On the Importance of Physically Correct Models for Protein-Ligand Binding

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Němčice, ENBIK 06/2022

Ligand Design via Quantum Chemical Scoring

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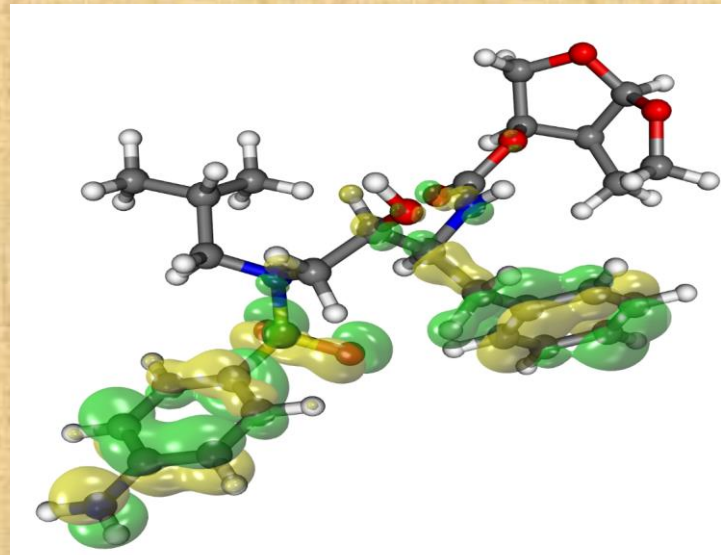
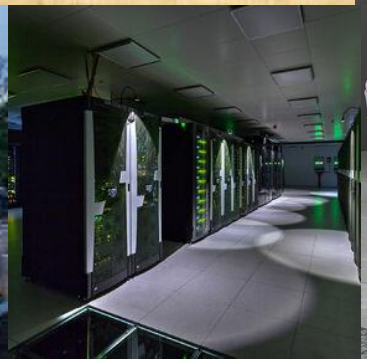
IOCB Prague, Czech Academy of Sciences

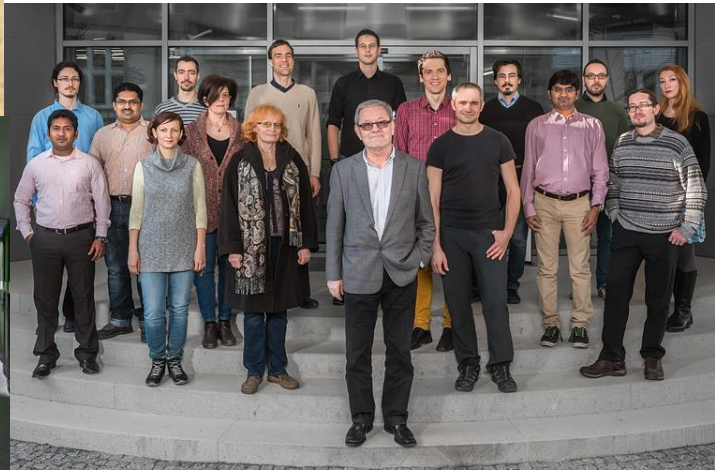


ÚOCHB AV ČR IOCB PRAGUE

IT4I: 20+ MCPU hours

IOCB Tech





Computer-Aided Drug Design

Structure-based approach

- Target/Receptor (protein)
- Ligand (small molecule / drug)

- 3D structures (X-ray crystallography, NMR, cryo-EM)

- non-covalent interactions governing the affinity

Aims

- prioritize compounds for synthesis
- exclude non-binders

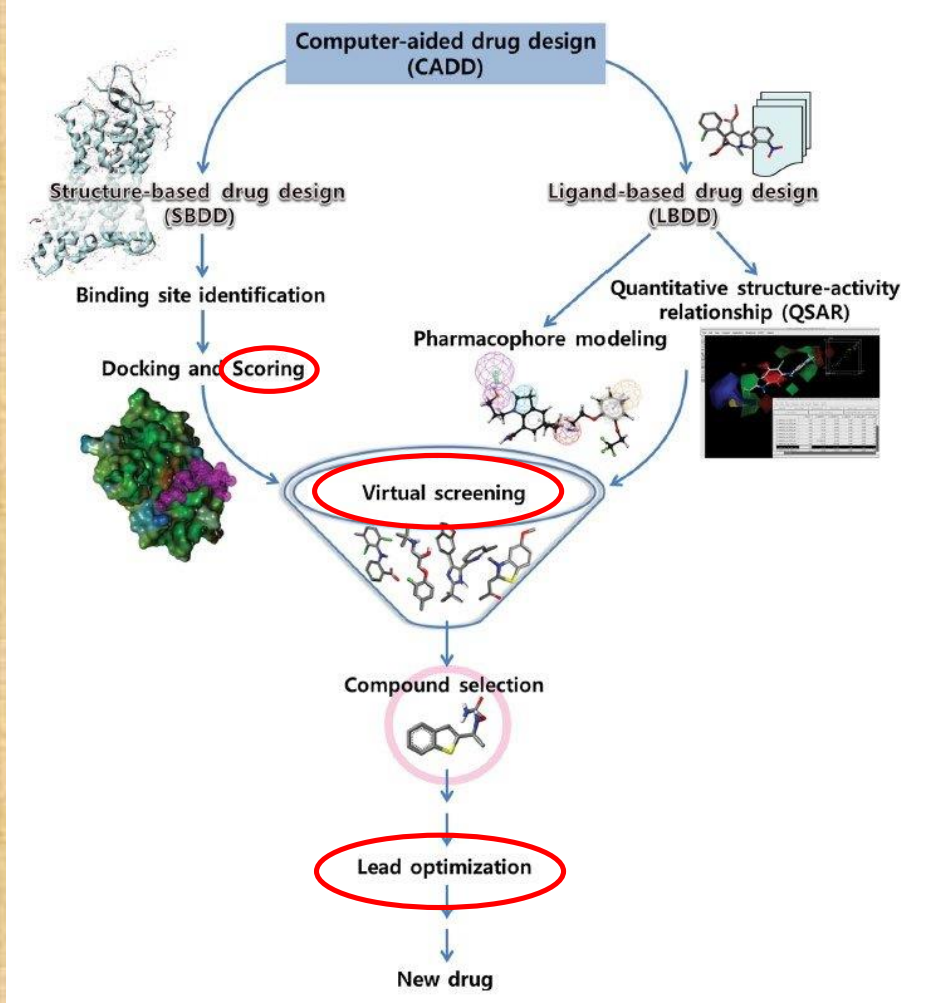


Image: Prajapat P, Agarwal S, Talesara GL, *J. Med Org Chem* **2017**

What is scoring?

