Current Development in Non-Equilibrium Switching: The Mapper Feature

Presented by Gaetano Calabró, PhD
Senior Scientific Software Developer
Thursday, June 30, 2022

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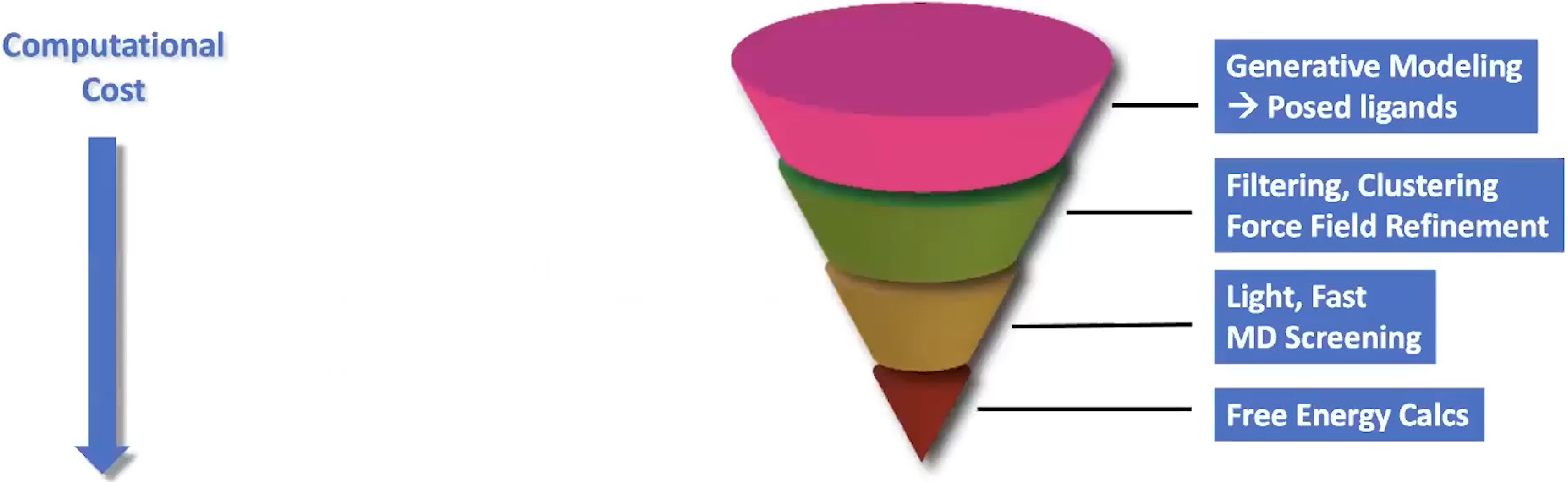
Overview

- Introduction and Background
- The OE Mapper Features
- The OE Mapper Validation
- Conclusions

MD in Structure-Based Lead Optimization



- Heavier MD methods staged to offer more value later in triaging

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MD in Structure-Based Lead Optimization

- Heavier MD methods staged to offer more value later in triaging

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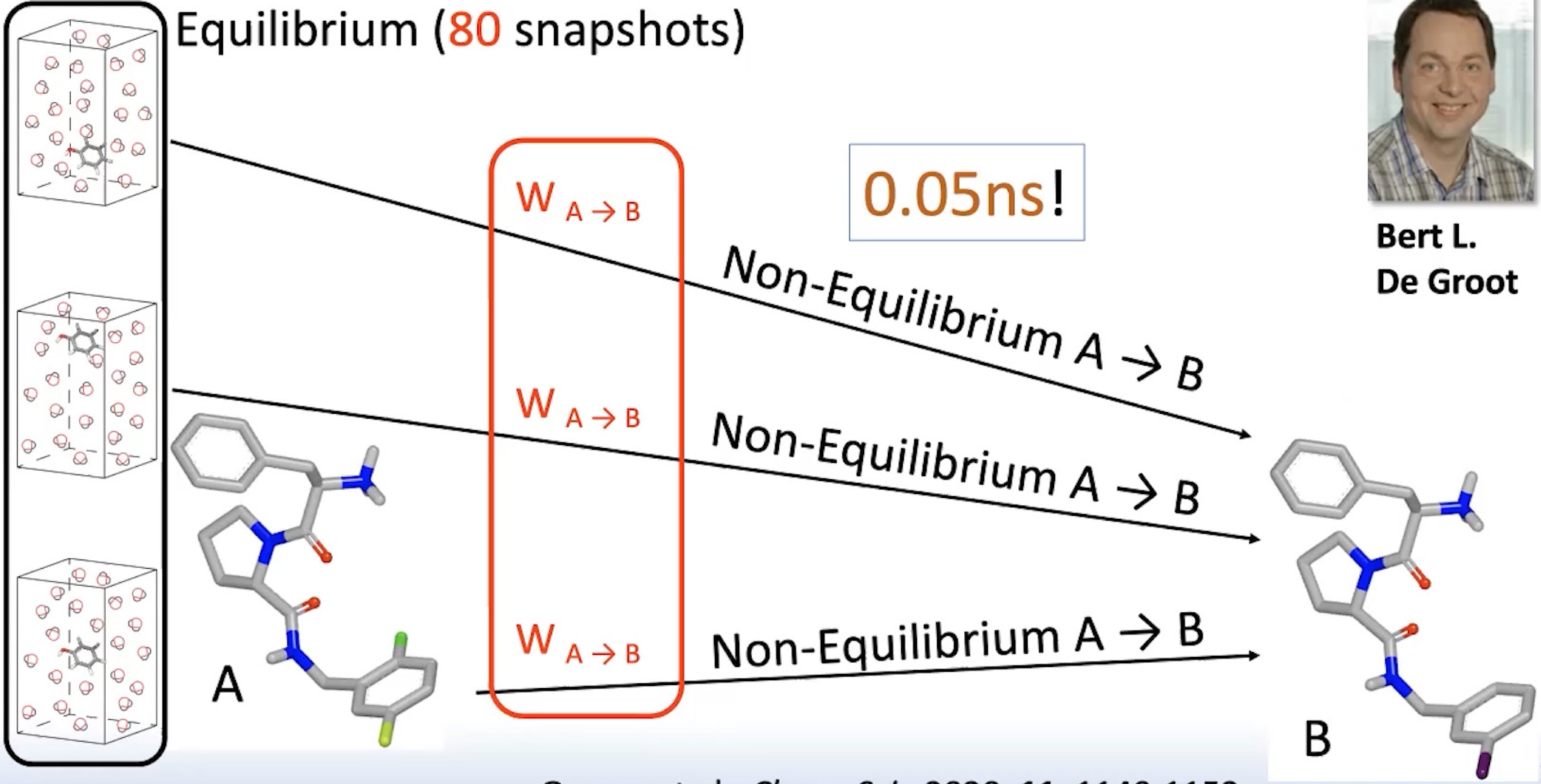
RBFE Methods NES (Non-Equilibrium Switching)

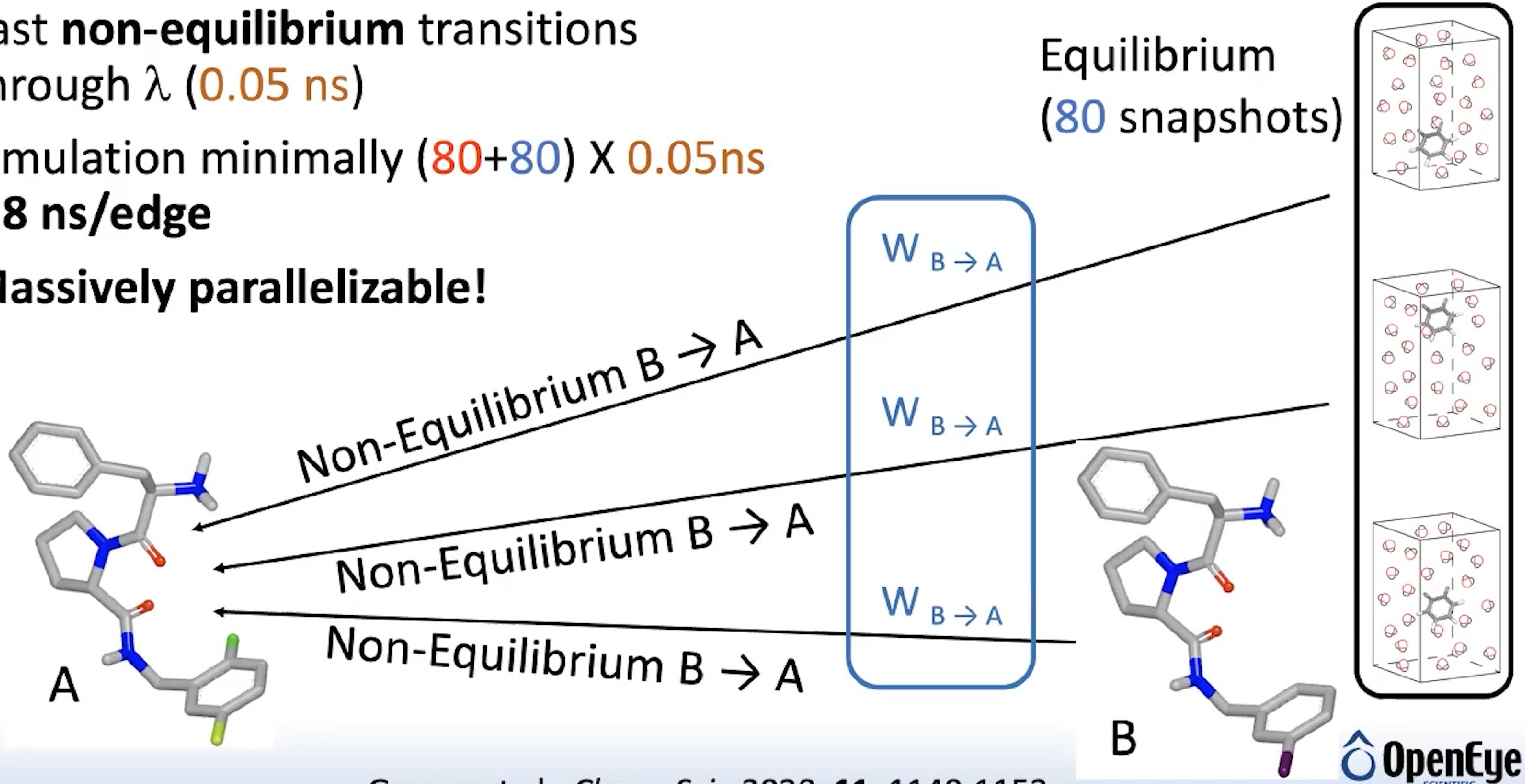


Bert L. De Groot   Vytautas Gapsys

Gapsys et al., *Chem. Sci.*, 2020, **11**, 1140-1152

RBFE Methods NES (Non-Equilibrium Switching)

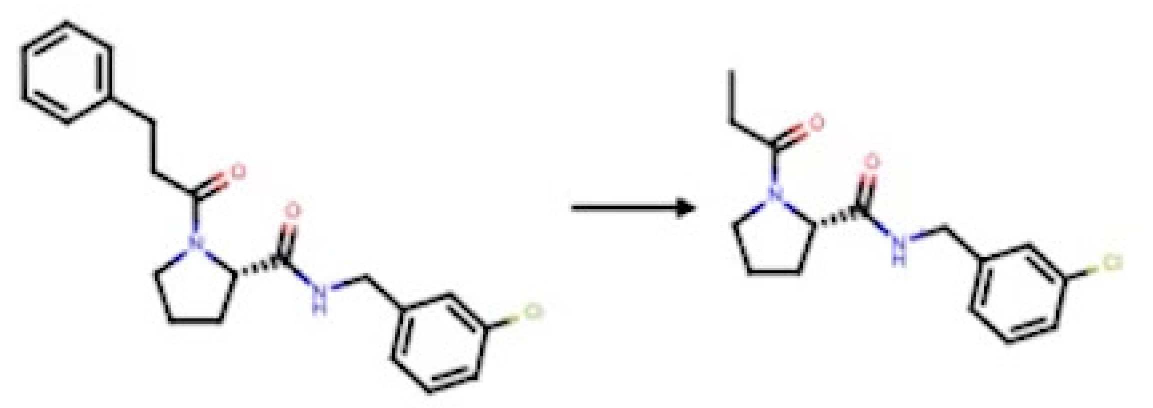
- Fast **non-equilibrium** transitions through λ (0.05 ns)
- Simulation minimally (80+80) X 0.05ns **= 8 ns/edge**
- **Massively parallelizable!**



