Jenke Scheen

A data-driven approach to relative Free Energy Perturbation reliability predictions for alchemical free energy calculations in drug design

MGMS
Young Modellers' Forum
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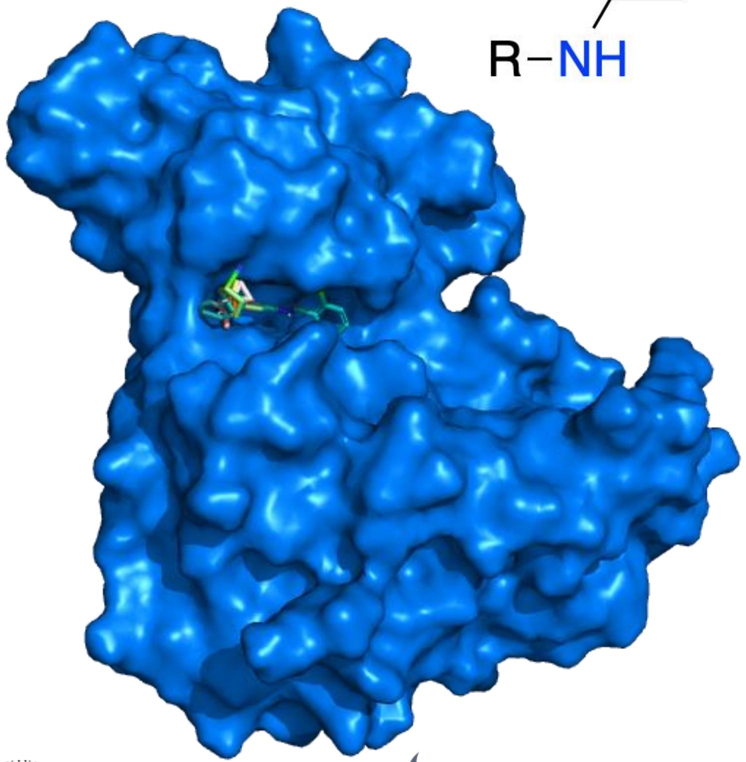
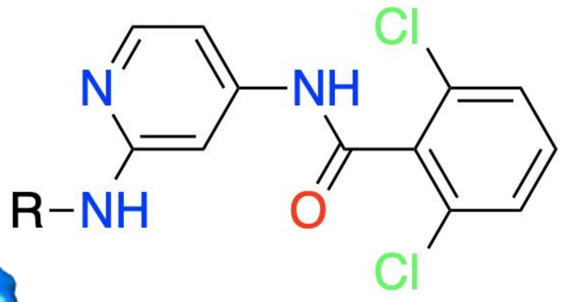
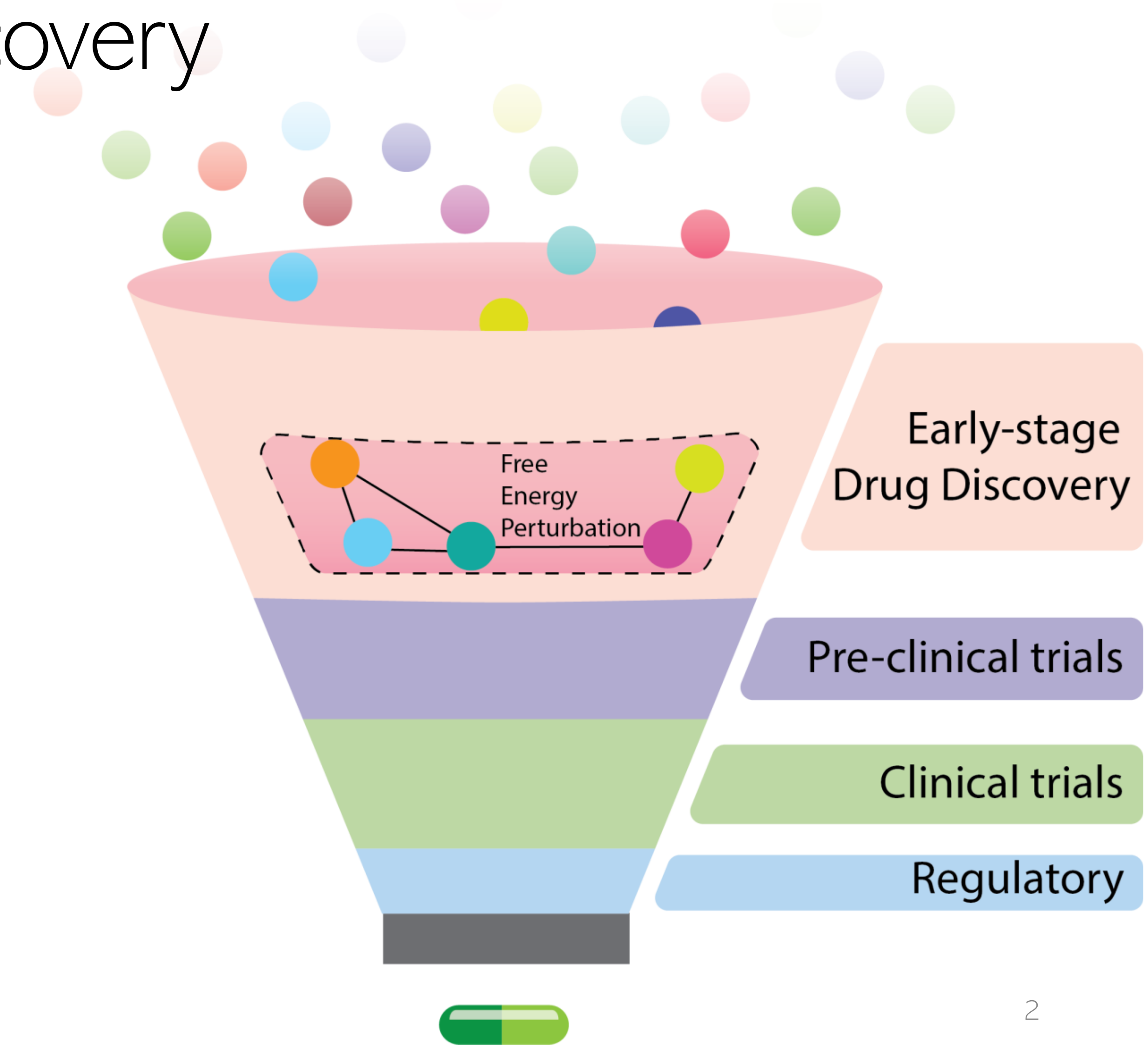
Free Energy Perturbation (FEP) is a a helpful tool in supporting ligand optimization in early-stage drug discovery







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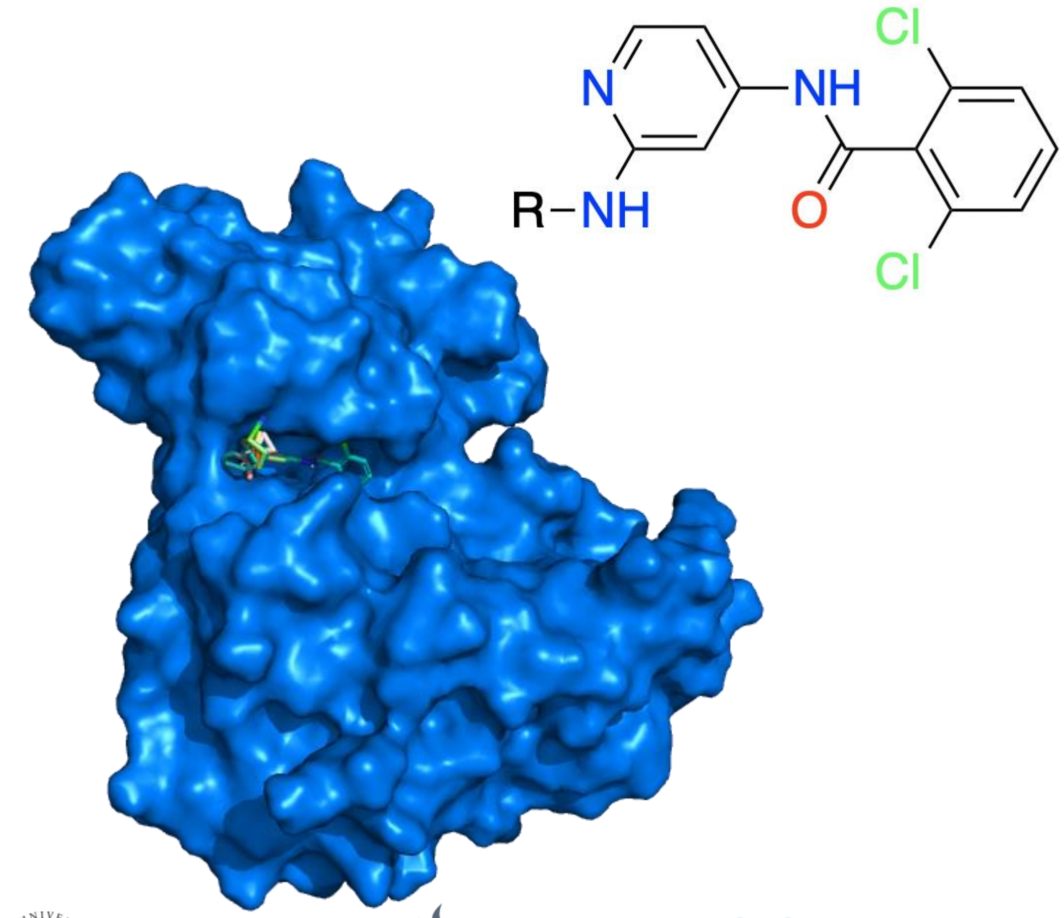
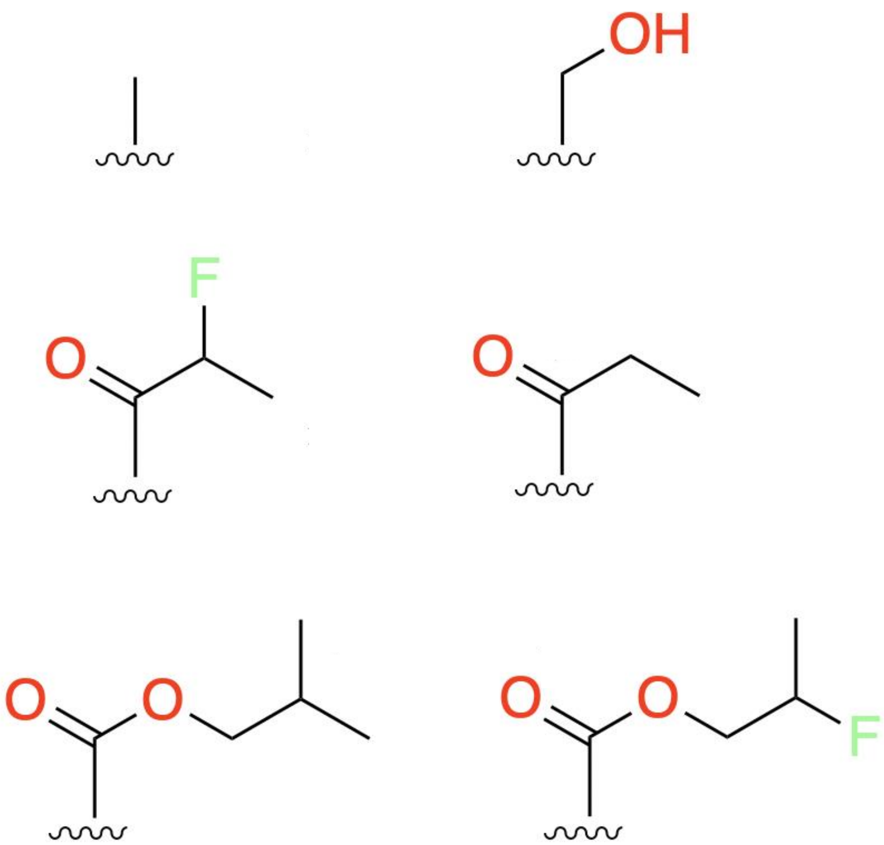
Free Energy Perturbation (FEP) can predict the relative binding free energy between ligands





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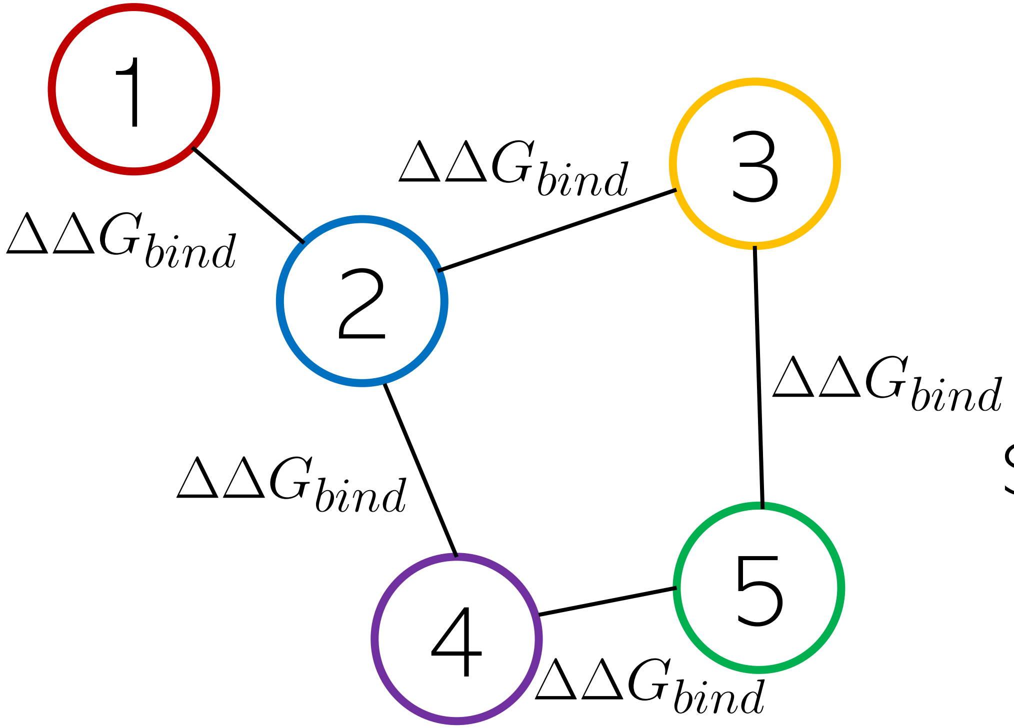
FEP calculations on ligand series require a graph of transformations through the series



Weighted Least Squares regression

$\Delta\Delta G_{bind,\ ligand\ 1} = ..$

$\Delta\Delta G_{bind,\ ligand\ 2} = ..$

$\Delta\Delta G_{bind,\ ligand\ 3} = ..$

$\Delta\Delta G_{bind,\ ligand\ 4} = ..$

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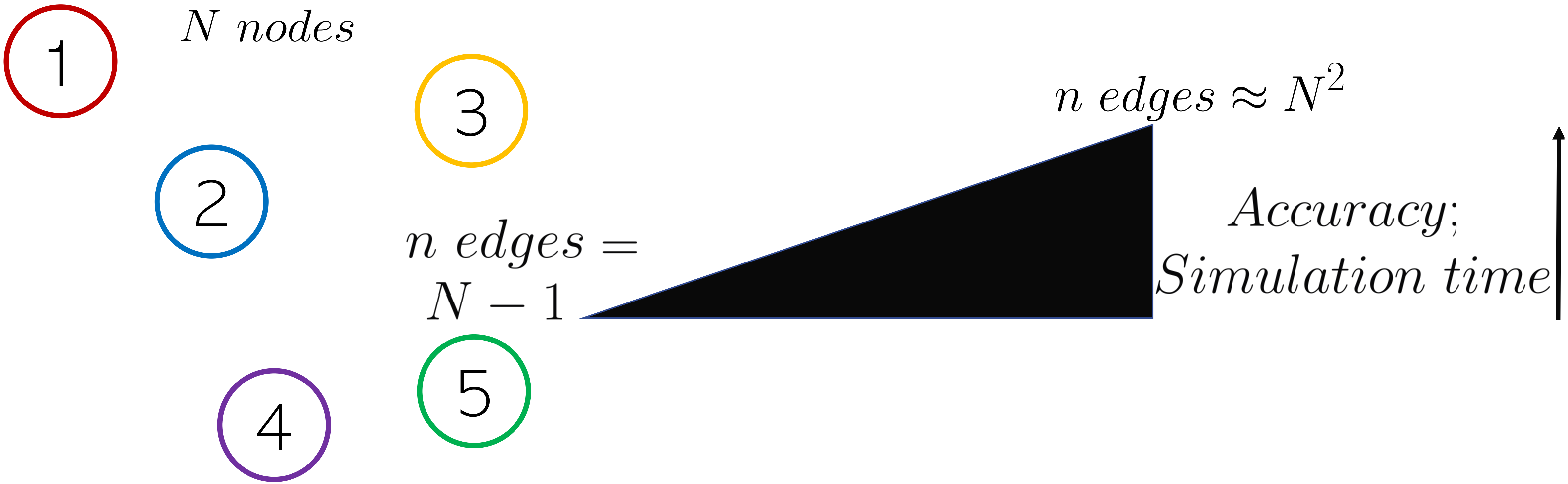
Problem statement – how do we pick a graph?



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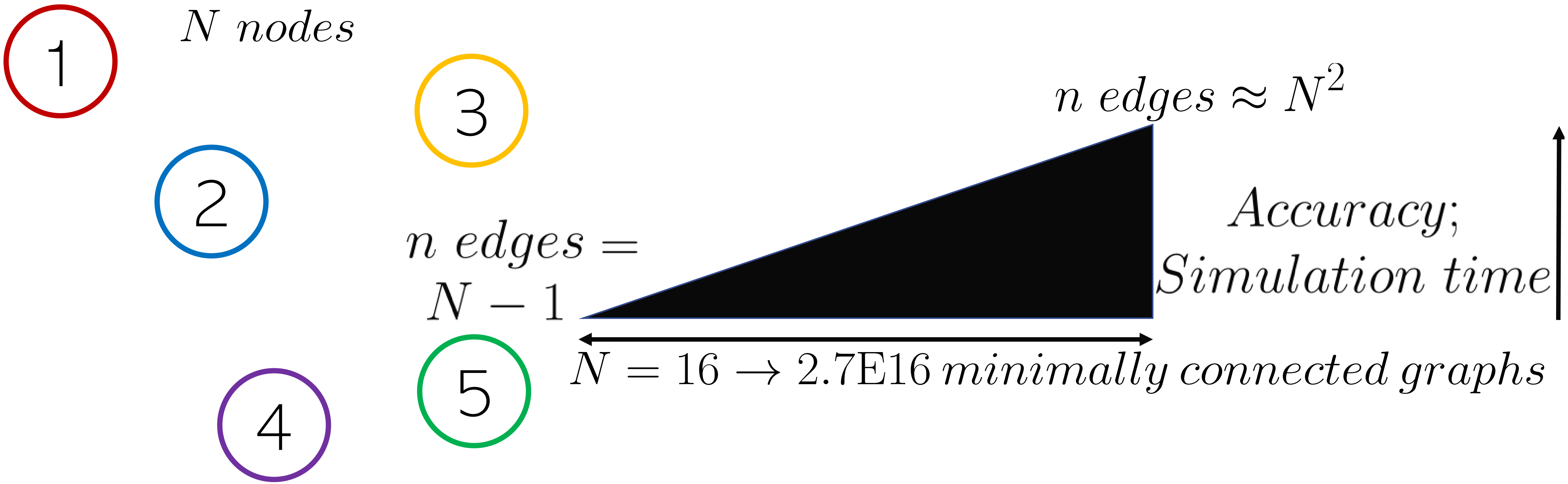
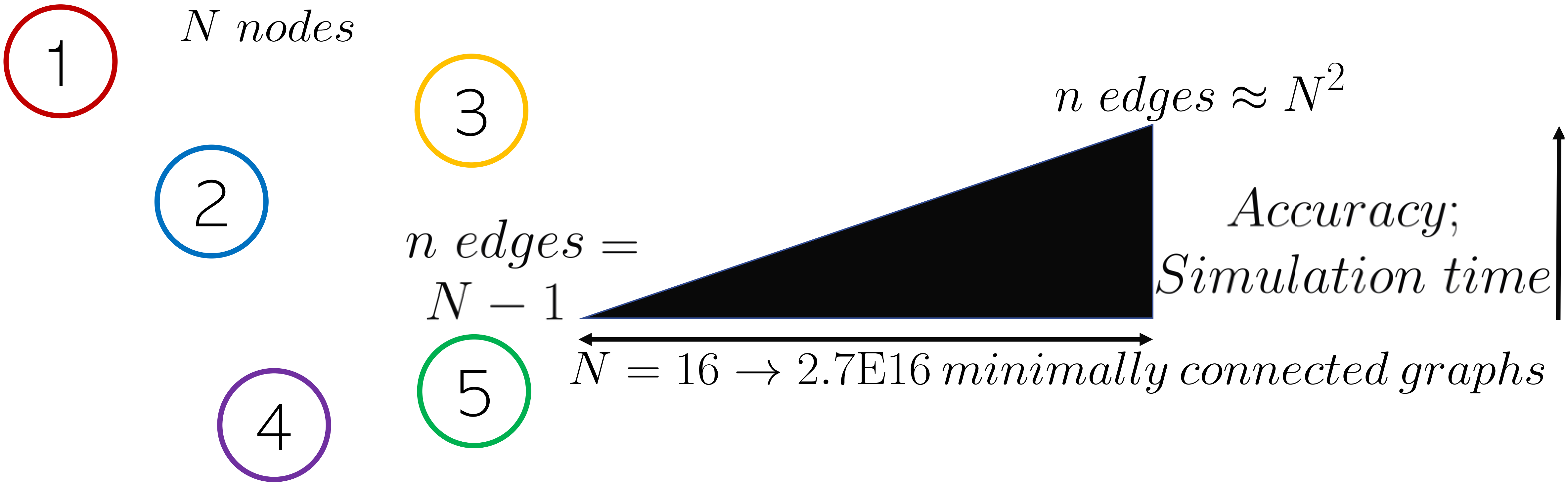
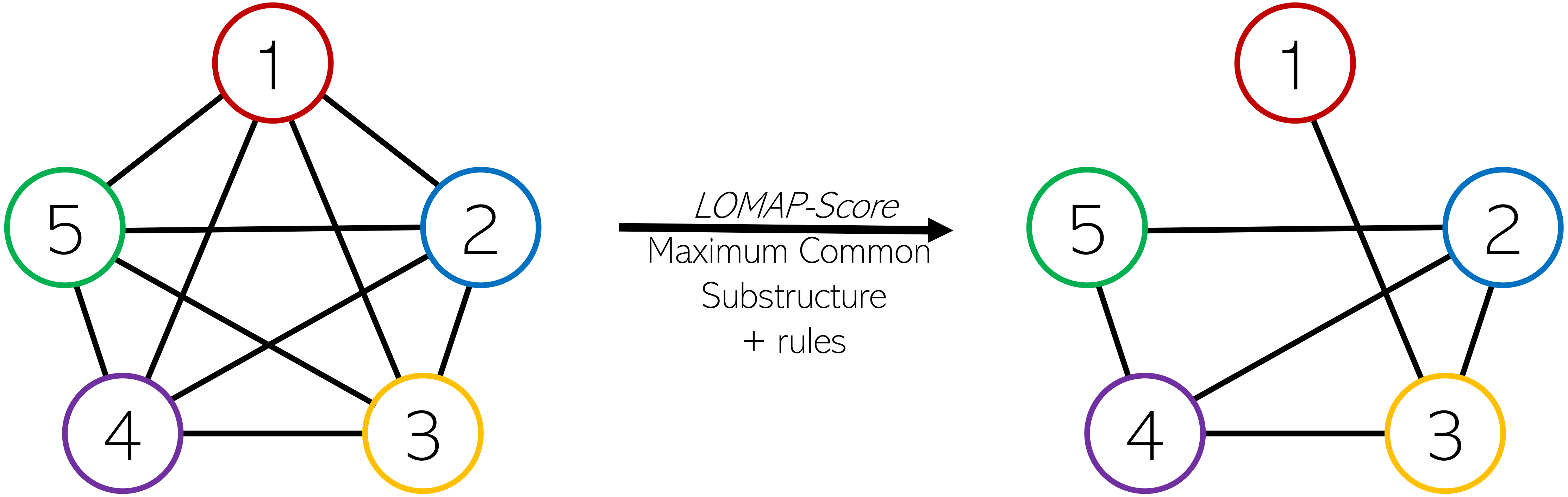


Problem statement – how do we pick a graph?



