Large Scale Binding Free Energy Screening of HSP90 Ligands

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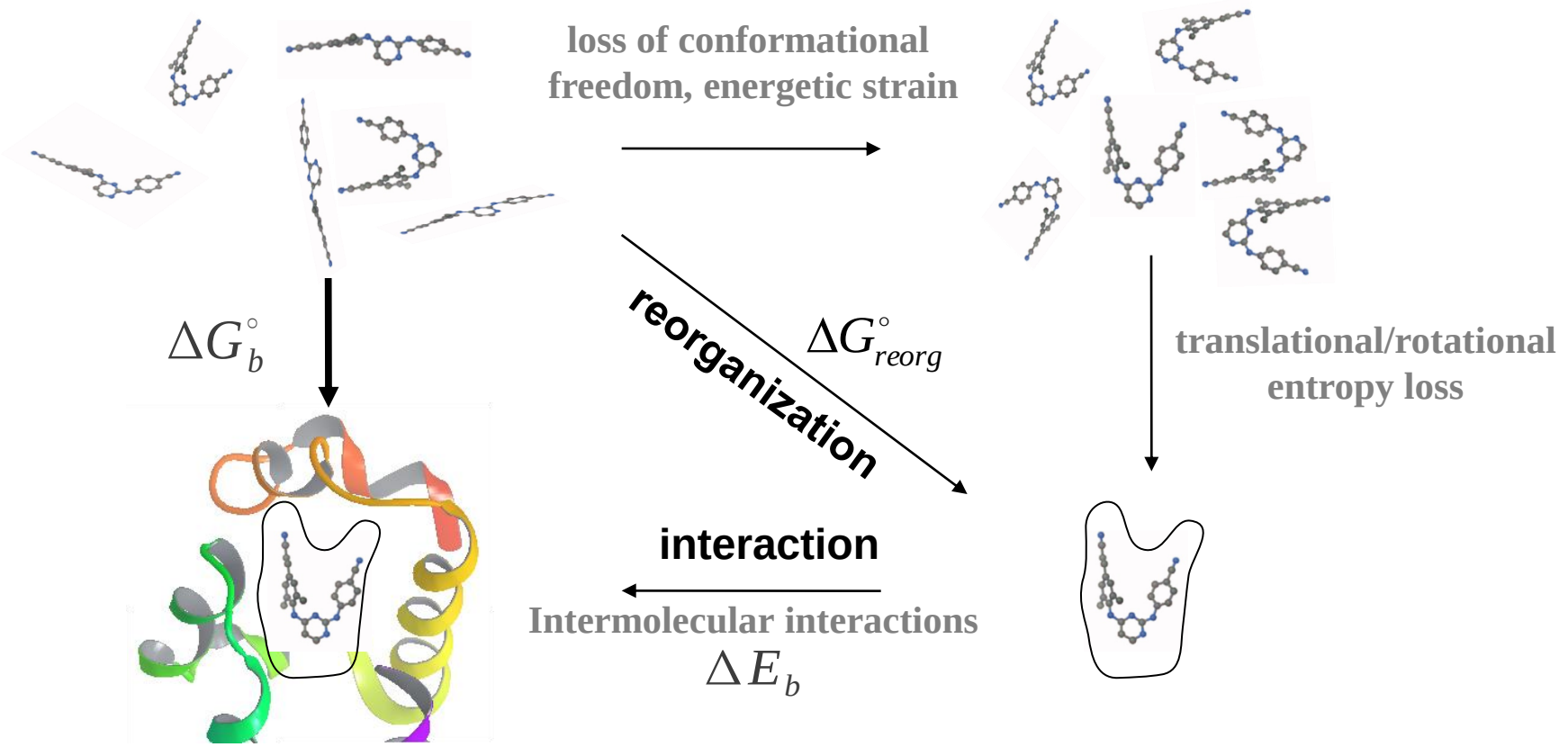
Outline

1. The BEDAM free energy method
2. Participation in previous SAMPL challenges
3. Screening results for HSP90 ligands
4. New development of BEDAM for binding pose prediction

Free Energy of Binding = Reorganization + Interaction

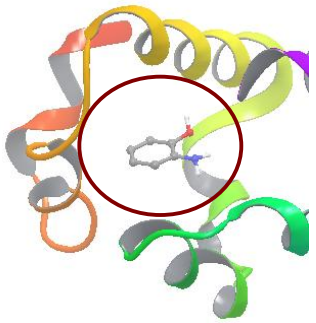


$$\Delta G^\circ_b = \Delta E_b + \Delta G^\circ_{\text{reorg}}$$

Can the inclusion of reorganization improve predictions?

BEDAM λ-Dependent Hybrid Potential

Implicit Solvation (OPLS/AGBNP2)



Hybrid potential: $U_\lambda(x) = U_0(x) + \lambda u(x)$

Effective Potential at uncoupled state
(both ligand and receptor interact only with solvent continuum)

Binding energy = perturbation
(effective energy change for moving ligand from solution to receptor site)

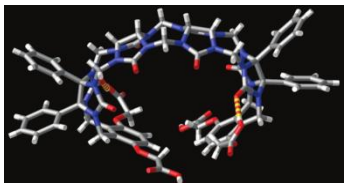
λ=0: uncoupled state
λ=1: coupled state

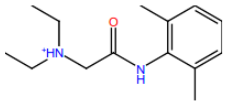
Direct transfer from implicit solvent environment to the complex.
(one simulation leg rather than two as with explicit solvation)

