

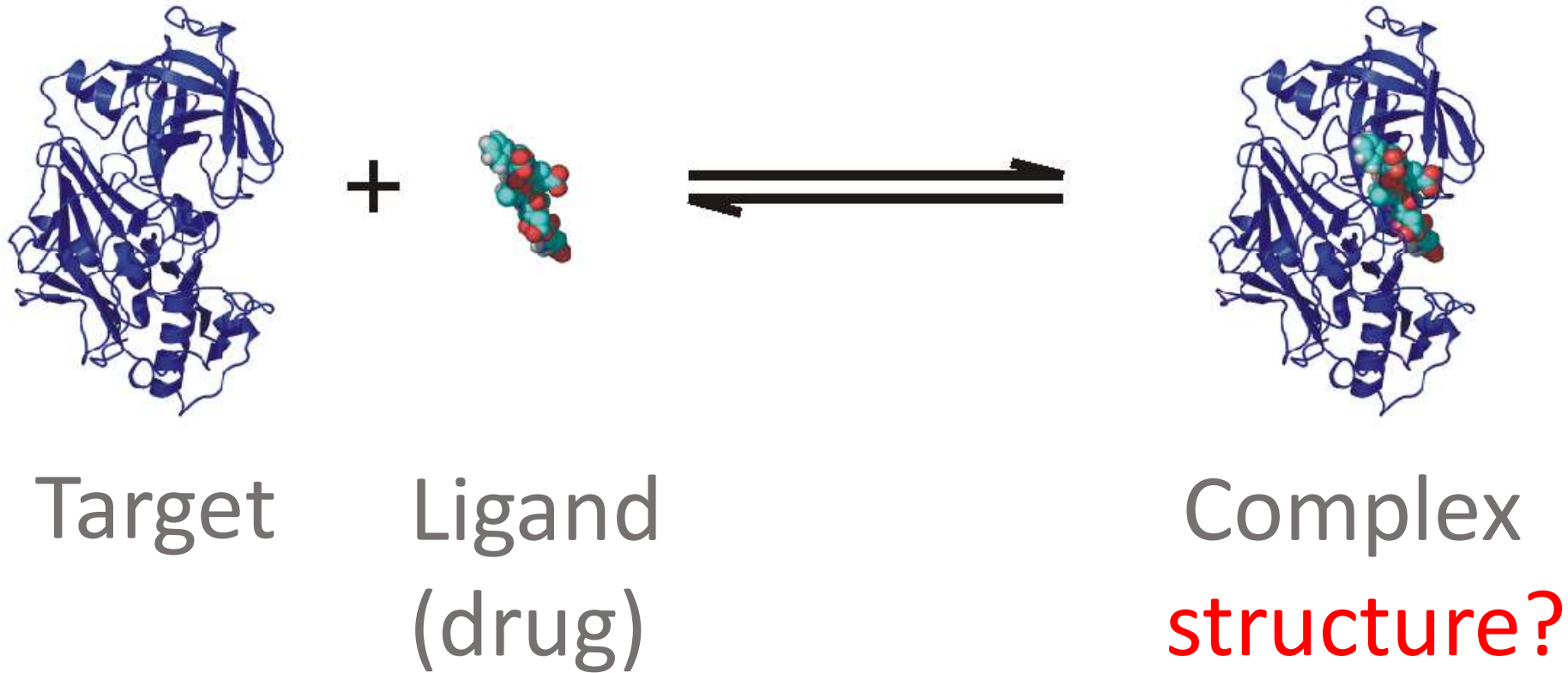
# **A Massively Parallelized, Systematic Method for Efficient Prediction of Multiple Drug Binding**

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University of Pécs, Hungary



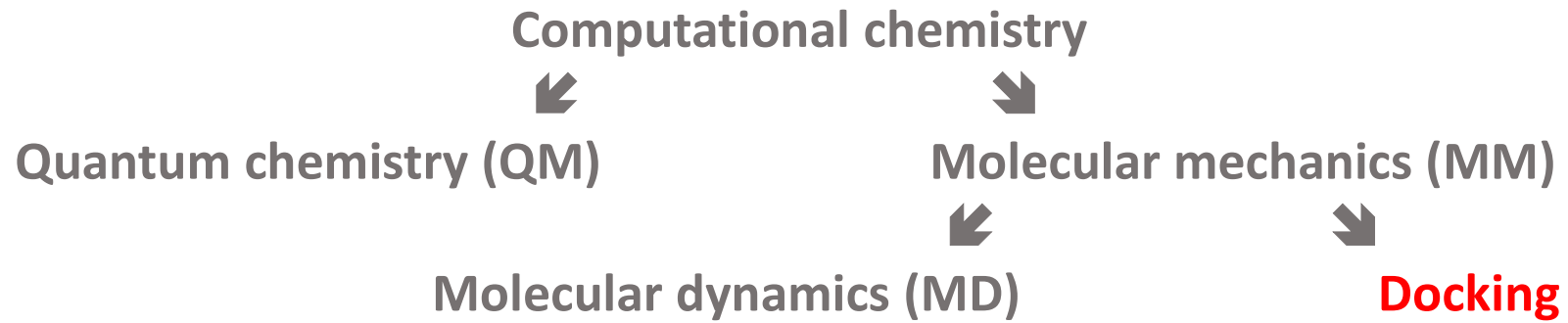
# Binding: the central event of drug action



Computational docking =



driving a ligand into its binding site



### Important difference

QM → atomic nuclei + electrons

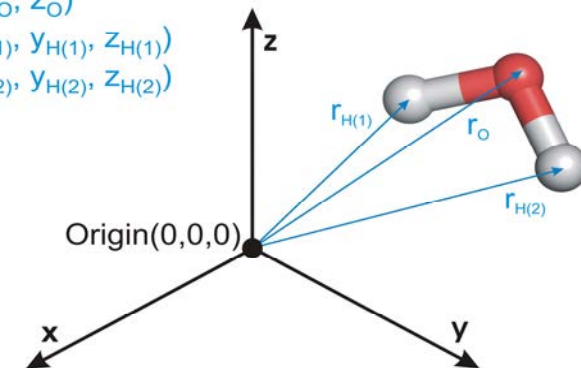
MM → connected atoms

Water molecule

$\mathbf{r}_O(x_O, y_O, z_O)$

$\mathbf{r}_{H(1)}(x_{H(1)}, y_{H(1)}, z_{H(1)})$

$\mathbf{r}_{H(2)}(x_{H(2)}, y_{H(2)}, z_{H(2)})$



Computational docking =  
Force field + Search algorithm

Force Field =  
V function + Parameter set

$$V(\vec{r}_1, \vec{r}_2, \dots, \vec{r}_N) = \sum_{bonds} \frac{1}{2} K_b (b - b_0)^2 + \sum_{angles} \frac{1}{2} K_\Theta (\Theta - \Theta_0)^2 + \sum_{dihedrals} K_\phi [1 + \cos(n\phi - \delta)] +$$
$$+ \sum_{pairs(i,j)} \left[ C_{12}(i,j) / r_{ij}^{12} - C_6(i,j) / r_{ij}^6 + q_i q_j / (4\pi\epsilon_0\epsilon_r r_{ij}) \right]$$

Blind docking vs.  
focused docking

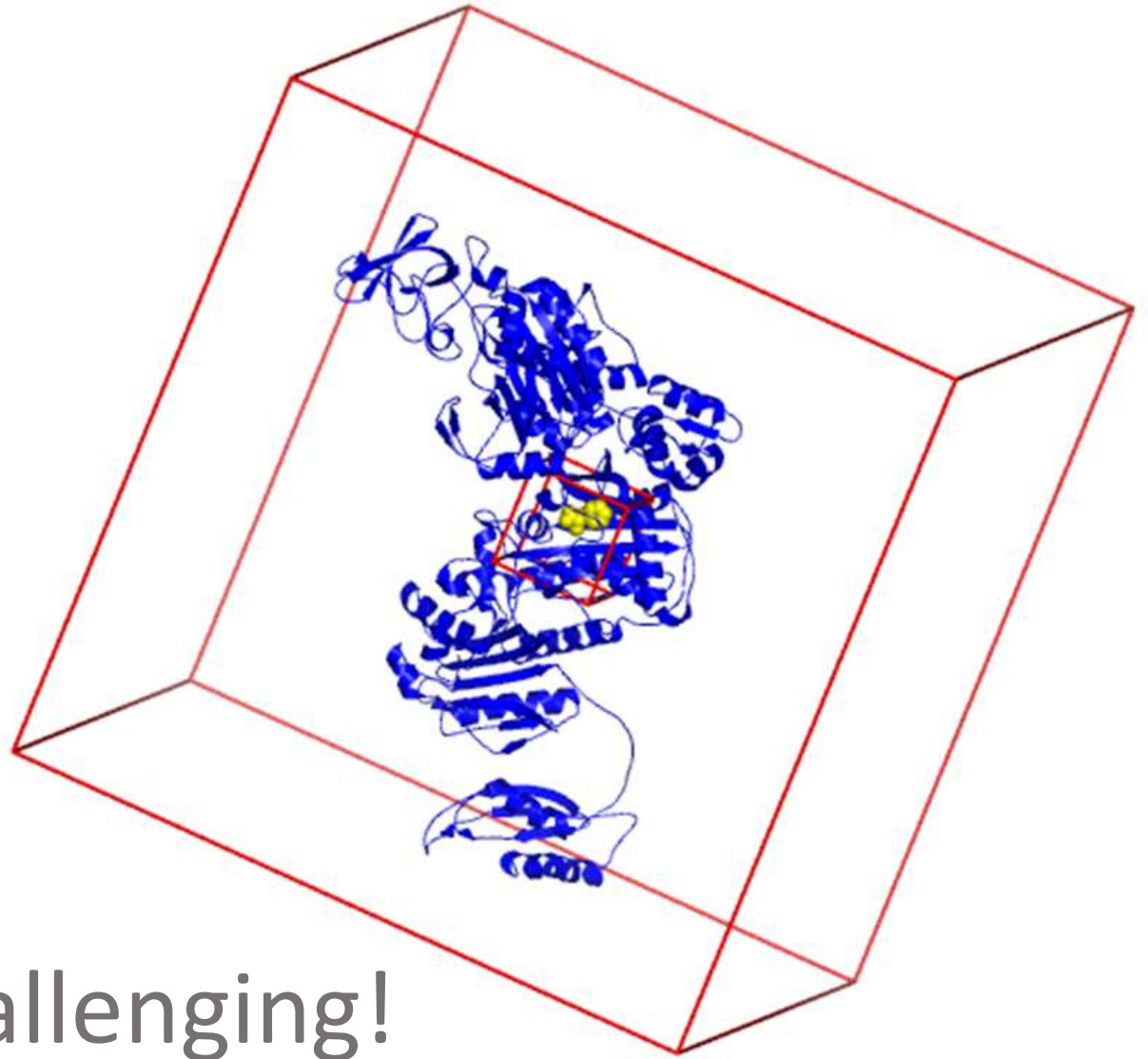
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Global search vs.  
local search

