SCHRÖDINGER

FEP+ Simulation Details and Results

System Details

Job name: absolute_binding_FEP_chosen_hits_new_2OWB_apo
Job type: absolute_binding
Perturbation: (Z2407952372 ↔ None)

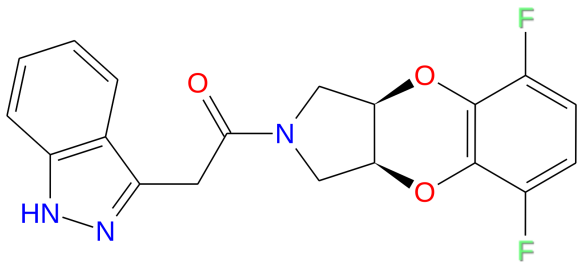
	Ensemble	Force Field	Temp. [K]	Sim Time [ns]	No. Atoms / Waters	ΔG [kcal/mol]
Solvent:	NPT	S-OPLS*	300.0	5.0	2830 / 929	-50.25 ± 0.05
Complex:	muVT	S-OPLS*	300.0	5.0	41245 / 10516	-39.42 ± 0.09
Corr. Term:						-9.38 ± 0.00

Absolute binding free energy (ΔΔG) is: -1.45 kcal/mol

Ligand Information

Name	HexID	No. Atoms / Heavy	Atomic Mass	Charge	Mol. Formula
Z2407952372	a58c2b1	42 / 27	371.3 au	0	C19H15F2N3O3

