Developing a Robust Method for Automated Assessment of Binding Affinity via FEP

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Introduction

There is a rising interest towards FEP (Free Energy Perturbation) calculations in the drug discovery community.[1,2] Such calculations are performed to predict the relative binding affinity changes (ΔΔG) within a congeneric ligand series.

This is achieved by non-physical ("alchemical") transformations, in which a molecule (A) is gradually converted into a structurally related molecule (B) through a number of discrete steps, the so-called λ windows. The ligand simulated in each window can be thought of as an alchemical (i.e., hybrid) molecule consisting of a 1-λ fraction of A and a λ fraction of B (Figure 1).

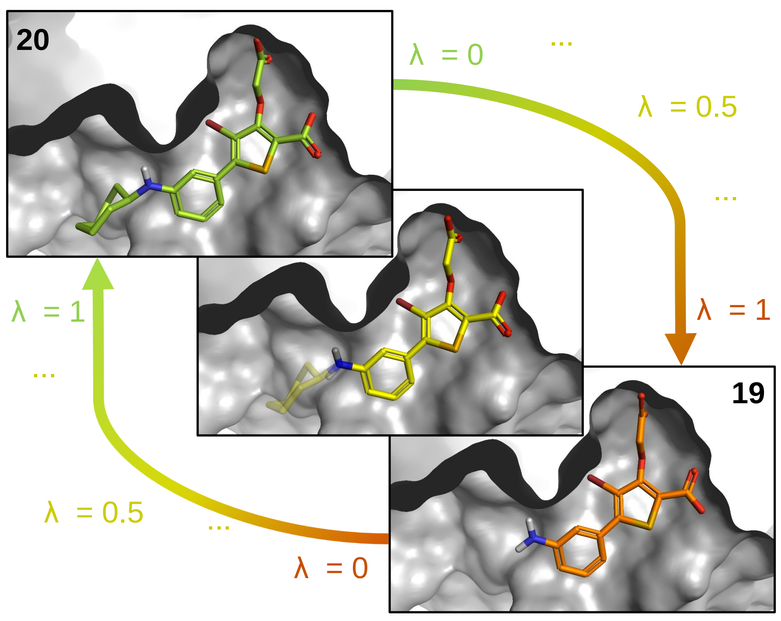

Figure 1: Ligands **20** (lime) and **19** (orange) bound to PTP1B. An artificial hybrid molecule is shown in beige. **20** has an additional cycloheptyl moiety.

The free energy difference between the end states of the transformation can be assessed by a variety of methods, such as the Multistate Bennett Acceptance Ratio (MBAR)[3], and corresponds to the binding affinity difference between the two molecules.

Extending this approach to a network of congeneric molecules leads to assessing the binding affinities of the corresponding ligand series (Figure 2). Accuracies of about 1 kcal/mol compared to experimental values can be achieved for larger data sets.

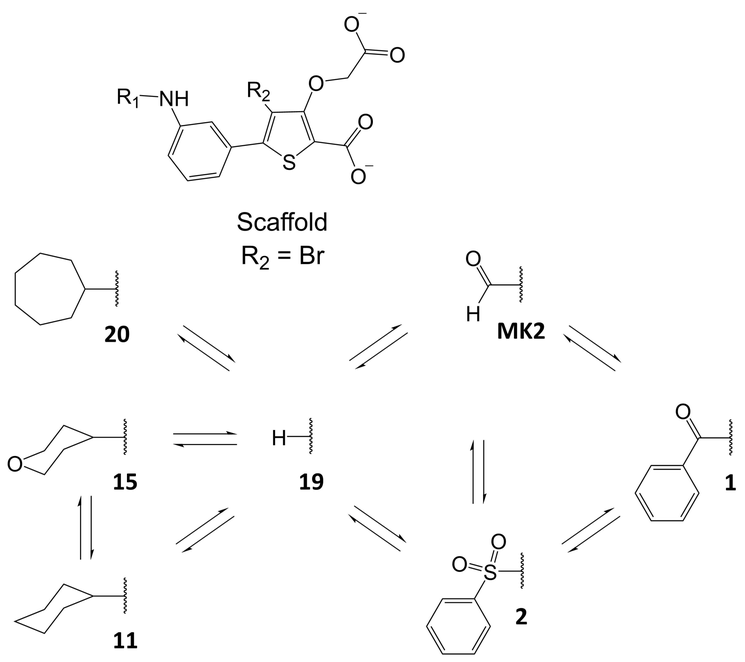

Figure 2: Excerpt of the perturbation network for the PTP1B subset, containing an additional molecule (MK2) not present in the original dataset.

However, the lack of automation for the various steps of the FEP calculations still hamper their routine use.

