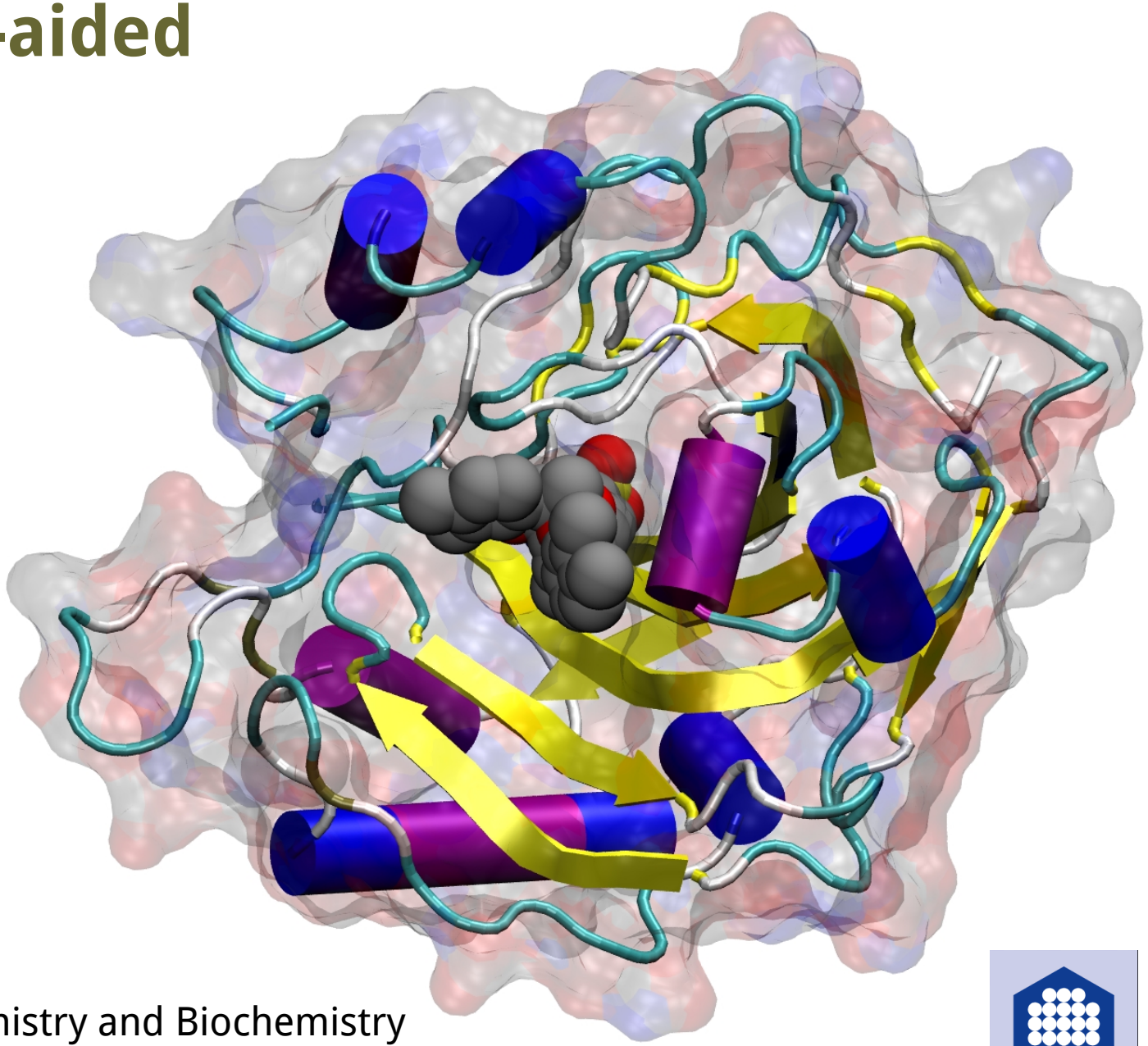
Large-scale quantum-mechanical calculations for computer-aided drug design



