New Horizons for RosettaLigand

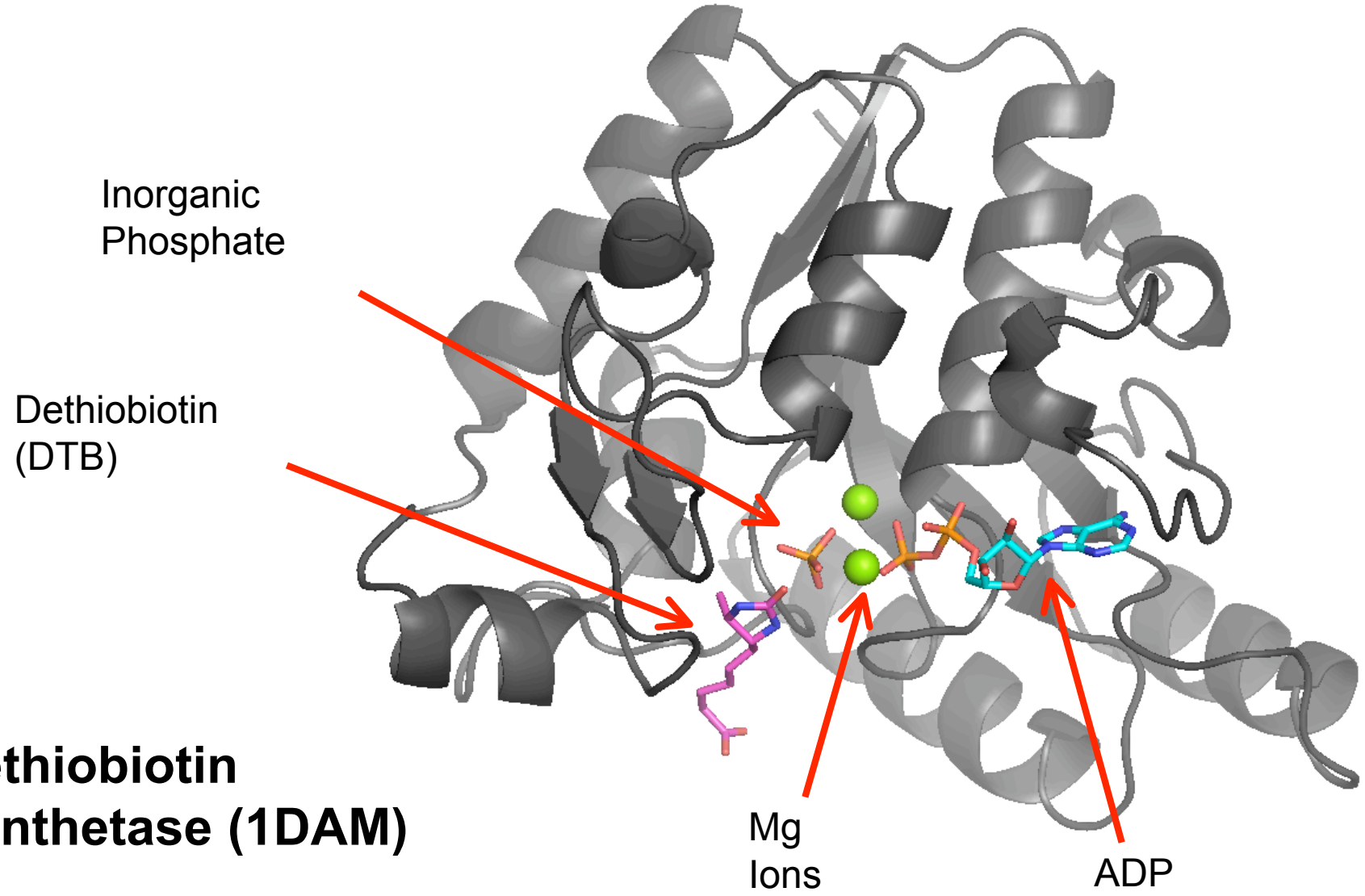
- Gordon Lemmon,
  Vanderbilt University

Overview

New features of RosettaLigand

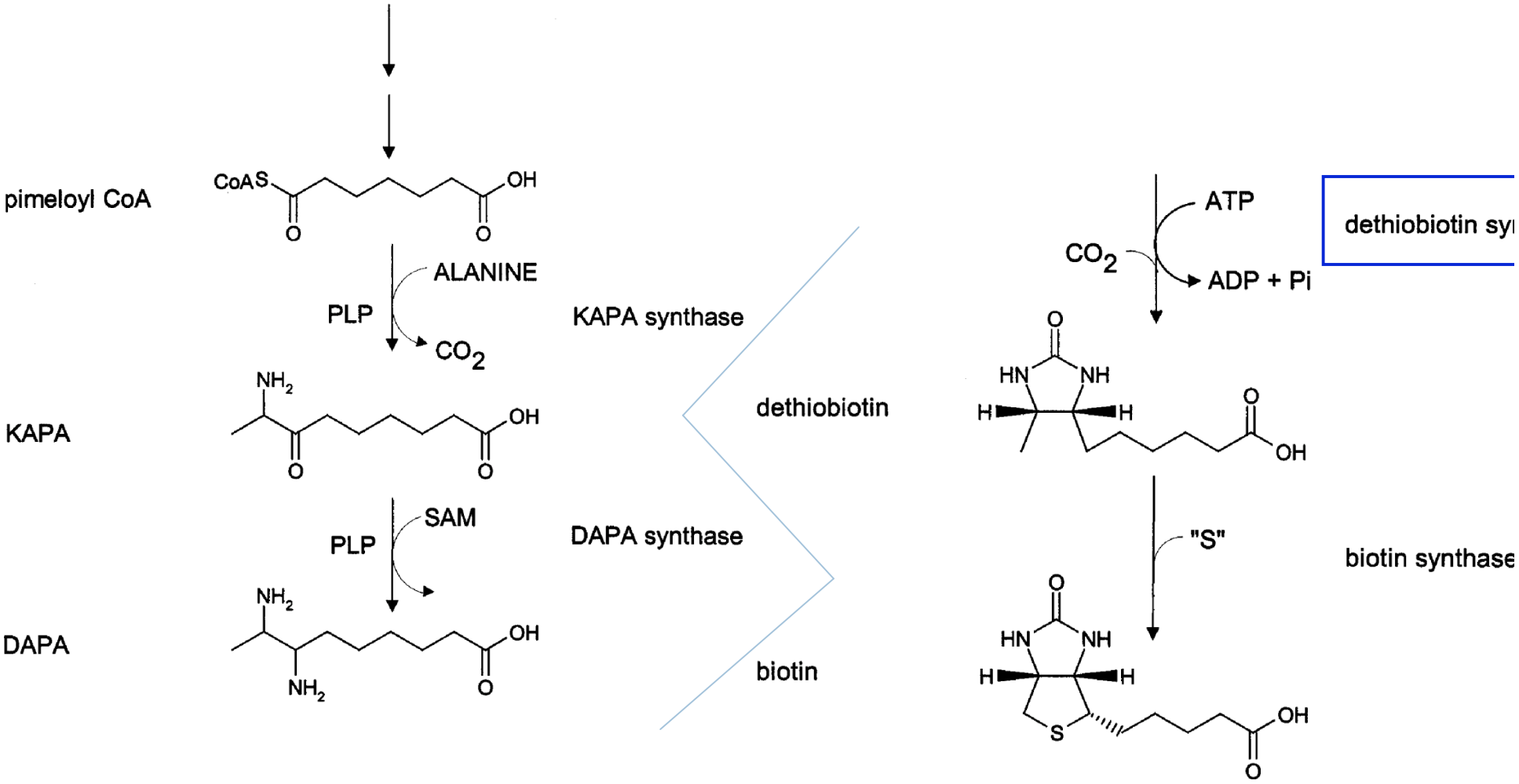
1. Simultaneous docking of multiple ligands
   - Proper placement of water molecules, ions
2. Use of Ligand residues/rotamers allows unrestricted ligand flexibility.
3. Interface design within RosettaLigand