Goal: find a graph that minimises the number of edges (n), while maximising prediction accuracy (versus experiment).

State-of-the-art: LOMAP-Score depends on MCS and expert-derived rules



Shuai Liu et al, Lead optimization mapper: automating free energy calculations for lead optimization, J Comput Aided Mol Des . 2013 Sep;27(9):755-70. doi: 10.1007/s10822-013-9678-y. Epub 2013 Sep 26.

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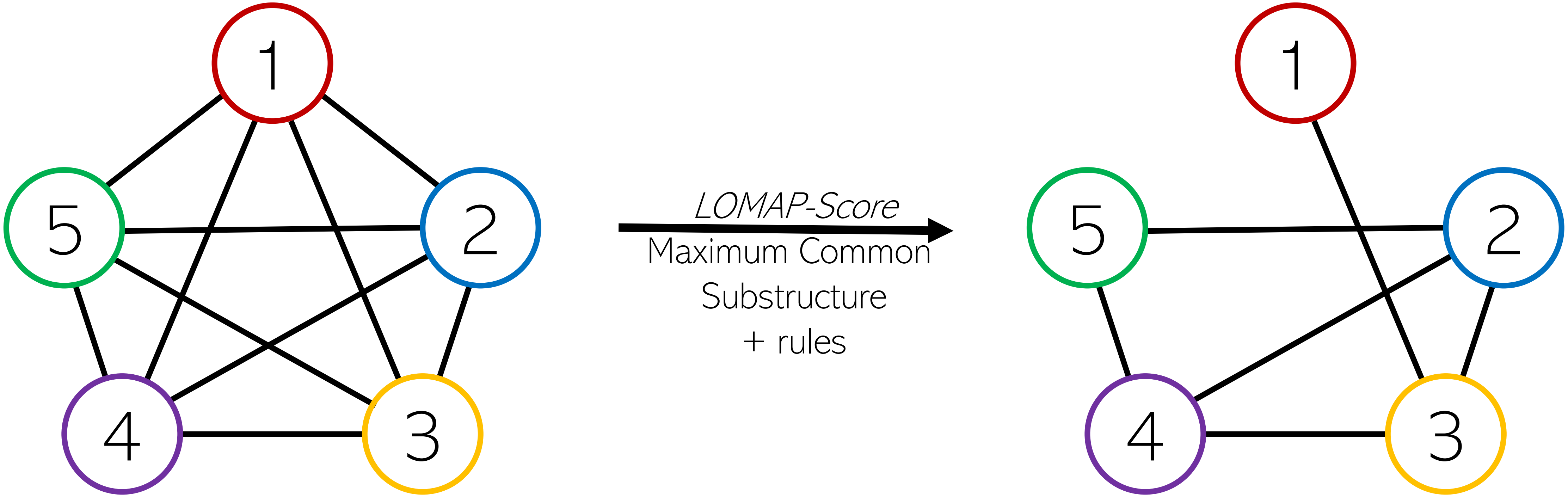

Extensively tweaked to perform adequately

Does not scale well to higher N (>50)

Limited transferability to other FEP codes

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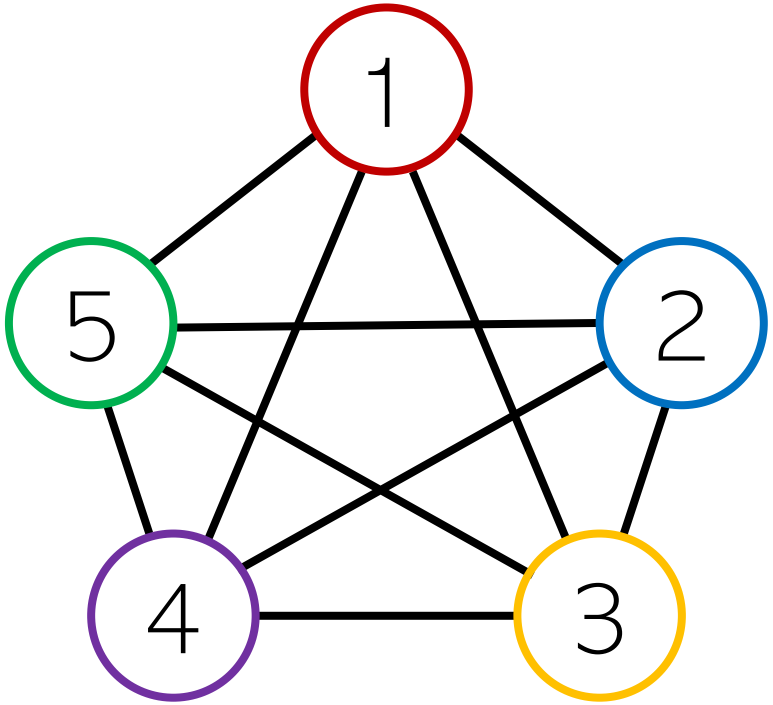
The ideal metric: $\Delta\Delta G_{offset}$



- Absolute differences between FEP predictions and experimental values

J Scheen et al, Hybrid Alchemical Free Energy/Machine-Learning Methodology for the Computation of Hydration Free Energies , J Chem Inf Model . 2020 Nov 23;60(11):5331-5339. doi: 10.1021/acs.jcim.0c00600.

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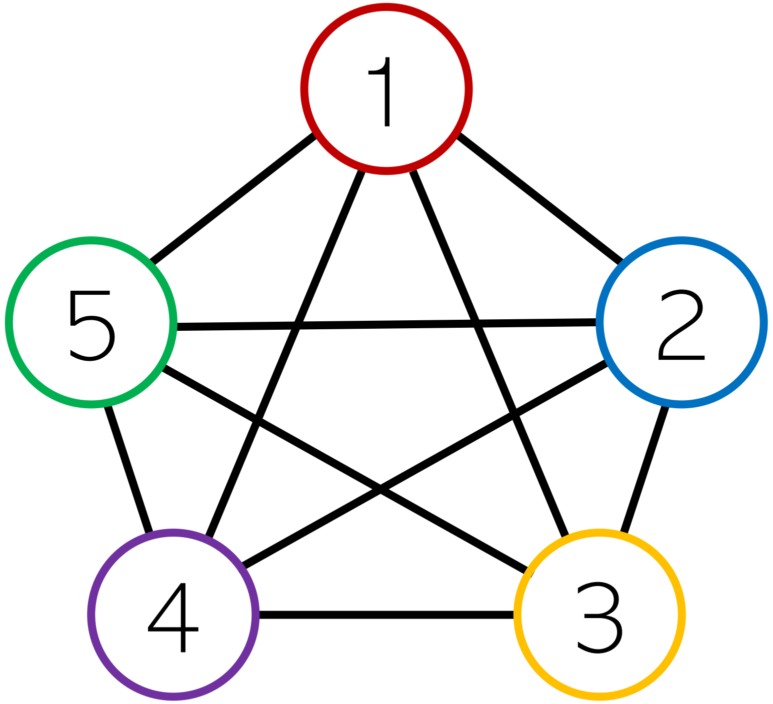
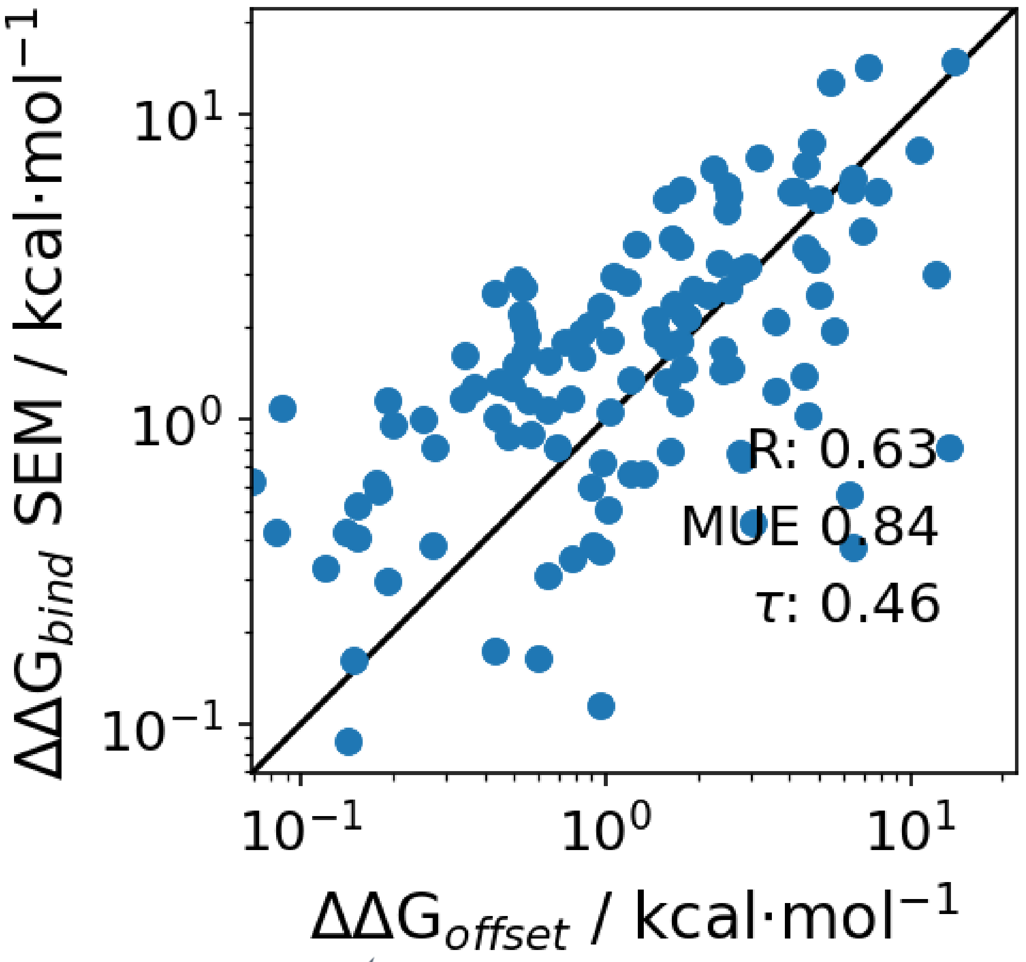


- Absolute differences between FEP predictions and experimental values
- Neither are known *a priori*
- Proposed graph has theoretically minimal FEP 'mistakes'

J Scheen et al, Hybrid Alchemical Free Energy/Machine-Learning Methodology for the Computation of Hydration Free Energies , J Chem Inf Model . 2020 Nov 23;60(11):5331-5339. doi: 10.1021/acs.jcim.0c00600.

A more practical metric: FEP uncertainty



- FEP standard error of the mean (SEM) tends to be low when offset is low
- No experimental data required
- Still require FEP simulations to obtain SEMs

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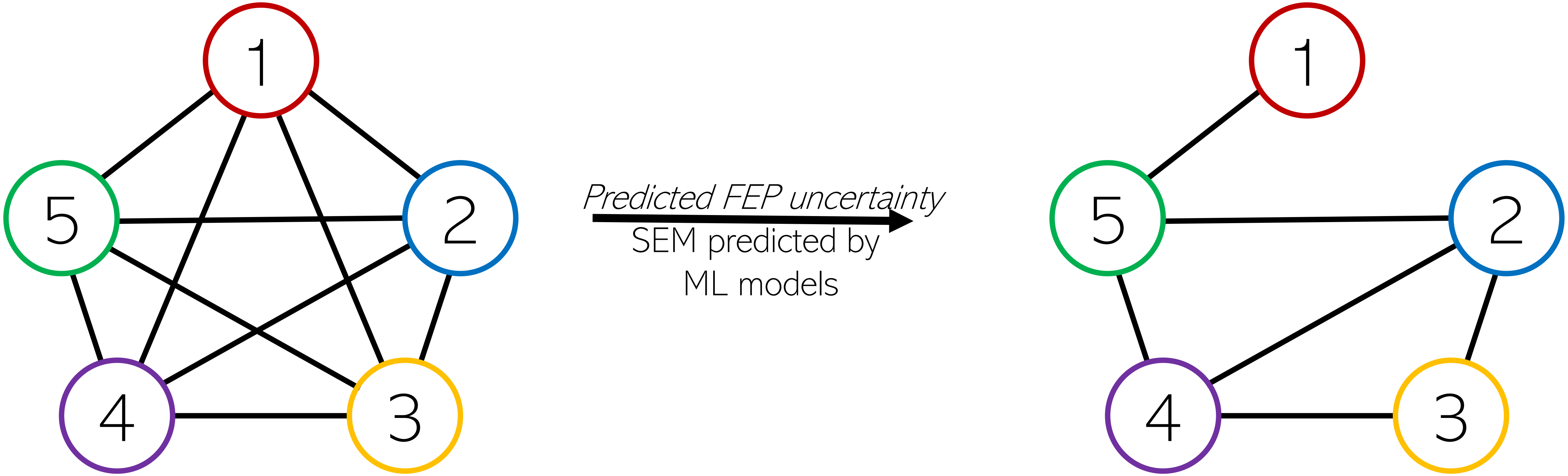
This work: predict FEP uncertainty with machine-learning models



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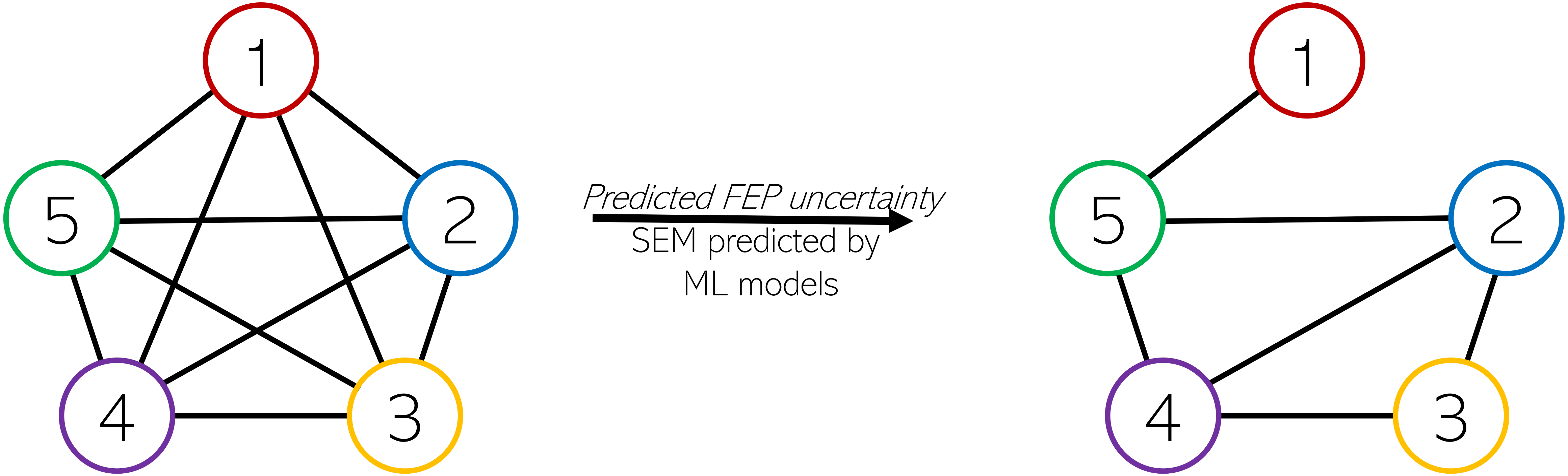

Can do a representative set of FEPs in advance

Fast, scalable estimation for large N

Does not require expert/subjective engineering

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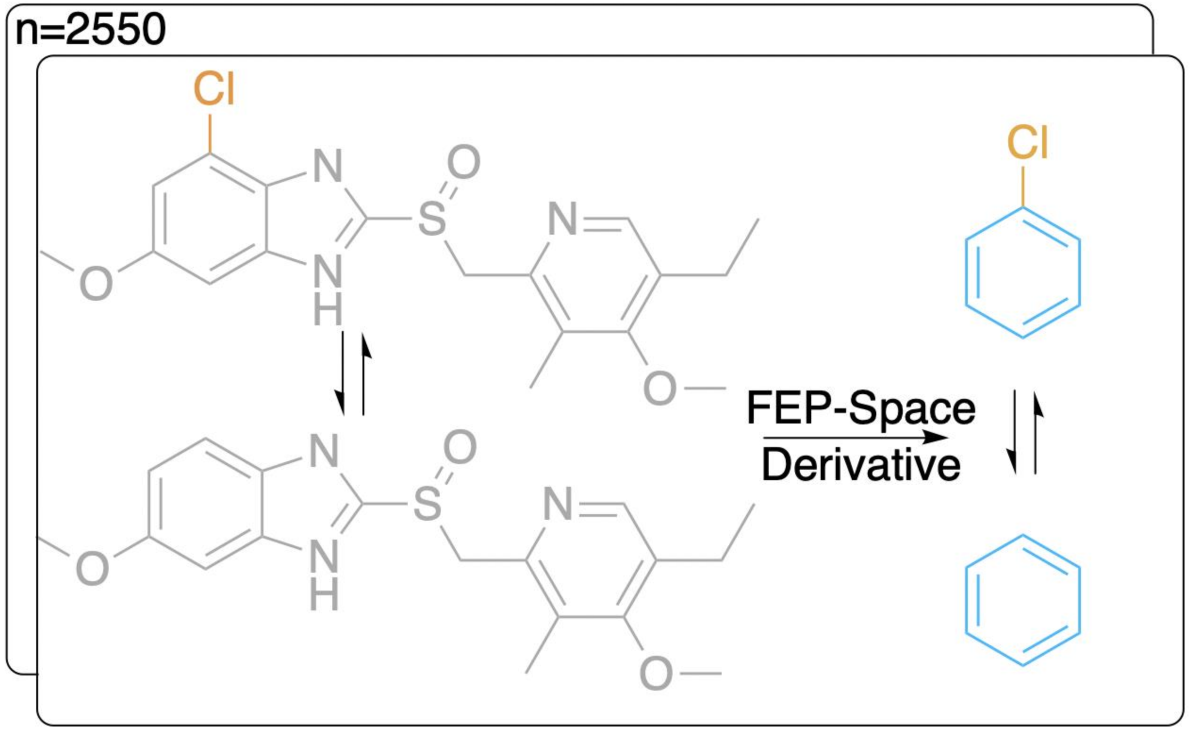
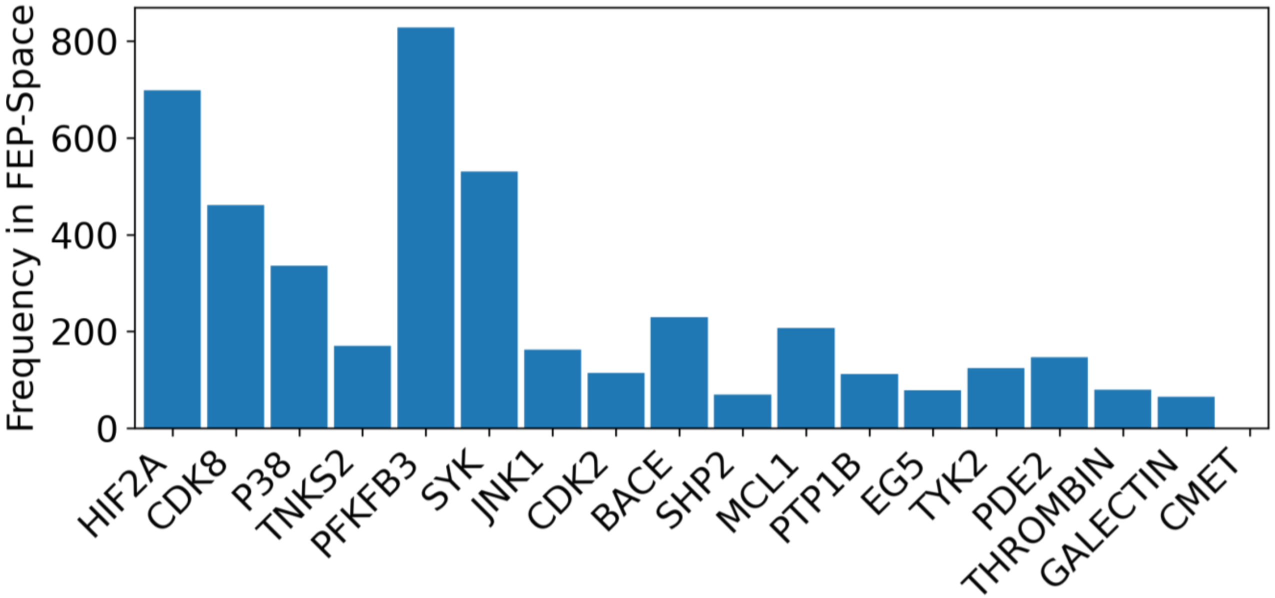
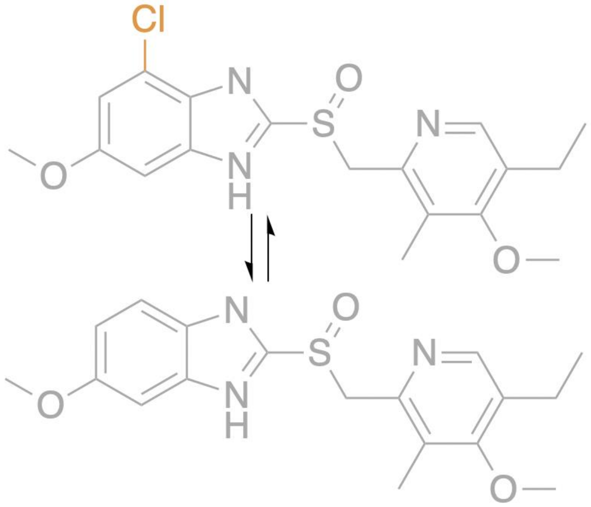
FEP-Space was created as a training set to represent all realistic FEP transformations