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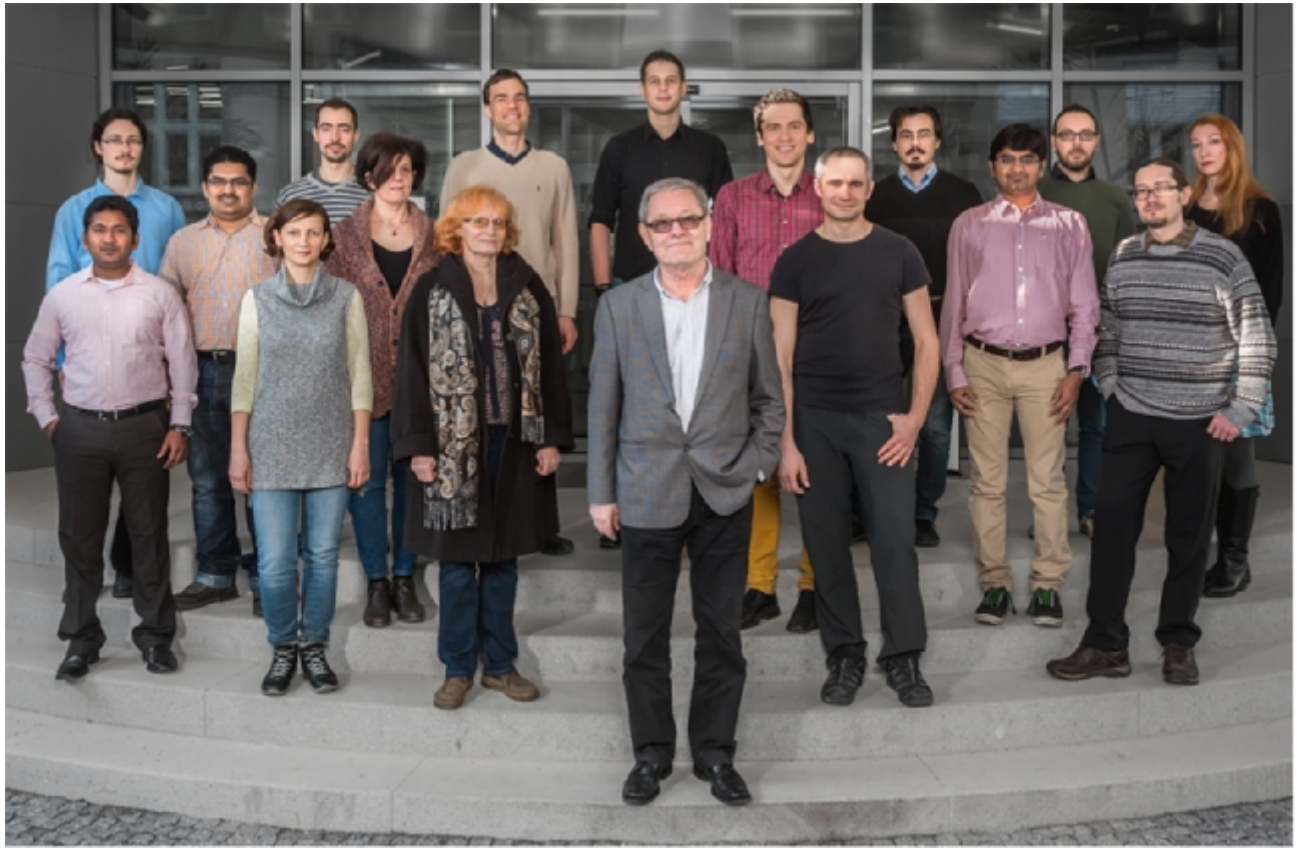

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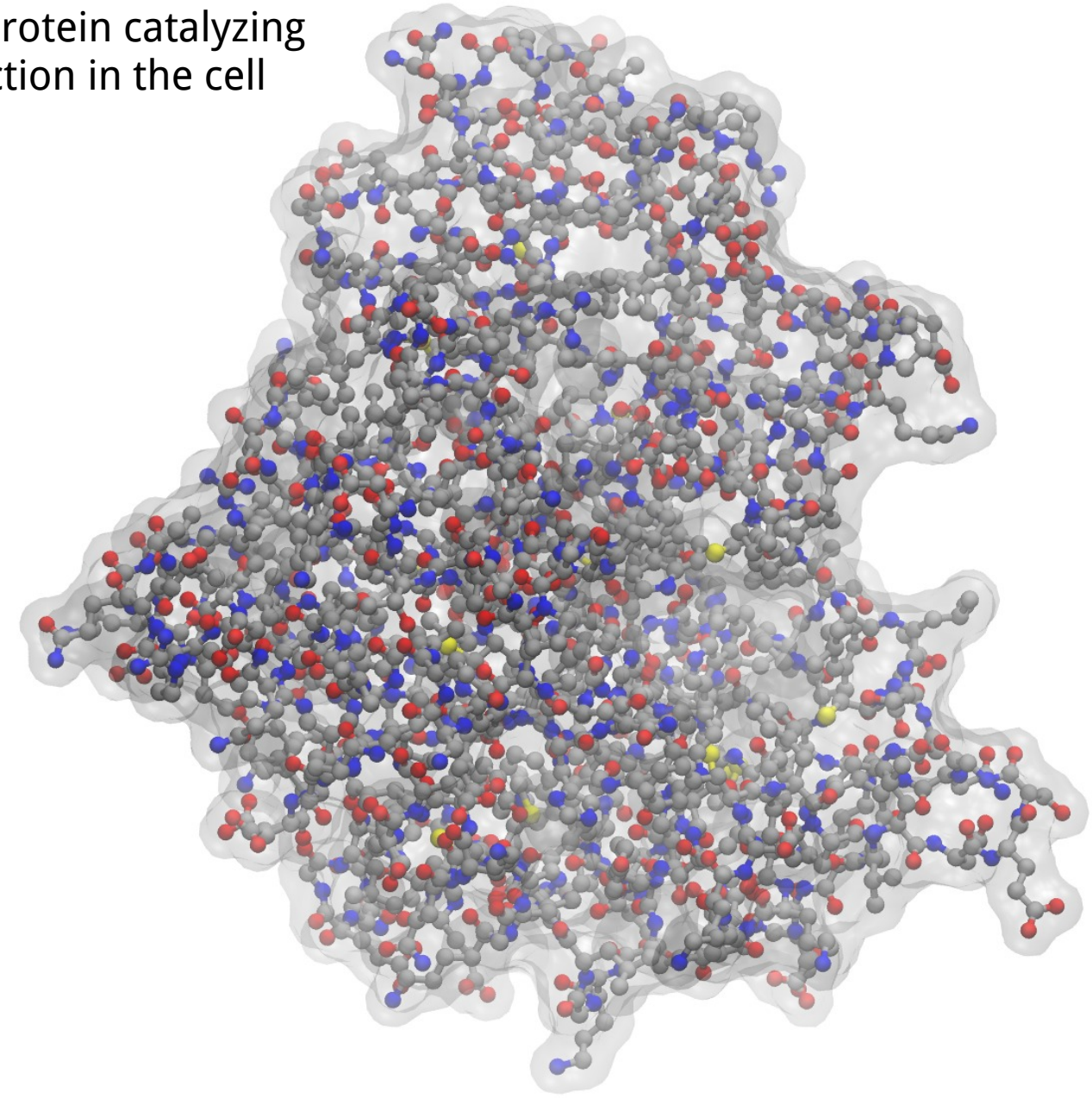
Enzyme inhibition