Protein/ligand interactions are complex



Dethiobiotin Synthetase (1DAM)

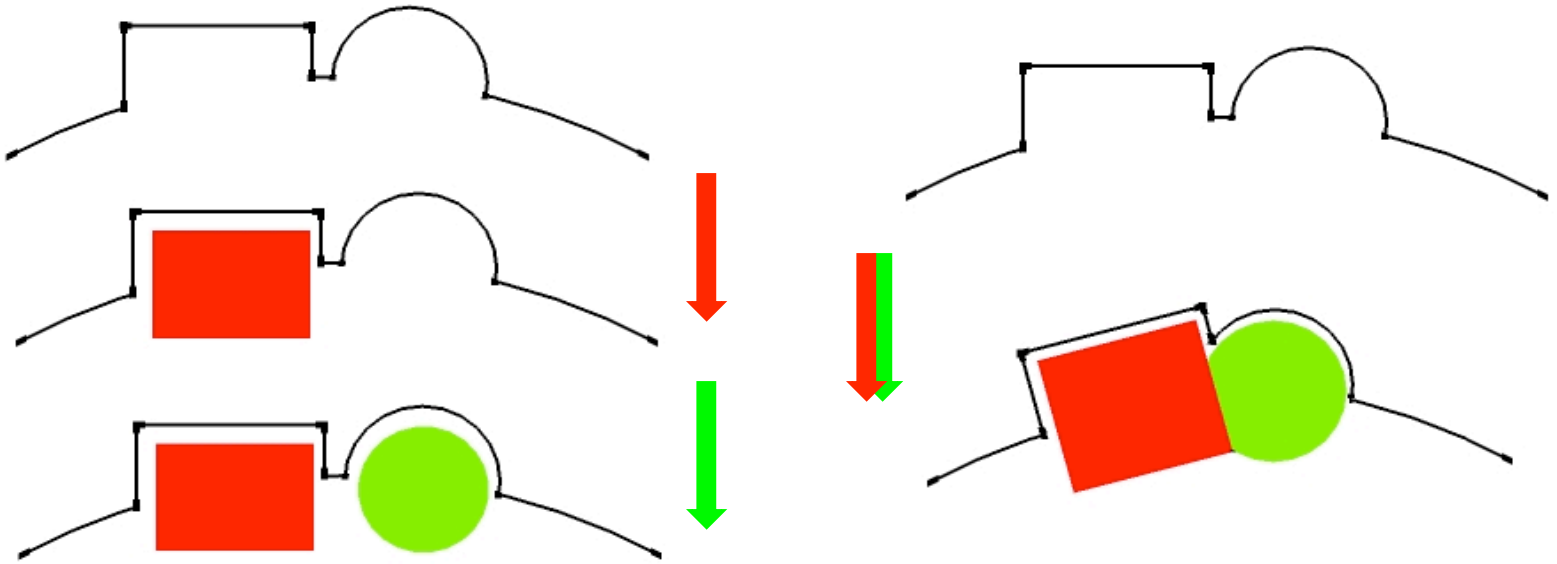
Role of Dethiobiotin Synthase



Dethiobiotin synthase:
ATP + 7,8-diaminononanoate + CO_2 ⇋ ADP + phosphate + dethiobiotin

Multiple Ligand Docking

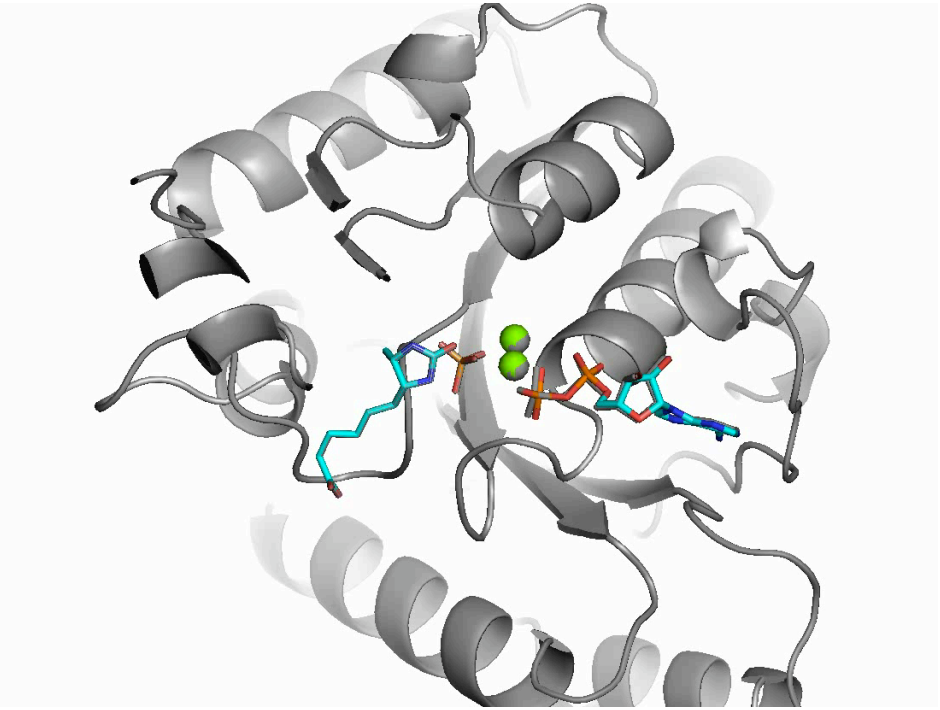
- Enzymes bind multiple ligands and cofactors
- Ligands and receptors are flexible so serial docking fails
- No software supports simultaneous docking