Predicting the strength of protein-ligand interaction from structure

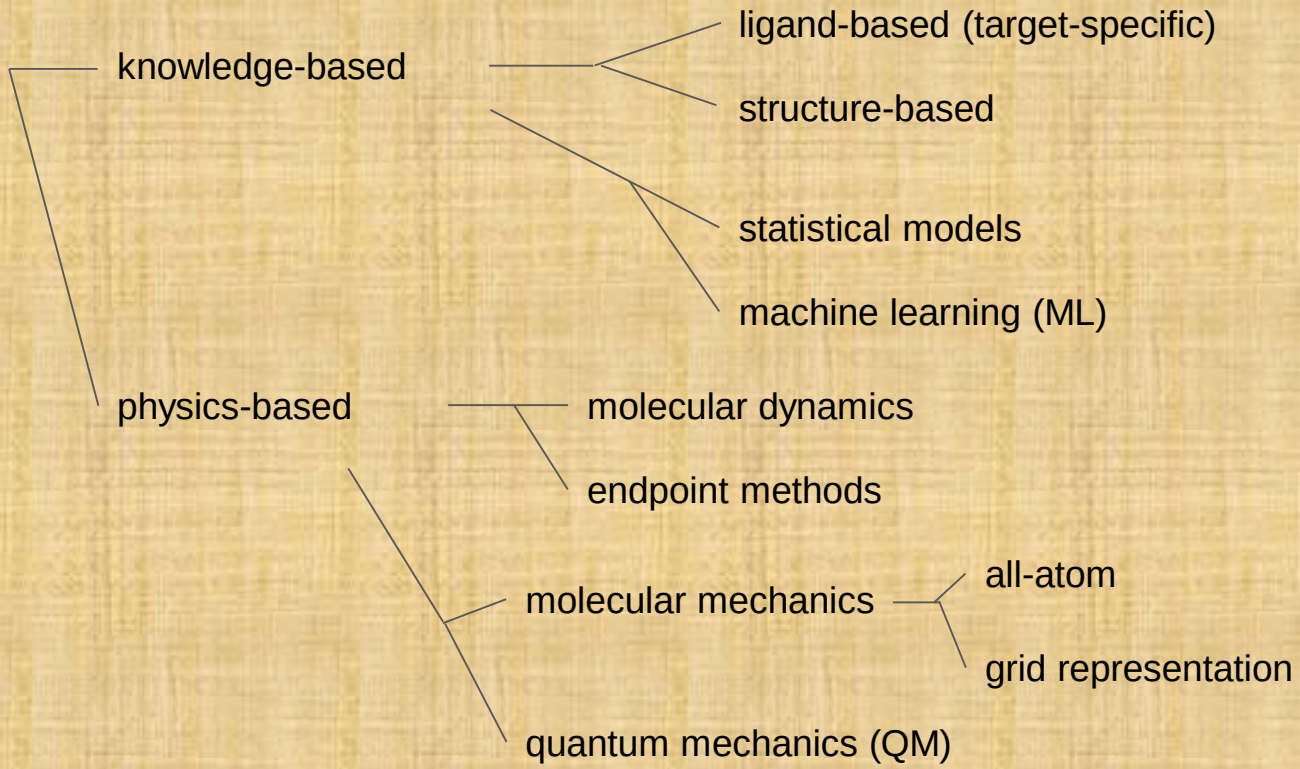
ΔG_{bind} = -12.456 kcal/mol

What is scoring?

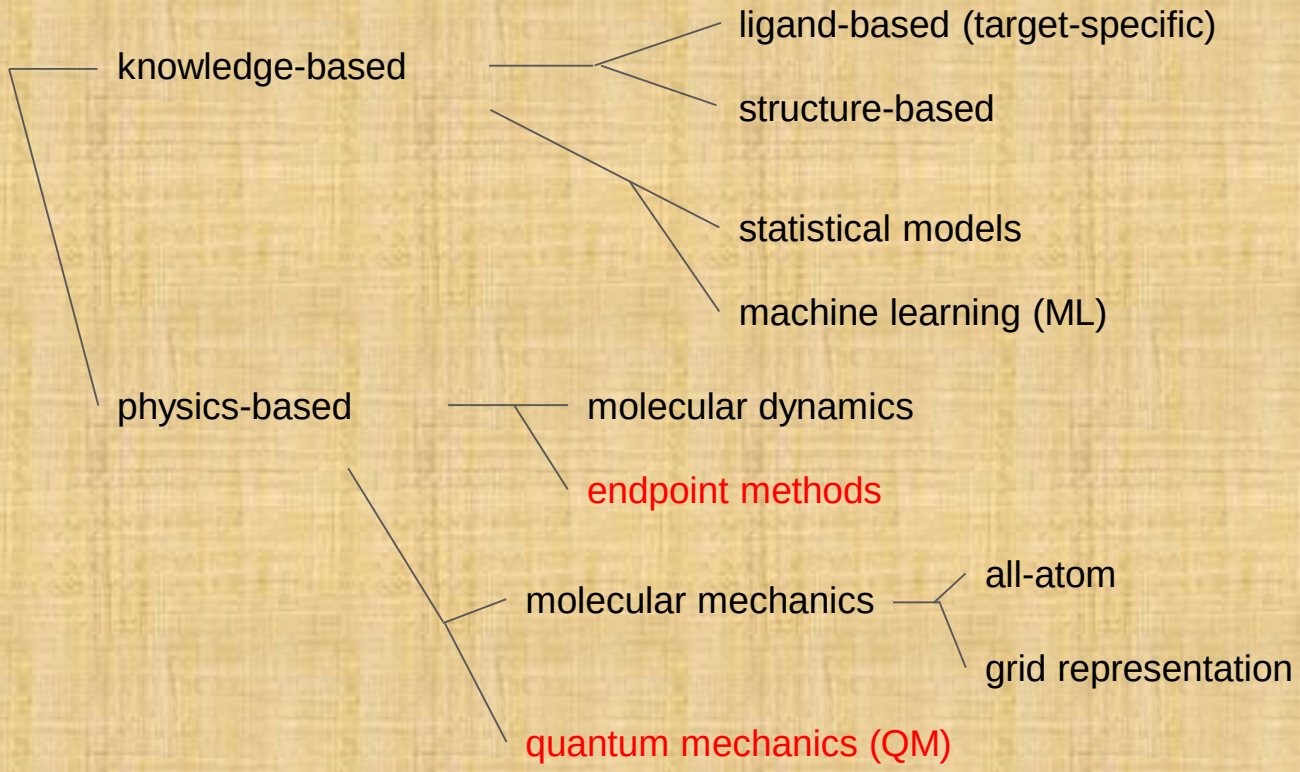
Predicting the strength of protein-ligand interaction from structure

Score = -42.01 units

Scoring function “taxonomy”



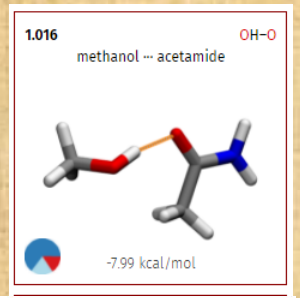
Scoring function “taxonomy”

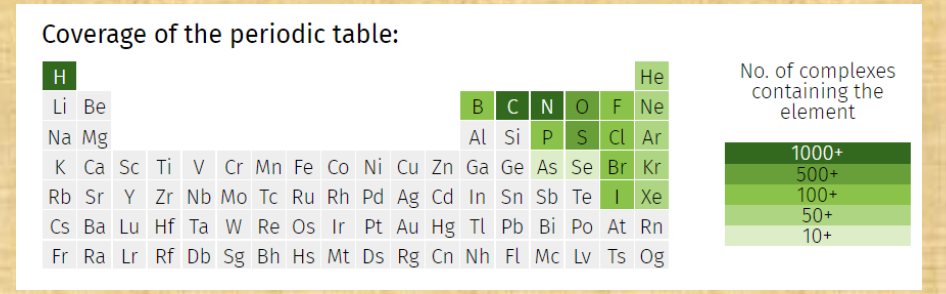


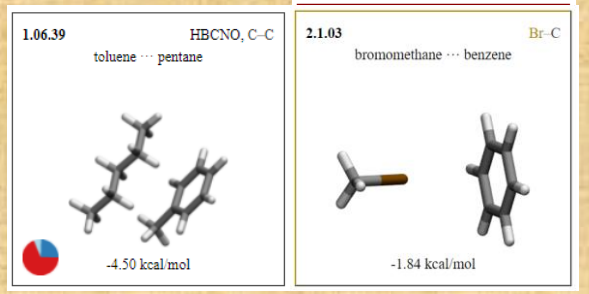
Universal Reliable Scoring Function

QM Methods for Non-covalent Interactions

- Small models, accurate calculations (CCSD(T)/CBS) in vacuum
- www.nciatlas.org (~ 20,000 data points)
- hydrogen bonding, dispersion, sigma-hole interactions,…..



