An Order-Invariant Structure Learning Method for Molecule Classification

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Objectives

Virtual high-throughput screening provides a strategy for prioritizing compounds for physical screens. Machine learning methods offer an ancillary benefit to make molecule predictions, yet the choice of representation has been challenging when selecting algorithms. We emphasize the effects of different levels of molecule representation. Then, we introduce N-gram graph, a novel representation for a molecular graph. We demonstrate that N-gram graph is able to attain most accurate prediction with several non-deep machine learning methods on multiple tasks.

Introduction

Molecule representation has become one of the biggest challenges in virtual screening tasks. Typically machine learning methods assume three levels of featurization as illustrated in Figure 1.

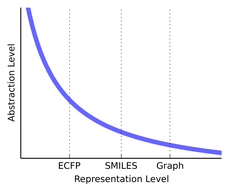


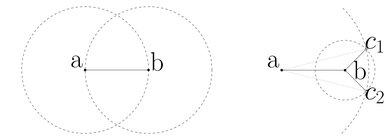
Figure 1: Pareto curve for feature representation and model understanding. From molecule graph to SMILES to ECFP, more information is lost, but the corresponding representation becomes more abstract adn easier for machine to understand.

- Extended Connectivity Fingerprint (ECFP) is a bit vector, where each bit represents one substructure.
- Simplified Molecular Input Line Entry System (SMILES) maps each molecule into a string.
- Molecule graph as input feature is first introduced in [1].

Figure 2: SMILES: c1cc(oc1C(=O)Nc2nc(cs2)C(=O)OCC)Br. ECFP: [000000...00100100100...000000].

Motivation

- Message passing based on adjacent matrix can help identify a molecule skeleton.
- Distance matrix maintains the information of a molecule shape.
- Combining both can keep all the key information in a molecule.



(a) stage 1, fix atom a and b locations. The distance between atoms is given by distance matrix.

(b) Stage 2, construct the molecule graph following the adjacent matrix. There are two possible locations for atom c.

(c) Stage 3, choose c_1 as atom C.

(d) Stage 4, all the remaining atoms will be uniquely defined in this 2D space after fixing first three atoms.

Figure 3: Illustrations on how adjacent matrix and distance matrix can be combined to recover a graph structure.

Graph Representation

Each molecule can be represented as a graph with at most m atoms. Each atom can be represented as a vector of $d-$dimension.

- Adjacent Matrix $\mathcal{A} \in \{0,1\}^{m\times m}$

$$\mathcal{A}_{i,j} = \begin{cases} 1, & \text{atom}_i \text{ and atom}_j \text{ are bonded} \\ 0, & \text{otherwise} \end{cases}$$

- Distance Matrix $\mathcal{D} \in \mathbb{R}^{m\times m}$

$$\mathcal{D}_{i,j} = \sqrt{(x_i - x_j)^2 + (y_i - y_j)^2 + (z_i - z_j)^2}$$

- Node Attribute Matrix $\mathcal{N} \in \{0,1\}^{d\times m}$. For each atom, the features are symbol, degree, # Hytrogeon, charges, is aromatic, is acceptor, is donor.

$$\mathcal{N}_{\cdot,i} = [\underbrace{\text{C}, \text{Cl}, \text{I}, \text{F}, \ldots}_{\text{atom symbol}}, \underbrace{0, 1, 2, 3, 4, 5, 6, \ldots}_{\text{atom degree}}]$$

Methods: N-Gram Graph

Candidate Set: $s = \{0,1\}^{m\times 1}$, each one bit in s represents if one atom is crucial for the target task.

Problem Relaxation:

- $\mathcal{N} \cdot s = c_1$
- $\mathcal{A} \otimes (s \cdot s^T) \cong c_2$
- $\mathcal{D} \otimes (s \cdot s^T) \cong c_3$

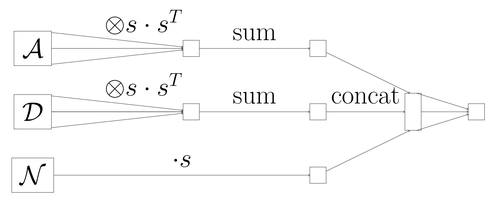


Figure 4: Pipeline for Graph-based Neural Network.

Segmented Random Projection:

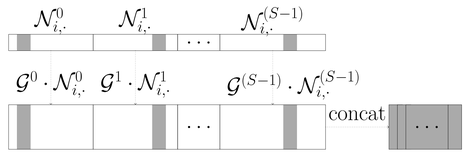


Figure 5: Segmented random projection on atom a_i. Each atom features can be split into S segments. Each group of feature with dimension d_s corresponds to a one-hot vector $N^s_{i,\cdot} \in \{0,1\}^{1\times d_s}$ (marked in grey). Multiply it by Gaussian random matrix $\mathcal{G}^s \in \mathbb{R}^{r\times d_s}$ as projection to a random space. For each randomized atom feature g_i, the only non-zero column in output matrix $\mathcal{G}^s \cdot \mathcal{N}^s_{i,\cdot}$ in each segment will be extracted and concatenated.

N-gram Path and N-gram Graph:

Let V be a path, and N-gram path (V_n) is the production of all n nodes in that path.

Let $\mathcal{V}_n \in \mathbb{R}^{r\times S}$, $p \in \{1, 2, \ldots, N\}$ represent the **N-gram path set**. It is defined as the sum of all N-gram paths with length n.

$$\mathcal{V}_n = \underbrace{\sum_{\forall V, \text{s.t.}\ |V|=n} \overbrace{\prod_{a_i \in V} \underbrace{f(a_i)}_{\text{segmented random projection}}}^{\text{n-gram path}}}_{\text{n-graph path set}}$$

N-gram graph for each molecule $\mathbb{G} = [\mathcal{V}_1, \mathcal{V}_2, \ldots, \mathcal{V}_n] \in \mathbb{R}^{N\times r\times S}$ is the concatenation of N-gram path sets with multiple length n.

Experiments

- Three regression tasks, Delaney, Malaria, and CEP.
- Six models are tested: RF, XGB, DNN, NEF [1], GCNN [2], Weave Net [3].

Table 1: RMSE on three regression tasks (test set). Top three results are **bolded** and the best performance is **underlined**. Baseline results (*) are from [1, 3].

Representation	Method	Delaney	Malaria	CEP
ECFP	RF	1.251	**1.011**	1.667
	XGB	1.120	**0.998**	1.442
	DNN (*)	1.40	1.13	2.00
Message-Passing Graph	NEF (*)	**0.52**	1.15	1.43
	GCNN	0.98	1.02	**1.17**
	Weave (*)	**0.46**	1.07	**1.10**
N-Gram Graph	RF	0.802	**1.011**	1.367
	XGB	0.771	**1.003**	**1.296**
	DNN	**0.665**	1.085	1.359

Conclusion and Discussion

- Another way to explore graph-like feature representation.
- No requirement for End-to-End deep neural networks.
- Current graph-based methods haven't fully utilized the comprehensive capacity of deep neural network.
- More advanced NLP strategies can be applied for both modeling and analysis.

References

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