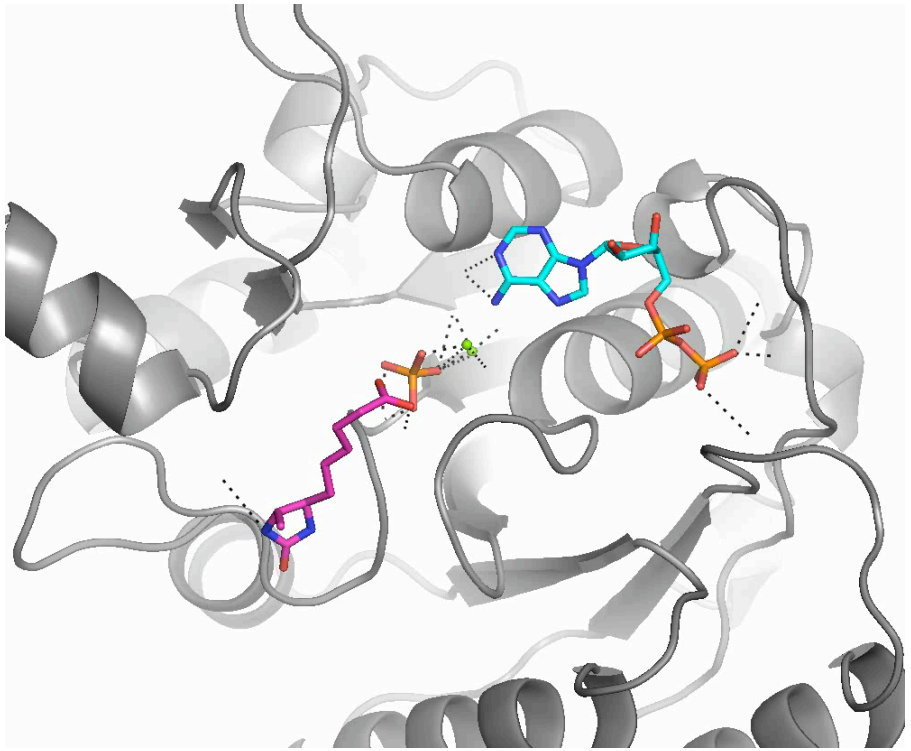
Serial Docking

Simultaneous Docking

Serial vs Simultaneous Docking



Serial Docking

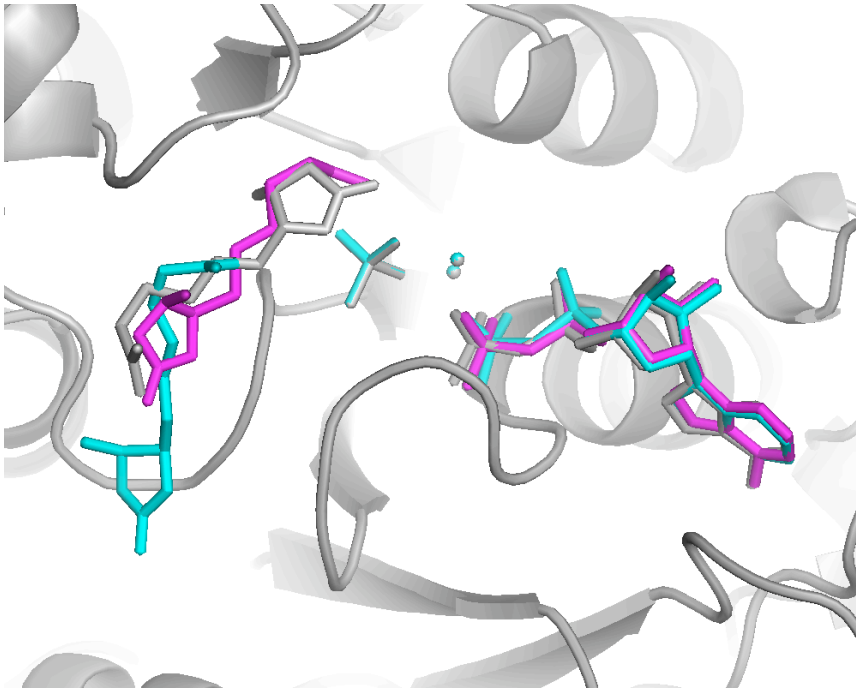


Simultaneous Docking

For each ligand 100 models rotated only, 100 translated up to 5A.

Serial vs Simultaneous Docking

- Colors…
  - Original
  - Best serial model
  - Best simultaneous model
- Time per struct:
  - 12 and 14 sec /22 sec
- Average totals (top 10%)
  - -569 (-582)
  - -601 (-614)

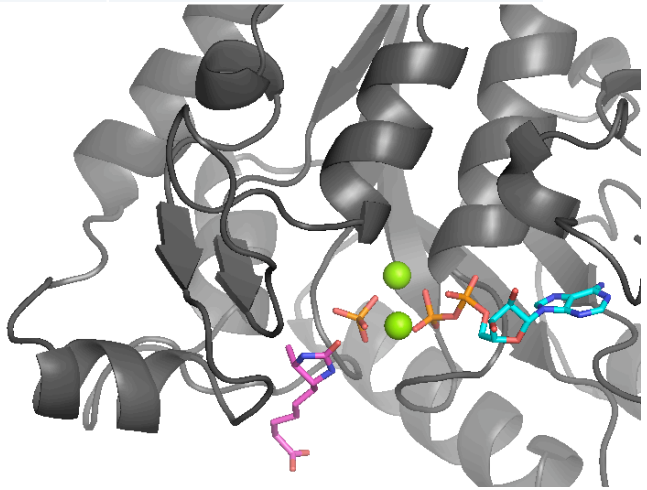


Top 10% by total score, top model by interface delta

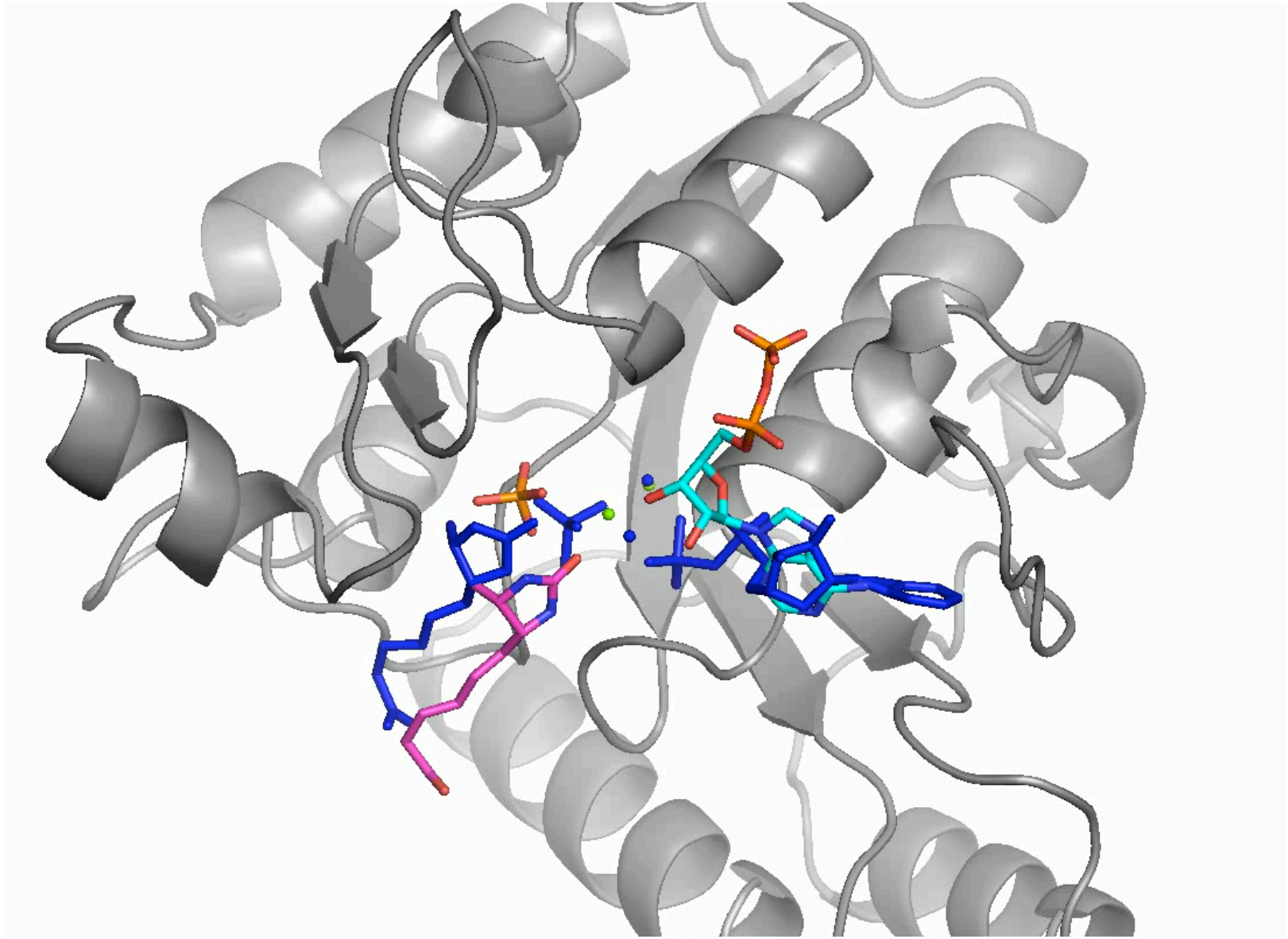
Recovery of Native Conformation

Type	RMS of #1	Rank below 2.5Å	RMS below 2.5Å
Serial ADP	0.44	1	0.44
Simultaneous ADP	0.41	1	0.41
Serial DTB	8.44	3	1.78
Simultaneous DTB	3.94	3	2.26

- Each study represents 200 models, 100 with a translate and rotate step and 100 with only a rotate step