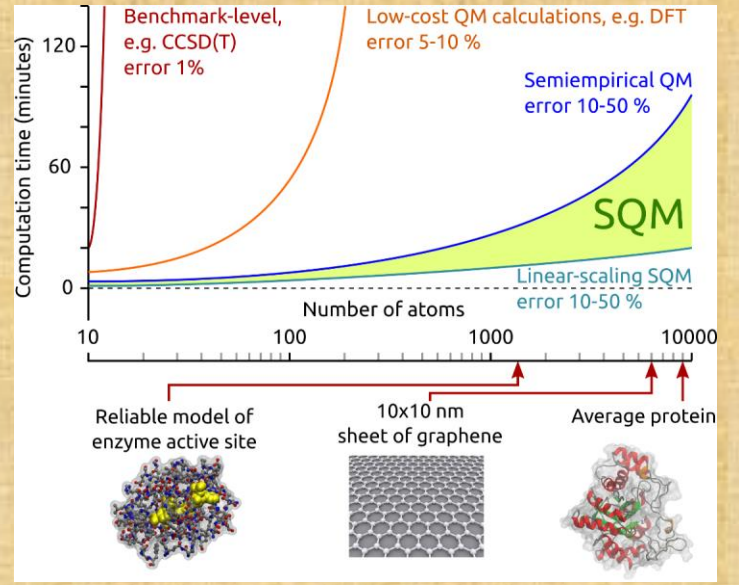




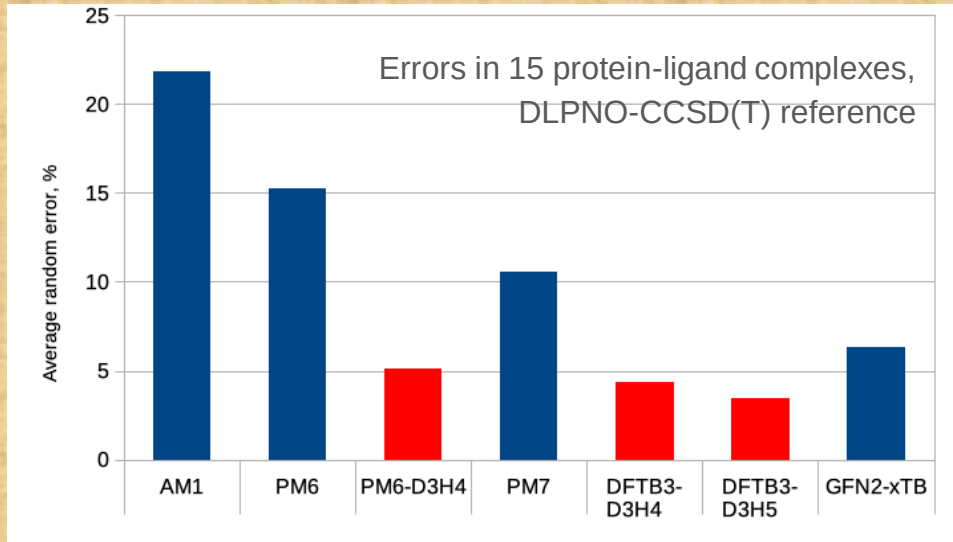
- Development of semiempirical QM methods - corrections for non-covalent interactions
  chemical accuracy (1 kcal/mol) in small dimers

Semiempirical QM methods

- Fast calculation
- Easy preparation
  (no system-specific parameters)
- Accuracy?



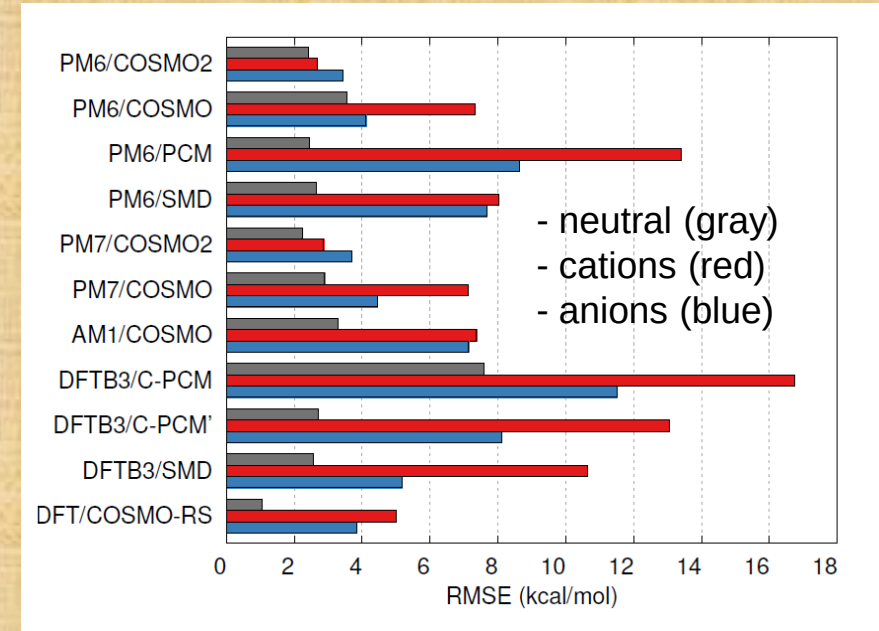
correcting SQM methods
for non-covalent interactions[1-3]



[1] Řezáč et al.; *J. Chem. Theory Comput.* **2009**, 5, 1749
[2] Řezáč and Hobza.; *J. Chem. Theory Comput.* **2012**, 8,141
[3] Řezáč; *J. Chem. Theory Comput.* **2017**, 13, 4804

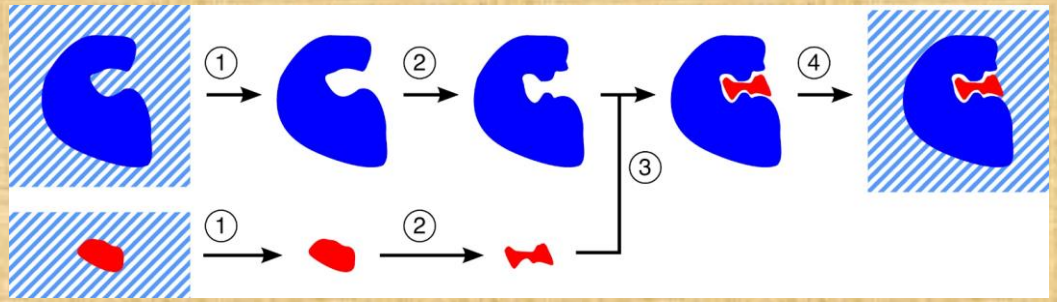
Implicit Solvation Models

- reparametrisation of COSMO → COSMO2



Kříž, Řezáč; *J. Chem. Inf. Model.* **2019**, 59, 229

SQM-based Scoring function



Modular physics-based approach:
components can be replaced if better alternative exists

Score = ΔE_{int} ← PM6-D3H4X + further corrections

+ $\Delta\Delta G_{solv}$ ← PM6/COSMO2

+ $\Delta G_{conf,w}(L)$ ← Optimized free molecule / optional conformation search

+ $\Delta G_{conf,w}(P)$

– $T\Delta S$ ← LM5 model fitted to QM data

Fanfrlík et al.; *J. Phys. Chem. B* **2010**, *114*, 12666
Lepšík et al.; *ChemPlusChem* **2013**, *78*, 921
Pecina et al.; *ChemPlusChem* **2020**, *85*, 2362

QM/MM Setup

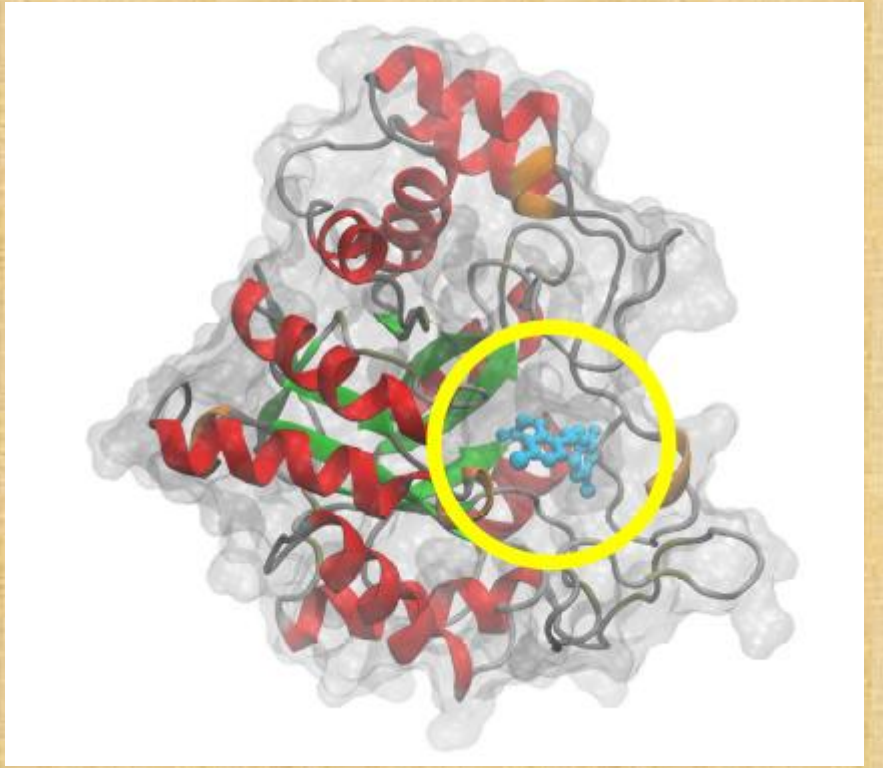
- Ligand ~ 10 to 100 atoms
- Protein ~ 10 000 atoms

- We consider model of the active site with ~1500 atoms
  (10 Å sphere around ligand)
- Proven to converge to the results obtained in the whole protein

- One protein conformation

for a series of ligands

- QM/MM geometry optimization
  + many more steps



Questions

Is SQM-score generally applicable?

How does it compare to commonly used scoring functions (SF) in academia/industry?

