FEbuilder: A comprehensive webserver to streamline FEP simulation setup in drug discovery

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Introduction

Relative binding free energy (RBFE) calculations are essential techniques in drug discovery. However, setting up alchemical simulations, particularly the creation of hybrid single-dual topologies, is often labor-intensive. To address this challenge, we propose FEbuilder, an open-source platform that streamlines the preparation of **free energy perturbation (FEP) simulations for small molecules as well as protein residues.**

- **Rapid System Setup**: Transforms a complex structure into ready-to-use CHARMM-format simulation files in a few seconds, facilitating high-throughput RBFE calculation setup.
- **User-Friendly Interface**: Offers an installation-free web interface; visualizes atom mapping for intuitive hybird topology editing; enables flexible adjustments of system modeling and simulation parameters.
- **Versatile Parametrization**: Integrates seamlessly with tools like CgenFF, MATCH, and SwissParam for automated ligand parametrization; supports various ligand file formats and biomolecular force fields.
- **Result Analysis**: Evaluates NAMD trajectory quality and convergence of forward and backward simulations to ensure data reliability.

FEbuilder liberates researchers from the complexities of simulation setup, accelerating lead optimization and innovative drug design.

Algorithm

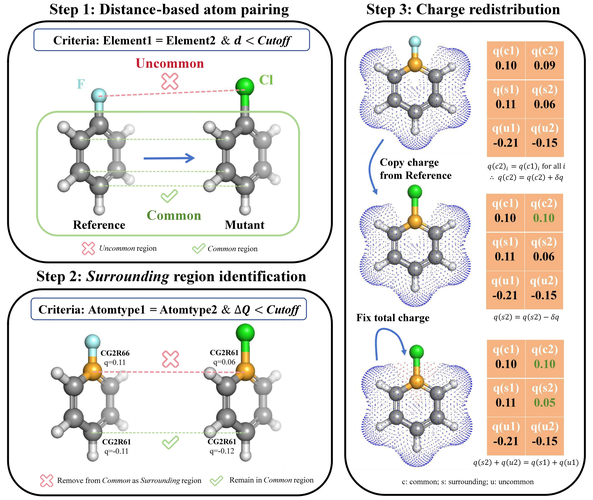
FEbuilder employs a **3D-distance-based atom mapping protocol assisted by force field parameters** to create the topology, addressing challenges like molecule symmetry, stereoisomerism, charge-changing perturbations and ring transformations:

Step1: Common Region. Find atom pairs that are within a distance cutoff and ensure they have the same element type. These atoms classified as *Common* region (the green box), while others are deemed *Uncommon* (F and Cl).

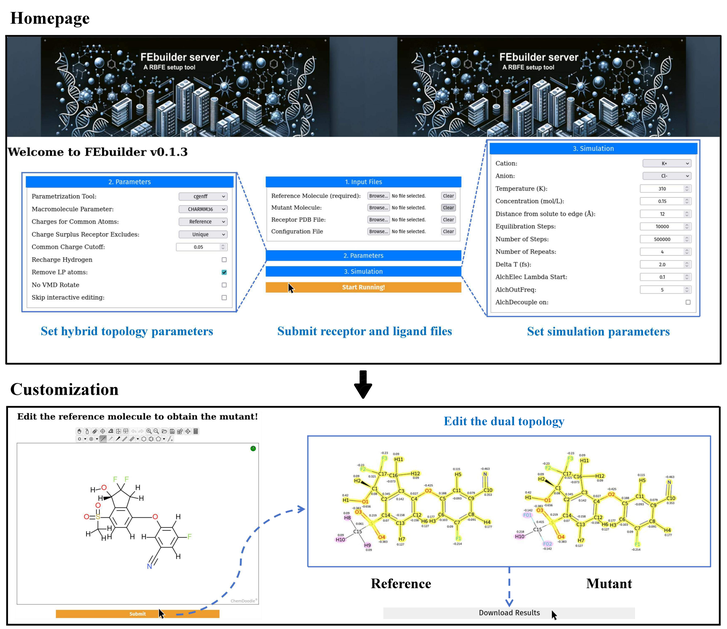
Step2: Surrounding Region. If a pair of common atoms do not share force field atom types or their charge differences are not within a cutoff, remove them from the *Common* region and put into *Surrounding* region (the orange carbon atom).