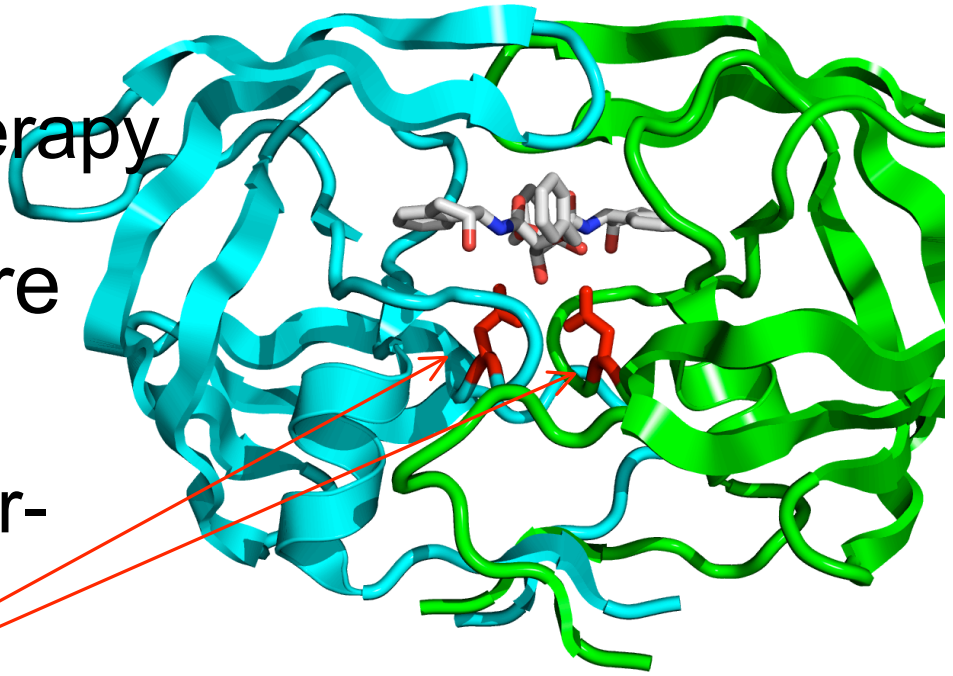


Simultaneous docking of 5 ligands



Ligand flexibility using fragments

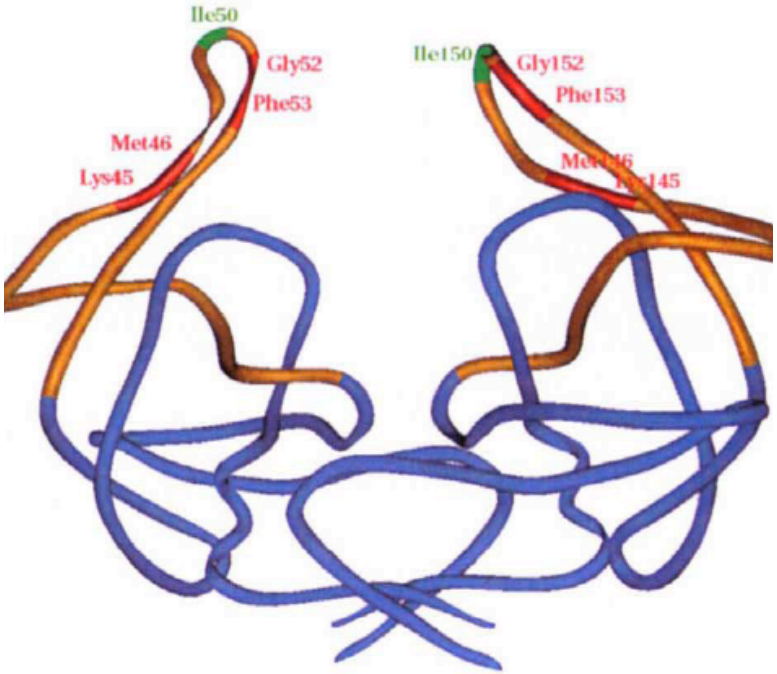
- HIV-1 protease
  - Vital for HIV life cycle
  - Cleaves polypeptide precursors
  - A key target for HIV therapy
- HIV-1 protease structure
  - Homodimer (99 AA)
  - Catalytic Triad (Asp-Thr-Gly)

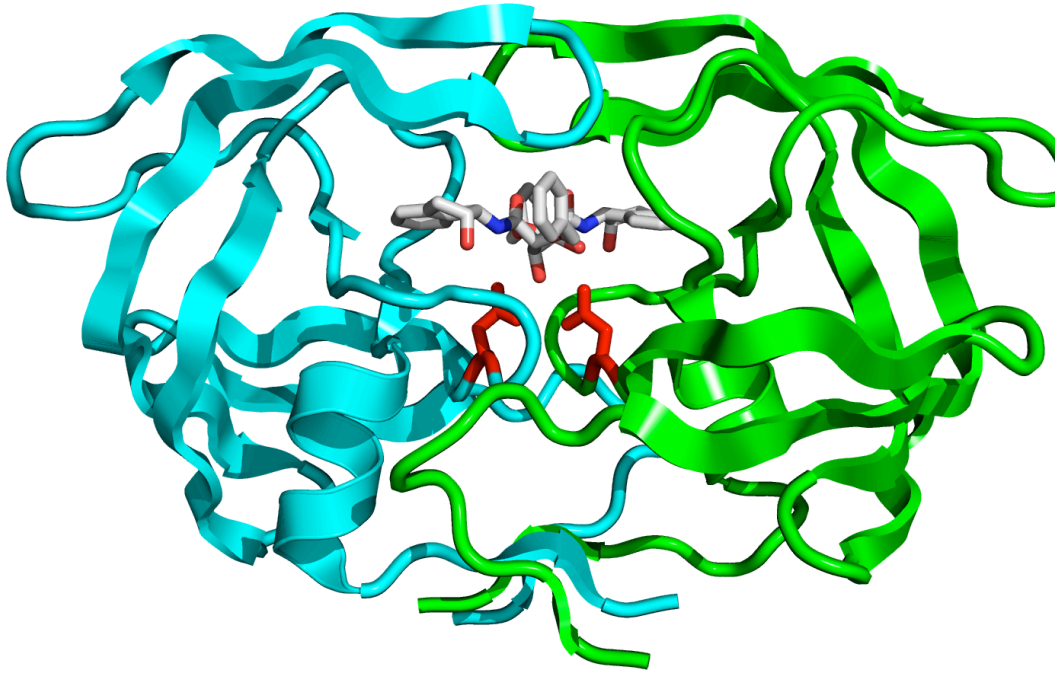


1EBY: protease bound to inhibitor.