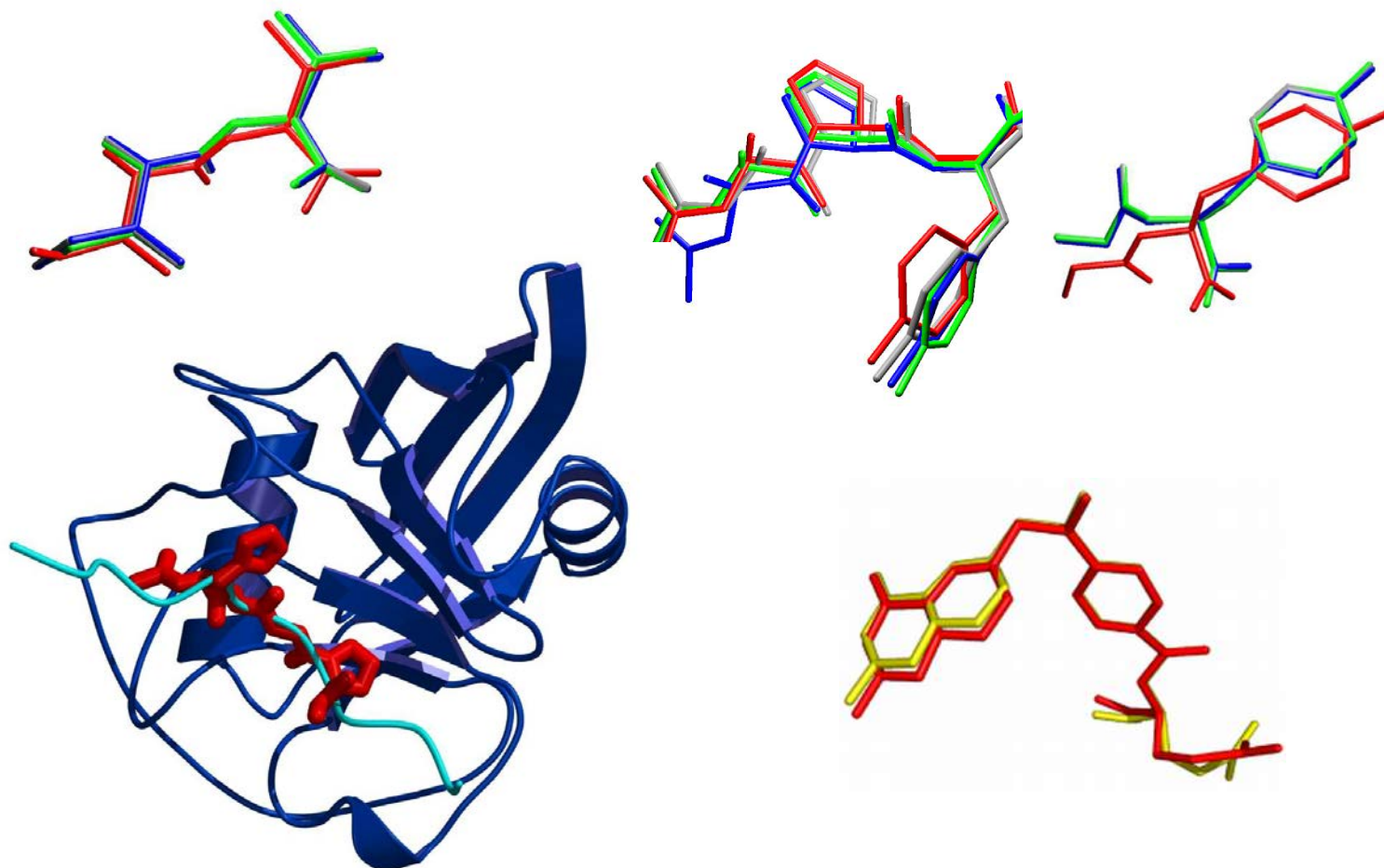
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Allosteric sites vs.  
orthosteric sites

Blind docking is challenging!



## Fast blind docking results





**Hetényi C\***, van der Spoel D (2011)

Toward prediction of functional protein pockets using blind docking and pocket search algorithms.

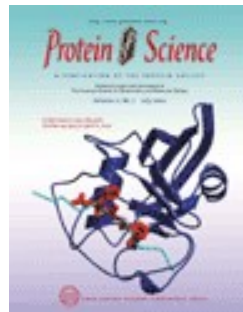
*Protein Sci* **20**, 880-93.



**Hetényi, C\***, van der Spoel, D. (2006)

Blind docking of drug-sized compounds to proteins with up to a thousand residues.

*FEBS Letters* **580** 1447-1450.



**Hetényi, C.** and van der Spoel, D\*. (2002)

Efficient docking of peptides to proteins without prior knowledge of the binding site.

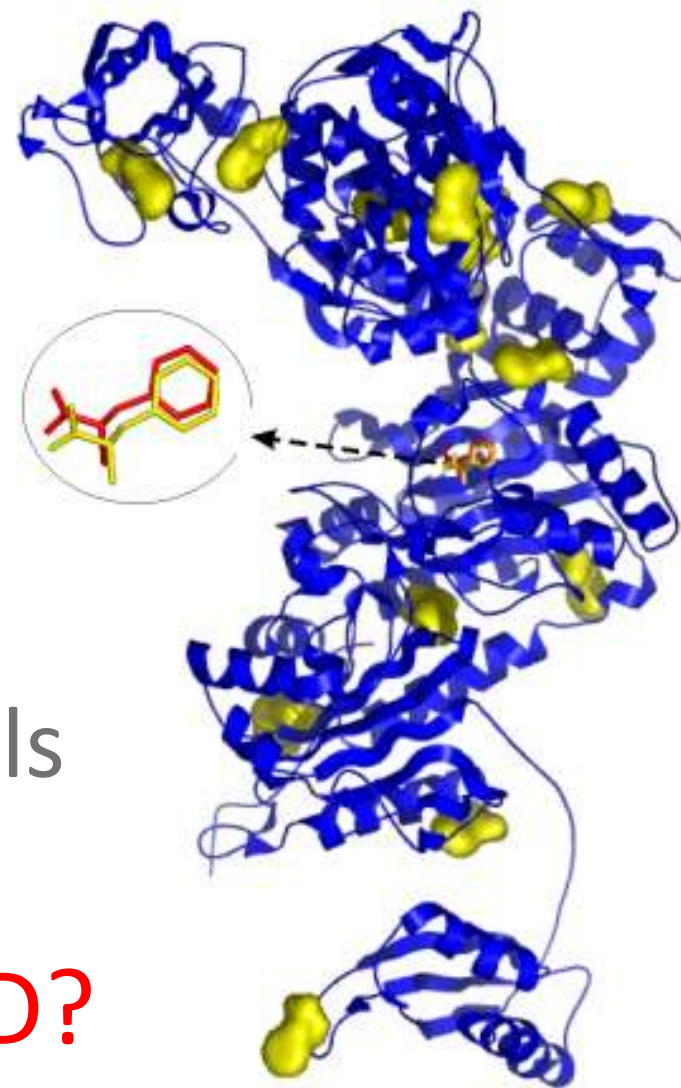
*Protein Science* **11** 1729-1737



# Limitations of fast blind docking approaches

- Heuristic search algorithms
- Simplified force fields
- Lack of explicit water models