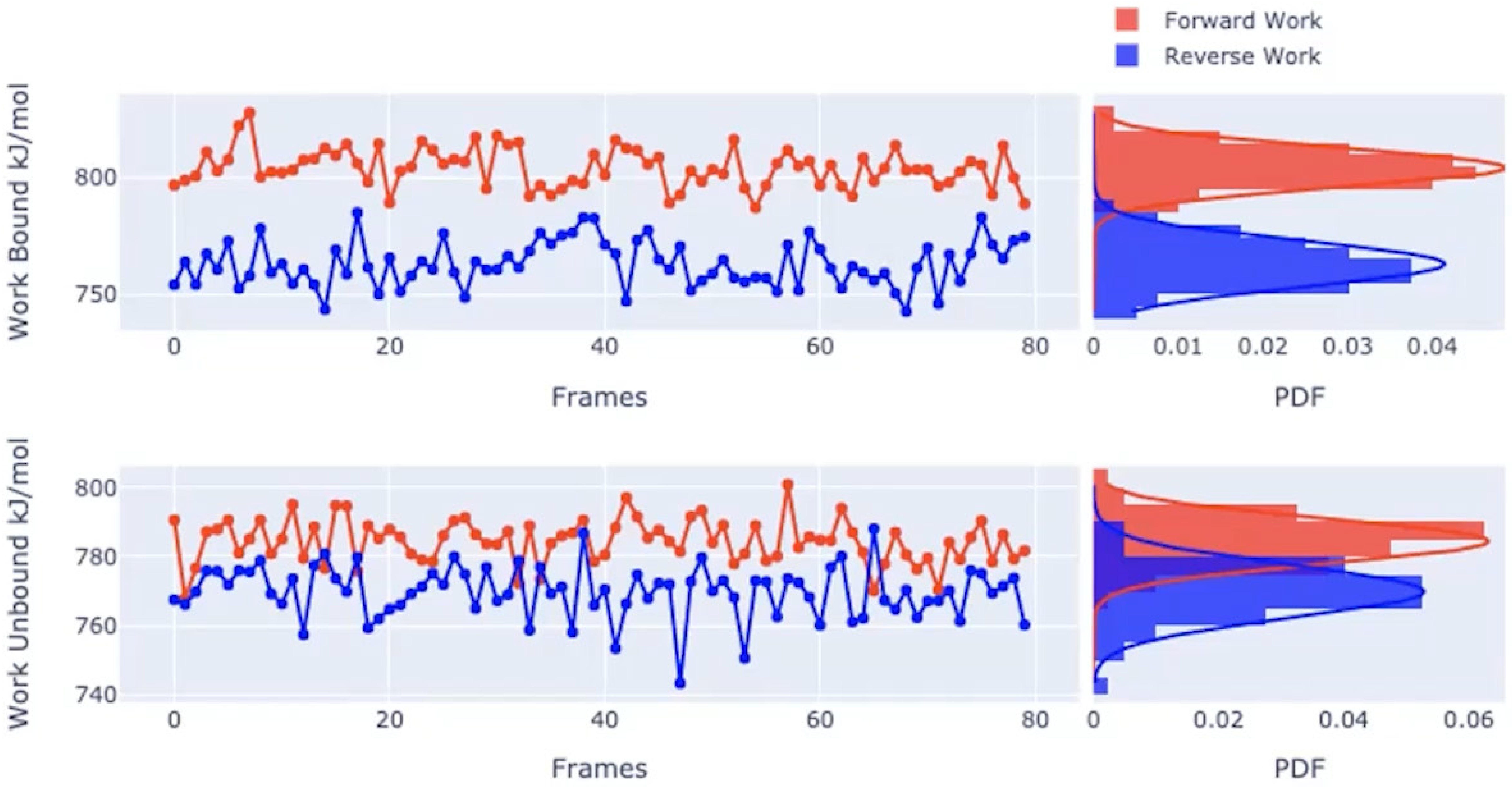
Gapsys et al., *Chem. Sci.*, 2020, **11**, 1140-1152

RBFE Methods NES (Non-Equilibrium Switching)

3K to 3B

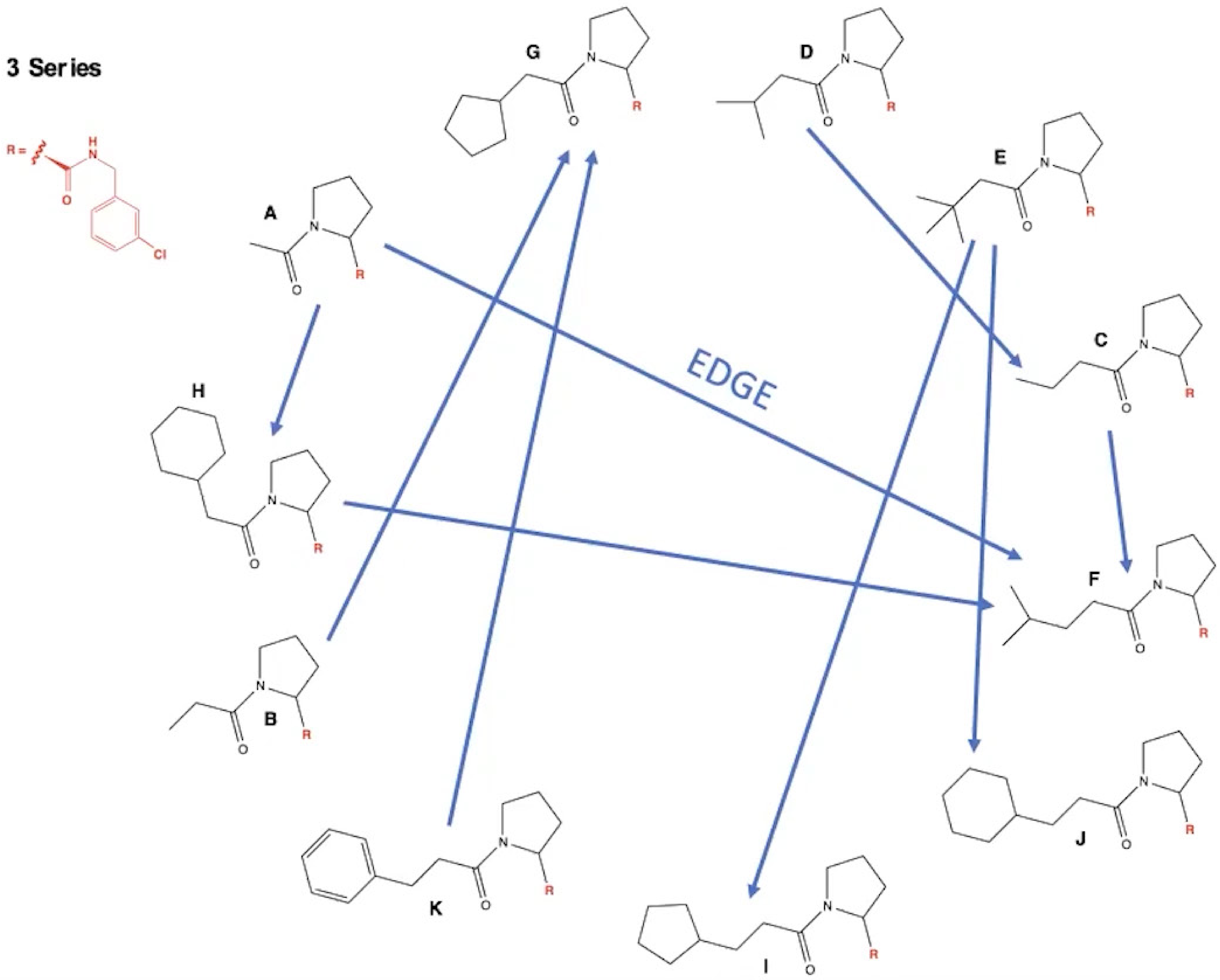


BAR score:
8.30 ± 1.02 kJ/mol



BAR: $$\sum_{i=1}^{n_f} \frac{1}{1+\exp\left(\ln \frac{n_f}{n_r} + \beta(w_i - \Delta G)\right)} = \sum_{j=1}^{n_r} \frac{1}{1+\exp\left(\ln \frac{n_r}{n_f} + \beta(w_j - \Delta G)\right)}$$

Why do we need a mapper?



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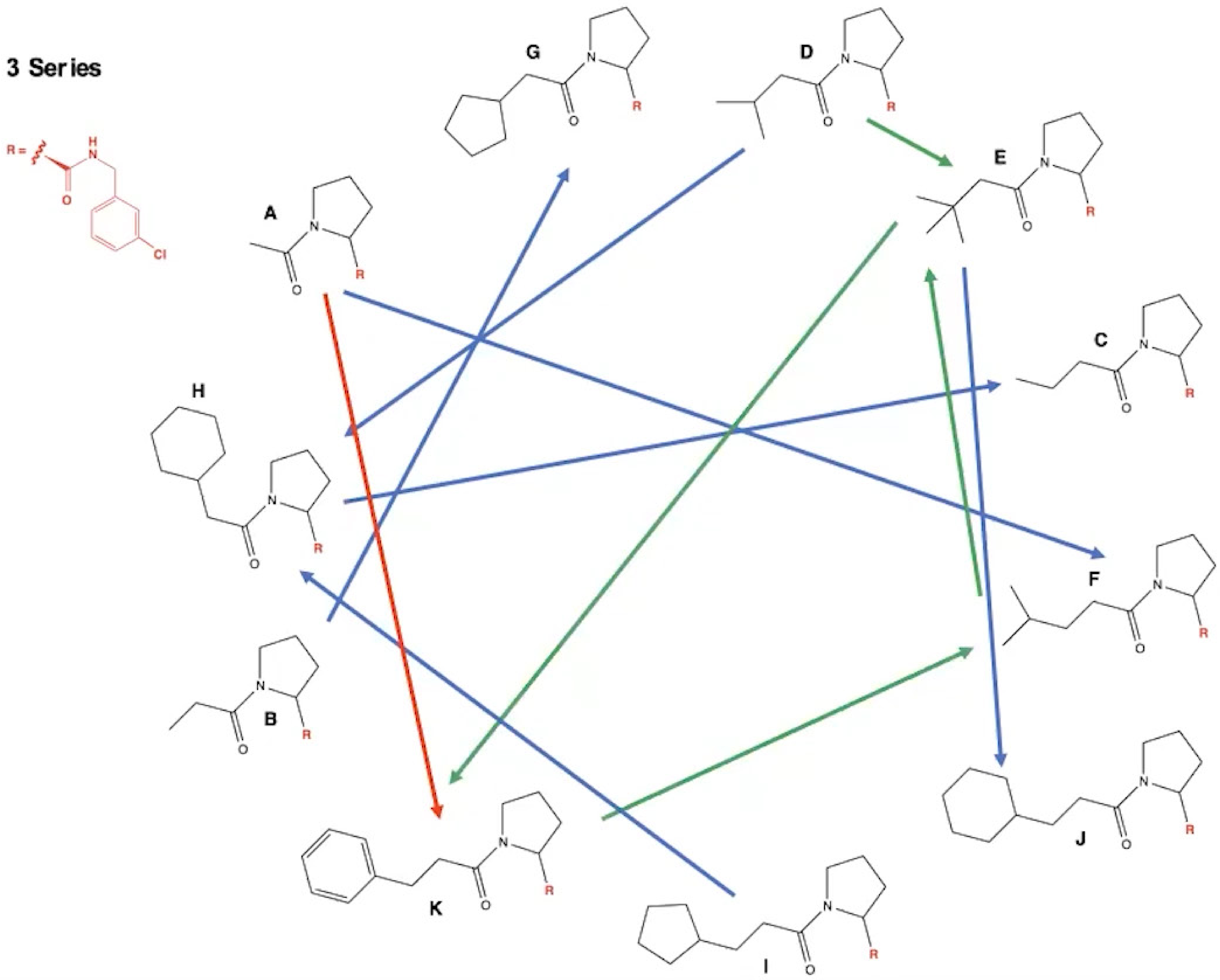
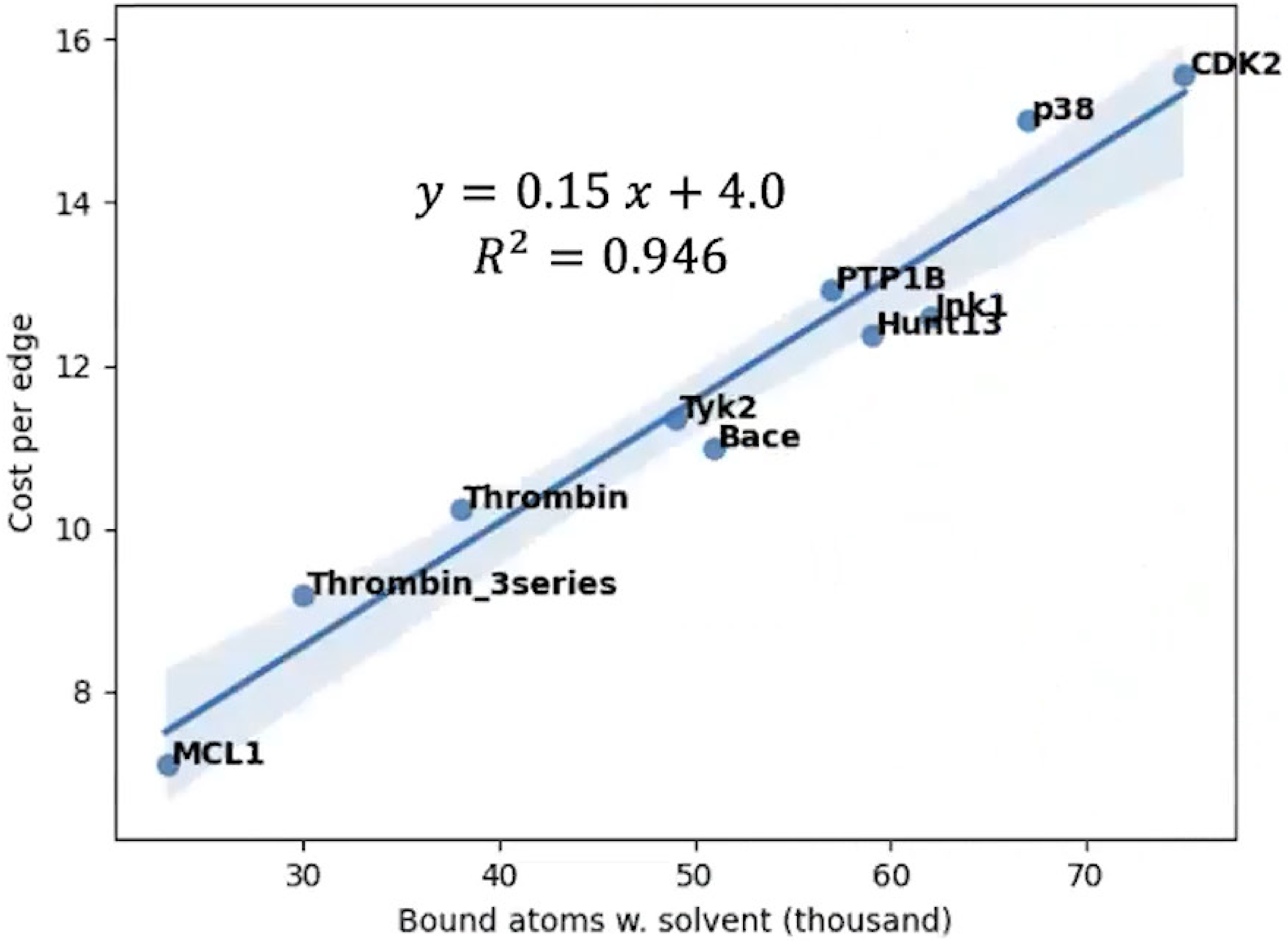


Why do we need a mapper?

