the convolutional layer. Scalar and vector features from the center node (orange) and neighborhood (blue) generate new features. Scalar-to-scalar (a) and vector-to-vector (c) operations combine coordinative features from the center and neighbor node. Vector-to-scalar operation (b) employs the scalar projection of vector feature from the neighboring node on the relative direction between the center and neighborhood to transform information as a scalar feature. Scalar-to-vector operation (d) expands the scalar feature of neighborhood to a vector feature by tensor product with the relative direction. W stands for weight matrix, b for bias, and $\sigma$ for nonlinearity.

Operations of scalar-to-scalar and vector-to-vector features combine two adjacent nodes by concatenating the features before the linear combination with rectified linear activation.
function (ReLU). Specifically, if you have scalar features, \( x_{i,s}^{(l)} \) and \( x_{j,s}^{(l)} \) from node \( i \) and \( j \) on layer \( l \), the updated scalar feature \( a_{j,s\to s}^{(l)} \) (scalar-to-scalar) is defined as

\[
a_{j,s\to s}^{(l)} = \text{ReLU} \left( W_{s\to s} \left( x_{i,s}^{(l)} \| x_{j,s}^{(l)} \right) + b_{s\to s} \right)
\]

or, with vector features \( x_{i,v}^{(l)} \) and \( x_{j,v}^{(l)} \), the updated vector feature \( a_{j,v\to v}^{(l)} \) (vector-to-vector) is represented as

\[
a_{j,v\to v}^{(l)} = \text{ReLU} \left( W_{v\to v} \left( x_{i,v}^{(l)} \| x_{j,v}^{(l)} \right) + b_{v\to v} \right)
\]

where \( \| \) is concatenation, \( W \) is trainable weights, and \( b \) is biases. It should be pointed out that the linear combination of vector-to-vector operation does not flatten the concatenated features to retain equal weights along the x, y, and z axes.

Next, we consider operations to interconnect the scalar and vector features that require changes in dimension. Transforming the features incorporates the relative direction between nodes to decrease or increase the rank, as the features differ only in whether the directionality exists or not. Scalar projection and tensor product are chosen for the operations, which relate the features with relative directions without significant loss of the original information. Formally,

\[
a_{j,v\to s}^{(l)} = \text{ReLU} \left( W_{v\to s} x_{j,v}^{(l)} + b_{v\to s} \right) \cdot r_{ji}
\]

\[
a_{j,s\to v}^{(l)} = \text{ReLU} \left( W_{s\to v} x_{j,s}^{(l)} + b_{s\to v} \right) \otimes r_{ji}
\]

where \( \cdot \) stands for dot product and \( \otimes \) for tensor product. Note that, unlike appositional operations, scalar-to-vector and vector-to-scalar operations employ neighborhood features only.

Once we have four operations on scalar and vector features, four updated features should be combined into two features for convolution along neighborhoods. Two updated features
for scalar and vector features each are in the concatenated and reduced dimension by linear combination with nonlinearity. Afterwards, the features of neighboring nodes are collected and averaged by the normalized adjacency matrix, generating $x^{(l+1)}_{i,s}$ and $x^{(l+1)}_{i,v}$.

$$x^{(l+1)}_{i,s} = \text{ReLU} \left( \sum_{j \in N(i)} \frac{1}{N_{ij}} \left( W_s \left( a^{(l)}_{j,s \rightarrow s} || a^{(l)}_{j,v \rightarrow s} \right) + b_s \right) \right)$$  \hspace{1cm} (5)

$$x^{(l+1)}_{i,v} = \text{ReLU} \left( \sum_{j \in N(i)} \frac{1}{N_{ij}} \left( W_v \left( a^{(l)}_{j,v \rightarrow v} || a^{(l)}_{j,s \rightarrow v} \right) + b_v \right) \right)$$  \hspace{1cm} (6)

At the end of the convolution cycles, information distributed on the entire graph should be accumulated to predict certain properties of a molecule. In the process of accumulation, all vector features from all nodes are summed to make molecule-level features independent from the number of atoms in the molecule. In addition, summation provides order invariance of atoms and bonds encoded in the input.

2.4 Datasets

For our experiments, we focused on regression tasks to evaluate the ability to quantitatively interpret molecular information which is necessary for further comparison on conformations. We trained our model with three publicly available and commonly used datasets.

**FreeSolv**  The Free Solvation Database (FreeSolv) is a dataset of experimental and calculated hydration free energies optimized by general AMBER force field (GAFF).\textsuperscript{34} Atomic coordinates used for GAFF hydration free energy calculations are included with structural information in the SMILES format. Experimental values are used for training our models, and the coordinates are used without modification.

**ESOL**  The ESOL dataset is a small collection of aqueous solubilities in $\log_{10}(mol/L)$ for 1128 compounds.\textsuperscript{35} The dataset targets prediction of log-valued solubilities from chemical structures provided as SMILES encoded strings. To obtain 3D coordinates of individual
atoms, we employed a conformer generation strategy with provided SMILES as previously described.\textsuperscript{50} Molecules that failed to generate stable conformers were excluded.

**BACE** The BACE dataset has experimental binding affinities ($p$IC$_{50}$) of 1522 small molecule inhibitors on human $\beta$-secretase 1, potential therapeutic target for Alzheimer’s.\textsuperscript{37} Individual values are collected from various laboratories in academia and pharmaceutical companies. The dataset focuses on modeling protein–molecule interactions. For 3D conformer generation, the same procedure as ESOL dataset was employed.

