Of graphs, sets, and molecules

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It's always graphs

- SMILES (or SELFIES, DeepSMILES, …) are a way to represent (and store) graphs as strings
- … but then again, "Transformers are Graph Neural Networks" [1]
- The baseline for GNNs applied to molecular property prediction is quite strong (when also adding RDKit descriptors)

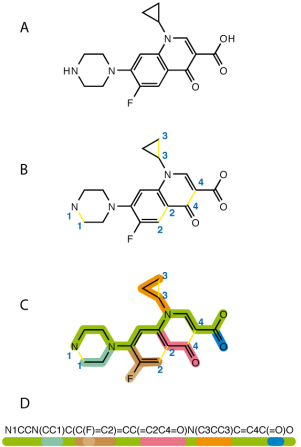


Figure 1: SMILES construction (Source: Wikipedia)

What about sets?

- … so we got (almost) rid of the bonds and thought of molecules as bags of atoms [2]
- This worked very well on the MoleculeNet benchmark… but everything does perform well on this

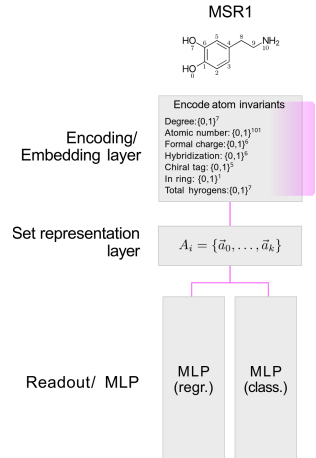


Figure 2: Molecular set representation architecture

What about sets?

Data Set	Metric	MGCN	SchNet	GCN	GIN	D-MPNN	MSR1
HIV	AUROC	73.8 ± 1.6	70.2 ± 3.4	71.6 ± 4.0	75.3 ± 1.9	75.0 ± 2.1	72.3 ± 2.2
BACE	AUROC	73.4 ± 3.0	76.6 ± 1.1	71.6 ± 2.0	70.1 ± 5.4	**85.3 ± 5.3**	75.5 ± 1.9
BBBP	AUROC	**85.0 ± 6.4**	84.8 ± 2.2	71.8 ± 0.9	65.6 ± 0.5	71.2 ± 3.8	71.4 ± 0.0
Tox21	AUROC	70.7 ± 1.6	**77.2 ± 2.3**	70.9 ± 2.6	74.0 ± 0.8	68.9 ± 1.3	72.1 ± 5.0
SIDER	AUROC	55.2 ± 1.8	53.9 ± 3.7	53.6 ± 3.2	57.3 ± 1.6	**63.2 ± 2.3**	61.4 ± 7.3
ClinTox	AUROC	63.4 ± 4.2	71.5 ± 3.7	62.5 ± 2.8	58.0 ± 4.4	**90.5 ± 5.3**	86.6 ± 1.2
ESOL	RMSE	1.27 ± 0.15	1.05 ± 0.06	1.43 ± 0.05	1.45 ± 0.02	0.98 ± 0.26	**0.59 ± 0.03**
FreeSolv	RMSE	3.35 ± 0.01	3.22 ± 0.76	2.87 ± 0.14	2.76 ± 0.18	2.18 ± 0.91	**1.94 ± 0.24**
Lipo	RMSE	1.11 ± 0.04	0.91 ± 0.10	0.85 ± 0.08	0.85 ± 0.07	**0.65 ± 0.05**	0.85 ± 0.03
QM7	MAE	77.6 ± 4.7	**74.2 ± 6.0**	122.9 ± 2.2	124.8 ± 0.7	105.8 ± 13.2	85.9 ± 13.1
QM8	MAE	0.022 ± 0.002	0.020 ± 0.002	0.037 ± 0.001	0.037 ± 0.001	**0.014 ± 0.002**	0.023 ± 0.010

What about sets of node embeddings?