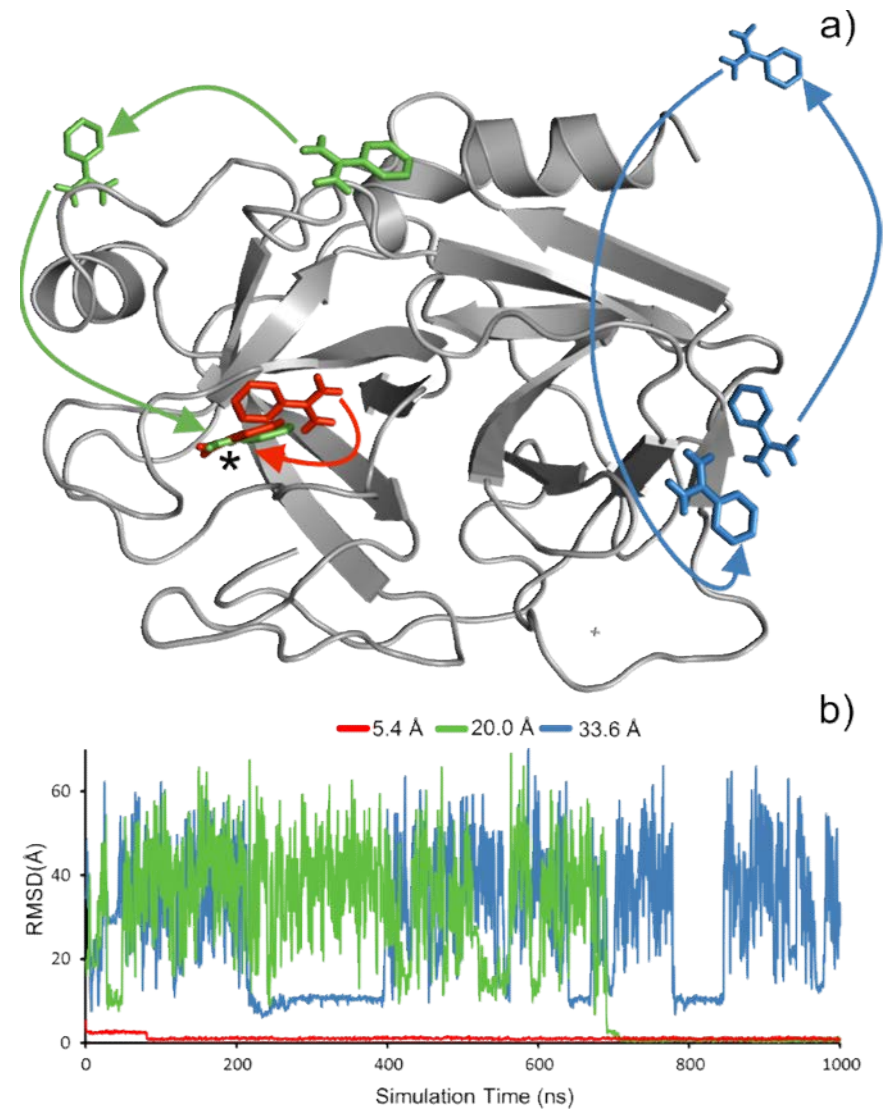
→ No systematic results. **MD?**

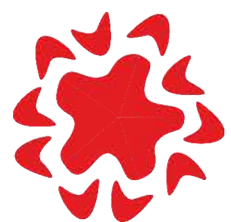


# Limitation of molecular dynamics (MD) approaches

- Heuristic or biased starting positions
- Simulation time is not predictable

→ No systematic results





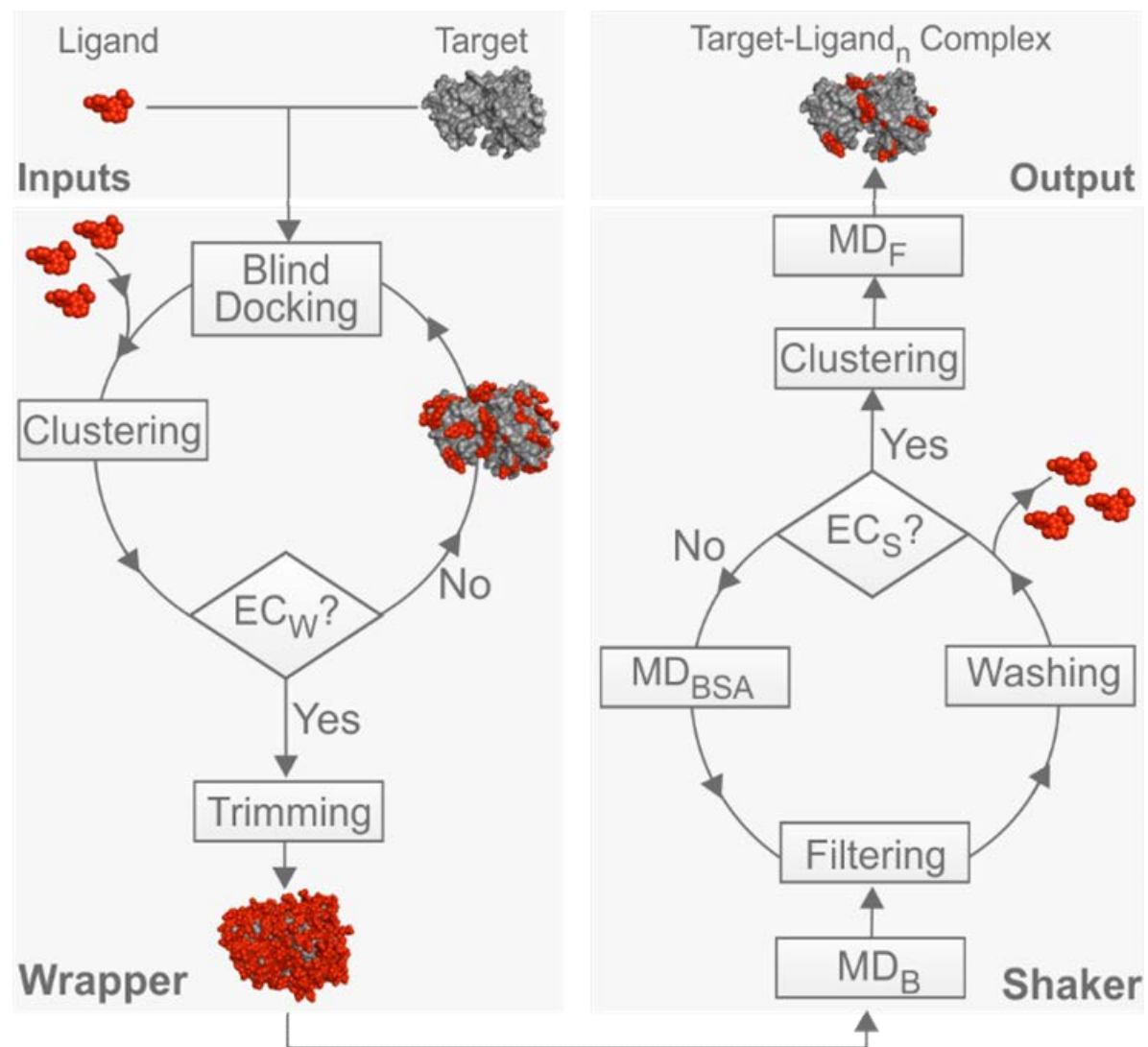
# WRAP 'N' SHAKE

[www.wnsdock.xyz](http://www.wnsdock.xyz)

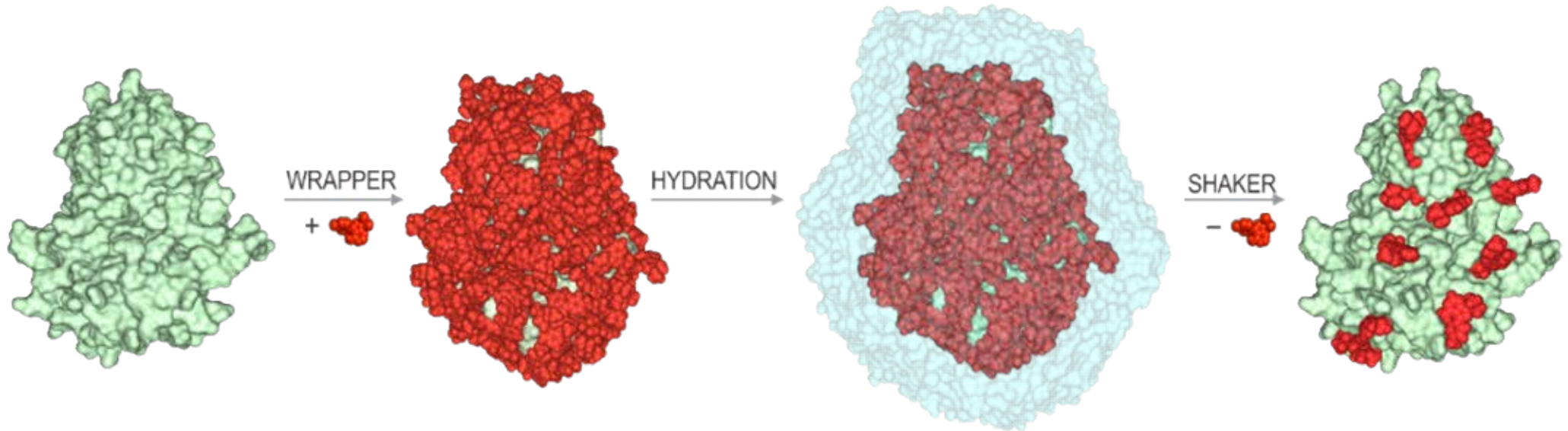
**Systematic exploration of multiple drug binding sites**

Bálint M, Jeszenői N, Horváth I, van der Spoel D and Hetényi C

Journal of Cheminformatics 2017 **9**:65



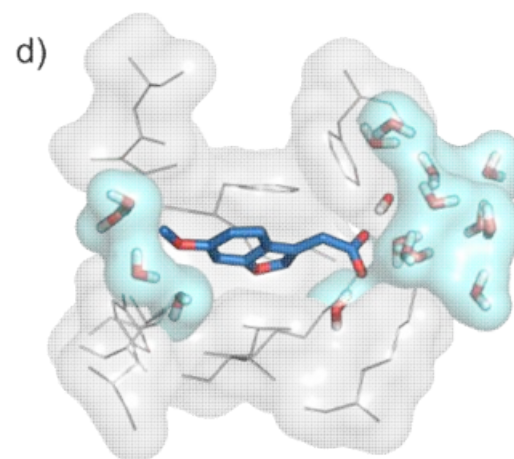
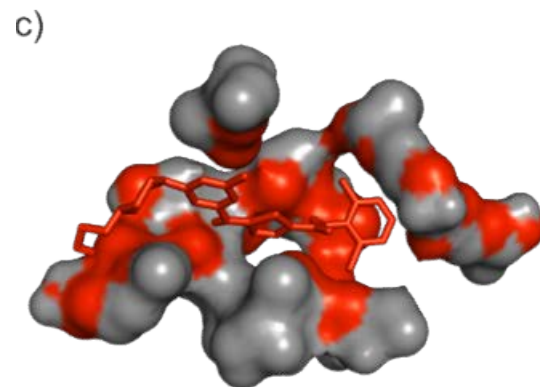
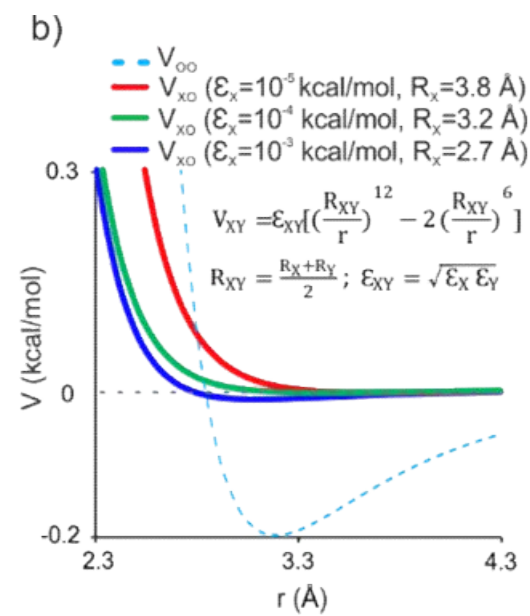
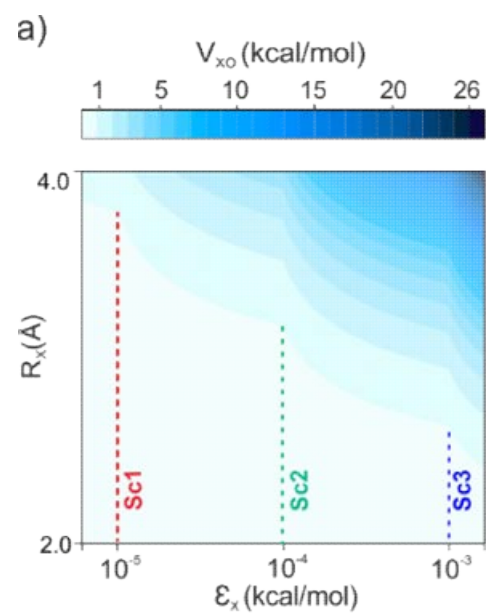
# Wrap 'n' Shake = Wrapper + Shaker



# Wrapper

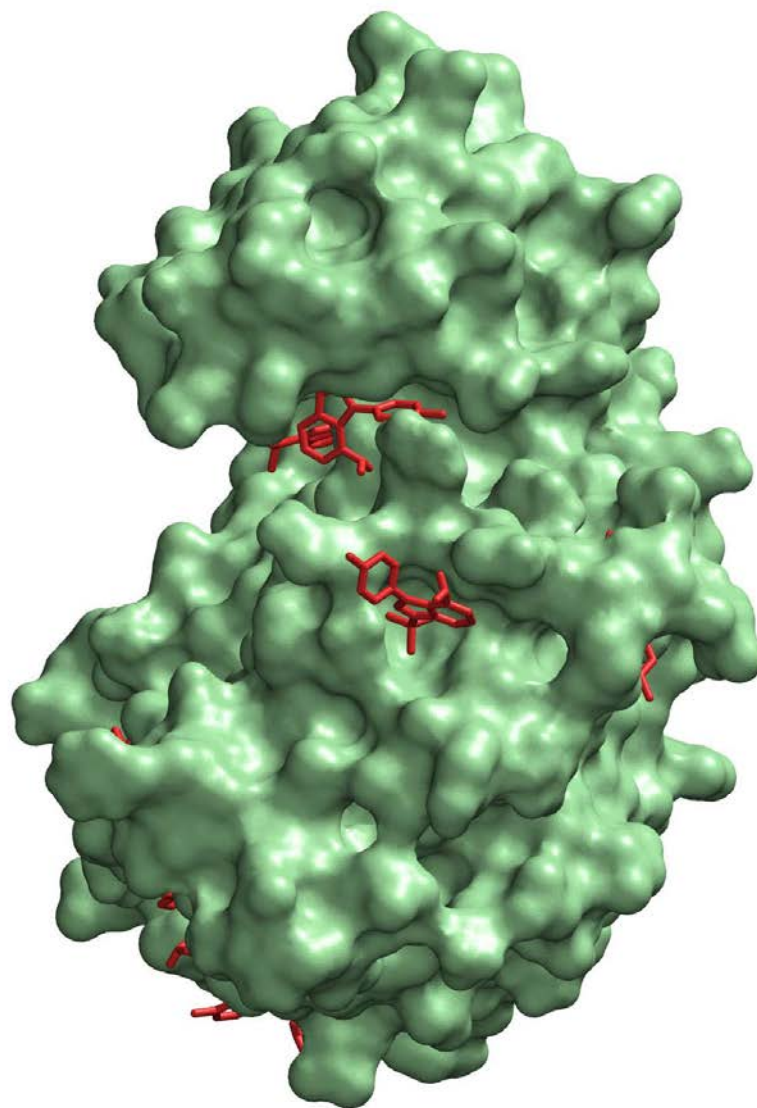
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several fast blind docking cycles