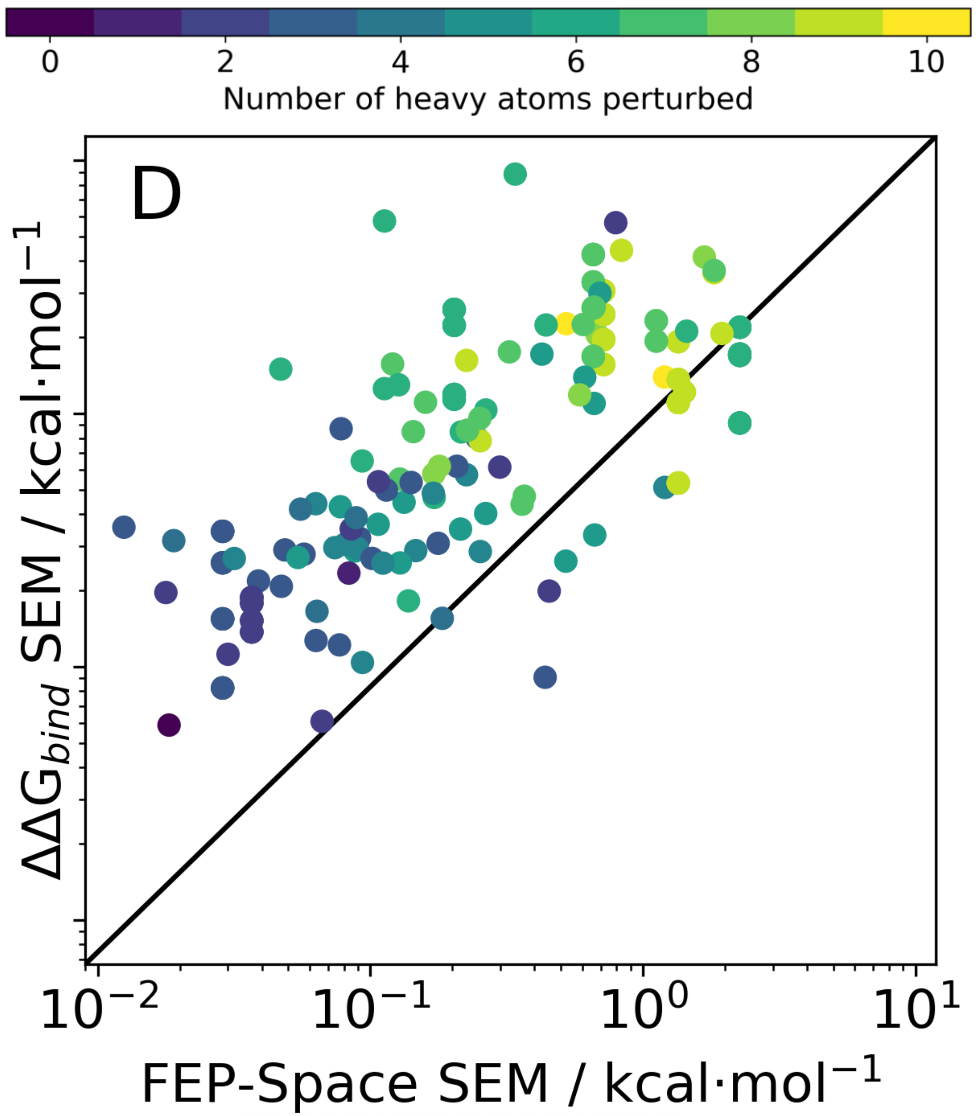


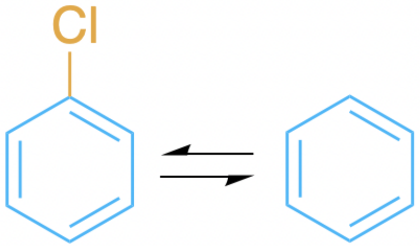


~25K GPUh

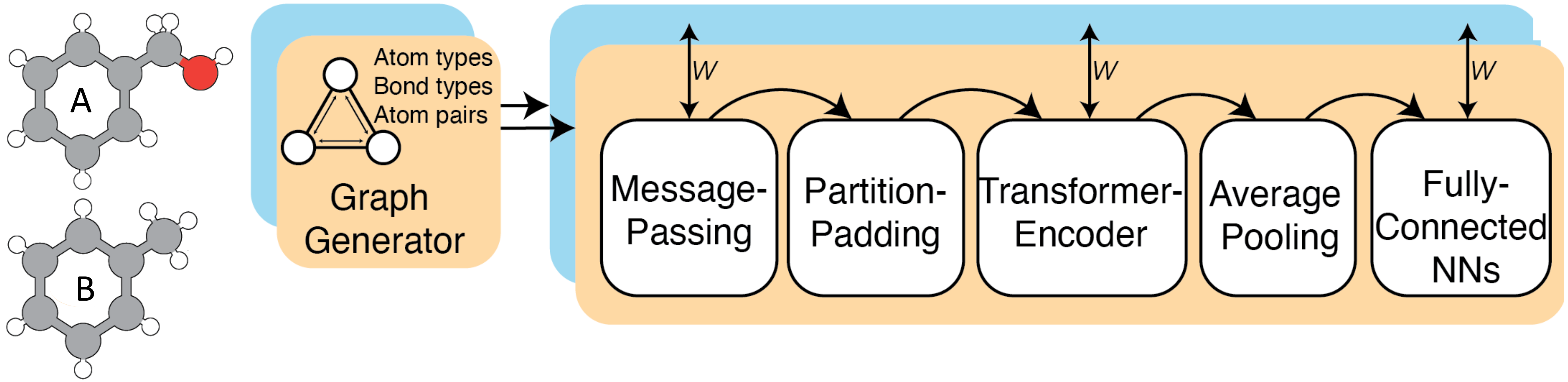
FEP-Space is a generalisable training domain at the cost of losing some correlation to its source SEM







FEP-NN: a graph neural network that trains on FEP-Space ligand pairs



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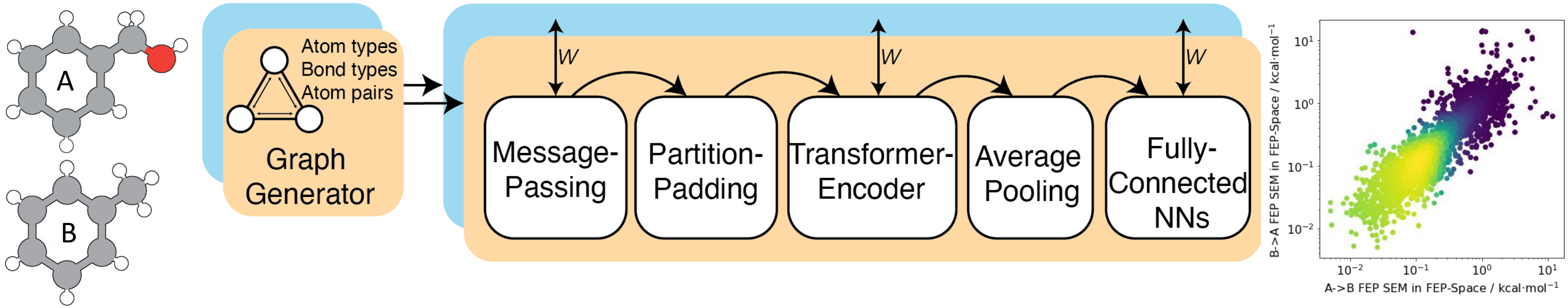

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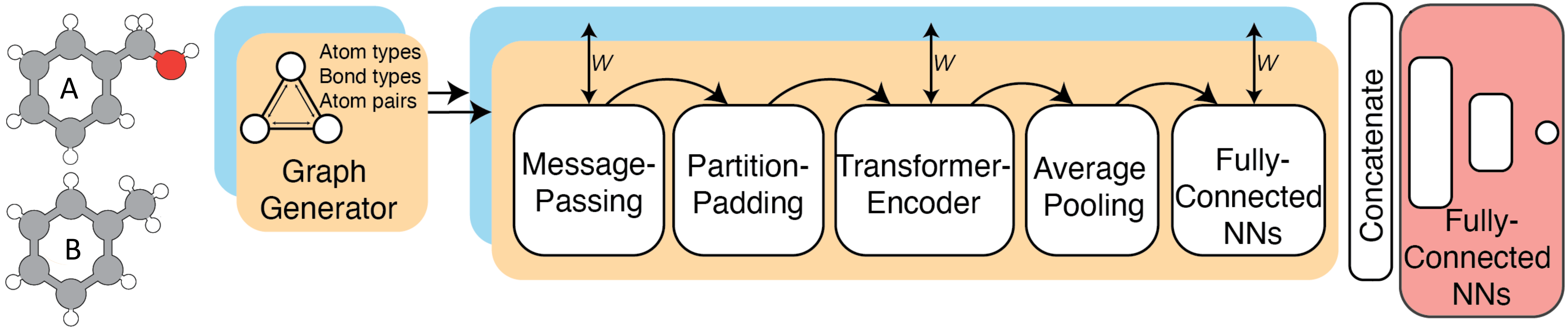

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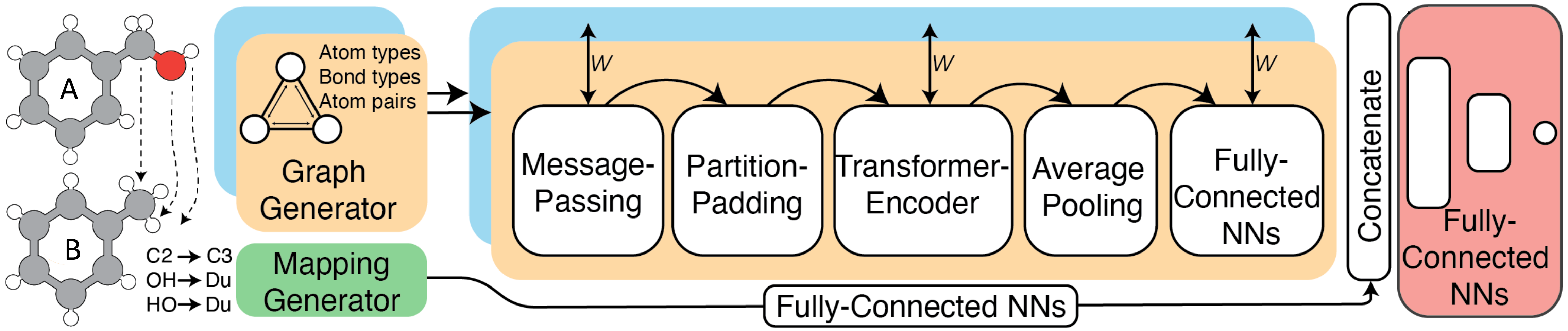

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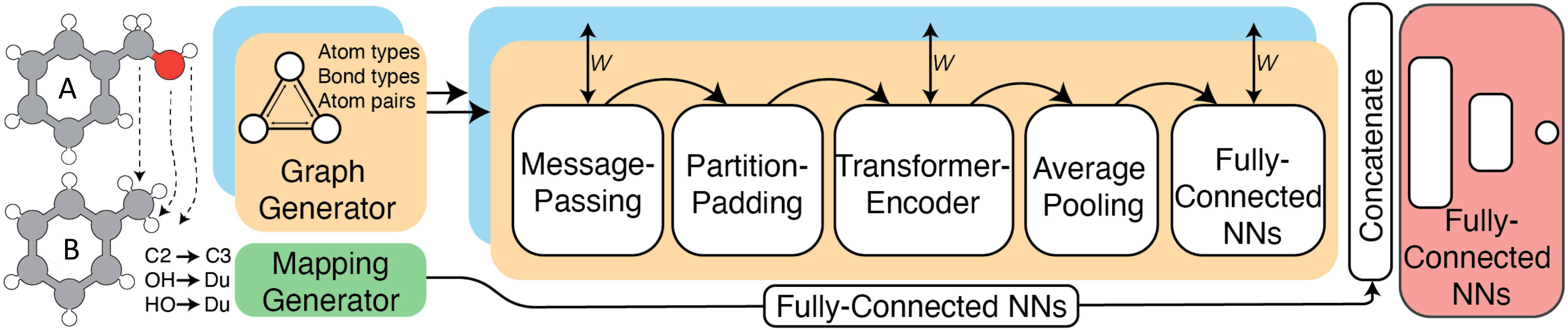

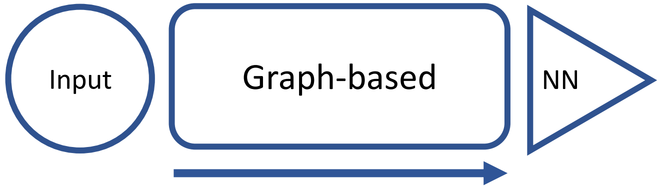

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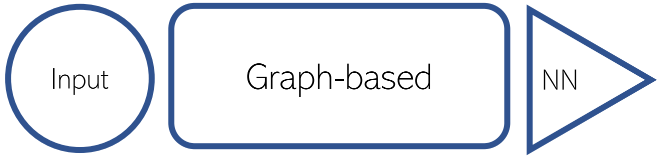
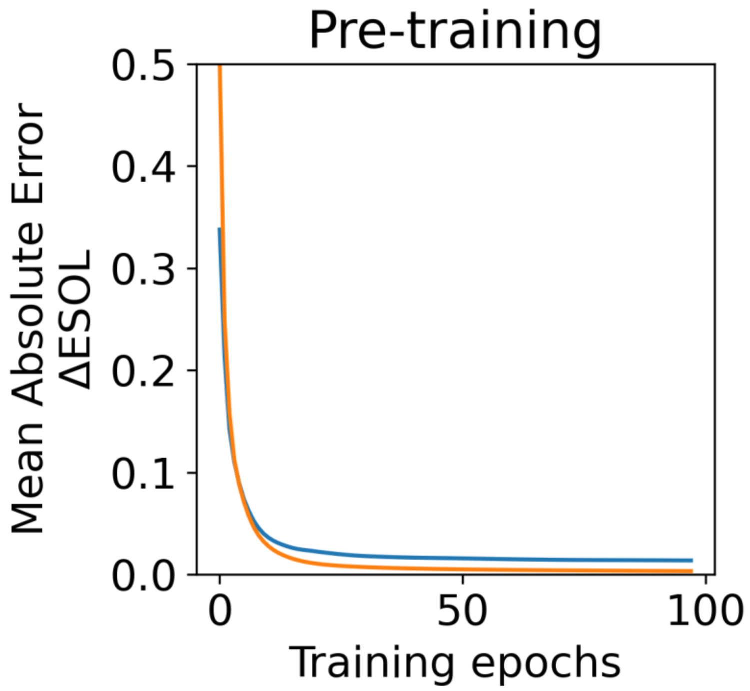
FEP-NN: training on FEP-space using a transfer-learning approach





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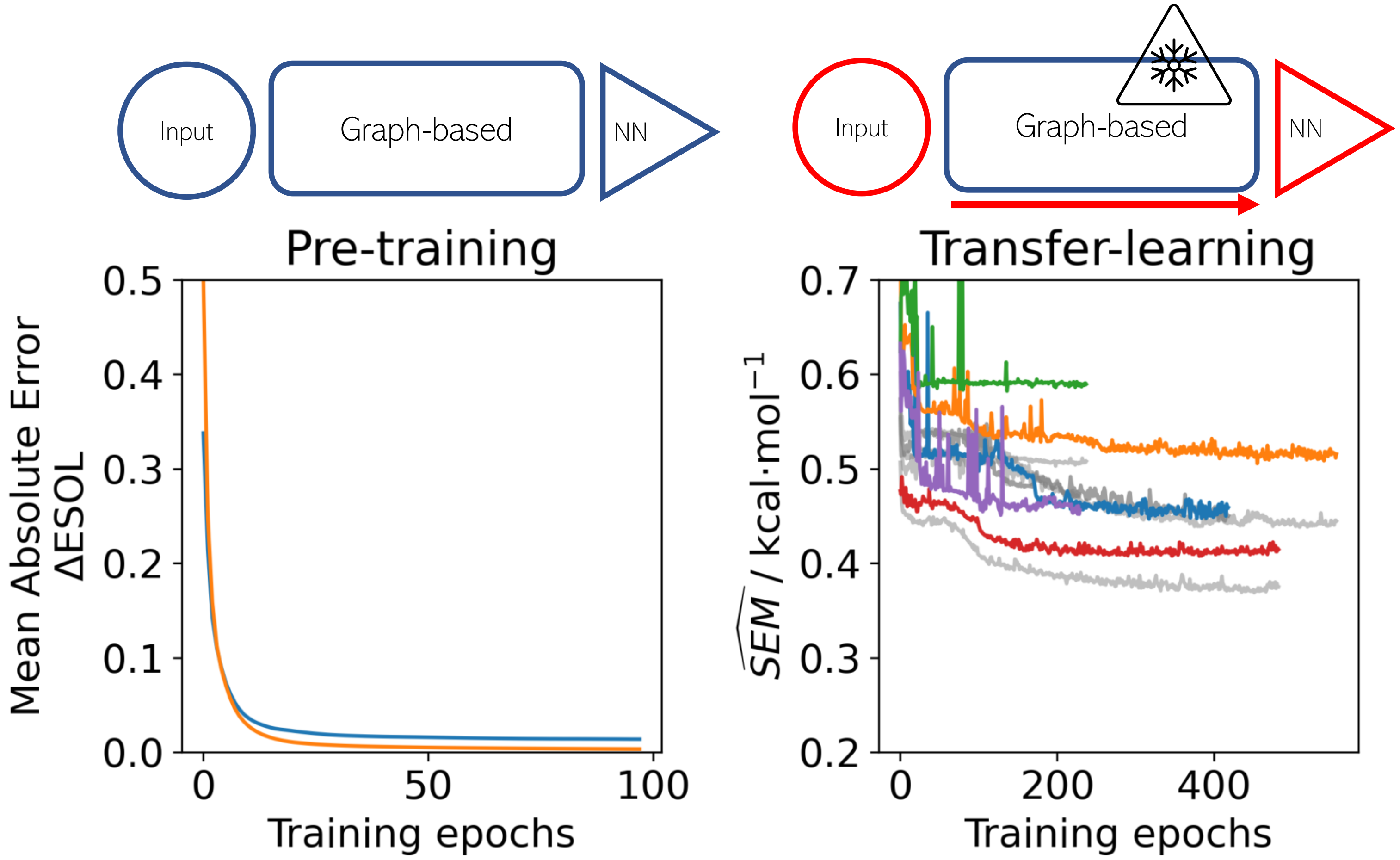