Step3: Charge Redistribution. Equalize partial charges in the *Common* region (copy from one of the ligands or take the average), with discrepancies uniformly redistributed across the *Surrounding* region to maintain the total charge of each ligand.

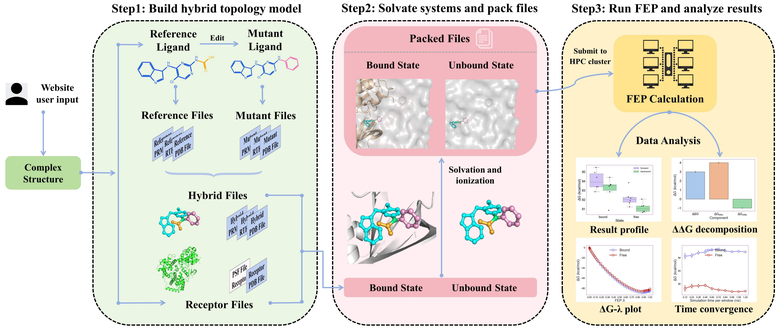
Note: both the *Surrounding* and *Uncommon* region is alchemically transformed.



Web Interface

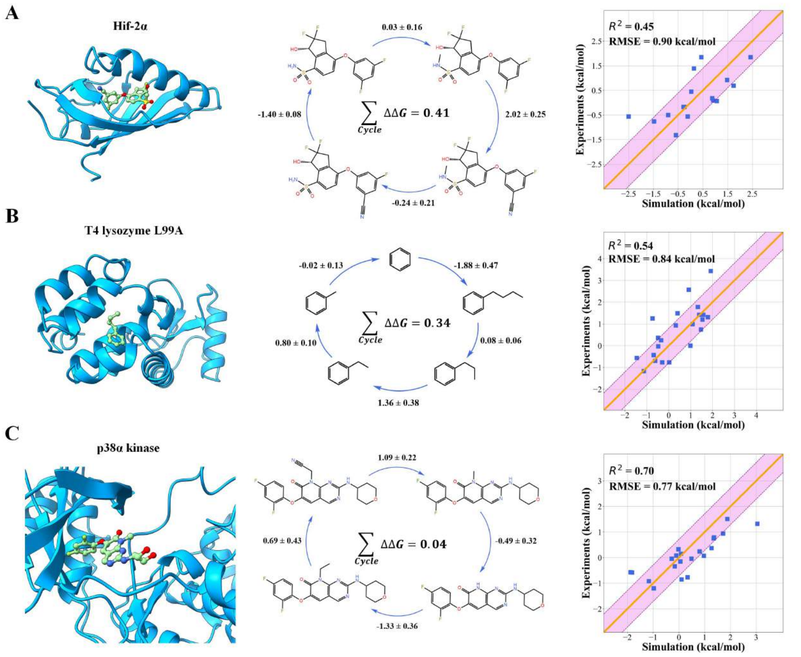


Workflow



Benchmarking

We selected three protein-ligand systems: Hif-2α, T4 lysozyme L99A mutant, and p38α kinase, with experimental affinity of their ligands available. For each system, we constructed ligand perturbation cycles based on structure similarity, and performed FEP calculations along them. We parametrized ligands with MATCH and protein with CHARMM36. Ideally, the cycle closure hysteresis should be zero, which was usually the case in our three systems. Root mean squared error (RMSE) compared to experimental data of the three systems were 0.90, 0.84, and 0.77 respectively, with most test cases showing an unsigned error within 1 kcal/mol. These findings underscore the robustness and reliability of FEP systems built by FEbuilder for relative free energy calculations.



References

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https://github.com/openforcefield/protein-ligand-benchmark

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