- What about combining the set representation approach with GNNs?
- Embedding nodes, followed by a set representation layer instead of global pooling
- Turns out, this works quite well on more representative benchmarks

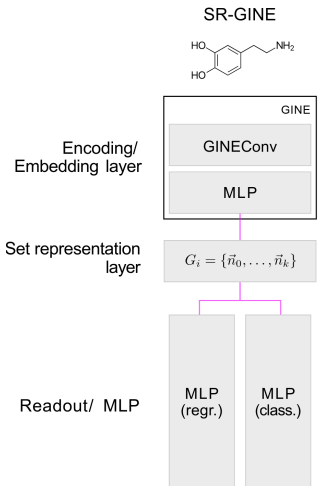


Figure 3: SR-GINE architecture

What about sets of node embeddings?

Data from Biogen ADME in vitro assays. The metric used is the Pearson correlation. Similar results on OCELOT chromophore data containing chemically diverse π-conjugated molecules [3], [4].

Endpoint	D-MPNN	D-MPNN+	MSR1	GINE	SR-GINE
HLM	0.65	**0.68**	0.58 ± 0.00	0.59 ± 0.01	**0.68 ± 0.01**
MDR1-MDCK ER	0.72	0.78	0.68 ± 0.02	0.67 ± 0.00	**0.80 ± 0.01**
Solubility	**0.64**	0.59	0.47 ± 0.04	0.55 ± 0.02	0.63 ± 0.02
RLM	0.72	**0.74**	0.57 ± 0.01	0.61 ± 0.02	0.70 ± 0.01
hPPB	0.74	**0.77**	0.68 ± 0.01	0.68 ± 0.02	**0.77 ± 0.01**
rPPB	0.70	0.70	0.55 ± 0.02	0.63 ± 0.02	**0.73 ± 0.02**
Average	0.695 ± 0.037	0.710 ± 0.064	0.588 ± 0.08	0.622 ± 0.05	**0.718 ± 0.06**

Sets of molecules (reactions)

Yield prediction on Buchwald-Hartwig reactions from high-throughput experiments (HTE) and extracted from an electronic laboratory notebook (ELN) [5], [6]. The metric used is R^2.

Data Set	Subset/Spilt	Yield-BERT	DRFP	YieldGNN	MSR2-RXN
HTE	Rand 70/30	0.95 ± 0.005	0.95 ± 0.005	0.96 ± 0.005	0.94 ± 0.005
	Rand 50/50	0.92 ± 0.01	0.93 ± 0.01	-	0.93 ± 0.01
	Rand 30/70	0.88 ± 0.01	0.89 ± 0.01	-	0.90 ± 0.01
	Rand 20/80	0.86 ± 0.01	0.87 ± 0.01	-	0.87 ± 0.01
	Rand 10/90	0.79 ± 0.02	**0.81 ± 0.01**	-	0.80 ± 0.02
	Rand 5/95	0.61 ± 0.04	0.73 ± 0.02	-	0.69 ± 0.03
	Rand 2.5/97.5	0.45 ± 0.05	**0.62 ± 0.04**	-	0.57 ± 0.05
	Avg. 1-4	**0.73**	0.71 ± 0.16	-	0.72 ± 0.15
ELN	-	−0.006 ± 0.11	**0.20 ± 0.05**	0.05 ± 0.07	0.13 ± 0.08

Speaking of sets and reactions ...

- We recently published an update on the differential reaction fingerprint (DRFP) where we set SOTA on the ELN data set
- See results on previous slide
- More on sets, molecules, and reactions coming soon ...

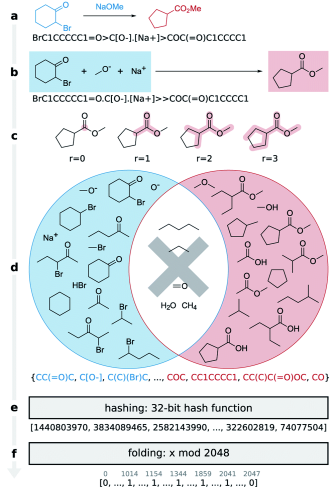


Figure 4: DRFP Scheme

Speaking of sets and reactions ...