Enzyme – a protein catalyzing chemical reaction in the cell



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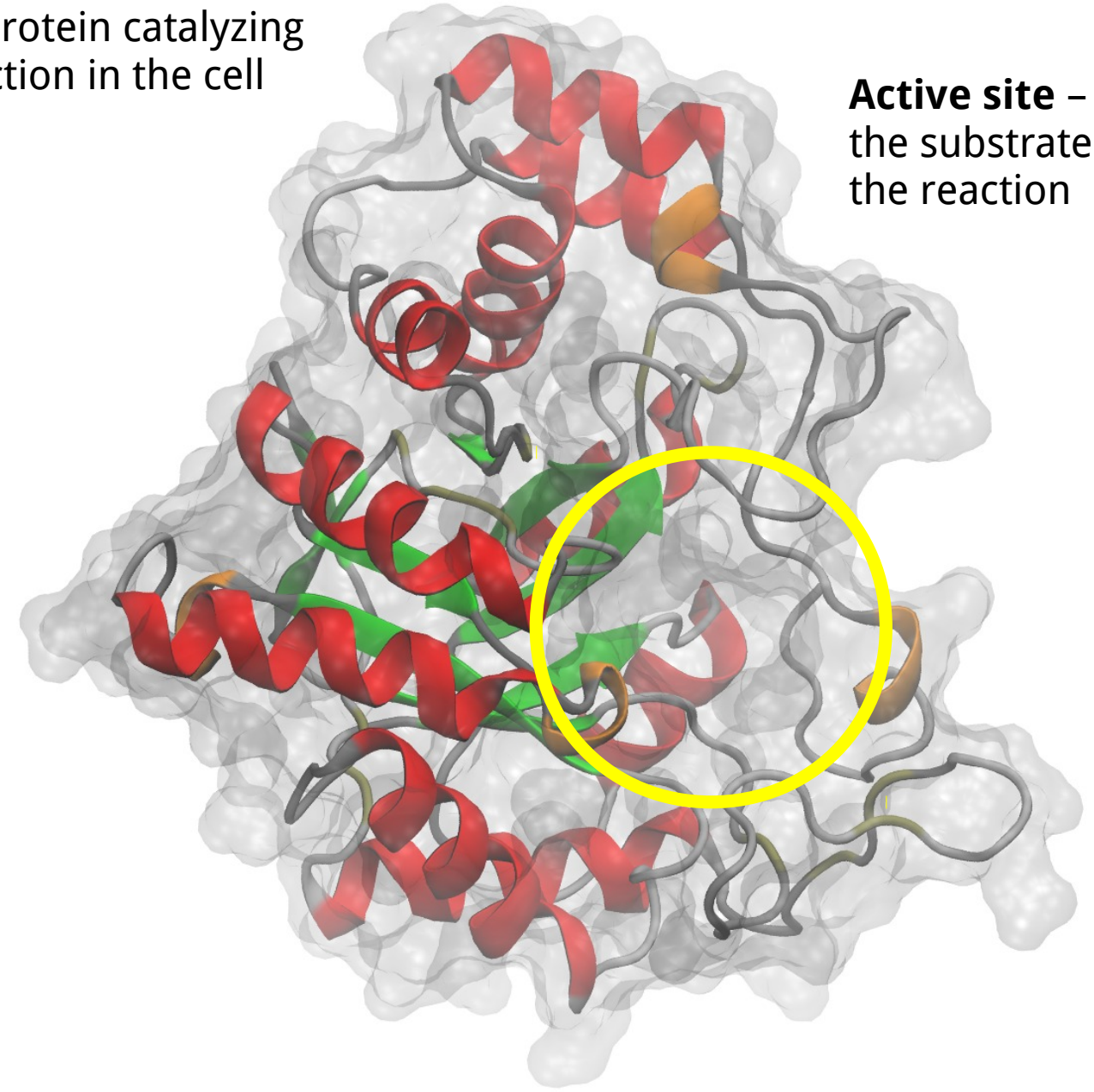