Ligand flexibility using fragments

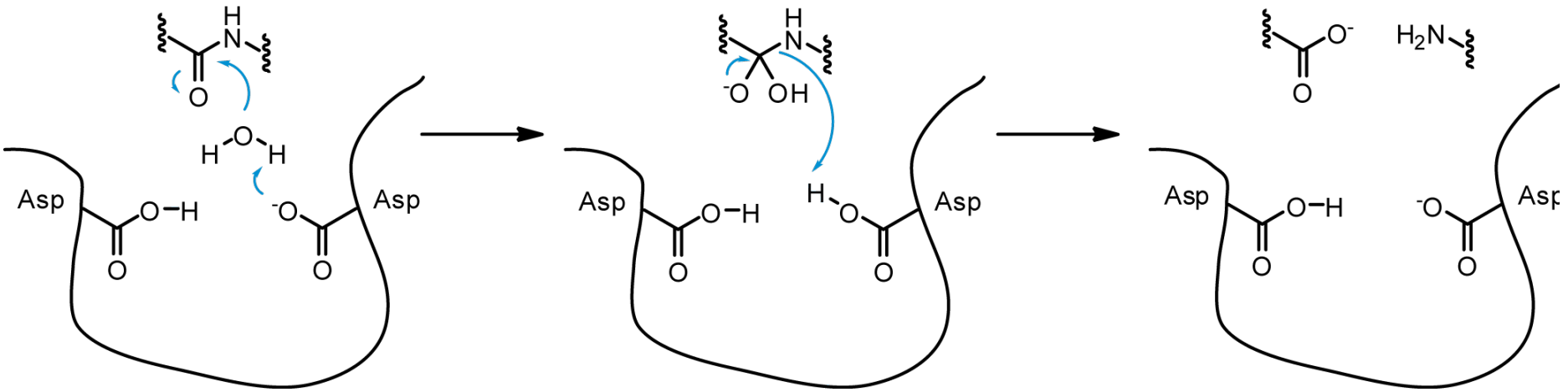
- HIV-1 protease



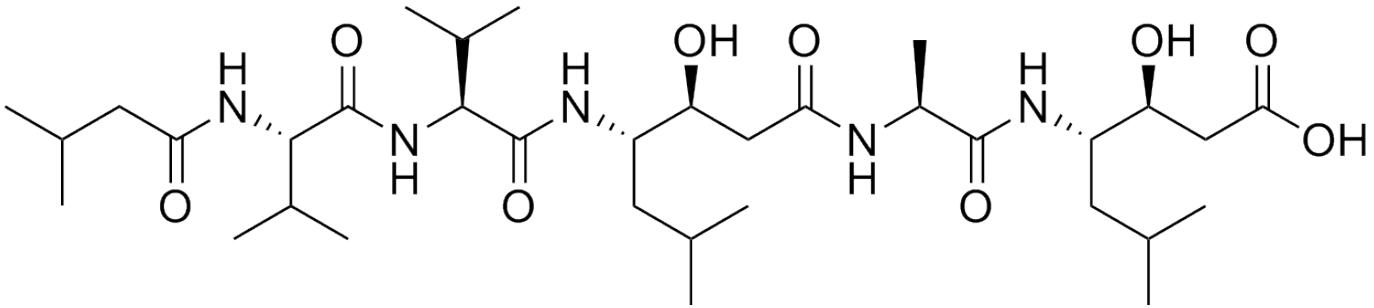


Collins, *Nature Structural Biology* **2**, 334 - 338 (1995)

Aspartyl Protease Mechanism



HIV Protease inhibitors are flexible



Pepstatin

Fragment Rotamer Libraries

Library Construction:

1.Search Cambridge Structural Database (CSD) for all atom pairs

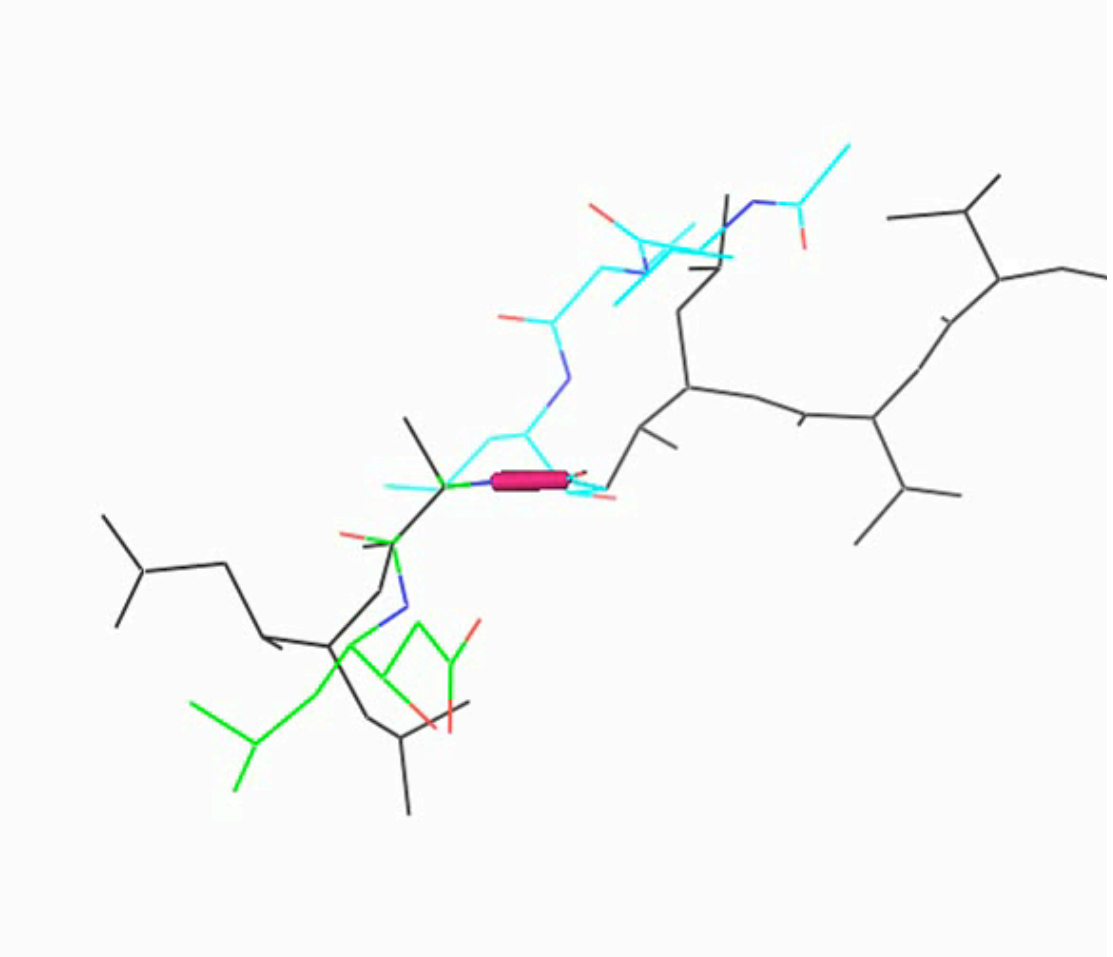
2.Collect atom pair torsion angles in 10 degree bins