Verification

Evaluation against experimental “truth” in multiple diverse data sets

- Input: Experimental structures or a reliable model
- Comparison with experimental affinities

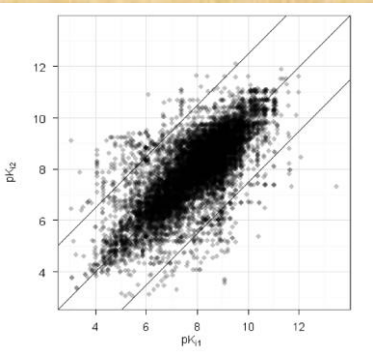
Experimental data

All data

PDBBind database ~20,000 systems

Reproducibility from multiple independent measurements - $R^2 = 0.8$

No time to prepare each system carefully



DOI: 10.1021/jm300131x

Reliable data

Reliable structures, preferably crystal

Measurements from one lab

Only tens of target / ligand series

Careful preparation of each protein

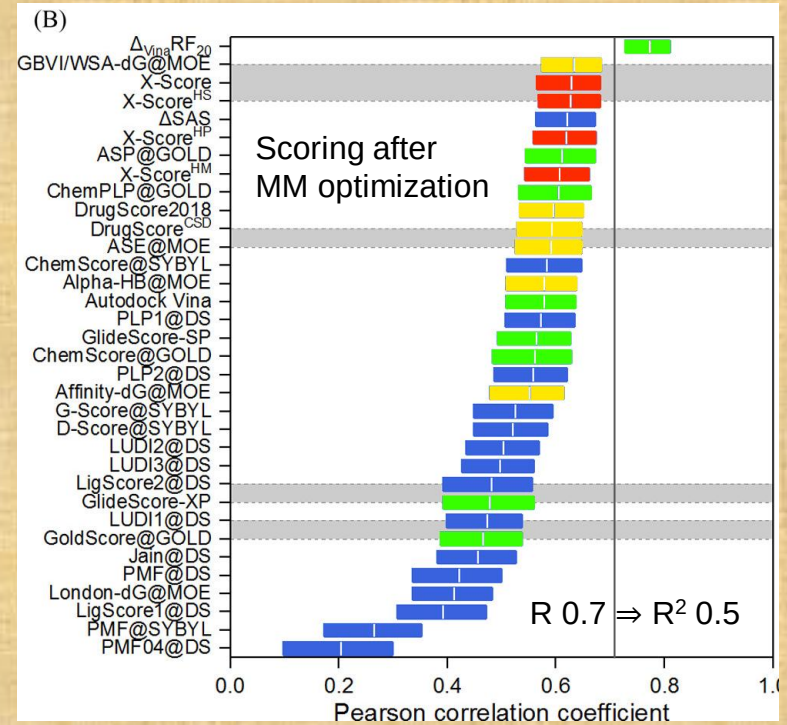
Current Status

- Best SFs in the CASF2016[1]
-
- Structure-based machine learning

× MD-based methods (FEP)

Timing:

- Empirical SFs <= seconds
- SQM-score ~ 30 minutes

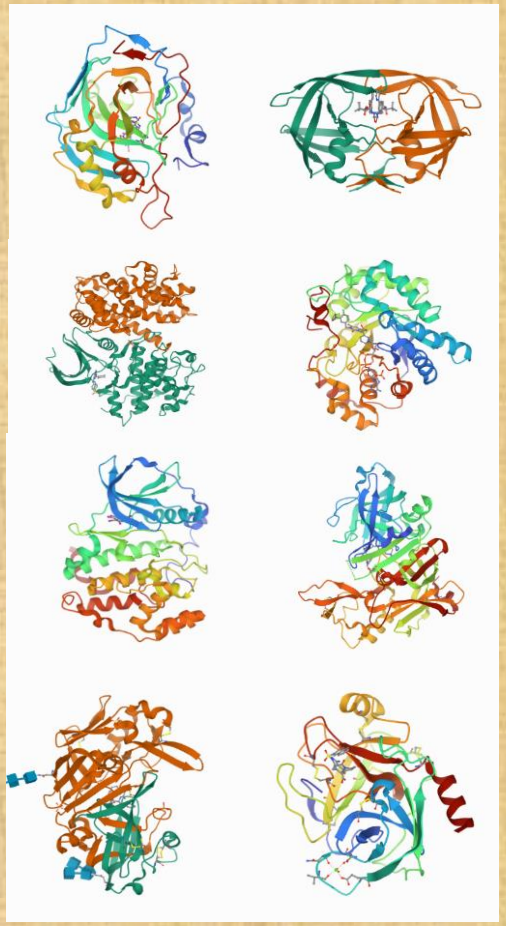


[1] M. Su, Q. Yang, Y. Du, G. Feng, Z. Liu, Y. Li, R. Wang, *J. Chem. Inf. Model.*, **2018**.

Diverse protein-ligand datasets

- consistent inhibition constants, IC_{50}
- reliable crystal structures

		Ligands	Similarity	Crystals	Expt.
001	Carbonic anhydrase 2	10	0.32	10	Ki
002	HIV protease	22	0.43	15+	Ki
003	CDK2	12	0.38	15	Ki
004	Casein kinase 2	9+	0.47	9+	Ki
006	Aldose reductase	14	0.47	14	Ki + IC50
010	CDK2	21	0.88	1	IC50
011	Cathepsin D	10	0.71	3	IC50
032	BACE1	16	0.48	20	IC50
038	JAK1	10	0.58	12	Ki
043	Trypsin	10	0.71	5	Ki