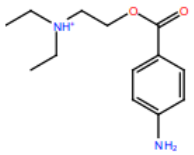
Gallicchio, Lapelosa, Levy, *JCTC* **(2010)** · Gallicchio & Levy, *Curr. Op. Struct. Biol.* **(2011)** · Gallicchio & Levy, *Adv. Prot. Chem.* **(2011)** · Lapelosa, Gallicchio, Levy, *JCTC* **(2012)** · Gallicchio, Levy *J. Comp. Aid. Mol. Design* **(2012)** · Tan, Gallicchio, Lapelosa, Levy *JCP* **(2012)** · Gallicchio, *Mol. Biosc* **(2012)** · Wickstrom, He, Gallicchio, Levy *JCTC* **(2013**), Gallicchio, Deng, He, Wickstrom, Perryman, Santiago, Forli, Olson, Levy *JCAM* **(2014).**

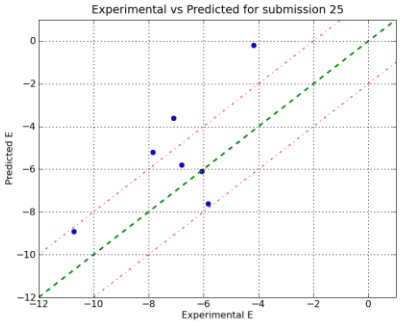
Participation in previous SAMPL challenges

Sampl3 host/guest

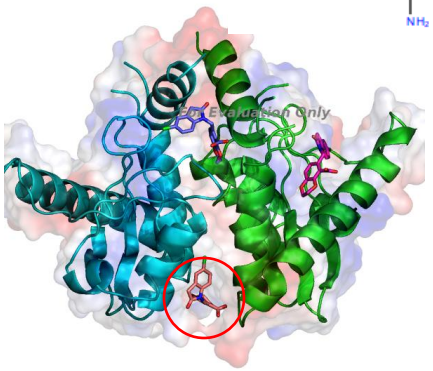




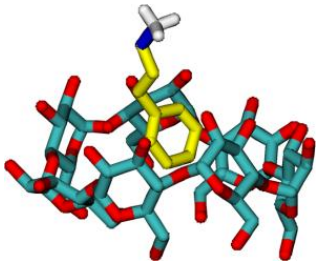




Sampl4



HIV-Integrase

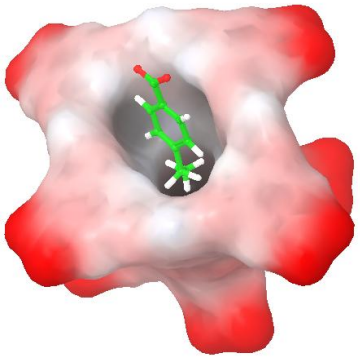


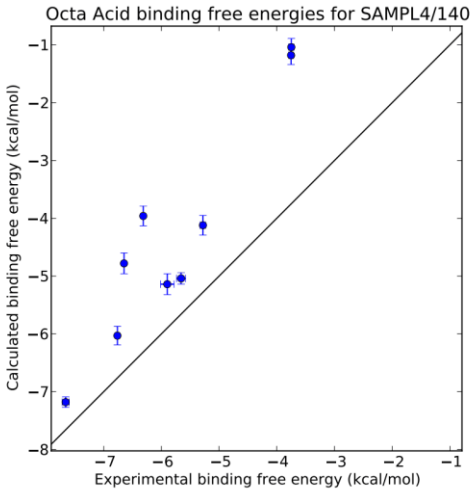
Host/Guest

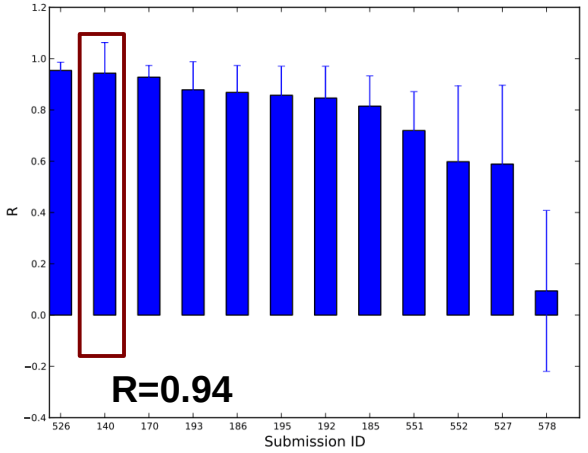
Sampl3 host-guest: 5th out of 15 (R^2)
Sampl4 host-guest: 2nd out of 12 (R^2)
Sampl4 Integrase ligands: 2nd out of 26 (enrichment at 10%)

Gallicchio, Levy *J. Comp. Aid. Mol. Design* **(2012),** Gallicchio, et al. *J. Comp. Aid. Mol. Design* **(2014)**
Gallicchio, et al. *J. Comp. Aid. Mol. Design* **(2015)**