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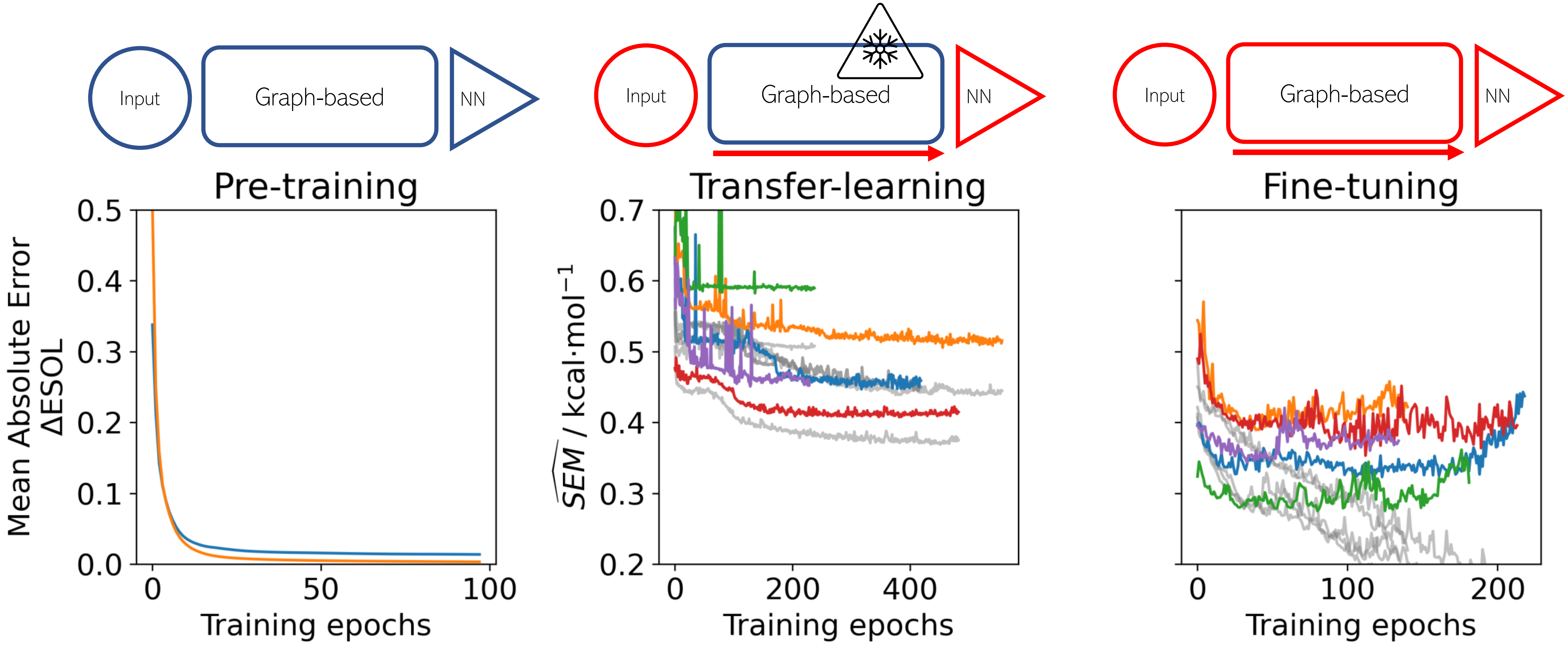

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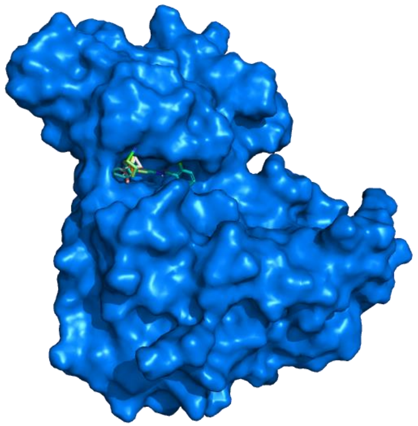
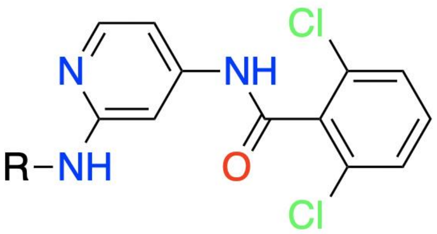
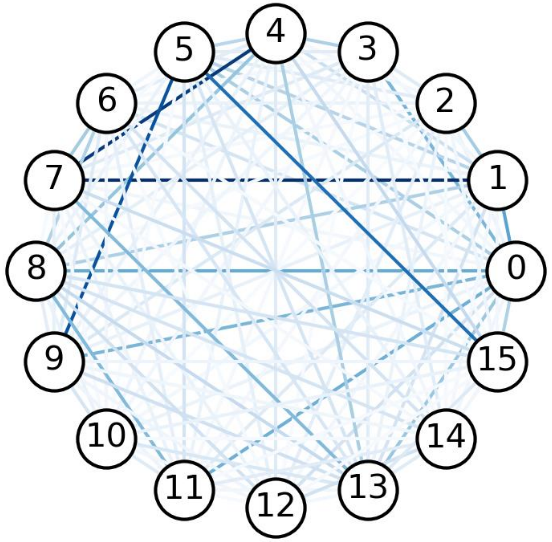
Applying trained model to test set – TYK2 methodology

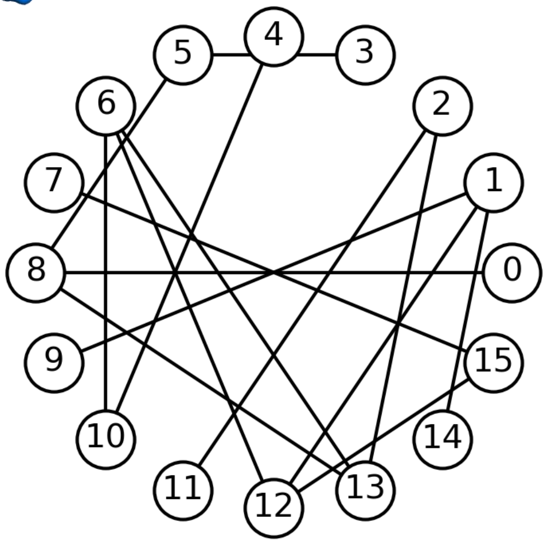




Fully-connected:



Generated graph:



Free Energy Predictions:

$$\Delta\Delta G_{bind,\ ligand\ 1} = ..$$

$$\Delta\Delta G_{bind,\ ligand\ 2} = ..$$

$$\Delta\Delta G_{bind,\ ligand\ 3} = ..$$

$$\Delta\Delta G_{bind,\ ligand\ 4} = ..$$

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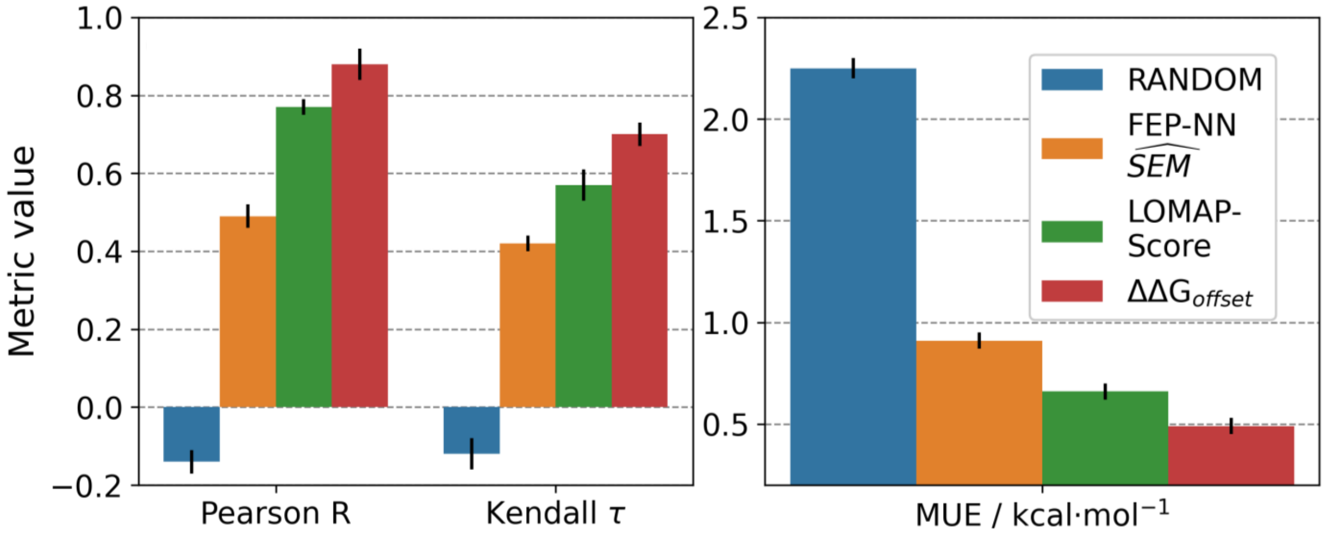
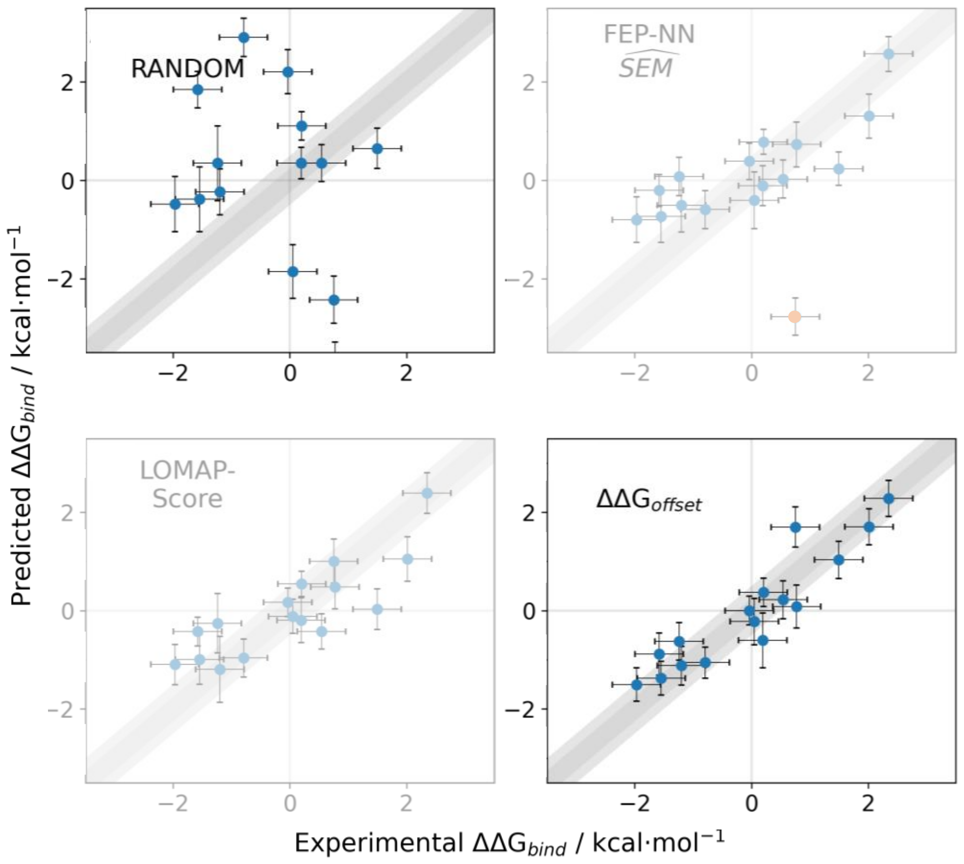
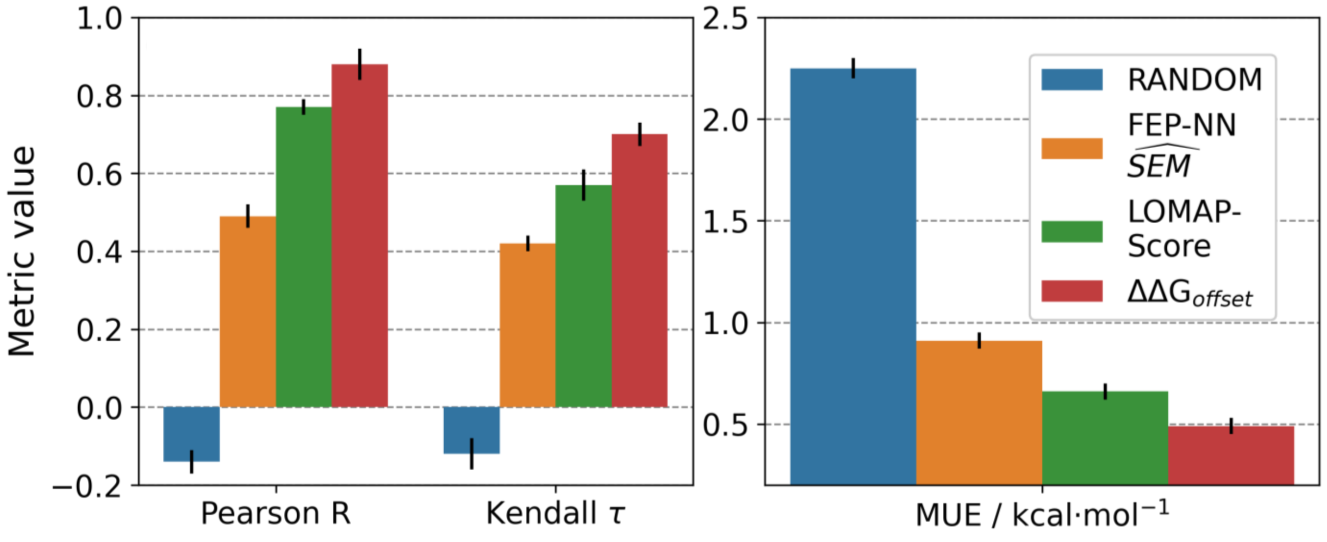
120 FEPs (5x): ~13K GPUh

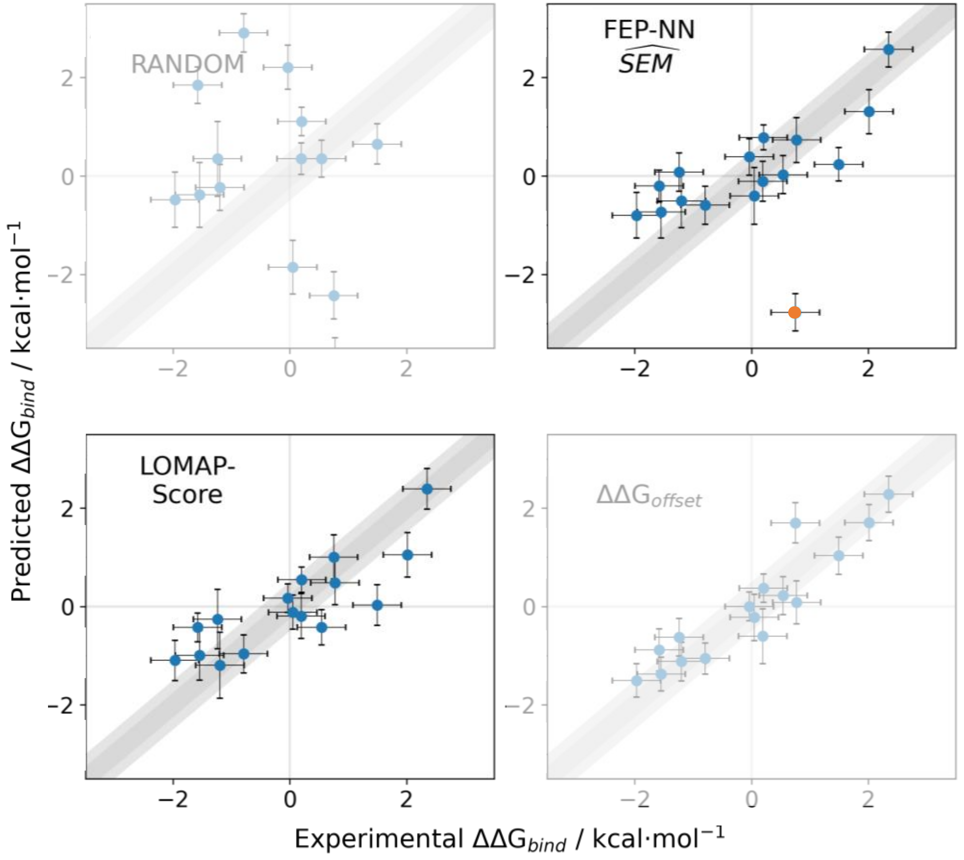
Applying trained model to test set – TYK2 results:





Applying trained model to test set – TYK2 results: FEP-NN graph contains an outlier





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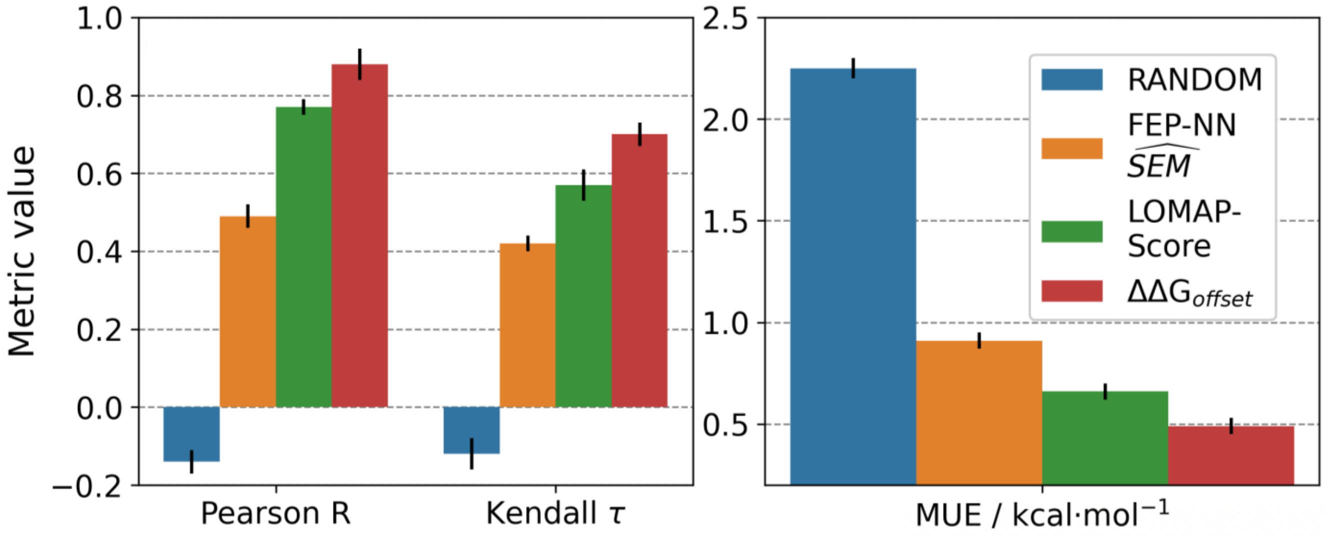

