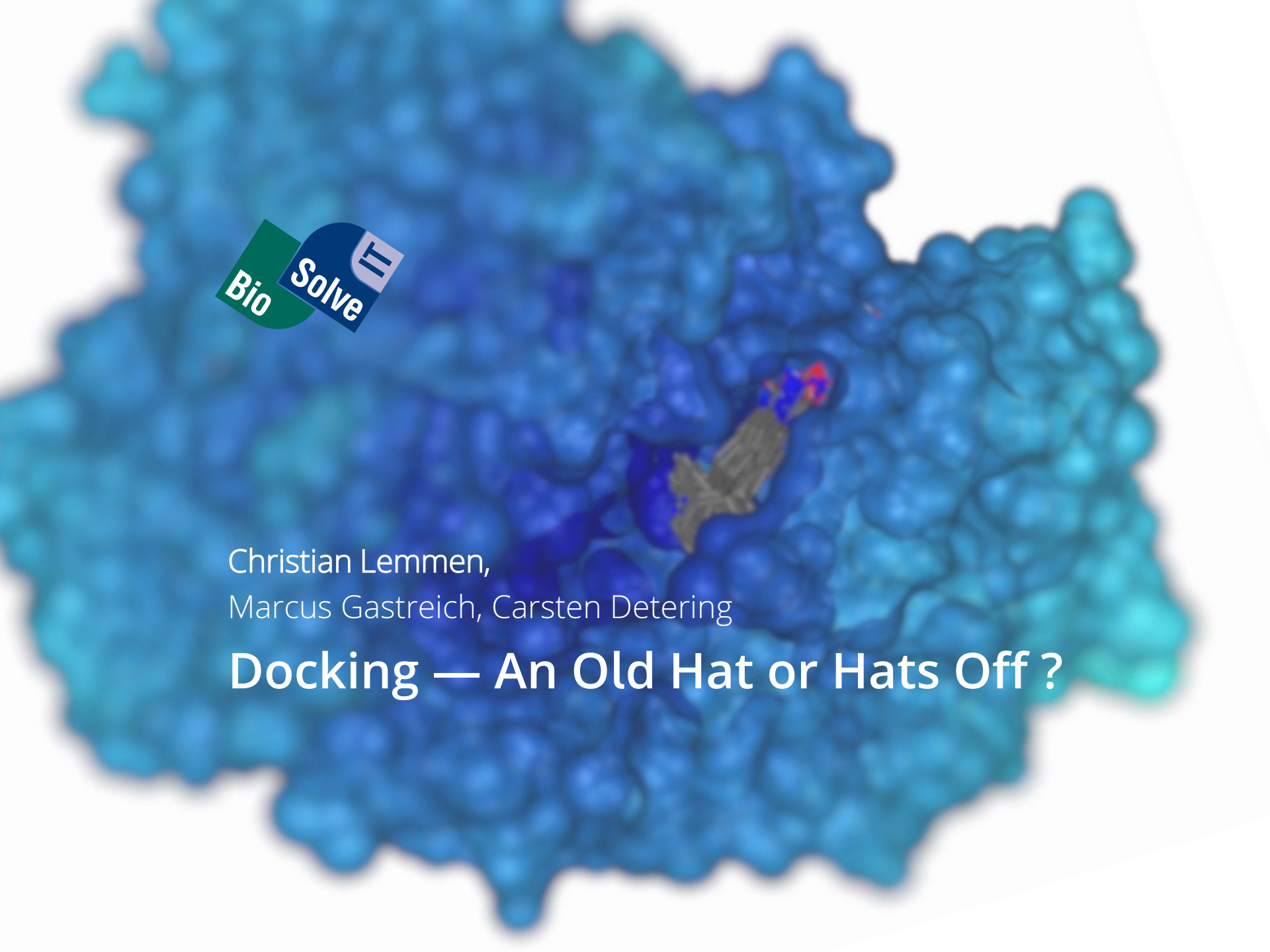


Christian Lemmen,
Marcus Gastreich, Carsten Detering

Docking — An Old Hat or Hats Off ?

“A grand challenge for all of us is how to best incorporate existing knowledge.

Martha S. Head, GSK, in 2009…

What a Traditional Docking Sees…

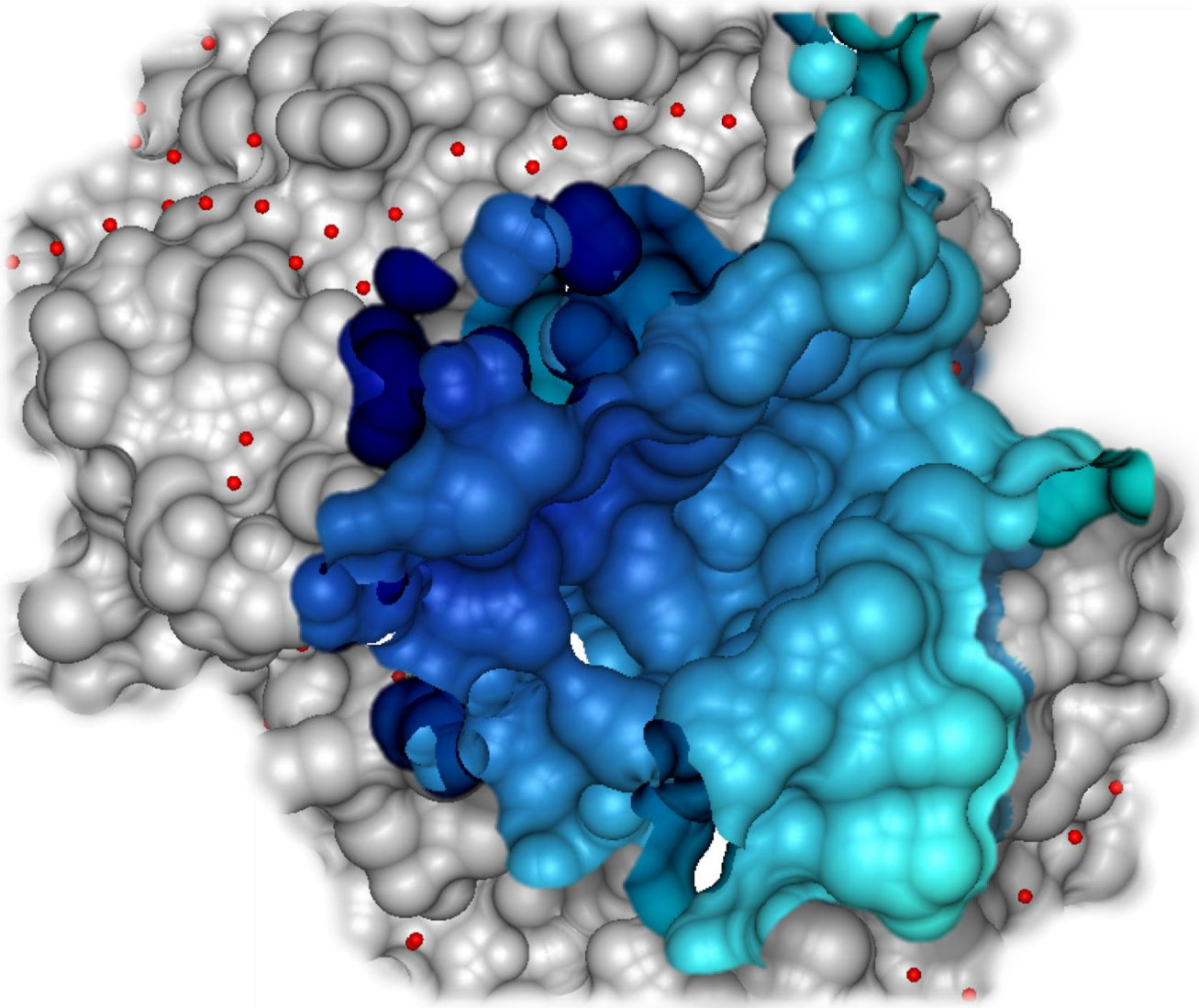


image ©reated with LeadIT

But We Know More…

For example:

- Hot spots, known recepter ph4s…

  => FlexX-Pharm[1] takes care of this

- Metal coordination chemistry

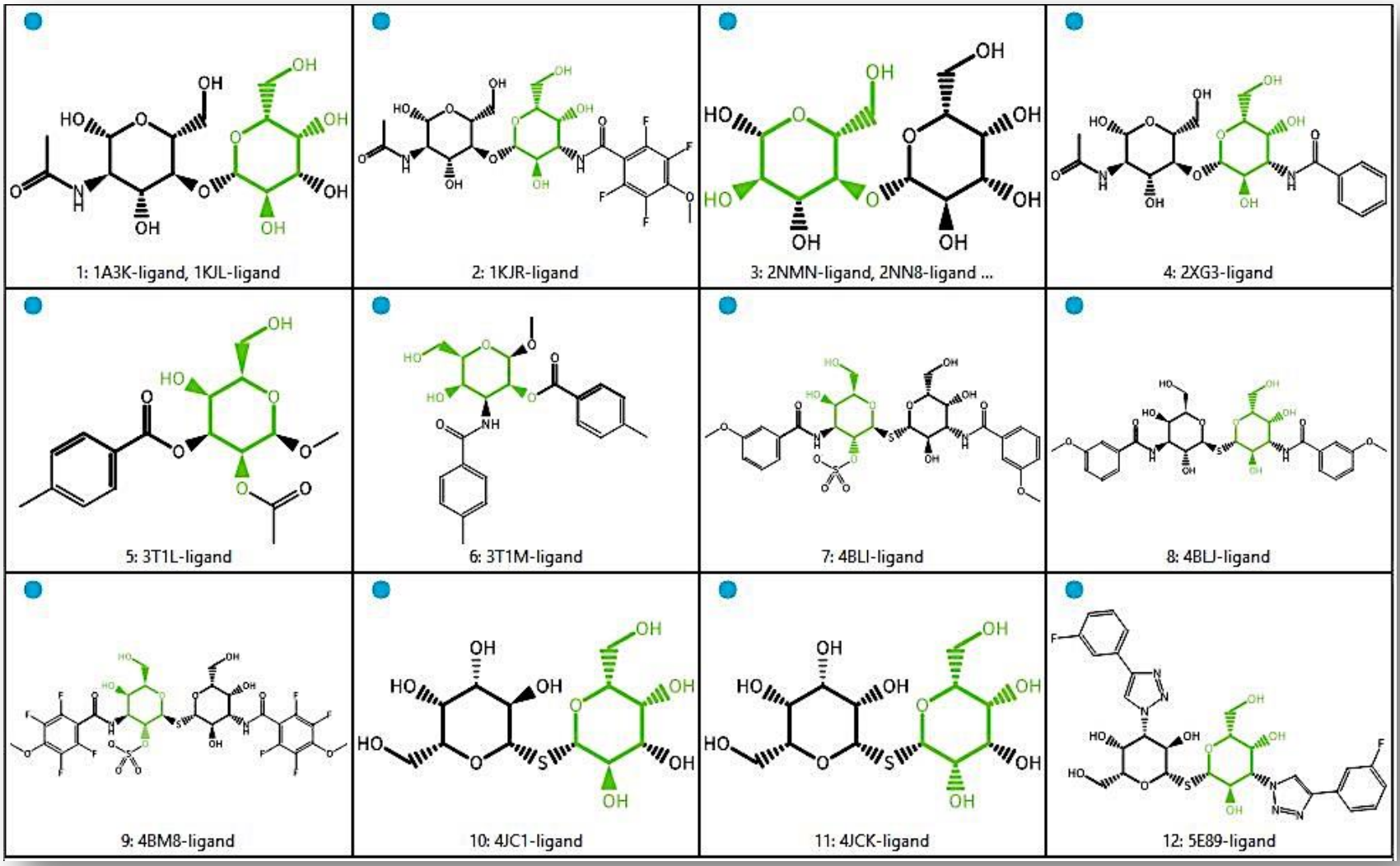
  => *Seebeck algorithm*[2] takes care of this

- Known binders, SAR, preferred motifs, … LIGAND knowledge

=> ??

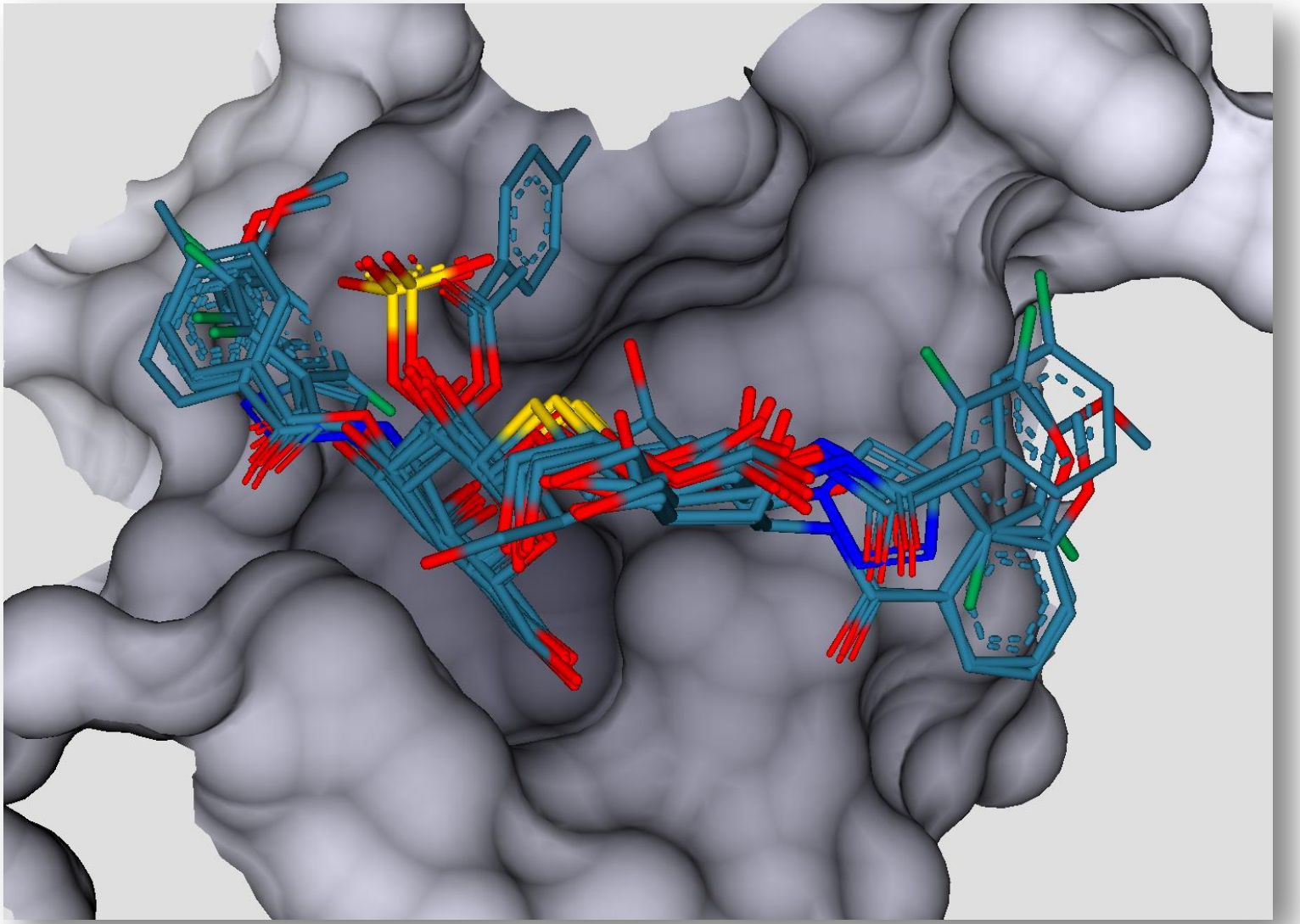
[1] Hindle et al. 2002, JCAMD, 16: 129–149
[2] Seebeck et al. 2008, Proteins **71**:1237–1254.