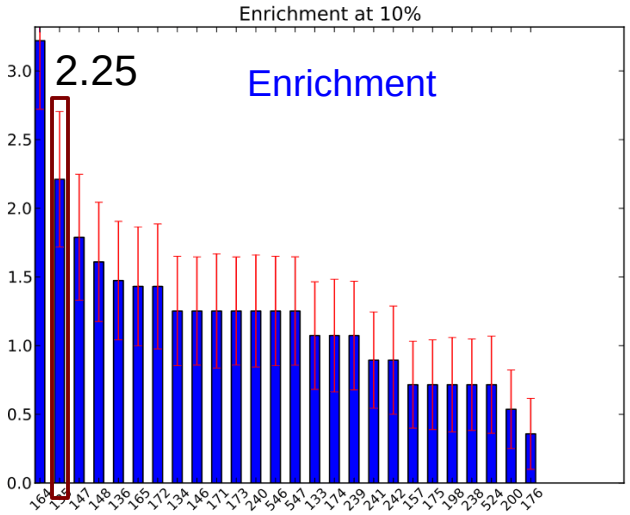
Sampl4: Host/Guest OctaAcid Results



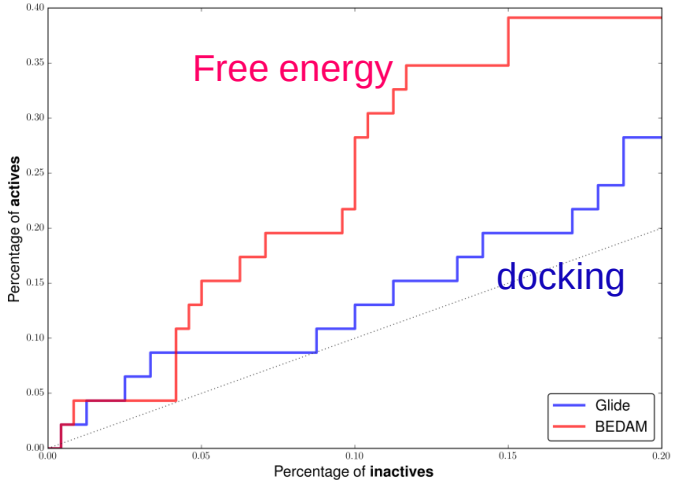




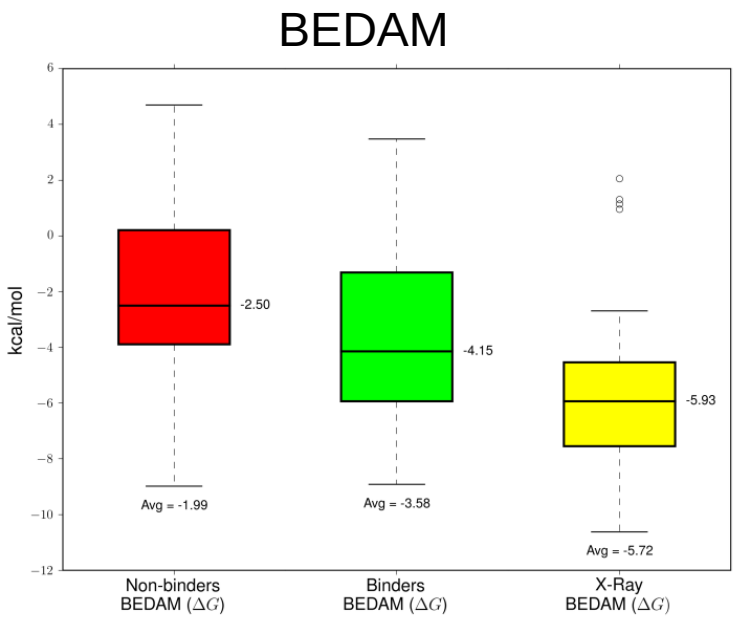
Free Energy Screening of the HIV Integrase Ligands - Enrichment Results in Sampl4

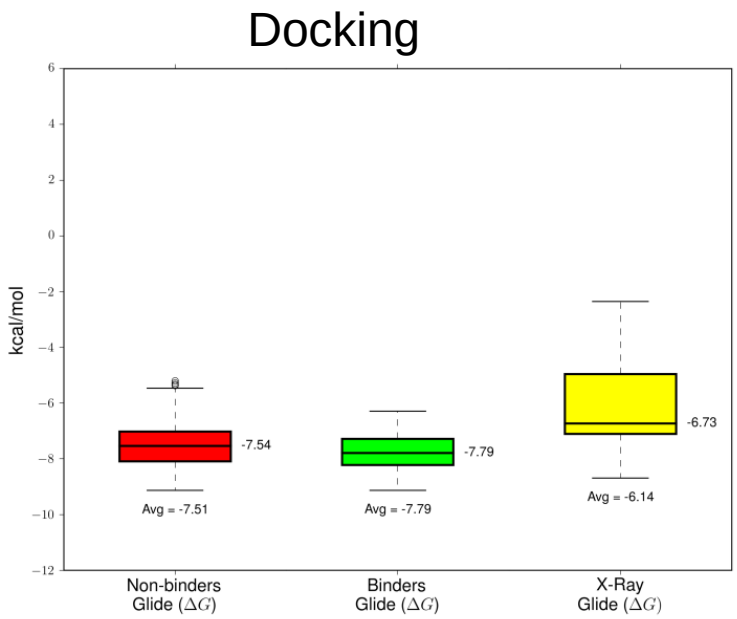


ROC



Sampl4 HIV Integrase Ligands: Distribution of ΔG for Actives vs. Inactive Compounds