Ligand

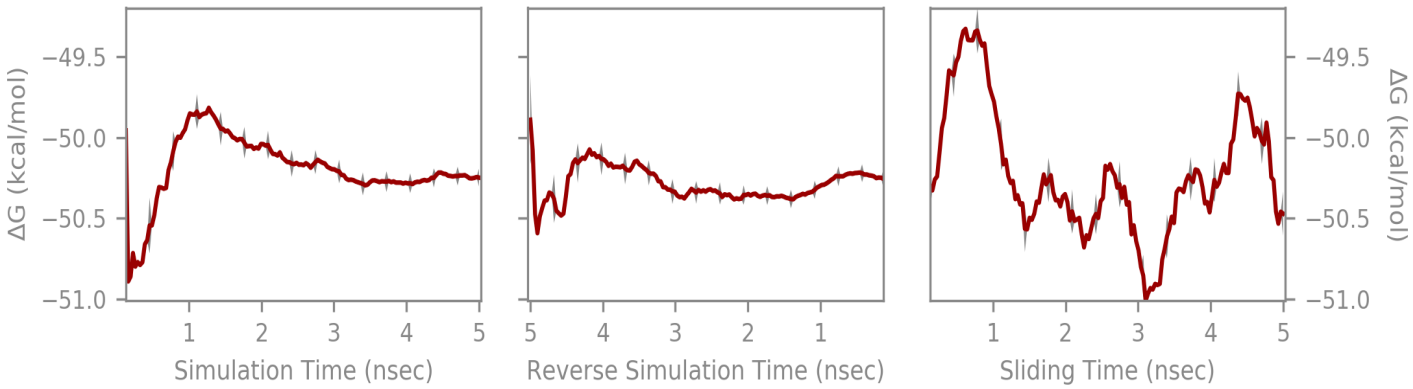


Protein Information

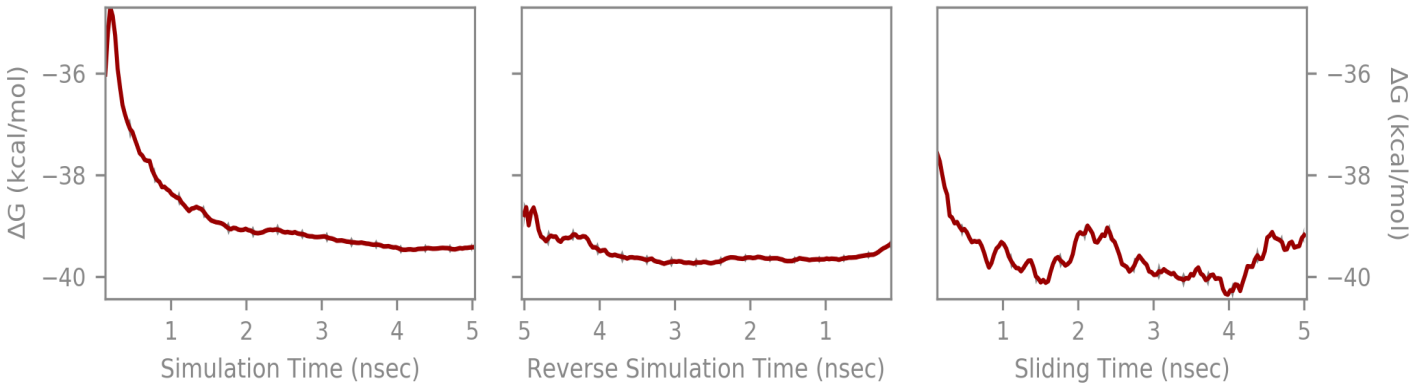
Name	Tot. Residues	Prot. Chain(s)	Res. in Chain(s)	No. Atoms	No. Heavy Atoms	Charge
2OWB_prepared_apo	294	'A'	294	4826	2379	+11