3.Create atom-pair energy profile as negative log of propensities

4.Generate conformers based on energy profile minima

5.Use Rosetta to filter clashes

Acetyl-pepstatin broken into 2 fragments

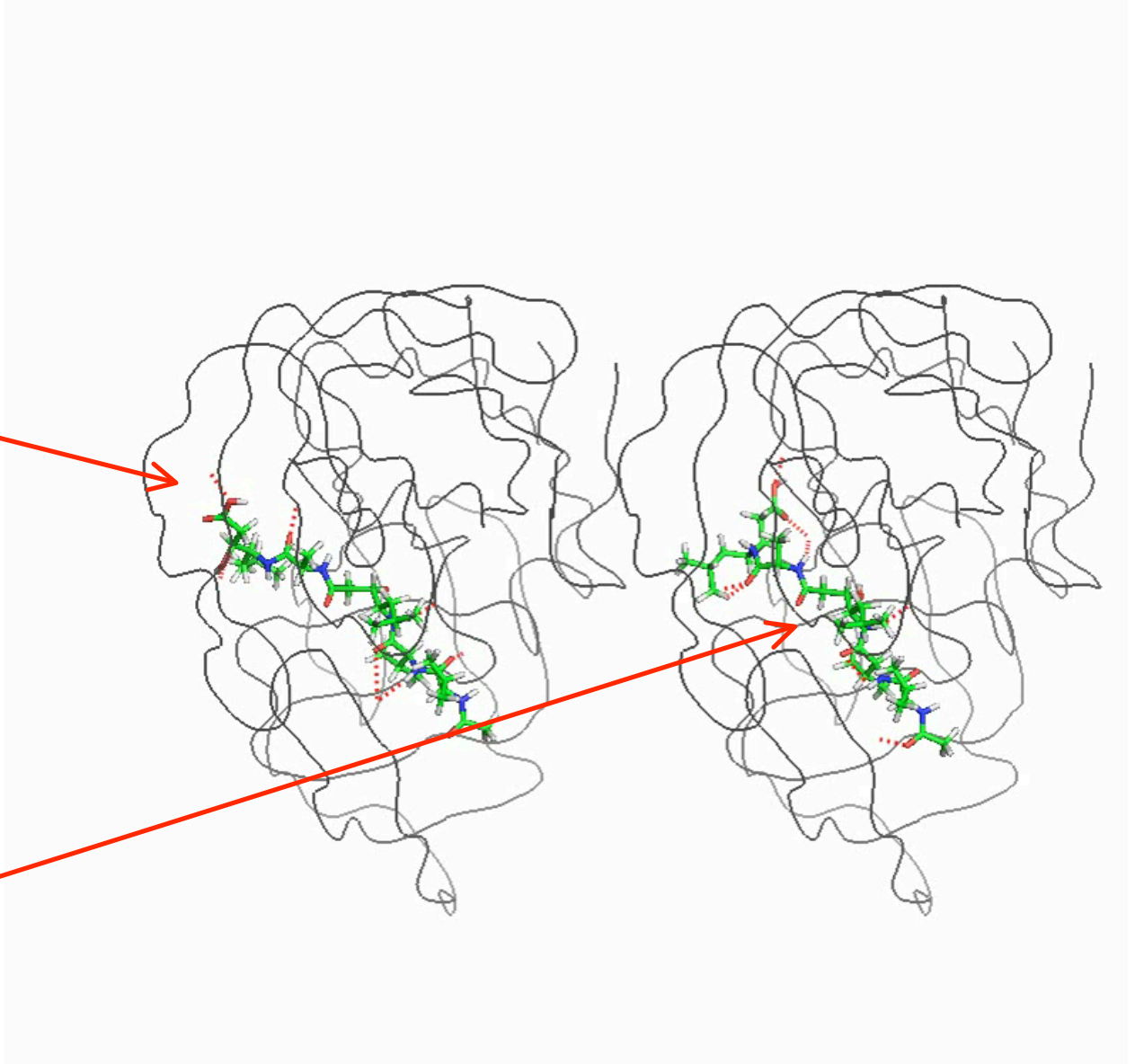


Conformer Sampling docking study

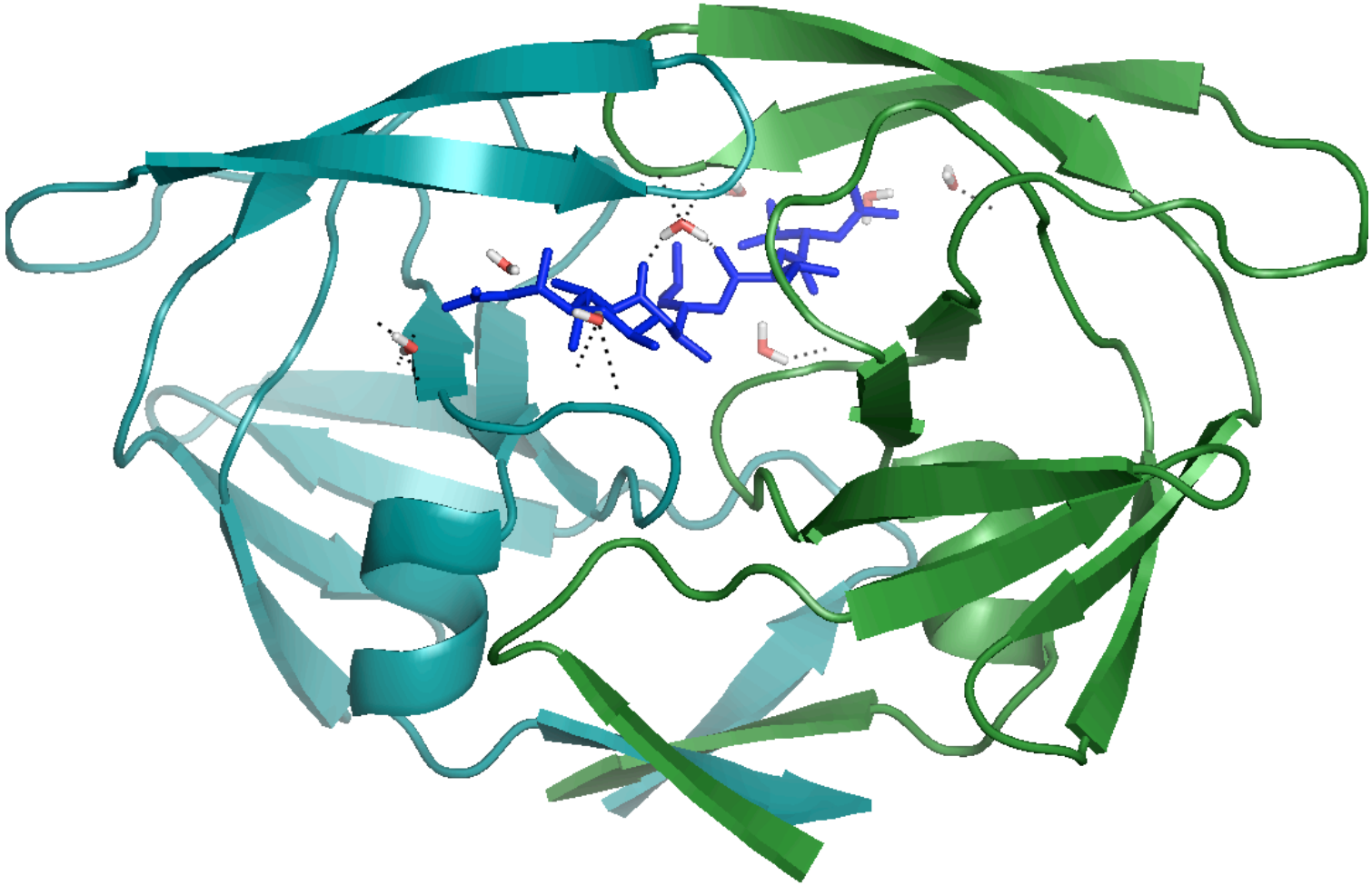
300 structs of Acetylpepstatin docking HIV-1 protease