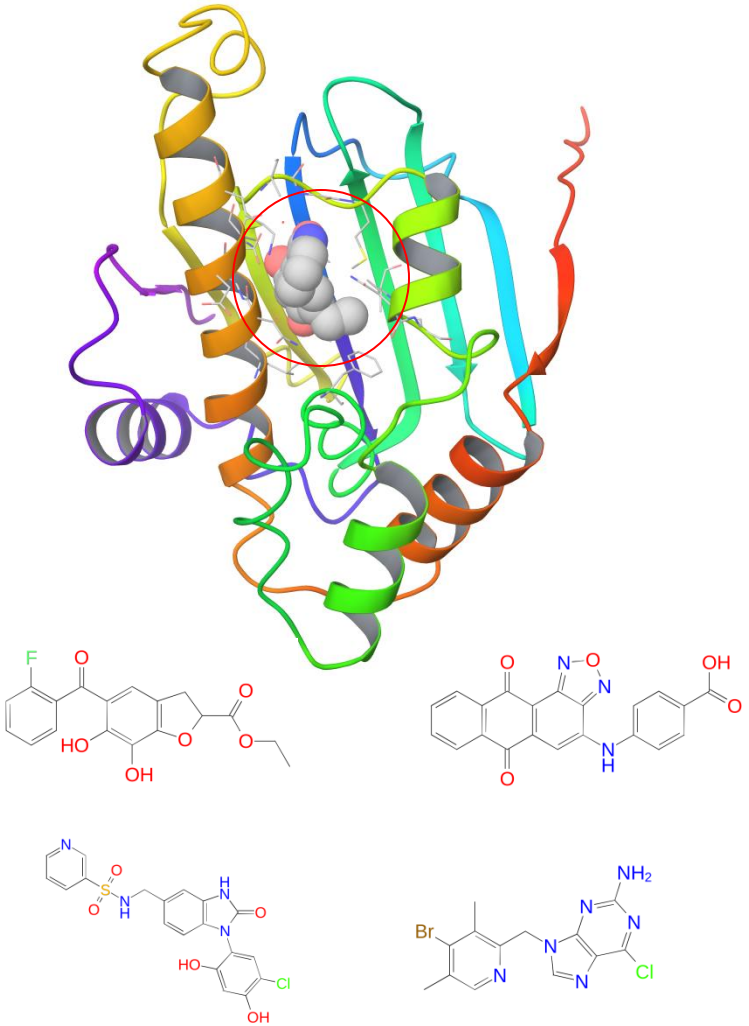




BEDAM free energy scoring is able to separate binders from non-binders.

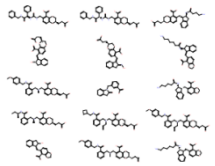
Virtual Screening of HSP90 Ligands: the Grand Challenge

- Hydrated binding site with varying number of bridging waters.
- Conformational changes noted near the binding pocket.
- 180 ligands, 33 inactives, 147 active compounds.
- The setting resembles lead optimization, rather than screening for hit identification as in the case of Sampl4.



BEDAM Free Energy Screening Workflow Used for Protein Targets in Sampl4 and Grand Challenge

Ligand Database (180)

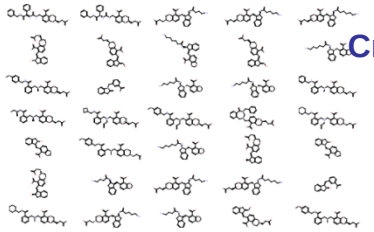


Protonation/ tautomerization expansion

LigPrep/Epik

(minutes)

Expanded Database (311)

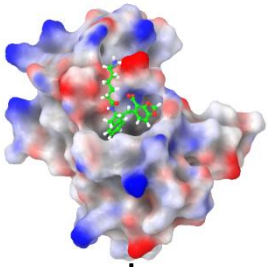


Crystal Structures Analysis + Ensemble Docking

Glide/Autodock

(5 hours)

Docked Complexes (~1,000)



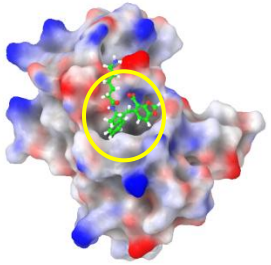
Filtering/Prioritization Structural Predictions

(1 day)

BEDAM Setup T-RE Conformational Analysis

(1 day)

Prepped Complexes



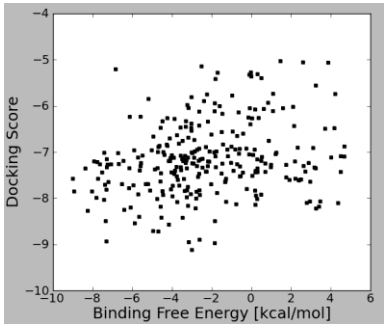
BEDAM parallel H-RE Calculations

(20 replicas, 22ns)

IMPACT/OPLS/AGBNP2

(2-3 weeks on Brooklyn Grid and Temple Grid)

Binding Free Energy Estimates



Ranking & Submission

AVX17557_3	1 yes	5
AVX101124_0	2 yes	5
AVX17556_3	3 yes	5
AVX17556_1	4 yes	5
AVX17734_3	5 yes	4
AVX17626_1	6 yes	4
AVX101133_0	7 yes	4
AVX17556_0	8 yes	4
AVX17285_0	9 yes	4
AVX38753_3	10 yes	4
AVX101124_1	11 yes	4
AVX38748_0	12 yes	4
AVX38789_2	13 yes	4
AVX101121_0	14 yes	4
AVX38747_5	15 yes	4
AVX38669_0	16 yes	4
AVX101119_0	17 yes	3
AVX17687_1	18 yes	3
AVX38748_6	19 yes	3
AVX40868_0	20 yes	3
AVX101133_1	21 yes	3
AVX38781_2	22 yes	3
AVX38672_1	23 yes	3
AVX101121_1	24 yes	3
AVX16980_0	25 yes	3
AVX17377_0	26 yes	2
AVX38669_1	27 yes	2
AVX38743_5	28 yes	2
GL5243104_0	29 yes	2
AVX17558_3	30 yes	2
AVX38748_4	31 yes	2
AVX17287_0	32 yes	2

HSP90 Results Using BEDAM Free Energy Scoring

Our Submission ID	Pearson R	Kendall Tau	Matthews (active/inactive, 1 uM cutoff)	ROC	AUC
564f8205a4c32	0.30	0.22	0.31	0.65	0.67

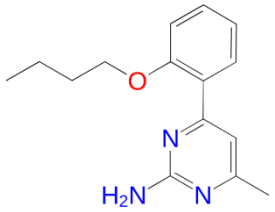
Results ranked12th out of 84 submissions

BEDAM performed better in enrichment than in rank ordering.