Free Energy Convergence

Solvent Leg



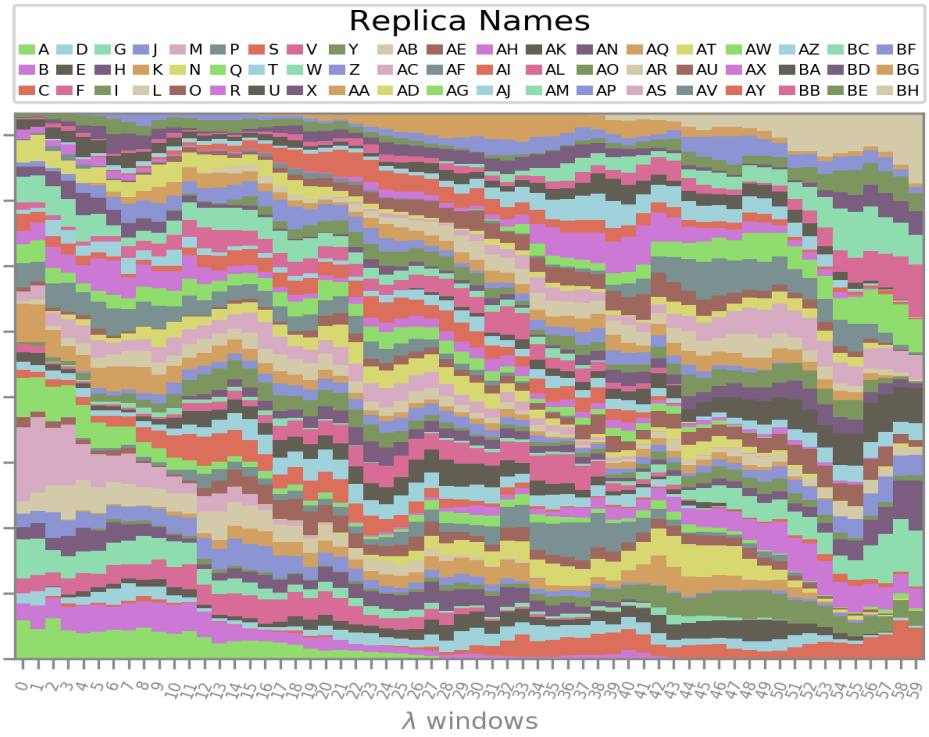
Complex Leg



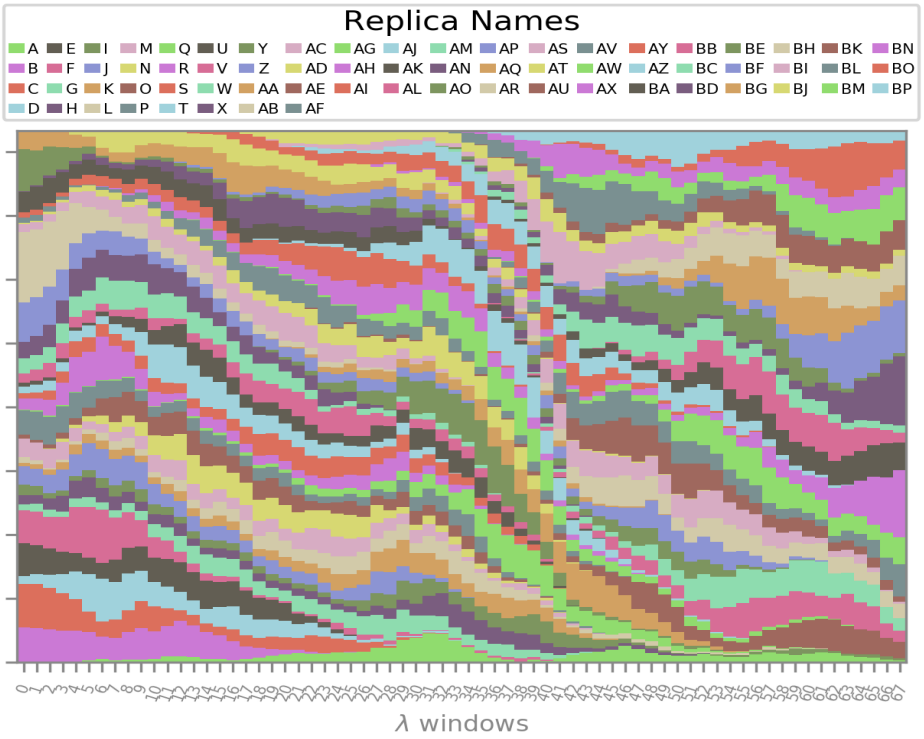
The total free energy differences between the two ligands (ΔG in *kcal/mol*) in solvent and complex legs are plotted as a function of time. Three plots for each leg show the accumulated data during different time window schemes: forward; reverse; and sliding window.

Exchange Density of FEP Replicas Over λ-Windows

Solvent Leg



Complex Leg

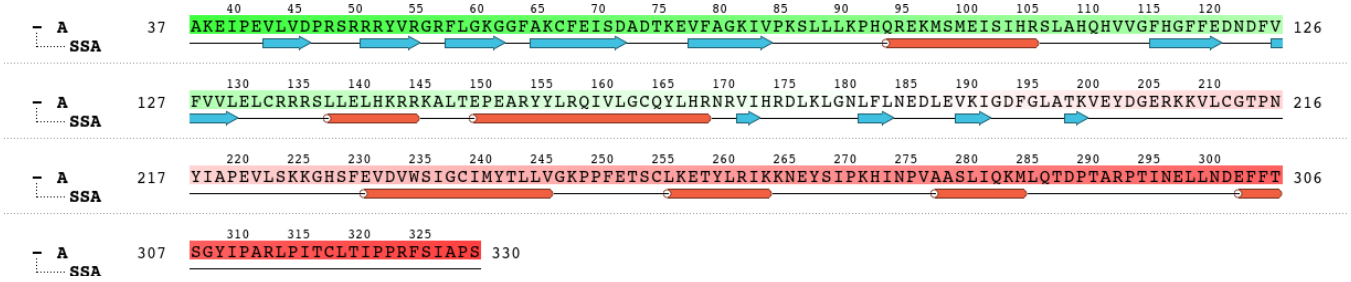


For both legs of the FEP simulation, each replica is color coded and the plot shows how it occupies different lambda windows during the course of the simulation. Ideally each replica will sample all lambda windows uniformly, however non-uniform sampling is sufficient in most instances.