Active site – cavity that binds the substrate and enables the reaction

Enzyme inhibition

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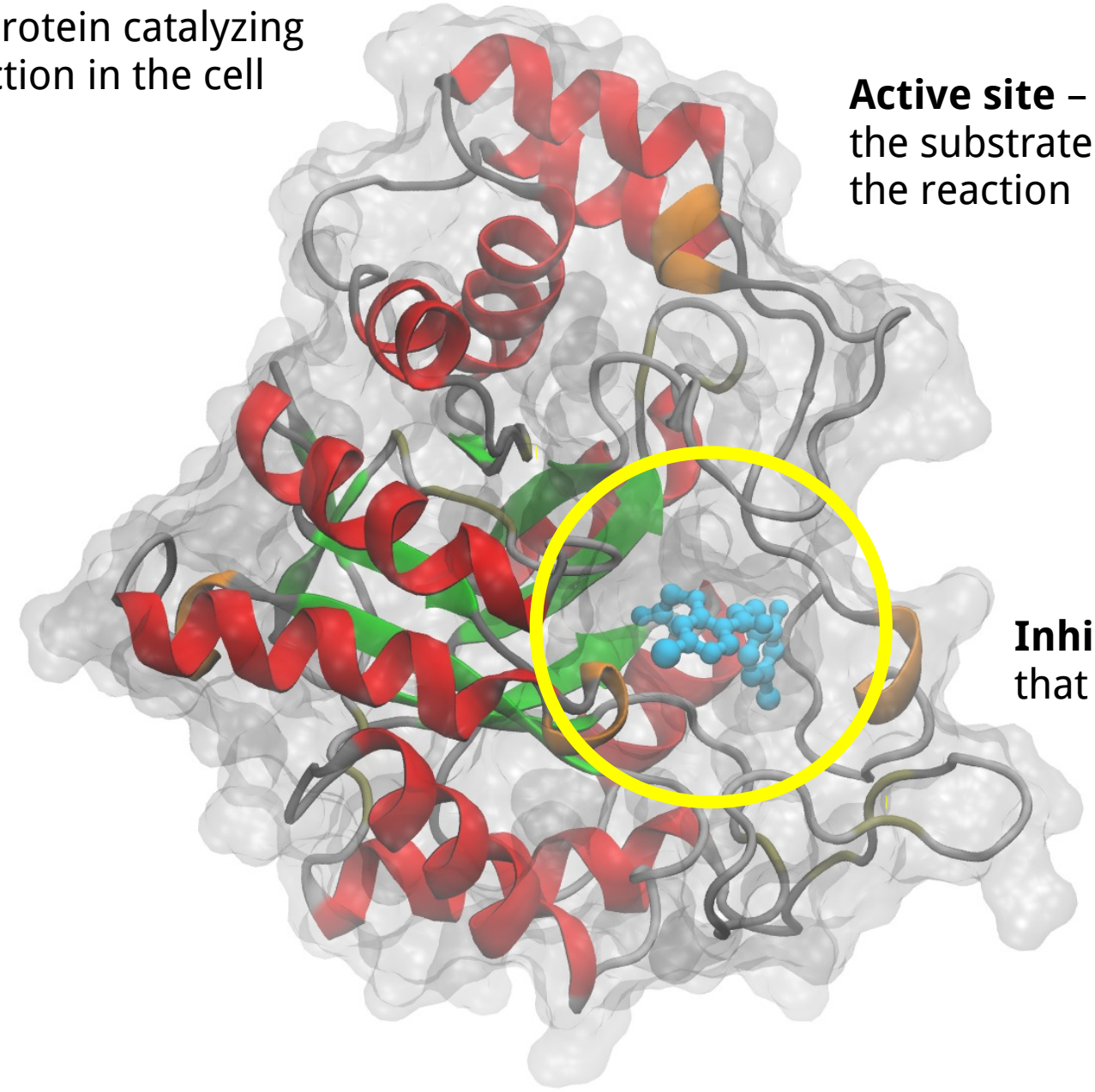

Active site – cavity that binds the substrate and enables the reaction

Inhibitor – molecule that blocks the active site

Rational drug design

- Identify metabolic pathways involved in the disease
- Identify structure and mechanism of a key enzyme
- Design an inhibitor of this enzyme
  - binds stronger than the substrate
  - specific to the target
  - can be delivered into the cell
  - is not toxic

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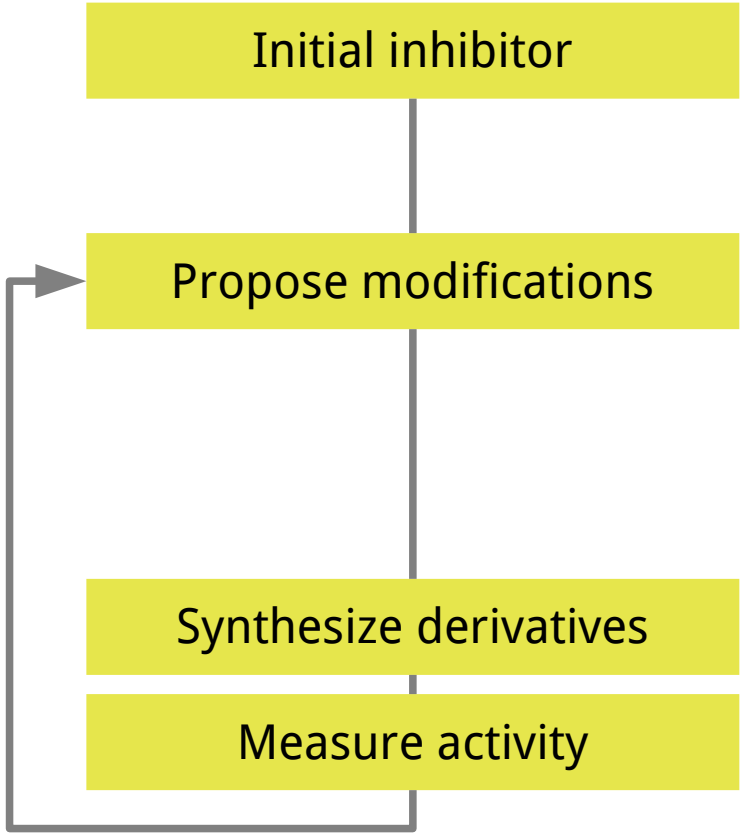

