Quantum chemistry on AI-generated structures of protein-ligand complexes

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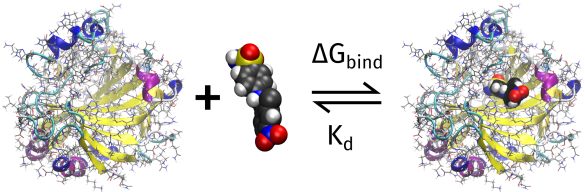
Binding energetics of protein-ligand complexes

- The cornerstone of every **structure-based** computer-aided drug design (CADD) workflow
- ΔG_{bind} hard to calculate
- Often replaced with approximate "scoring function"
- **Our approach:**
  - Physics-based computational chemistry methods
  - Fast enough for practical use



Semiempirical QM methods

- Conserves QM formalism
- No system-specific parameters
- **Fast, can handle large systems**

- Approximations limiting accuracy
- **Strong effect on NCIs**

  ↓

  Empirical corrections,
  PM6[1]**-D3H4X**[2,3]

[1] Stewart; J. Mol. Model. 2007
[2] Řezáč and Hobza; J. Chem. Theory Comput. 2012
[3] Řezáč and Hobza; Chem. Phys. Lett. 2011

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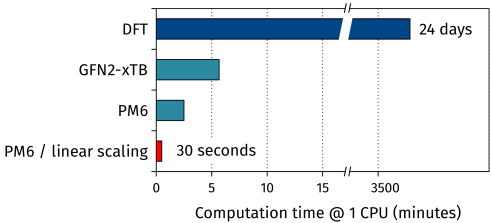
Time to compute 1000 atoms
(smallest reliable model
of protein active site)



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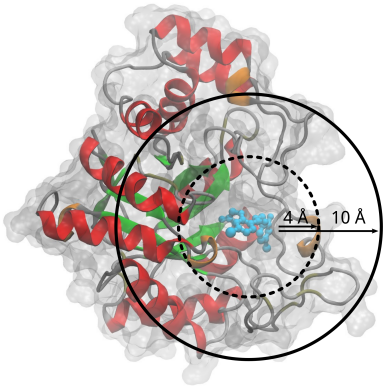
SQM2.20 computational model

Single-structure approach

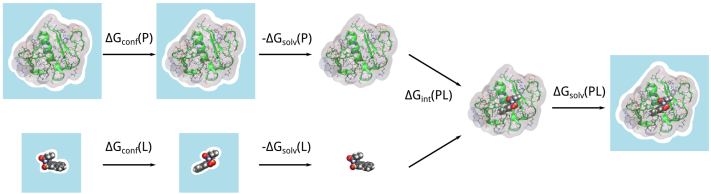
- Crucial for efficiency
- Works better than expected

Obtaining representative P-L structure

- Benchmarking on quality crystals
- Large model, active site optimized for each ligand (SQM/MM)
- Modeling new systems - multiple poses help, and we can select the best one



SQM2.20 scoring function



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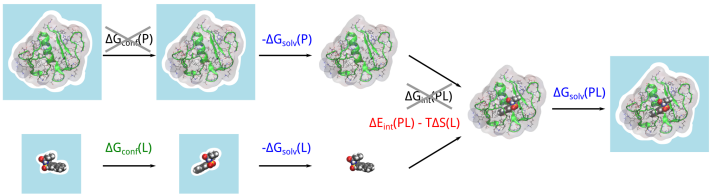


Score = $\Delta E_{int}(PL) - T\Delta S(L) + \Delta\Delta G_{solv}(PL) + \Delta G_{conf}(L) + \Delta G_{H+}$

ΔE_{int}: PM6-D3H4X
ΔG_{solv}: PM6/COSMO2[1]
$-T\Delta S$: LM5 model[2]

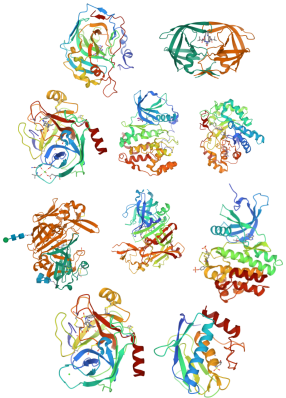
SQM/MM geometry optimization
Complete model SQM singlepoint
$\sim$ 30 minutes @ 1 CPU core

[1] Kříž and Řezáč; J. Chem. Inf. Model. 2019, 59, 229.
[2] Chan, Morris and Hutchison; J. Chem. Theory Comput. 2021, 17, 2099.