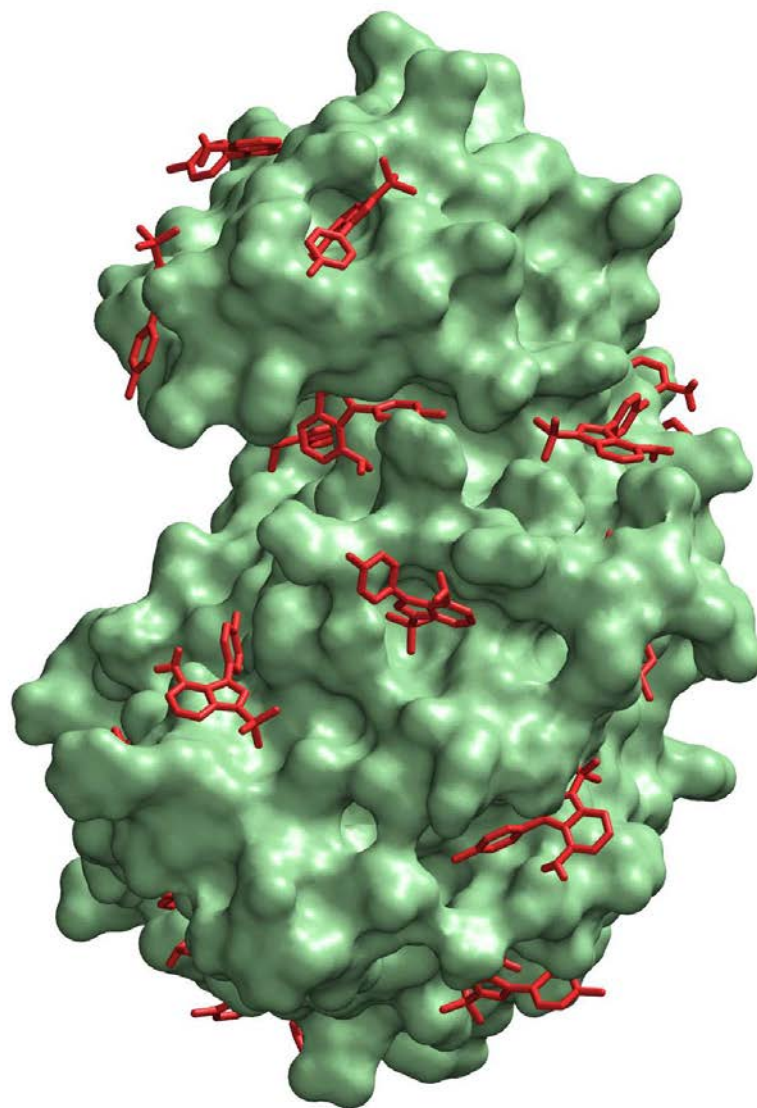




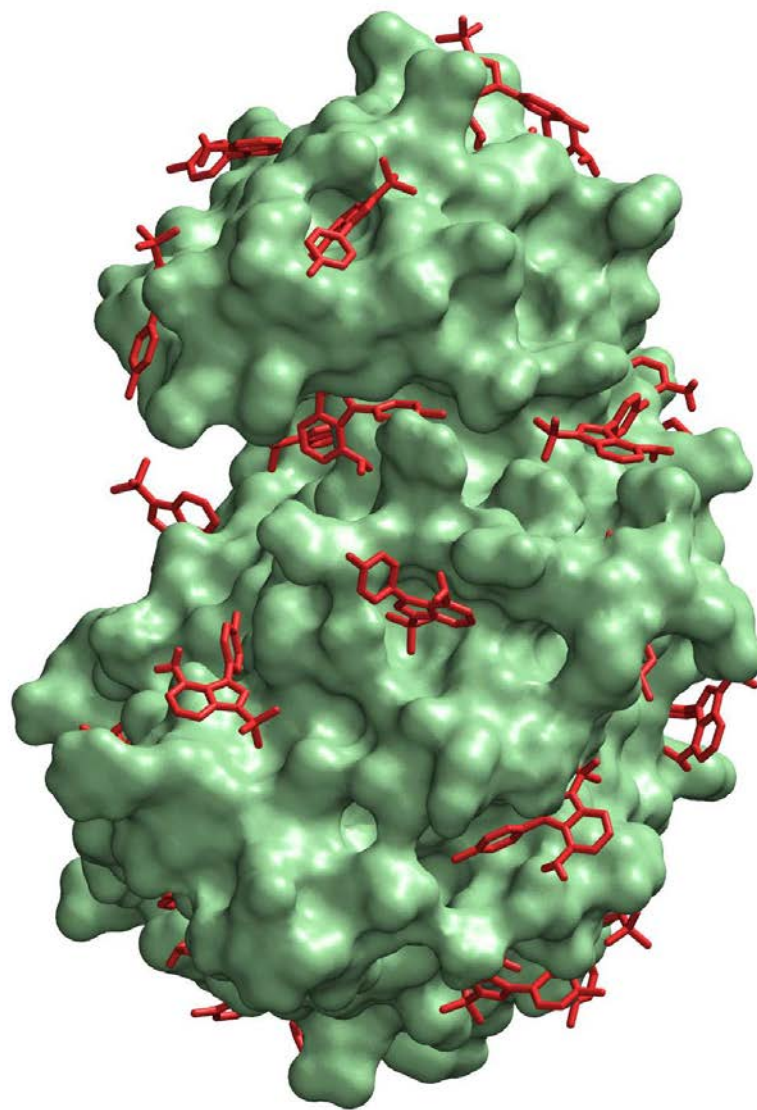
Cycle 1



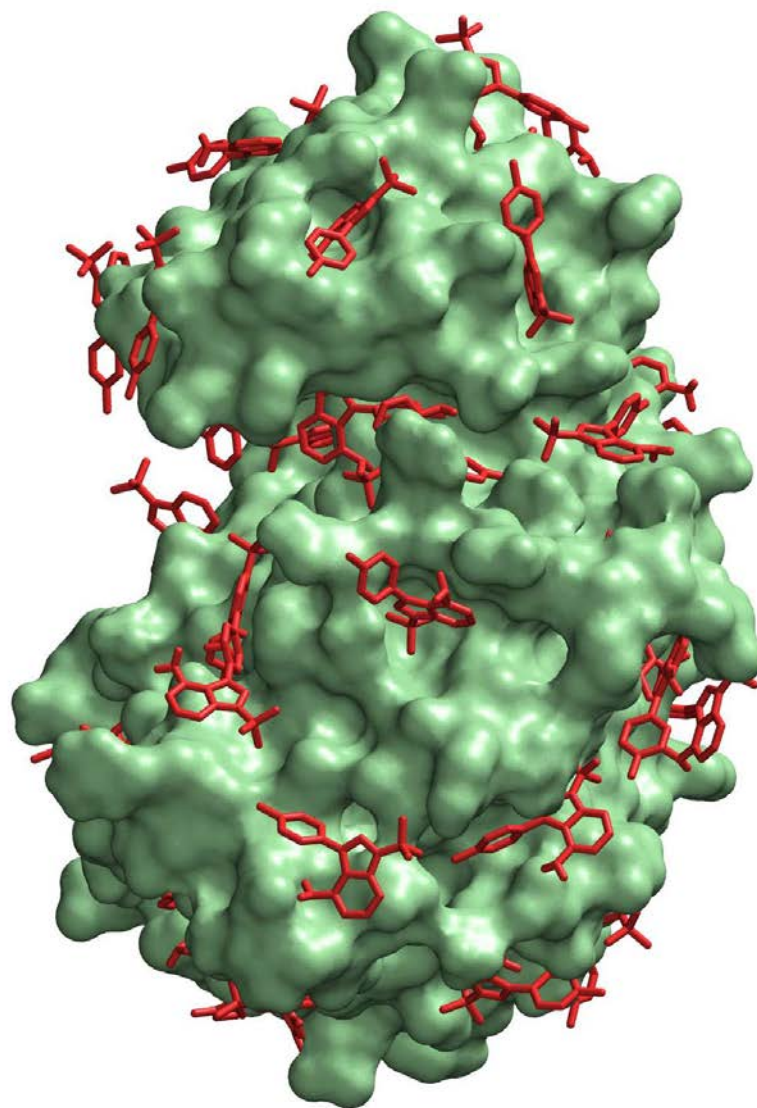
Cycle 2



Cycle 3

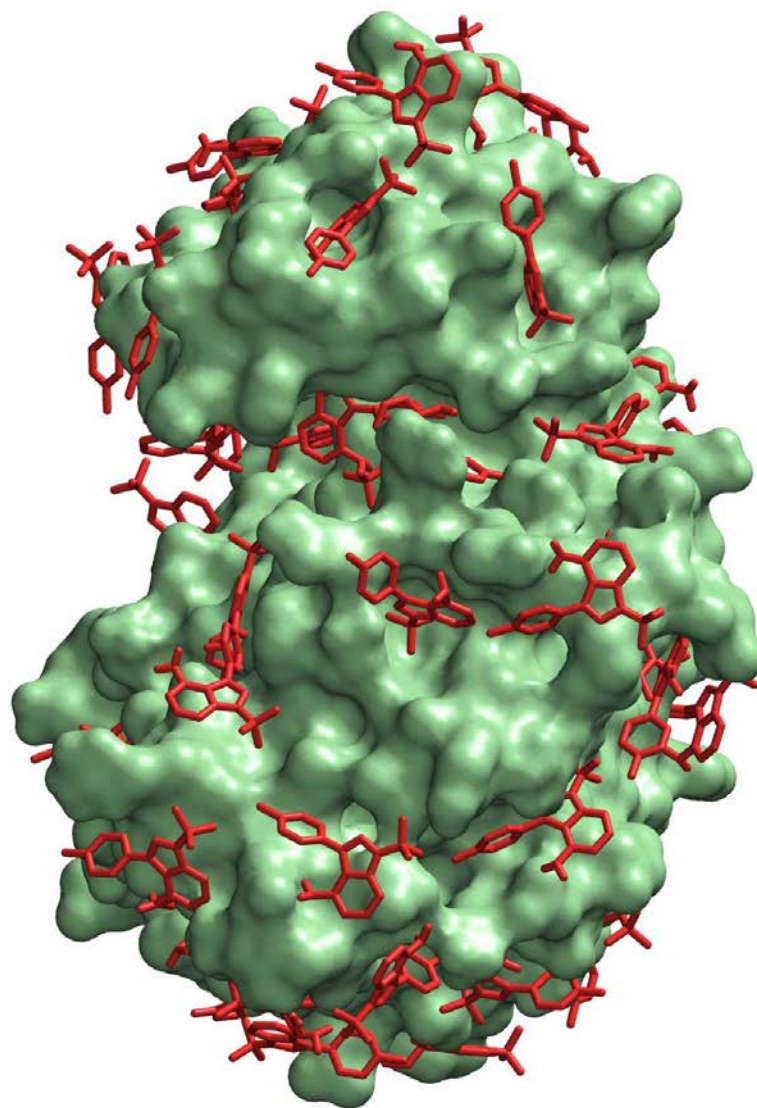


Cycle 4

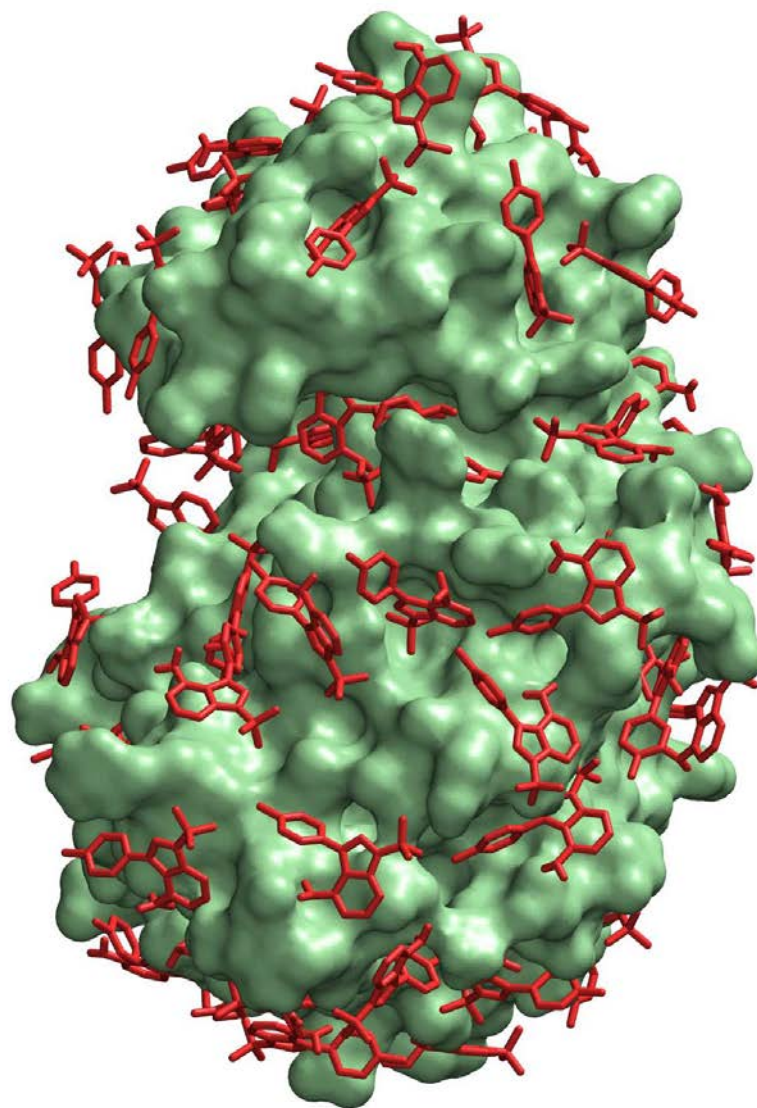