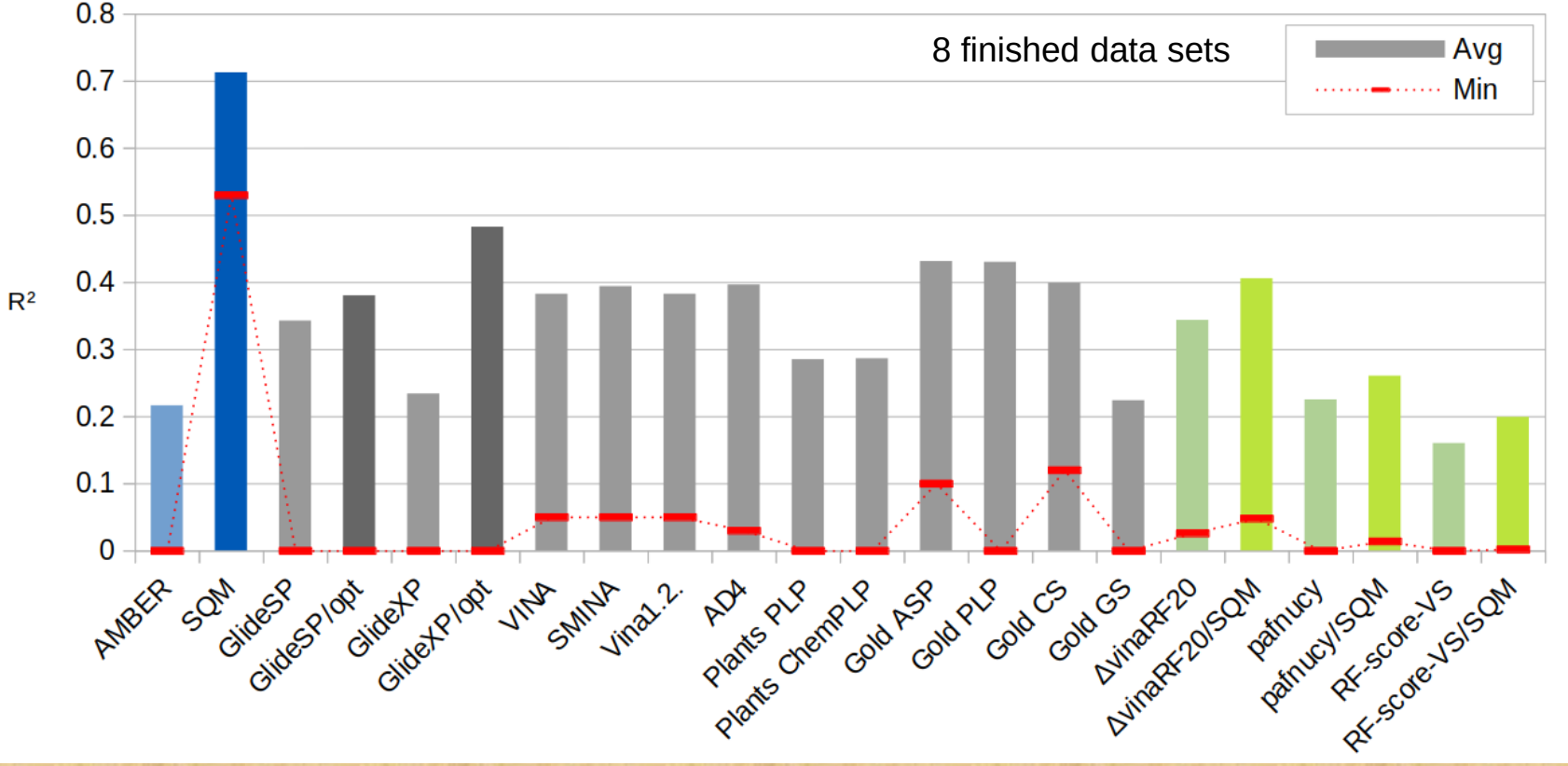
SQM-score Performance

$$\Delta G_{bind} = RT \ln K_i$$

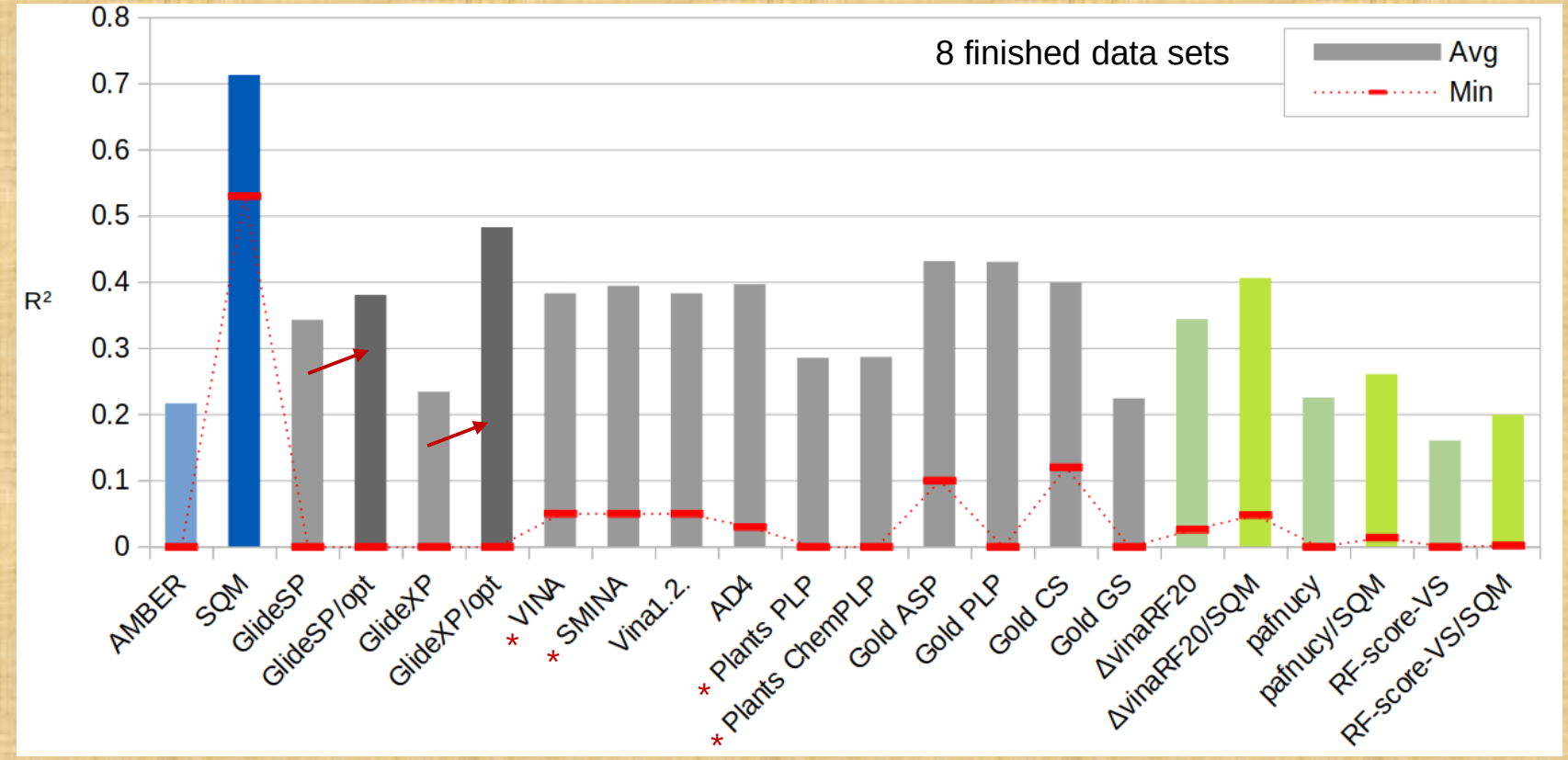
R^2 to experiment			
	Ligands	v 1.02	v 2.19
001-CA2	10	0.21	0.66
002-HIV-PR	12	0.41	0.55
003-CDK2	12	0.53	0.83
004-CK2_Dobes	9	0.64	0.65
006+037-AR	14	0.61	0.78
010-CDK2-biphenyls	21	0.55	0.84
011-Cath-D	10	0.62	0.75
032-BACE1-challenge	16	0.01	0.56
38-JAK1	10	0.04	0.83
AVERAGE		**0.40**	**0.72**

- **multi-step optimization protocol,** focus on fixing H-bond networks
- tight control of SQM calculation
- **reparametrized H4 and X corrections**
- additional corrections for sulfur
- halogen bonding correction in MM