- In general, given N compounds N(N-1)/2 possible edges



11 Thrombin inhibitors (55 edges) ~ $550
32 Bace inhibitors (496 edges) ~ $5500

Why do we need a mapper?

- The mapper should avoid “difficult” edges
- Cycles closure help in the Affinity prediction introducing redundances
- To expensive running all the edges

The OE Mapper

- **The Mapper goal** is to produce a set of edges where the transformed pair of compounds are “similar”: the RBFE edge calculation is likely to be successful and accurate

- The OE Mapper is mainly based on LOMAP(*)
    - LOMAP uses the chemical graph only (MCS)

(*) Liu, Y. Wu, et al, (2013), “Lead Optimization Mapper: Automating free energy calculations for lead optimization”, J. Comput. Aided Mol. Design, 27(9):755-770

The OE Mapper floe report

The Mapper Score

(With OpenEye variations)

- The similarity Matrix Scoring

$$\begin{array}{c|ccccc} & C_1 & C_2 & \dots & & C_n \\ C_1 & 1 & S_{1,2} & S_{1,3} & \dots & S_{1,n} \\ C_2 & S_{2,1} & 1 & S_{2,3} & \dots & S_{2,n} \\ \dots & \dots & \dots & \dots & \dots & \dots \\ & \dots & \dots & \dots & \dots & \dots \\ C_n & S_{n,1} & S_{n,2} & S_{n,3} & \dots & 1 \end{array}$$

$$S_{ij} \in [0,1]$$

$$S_{ij} = S_{ji}$$

$$S_{i,j} = \prod_{k=1}^{M} R_k(i,j)$$

- R_k Charge Based
  - If C_i and C_j same charge 1 else 0
- R_k MCSS Based (GMX biased)
  - (a) $H(mcs_{hw} - ths)$
  - (b) $e^{-\beta(Nhw_i + Nhw_j - 2mcs_{hw})}$
- R_k ROCS Based
  - Shape and Color

The Mapper Score

- The similarity Matrix Scoring

(With OpenEye variations)

$$
\begin{array}{c} \\ C_1 \\ C_2 \\ \dots \\ \\ C_n \end{array}
\begin{array}{c}
\begin{array}{ccccc} C_1 & C_2 & \dots & & C_n \end{array} \\
\begin{pmatrix}
1 & S_{1,2} & S_{1,3} & \dots & S_{1,n} \\
S_{2,1} & 1 & S_{2,3} & \dots & S_{2,n} \\
\dots & \dots & \dots & \dots & \dots \\
\dots & \dots & \dots & \dots & \dots \\
S_{n,1} & S_{n,2} & S_{n,3} & \dots & 1
\end{pmatrix}
\end{array}
\quad S_{ij} \in [0,1] \quad S_{ij} = S_{ji}
$$

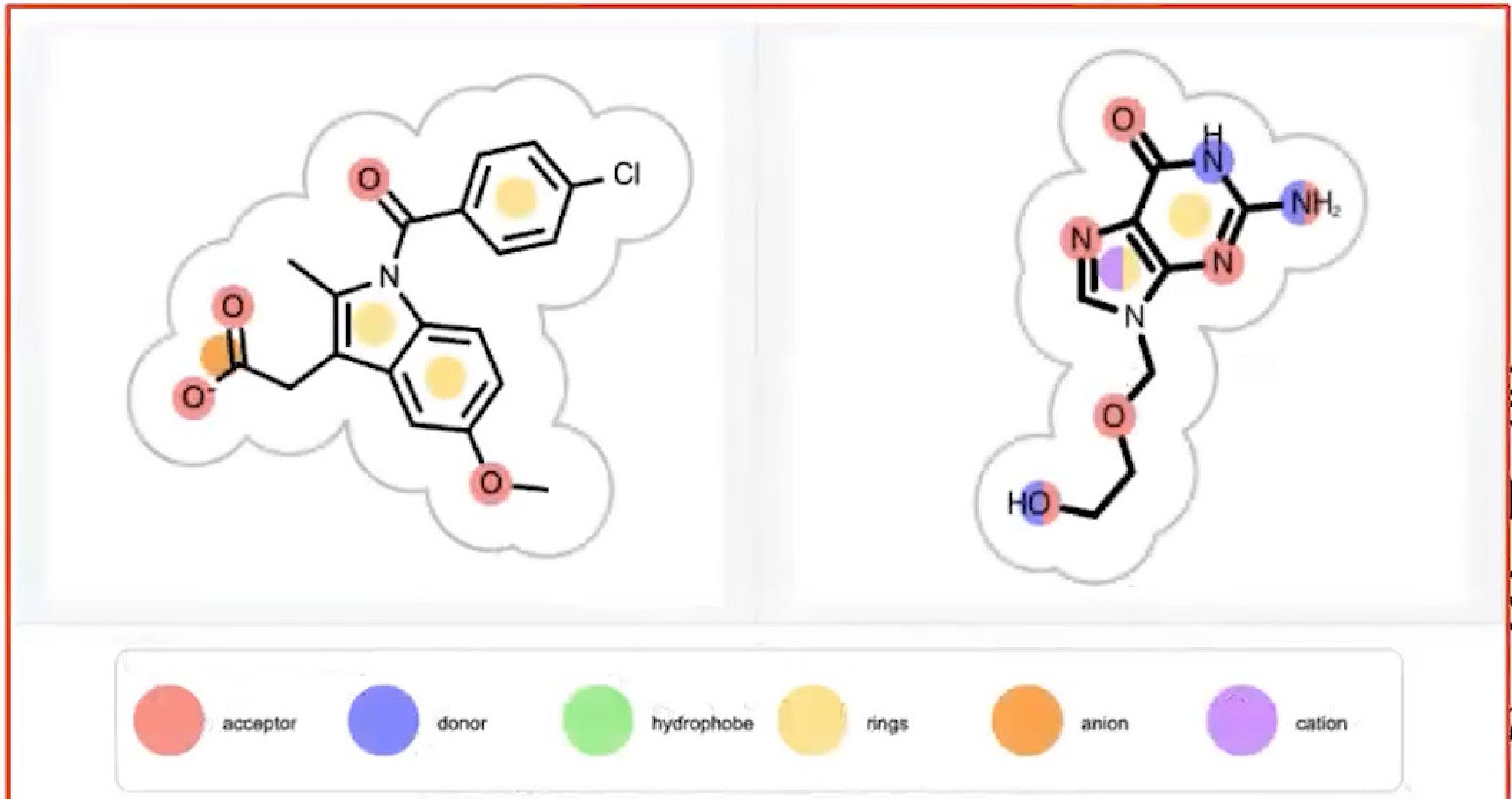


Figure 2. Color-coding of chemical features

ge Based

nd C_j same charge 1 else 0

S Based (GMX biased)

$$H(mcs_{hw} - ths)$$

$$e^{-\beta(Nhw_i + Nhw_j - 2mcs_{hw})}$$

- R_k ROCS Based
  - Shape and Color

The Mapper Score

- The similarity Matrix Scoring

(With OpenEye variations)

$$
\begin{array}{c} \\ C_1 \\ C_2 \\ \dots \\ \\ C_n \end{array}
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\begin{pmatrix}
1 & S_{1,2} & S_{1,3} & \dots & S_{1,n} \\
S_{2,1} & 1 & S_{2,3} & \dots & S_{2,n} \\
\dots & \dots & \dots & \dots & \dots \\
\dots & \dots & \dots & \dots & \dots \\
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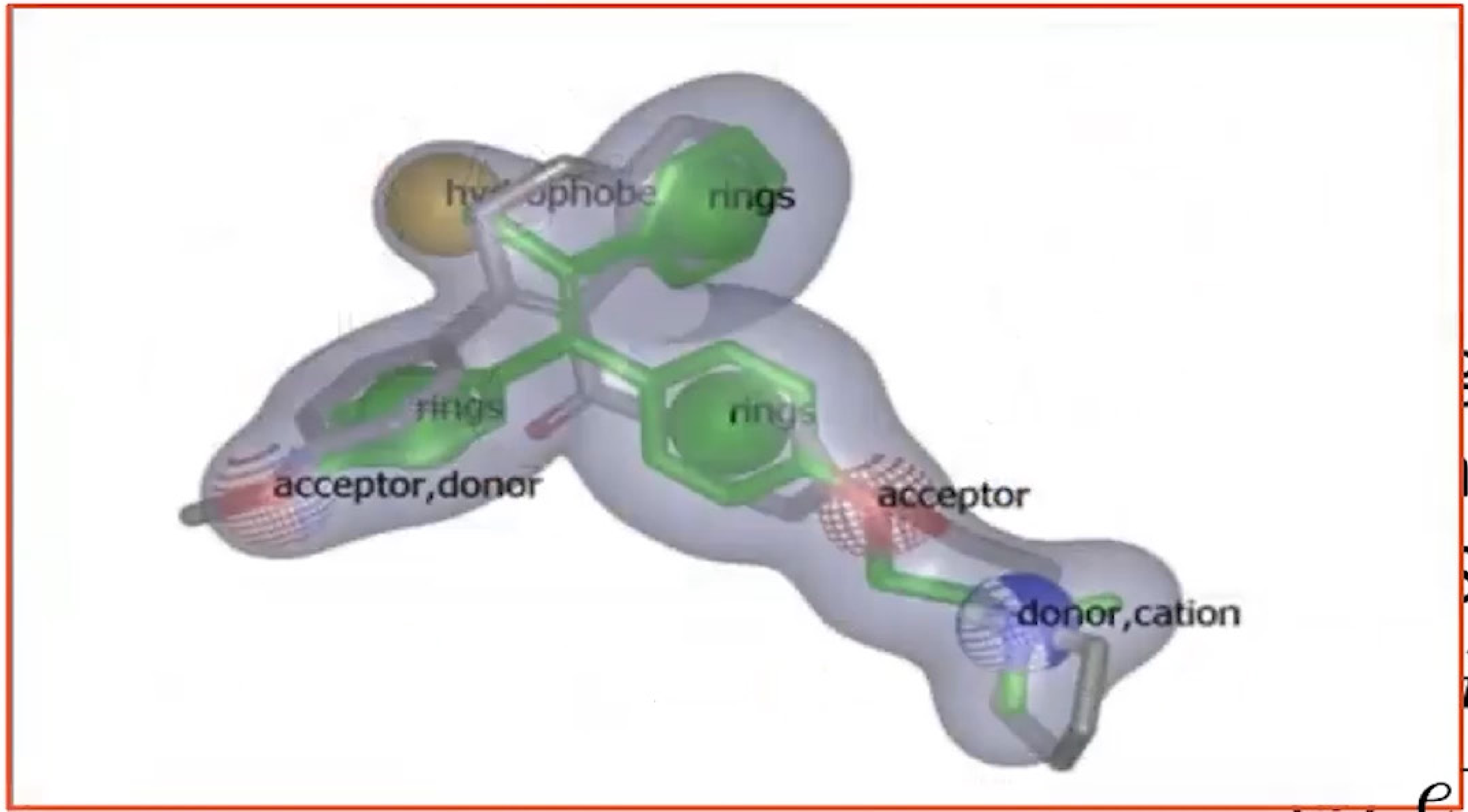

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$H(mcs_{hw} - ths)$

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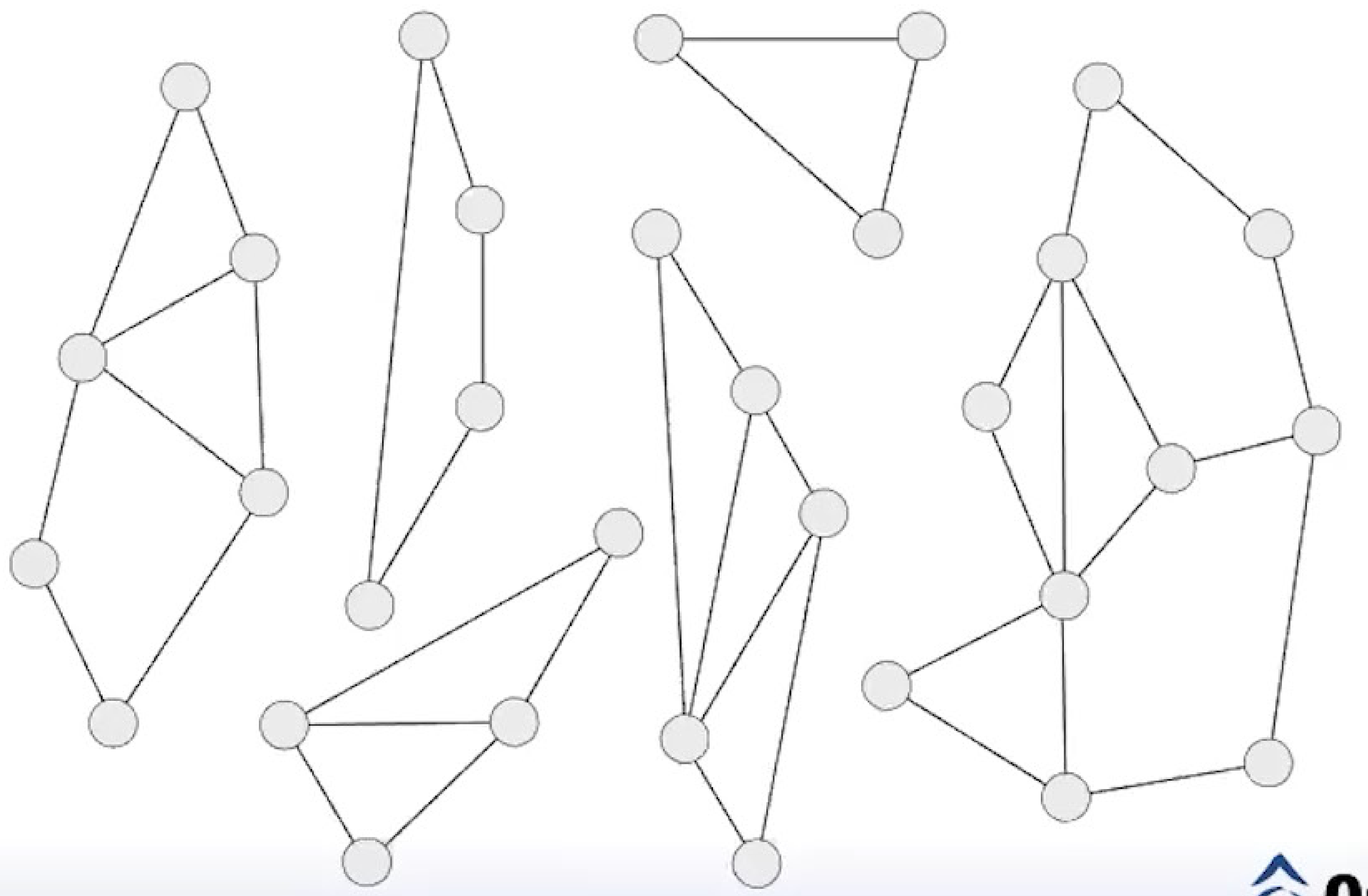
The Mapper Graph