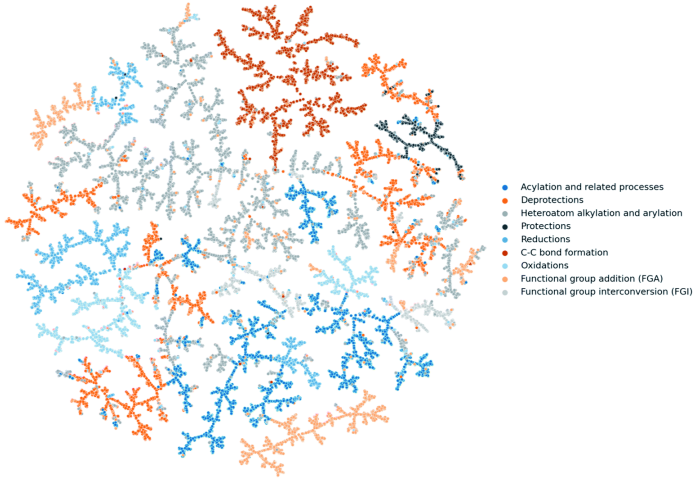


Figure 5: DRFP-encoded USPTO subset visualised using TMAP.

Mass spectra as graphs

- Mass spectra are commonly binned to account for different numbers of peaks between samples
- Why not represent them as graphs and predict the quantitative estimate of drug-likeness (QED)?
- Intensities as node attributes and m/z differences as edge weights [7]

Model	Params	MAE (↓)	RMSE (↓)	Pearson's r (↑)	R^2 (↑)
MLP	11.0 M	0.145 ± 0.008	0.200 ± 0.008	0.736 ± 0.011	0.437 ± 0.043
SetTransformer	0.4 M	0.134 ± 0.002	0.174 ± 0.001	0.758 ± 0.004	0.572 ± 0.006
GNN (GAT)	12.6 M	**0.110 ± 0.006**	**0.144 ± 0.006**	**0.843 ± 0.015**	**0.709 ± 0.025**

Molecular dynamics as graphs

- Idea: Combine structure and dynamics in a heterogeneous graph [8]
- 8 ns MD per protein (or complex) from the MISATO data set [9]
- Significant performance improvements in binding site detection, binding affinity prediction, and atomic adaptability prediction

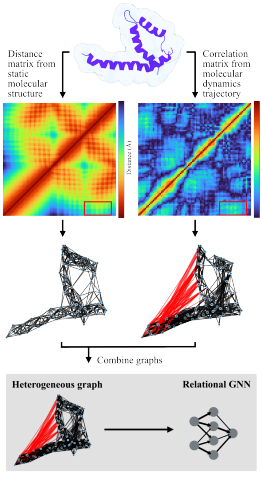


Figure 6: DRFP Scheme

Molecular dynamics as graphs

- Hypothesis: In addition to the dynamics information, dynamics edges reduce over-squashing and improve long-range information propagation
- More recent research showed that random edges do not have a similar effect on performance