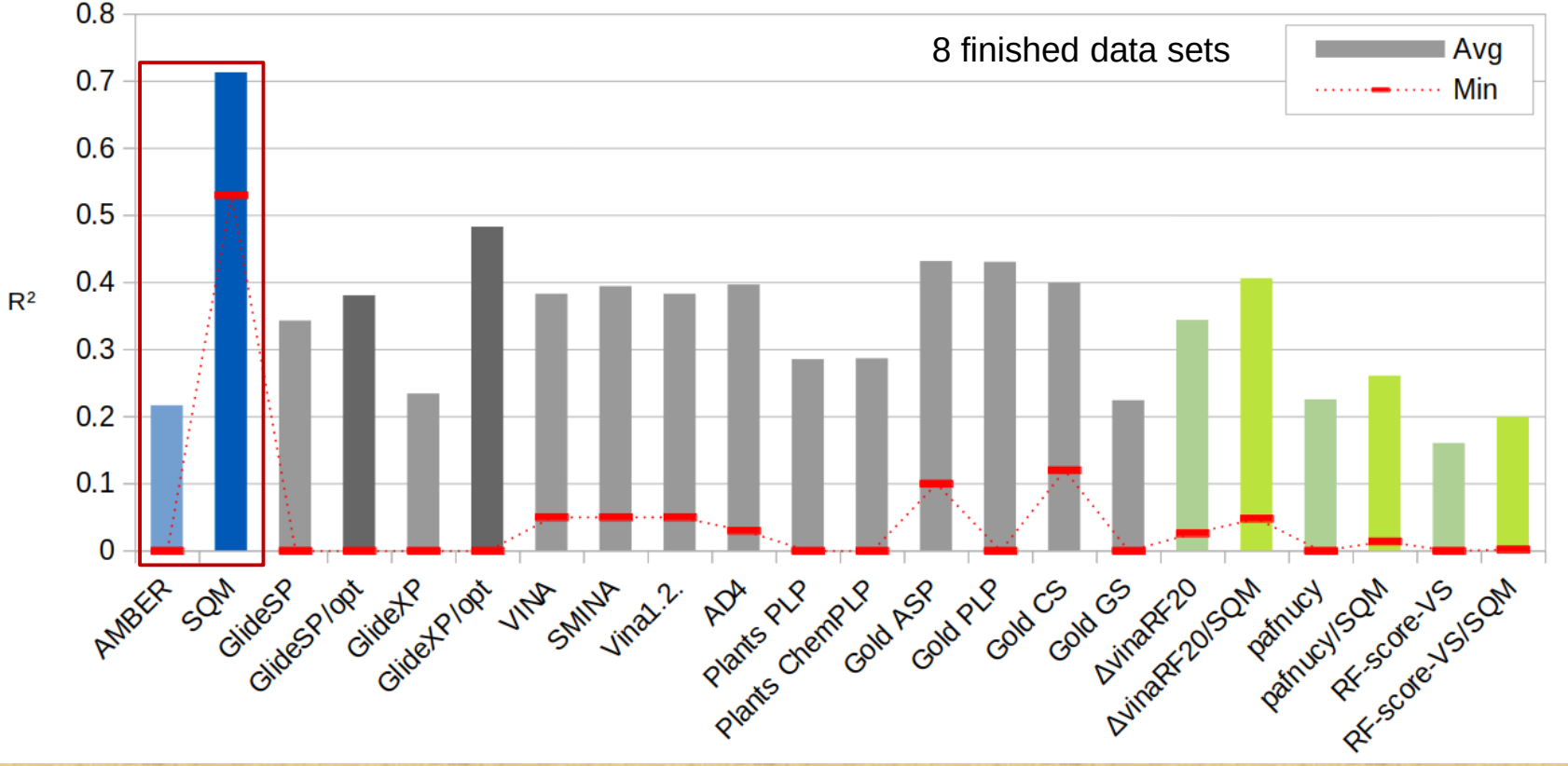
Scoring Function Performance



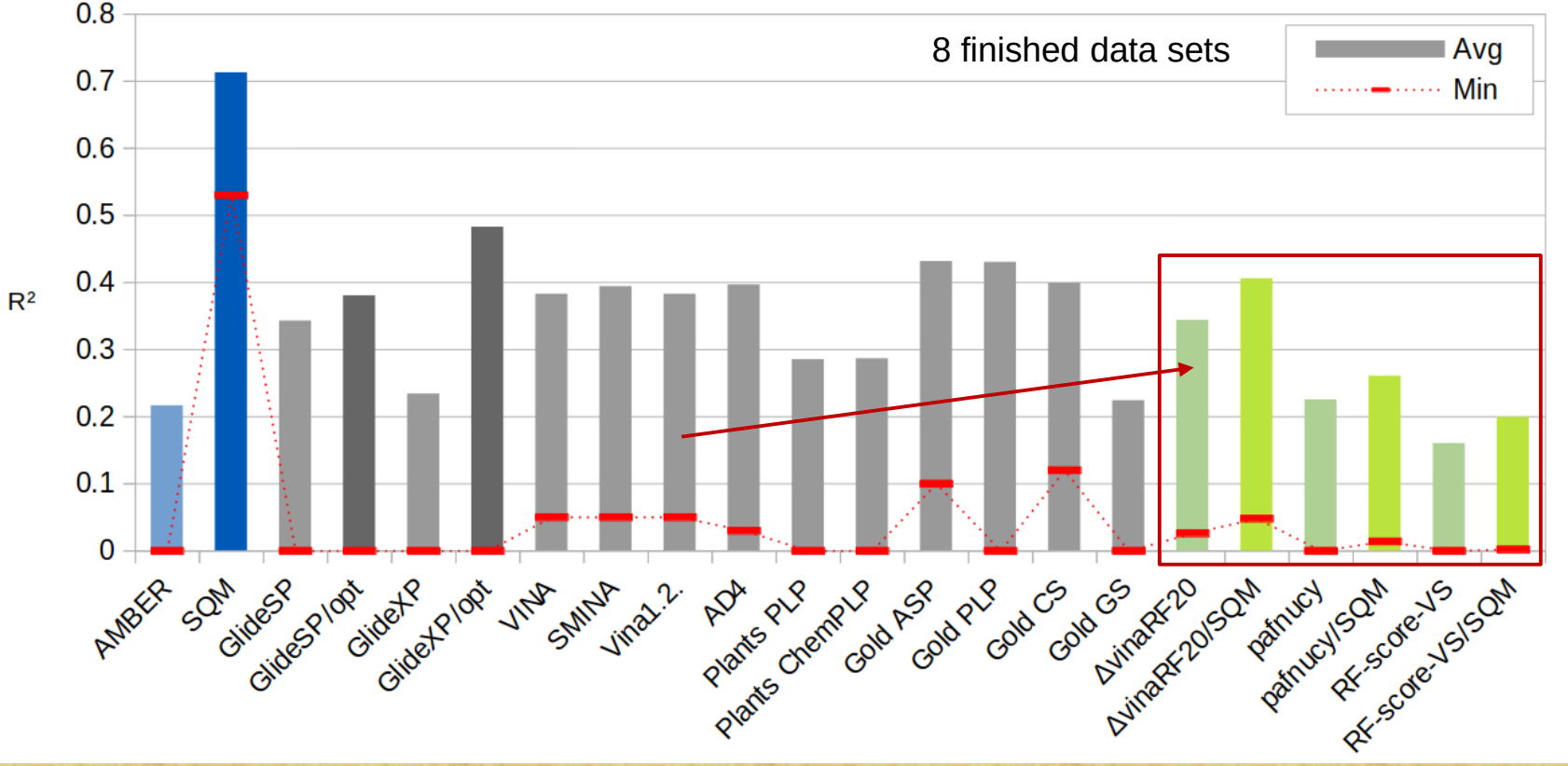
Scoring Function Performance



Scoring Function Performance

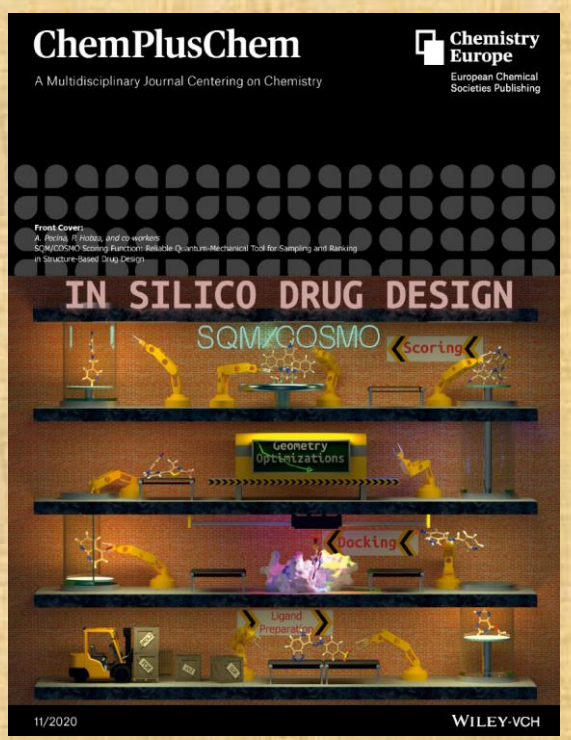


Scoring Function Performance



Summary

- SQM-score outperforms classical and ML scoring functions
- reasonable computational cost (20 min/1 CPU)
- prototype software licensed to US-based pharma company
- Heading towards marketable, stand-alone implementation



Acknowledgements

- IOCB internal grant
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EUROPEAN UNION
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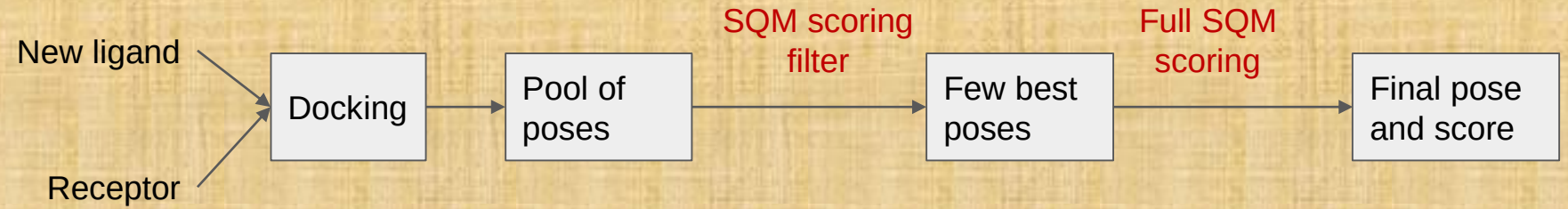
MINISTRY OF EDUCATION, YOUTH AND SPORTS

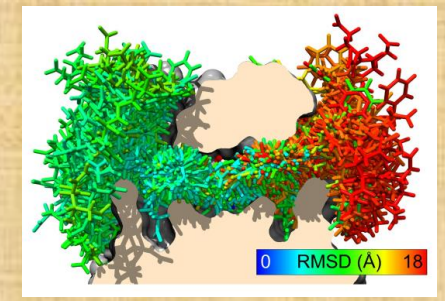
Reviews:
Lepšík et al.; *ChemPlusChem* **2013**, *78*, 921
Pecina et al.; *ChemPlusChem* **2020**, *85*, 2362

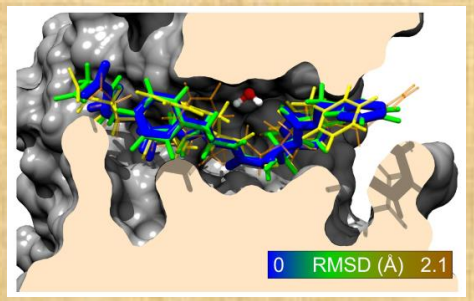
Towards realistic use case

Unknown structure of the complex - ability to calculate new molecules

- faster protocol for selecting best geometries (poses) from docking[1]