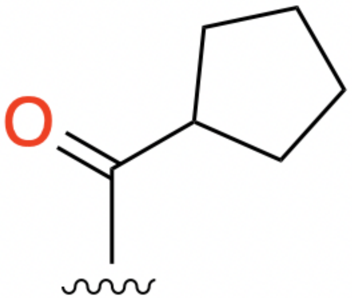

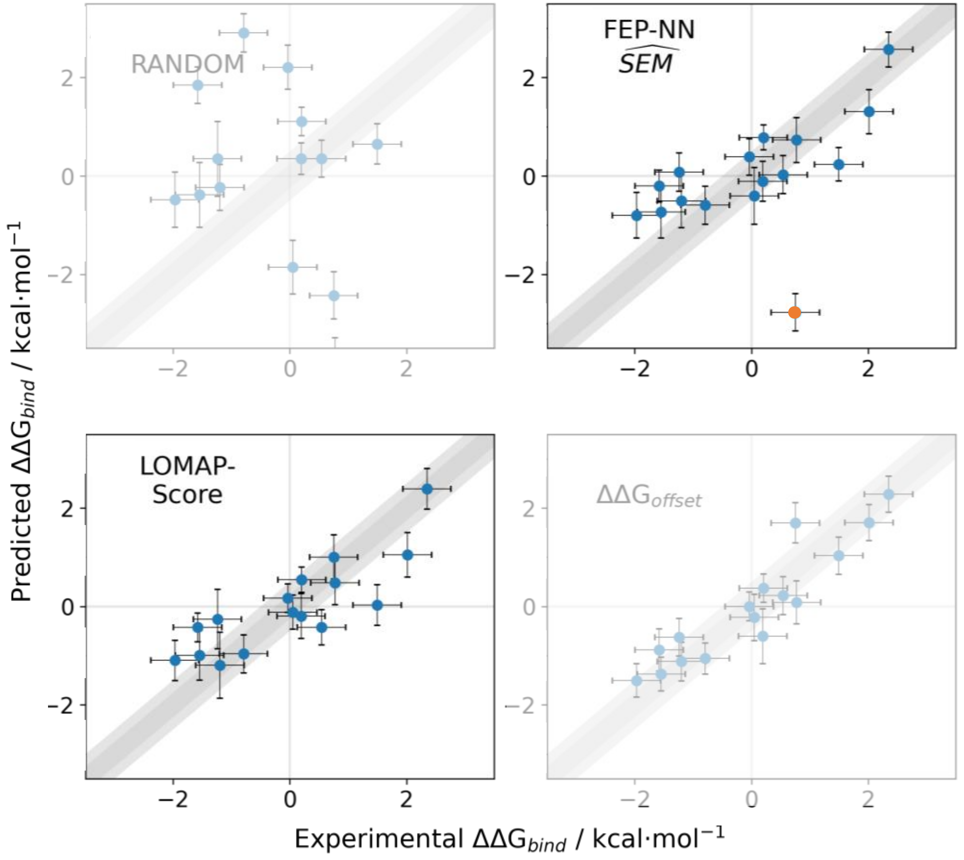

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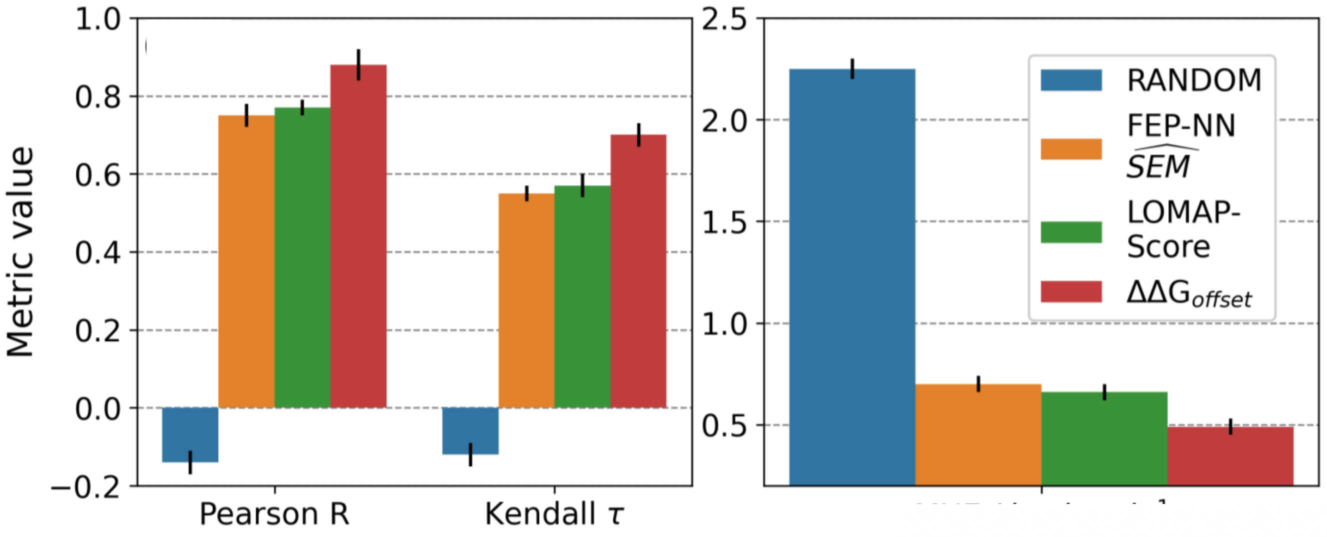
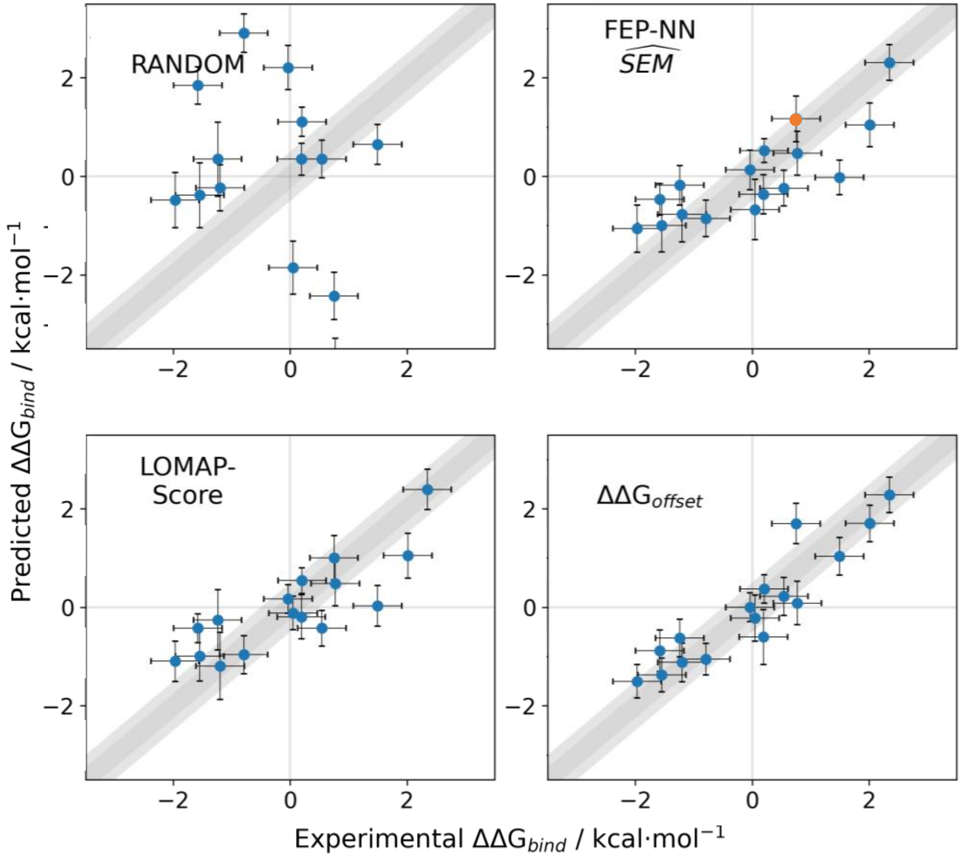
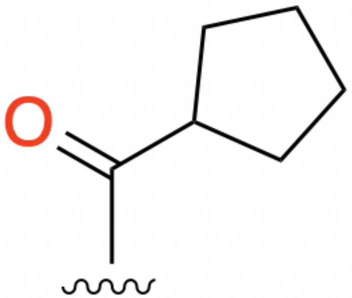
Applying trained model to test set – TYK2 results: corrected FEP-NN graph performs competitively with state-of-the-art LOMAP-Score

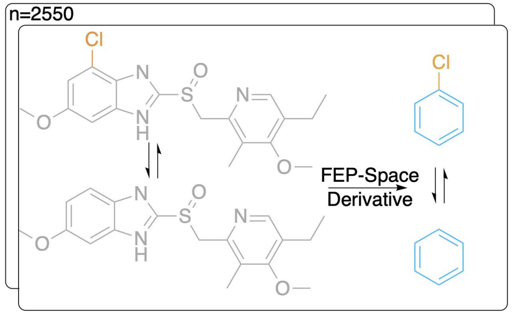






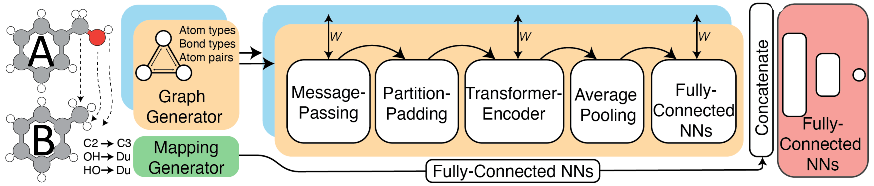
Take-home messages

FEP-Space publicly Available to advance ML for FEP

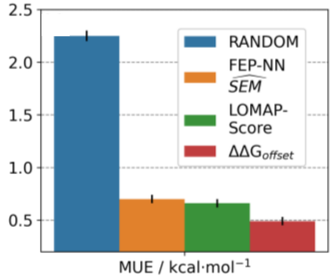


https://github.com/michellab/data_driven_fep_reliabilities

First Siamese-NN-type implementation in FEP



Data-driven network generator is competitive with state-of-the-art generators



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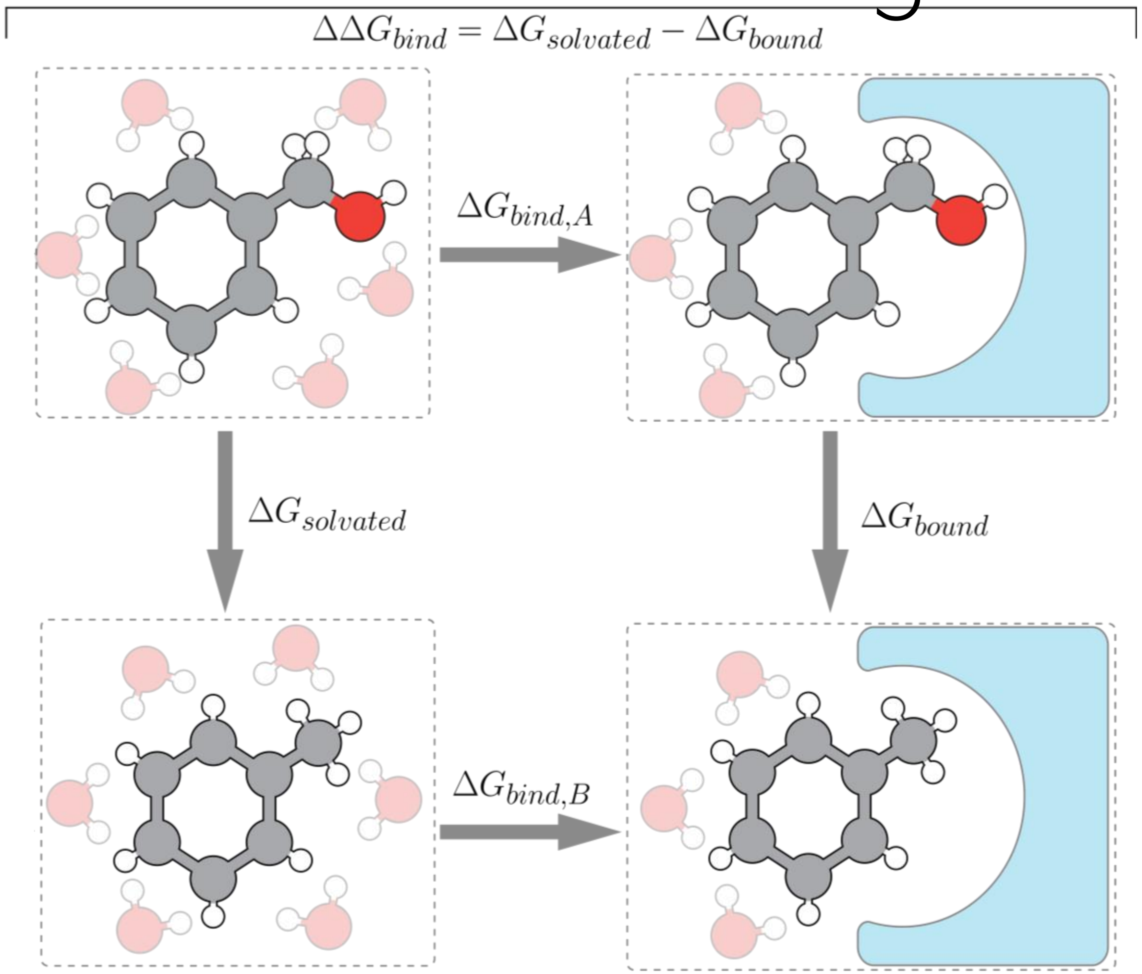
Thermodynamic cycle is the core concept in FEP methodologies



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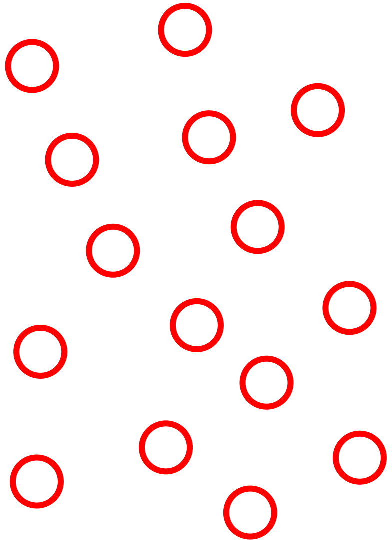
Under the hood: LOMAP scores edges based on expert-knowledge



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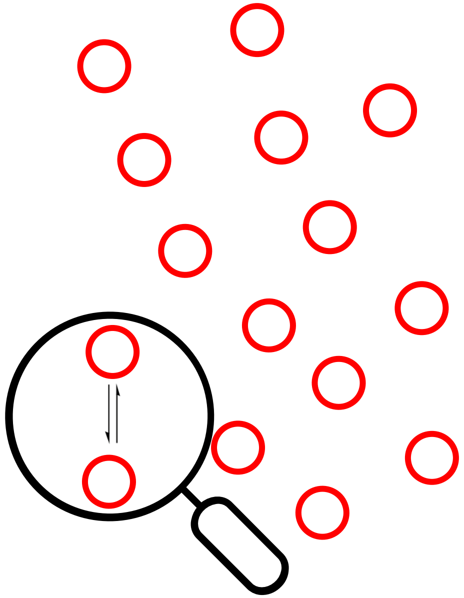
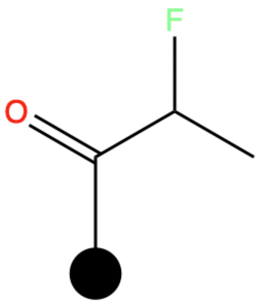
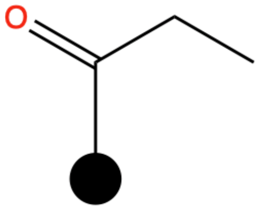
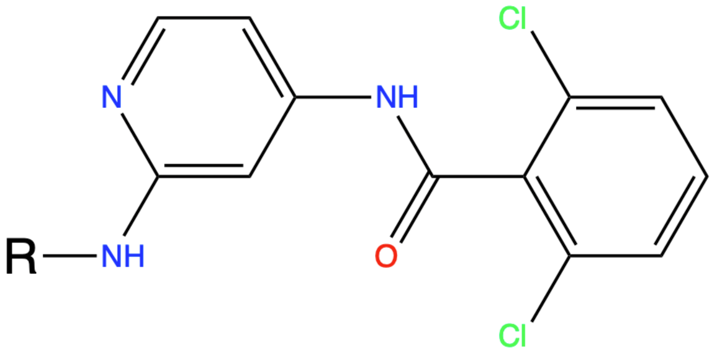






- 4 shared HAs
- 1 added HA



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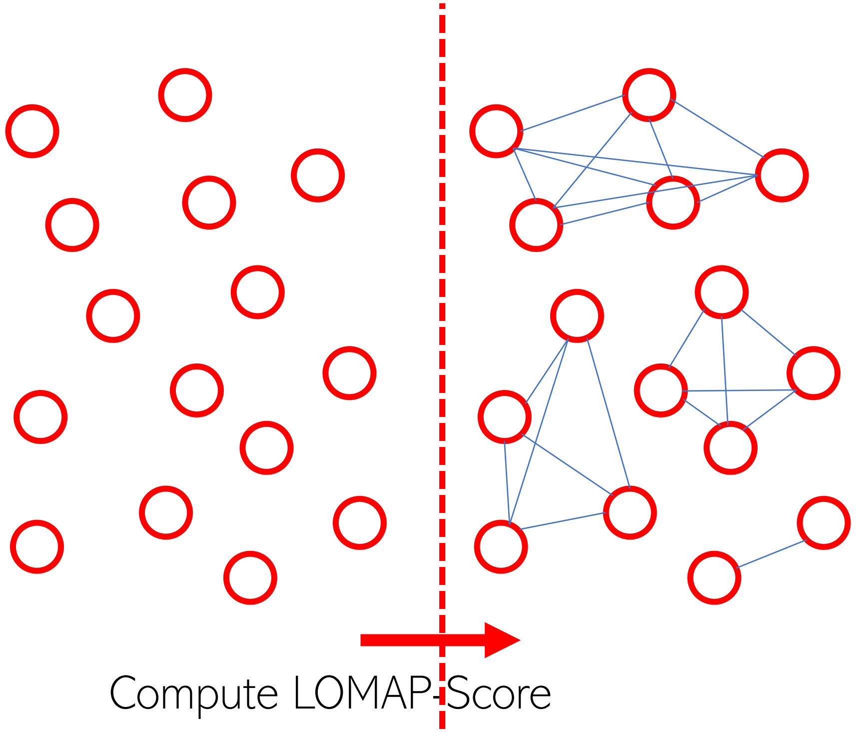

Compute LOMAP Score
(models FEP uncertainty);
keep edges above threshold

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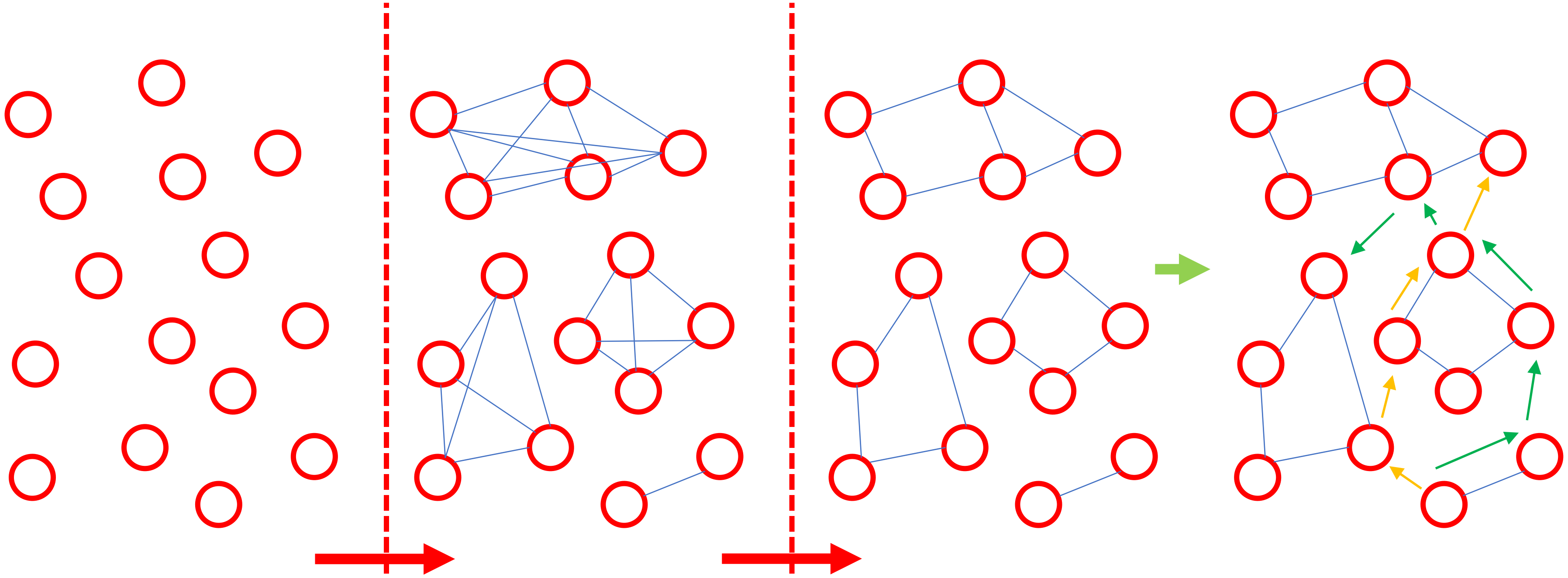
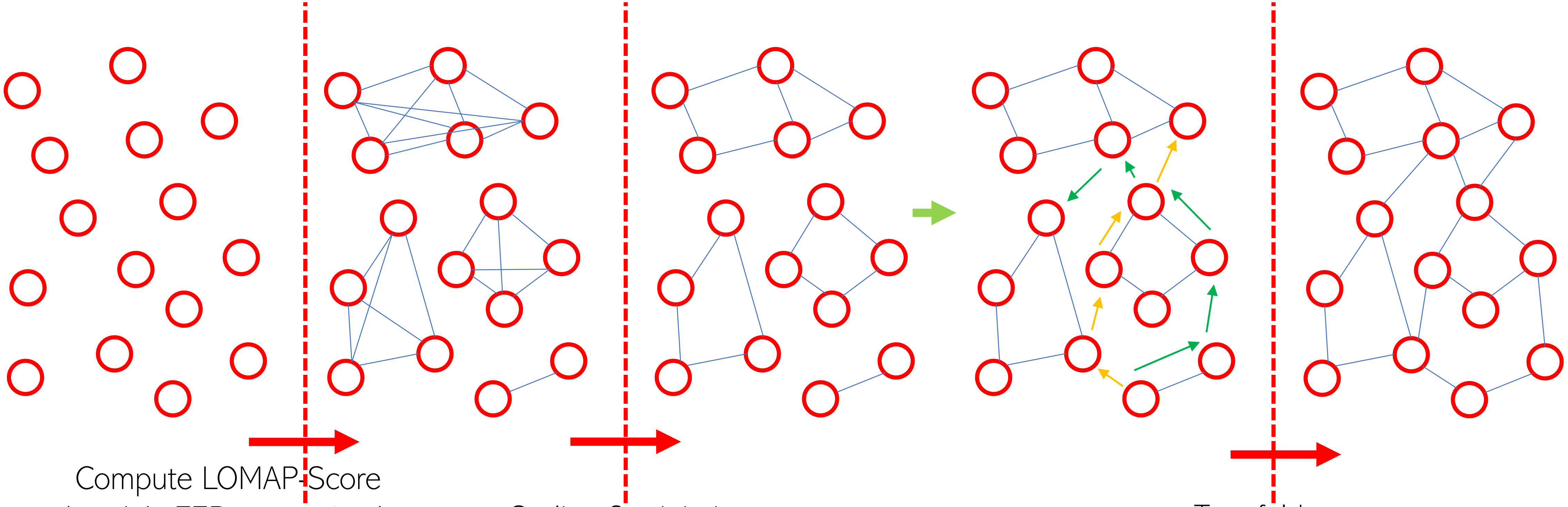


Compute LOMAP-Score (models FEP uncertainty); keep edges above threshold

Cyclize & minimize clusters

Shuai Liu et al, Lead optimization mapper: automating free energy calculations for lead optimization, J Comput Aided Mol Des 2013 Sep;27(9):755-70. doi: 10.1007/s10822-013-9678-y. Epub 2013 Sep 26.