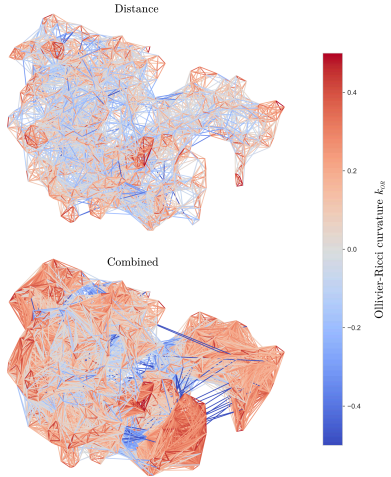


Figure 7: Ollivier-Ricci curvature

Modelling protein conformations

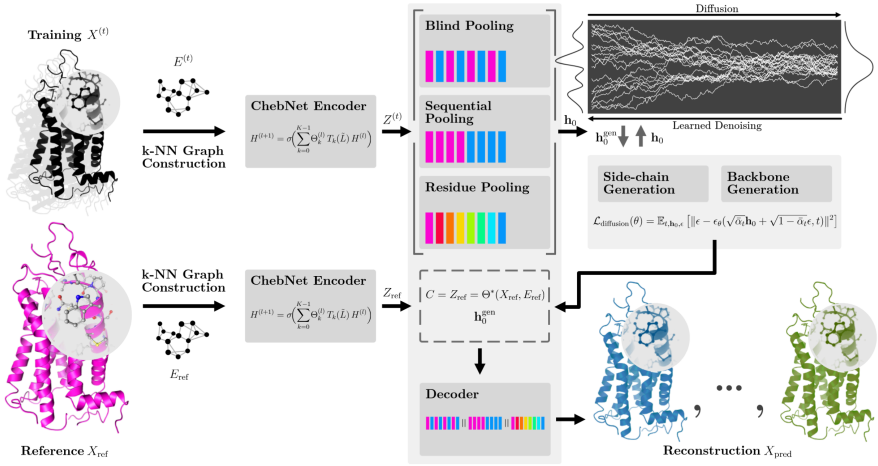


Figure 8: Schematic of the LD-FPG framework.

Modelling protein conformations

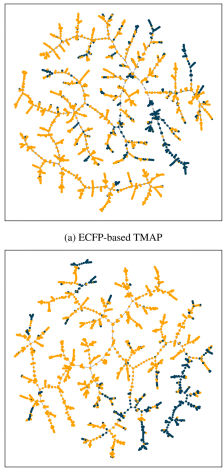
- Autoencoder architecture utilising **ChebNet** combined with residue-based pooling [10]
- As it turns out, ChebNet performs well compared to other GNN architectures on long-range tasks
- But you have probably heard enough about protein ensemble generation already …

Back to SMILES and … GZIP

Model		RMSE	MAE	R
GraphDTA	GCN	1.735 ± 0.034	1.343 ± 0.037	0.613 ± 0.016
	GAT	1.765 ± 0.026	1.354 ± 0.033	0.601 ± 0.016
	GIN	1.640 ± 0.044	1.261 ± 0.044	0.667 ± 0.018
	GAT-GCN	1.562 ± 0.022	1.191 ± 0.016	0.697 ± 0.008
GNN-based	GNN-DTI	1.492 ± 0.025	1.192 ± 0.032	0.736 ± 0.021
	D-MPNN	1.493 ± 0.016	1.188 ± 0.009	0.729 ± 0.006
	MAT	1.457 ± 0.037	1.154 ± 0.037	0.747 ± 0.013
	DimeNet	1.453 ± 0.027	1.138 ± 0.026	0.752 ± 0.010
	CMPNN	**1.408 ± 0.028**	**1.117 ± 0.031**	**0.765 ± 0.009**
Compression-based	MolZip	1.508 ± 0.000	1.190 ± 0.000	0.720 ± 0.000
	MolZip Aug	1.422 ± 0.017	1.131 ± 0.014	0.757 ± 0.007

Back to SMILES and … GZIP

- Based on the normalised compression distance
- $\mathrm{NCD}(x,y) = \frac{0.5(C(xy)+C(yx))-\min\{C(xx),C(yy)\}}{\max\{C(xx),C(yy)\}}$
- approximates normalised information distance, specifically the Kolmogorov complexity, which is uncomputable ($\longrightarrow$ halting problem) in
- $\mathrm{NID}(x,y) = \frac{\max\{K(x|y),K(y|x)\}}{\max\{K(x),K(y)\}}$
- Based on this, we build kNN classifiers and regressors [11]



(a) ECFP-based TMAP

(b) MolZip-based TMAP

Figure 9: TMAPs of BBBP

Thanks!

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- probstlab.science
- github.com/daenuprobst/talks

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