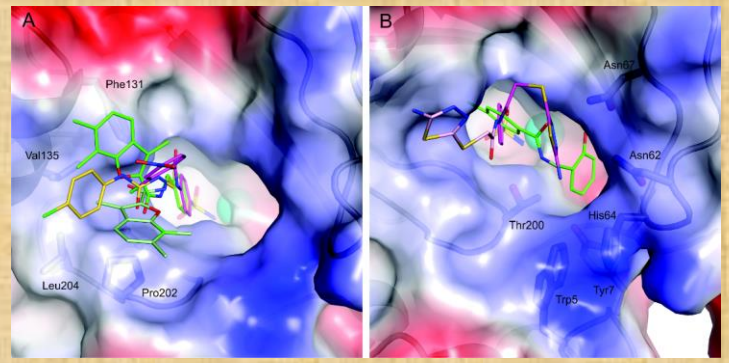


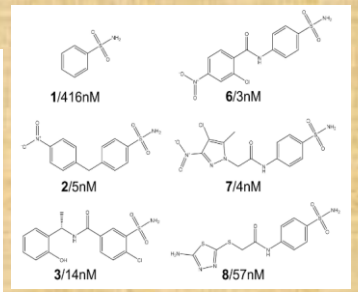


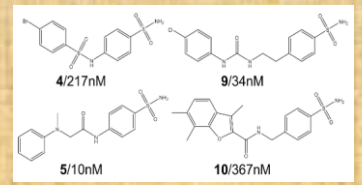
[1] A. Pecina, R. Meier, J. Fanfrlík, M. Lepšík, J. Řezáč, P. Hobza, C. Baldauf; Chem. Commun. 2016

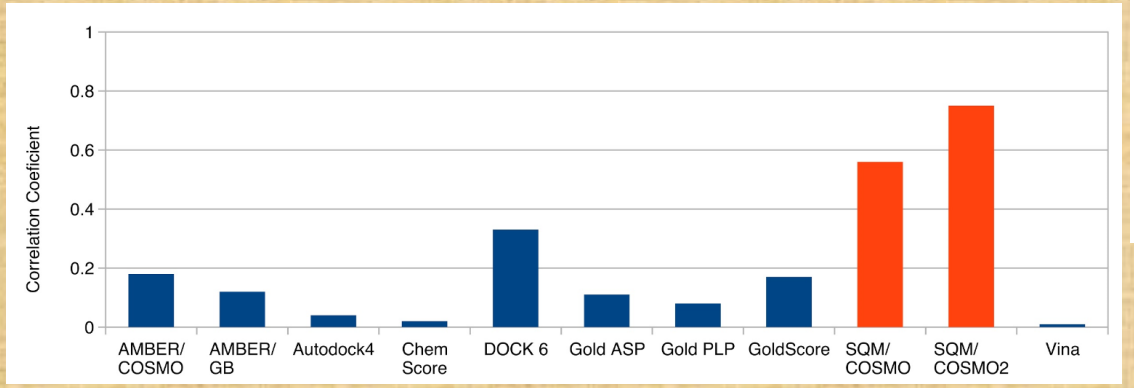
Case Study 1: Ranking - Carbonic anhydrase II

- Set of 10 inhibitors
  binding to carbonic anhydrase II through Zn^{2+}
- 10 high-resolution (1.1–1.4 Å) crystal structures
- Consistent inhibitory constant (K_i) values
  measured at IOCB
- Score vs. $\Delta G_{bind} = RT \ln K_i$





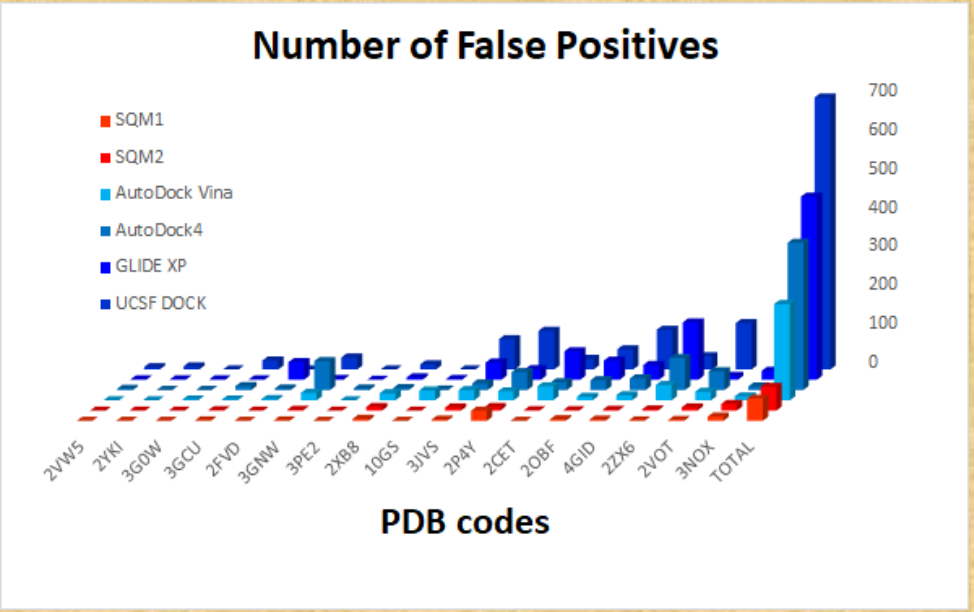




Pecina et al.; *ChemPhysChem* **2018**, 19, 873

Case Study 2: Sampling (Native Pose Identification)

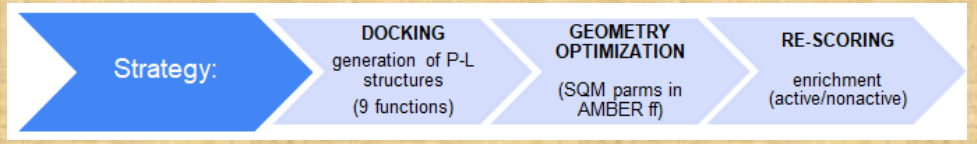
- diverse set of 21 protein-ligand systems (17 shown here)
- crystal structures available in PDB
- two SQM methods: SQM1=DFTB-D3H4X/COSMO
  SQM2=PM6-D3H4X/COSMO
- compared to 4 standard scoring functions
- evaluation:
  false positive = a pose with better score than crystal
  (ideal: zero false positives)
- SQM has 4-12-times less FPs than the standard SFs

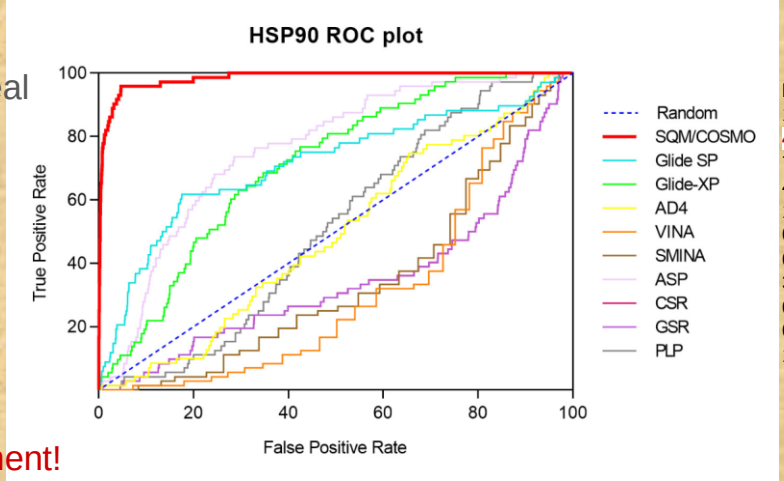


Pecina et al.; *Chem. Commun.* **2016**, 52, 3312
Pecina et al.; *J. Chem. Inf. Model.* **2017**, 57, 127
Ajani et al.; *ACS Omega* **2017**, 2, 4022

Case Study 3: Virtual screening (Library enrichment)

- Heat shock protein (HSP90); important for cancer and immunity
- 72 biologically active compounds + 4469 structurally similar compounds (DUD-E decoys)
- Enrichment factor (EF_1) and ROC curves (AUC%), where random is (1, 50%) and ideal (63, 100%)
- Standard docking provides good poses but standard SFs fail in their correct ranking
- Rescoring by SQM increases enrichment significantly
- Combination of SQM geometries and SQM/COSMO SF leads to the best enrichment!





