THRUST 1

Bi-Level Contrastive Learning for Knowledge-Enhanced Molecule Representations

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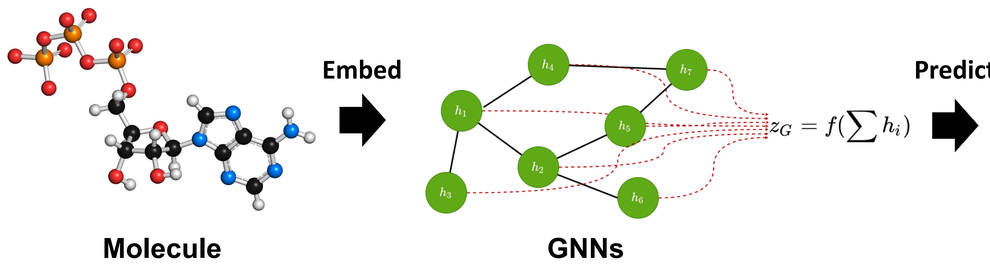
Motivation

Most previous approaches use graph neural networks (GNNs) to only learn the structure information in molecules, to predict molecule's property (e.g., BBBP, toxicity).



BBBP:
- "Can it cross the blood-brain barrier?"

Toxicity:
- "Is it toxic in high doses?"

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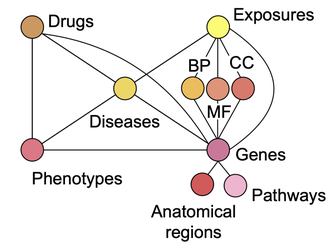
However, publicly available biochemical knowlegde bases remained largely unused (e.g., PubChem, PrimeKG) for this task.

