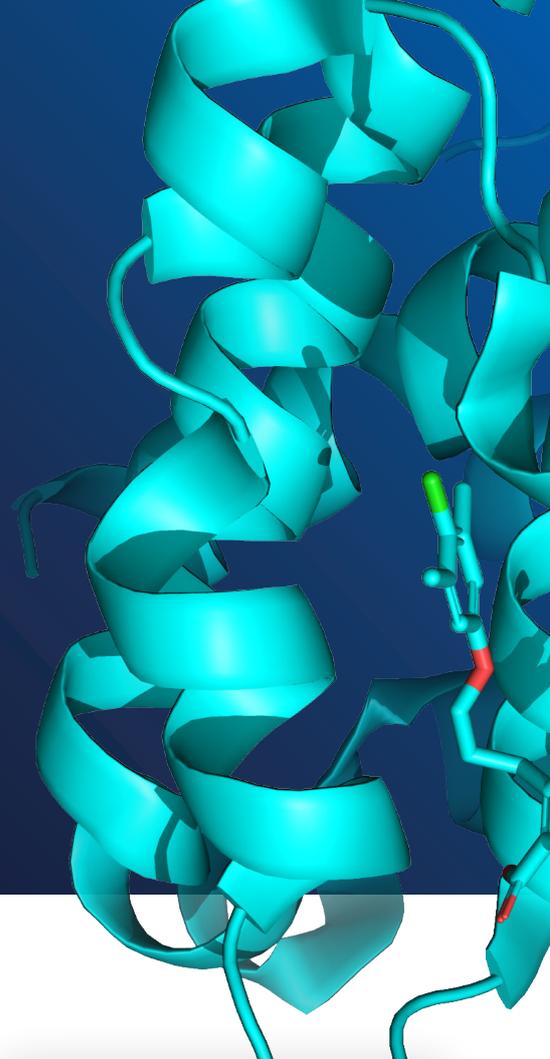# FEP+ Protocol Builder

ML-powered optimization of FEP+ models for challenging targets

FEP+ Protocol Builder is an automated machine learning workflow for FEP+ model optimization. It saves scientists time and improves the chances of successfully enabling discovery with FEP+ by identifying an optimized predictive model for your target.

Improve FEP+ accuracy with physics-driven machine learning for the most challenging targets to confidently use FEP+ prospectively in your program

Reduce compute cost across the lifetime of your project with automated cost optimization of FEP+ models

Generate optimized FEP+ models 4x faster than manual optimization, saving weeks of researcher time across diverse disease areas through efficient exploration of parameter space

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FEP+ Protocol Builder models routinely outperform those from human experts across diverse protein targets

In a recent study, FEP+ Protocol Builder outperformed human experts in producing a predictive model across ten diverse targets where default FEP+ settings did not produce an appropriately accurate protocol (RMSE > 2.5 kcal/mol) and were able to generate FEP+ models for systems where experts failed.

FEP+ Protocol Builder was run in a completely automated fashion following a rigorous training/test set split. On average, the reduction in turnaround time for the final optimization model went from 27 days to 7 days, a **4x acceleration**, saving on average 20 days per project.

Disease area	Target class	Target	Expert Protocol RMSE (kcal/mol)	FEP+ Protocol Builder RMSE (kcal/mol)
Oncology	Bcl-2	MCL1	1.5	**1.1**
Neurology	ATPase	P97	1.3	**1.0**
Oncology	Nuclear receptor	ESR1	3.1	**2.0**
Pain, addiction, oncology	GPCR	mOR	2.4	**2.2**
Pain, addiction	GPCR	dOR	2.2	**1.3**
Hematology, oncology	ADP-ribosyltransferase	TNKS2	2.2	**1.1**
Pain, addiction, neurology	GPCR	KOR	2.1	**1.7**
Renal	Aspartic protease	Renin	1.8	**1.6**
Oncology and rheumatology	Cysteine protease	MALT1	2.5	**1.5**
Oncology	Receptor tyrosine kinase	RET	1.9	**0.8**

Recommended inputs

- One experimentally resolved protein-ligand structure or a computationally generated protein-ligand binding mode hypothesis
- 10 or more congeneric ligands, ideally 20 for better statistics, are needed. The ligands should have known affinity data spanning at least two to three orders of magnitude
- FEP+ Protocol Builder is bundled with FEP+ and requires a minimum of 20 licenses for optimal use

Available as software or a service

Leverage your internal resources or work with Schrödinger's team of experts and large-scale computational resources to optimize your next FEP+ model.

Contact us at sales@schrodinger.com

Publications

- FEP Protocol Builder: Optimization of free energy perturbation protocols using active learning. de Oliveira C, et al. *J. Chem. Inf. Model*. 2023, 63, 17, 5592–5603.
- Advancing drug discovery through enhanced free energy calculations. Abel R, et al. *Acc. Chem. Res.* 2017, 50, 7, 1625–1632.
- Accurate and reliable prediction of relative ligand binding potency in prospective drug discovery by way of a modern free-energy calculation protocol and force field. Abel R, et al. *J. Am. Chem. Soc.* 2015, 137, 7, 2695–2703.

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