
Non-equilibrium molecular geometries in graph neural networks

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Abstract

Graph neural networks have become a powerful framework for learning complex structure-property relationships and fast screening of chemical compounds. Recently proposed methods have demonstrated that using 3D geometry information of the molecule along with the bonding structure can lead to more accurate prediction on a wide range of properties. A common practice is to use 3D geometries computed through density functional theory (DFT) for both training and testing of models. However, the computational time needed for DFT calculations can be prohibitively large. Moreover, many of the properties that we aim to predict can often be obtained with little or no overhead on top of the DFT calculations used to produce the 3D geometry information, voiding the need for a predictive model. To be practically useful for high-throughput chemical screening and drug discovery, it is desirable to work with 3D geometries obtained using less-accurate but much more efficient non-DFT methods. In this work we investigate the impact of using non-DFT conformations in the training and the testing of existing models and propose a data augmentation method for improving the prediction accuracy of classical forcefield-derived geometries.

1 Introduction

Computational screening can accelerate drug discovery by efficiently exploring a much larger space of compounds and identifying promising candidates for experimental testing. In recent years machine learning (ML) has achieved great success in the fast screening of chemical structures. It is more efficient than physics-based methods and more accurate than traditional rule-based methods (1)(2)(3). Graph neural networks (GNNs) have been considered as the ML method of choice for such problems because they conveniently take molecular graphs as input to learn continuous embeddings, without the need for feature engineering. Recent developments in GNNs have incorporated geometry information. It is a common practice for such methods to report their performance by training and testing the proposed models using optimized equilibrium 3D molecular geometries. Obtaining minimum-energy atomic coordinates, e.g., using density functional theory (DFT), for a new molecule is a computationally intensive task and impractical for fast chemical screening. Even if the time required is not critical, and computationally expensive procedures are acceptable in exchange for better accuracy, the properties we are interested in predicting can often be obtained with little or no overhead on top of the computation needed for obtaining the 3D geometry. In such cases, it is preferable to directly obtain these properties using DFT as opposed to using machine learning, which uses DFT computed geometries to make relatively less accurate predictions. As such, we

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argue that, to be practically useful, ML models should work with geometries obtained using methods that do not require computationally expensive operations like DFT. This, however, is not the common practice in the literature. In this work, we examine the impact of using non-equilibrium geometry with state-of-the-art GNN models, trained using DFT or non-DFT geometries. Furthermore, we propose a simple scheme of data augmentation to make the models more robust and improve the prediction accuracy using non-equilibrium geometries computed by efficient non-DFT methods.

2 Background

Graph Neural Networks. Graph neural networks (GNNs) have been developed to process graph data (4)(5), such as the graph representations of molecular structures (with atoms as nodes and chemical bonds as edges). GNNs follow a message passing (recursive neighborhood aggregation) scheme by embedding each node in a high-dimensional space and aggregating feature vectors (node and/or edge embedding) of its neighbors to compute its new feature vector (6). After T iterations, each node has structural information of its T -hop neighborhood (or local bonding environment). Original GNNs were defined for regular graph structures (2D graphs). Recently, new GNN architectures have been proposed to use 3D molecular graphs, which include the 3D coordinates for each node in addition to the bonding information. These models incorporate the distances and angular information derived from the 3D geometry of the graph to enhance the message passing between neighbors. See Table 1 for a summary of these works.

3D-conformation of molecules. Molecules are intuitively represented as 3D graphs. For molecules with flexible/rotatable bonds, there may exist multiple locally-optimal spatial configurations, known as conformations. Molecular conformations may be determined experimentally; this, however, is time-consuming and requires special instrumentation. The prevailing technique for calculating accurate conformations is density functional theory (DFT), which seeks a numerical solution to the Schrödinger equation under the Born-Oppenheimer approximation. The trade-off for the accuracy of DFT methods is computational expense, with time complexity $O(e^3)$ where e is the number of electrons in the system. For larger molecules or molecules containing heavy atoms, runtime becomes impractical for high-throughput screening. Classical methods for obtaining conformations minimize, with respect to atomic coordinates, a force-field energy function based on, e.g. the Lennard-Jones interaction potential. Although these classical methods provide relatively cruder approximations of molecular structure (15), their efficiency renders them highly practical for generation of conformer ensembles for use in rapid computational screening of novel structures.