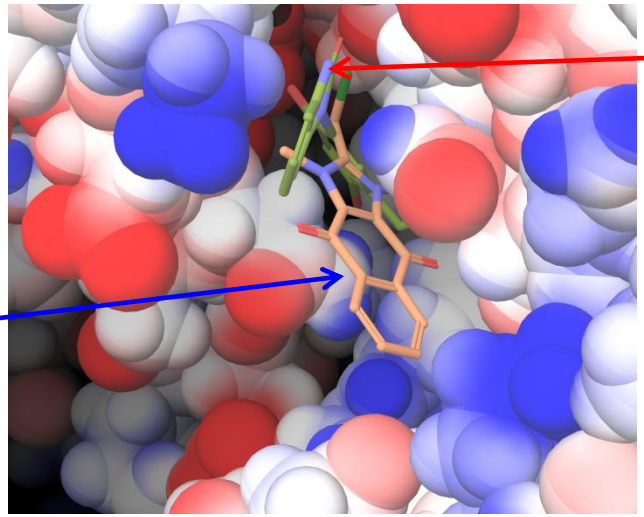
Analysis of Correctly/Incorrectly Predicted Binders

- Binding free energies of the aminopyrimidine compounds are underestimated.
- Many of the most prominent false negatives are due to failure in obtaining a good initial docked pose.
- Without good initial docked structures most of the binding free energies are incorrect

hsp90_63



ΔG(calc) = -2.8 kcal/mol
ΔG(expt) = -6.9 kcal/mol



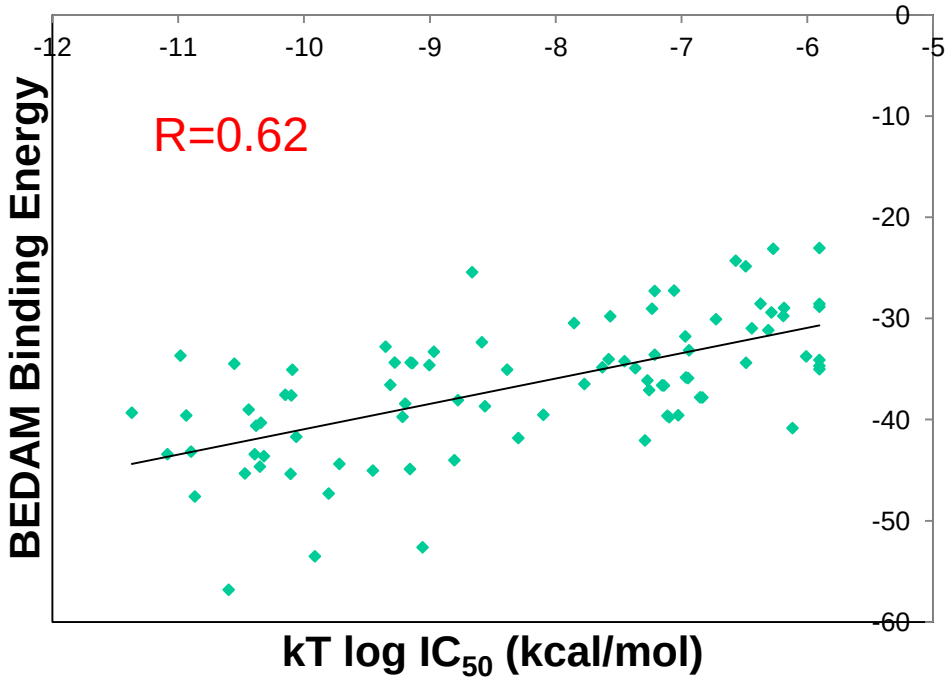
Hsp90_40
Correctly docked

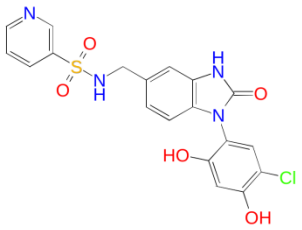
ΔG(calc) = -13 kcal/mol
ΔG(expt) = -10 kcal/mol

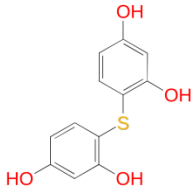
Hsp90_128
incorrectly docked

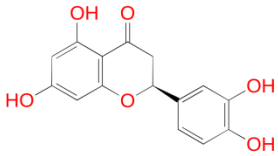
ΔG(calc) = 8 kcal/mol
ΔG(expt) = -10.7 kcal/mol