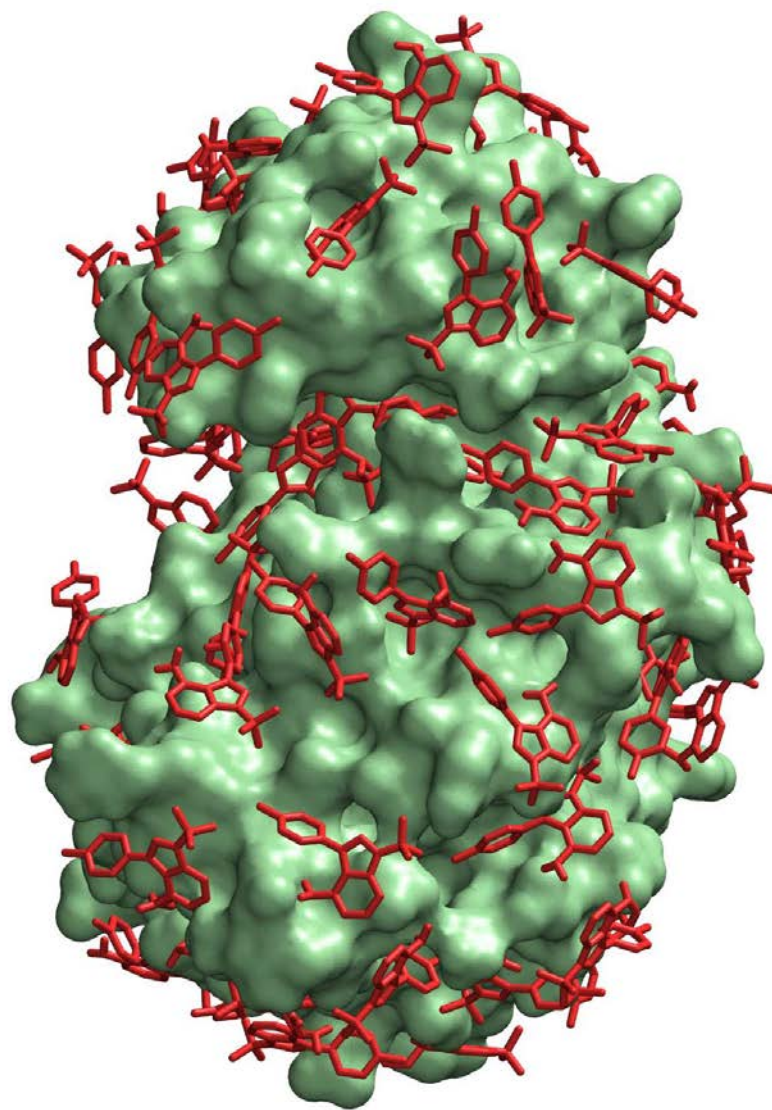
Cycle 5



Cycle 6

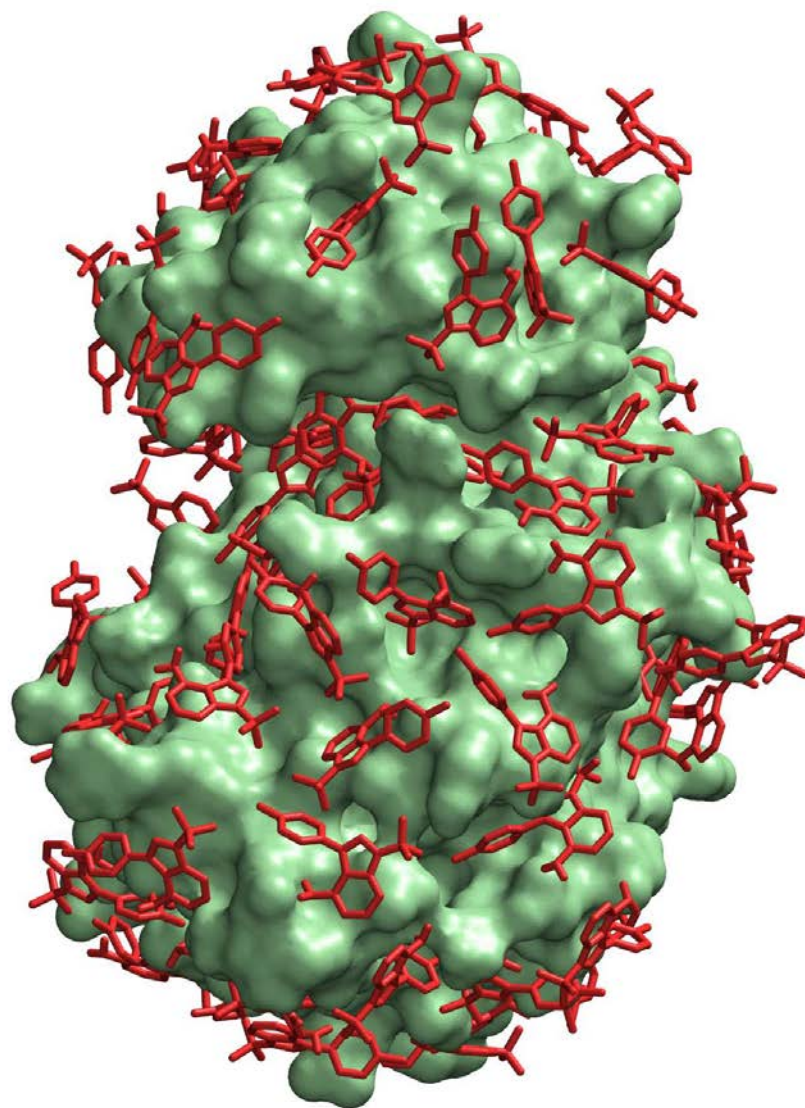


Cycle 7

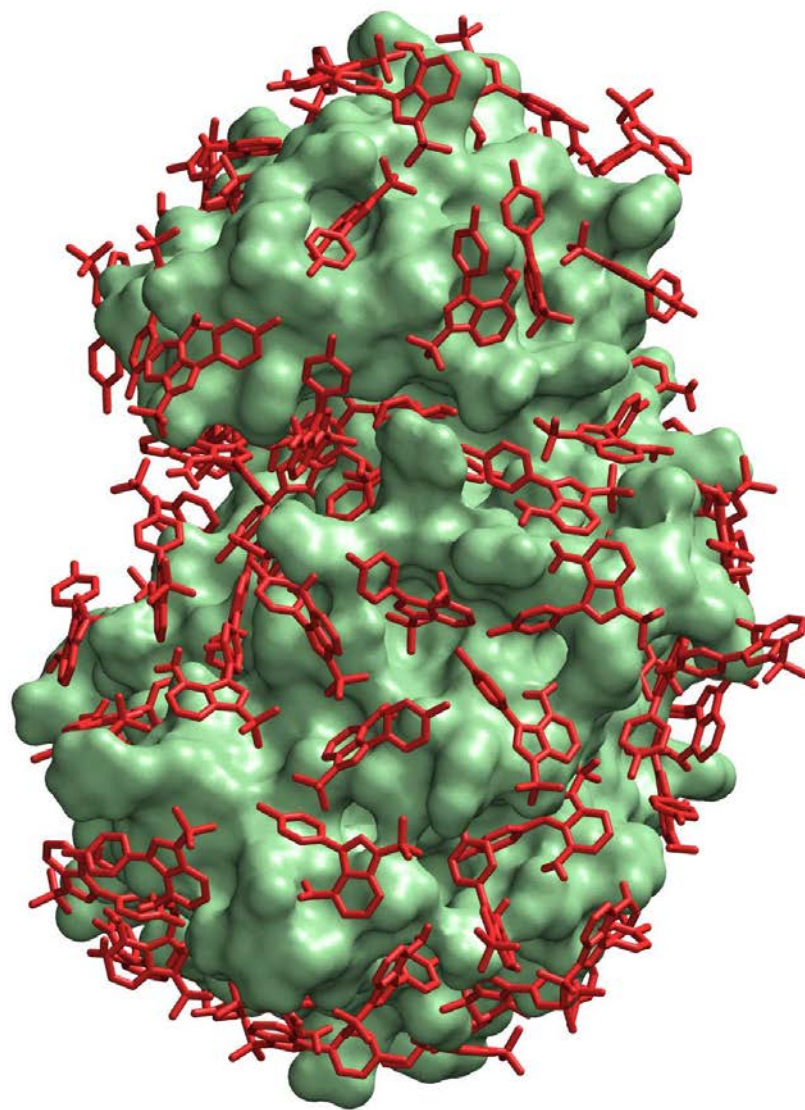




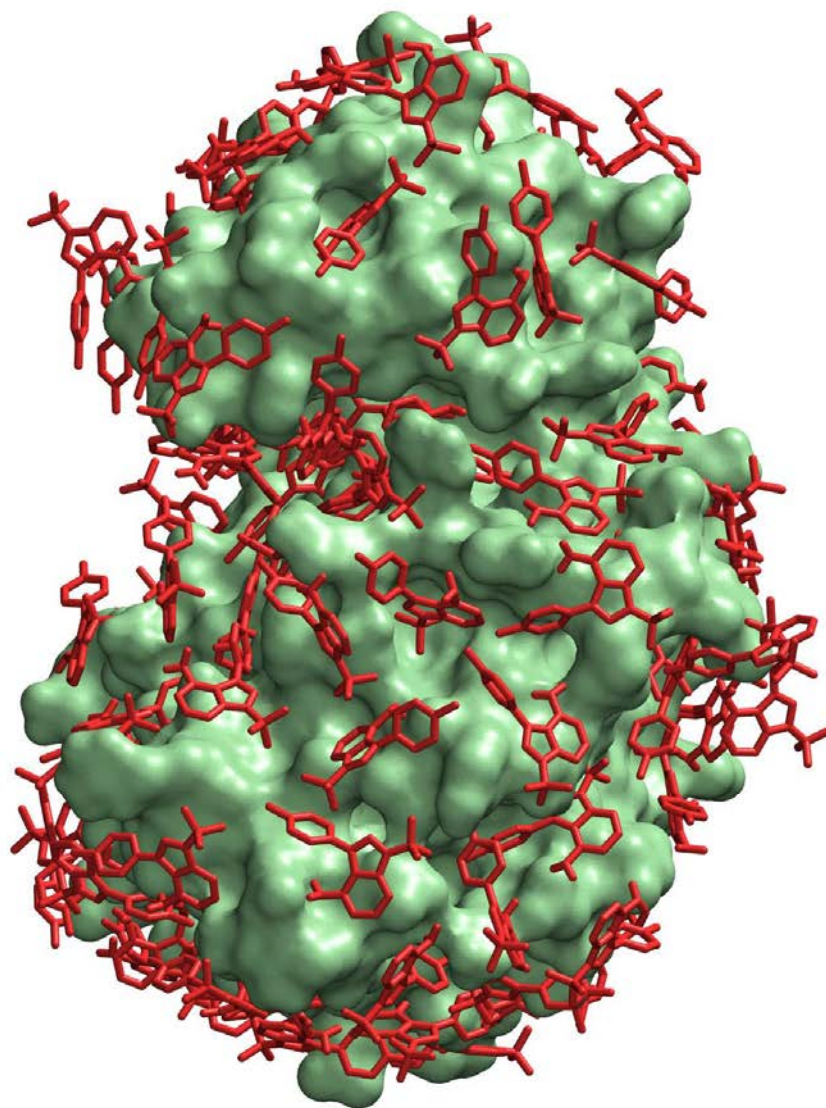
Cycle 8



Cycle 9