“Pareto’s 80%”: Compound Series or Focused Libraries

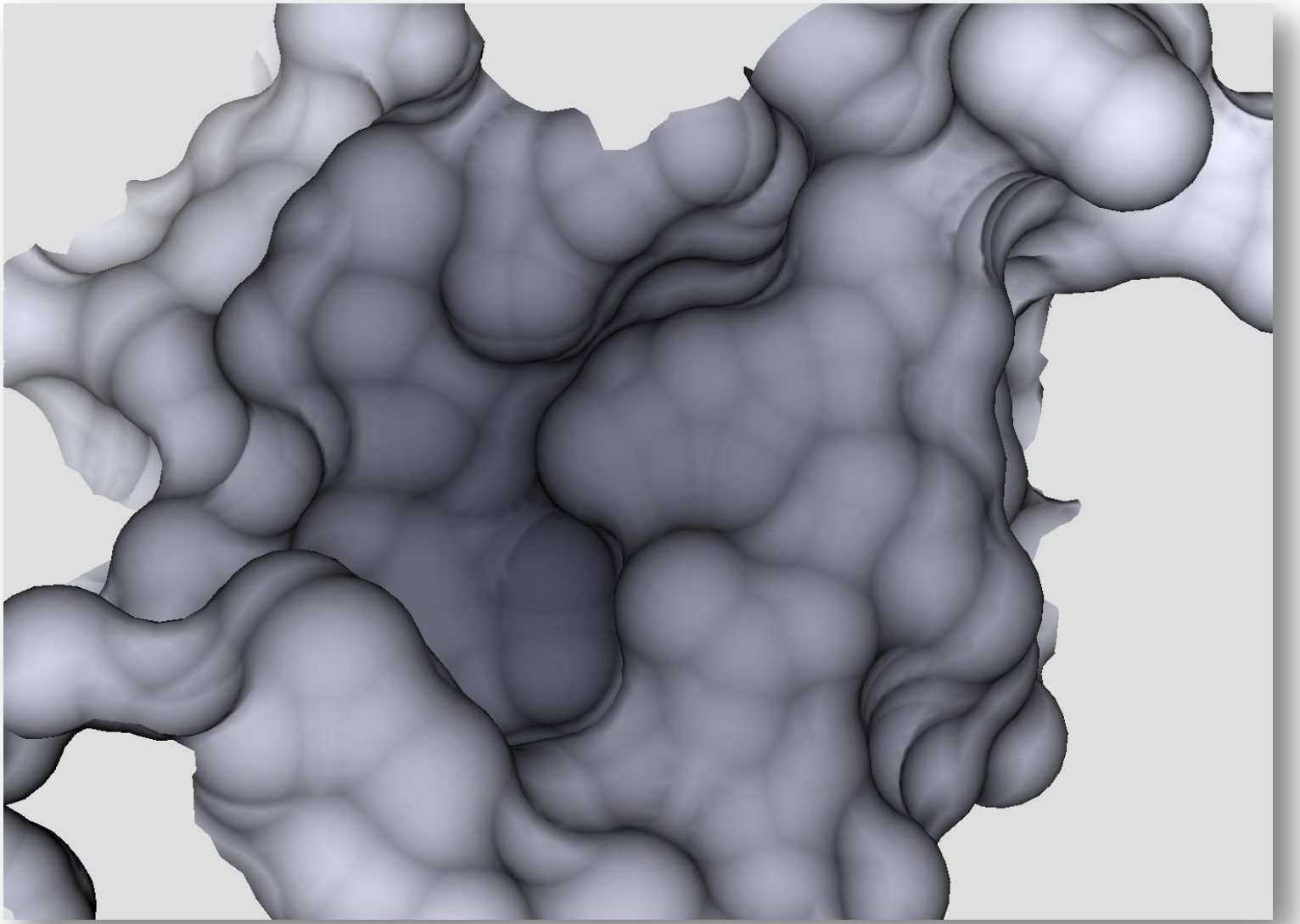


©reated with MONA

So For a Problem Like This…



Instead Of Discarding All Knowledge…



… Let's Use It Cleverly!

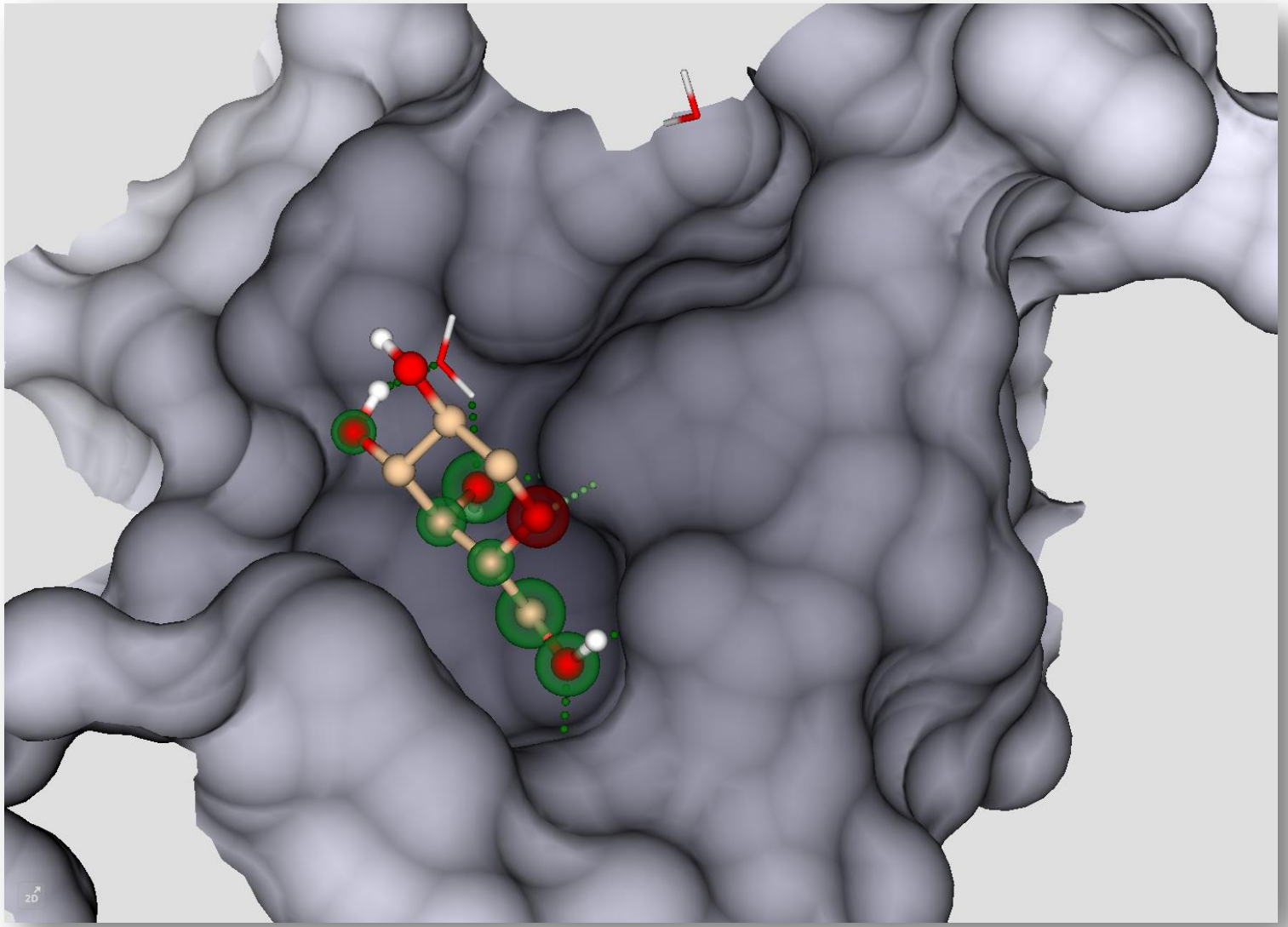
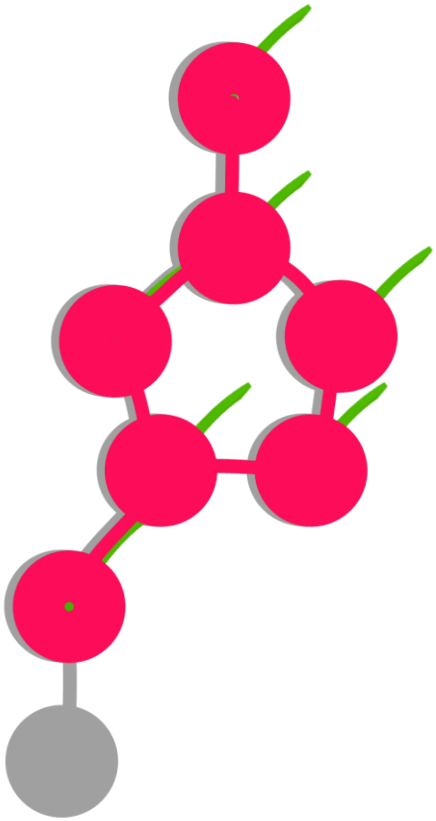
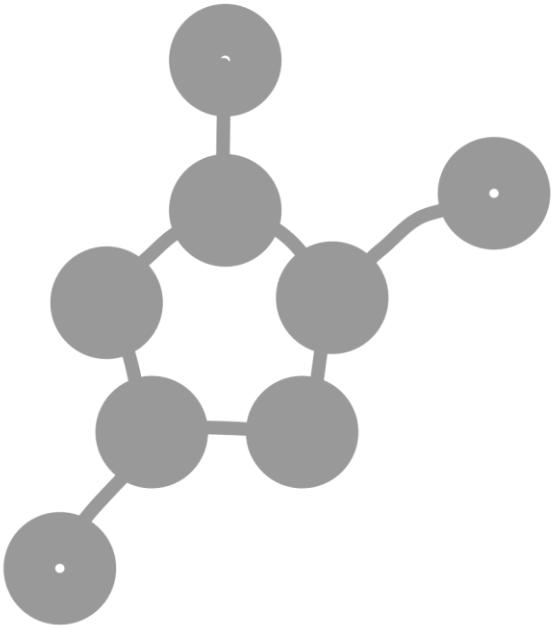