PL-REX data set[1]

10 targets / 164 complexes
quality X-ray structures + few modeled
measurements from the same lab

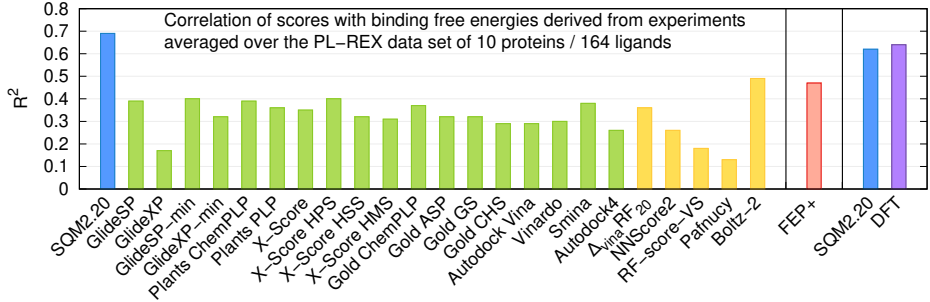
System	Ligands	Tanimoto	pK_i range	Expt. R^2	Charges
001-CA2	10	0.32	2.19	0.73	-1*
002-HIV-PR	22	0.51	5.09	0.89	0,1
003-CK2	16	0.32	1.92	0.51	-1,0
004-AR	14	0.47	2.80	0.70	-1
005-Cath-D	10	0.71	3.52	0.88	0
006-BACE1	16	0.48	3.62	0.76	0,1
007-JAK1	12	0.55	3.37	0.77	0,1
008-Trypsin	15	0.46	4.41	0.89	0*,1,2
009-CDK2	31	0.69	3.61	0.81	-1,0
010-MMP12	18	0.47	3.85	0.83	0
Average	16	0.50	3.44	0.78	



[1]Pecina, Fanfrlík, Lepšík and Řezáč, *Nat. Commun.* 2024, 15 (1), 1127.

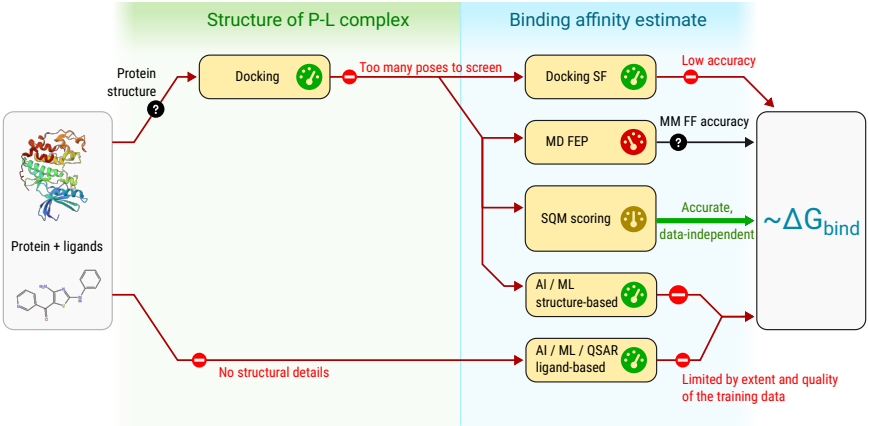
PL-REX SQM2.20 scoring[1]

- PL-REX dataset: 10 proteins with a series of ligands, 164 systems total
- Calculations evaluated by **correlation with experimental affinities**
- Comparison to DFT and FEP+

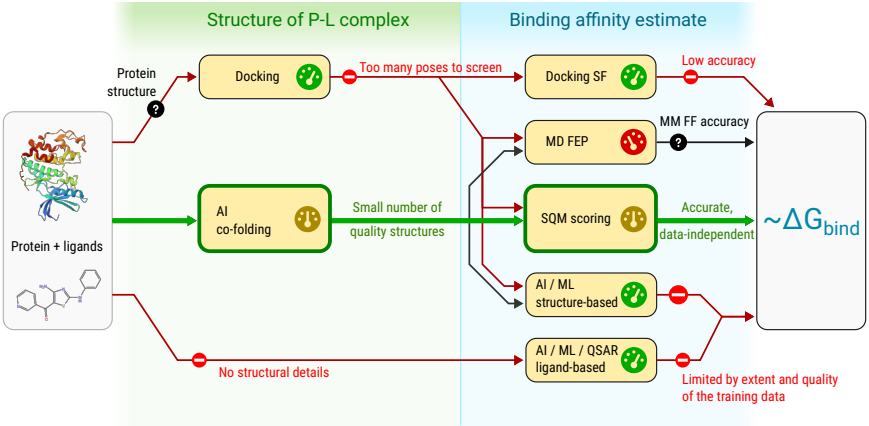


[1] A. Pecina, J. Fanfrlík, M. Lepšík and J. Řezáč, *Nat. Commun.* 2024, 15 (1), 1127.