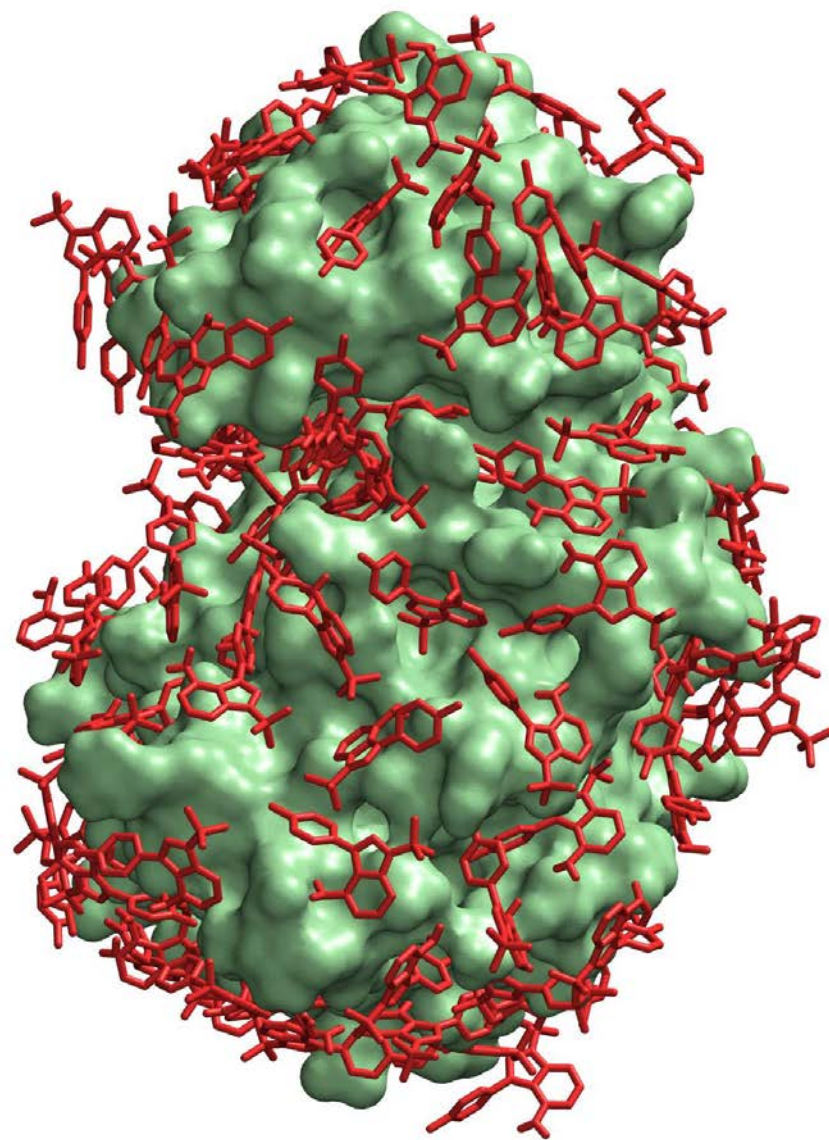


Cycle 10

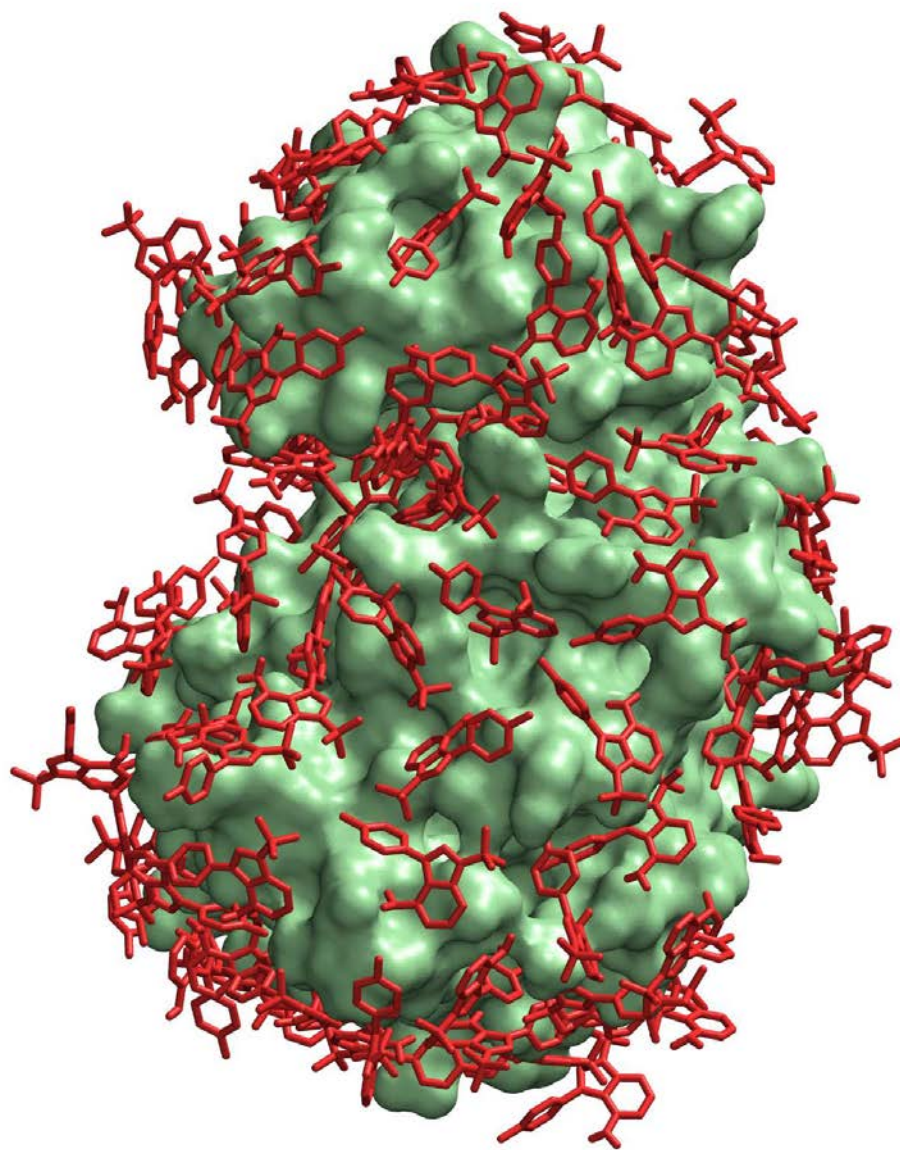




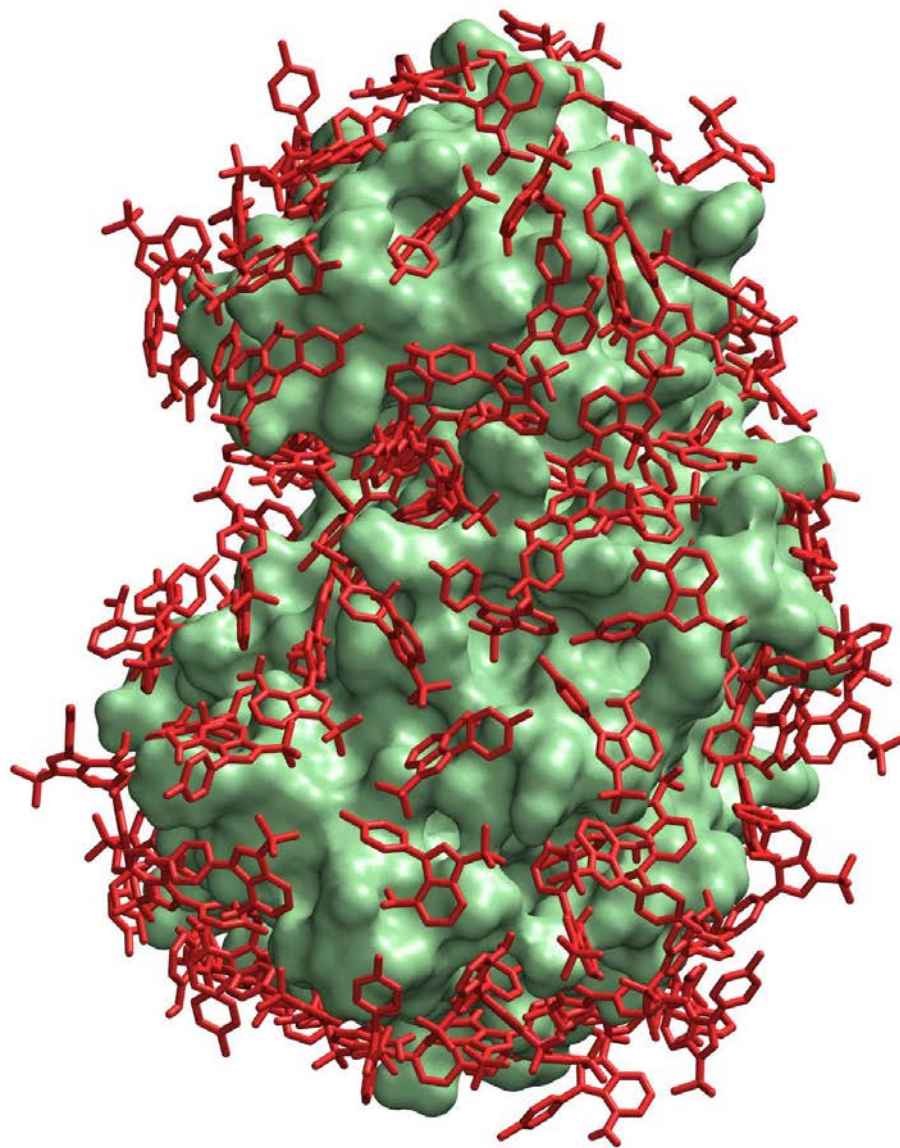
Cycle 11



Cycle 12

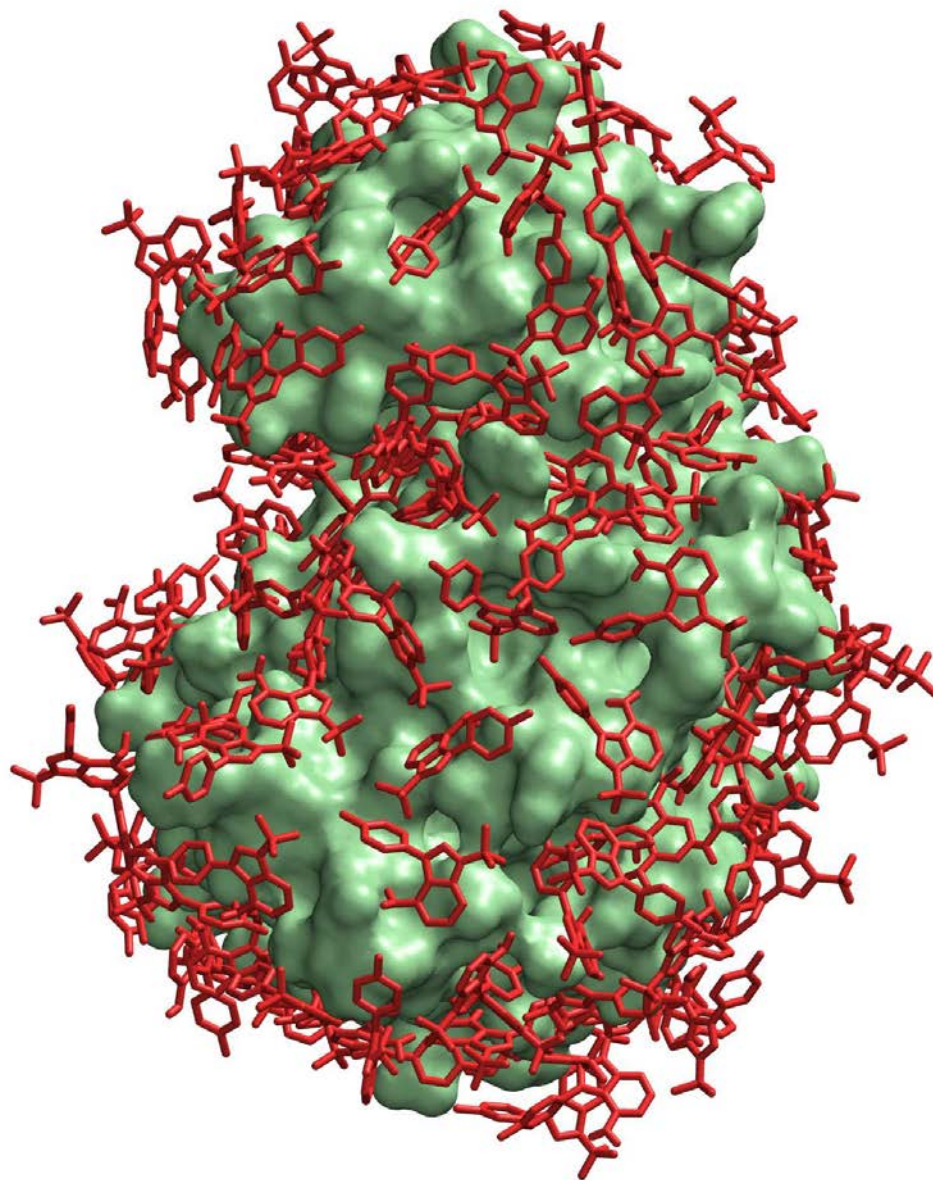


Cycle 13



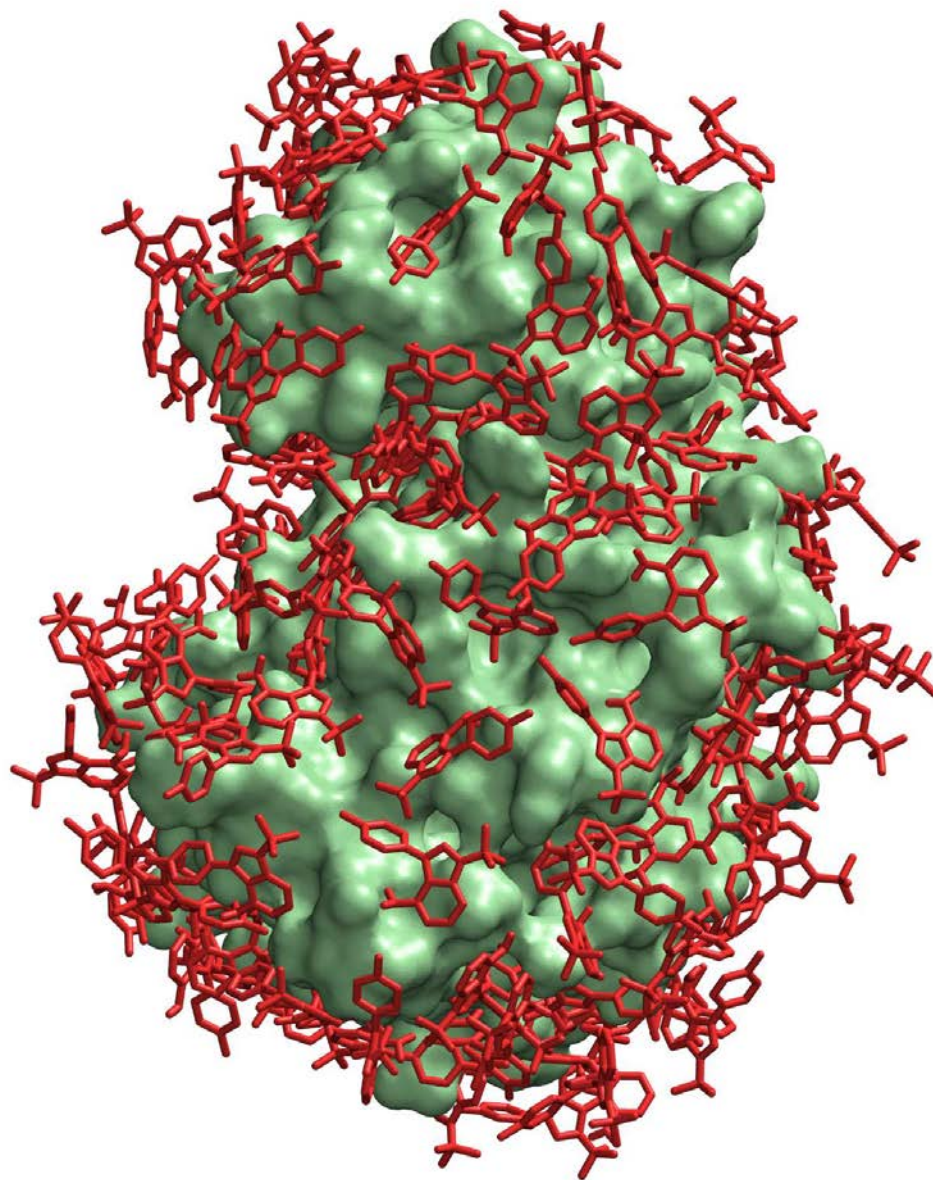