Single Fragment

Multiple Fragment

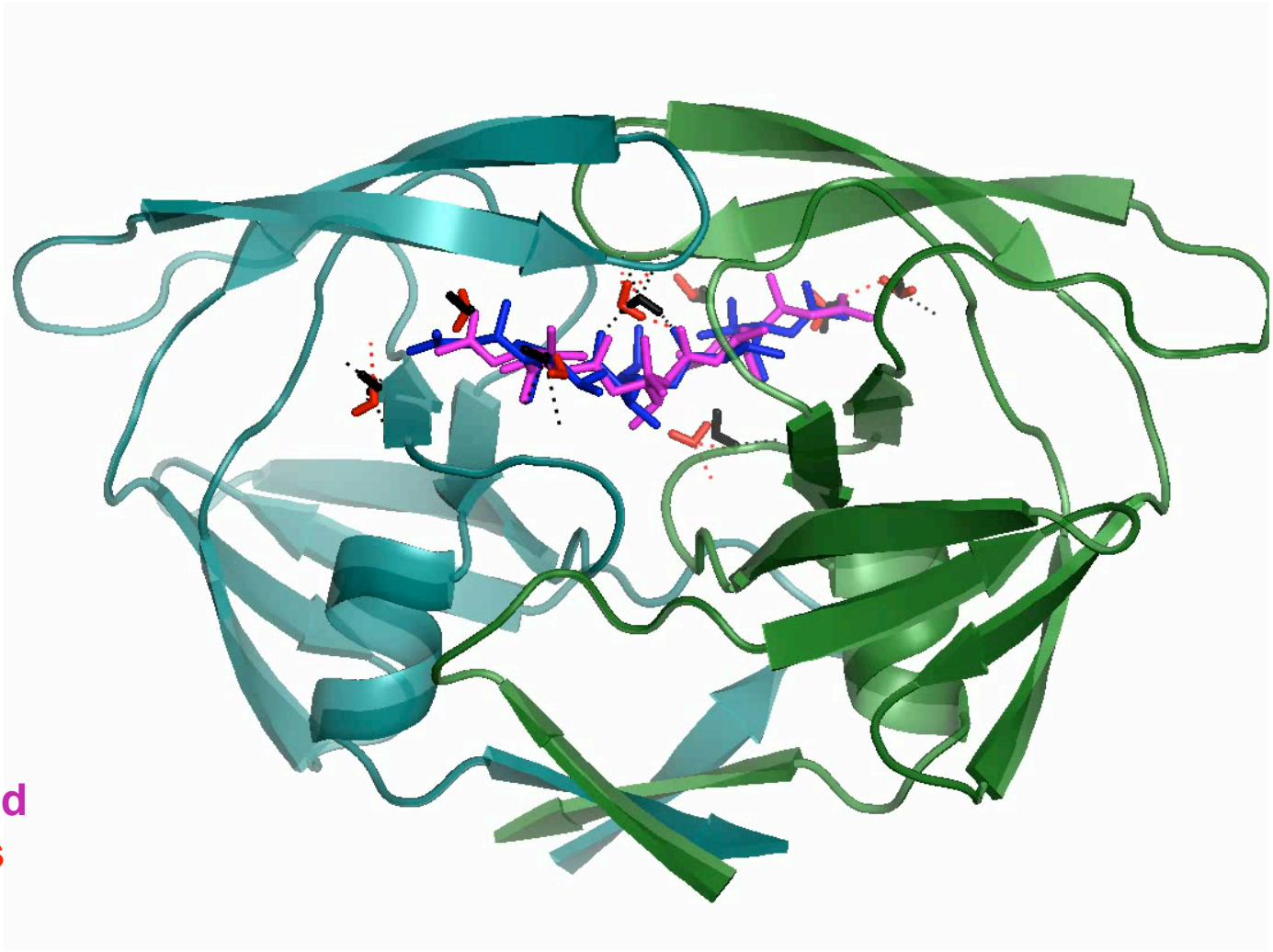


Treating H_2O as a ligand



5HVP: HIV-1 protease bound to Acetylpepstatin.
8 water molecules shown

Treating H_2O as a ligand



Color Legend:
PDB ligand
PDB H_2Os
Docked ligand
Docked H_2Os

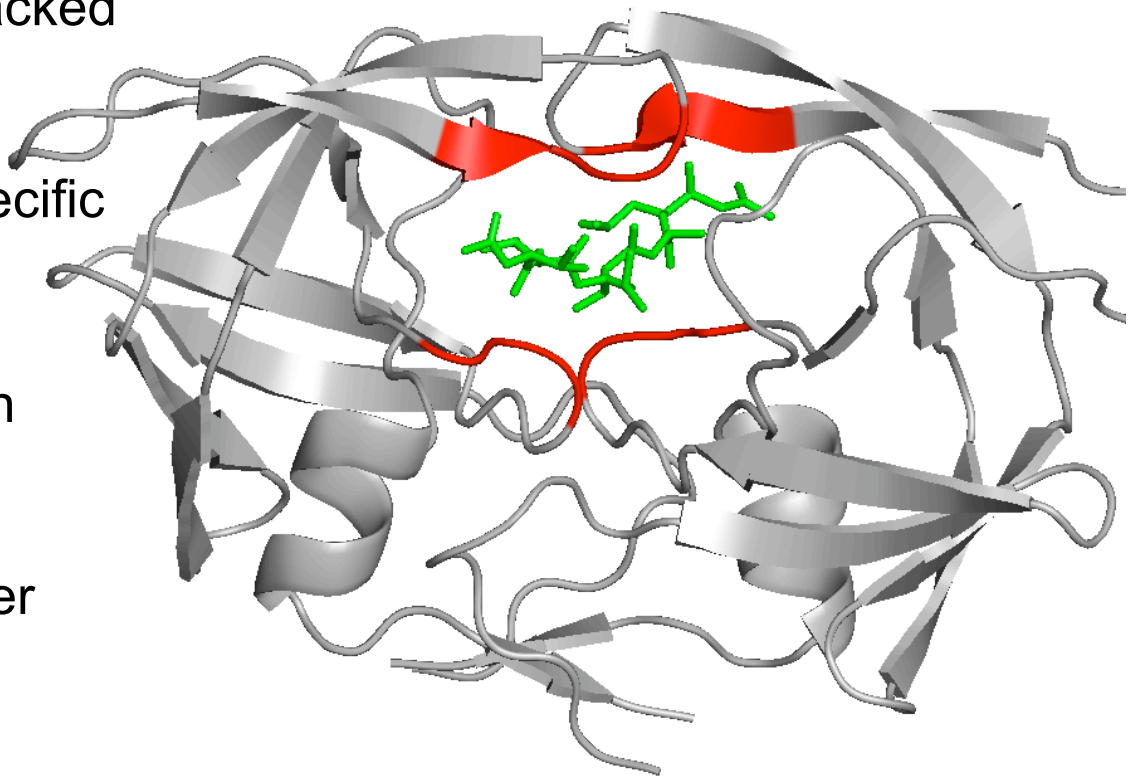
5HVP: HIV-1 protease bound to Acetylpepstatin.
100 models of 8 waters docked simultaneously

Ligand Docking with Interface Design

- Default docking interface: rotamers within 7 Å of the ligand are repacked

- Resfile support: user defines interface, allowing design at specific residues.

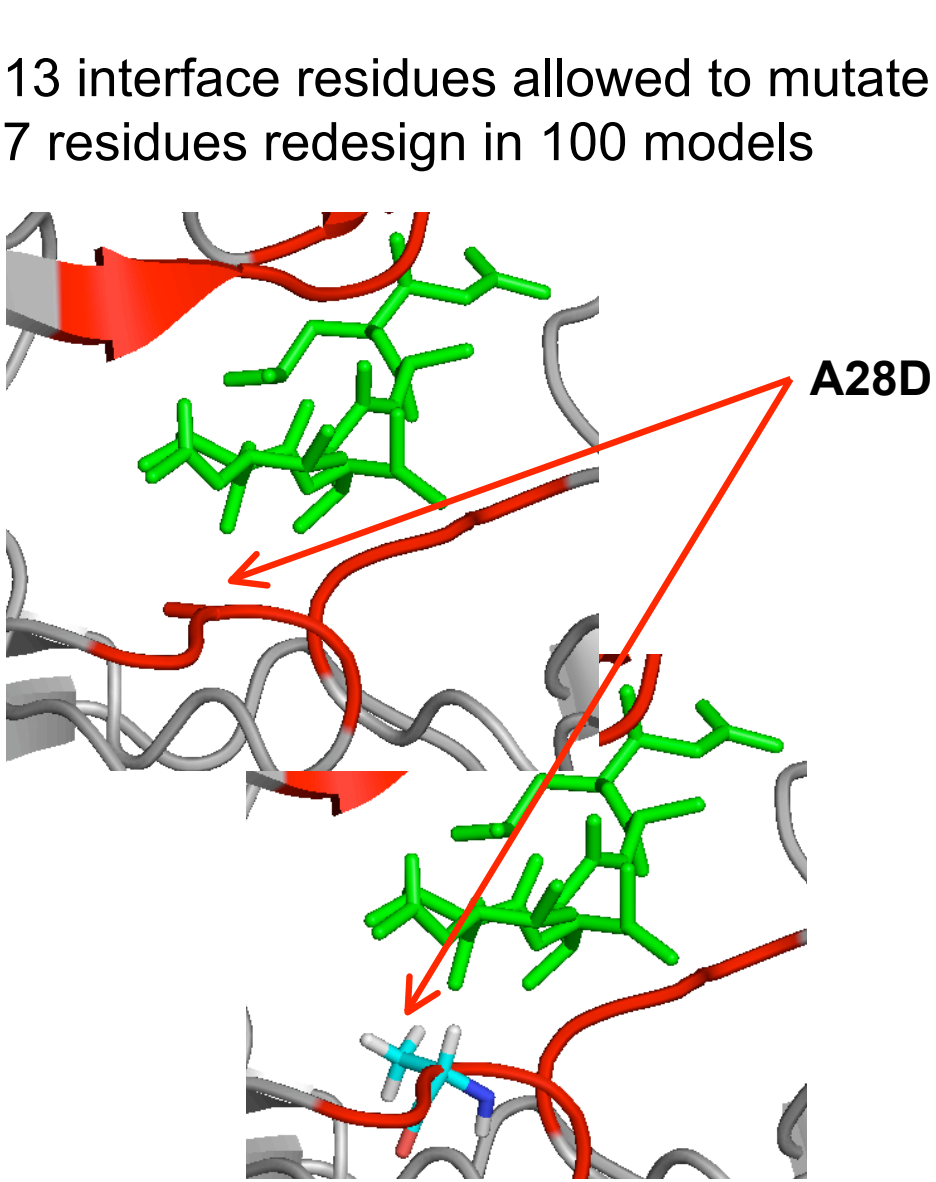
- Combine interface design with
  - Ligand flexibility
  - Backbone flexibility
  - Placement of Ions and water H_2O