References

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Method

Albeit several open-source applications are available to assist in different parts of the FEP workflow, installing and using these relatively complex tools requires expertise. In order to make FEP more accessible, a number of packages will be included in the upcoming version (3.0) of Cresset's drug design software **Flare** (Figure 3).

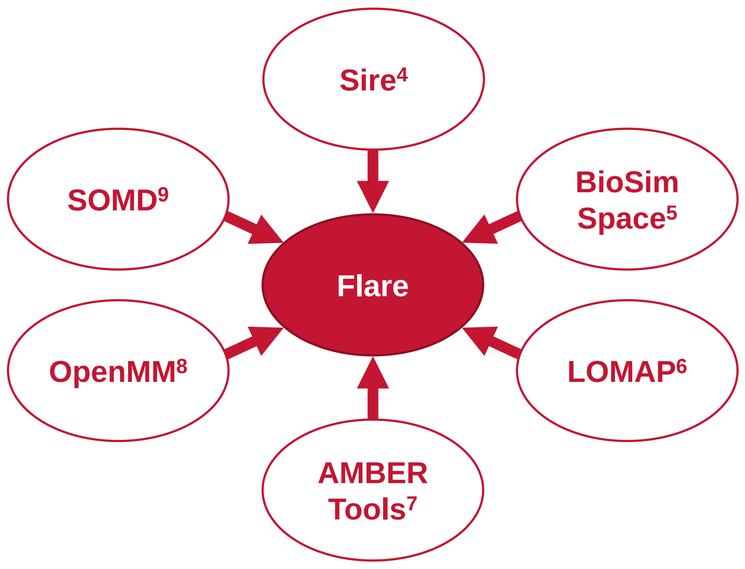

Figure 3: Applications used for FEP calculations

FESetup[10] was also used initially, but it will be replaced by the BioSimSpace utility prepareFEP in the final release version.

The automated workflow for performing FEP calculations is currently under development (Figure 4).

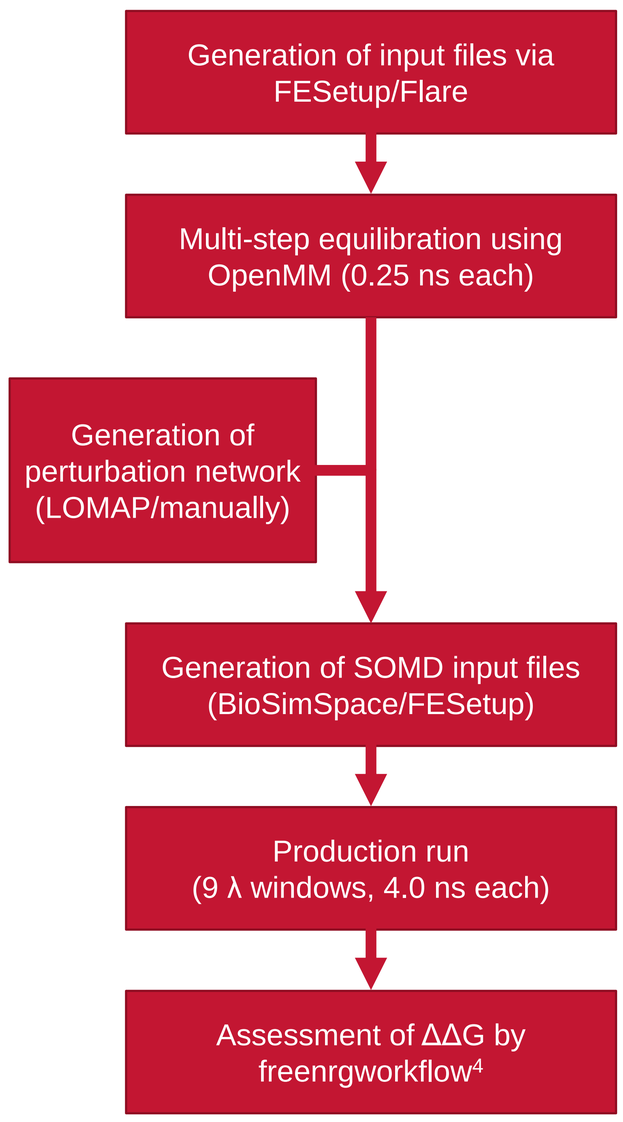

Figure 4: Preliminary automated workflow.

The workflow was run using different development versions of Sire and BioSimSpace. Therefore, the results may deviate slightly from the ones obtained with the final version.

Dataset and Benchmarks

The entire dataset to be investigated contains 199 ligands and consists of eight protein subsets of variable size. It was originally published by Wang et al.,[2] who used the OPLS 2.1 force field implemented in FEP+.

Recently, an additional benchmark was made available by Song et al.,[11] who used AMBER's GPU-TI and the AMBER FF14SB force field. In both cases a dual-topology approach was used.