Cycle 14





Cycle 15

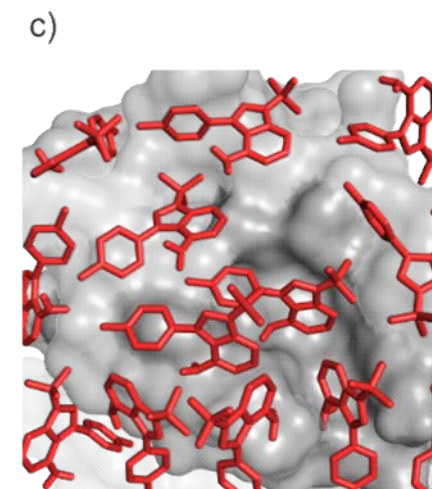
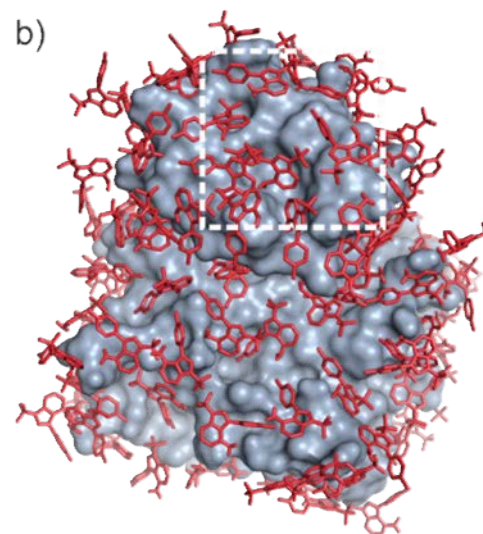
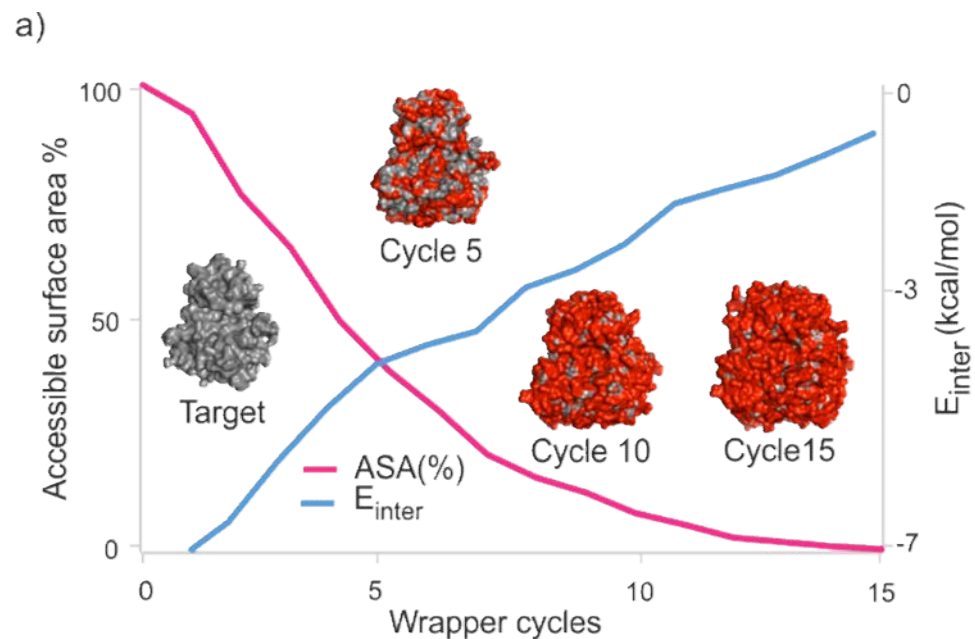


Now, we have a target, systematically wrapped in ligand copies