image ©reated with SeeSAR

Exploiting The Common-ness of Scaffolds

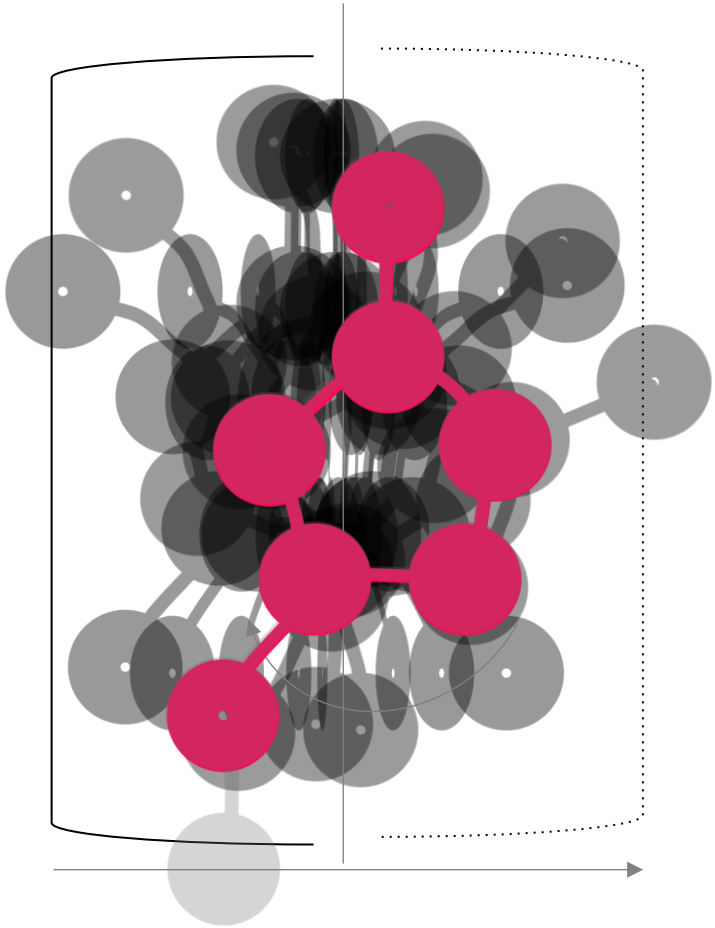


Template



MCS — Maximum Common Substructure

Beware Of Multiple Mappings!



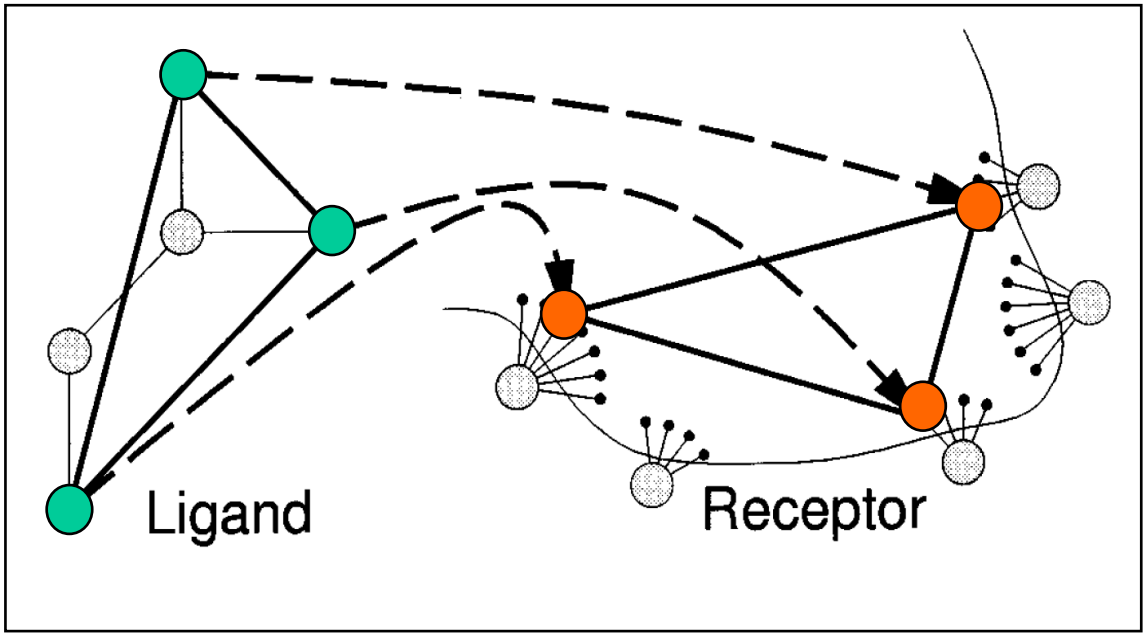
Technically We Do The Following

1. Specify "knowledge" (i.e. a template molecule)
2. Determine MCS including all possible mappings
3. Superpose common fragment considering all conformers
4. Fast incremental build-up

To Be On The Safe Side…

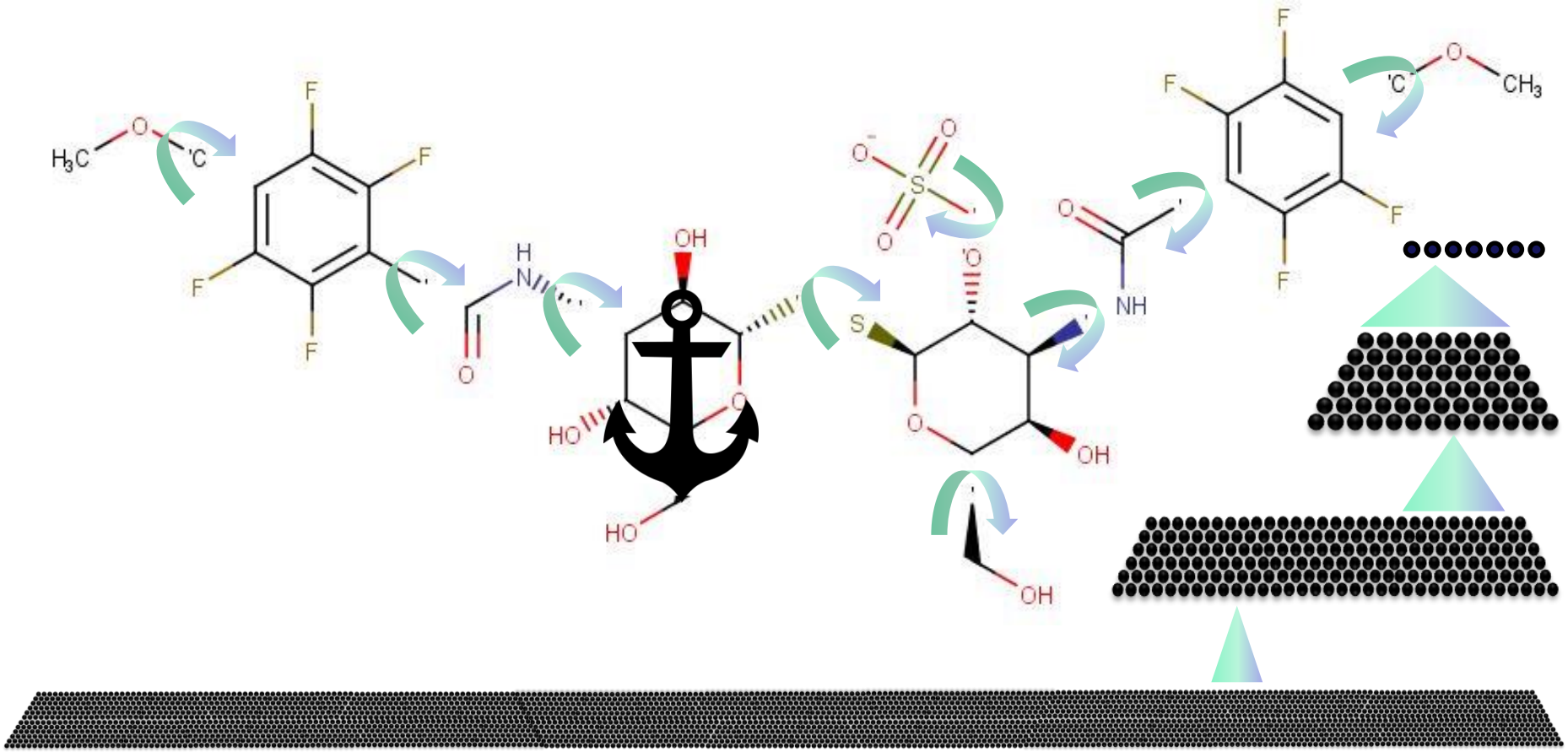
We use the existing docking strategy as a backup:

- Mappings of triangles (traditional FlexX)
- "New" SIS (single interaction scan)



Rarey et al JMB 1996

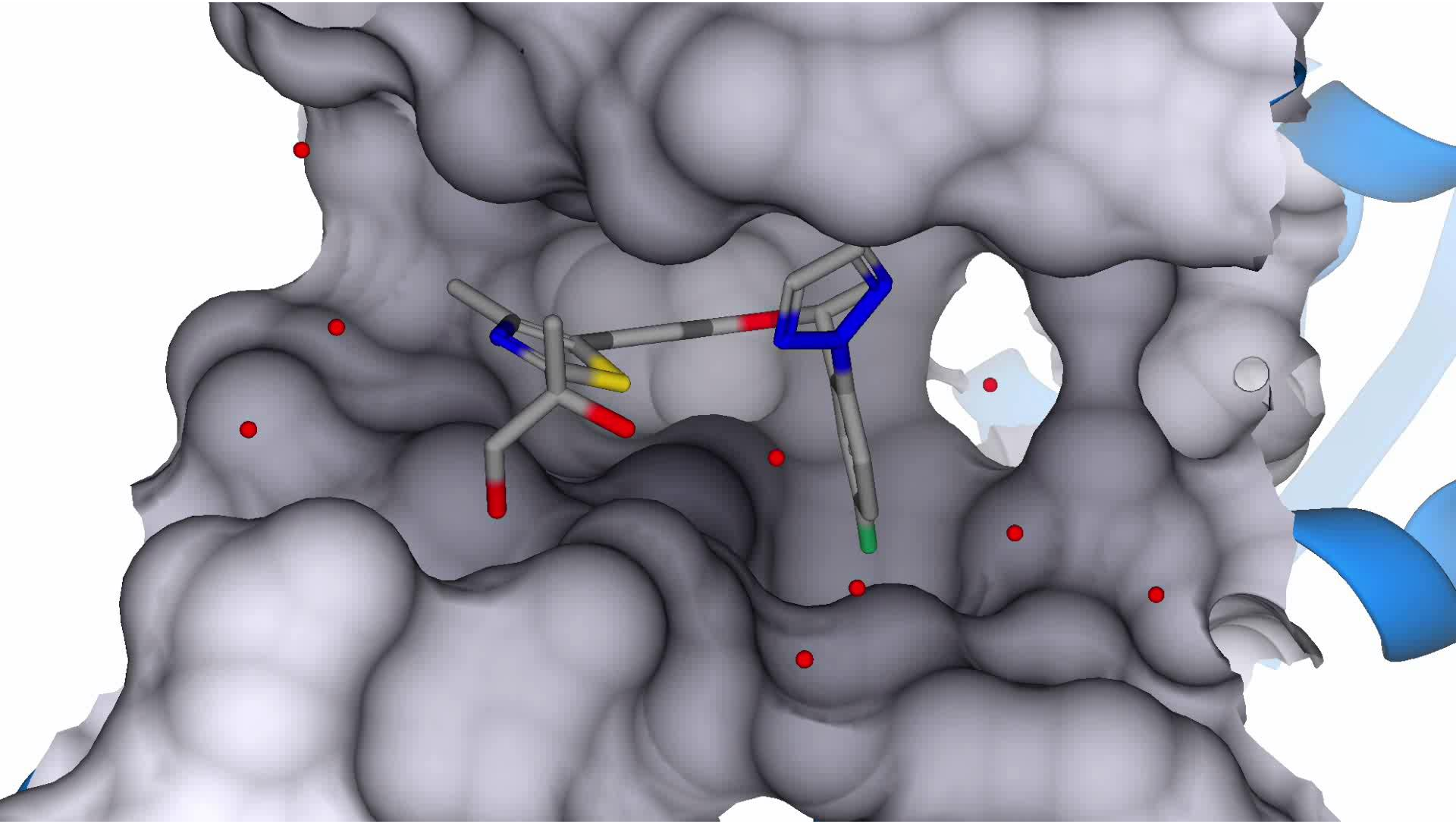
Incremental Build-Up



Considering all possible torsions

12 valid angles => 12^9 = 5.159.780.352 conformations!!

In ALK (4CD0.pdb, Pfizer)



Putting Things Together

- We exploit prior *knowledge*
  => MCS-guided template docking

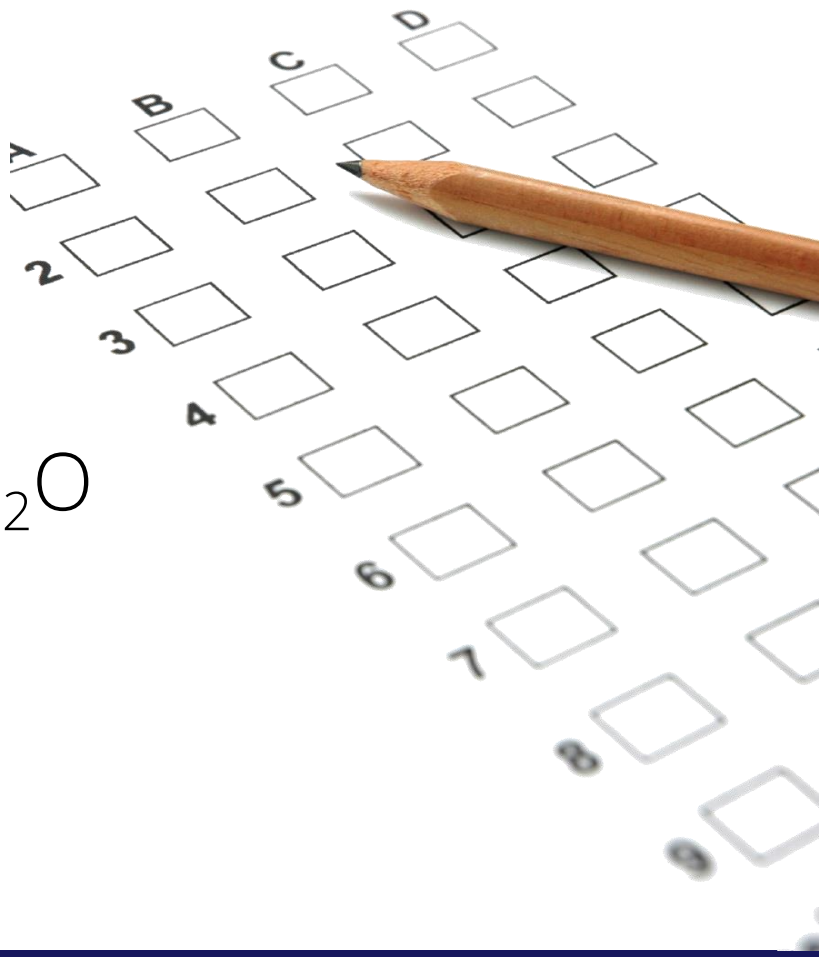
- *Combining* with extended traditional FlexX-posing
  => Best of both worlds

- Trusted *incremental* build-up
  => Quick, fully flexible placement

Remaining "challenges":

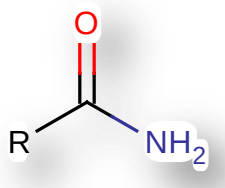
H-bond network refinement, H_2O, and scoring of course

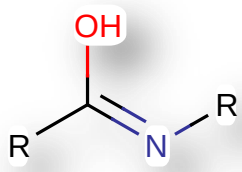
Protonation, Tautomers, H_2O



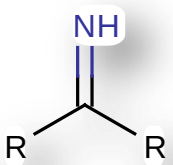
Tautomer/Protonation-Refinement

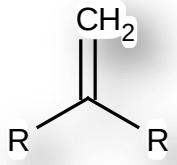
We optimize the assignment (H^+/H_2O) for <u>every</u> pose in ms!