Challenge: new compound, P–L structure unknown

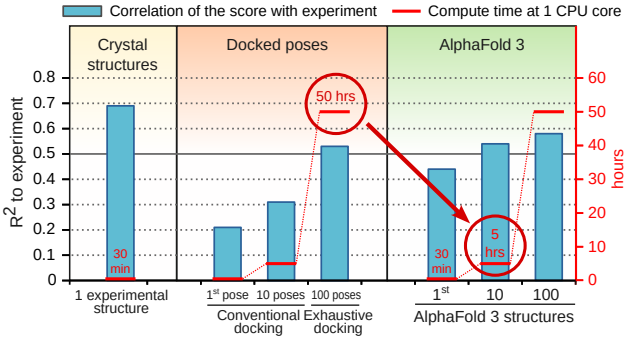


Generative AI co-folding models



Docking vs. AlphaFold 3

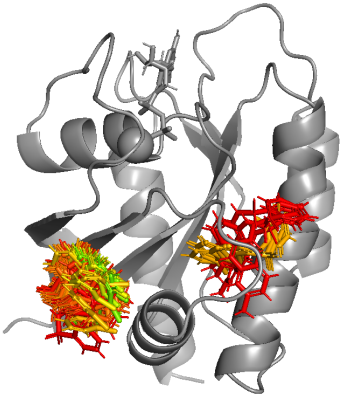
- PL-REX dataset
- Ligand poses from AlphaFold 3, experimental protein structure
- **Overlap with training set!**



Validation in new targets

- Ligands not known in training
- 10 P–L series selected using objective criteria

- 32 crystals
- AlphaFold 3 structures:
  27 (85%) structures with RMSD < 2 Å
- Boltz-2 structures:
  21 (63%) structures with RMSD < 2 Å
  (affinities not reliable, correlation in 2 out of 10 series)



Validation in new targets

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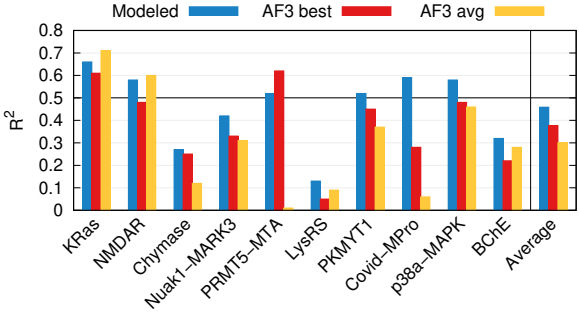
- **Modeling + SQM** scoring succeeds in 6 cases ($R^2 > 0.5$), average $R^2 = 0.46$
- **SQM scoring on AF3 structures** succeeds in 2 cases, average $R^2 = 0.37$



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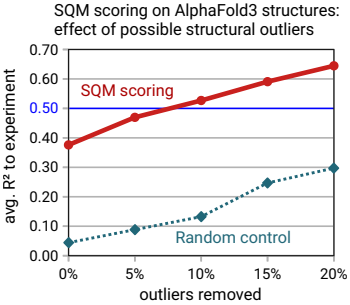
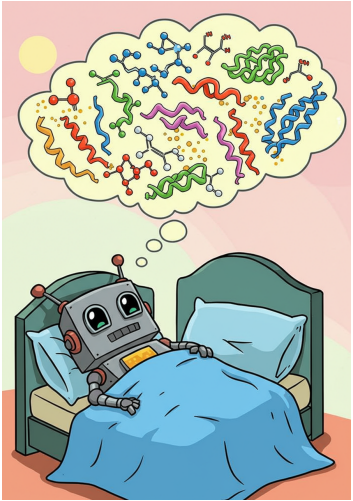


Summary

- AI co-folding advantages
  - Much more effective than docking
  - Access to systems without structure
  - Protein structure adapts to the ligand
  - Reasonable computational cost
- Limitations
  - Wrong structures with high confidence scores
  - Independent, rigorous validation catching up only slowly
- **Useful tool, but not a black box**



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- Thanks to
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  - other colleagues and collaborators

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