Better Performance for the Subset of 96 Phenolic Compounds

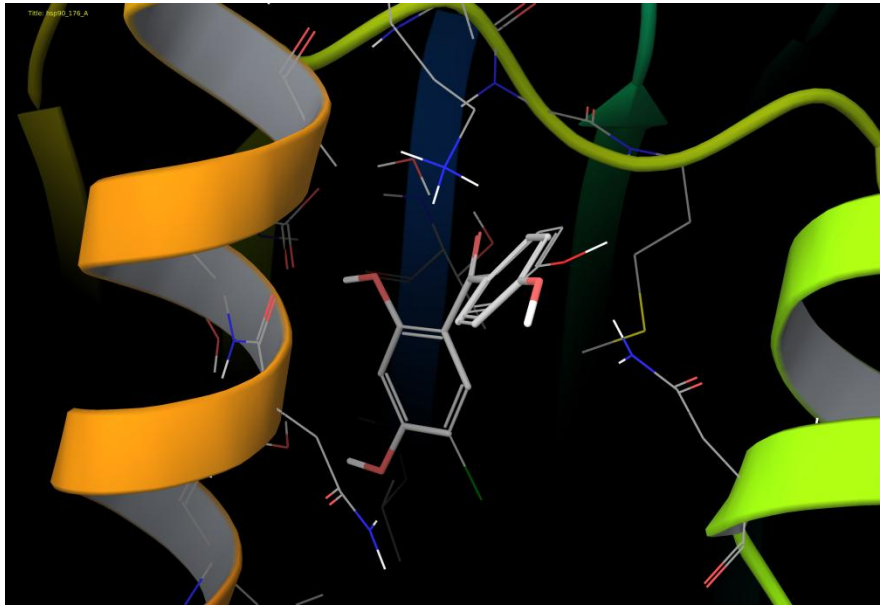




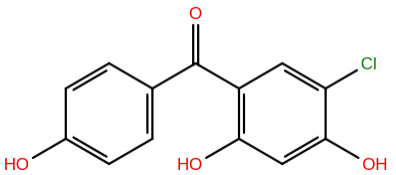




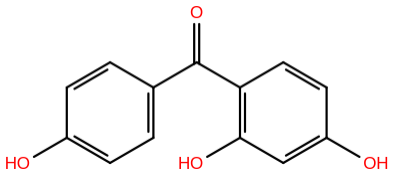
Result that raises a question about experimental activities



154



176



Binding modes of compounds 154 vs. 176 from docking

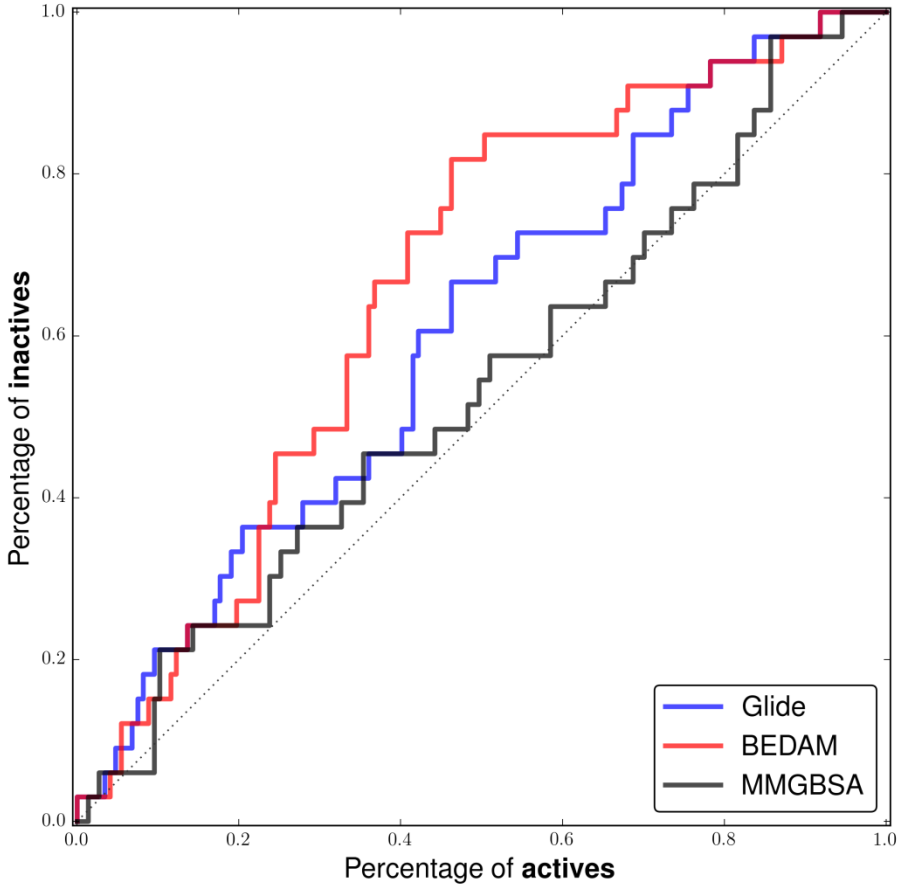
Compound154: $\Delta G(expt) = -8.3$, $\Delta G(calc) = -8.3$

Compound 176: experimentally inactive, $\Delta G(calc) = -9.0$

For these two very similar compounds, why is one a μM binder and the other a non-binder?