- Building the graph
  1. Create edges where $S_{ij} \geq Cut_{Off} > 0$

$$\begin{pmatrix} 1 & S_{1,2} & S_{1,3} & \dots & S_{1,n} \\ S_{2,1} & 1 & S_{2,3} & \dots & S_{2,n} \\ \dots & \dots & \dots & \dots & \dots \\ \dots & \dots & \dots & \dots & \dots \\ S_{n,1} & S_{n,2} & S_{n,3} & \dots & 1 \end{pmatrix}$$



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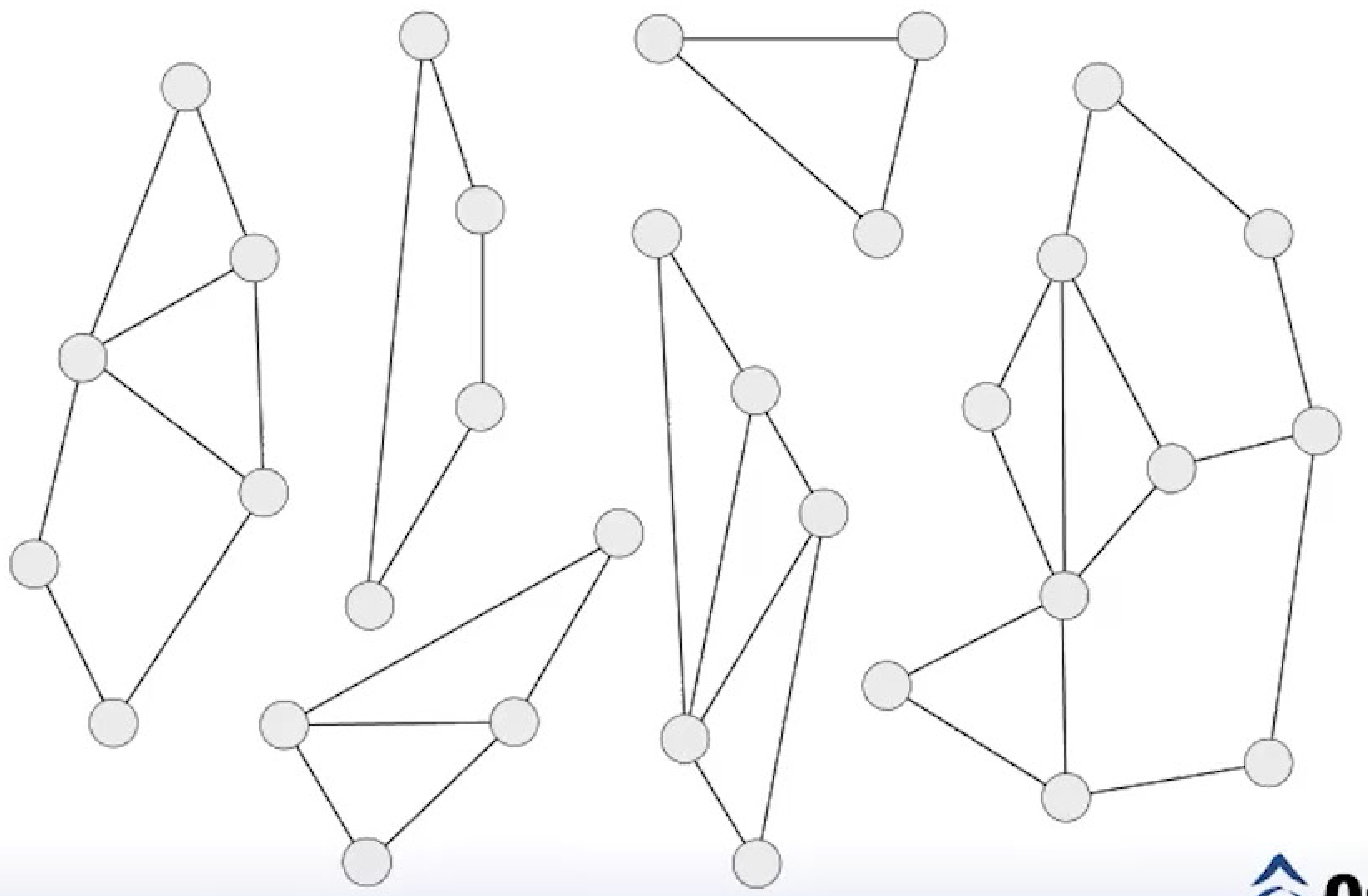
The Mapper Graph

- Building the graph
  - For each one of the cluster minimize:
    - Cycles and MAXDIST constraints

$$\begin{pmatrix} 1 & S_{1,2} & S_{1,3} & \ldots & S_{1,n} \\ S_{2,1} & 1 & S_{2,3} & \ldots & S_{2,n} \\ \ldots & \ldots & \ldots & \ldots & \ldots \\ \ldots & \ldots & \ldots & \ldots & \ldots \\ S_{n,1} & S_{n,2} & S_{n,3} & \ldots & 1 \end{pmatrix}$$



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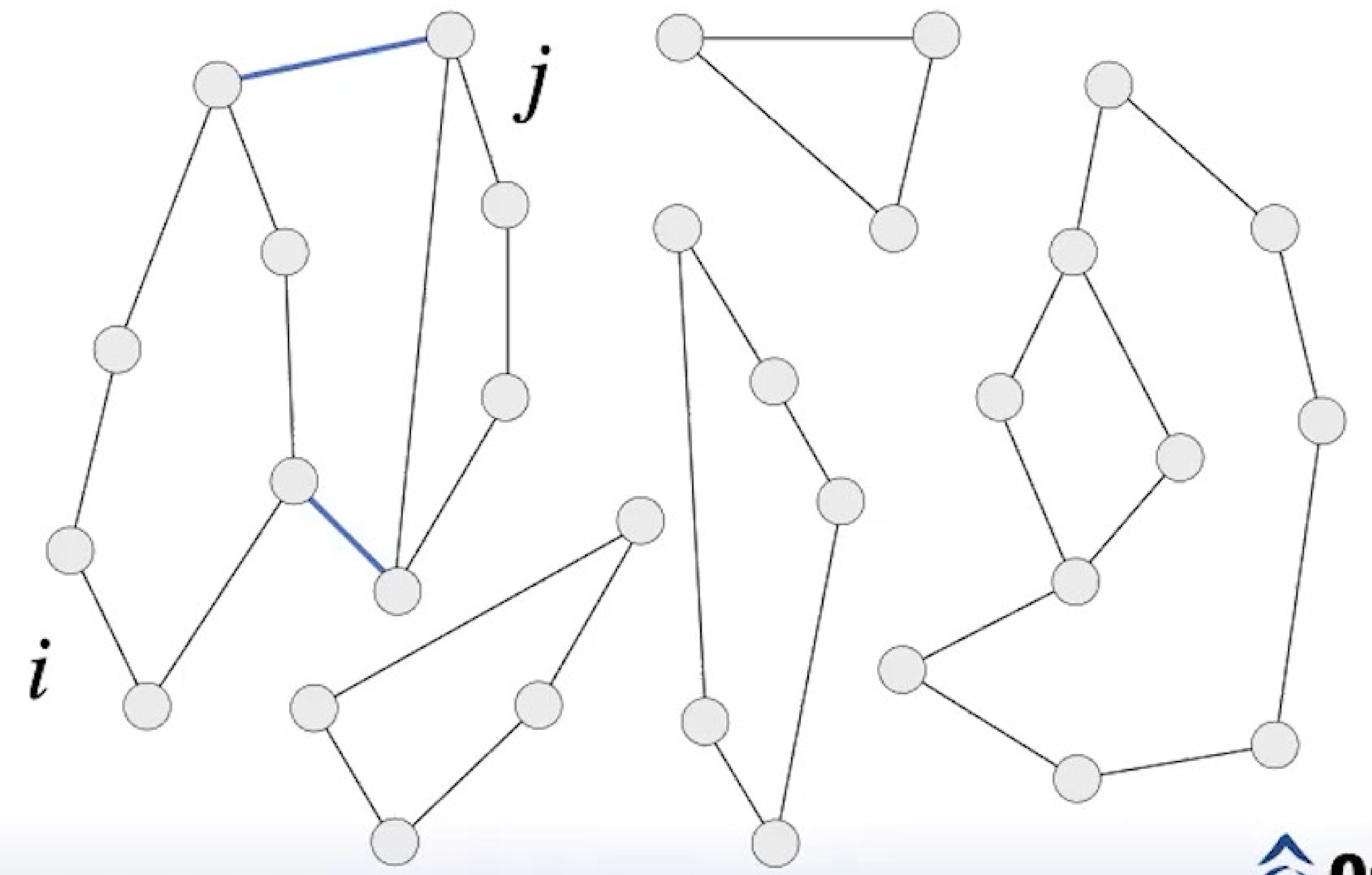
The Mapper Graph

- Building the graph
  - Connect the Subgraphs:
    - (a) $\forall Cl_i, Cl_j \; e_{ij} \mid S_{i,j} = \max\limits_{S_{Ci,Cj}}$
    - (b) $\forall Cl_h, Cl_k \; e_{hk} \mid S_{h,k} = \max\limits_{S_{Ch,Ck}-e_{ij}}$

$$\begin{pmatrix} 1 & S_{1,2} & S_{1,3} & \dots & S_{1,n} \\ S_{2,1} & 1 & S_{2,3} & \dots & S_{2,n} \\ \dots & \dots & \dots & \dots & \dots \\ \dots & \dots & \dots & \dots & \dots \\ S_{n,1} & S_{n,2} & S_{n,3} & \dots & 1 \end{pmatrix}$$



NES Protocol mainly followed Gapsys et al.*

(With OpenEye variations)

- GROMACS 2020
- OpenFF 2.0 (Sage) with Amber ff14
- Equilibrium runs done separately
  - Bound and unbound ligand
  - 1X 6 ns, no clustering
  - No NES knowledge embedded
- NES runs: 80 frames with 50ps switching per frame
  - OpenEye alchemical chimeric A/B ligands
  - $\Delta\Delta G$ correlations symmetrized around A→B | B→A
- Schrodinger JACS ‘15 datasets: 8 targets
- Hunt ‘13 Bace dataset and Calabro Thrombin 3-series dataset

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Compare:
- **OE Mapper**
- **Literature maps (FEP+)**

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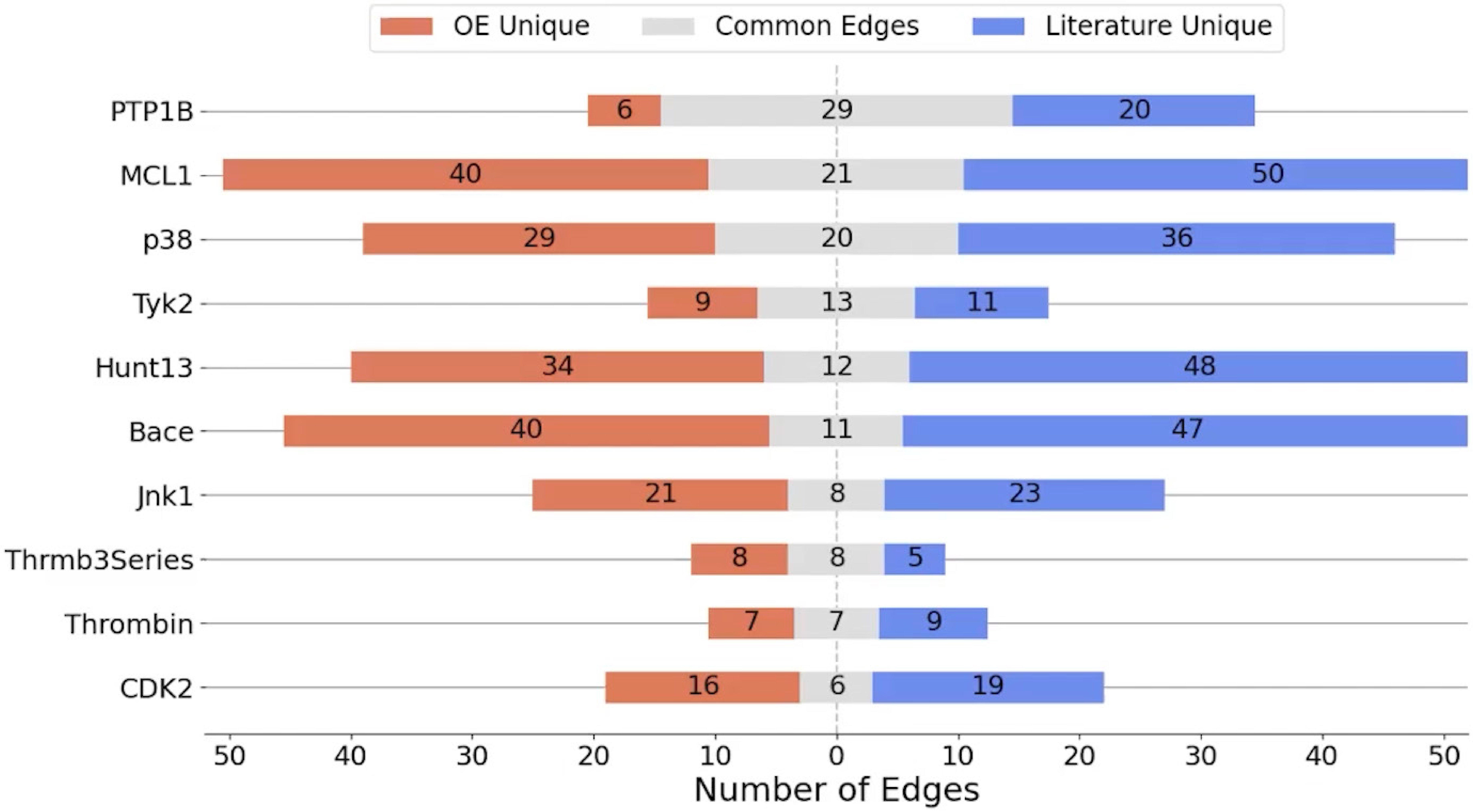
*Gapsys et al., *Chem. Sci.*, 2020, **11**, 1140-1152

