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Automated Free Energy Perturbation calculations in Flare

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Free Energy Perturbation (FEP) calculations allow for prediction of relative binding affinity changes within a congeneric ligand series.¹ In these calculations a molecule is gradually converted into a structurally closely related analogue via a non-physical ('alchemical') pathway. By assessing the free energy difference ($\Delta\Delta G$) between the end states of such transformations, accuracies of about 1 kcal/mol compared to experimental values can be achieved for large datasets.^{2,3}

The implementation of FEP in Flare,⁴ Cresset's structure-based design platform, builds on top of open-source tools (such as AMBER tools,⁵ OpenMM,⁶ LOMAP,⁷ Sire^{8,9} and BioSimSpace¹⁰) and of Cresset's unique expertise of delivering intuitive software. Our aim is to provide our users with an accessible and user friendly interface to a fully automated FEP workflow. The latter was internally validated on various datasets, including the FEP+ dataset as a reference benchmark.^{2,3} Full control over the simulation parameters both within the Flare graphical user interface (GUI) and through the Flare Python API facilitates the exploration and identification of the ideal conditions for a given set of ligands and their target protein.

In this seminar, I will provide a brief overview of the validation work performed by Cresset in collaboration with the University of Edinburgh, and present the FEP GUI within Flare.

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