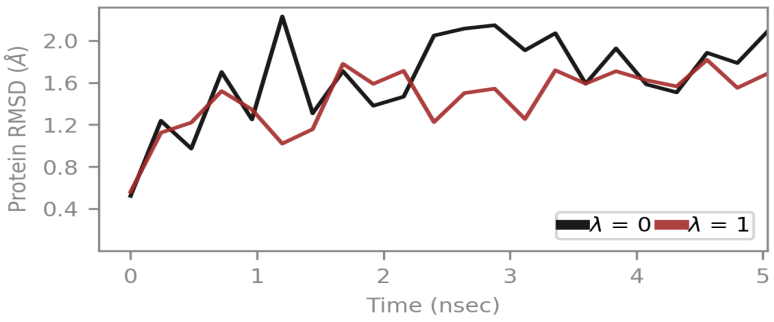
Protein Analysis for End-Point λ-Replicas

Protein Information

Name	Tot. Residues	Prot. Chain(s)	Res. in Chain(s)	No. Atoms	No. Heavy Atoms	Charge
2OWB_prepared_apo	294	'A'	294	4826	2379	+11

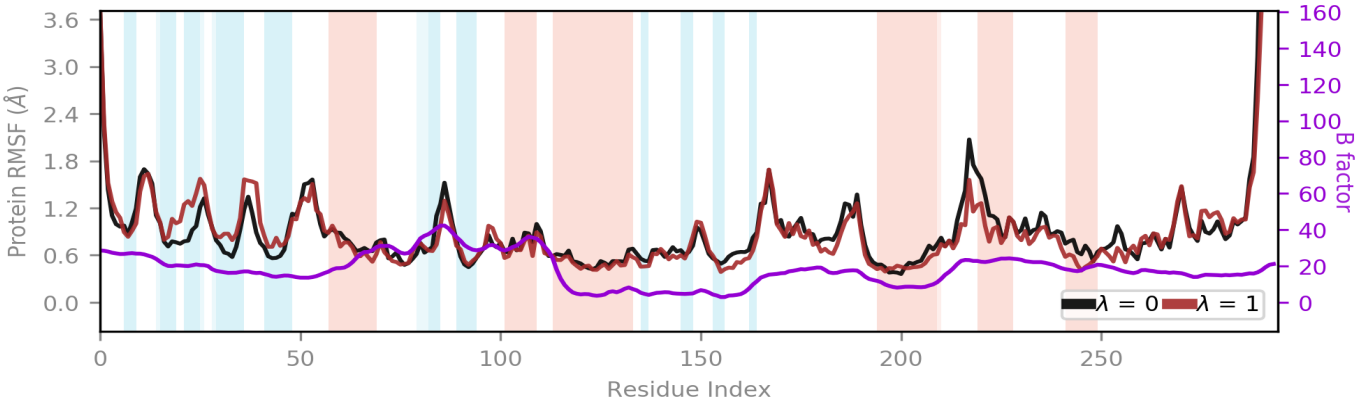


Protein RMSD



The Root Mean Square Deviation (RMSD) of a protein is measured here over the backbone atoms. Monitoring protein RMSD for two end-points in the FEP simulation may give insights of its structural stability. Values of the order of 1-3 Å are perfectly acceptable for medium-size, globular proteins. Changes much larger than that, however, indicate that the protein is undergoing a larger than expected conformational changes for an equilibrated system, during the simulation.