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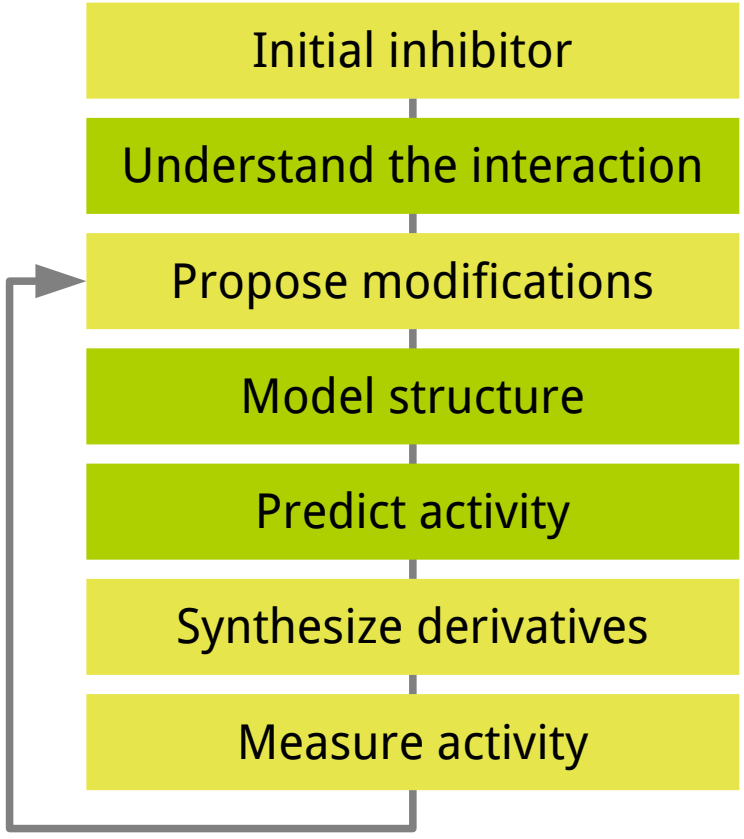
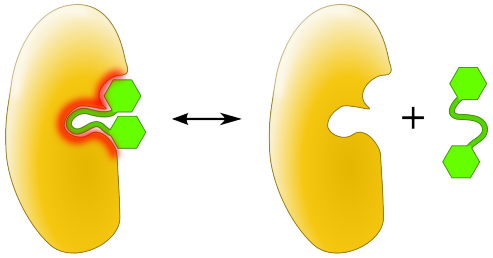
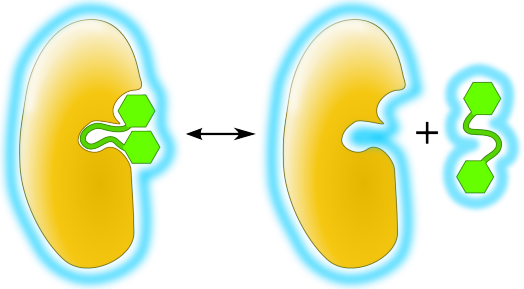


Modeling protein-ligand binding

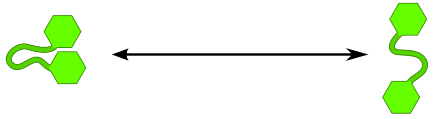
- Protein structure – X-ray data + modeling
- Geometry of the protein-ligand complex – **docking**
- Binding free energy calculation – **scoring**



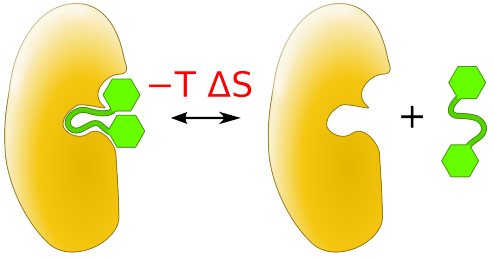
Binding energy



Solvation



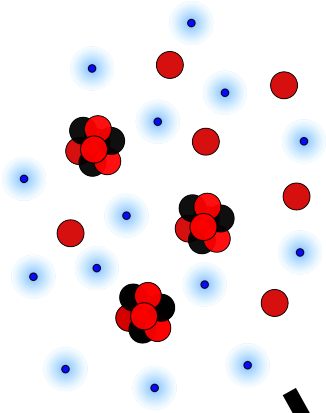
Geometry changes



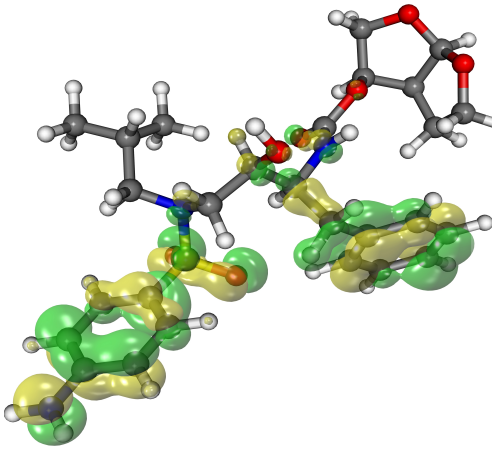
Entropy

Computational approaches

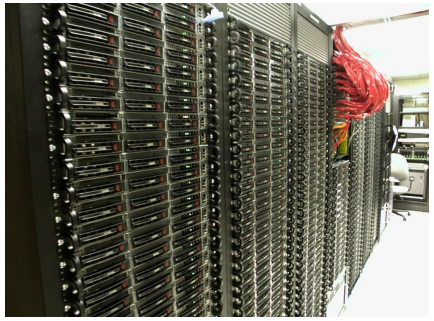
- Statistics-based models
- Molecular mechanics – approximate empirical models
- Quantum-mechanical calculations



$$\hat{H}\Psi = E\Psi$$



$$E = 2\sum_{i=1}^{N} H_{ii} + \sum_{i=1}^{N}\sum_{j=1}^{N}\left(2J_{ij} - K_{ij}\right)$$