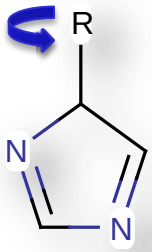


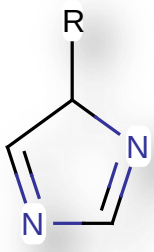
Tautomerism





Element assignments,
esp. Gln & Asn

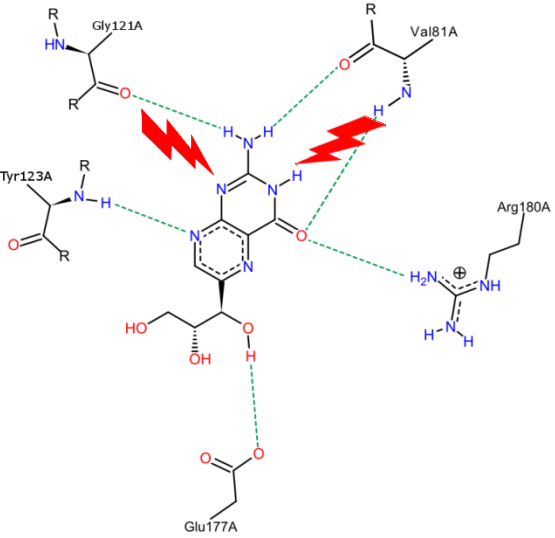




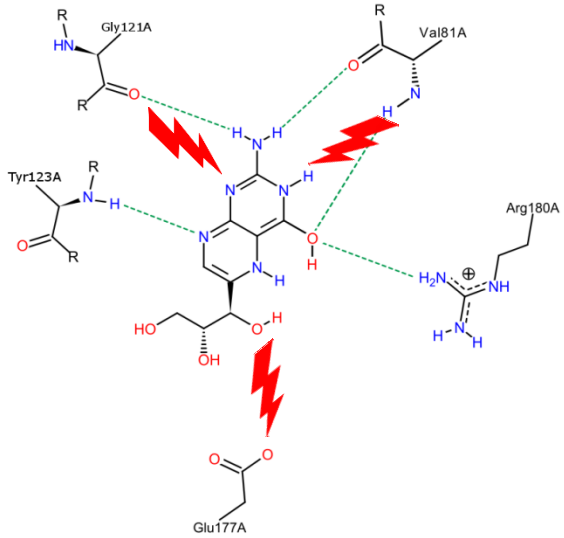
Pseudo-rotation and
protonation, esp. His

ProToss (Proposals in ms); see Bietz et al., 2014, JChemInf **6** 12

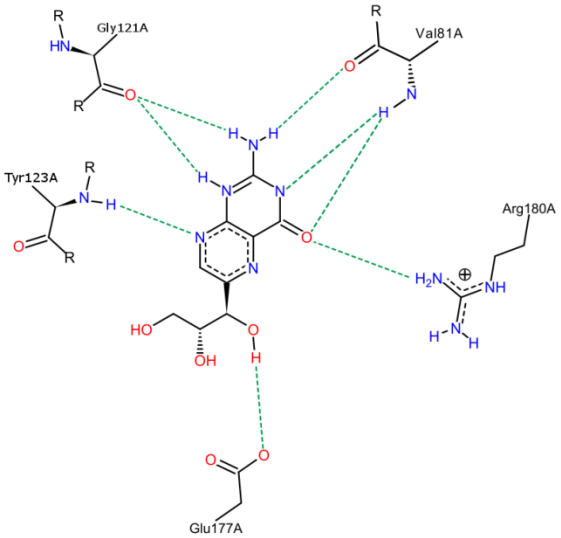
Doing This Right is Not Trivial



Yasara:
Repulsive interactions



Protonate3D:
Missing H-bonds



ProToss:
Perfect network

ProToss optimizes the entire H-bonding network…

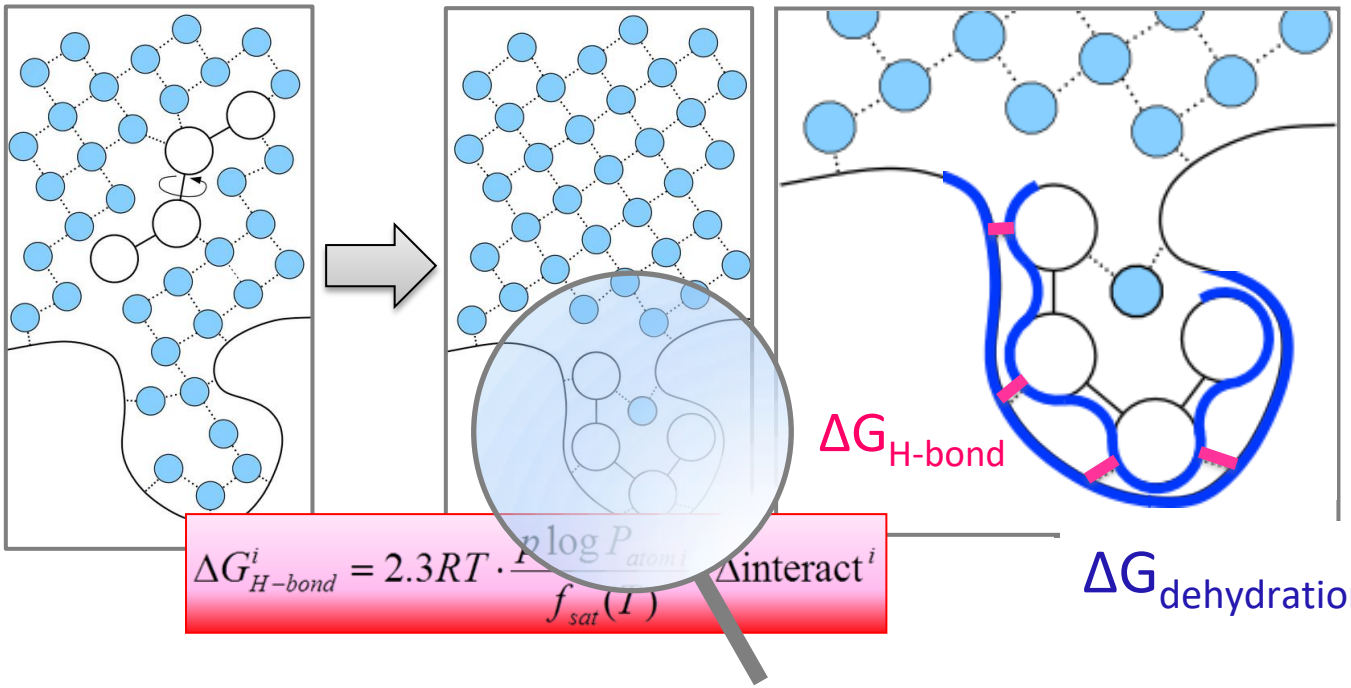
=> correctly most of the time and a in split-second

PDB: 1BR5

Energetics

HYDE: Fast, Visual ΔG

$$\Delta G_{\text{HYDE}} = \sum_{\text{atom } i} \Delta G^{i}_{\text{dehydration}} + \Delta G^{i}_{\text{H-bond}}$$