Screening HSP90 Ligands: Compare BEDAM with Docking and MM-GBSA

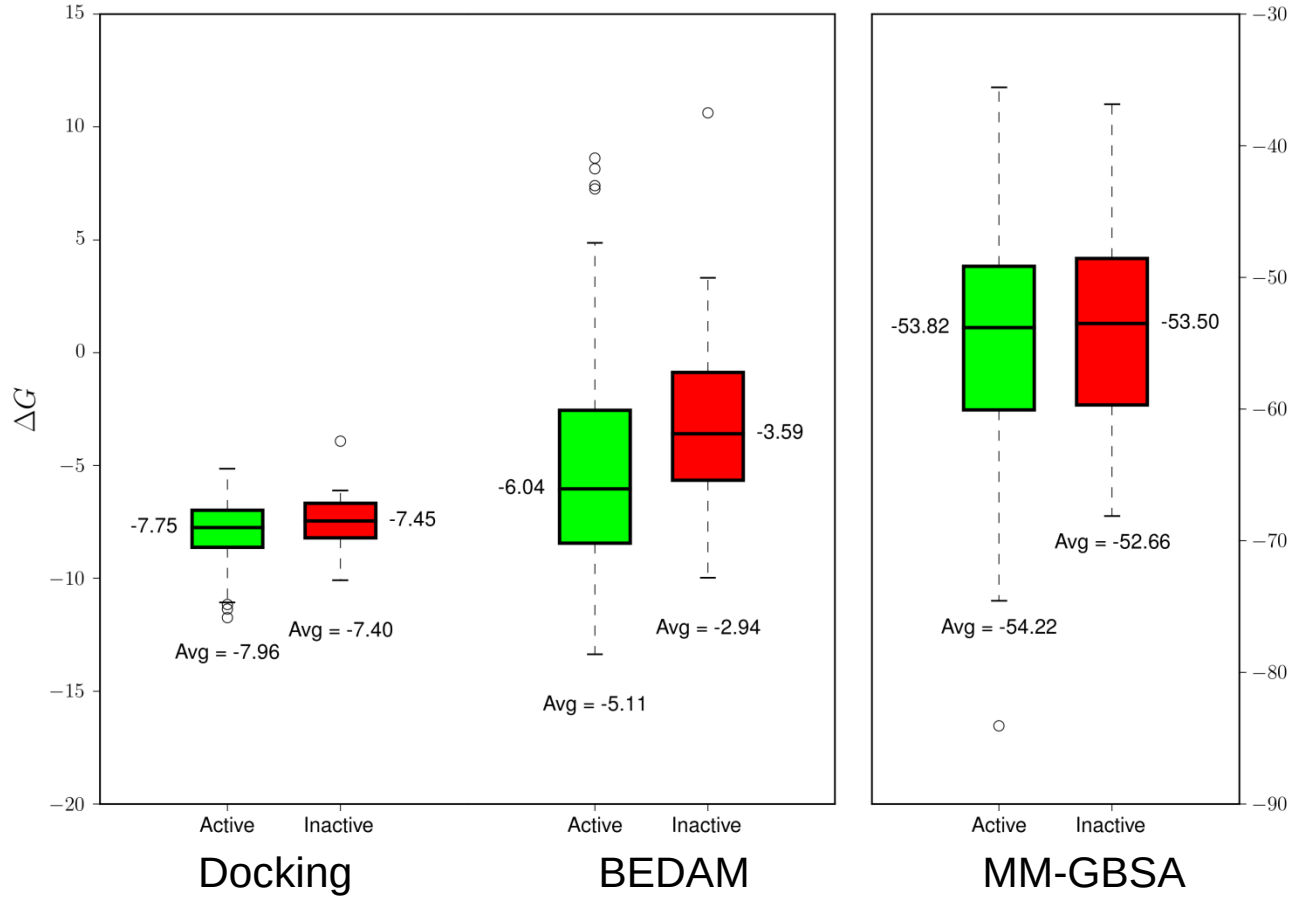
ROC



AUC

Docking	0.60 ± 0.079
BEDAM	0.66 ± 0.082
MM-GBSA	0.53 ± 0.082

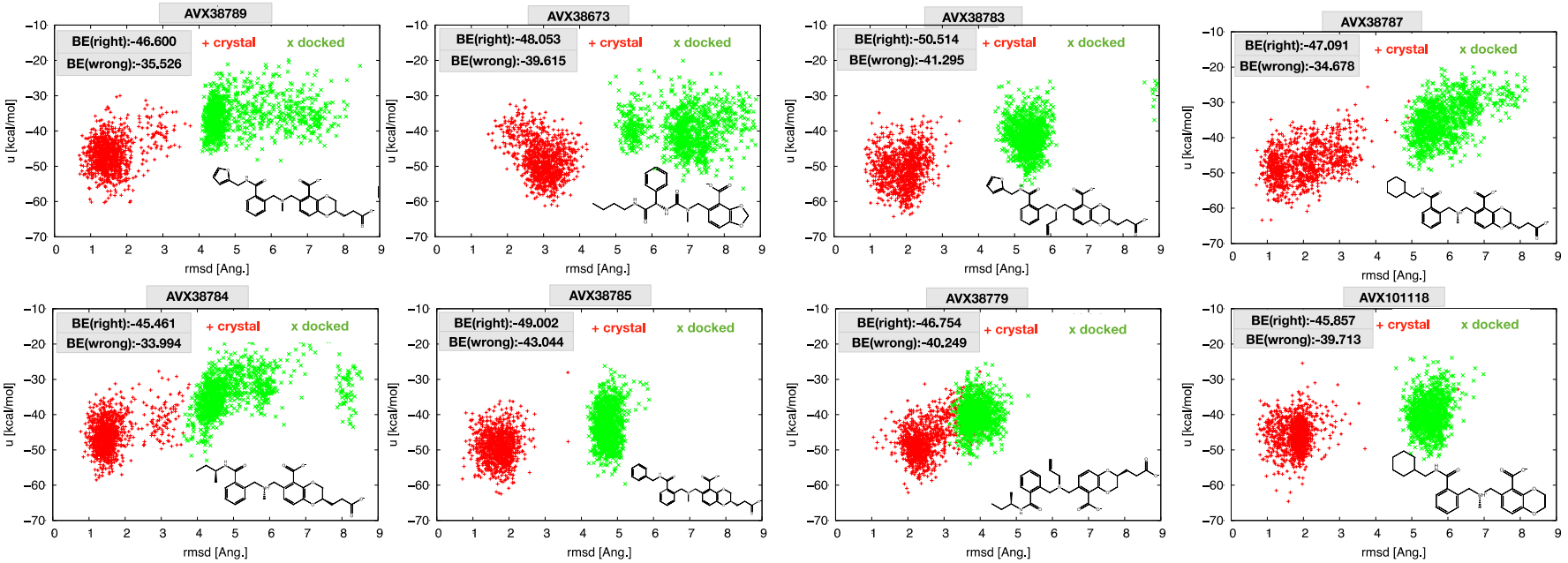
Screening HSP90 Ligands: Distribution of ΔG for Actives vs. Inactive Compounds



Compared with docking and MM-GBSA, BEDAM shows better separation of active and inactive compounds.

Improving binding prediction in virtual screening: binding energy landscape analysis

- In Sampl4 blind challenge, many false negatives are associated with bad initial docked poses.
- Majority of the ligands have funneled binding energy landscape favoring the crystallographic binding pose, implying that it is possible to use the BEDAM energy function to sample the correct pose starting from an incorrect one.