theoretical approximations

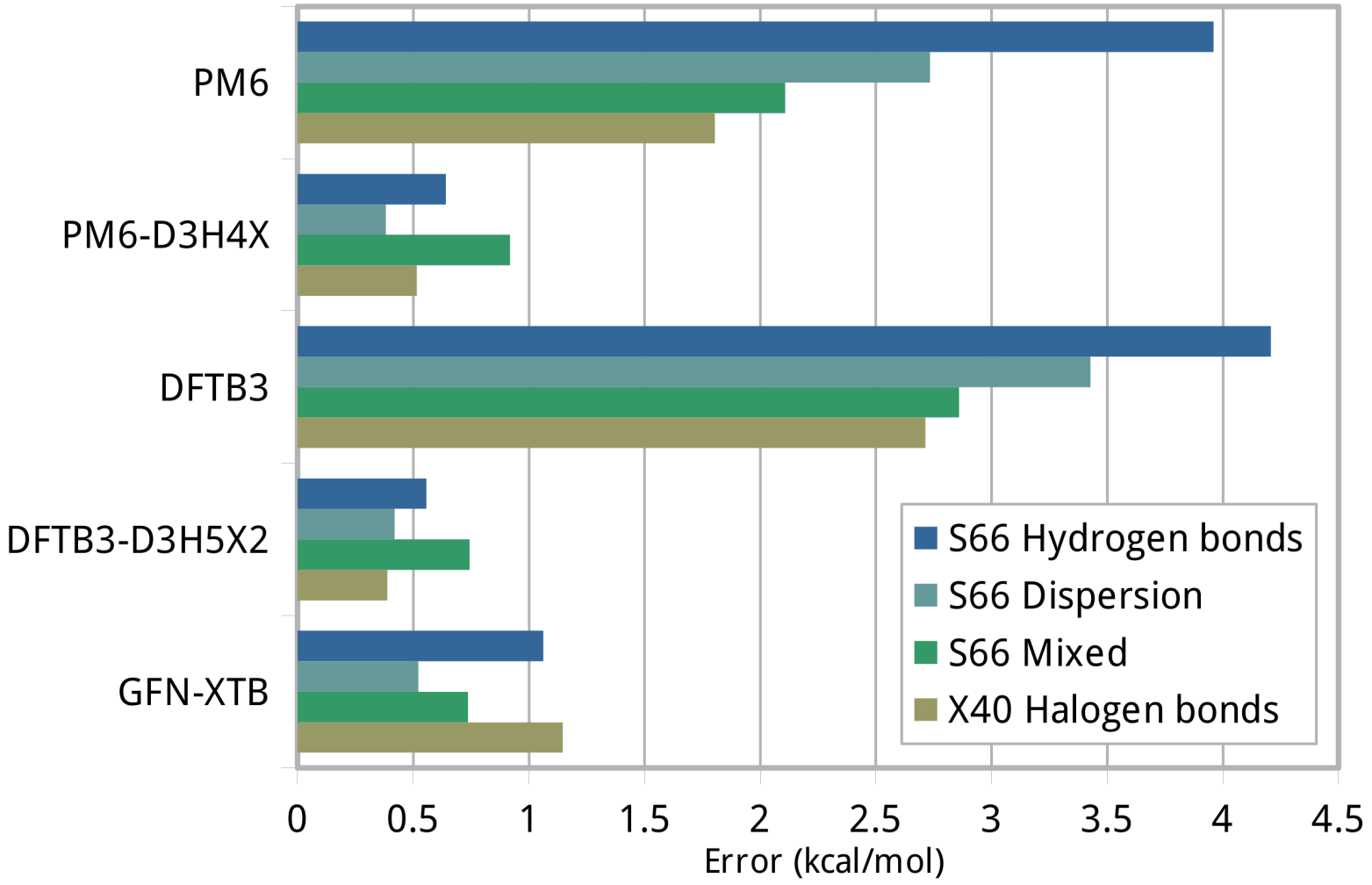
numerical calculations

Semiempirical QM methods

- Full QM to demanding for large-scale applications
- Semiempirical methods
  - Approximations compensated with empirical parameters
  - 1000s of atoms computed in minutes
  - No system-specific parameterization
  - Covers all phenomena using appropriate physics
- Limitations
  - Poor description of non-covalent (intermolecular) interactions

Method development

- Corrections for PM6 and DFTB methods
- Fixing London dispersion, hydrogen and halogen bonds



Our method development

- Corrections for description of non-covalent interactions[1-5]
- Benchmark calculations for their parametrization[6]
- Solvation model improvements

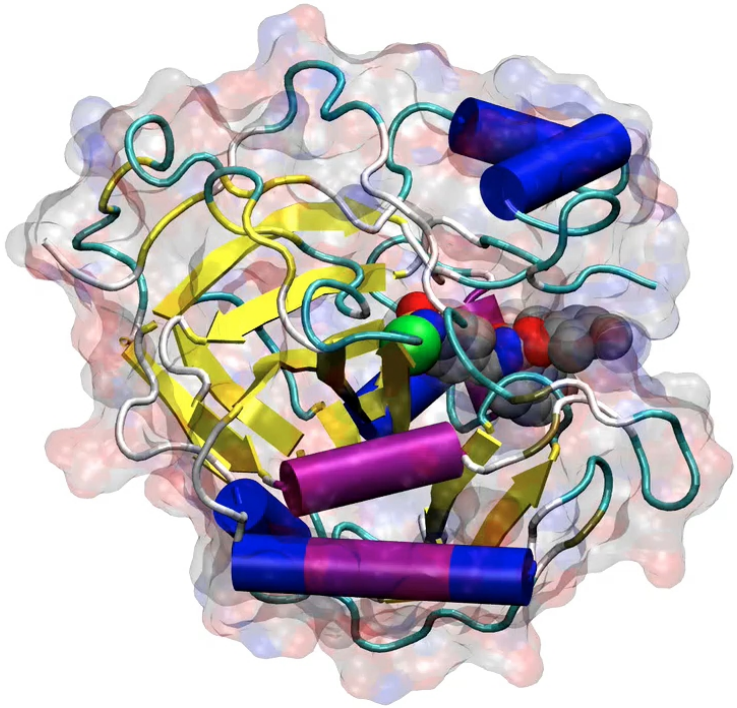
- Computational drug design protocol based on SQM[7]
- Software framework for automating the calculations[8]