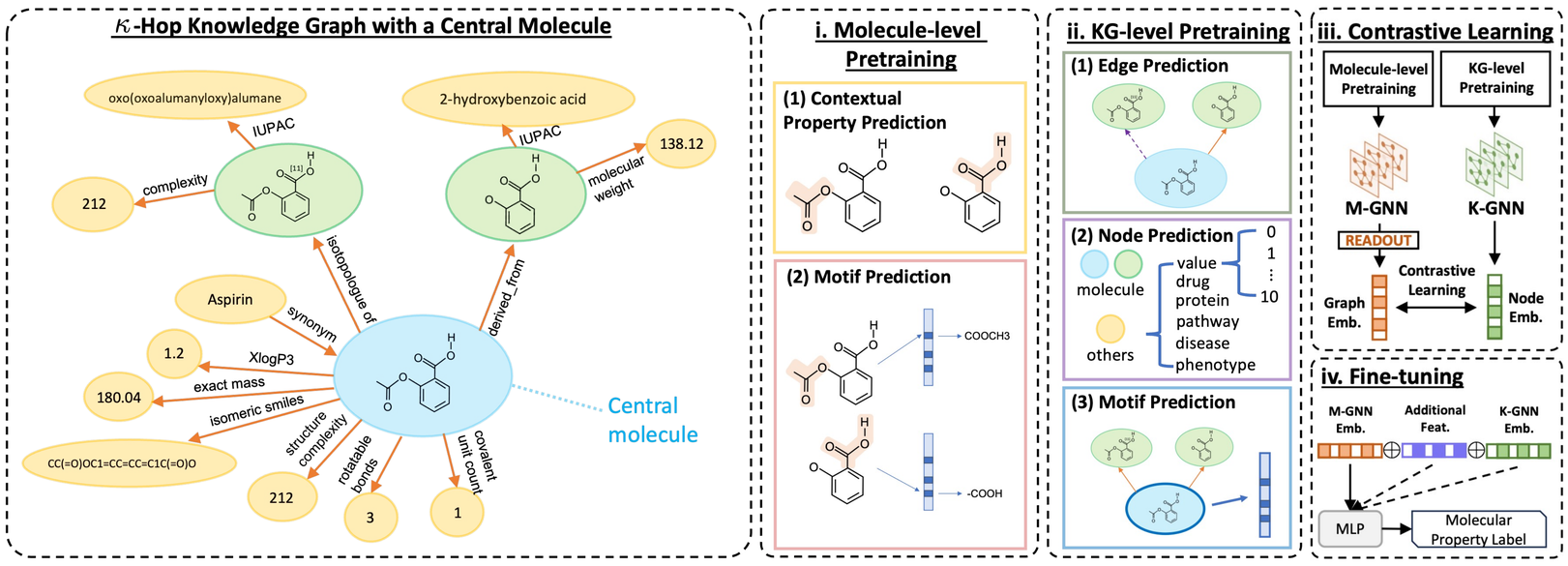
PubChem

PrimeKG



"Can we leverage the available biochemical knowledge for molecular property prediction?"

Method: Gode (Graph as a Node) Framework



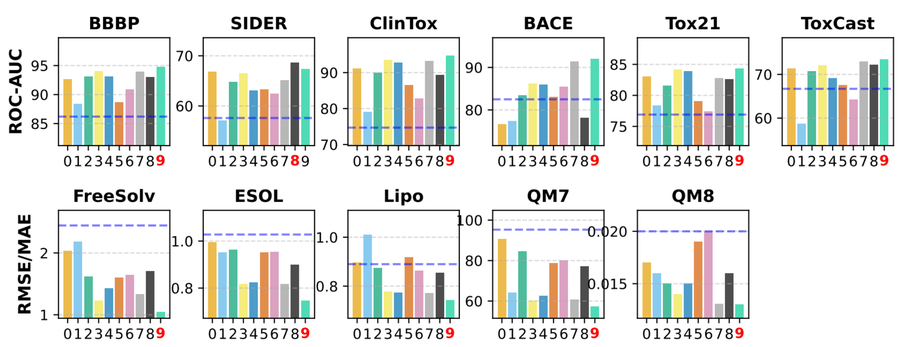
- ❑ We construct MolKG – a molecule-centric biochemical knowledge graph dataset
  - ❖ Each molecule corresponds to its central sub-graph in MolKG
- ❑ We conduct GNN pre-training at two levels: molecule-level and KG-level
  - ❖ At molecule-level, a molecule is a graph
  - ❖ At KG-level, a molecule is a node
- ❑ We align bi-level molecule representations via contrastive learning
- ❑ The pre-trained and aligned molecule embedding can then be fine-tuned to any downstream tasks

Results across 11 Molecular Property Prediction Tasks:

	Classification (Higher is Better)						Regression (Lower is Better)				
Dataset	**BBBP**	**SIDER**	**ClinTox**	**BACE**	**Tox21**	**ToxCast**	**FreeSolv**	**ESOL**	**Lipophilicity**	**QM7**	**QM8**
# Molecules	2039	1427	1478	1513	7831	8575	642	1128	4200	6830	21786
# Tasks	1	27	2	1	12	617	1	1	1	1	12
GCN	71.8 ± 0.9	53.6 ± 0.3	62.5 ± 2.8	71.6 ± 2.0	70.9 ± 0.3	65.0 ± 6.1	2.870 ± 0.140	1.430 ± 0.050	0.712 ± 0.049	122.9 ± 2.2	0.037 ± 0.001
GIN	65.8 ± 4.5	57.3 ± 1.6	58.0 ± 4.4	70.1 ± 5.4	74.0 ± 0.8	66.7 ± 1.5	2.765 ± 0.180	1.452 ± 0.020	0.850 ± 0.071	124.8 ± 0.7	0.037 ± 0.001
SchNet	84.8 ± 2.2	54.5 ± 3.8	71.7 ± 4.2	76.6 ± 1.1	76.6 ± 2.5	67.9 ± 2.1	3.215 ± 0.755	1.045 ± 0.064	0.909 ± 0.098	74.2 ± 6.0	0.020 ± 0.002
MPNN	91.3 ± 4.1	59.5 ± 3.0	87.9 ± 5.4	81.5 ± 4.4	80.8 ± 2.4	69.1 ± 1.3	1.621 ± 0.952	1.167 ± 0.430	**0.672 ± 0.051**	111.4 ± 0.9	**0.015 ± 0.001**
DMPNN	91.9 ± 3.0	63.2 ± 2.3	89.7 ± 4.0	85.2 ± 5.3	**82.6 ± 2.3**	71.8 ± 1.1	1.673 ± 0.082	1.050 ± 0.008	0.683 ± 0.016	103.5 ± 8.6	**0.016 ± 0.001**
MGCN	85.0 ± 6.4	55.2 ± 1.8	63.4 ± 4.2	73.4 ± 3.0	70.7 ± 1.6	66.3 ± 0.9	3.349 ± 0.097	1.266 ± 0.147	1.113 ± 0.041	77.6 ± 4.7	0.022 ± 0.002
N-GRAM	91.2 ± 1.3	63.2 ± 0.5	85.5 ± 3.7	87.6 ± 3.5	76.9 ± 2.7	-	2.512 ± 0.190	1.100 ± 0.160	0.876 ± 0.033	125.6 ± 1.5	0.032 ± 0.003
HU. et.al	70.8 ± 1.5	62.7 ± 0.8	72.6 ± 1.5	84.5 ± 0.7	78.7 ± 0.4	65.7 ± 0.6	2.764 ± 0.002	1.100 ± 0.006	0.739 ± 0.003	113.2 ± 0.6	0.022 ± 0.001
$\text{GROVER}_{\text{Large, GTrans}}$	86.2 ± 3.9	57.6 ± 1.6	74.7 ± 4.4	82.5 ± 4.4	76.9 ± 2.3	66.7 ± 2.6	2.445 ± 0.761	1.028 ± 0.145	0.890 ± 0.050	95.3 ± 5.6	0.020 ± 0.003
MGSSL	70.5 ± 1.1	64.1 ± 0.7	80.7 ± 2.1	79.7 ± 0.8	76.4 ± 0.4	64.1 ± 0.7	-	-	-	-	-
MolCLR	73.3 ± 1.0	61.2 ± 3.6	89.8 ± 2.7	82.8 ± 0.7	74.1 ± 5.3	65.9 ± 2.1	2.301 ± 0.247	1.113 ± 0.023	0.789 ± 0.009	90.0 ± 1.7	0.019 ± 0.013
$\text{MolCLR}_{\text{GTrans}}$	76.7 ± 2.2	63.3 ± 2.5	89.3 ± 3.1	87.7 ± 1.8	80.2 ± 3.2	70.4 ± 2.1	2.124 ± 0.223	0.982 ± 0.109	0.767 ± 0.064	88.9 ± 4.8	0.018 ± 0.002
$\text{KGE\_NFM}_{\text{w/ MolKG}}$	92.4 ± 2.4	**65.3 ± 1.4**	87.3 ± 2.0	78.1 ± 2.1	79.8 ± 3.3	**72.6 ± 1.8**	1.942 ± 0.441	1.027 ± 0.201	0.877 ± 0.071	87.6 ± 3.2	**0.016 ± 0.001**
$\text{KANO}_{\text{CMPNN}}$	**92.6 ± 1.8**	**65.5 ± 1.6**	**92.9 ± 1.1**	**90.7 ± 3.1**	81.8 ± 1.1	**72.5 ± 1.9**	**1.320 ± 0.244**	**0.902 ± 0.104**	**0.641 ± 0.012**	**66.5 ± 3.7**	**0.013 ± 0.001**
$\text{KANO}_{\text{GTrans}}$	**93.7 ± 2.3**	63.8 ± 1.2	**93.6 ± 0.7**	**90.4 ± 1.5**	**81.2 ± 1.8**	**72.5 ± 1.5**	**1.443 ± 0.315**	**0.914 ± 0.092**	**0.651 ± 0.018**	**63.6 ± 4.1**	**0.013 ± 0.002**
GODE (ours)	**94.8 ± 1.9**	**67.4 ± 1.4**	**94.7 ± 2.9**	**92.0 ± 2.2**	**84.3 ± 1.2**	**73.4 ± 0.9**	**1.048 ± 0.314**	**0.746 ± 0.128**	0.743 ± 0.043	**57.2 ± 3.0**	**0.013 ± 0.001**