EF_1	AUC%
1	50
47	98
7	75
4	71
1	49
0	30
0	34
3	76
0	34
0	60
1	51

Eyrilmez et al.; ChemPhysChem **2019**, 20, 2759

Polarisation in Classical Molecular Dynamics (MD) of Protein/Ion/Ligand Complexes

M. Lepšík, S. Kuhaudomlarp, P. Jungwirth, A. Imberty

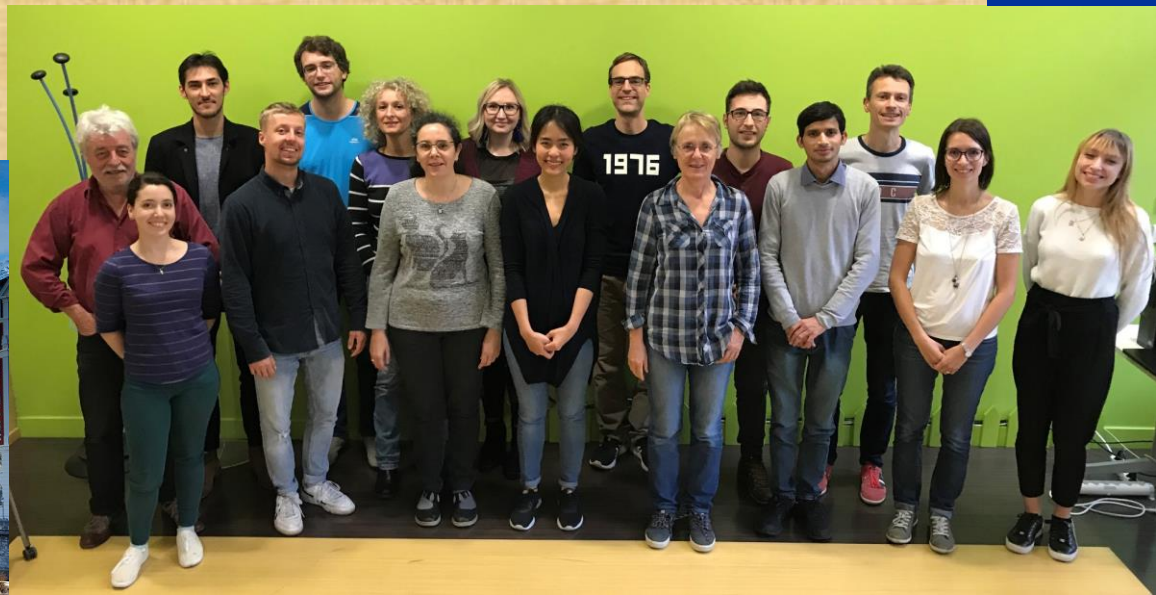
CERMAV, CNRS, Grenoble, France

Marie Sklodowska-Curie

Individual Fellowship

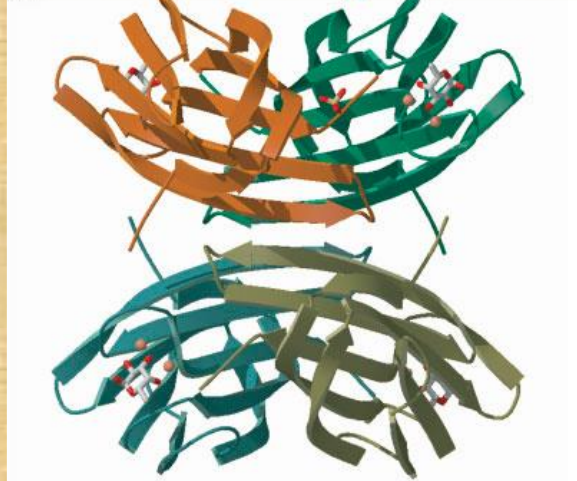
“CaLecLig”

2018-2020

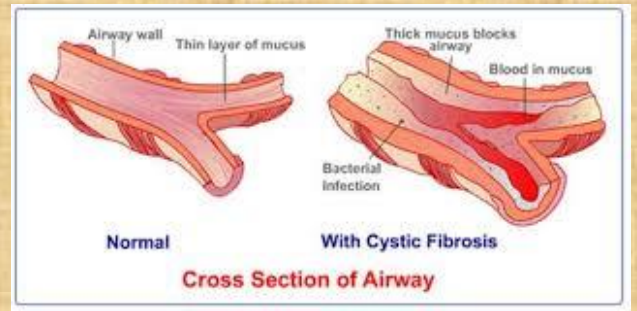


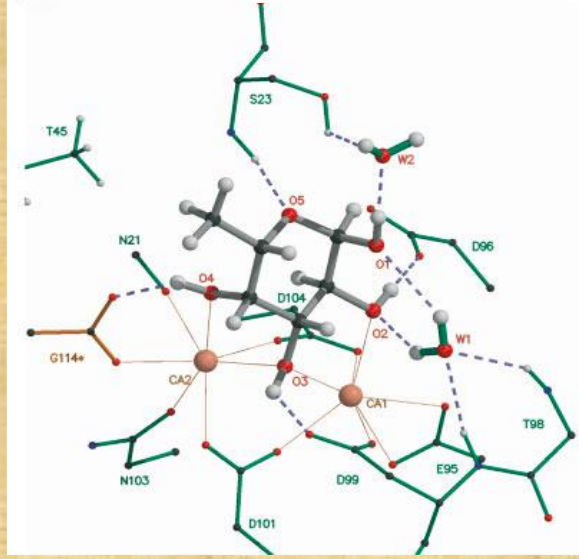
Bacterial Infection: Virulence Lectins

- Biofilm, virulence factors
- LecA, LecB lectins
- tetramers
- Ca^{2+} in binding site
- Bind human oligosaccharides



- *Pseudomonas aeruginosa*
- cystic fibrosis





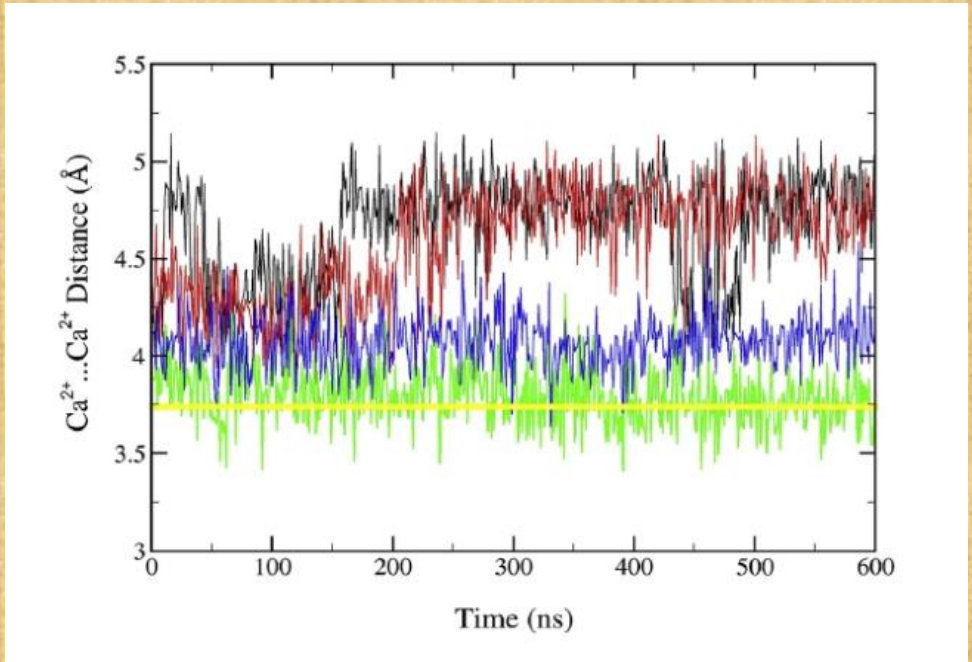
E. Mitchell, et al., *Nat. Struct. Biol.,* 2002, 9, 918

Electronic Continuum Correction for MD

- classical fixed-charge non-polarizable force fields miss electronic polarization, screening of charges

- charge scaling by inverse of square-root of water permittivity at high frequency

$$q_r = \frac{q}{\sqrt{\epsilon_r}}$$



(2+ charge Ca^{2+} - black, red; scaled Ca^{2+} parameters – blue, green), crystallographic value (yellow)

B.J. Kirby & P. Jungwirth, *J. Phys. Chem. Lett.*, **10**, (2019), 7531

M. Lepsik, et al., *Eur. J. Med. Chem.*, **177**, (2019), 212