1) Řezáč, J.; Fanfrlík, J.; Salahub, D.; Hobza, P. J. Chem. Theory Comput. 2009, 5 (7), 1749–1760.
2) Korth, M.; Pitoňák, M.; Řezáč, J.; Hobza, P. J. Chem. Theory Comput. 2010, 6 (1), 344–352.
3) Řezáč, J.; Hobza, P. Chem. Phys. Lett. 2011, 506 (4-6), 286–289.
4) Řezáč, J.; Hobza, P. J. Chem. Theory Comput. 2012, 8 (1), 141–151.
5) Hostaš, J.; Řezáč, J.; Hobza, P. Chem. Phys. Lett. 2013, 568–569, 161–166.
6) Řezáč, J.; Hobza, P. Chem. Rev. 2016, 116 (9), 5038–5071.
7) Lepšík, M.; Řezáč, J.; Kolář, M.; Pecina, A.; Hobza, P.; Fanfrlík, J. ChemPlusChem 2013, 78 (9), 921–931.
8) http://cuby4.molecular.cz

Virtual screening capabilities

- Docking
  - large databases of compunds
  - **10^6 structures** generated
- Fast filtering – SQM scoring on fixed geometry
  - from 5 minutes
  - **100 000 calculations** / project
- Full scoring – including SQM optimization
  - few days
  - **1000 calculations** / project

Carbonic anhydrase II



- Perfect model with accurate experimental data for 10 inhibitors[1]
- Zinc metaloprotein

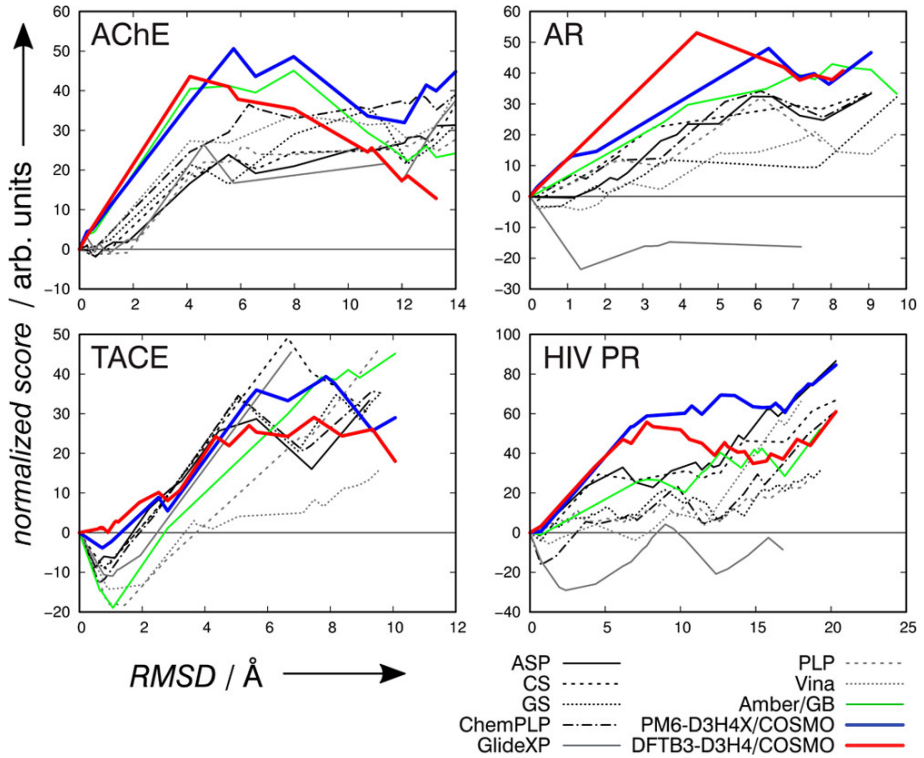
- New solvation model COSMO2[2]

Crystal waters	YES		NO	
	R^2	PI	R^2	PI
SQM/COSMO	0.58	0.87	0.45	0.73
SQM/COSMO2	0.68	0.91	0.69	0.75
AMBER/GB	0.09	0.45	0.13	0.3
Vina	0.39	0.67	0.07	0.2
DOCK 6	0.38	0.5	0.1	-0.22
Autodock 4	0.19	0.53	0.09	0.06
Gold ASP	0.15	0.47	0.12	0.35
GoldPLP	0.12	0.39	0.13	0.39
GoldScore	0.01	0.15	0.01	-0.1
Chemscore	0.01	0.08	0.01	-0.1

1) Pecina A., Řezáč, J. et al. ChemPhysChem 2018.
2) Kříž K., Řezáč J.; submitted manuscript

Identification of Native Protein–Ligand Poses

- Can SQM identify native geometry of P-L complex?
- large set of structures from docking
- Native pose should be energy minimum
- SQM tested against multiple scoring functions used in the field



1) Pecina, A.; Haldar, S.; Fanfrlík, J.; Meier, R.; Řezáč, J.; Lepšík, M.; Hobza, P. J. Chem. Inf. Model. 2017.