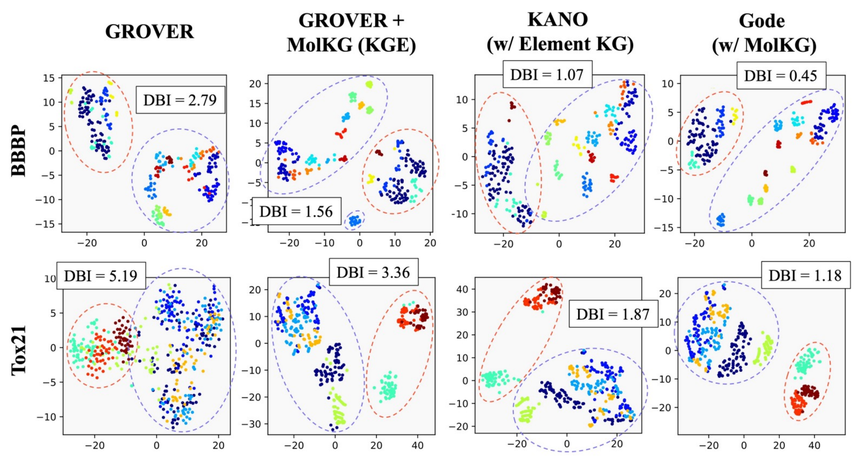
→ **Gode** achieves state-of-the-art performance on 10/11 tasks, outperforming all the previous baselines (including KANO, which leverages chemical element knowledge)

Case	KGE	κ	Pret.	Cont.	Embedding
0	✓	–	✗	✗	$\mathbf{h}_{\text{MG}} \oplus \mathbf{h}_{\text{KGE}}$
1	✗	2	✓	✓	$\mathbf{h}_{\text{MG}} \oplus \mathbf{h}_{\text{KG}}$
2	✓	2	✓	✗	$\mathbf{h}_{\text{MG}} \oplus \mathbf{h}_{\text{KG}}$
3	✓	2	✓	✓	$\mathbf{h}_{\text{MG}} \oplus \mathbf{h}_{\text{KG}}$
4	✓	2	✓	✓	$\mathbf{h}_{\text{MG}}$
5	✓	3	✓	✓	$\mathbf{h}_{\text{MG}} \oplus \mathbf{h}_{\text{KG}}$
6	✓	3	✓	✓	$\mathbf{h}_{\text{MG}}$
7	✓	2	✓	✓	$\mathbf{h}_{\text{MG}} \oplus \mathbf{h}_{\text{f}}$
8	✓	–	✗	✗	$\mathbf{h}_{\text{MG}} \oplus \mathbf{h}_{\text{f}} \oplus \mathbf{h}_{\text{KGE}}$
9	✓	2	✓	✓	$\mathbf{h}_{\text{MG}} \oplus \mathbf{h}_{\text{f}} \oplus \mathbf{h}_{\text{KG}}$



→ We conduct extensive ablation studies to show the effectiveness of each component in Gode.

Visualization



The learned **Gode** embedding has the most distinct clusters for different scaffolds (shown as different colors).
→ Highest representational power

Future Directions

- ❑ Applications in Drug Discovery
- ❑ Inclusion of Generative AI's power

Paper: https://pat-jj.github.io/assets/pdf/gode.pdf
Code: https://github.com/pat-jj/Gode

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