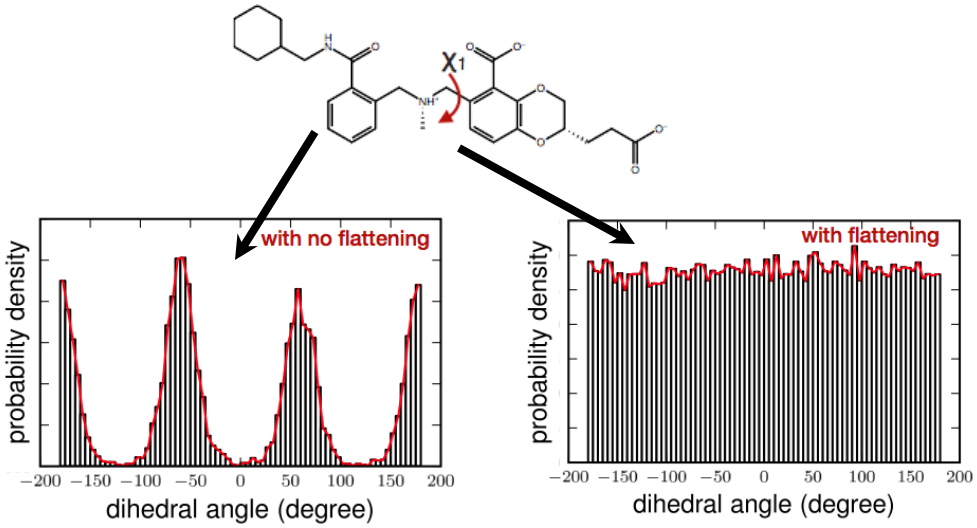


Mantes, Deng, Vijayan, Xia, Gallicchio, Levy, Binding Energy Distribution Analysis Method (BEDAM): Hamiltonian replica exchange with torsional flattening for binding mode prediction and binding free energy estimation. Submitted.

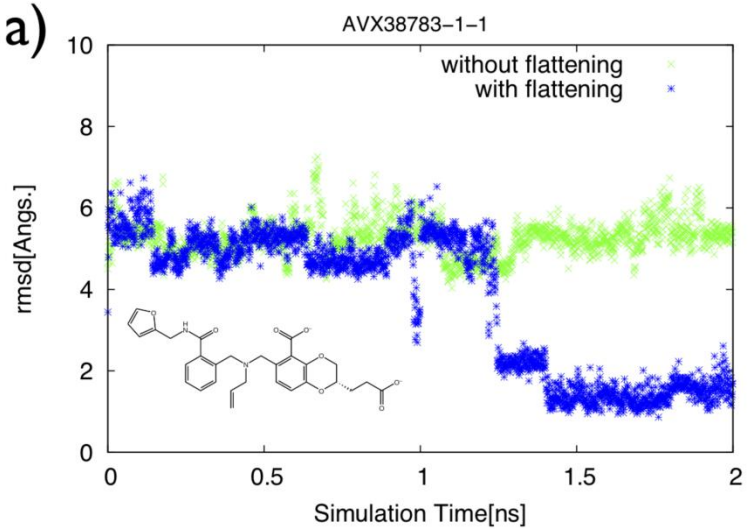
BEDAM with torsional flattening for binding mode prediction

Torsional flattening Hamiltonian

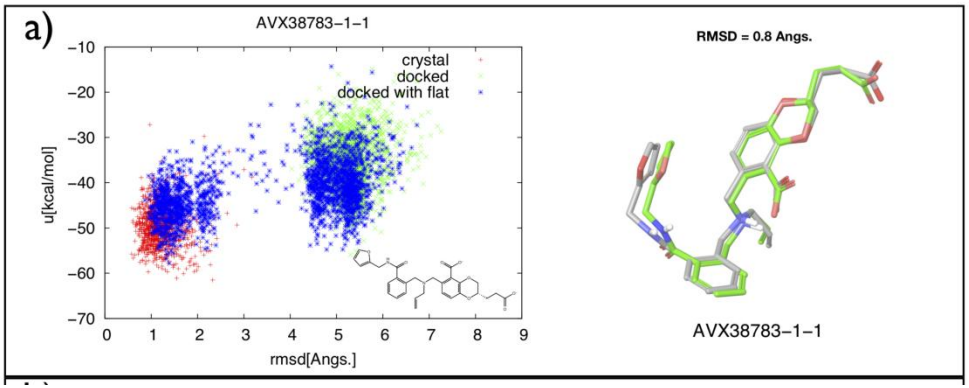
$$V_{\lambda_b}(r) = V_0(r) + \lambda_b u(r) - \lambda_D V_{Dihe}(r)$$



BEDAM simulation of a false negative with torsional flattening



The crystallographic binding pose is recapitulated starting from an incorrect docked pose



Summary

- With implicit solvation, BEDAM can be used to screen focused virtual libraries of hundreds of ligands using free energy calculations which include reorganization.
- It occupies a niche between docking and FEP/DDM in explicit solvent.

Why we were not doing as well on the Hsp90 target compared with Sampl4?

- The conformational changes near the binding site not adequately accounted for in both docking and BEDAM.
- Presence of structured waters in the binding pocket need to be better treated in BEDAM.
- Problems in the force field/solvation model with the aminopyrimidine compounds.

Acknowledgements

- Temple university team
  - Bill Flynn, Junchao Xia, R.S.K. Vijayan, Peng He, Ahmet Mantes and Ronald M. Levy
- CUNY Brooklyn college team
  - Baofeng Zhang, Emilio Gallicchio,
- Schrödinger
  - OPLS2005, Atomtyping, Maestro, LigPrep/Epik, ProteinPrep
- Funding
  - NIH P50; NIH R01; XSEDE resource

SAMPL5/Grand Challenge organizers