Under the hood: LOMAP scores edges based on expert-knowledge



Compute LOMAP-Score (models FEP uncertainty); keep edges above threshold

Cyclize & minimize clusters

Two-fold non-overlapping *Minimum-Spanning Trees*

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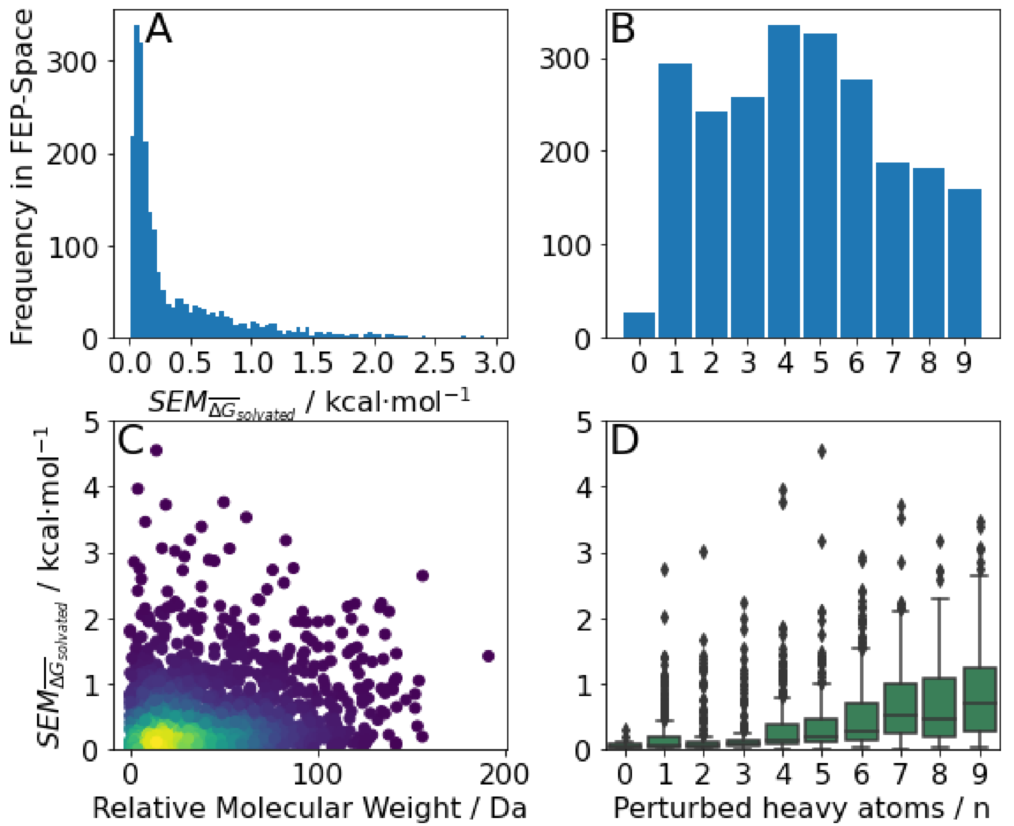
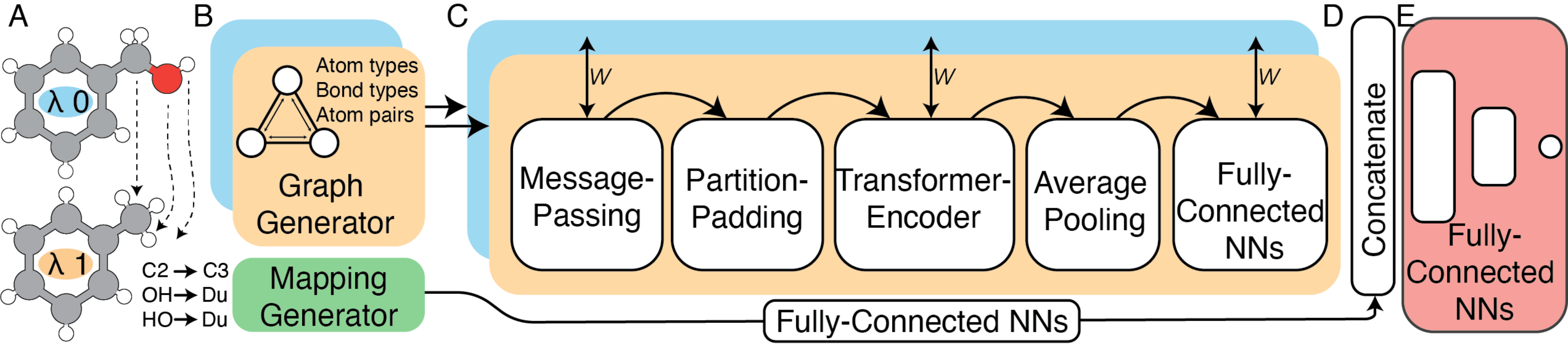
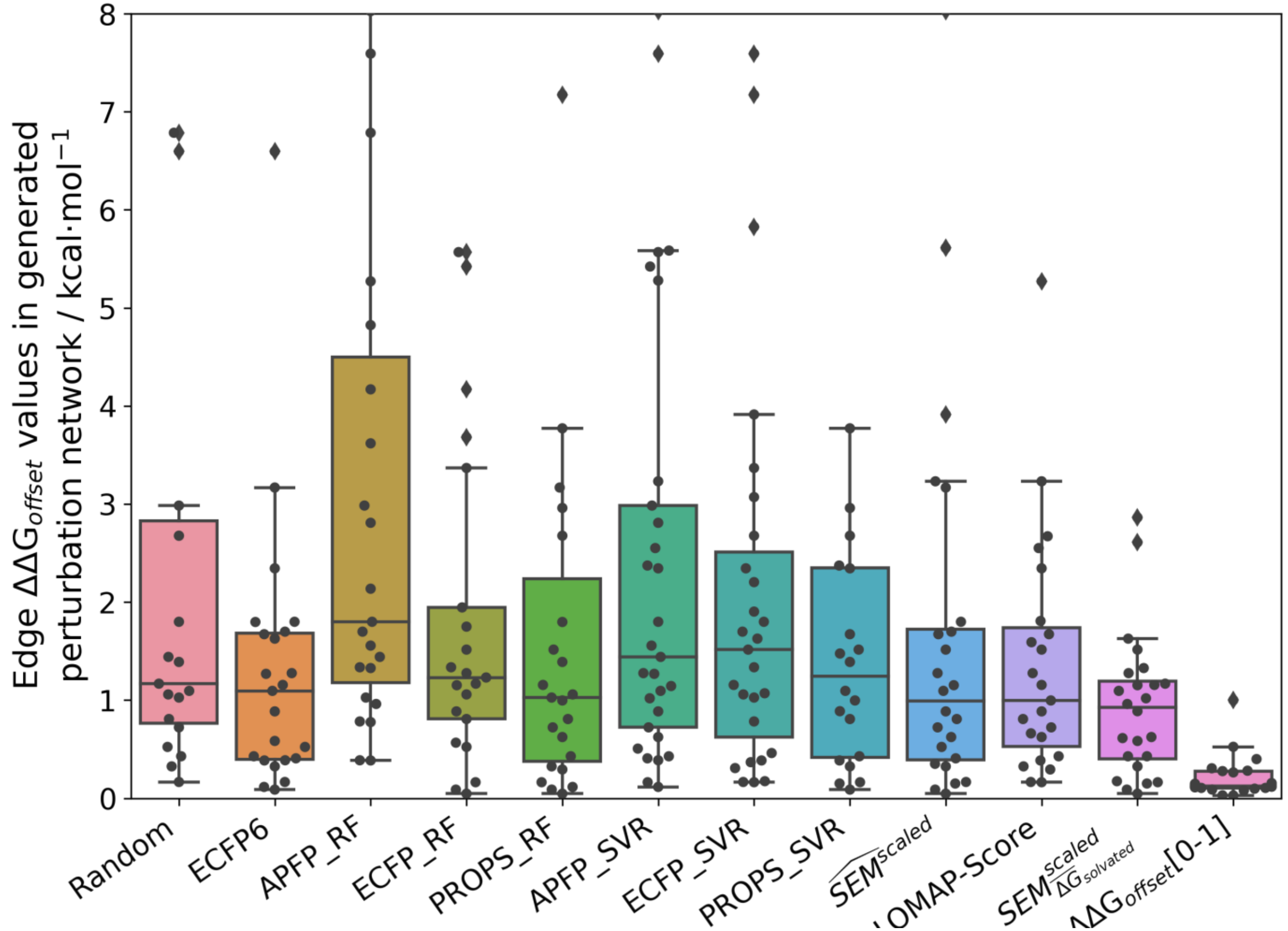
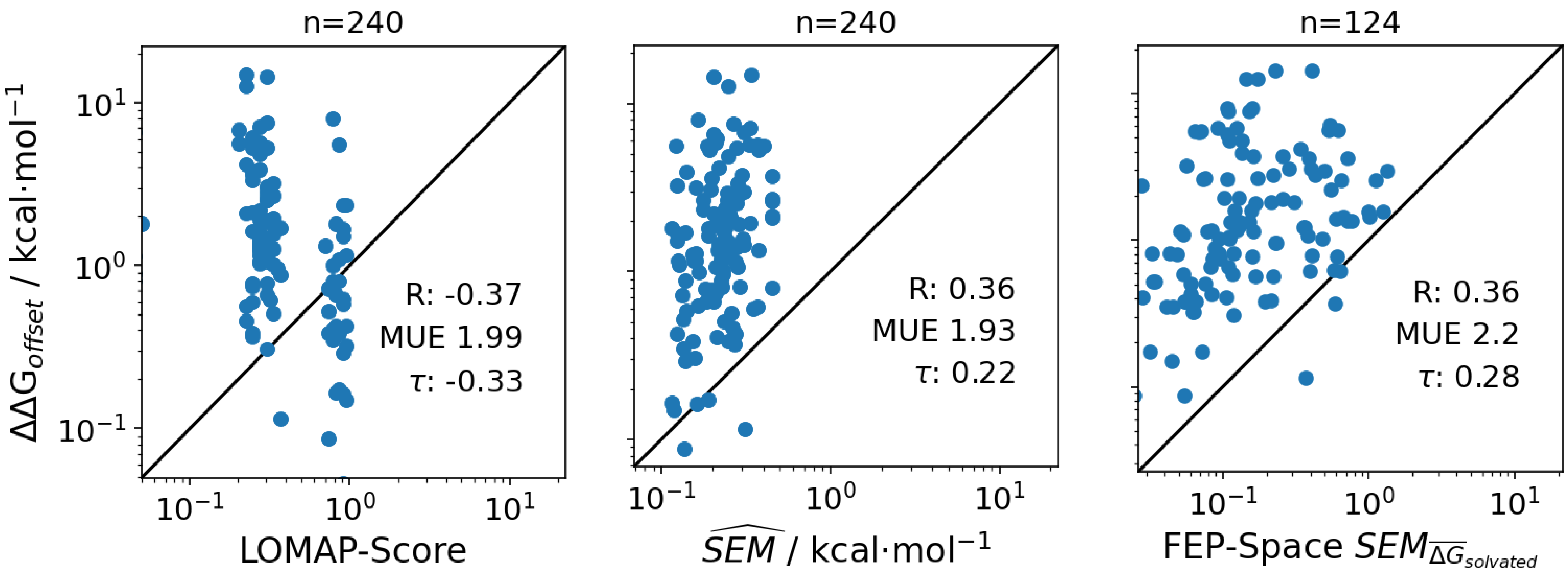
Shuai Liu et al, Lead optimization mapper: automating free energy calculations for lead optimization, J Comput Aided Mol Des 2013 Sep;27(9):755-70. doi: 10.1007/s10822-013-9678-y. Epub 2013 Sep 26.


A
B
C
D
Frequency in FEP-Space
$SEM_{\overline{\Delta G}_{solvated}}$ / kcal·mol^{-1}
Relative Molecular Weight / Da
Perturbed heavy atoms / n


A
B
C
D
E
λ 0
λ 1
C2 → C3
OH → Du
HO → Du
Atom types
Bond types
Atom pairs
Graph Generator
Mapping Generator
W
W
W
Message-Passing
Partition-Padding
Transformer-Encoder
Average Pooling
Fully-Connected NNs
Concatenate
Fully-Connected NNs
Fully-Connected NNs



Edge ΔΔG_offset values in generated perturbation network / kcal·mol⁻¹
0
1
2
3
4
5
6
7
8
Random
ECFP6
APFP_RF
ECFP_RF
PROPS_RF
APFP_SVR
ECFP_SVR
PROPS_SVR
SEM^scaled
OMAP-Score
SEM^scaled ΔG_solvated
ΔG_offset[0-1]



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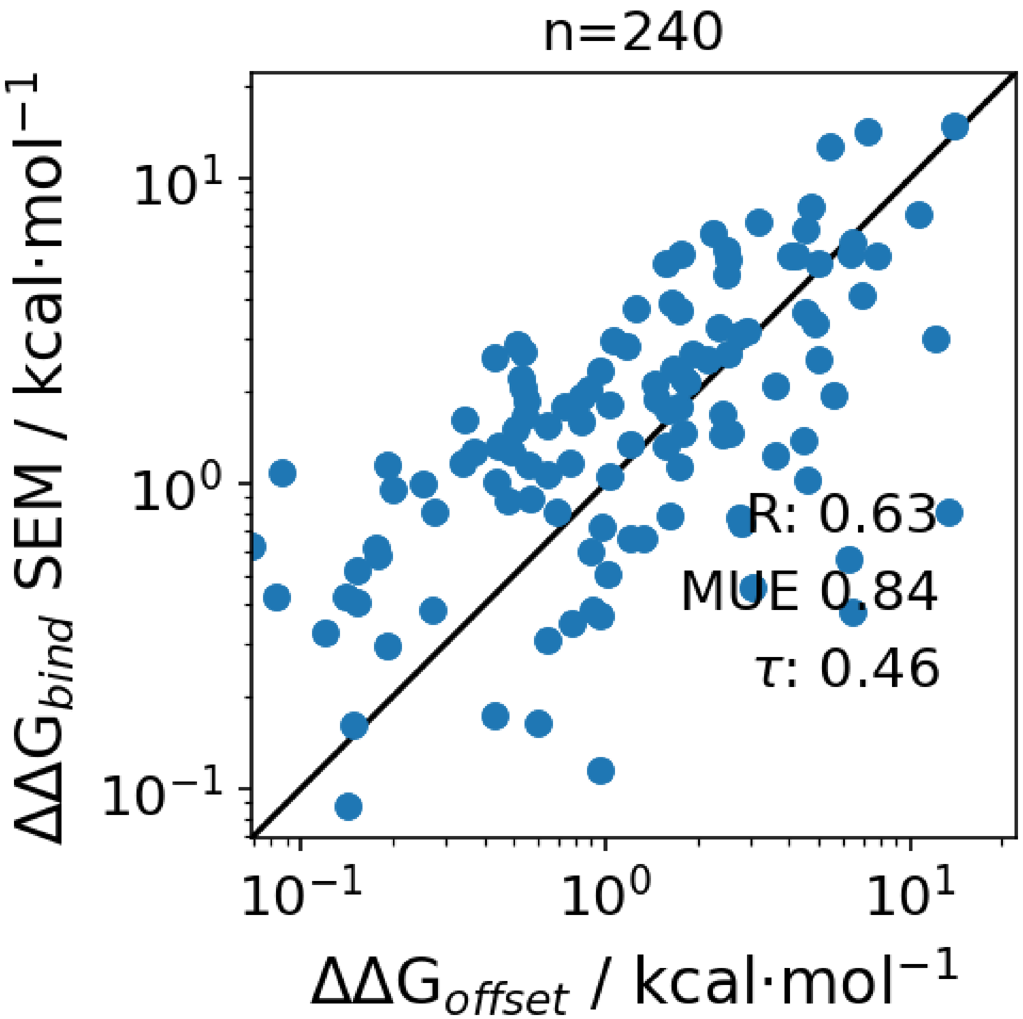
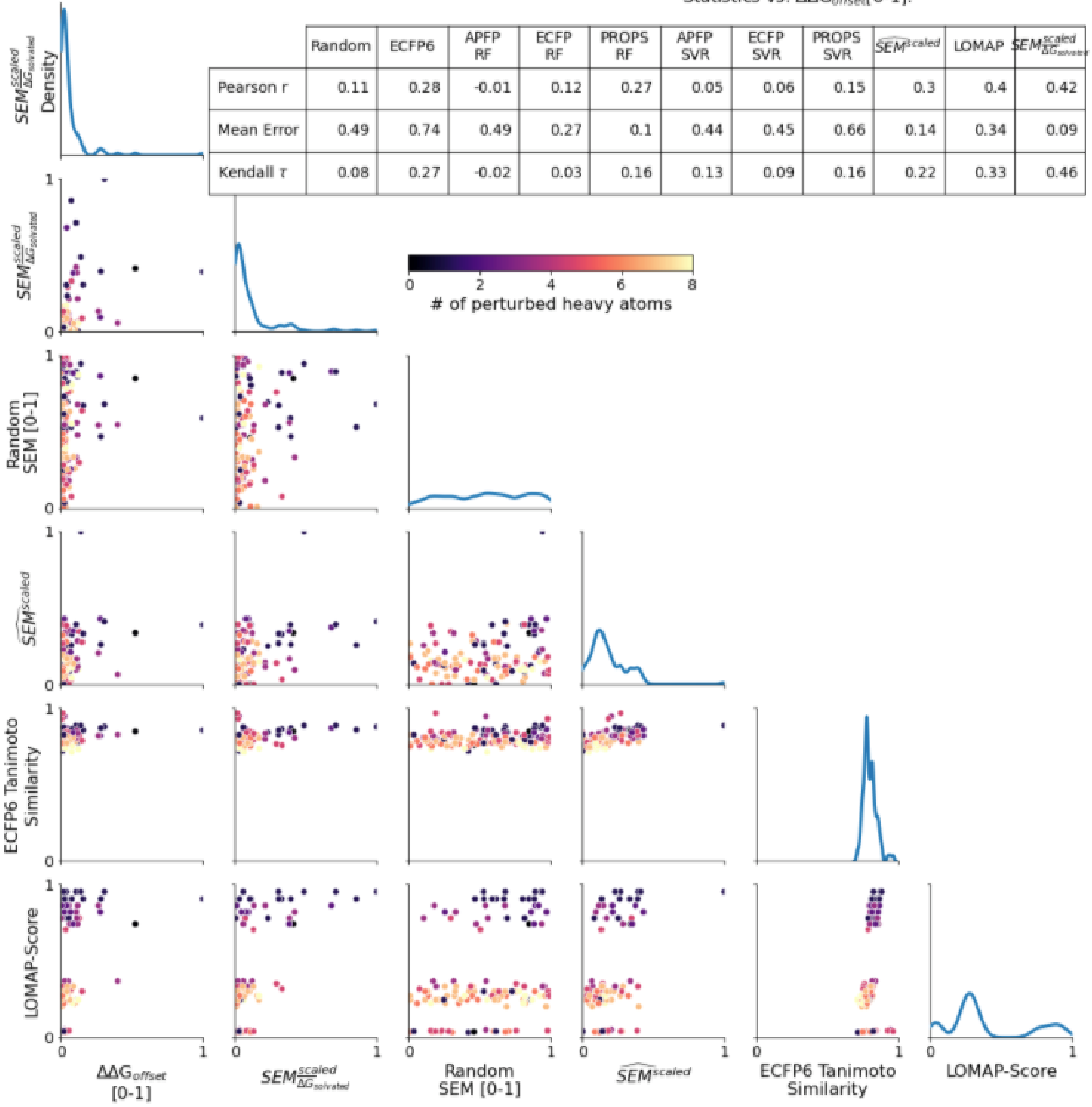


n=240
R: 0.63
MUE 0.84
τ: 0.46
10^{1}
10^{0}
10^{-1}
10^{-1}
10^{0}
10^{1}
$\Delta\Delta G_{bind}$ SEM / kcal·mol^{-1}
$\Delta\Delta G_{offset}$ / kcal·mol^{-1}

Statistics vs. $\Delta\Delta G_{offset}$[0-1]:

	Random	ECFP6	APFP RF	ECFP RF	PROPS RF	APFP SVR	ECFP SVR	PROPS SVR	$\widehat{SEM}^{scaled}$	LOMAP	$SEM^{scaled}_{\Delta G_{solvated}}$
Pearson r	0.11	0.28	-0.01	0.12	0.27	0.05	0.06	0.15	0.3	0.4	0.42
Mean Error	0.49	0.74	0.49	0.27	0.1	0.44	0.45	0.66	0.14	0.34	0.09
Kendall τ	0.08	0.27	-0.02	0.03	0.16	0.13	0.09	0.16	0.22	0.33	0.46