Common Edges Diverging Diagram



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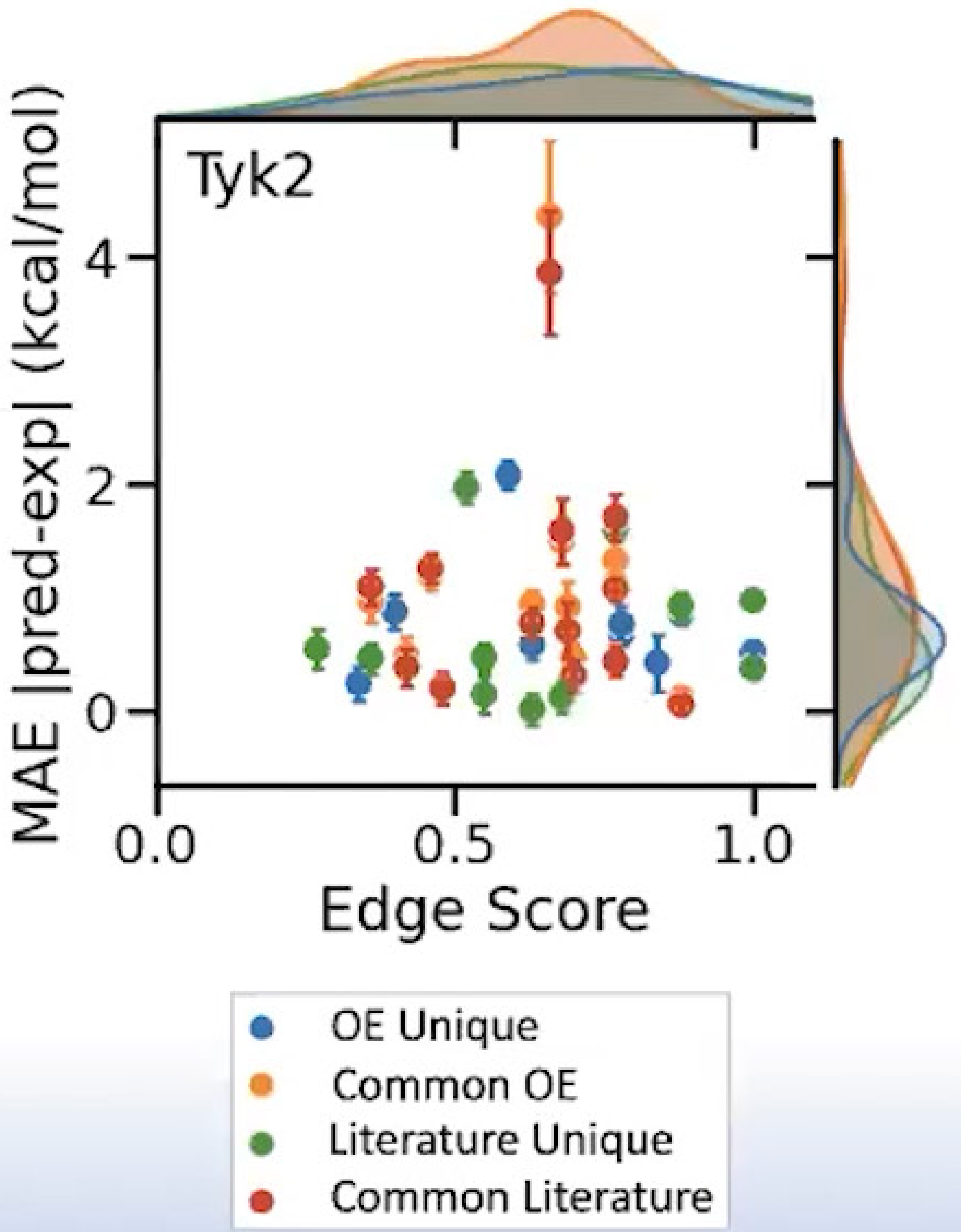
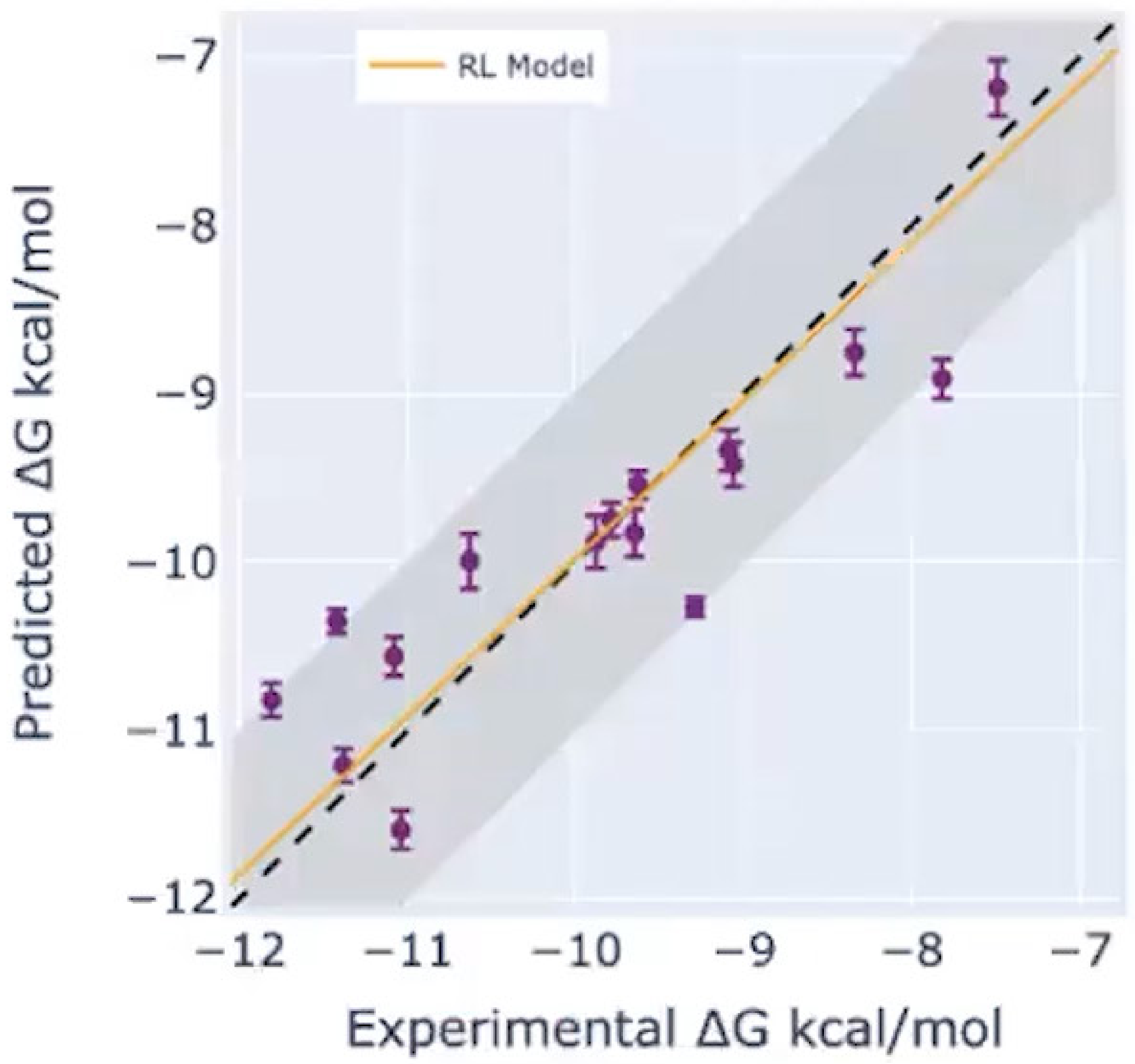
Tyk2

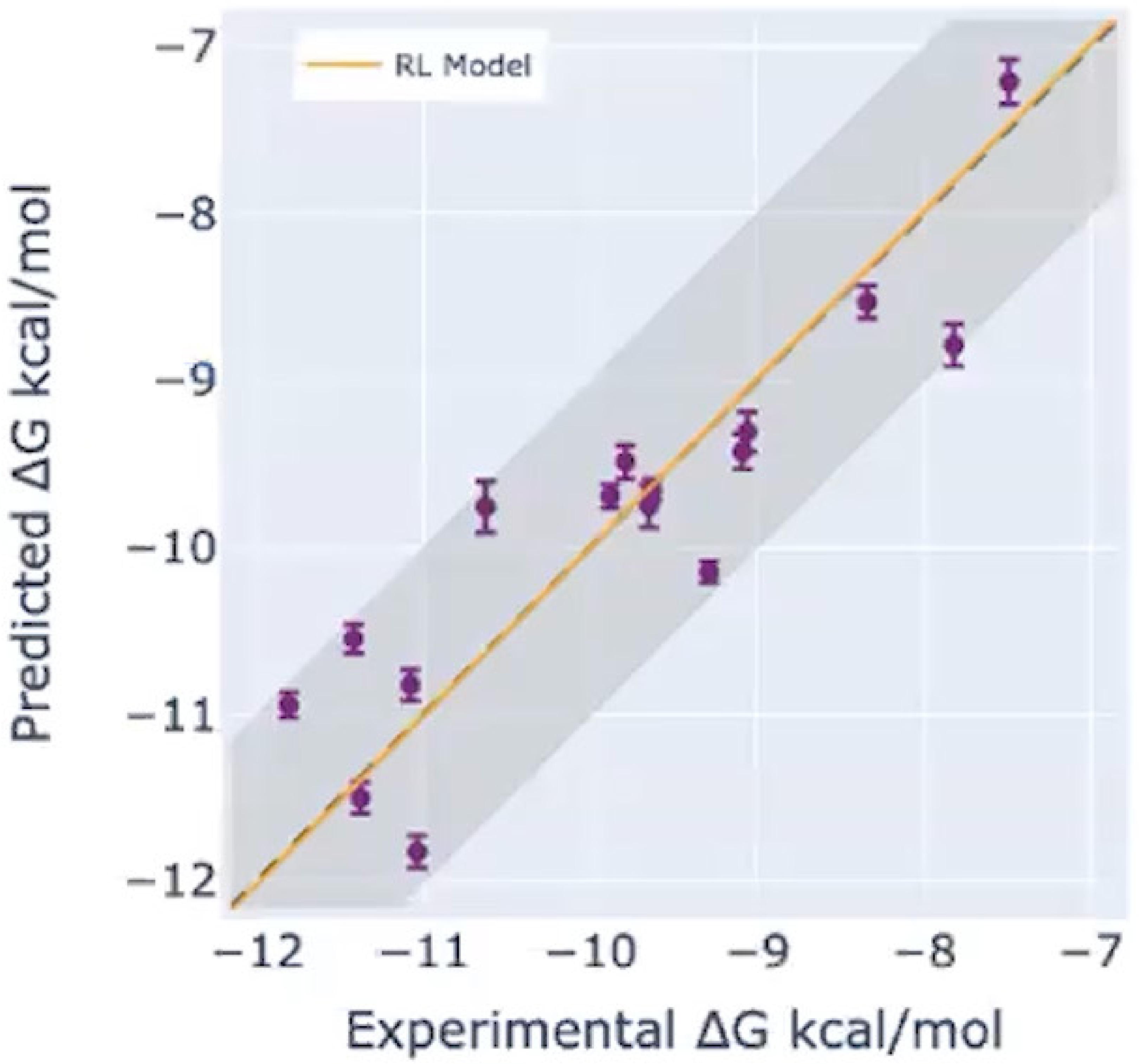
Metric	OE Mapper	Literature Mapper
Ligands	16	
Edges	22	24



OE Mapper



Literature Mapper



Metric	OE Mapper	Literature Mapper
Pearson's r^2	0.783 ± 0.075	0.804 ± 0.074
Kendall's τ	0.750 ± 0.102	0.733 ± 0.114
MAE[a]	0.477 ± 0.092	0.454 ± 0.088
RMAE[b]	0.456 ± 0.091	0.434 ± 0.097

[a]Mean Absolute Error in kcal/mol.
[b]MAE divided by the Mean Absolute Deviation of Experimental ΔG.