### 2.5 Model Training and Evaluation

The 3DGCN was implemented in Python using open-source machine learning library Keras\textsuperscript{45} 2.1.6 with TensorFlow\textsuperscript{39} 1.5 as a backend. Training was controlled by learning rate decay and early-stopping techniques, which observed the validation error to lower the learning rate or stop the training. The learning rate was decreased by a factor of 0.9 when the loss reached plateau, with a patience of 5, and the termination was determined with a patience of 25. Enough epochs were set to prevent termination by the end of epochs, not by the early-stopping mechanism. The models were evaluated by mean squared error (MSE) with 10-fold stratified cross-validation (CV). For each fold, the dataset was randomly split into a training set (80%), validation set (10%), and test set (10%).

### 3. Results and Discussion

We demonstrated the proof-of-concept of the 3DGCN via studies on small molecules and their nonlocal properties that are derived from the structures. Three datasets on physical property prediction and biophysics estimation tasks were selected to verify our architecture to learn three-dimensional graph representations. FreeSolv and ESOL datasets are commonly used target for benchmarking deep learning models based on aqueous solubility. Aqueous solubility
is a well-known physical property of molecules, which is highly influenced by local motifs such as functional groups. Typical hydrophilic and hydrophobic molecules share their motifs, and integrating the information over the molecule is the key challenge to predict the solubility. Based on these goals, we trained 3DGCN with three-dimensional graph representations of molecules to learn normalized hydration free energies and solubilities.

In addition, though there is ongoing controversy over the effectiveness of three-dimensional structures on deep learning models, protein–ligand interaction is known to be highly influenced by the conformations. Expanding the target scope of the 3DGCN from solubility tasks, we tested our model’s ability of interpreting the relationship between molecular structure and protein. The BACE dataset is a good target for examining the power to learn molecular effectiveness on a β-secretase 1 enzyme, representing structural suitability on the active center of the enzyme. As BACE dataset provides both binary labels of effectiveness and $pIC_{50}$ values, we trained our model on $pIC_{50}$ values to measure the closeness of predictions and observed the structural relationships. The evaluation results using the 3DGCN for the datasets are listed in Table 2.

| Datasets | Compounds | MAE Validation | MAE Test | RMSE Validation | RMSE Test |
|----------|-----------|----------------|----------|-----------------|----------|
| FreeSolv | 643       | 0.642 ± 0.062  | 0.651 ± 0.070 | 0.875 ± 0.100  | 0.911 ± 0.103 |
| ESOL     | 1128      | 0.490 ± 0.030  | 0.494 ± 0.037 | 0.623 ± 0.028  | 0.625 ± 0.056  |
| BACE     | 1522      | 0.545 ± 0.042  | 0.577 ± 0.046 | 0.654 ± 0.049  | 0.691 ± 0.056  |

The 10-fold cross-validation results show that the 3DGCN model achieves a mean RMSE of 0.911 on FreeSolv; in comparison, the state-of-the-art GCNs show RMSEs of over 1 kcal/mol. A method is generally considered to be comparable with the ab initio prediction, when its RMSE reaches 1.5 kcal/mol. On the ESOL task, our 3DGCN has an RMSE of 0.625, which is similar to or slightly higher than the results of modern GCNs. Moving beyond the predictions on unimolecular properties, the 3DGCN successfully proves its capability of simulating the interactions between beta-secretase and inhibitors, with an RMSE of 0.691. It
should be noted that the molecules in the BACE dataset are relatively larger in size compared with those in the solubility datasets, and the targeted property relies on the structural information on the fragments of molecules.

Figure 2: (a) Confusion plots for the test subsets of FreeSolv (red), ESOL (orange), and BACE (blue) datasets with Root Mean Squared Errors (RMSE). Trend lines for each predicted set are shown as solid lines, and dashed lines indicate identity lines. The most underpredicted and overpredicted molecules are indicated by black triangles. (b) Molecular structures of the outliers marked in (a) with experimental and predicted values. Units for the datasets are kcal/mol, log(mol/L), and log(mol/L), respectively.

The distribution graphs of the predicted values vs. true ones, as a visualization of the overall predictions, show linear-like relationship on all the tasks (Fig 2A). Test subsets are selected from the cross-validation trial, which show the closest performance to the averaged RMSE. The molecules with the most underpredicted and overpredicted values are marked on
the distribution, and their structures are shown in Fig 2B. Relatively large errors on FreeSolv in terms of mean RMSE compared with the other datasets, are distributed in the marginal area of the dataset where the number of molecules for training may be insufficient.

4. Conclusions

Molecular interactions take place in a three-dimensional space and are highly influenced by conformations and relative orientations, which are not represented in the conventional graph structure. In this work, we propose a three-dimensionally embedded graph convolutional network (3DGCN) that incorporates three-dimensional graph topology with a graph convolutional neural network. As far as we know, there have been several attempts to incorporate spatial information of a molecule, but the 3DGCN is the first model that uses the innate architecture that handles relative position vectors. We observe the capabilities of predicting basic molecular properties as well as protein-molecule interactions in our experiments. Our key insight is that the 3DGCN has various potential applications for learning conformation- and orientation-dependent phenomena in intermolecular dynamics, protein–ligand interaction predictions, and the simulation of chemical reactions.

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