Results

Dataset	Cresset/ UoE		Wang et al.[2]		Song et al.[11]	
	R	MUE	R	MUE	R*	MUE*
Thrombin	**0.88 ± 0.04**	**0.35 ± 0.04**	0.71 ± 0.24	0.76 ± 0.13	0.76	0.46
TYK2	**0.87 ± 0.02**	**0.60 ± 0.04**	0.89 ± 0.07	0.75 ± 0.11	0.57	1.07
PTP1B	**0.83 ± 0.04**	**0.84 ± 0.06**	0.80 ± 0.08	0.89 ± 0.12	0.71	1.06
JNK1	**0.81 ± 0.02**	**0.85 ± 0.04**	0.85 ± 0.07	0.78 ± 0.12	0.47	1.07
MCL1	**0.79 ± 0.02**	**1.30 ± 0.06**	0.77 ± 0.05	1.16 ± 0.10	0.65	1.52
BACE	**0.78 ± 0.03**	**1.08 ± 0.05**	0.78 ± 0.07	0.84 ± 0.08	0.43	1.20
p38	**0.72 ± 0.04**	**1.44 ± 0.05**	0.65 ± 0.09	0.80 ± 0.08	0.38	1.20
CDK2	**0.69 ± 0.09**	**1.02 ± 0.08**	0.48 ± 0.19	0.91 ± 0.12	0.47	0.97

Table 1: Preliminary results for the eight subsets in the FEP+ dataset. R: Pearson's correlation coefficient, MUE: mean unsigned error; *errors not specified

The prediction errors for the PTP1B subset were below 0.8 kcal/mol except for three ligands (**2**, **20** and **21**).

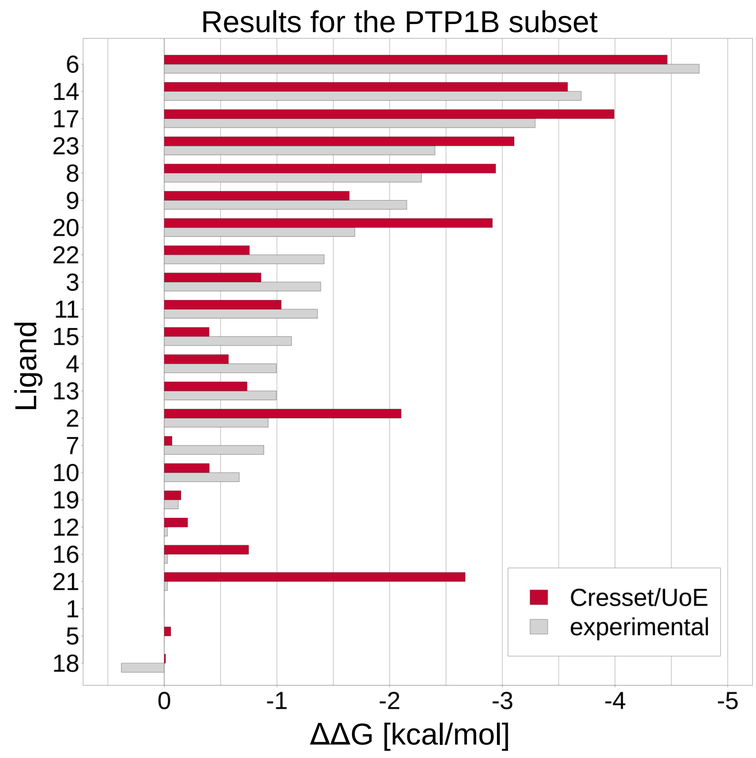

Figure 5: Bar plot comparing the computed and experimental affinities for the PTP1B subset.

Unlike all other molecules, ligand **21** has no R_2 substituent (R_2 = H), which makes it not suitable for binding (cf. Figure 6).

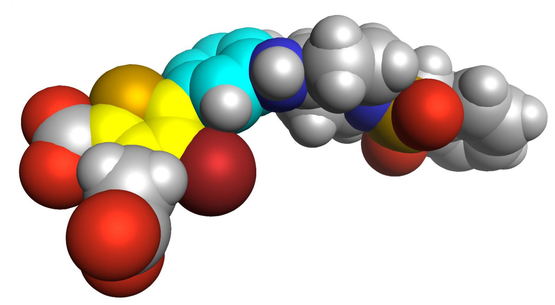

Figure 6: The bromine atom at the R_2 position (shown in dark red) enforces a non-planar orientation of the thienyl (yellow) and the phenyl (cyan) rings.

Conclusion & Outlook

- Results obtained with our method on all datasets processed so far were broadly comparable to or better than two previously published benchmarks.
- The ideal settings for a given set of ligands and their target protein are difficult to predict in advance.
- Power users will be able to further optimise the parameters via Flare's GUI and Python API in the final FEP implementation.