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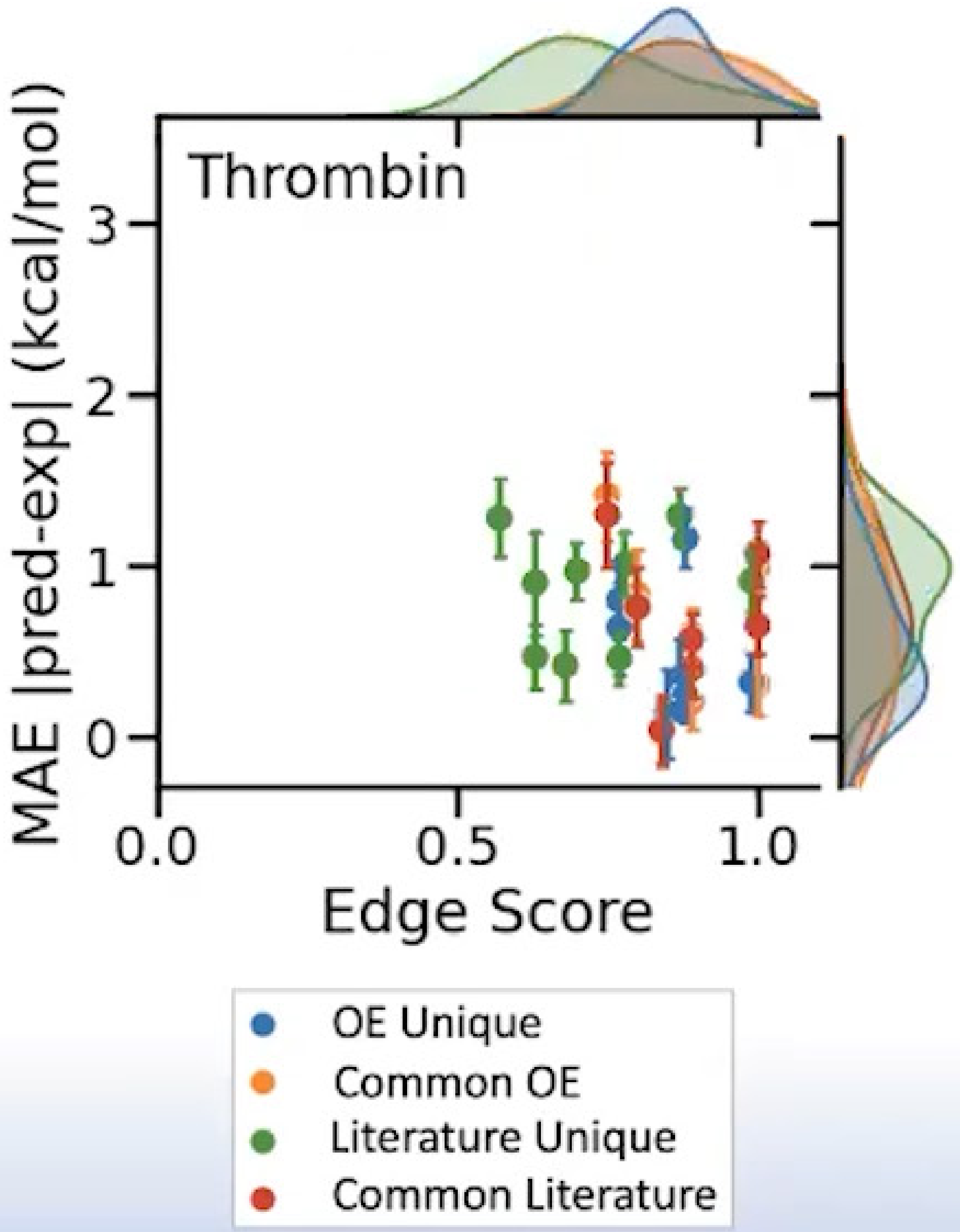
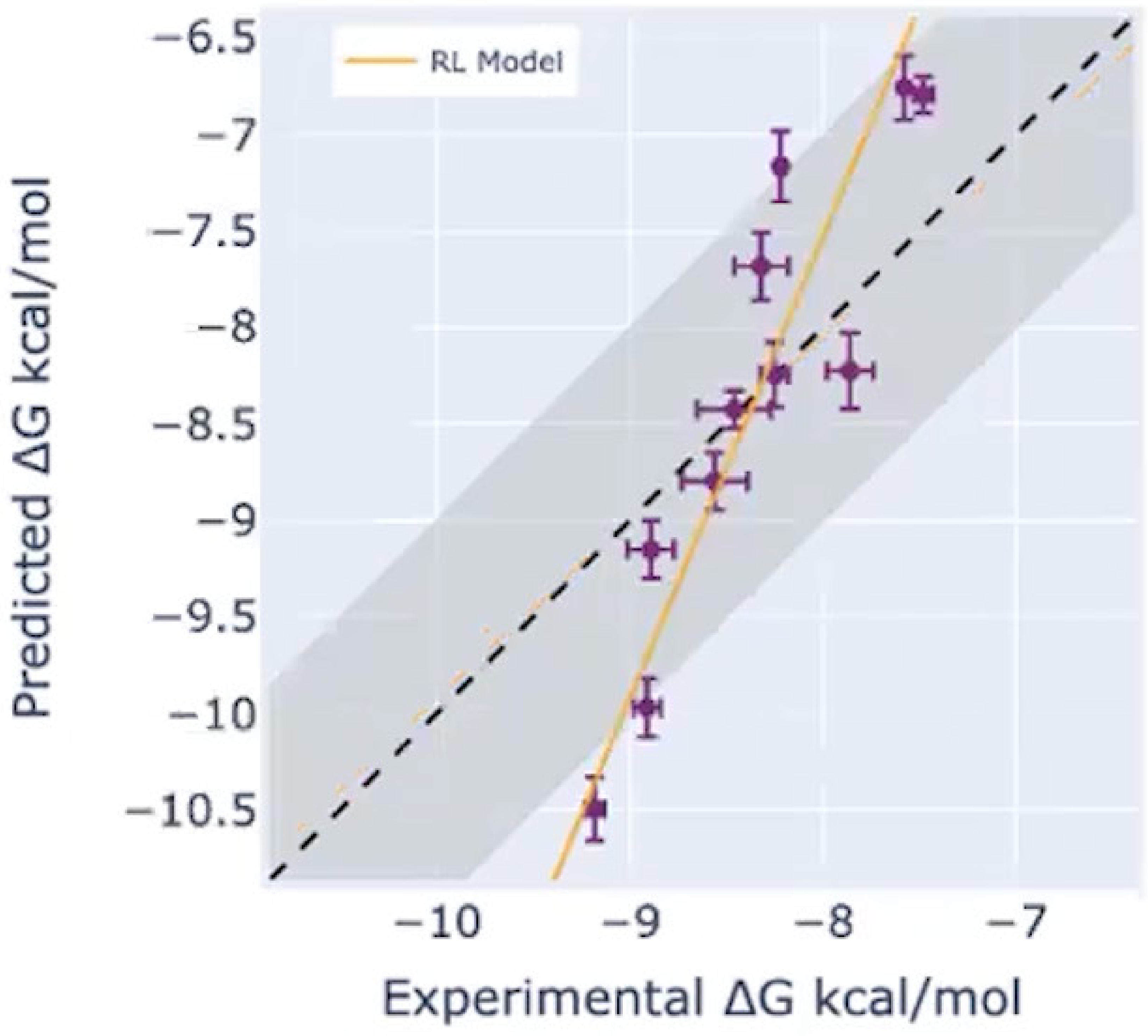
Thrombin

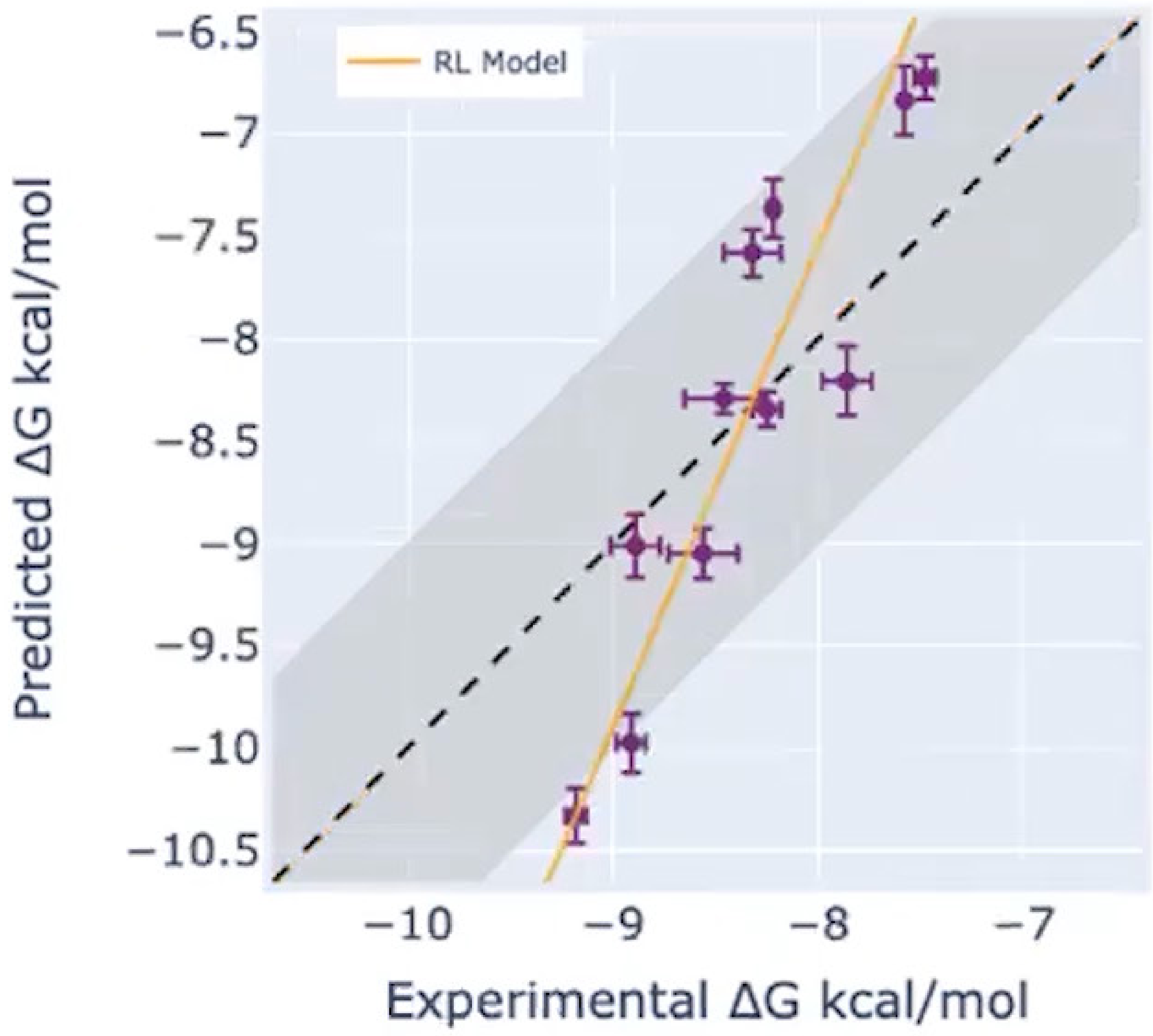
Metric	OE Mapper	Literature Mapper
Ligands	11	
Edges	14	16



OE Mapper



Literature Mapper



Metric	OE Mapper	Literature Mapper
Pearson's r^2	0.827 ± 0.113	0.824 ± 0.114
Kendall's τ	0.855 ± 0.119	0.818 ± 0.127
MAE[a]	0.588 ± 0.125	0.594 ± 0.113
RMAE[b]	1.399 ± 0.445	1.412 ± 0.381

[a]Mean Absolute Error in kcal/mol.
[b]MAE divided by the Mean Absolute Deviation of Experimental ΔG.

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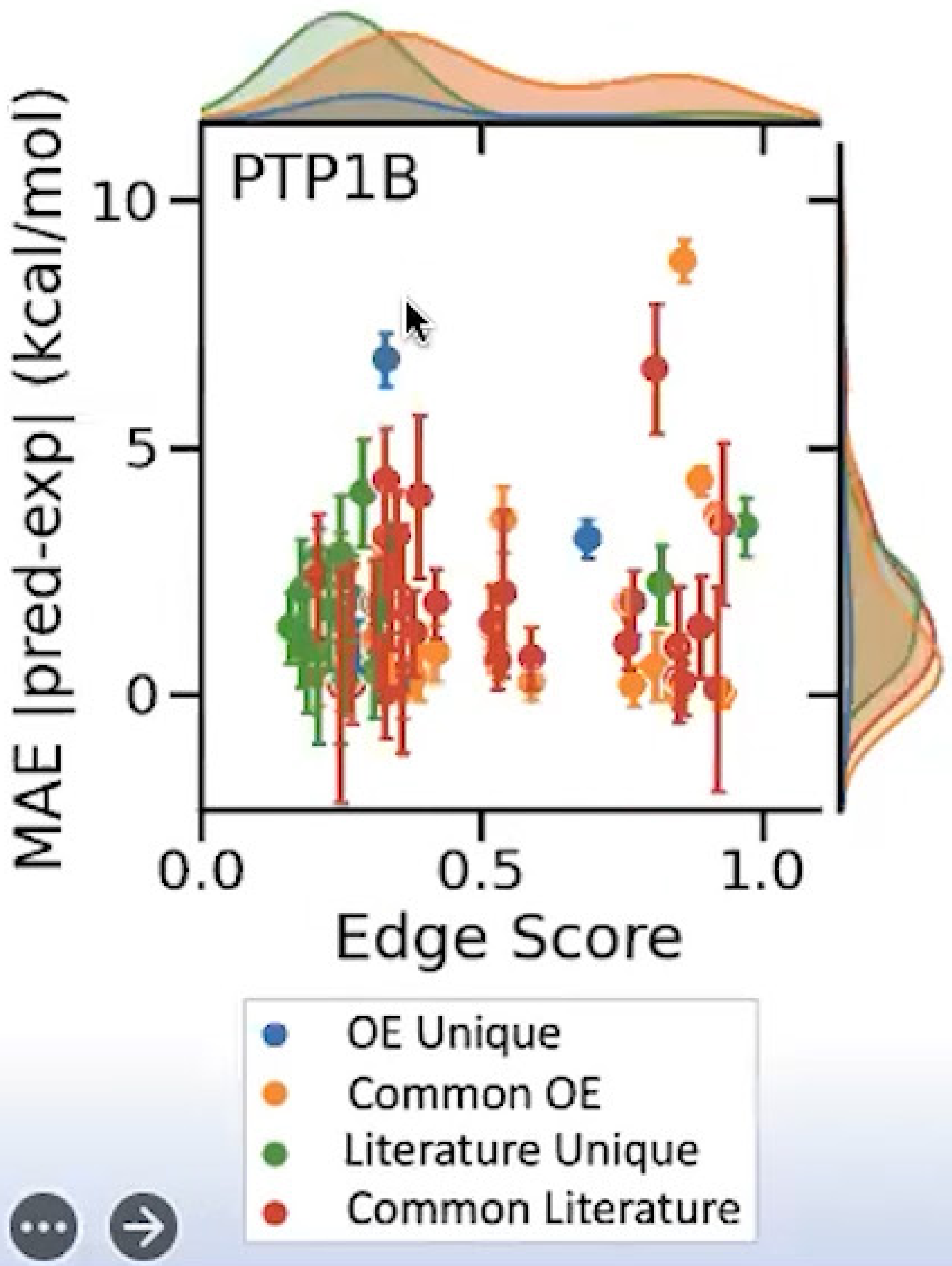
PTP1B