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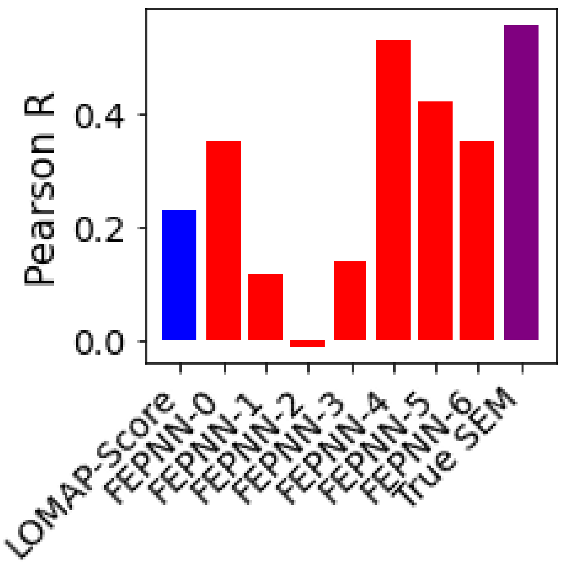
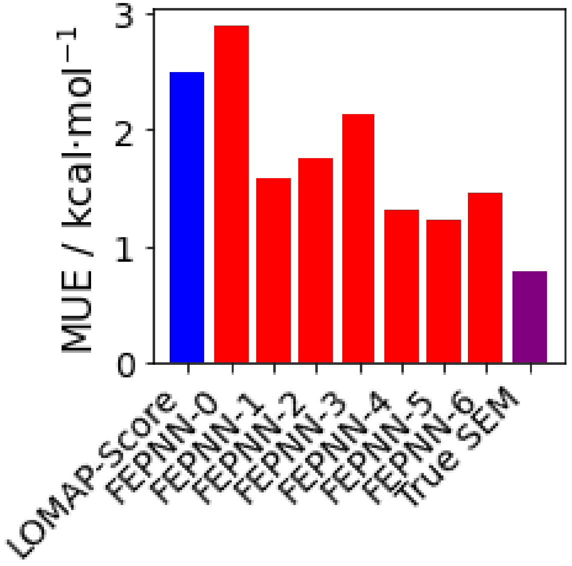
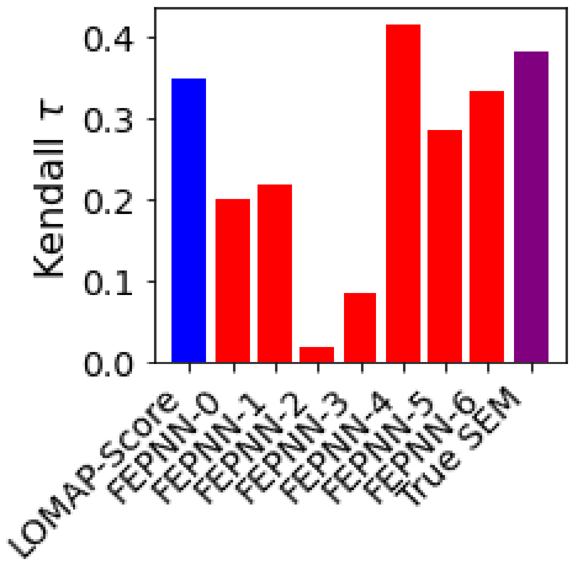
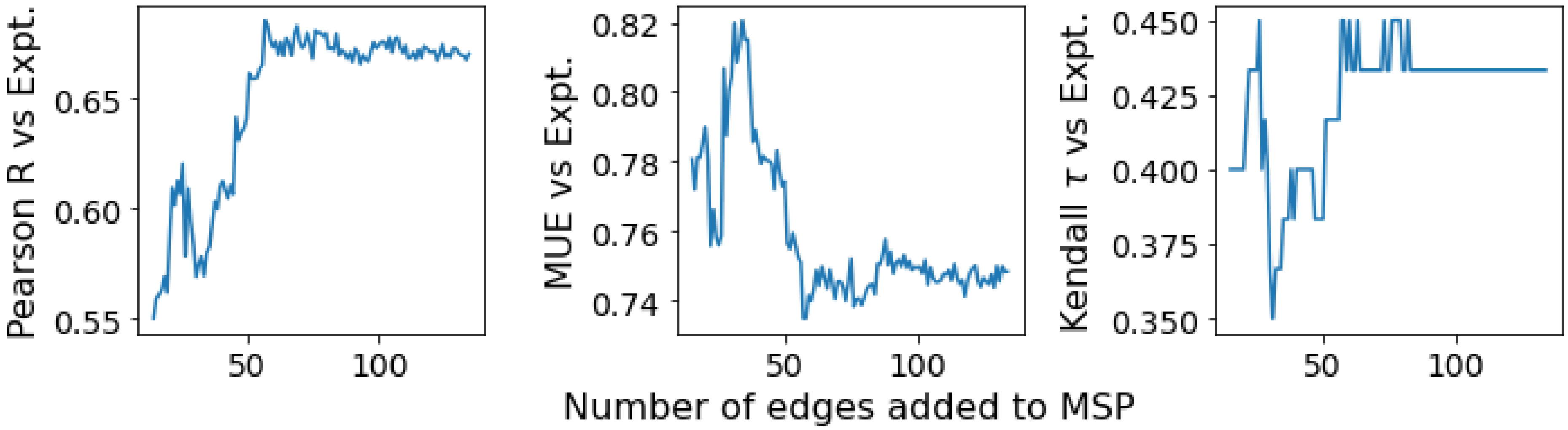
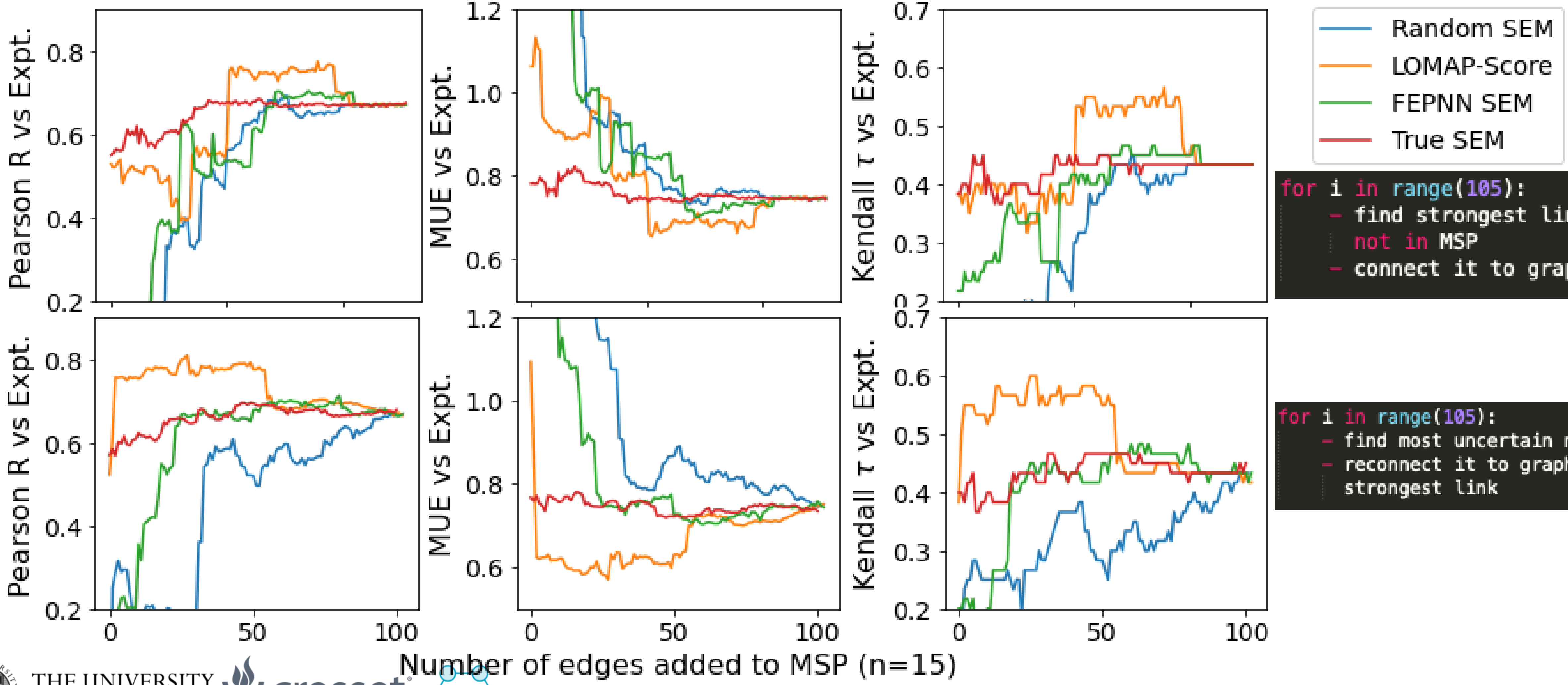

Pearson R
0.0
0.2
0.4
LOMAP-Score
FEPNN-0
FEPNN-1
FEPNN-2
FEPNN-3
FEPNN-4
FEPNN-5
FEPNN-6
True SEM


MUE / kcal·mol^{-1}
0
1
2
3
LOMAP-Score
FEPNN-0
FEPNN-1
FEPNN-2
FEPNN-3
FEPNN-4
FEPNN-5
FEPNN-6
True SEM

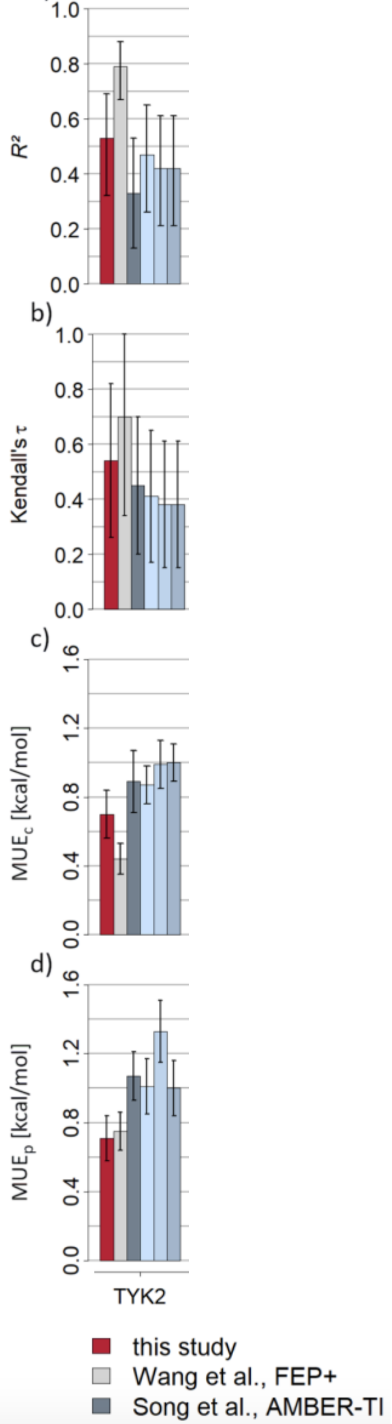

Kendall τ
0.0
0.1
0.2
0.3
0.4
LOMAP-Score
FEPNN-0
FEPNN-1
FEPNN-2
FEPNN-3
FEPNN-4
FEPNN-5
FEPNN-6
True SEM


Pearson R vs Expt.
0.65
0.60
0.55
50
100
MUE vs Expt.
0.82
0.80
0.78
0.76
0.74
50
100
Kendall τ vs Expt.
0.450
0.425
0.400
0.375
0.350
50
100
Number of edges added to MSP




```
for i in range(105):
    - find strongest link
      not in MSP
    - connect it to graph
```

```
for i in range(105):
    - find most uncertain node
    - reconnect it to graph at
      strongest link
```



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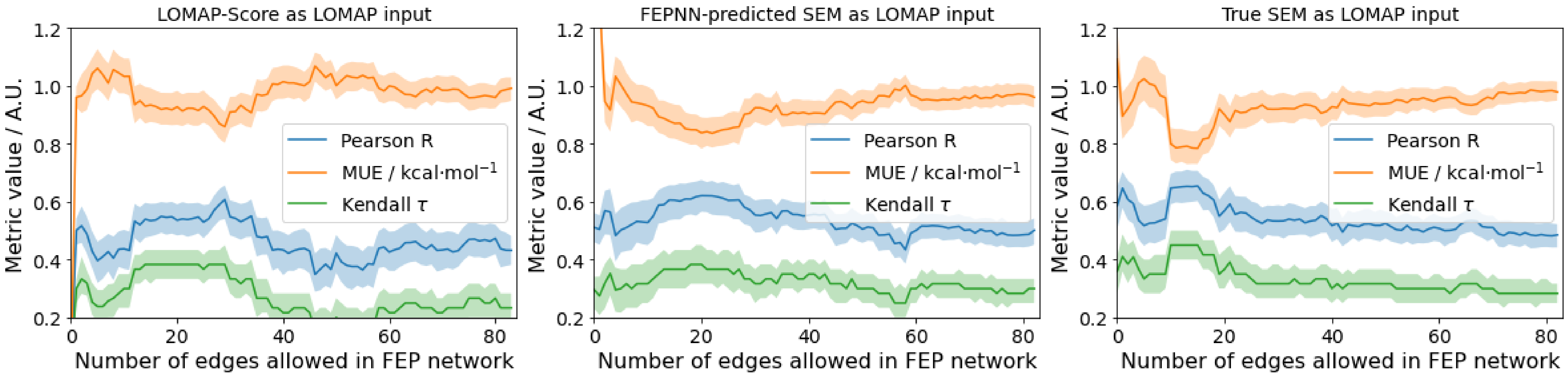

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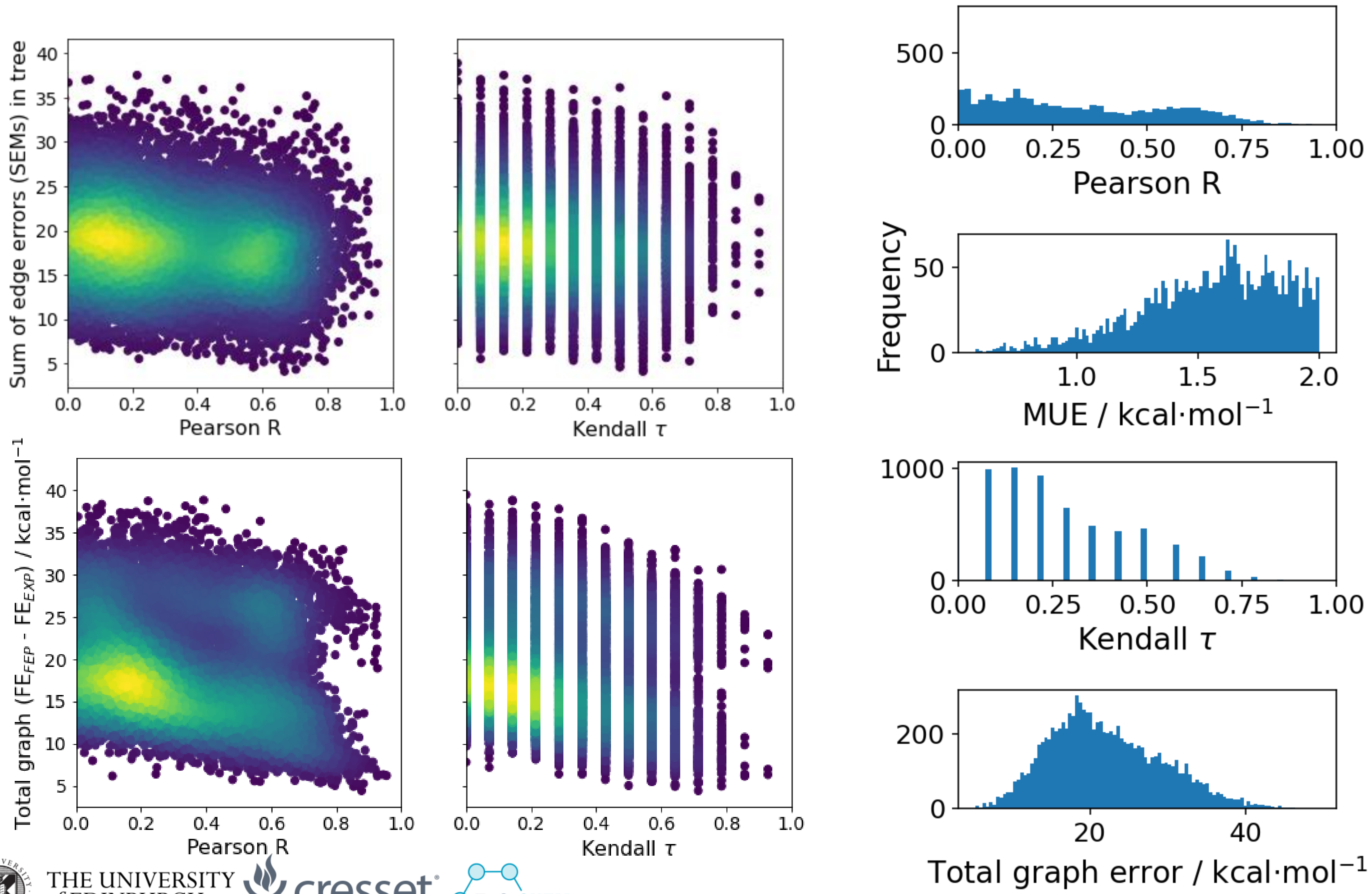

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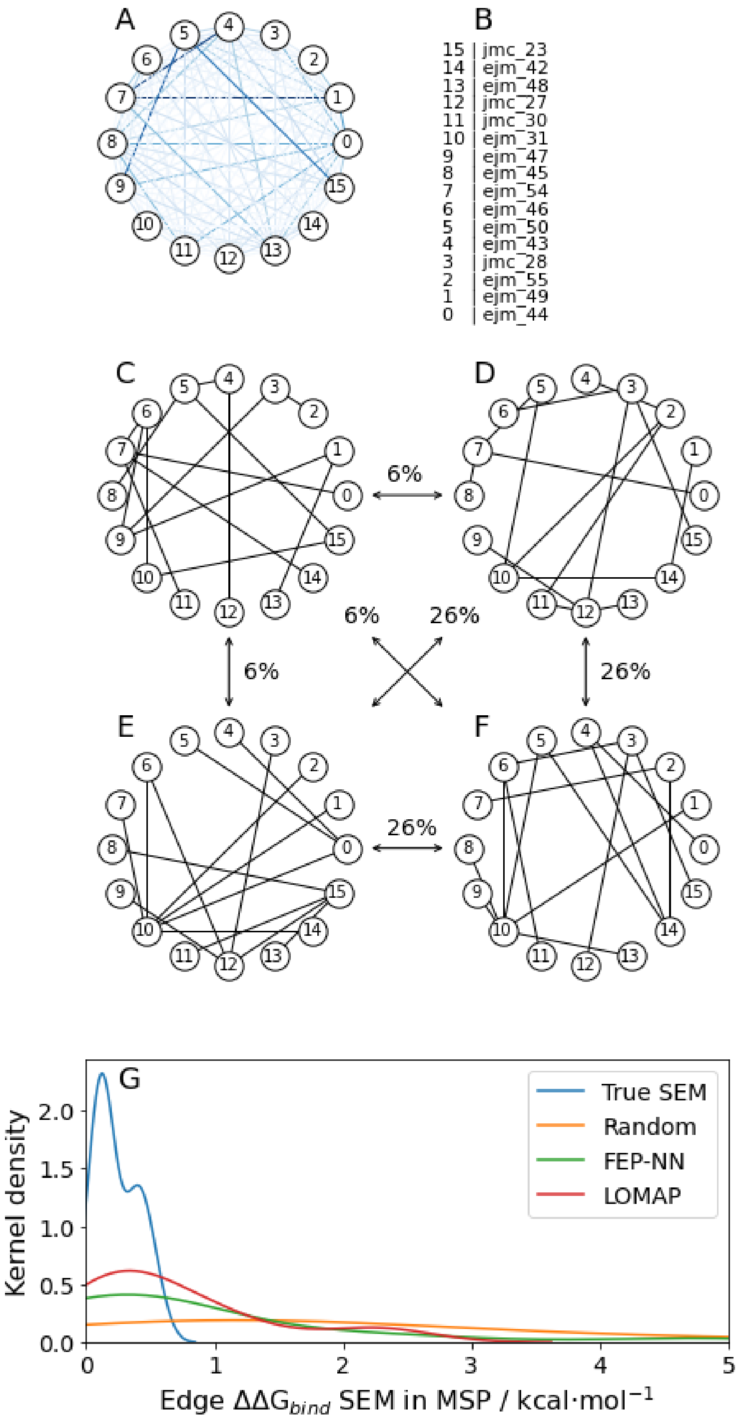
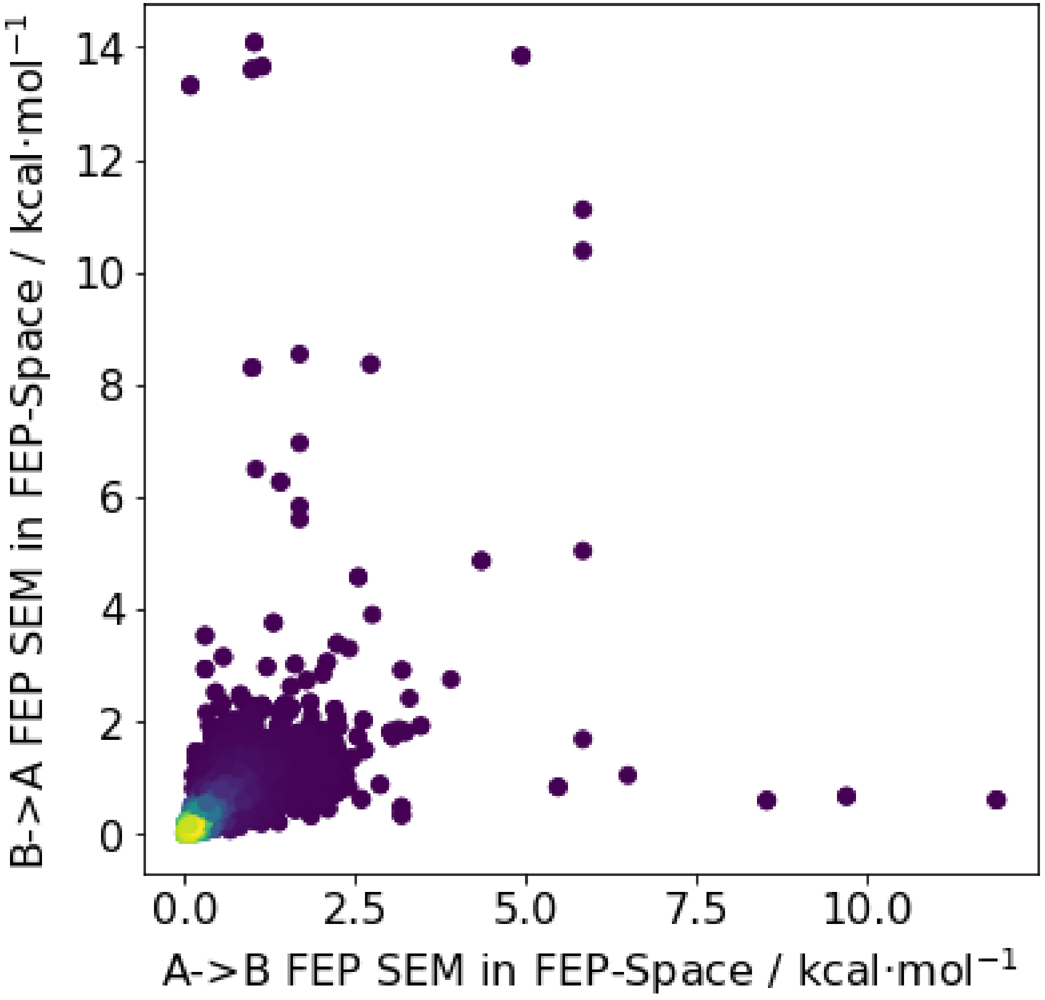
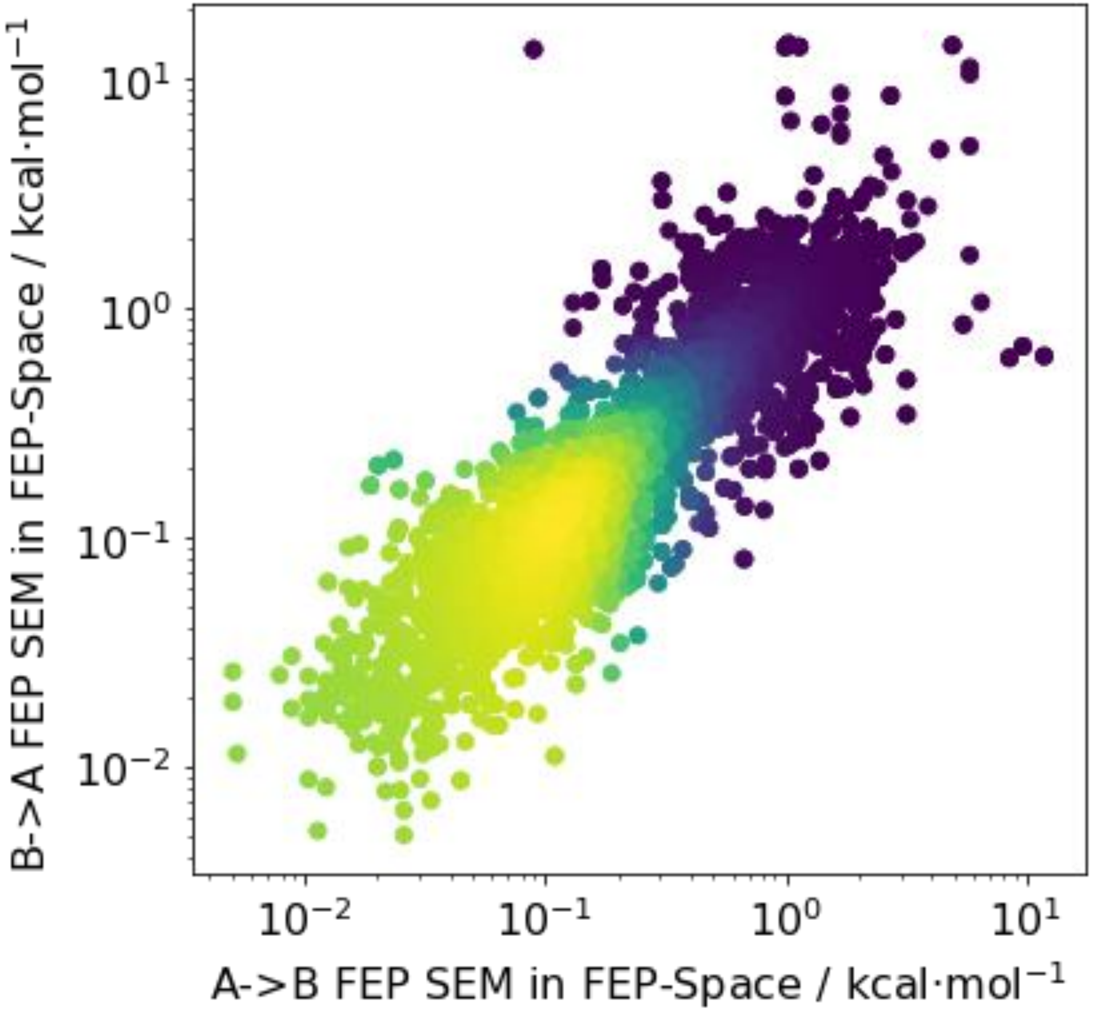