3 Impact of conformations

It is common practice to use DFT conformations to train GNN models; however, with DFT being computationally expensive, we are interested in understanding how well different models can work when applied with 3D conformations obtained using more efficient but less optimal non-DFT methods. In other words, do we see similar performance benefit from using distances/angular in-

Name	Approach	Dataset used
SchNet (7)	distance information using continuous-filter convolutional layers	QM9 (8), MD17 (9), ISO17 (10)
PhysNet (11)	integrates both the node features and distance information in the proposed interaction block	QM9, MD17, ISO17, SN2 (11)
DimeNet (12)	include distance and angle information in the interaction block	QM9, MD17
SphereNet (13)	use radial distance, polar angle, and the azimuthal angle	QM9, Open Catalyst (14), MD17

Table 1: Recently proposed GNNs for 3D graphs that use molecular geometry for more accurate predictions.

Model	Method	Target (Unit)						
		μ (D)	α (a_0^3)	ϵ_{HOMO} (meV)	ϵ_{LUMO} (meV)	$\Delta\epsilon$ (meV)	$\langle R^2 \rangle$ (a_0^2)	ZPVE (meV)
GCCN	B/B	0.621	0.947	269	404	615	100.7	26.04
SchNet	B/B	0.923	1.737	393	727	801	154.3	36.83
	DFT/DFT	0.033	0.235	41	34	63	0.073	1.7
	DFT/OB	0.875	0.723	131	164	200	49.7	12.21
	OB/OB	0.477	0.364	99	96	119	19.5	4.23
DimeNet	B/B	0.676	0.814	254	576	600	30.5	22.9
	DFT/DFT	0.029	0.047	27.8	19.7	34.8	0.331	1.29
	DFT/OB	0.718	1.08	169	206	197	45.9	50
	OB/OB	0.351	0.197	72	69.4	97.5	15.9	3.6

Table 2: Quantitative results

formation when using less accurate conformations? Specifically, we examine two types of models: models trained on DFT conformations and models trained on non-DFT conformations; and test their performances in a practically relevant scenario where only non-DFT conformations are available during testing.

GNN models used. We experiment with recently proposed SchNet (7) and DimeNet (12) models. SchNet incorporates relative distances based on atomic positions. DimeNet embeds atoms via a set of messages (i.e., edge embeddings) and leverages the directional information by transforming messages based on the angle between them. To compare these models to those that only consider the bond graph, we also create a modified version of both SchNet and DimeNet to keep their respective architecture but only use the bonding information and compare them with Gated Graph Sequence Neural Networks (GGCN) (16), which does not consider 3D geometries of the molecules.

Dataset. We use the QM9 computational dataset, a widely used benchmark dataset for molecular property prediction consisting of density functional theory (DFT)-optimized 3D coordinates and energies (8). QM9 contains geometric, energetic, electronic, and thermodynamics properties for a subset of GDB-17 structures (17) comprising up to 9 non-hydrogen atoms. All physical properties are computed with the B3LYP functional and 6-31G(2df,p) basis set (8). The dataset is split into three sets, where the training set contains 83,092, the validation set contains 10,386, and the test set contains 10,387 molecules. We use Open Babel (OB) (18) to generate non-DFT conformations for the QM9 dataset. Open Babel is a chemical toolbox that offers support for molecular mechanics and provides the ability to generate a reasonable 3D structure given the connectivity (bonding) information by following a series of steps (19). First, it uses a combination of rules and fragment templates to generate a 3D structure. This 3D structure is subsequently cleaned (conformer searching) without altering the stereochemistry. Conformer searching algorithms adopt a torsion-driving approach by setting torsion angles to one of the allowed values. Initial 3D structure is cleaned by a) steepest descent geometry optimization with the MMFF94 forcefield, b) weighted rotor conformational search and c) conjugate gradient geometry optimization. All of these steps ensure that the generated conformation is likely to be the minimum energy conformer.