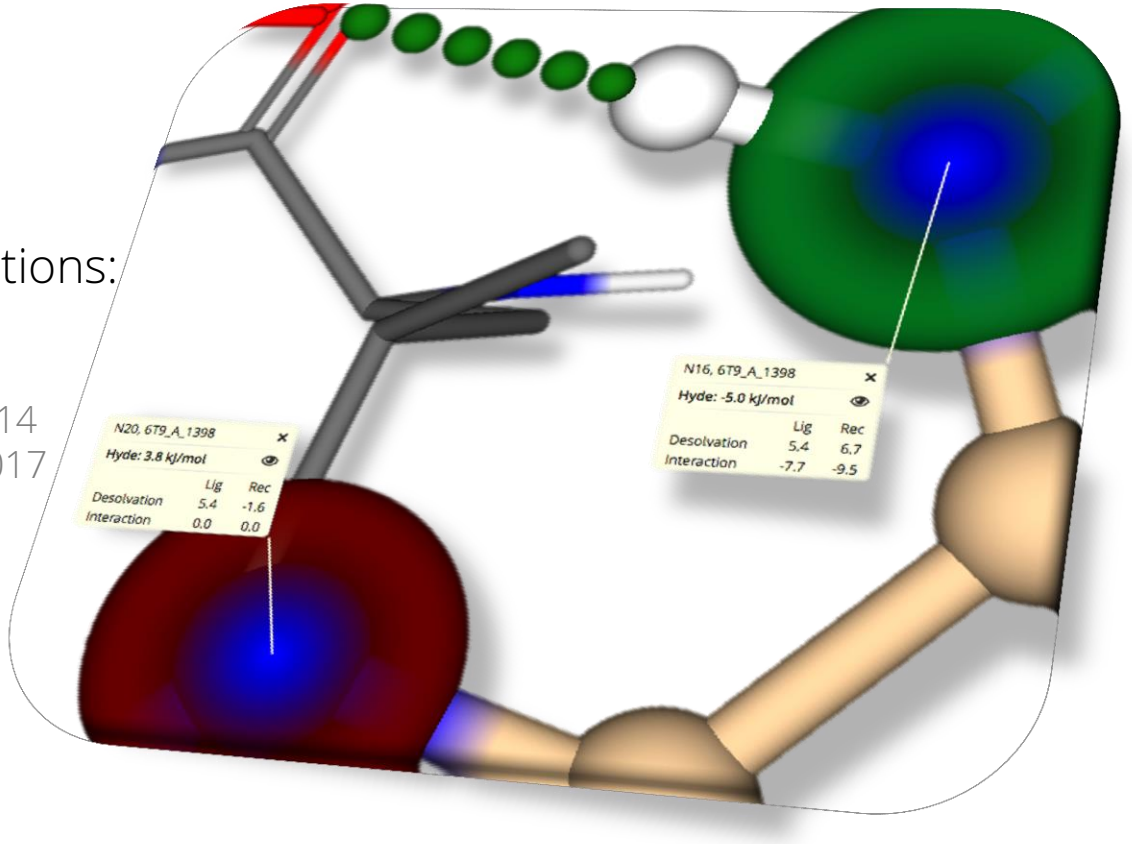


$$\Delta G^{i}_{dehydration} = -2.3RT \cdot p \log P_{atom\,i} \cdot \Delta\text{accessibility}^{i}$$

A BAYER & Univ. Hamburg Collaboration; cp. for ex. Schneider et al. 2013, JCAMD 27(1):15-29.

HYDE: ΔG Approximations in Seconds

- The logP connects dehydration and H-bonds in a natural way
  => No unphysical parameters (only 8 logPs, f_{sat})
- Computation is super fast (~ very few seconds; others need days!)
  => Interactive L.O.
- Atomic increments
  => Visual atomic affinities
- Works! Prospective applications:
  - Mondal et al, Angew. 2014
  - Barho et al., ChemMedChem 2014
  - Tzvetkov et al., EurJMedChem 2017
  - Rodeschini et al, JMC 2017 (submitted)



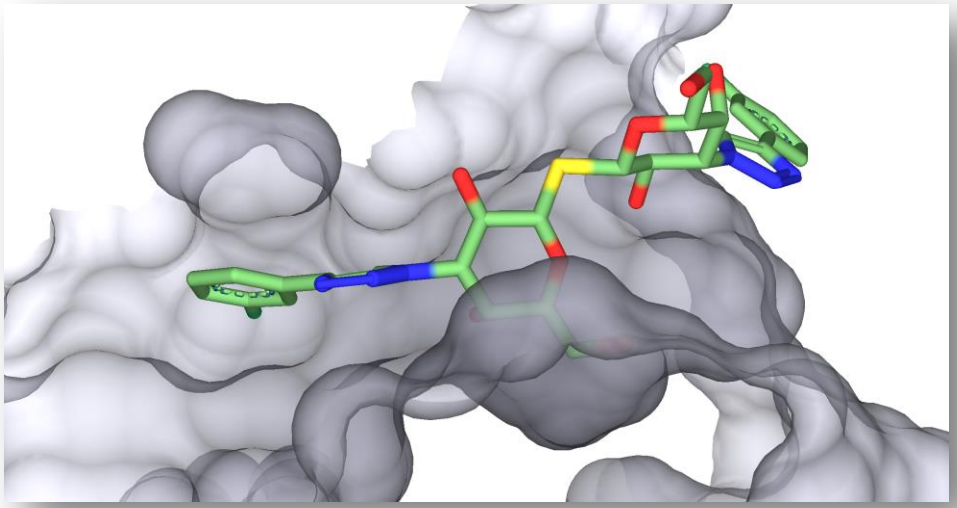
Application Scenarios

Sugar — Tough Stuff for Docking

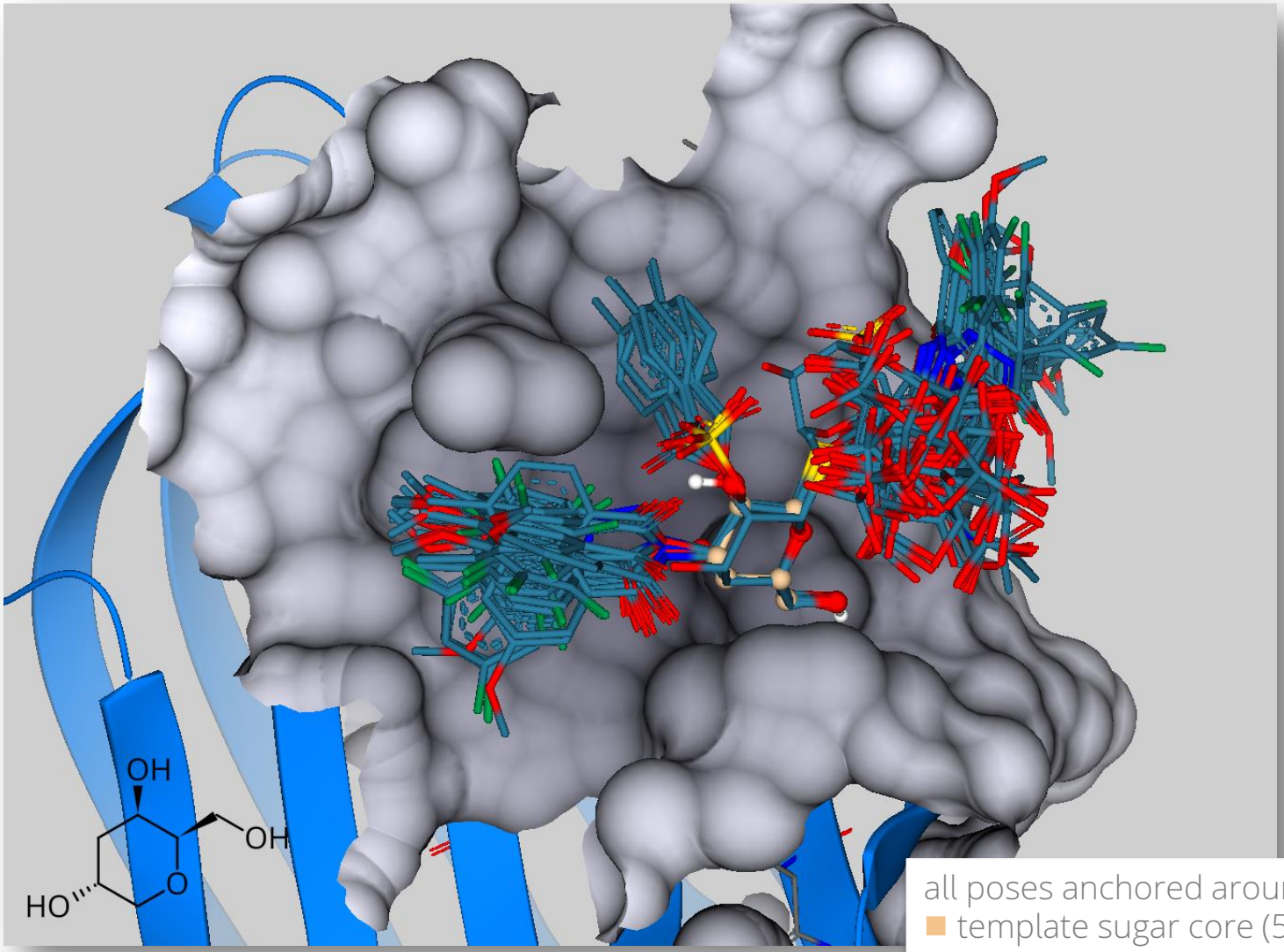
Sugars / glycosylic compounds:

- Exhibit many multifunctional (D/A) hydroxyl groups
- Tend to bind on shallow target surfaces
- Very flexible and (close-to-)symmetric

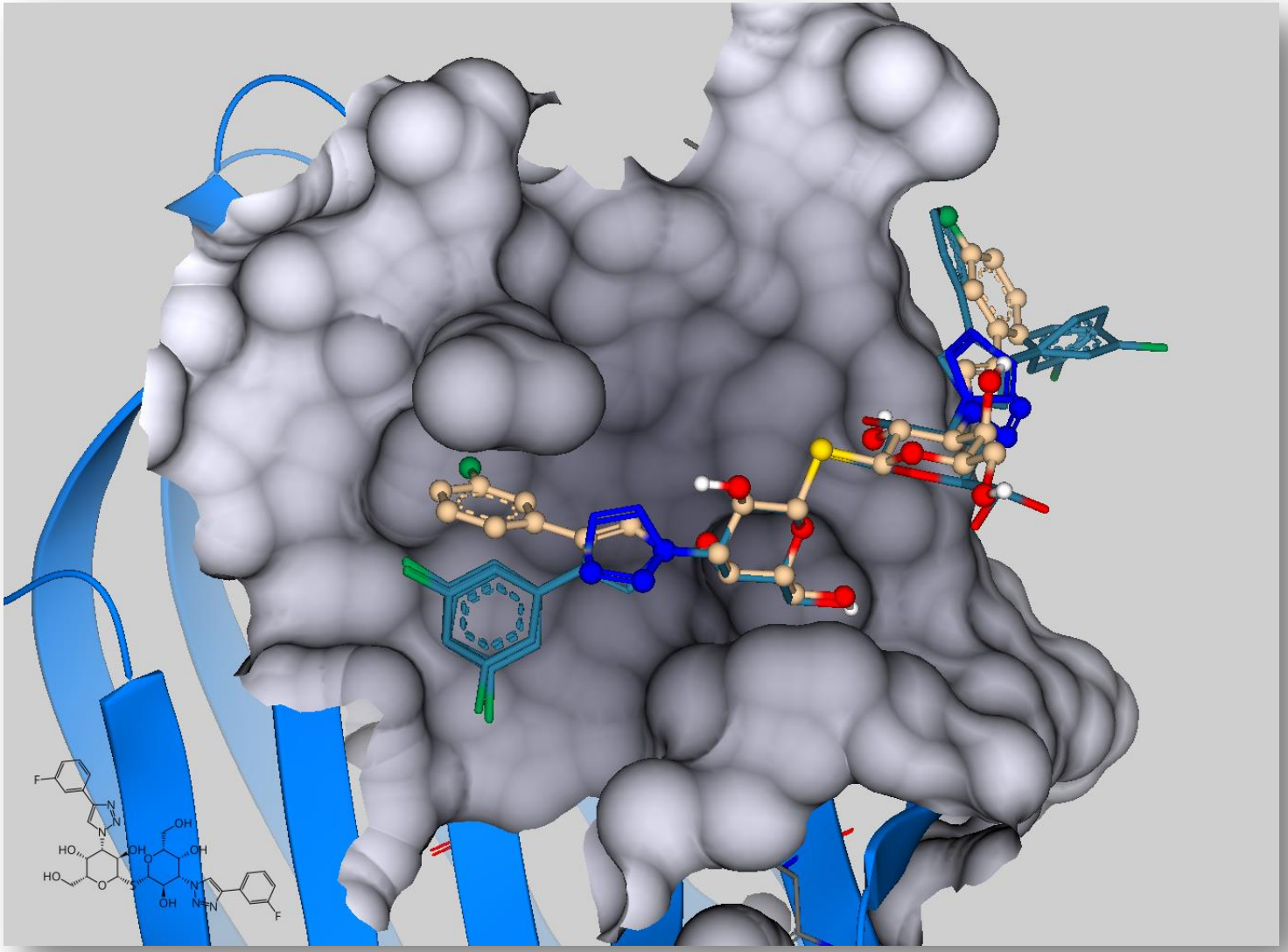
=> Traditional
docking often fails.



12 Galectin Inhibitor Series Docked: Pocket & ConfSpace Well Sampled

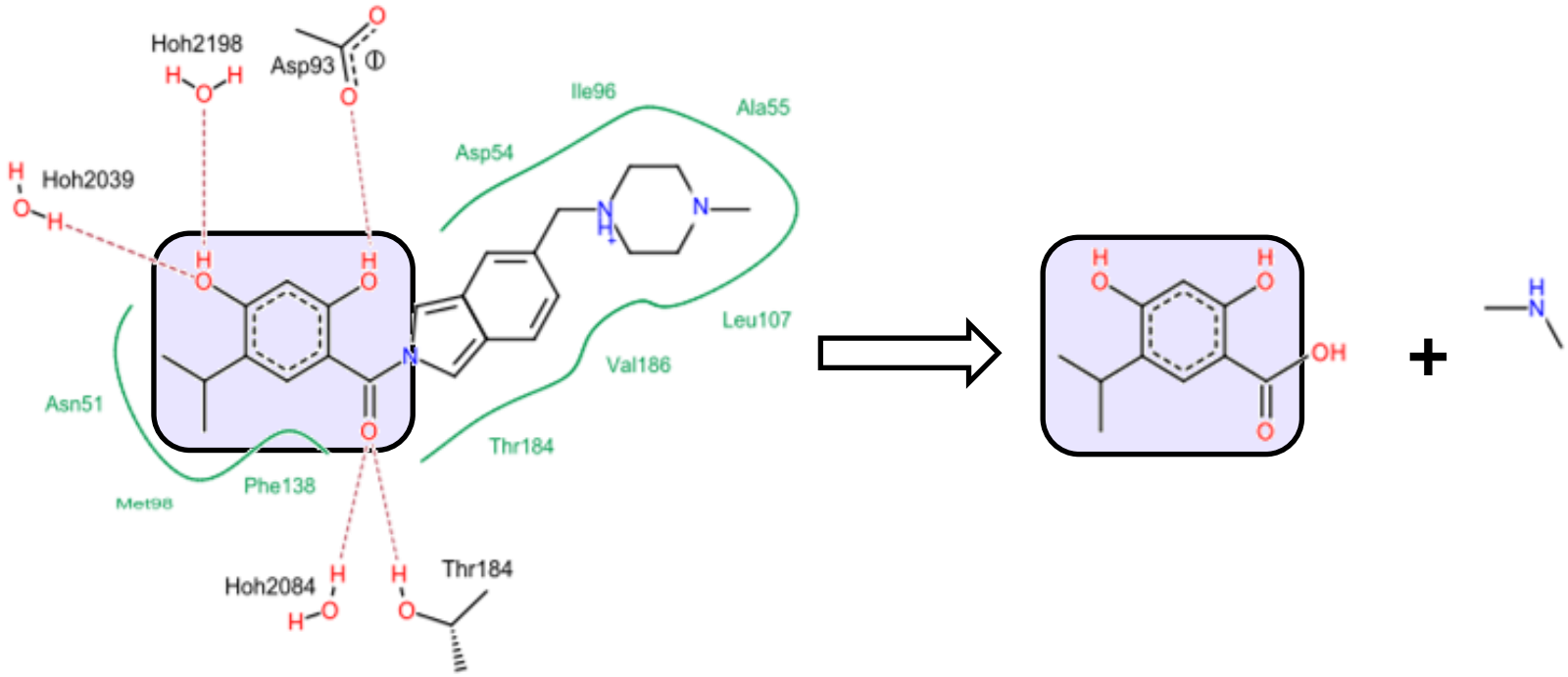


Docking In Good Agreement With Crystal (5e89)



Future Directions

I Library-Based Pocket Exploration



II MedChem Style Analoging

The Idea:

1. Use any promising compound as a starting point
2. Apply typical MedChem transformations
3. Rapidly (template!-) dock & score the new compouds

see www.biosolveit.de/KNIME (free)

Hats Off to Knowledge-Inspired Docking!

- Soon available in SeeSAR

  biosolveit.com/download