A
B
15 | jmc_23
14 | ejm_42
13 | ejm_48
12 | jmc_27
11 | jmc_30
10 | ejm_31
9 | ejm_47
8 | ejm_45
7 | ejm_54
6 | ejm_46
5 | ejm_50
4 | ejm_43
3 | jmc_28
2 | ejm_55
1 | ejm_49
0 | ejm_44
C
D
E
F
6%
6%
26%
6%
26%
26%
G
True SEM
Random
FEP-NN
LOMAP
Kernel density
Edge ΔΔG$_{bind}$ SEM in MSP / kcal·mol^{-1}





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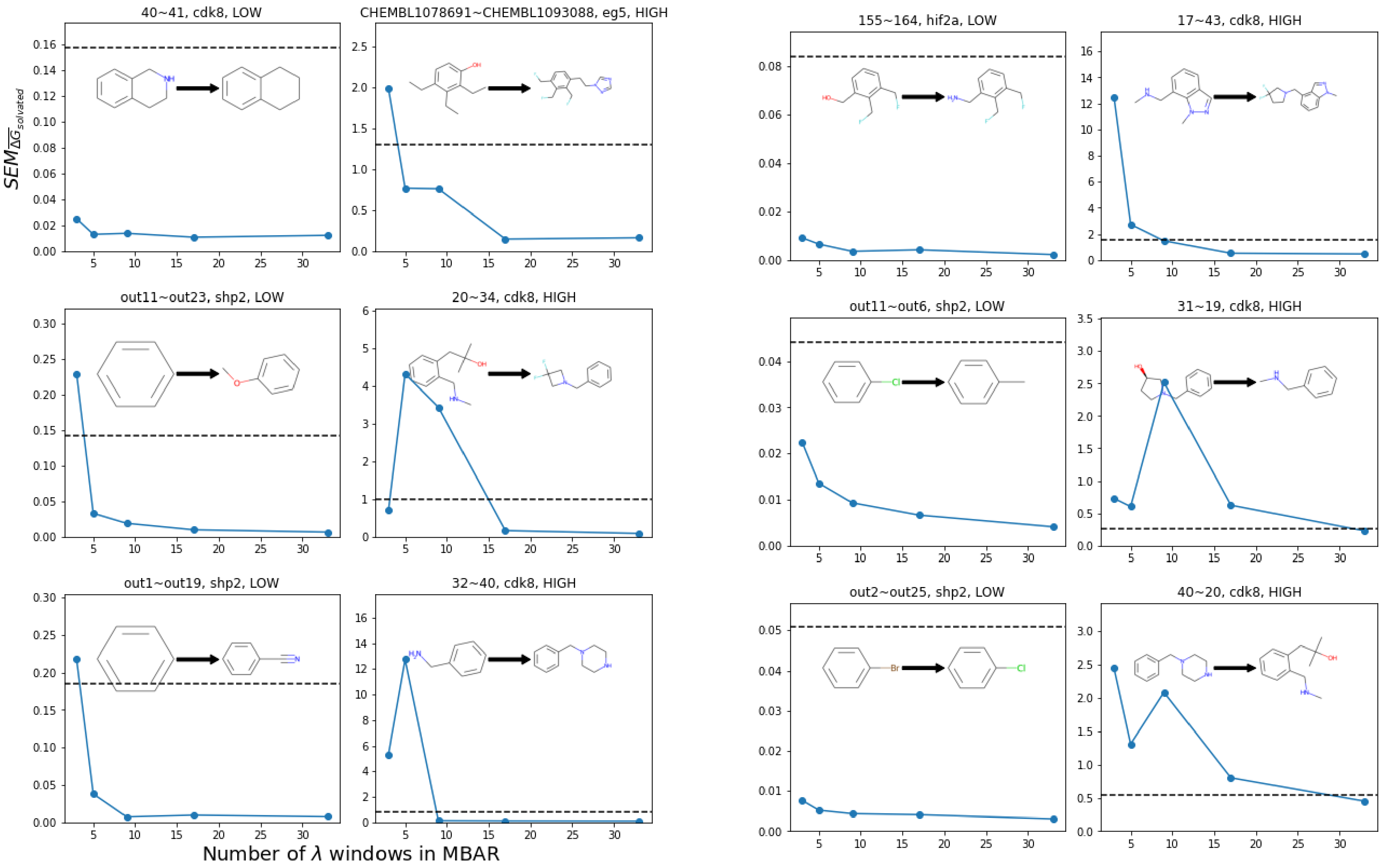
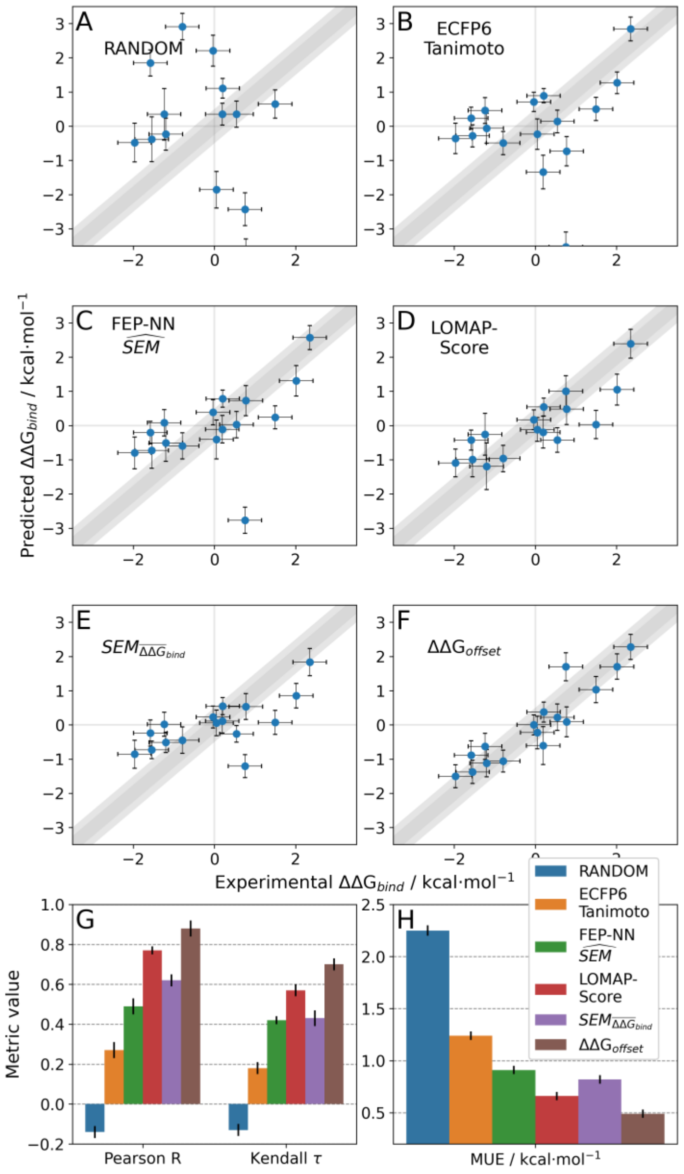
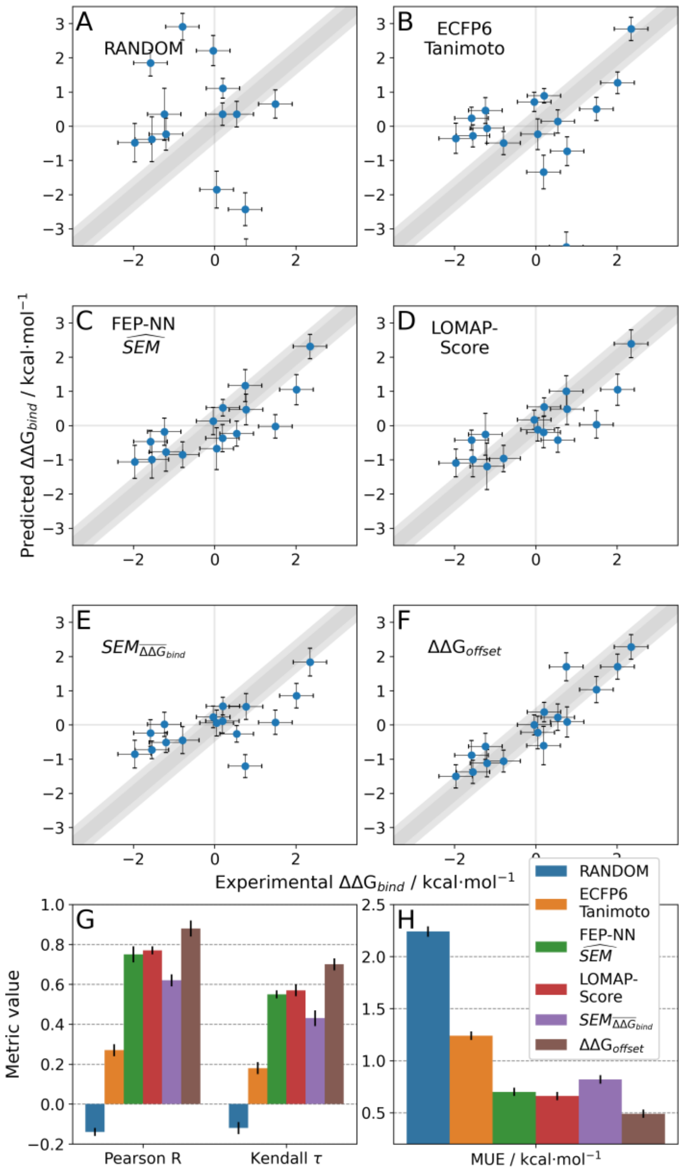

40~41, cdk8, LOW
CHEMBL1078691~CHEMBL1093088, eg5, HIGH
155~164, hif2a, LOW
17~43, cdk8, HIGH
out11~out23, shp2, LOW
20~34, cdk8, HIGH
out11~out6, shp2, LOW
31~19, cdk8, HIGH
out1~out19, shp2, LOW
32~40, cdk8, HIGH
out2~out25, shp2, LOW
40~20, cdk8, HIGH
$SEM_{\overline{\Delta G}_{solvated}}$
Number of λ windows in MBAR





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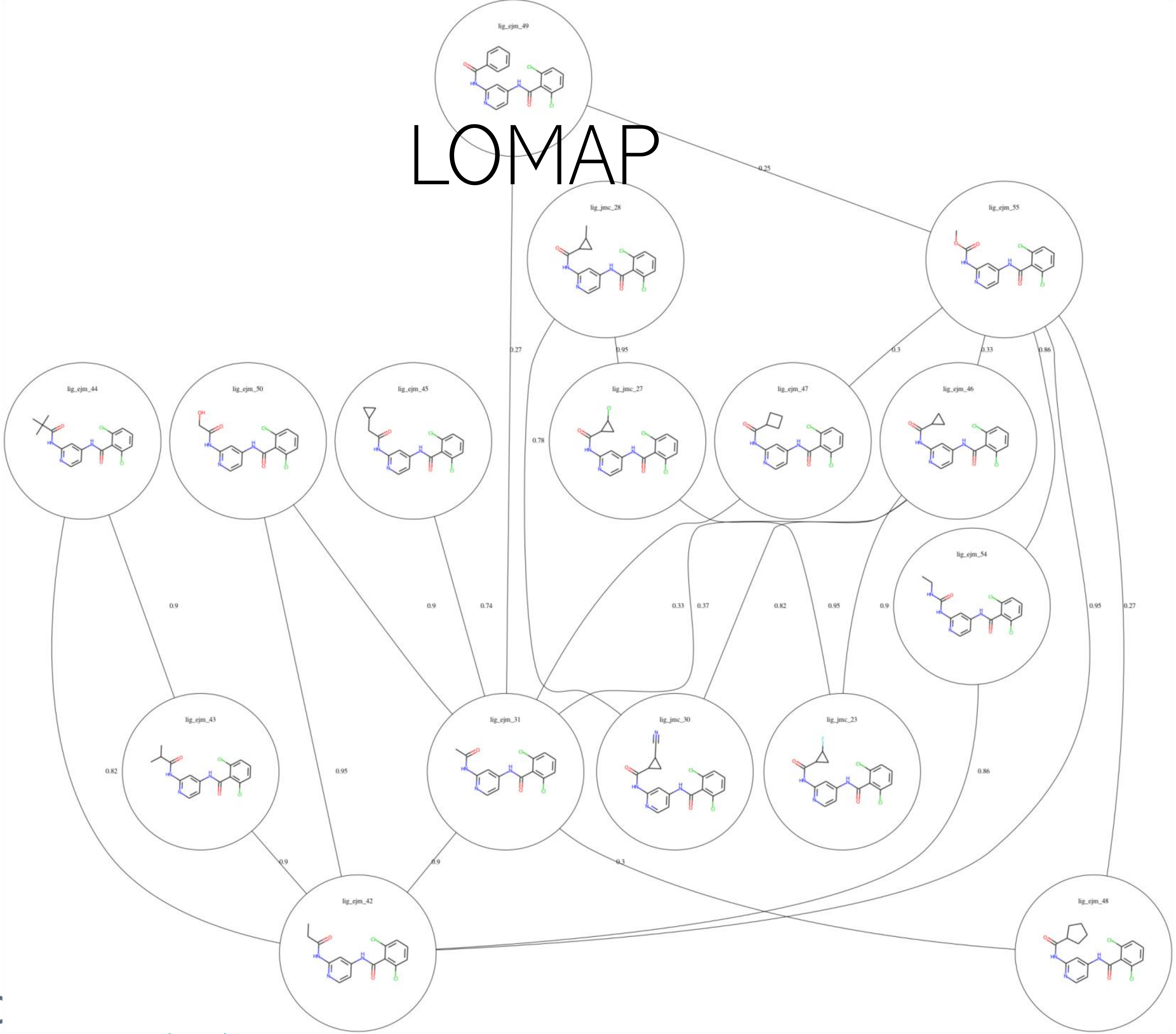
LOMAP



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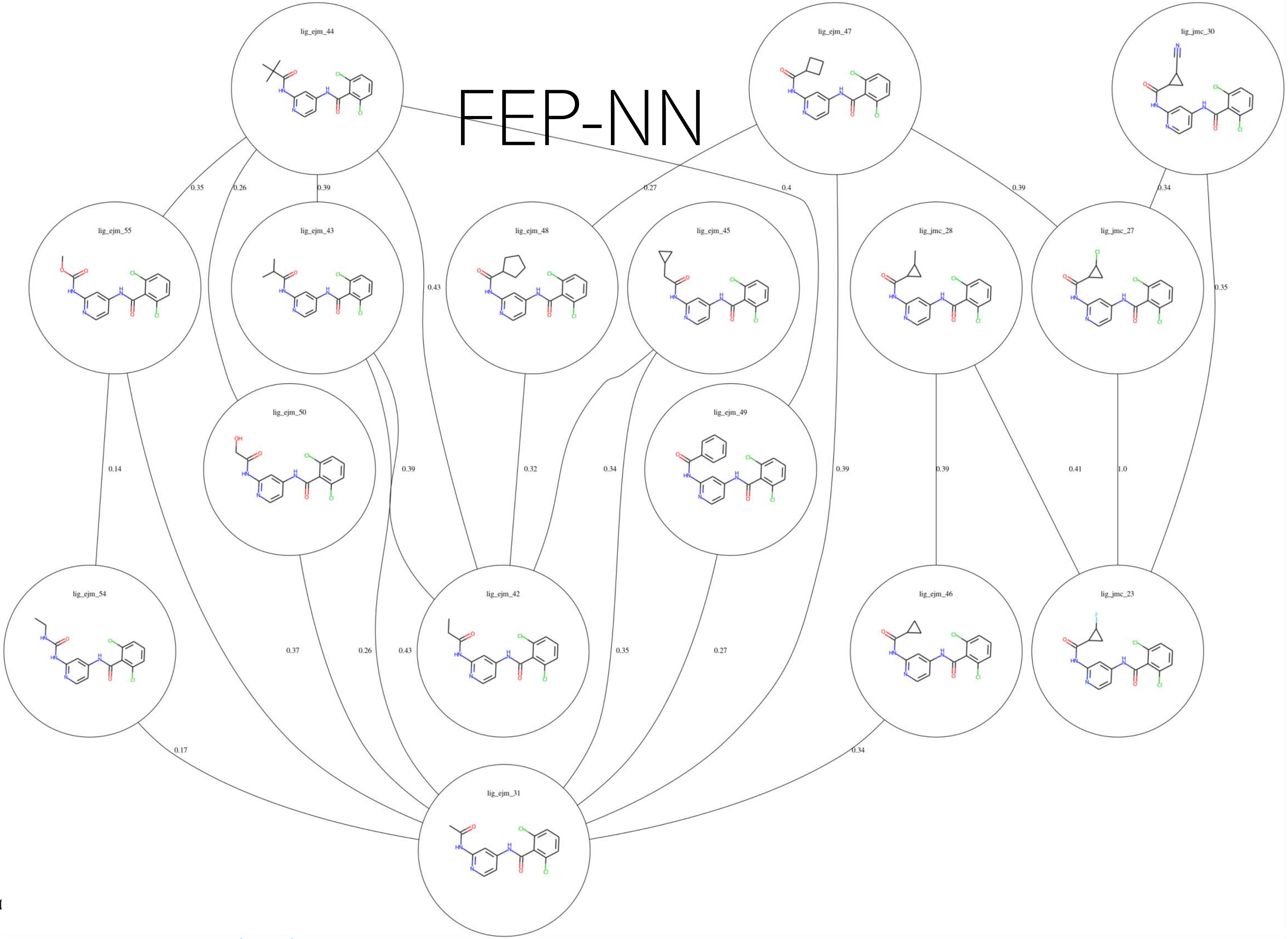
FEP-NN


lig_ejm_44
lig_ejm_47
lig_jmc_30
lig_ejm_55
lig_ejm_43
lig_ejm_48
lig_ejm_45
lig_jmc_28
lig_jmc_27
lig_ejm_50
lig_ejm_49
lig_ejm_54
lig_ejm_42
lig_ejm_46
lig_jmc_23
lig_ejm_31
0.35
0.26
0.39
0.43
0.27
0.4
0.39
0.34
0.35
0.14
0.39
0.32
0.34
0.39
0.39
0.41
1.0
0.37
0.26
0.43
0.35
0.27
0.17
0.34