Metric	OE Mapper	Literature Mapper
Ligands	23	
Edges	35	49



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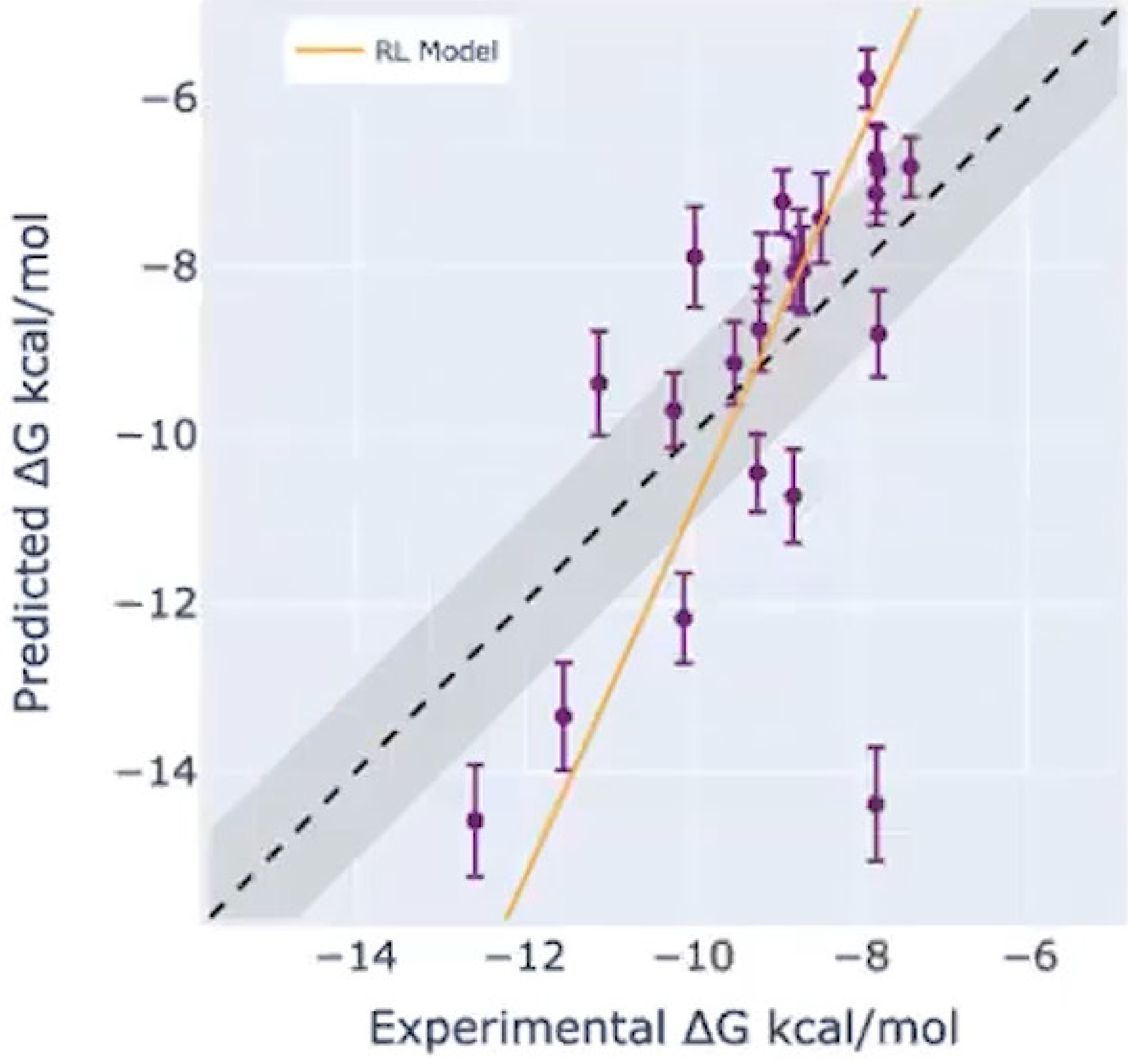
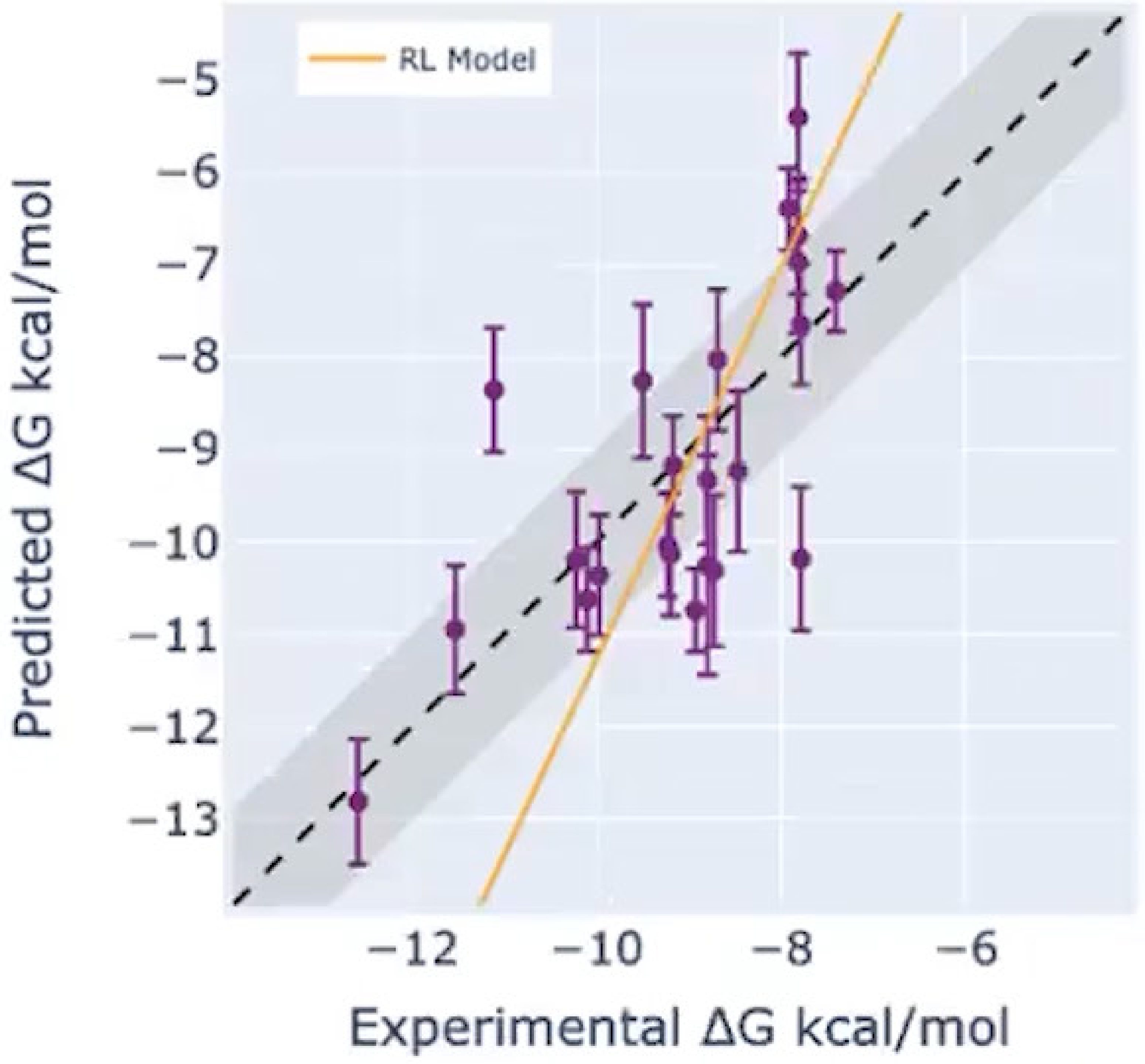


Literature Mapper



Metric	OE Mapper	Literature Mapper
Pearson's r^2	0.385 ± 0.248	0.481 ± 0.170
Kendall's τ	0.503 ± 0.147	0.487 ± 0.133
MAE[a]	1.445 ± 0.251	0.995 ± 0.157
RMAE[b]	1.437 ± 0.373	0.989 ± 0.284

[a]Mean Absolute Error in kcal/mol.
[b]MAE divided by the Mean Absolute Deviation of Experimental ΔG.