Protein RMSF



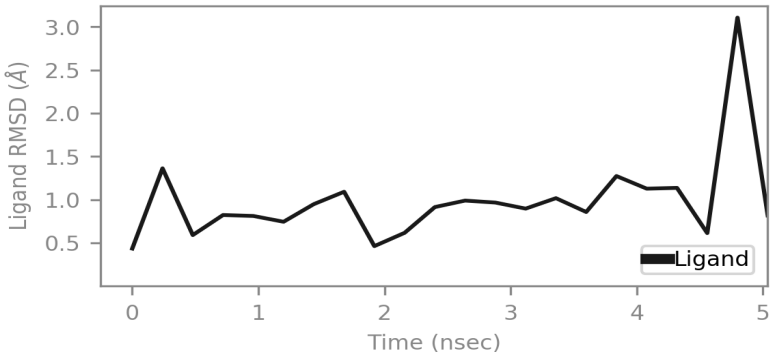
The Root Mean Square Fluctuation (RMSF) is useful for characterizing local changes along the protein chain. Protein backbone RMSF is shown in this plot. Typically you will observe that the tails (*N*- and *C*-terminal) fluctuate more than any other part of the protein. Secondary structure elements like alpha helices and beta strands are usually more rigid than the unstructured part of the protein, and thus fluctuate less than the loop regions. Experimental B factors extracted from PDB is overlaid alongside with RMSF values. RMSF and B factors fluctuations should correlate, but not necessarily follow each other.

Alpha-helical and beta-strand regions are highlighted in red and blue backgrounds, respectively. These regions are defined by helices or strands that persist over 70% of the entire simulation. One should expect secondary structure elements to be in the low-fluctuating RMSF region.

Ligand Analysis for End-Point λ-Replicas

Title	PDB Name	No. Atoms	No. Heavy	No. Hot Atoms	Rot. Bonds	Atomic Mass	Charge
Z2407952372	'UNK'	42	27	42	3	371.3 au	0

Ligand RMSD in complex

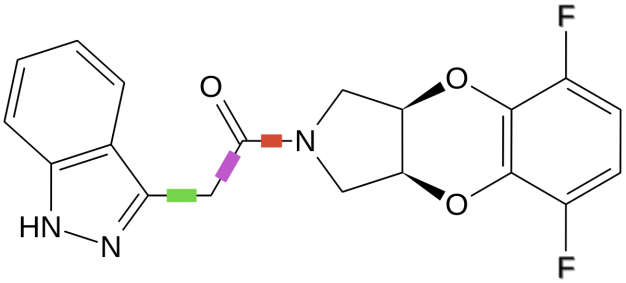


The Root Mean Square Deviation (RMSD) of a ligand is measured with respect to the input ligand pose by first aligning the complex on the protein. If the values observed are significantly larger than the RMSD of the protein (See the *Protein Analysis Report*), then it is likely that the ligand has diffused away from its initial binding site. Remember that since the FEP caculation is in the *'REST'* mode, the fluctuations may be larger than observed for typical *MD* jobs.