Results. Quantitative results are shown in Table 2. Results for training and testing using DFT conformations (DFT/DFT) for SchNet and DimeNet are provided by the original papers. When we test on the OB conformations with models trained on DFT conformations (DFT/OB), not surprisingly there is a significant loss of accuracy for all targets and models. Interestingly, DimeNet appears to be more severely affected compared to SchNet, possibly due to its complex architecture being more rigid and prone to overfitting to the DFT conformations. Nonetheless, in most cases, DFT/OB still performs better than completely ignoring the geometry information and using only the bonding graphs (B/B).

Model	Method	Target (Unit)						
		μ (D)	α (a_0^3)	ϵ_{HOMO} (meV)	ϵ_{LUMO} (meV)	$\Delta\epsilon$ (meV)	$\langle R^2 \rangle$ (a_0^2)	ZPVE (meV)
SchNet	OB/OB	0.477	0.364	99	96	119	19.5	4.23
	DA/OB	0.459	0.259	92.9	89	125	20.68	4.45
DimeNet	OB/OB	0.351	0.197	72	69.4	97.5	15.9	3.6
	DA/OB	0.337	0.176	63.8	58.46	91.9	14.6	3.2

Table 3: Using data augmentation (DA) to improve prediction accuracy for non-DFT conformations

When models are both trained and tested on OB conformations (OB/OB), we obtain better performance compared to DFT/OB and also DimeNet performs better than SchNet. The OB/OB results show that in practice, where a new chemical compound with non-DFT conformations is considered for fast screening, the deployed models should be trained using non-DFT conformations. Furthermore, the community should shift their practice and report results of using non-DFT conformations to reflect what to expect in practice.

4 Data augmentation for improved robustness/generalization

The results in Section 3 show that when using 3D geometry information in modeling, it is preferable to train your model using conformations that you expect to test on. Unfortunately, this implies that we will need to retrain our model if a different method is used for generating the conformation in testing. Can we remove this need for re-training by making training more robust? Toward this goal, we propose a simple strategy based on data augmentation that can reduce the sensitivity of the trained model to the specific conformations used and improve robustness and generalization.

The key idea is to augment each training example with multiple low-energy conformations to increase the diversity of the training and reduce the sensitivity to the variations in conformations. Each conformation is a plausible spatial arrangement at a local energy minimum, collectively representing an ensemble of observable states (i.e. likely model inputs) for the molecule. In principle, this augmentation expected to result in decreased dependence of the model on exact geometry information. Additionally, the model should learn to generate more consistent predictions for ground-state molecular properties when conformations other than the global energy minimum are given as input.

We use confab (20) to generate multiple low-energy conformers for each QM9 molecule. Confab uses the torsion-driving approach to generate conformations. It iterates through the set of allowed torsion angles for each rotatable bond. Energy is evaluated using the MMFF94 forcefield. Diversity is measured using the heavy-atom root-mean-square deviation (RMSD) relative to the already stored conformers. We use the DFT conformation as the initial conformation for confab. We use 50.0 kcal/mol as energy cutoff and 0.5 as RMSD cutoff. Depending on the structure’s rotatable bonds, confab generates 1 to 400 conformations for each QM9 molecule. We randomly select 30 conformations at most for each molecule. Each conformation of a molecule will serve as a different graph datum (training example) with the same target value. Data augmentation results in an increase of training data size from 83,092 to 519,655 graphs.

Results of using data augmentation (DA/OB) to effectively train models are shown in Table 2. SchNet-DA/OB performs better than OB/OB on 4 properties, and DimeNet-DA/OB achieves better accuracy than OB/OB on all 7 properties. DimeNet is a complex model with many layers. It uses both distances between nodes and angles between edges. This might be the reason why DimeNet is more sensitive to conformations being used for training/testing as well as benefits more from the augmentation than SchNet which only uses distance information.

5 Conclusion and discussion

It is a common practice in the literature to use DFT-optimized 3D geometries in GNNs. Machine learning models, to be practically useful for fast screening of chemical compounds, should work with geometries not obtained using computationally expensive methods like DFT. We show that there is a significant loss of accuracy when new chemical compounds with non-DFT conformations are tested with models trained on only DFT-conformations. Deployed models should be trained and tested using geometries from the same level of theory as what is expected in the predictive application. Additionally, we propose a data augmentation scheme to reduce the sensitivity of the trained models to the specific conformations and improve robustness and generalization.

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