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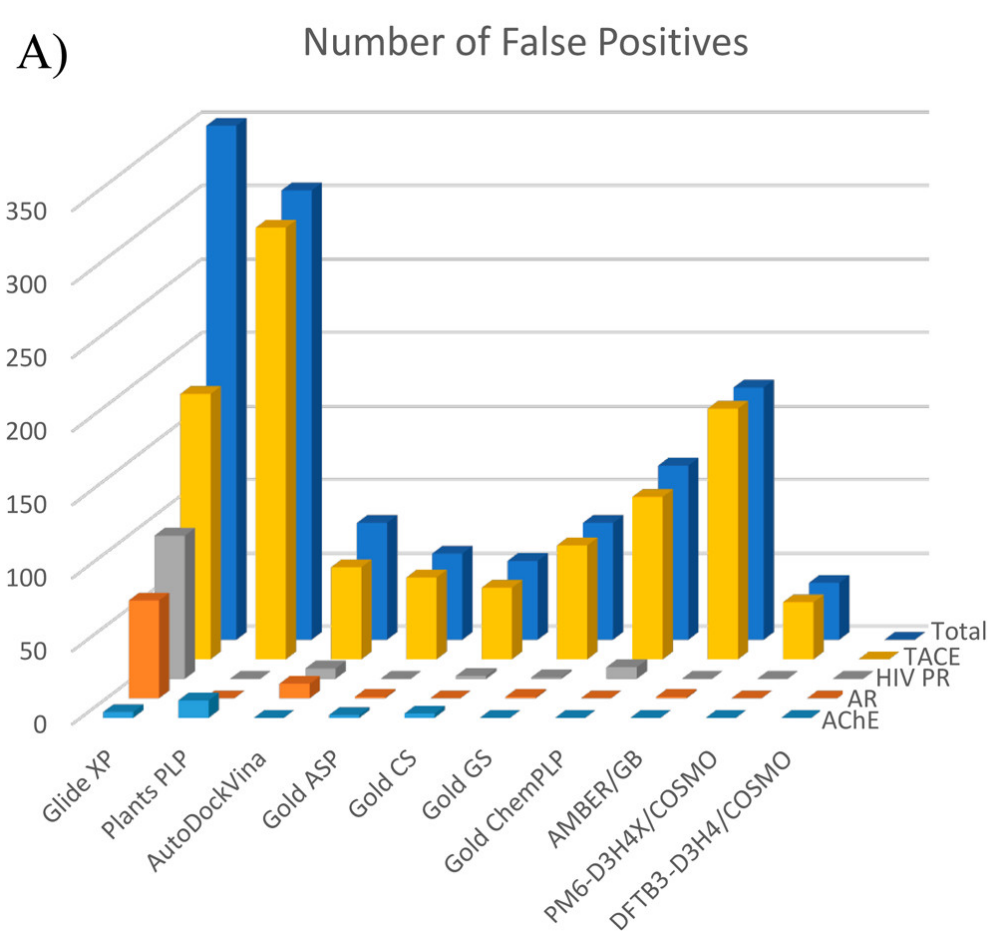

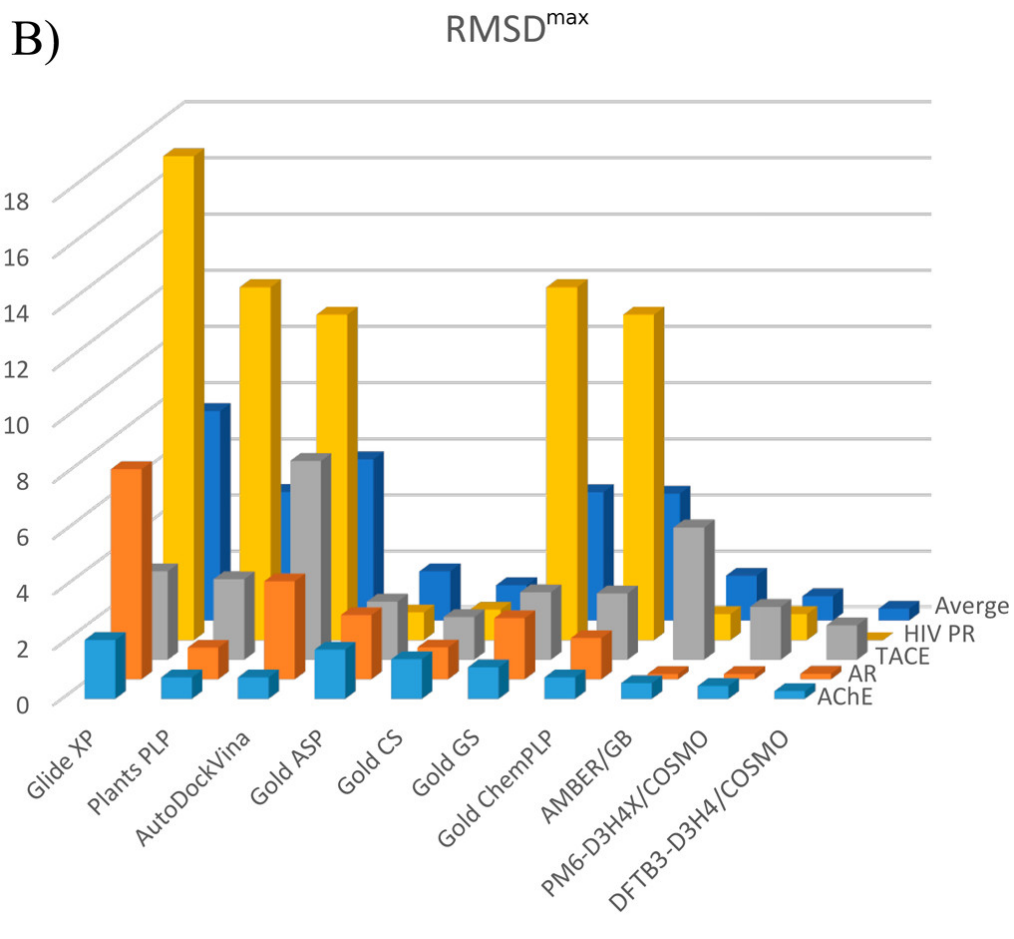

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Conclusions

- SQM method perform significantly better than standard scoring functions and molecular mechanics
- The computational cost is well justified
- Synergy between method development and applications

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