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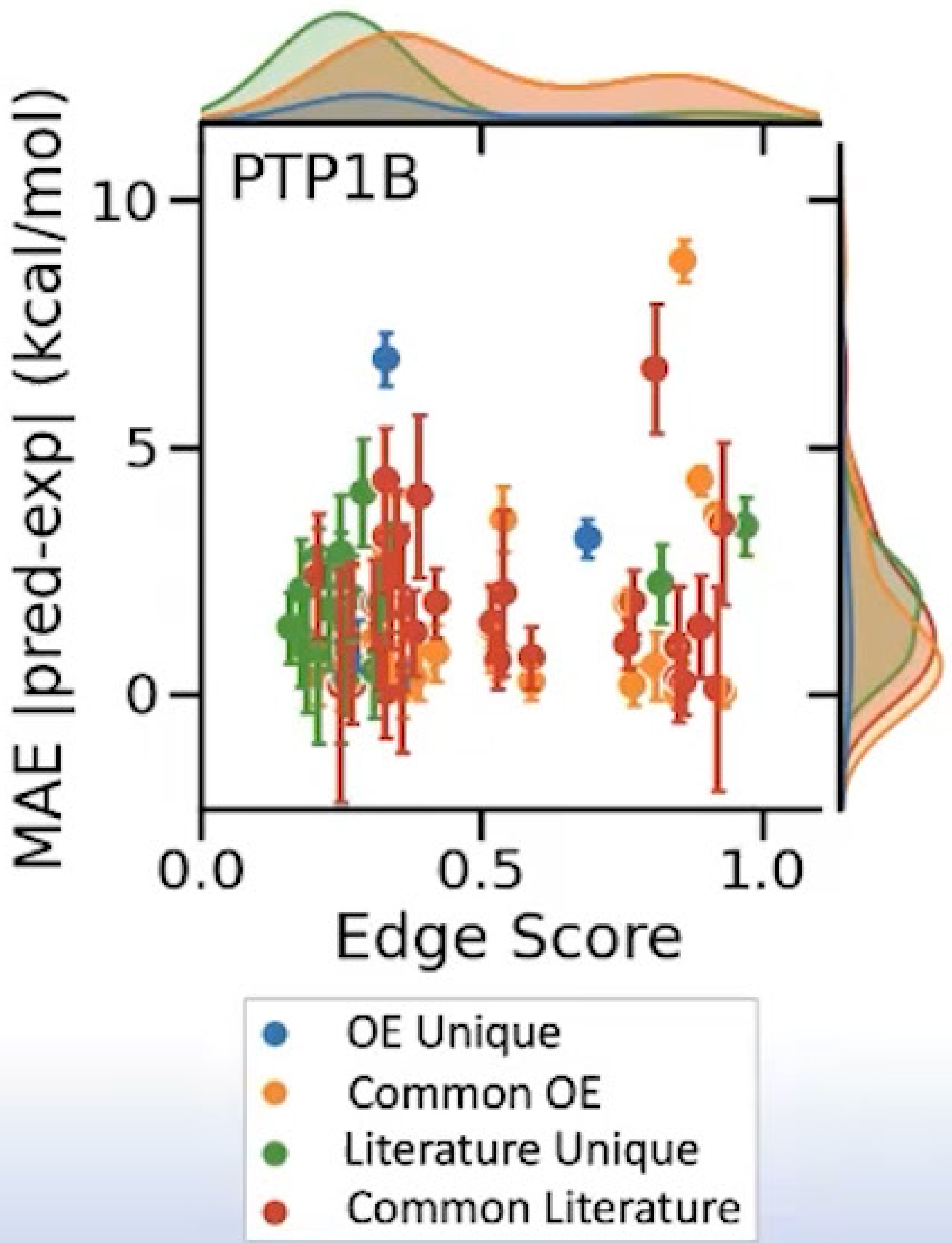
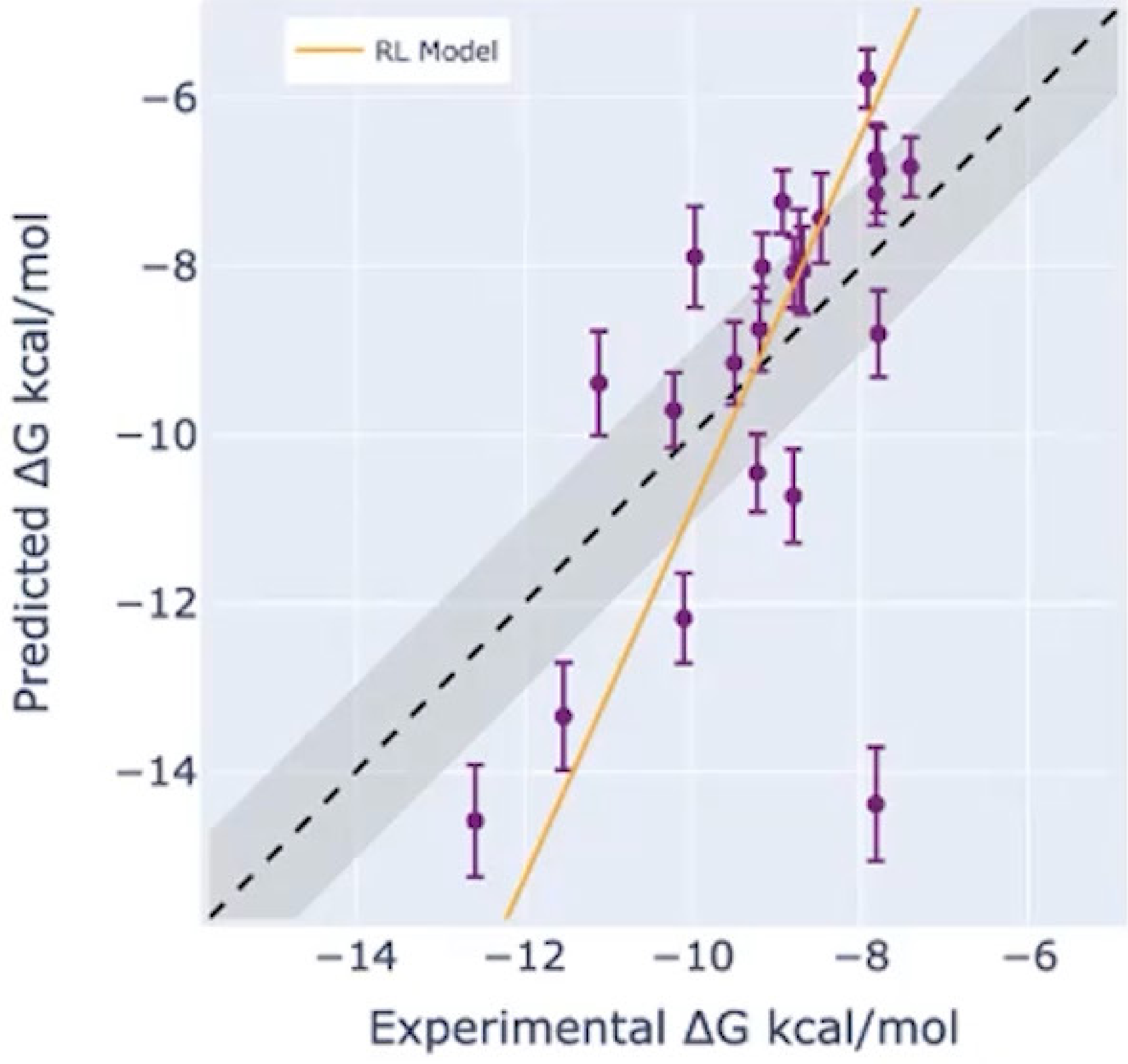
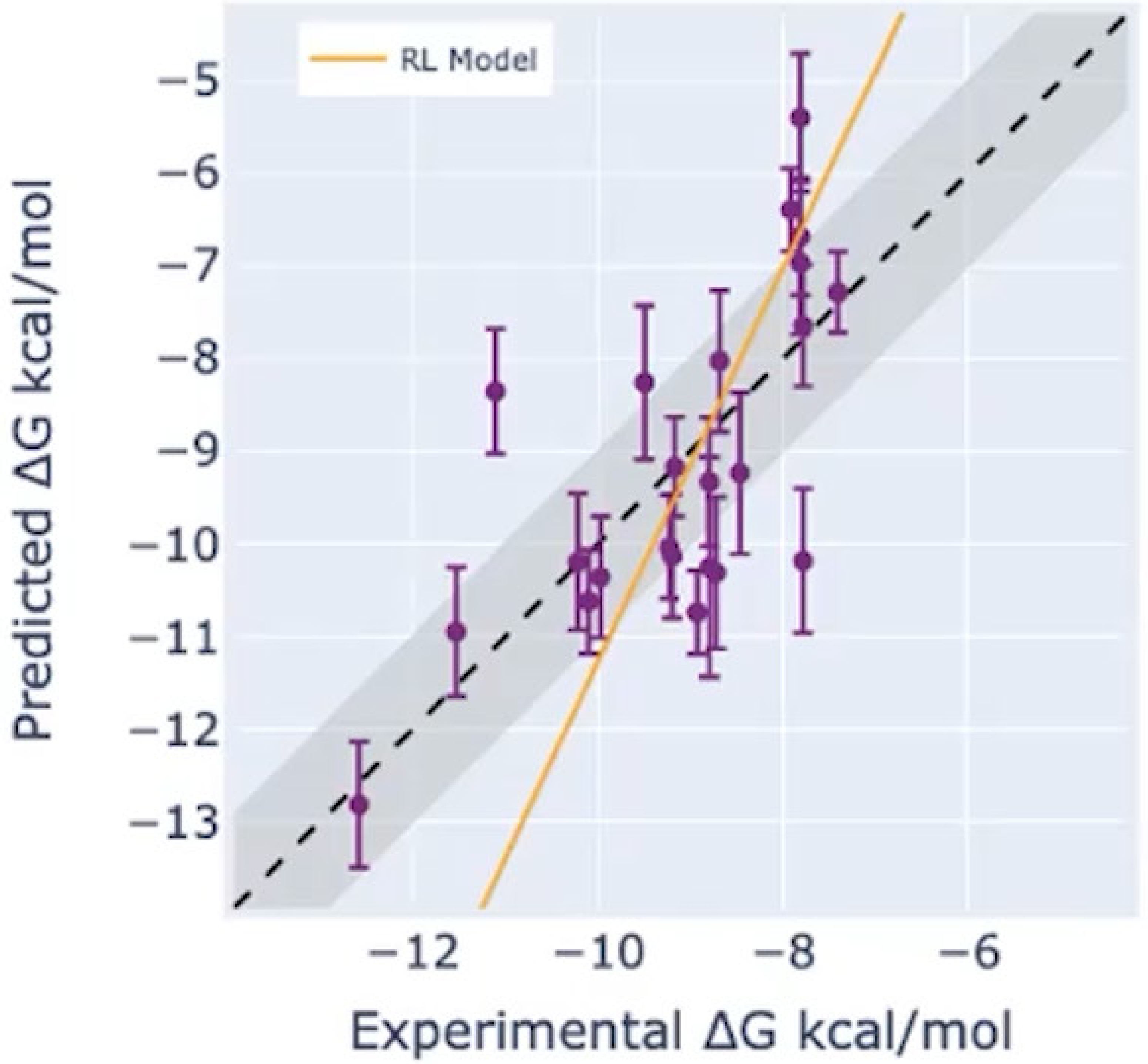


OE Mapper



Literature Mapper



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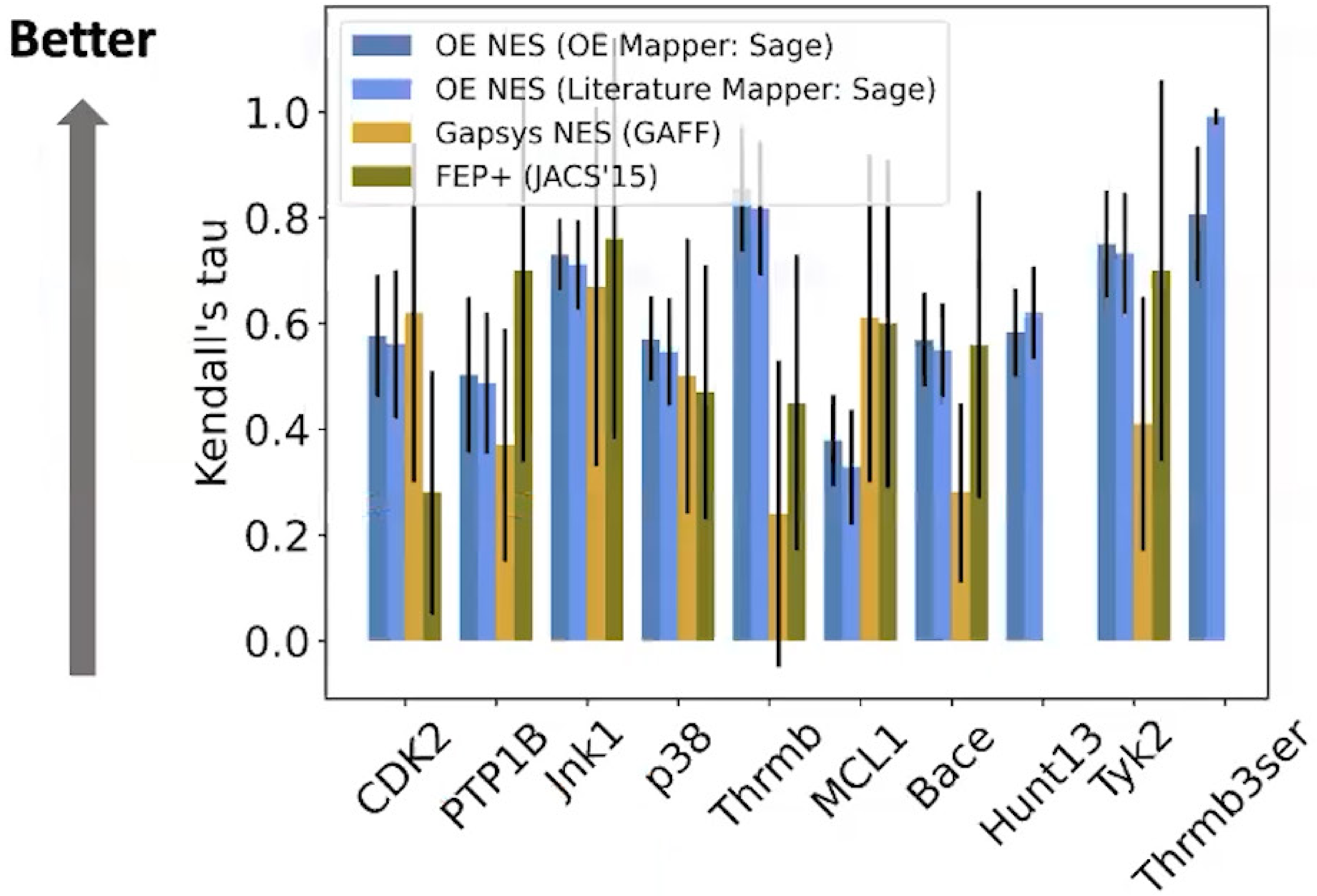
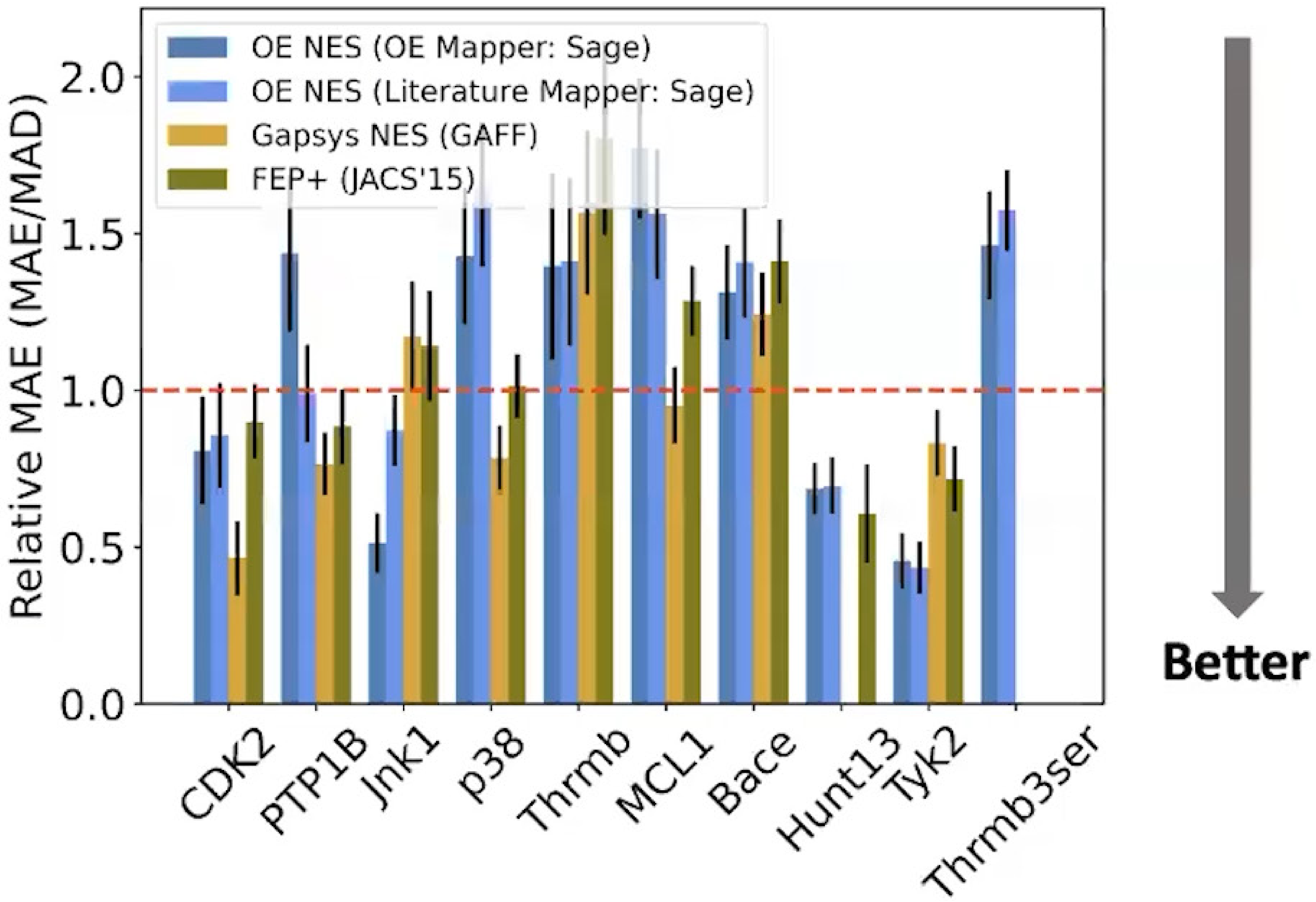
Direct Predictions of ΔG : 9 Datasets





- OE NES has comparable accuracy to literature RBFE benchmarks

Conclusions

- The starting OE Mapper implementation performs as expected compared to literature maps
- Still the edge scoring sometimes does not reflect the accuracy of the calculation

Plans: include equilibrium information in the mapper scoring

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- Christopher Bayly
- Agnes Huang
- Hyesu Jang
- Geoff Skillman


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