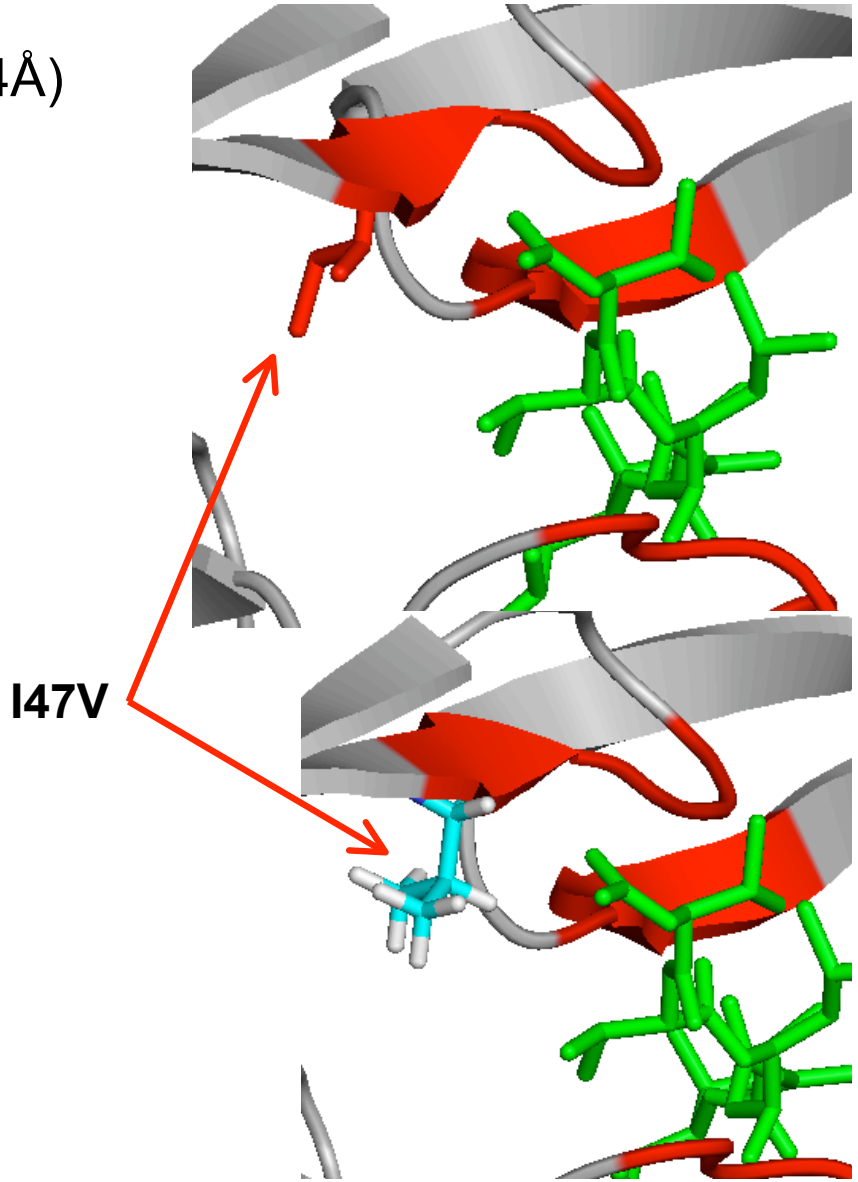


Residues selected for design shown in **red**

Resfile support in RosettaLigand

- 13 interface residues allowed to mutate (4Å)
- 7 residues redesign in 100 models



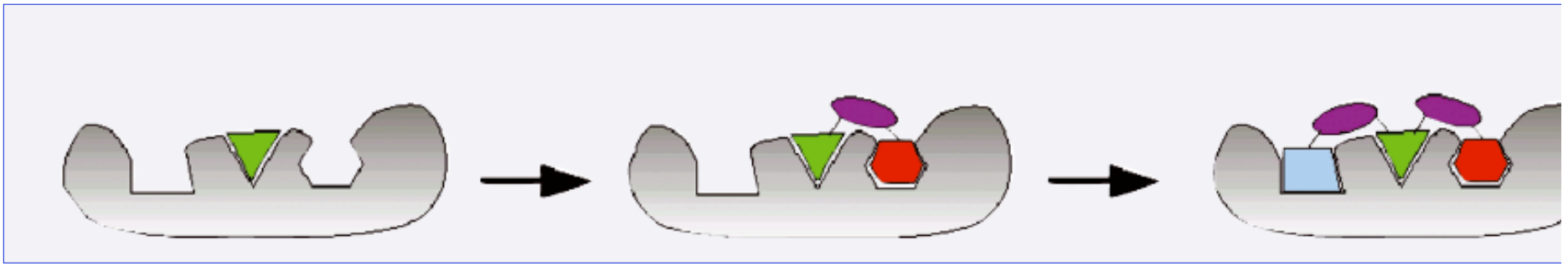


Top down design: code demonstrates algorithm

```
1  command_map_.parse_default_ligand_option_file(pose);

2  command_map_[ligand_options::random_conformer]->apply();

3  command_map_[ligand_options::start_from]->apply();

4  command_map_[ligand_options::translate]->apply();

5  command_map_[ligand_options::rotate]->apply();

5  command_map_[ligand_options::minimize_ligand]->apply();
                          // Setup ligand torsion restraints
6  command_map_[ligand_options::slide_together]->apply();

7  command_map_[ligand_options::minimize_backbone]->apply();
                          // Reorder backbone around mobile regions
8  command_map_[ligand_options::tether_ligand]->apply();

9  command_map_[ligand_options::protocol]->apply();
                          // Cycles of move, minimize, pack, accept/reject
11 final_minimize(pose);
```

Future Work: Ligand design

- Generate fragment libraries based on structures seen in the Cambridge Structural Database
- Use *Fragment Extension* to grow a ligand



Acknowledgements

- Jens Meiler
- Ian Davis
- Kristian Kaufmann
- Rosetta Community

Ligand Soft rep weights

hbond_lr_bb 1.2
hbond_sr_bb 1.2
hbond_bb_sc 1.2
hbond_sc 1.2
p_aa_pp 0.32
dslf_ss_dst 1.0
dslf_cs_ang 1.0
dslf_ss_dih 1.0
dslf_ca_dih 1.0
omega 0.5

pro_close 1.0
fa_atr 0.8
fa_rep 0.6
fa_sol 0.5
fa_intra_rep 0.3
fa_pair 0.5
fa_plane 0
fa_dun 0.32
ref 1