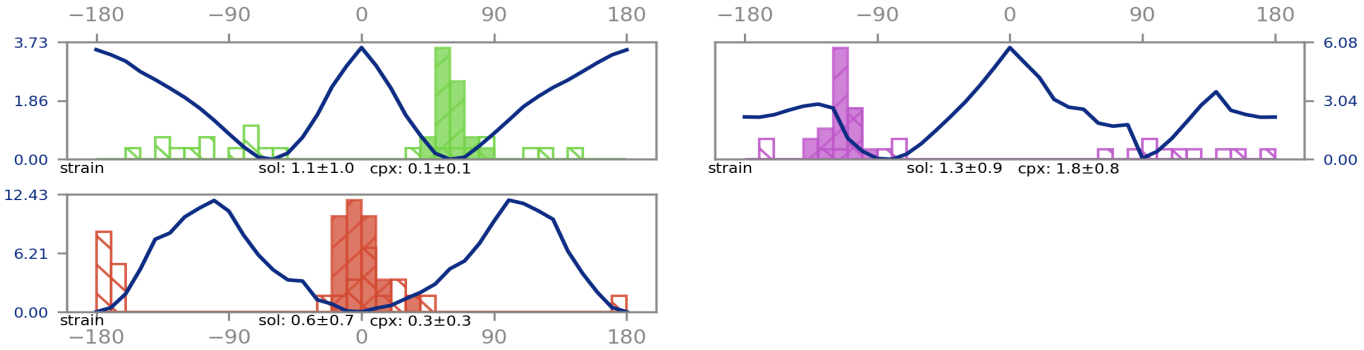
Ligand Misc. Properties

	Units	Solvent Leg	Complex Leg
RMSD	Å	2.0 ± 0.48	1.0 ± 0.52
Radius of gyration	Å	3.8 ± 0.61	3.6 ± 0.05
Molecular SA	$Å^2$	302.0 ± 19.17	299.2 ± 3.83
Solvent-accessible SA	$Å^2$	549.5 ± 40.44	40.2 ± 10.55
Polar SA	$Å^2$	97.8 ± 10.72	110.2 ± 3.13
Intramolecular HB	#	0.0 ± 0.00	0.0 ± 0.00
Number of waters	#	N/A	7.0 ± 2.99
Ligand strain	kcal/mol	3.1 ± 1.36	2.2 ± 0.89

Ligand Conformation Analysis

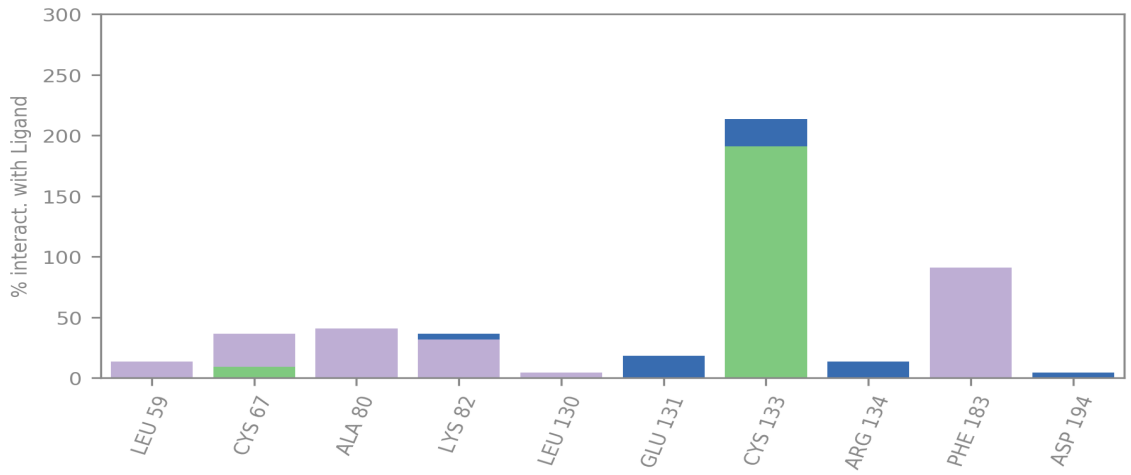


Z2407952372



Rotatable bonds (Rb) in both ligands are enumerated and color-coded. For each Rb, a representative dihedral angle is monitored throughout the complex and solvent simulation legs, their distributions are then plotted. Hollow bars show **solvent** and filled bars show **complex** leg distributions. Input starting conformation is marked as a gray vertical line. Potential energy around each Rb overlays the plot with the dark-blue curve and corresponding labels on the Y-axis. Local strain energies are shown below the plot. The units are in *kcal/mol*.

Protein-Ligand Interactions



Above bar chart illustrates the type of interactions the protein residues make with the ligand. Multiple types of specific interactions are monitored throughout the simulation and provide a way to examine and compare how the protein interacts with the ligand. The specific interactions types monitored and displayed are: **hydrogen bond**, **hydrophobic**, **ionic** and **water bridges**. The stacked bar charts are normalized over the course of the trajectory. More information about the geometry and the different interaction subtype categories can be found in the Schrödinger's *Desmond User Manual*, under 'Simulation Interactions Diagram' (SID) section. ***Note:*** The values may exceed 100% as the residue can make multiple contacts of the same type with the ligand.