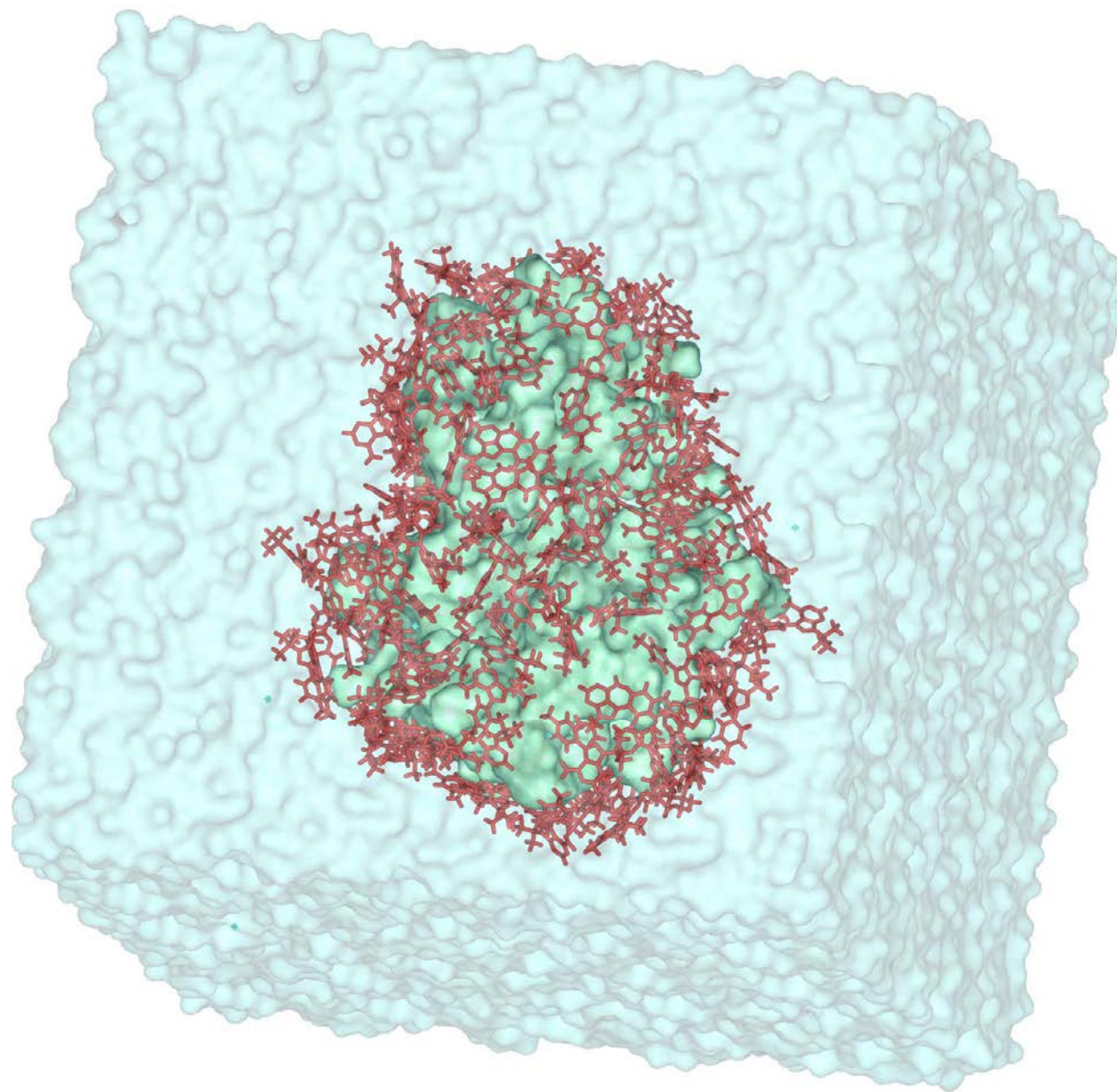
Target  
haematopoietic cell kinase (HCK)

Ligand  
1-ter-butyl-3-p-tolyl-1 h-pyrazolo[3,4-d]pyrimidin- 4-ylamine (PP1)

PDB 1QCF



Adding some water  
molecules

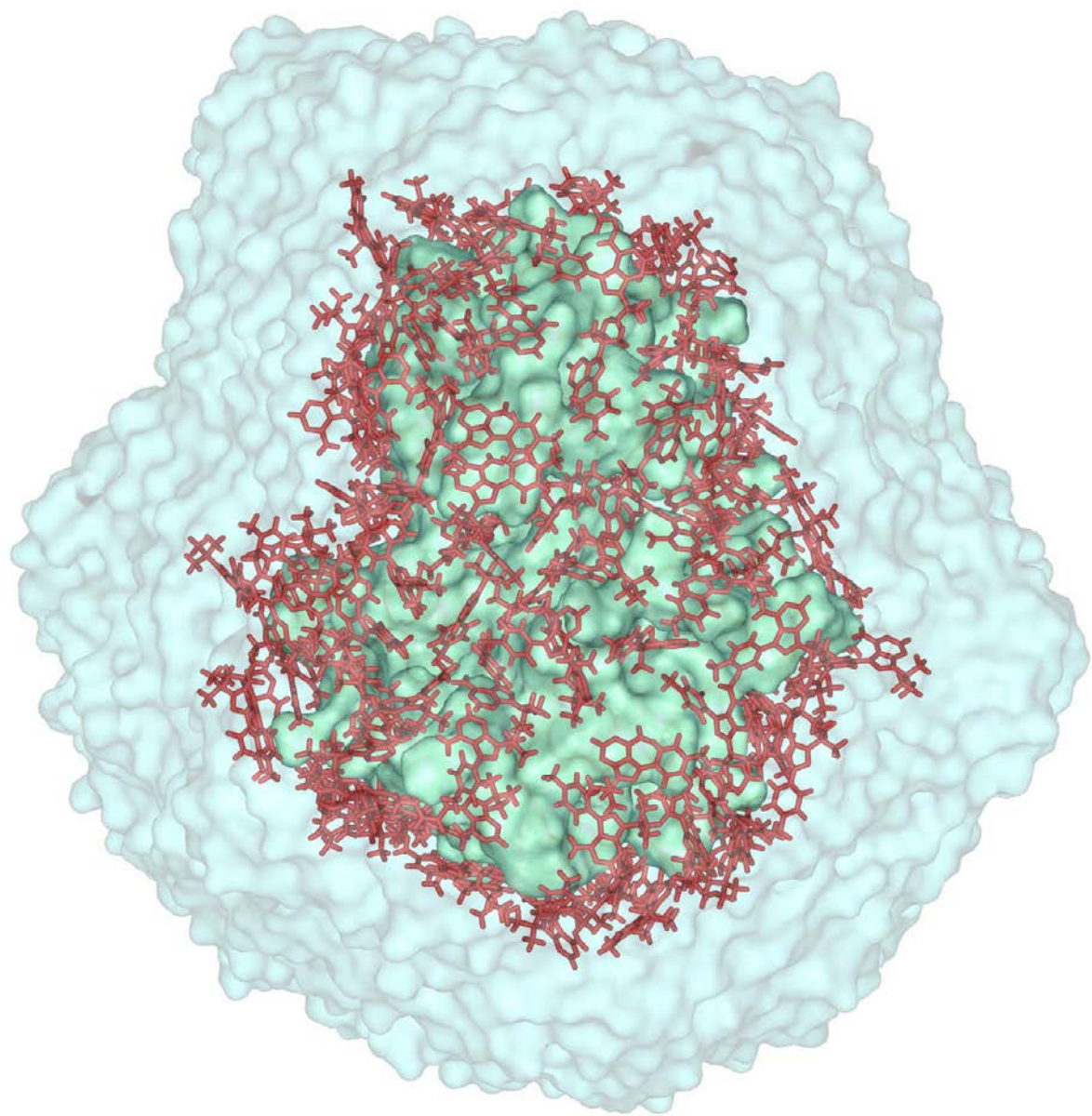


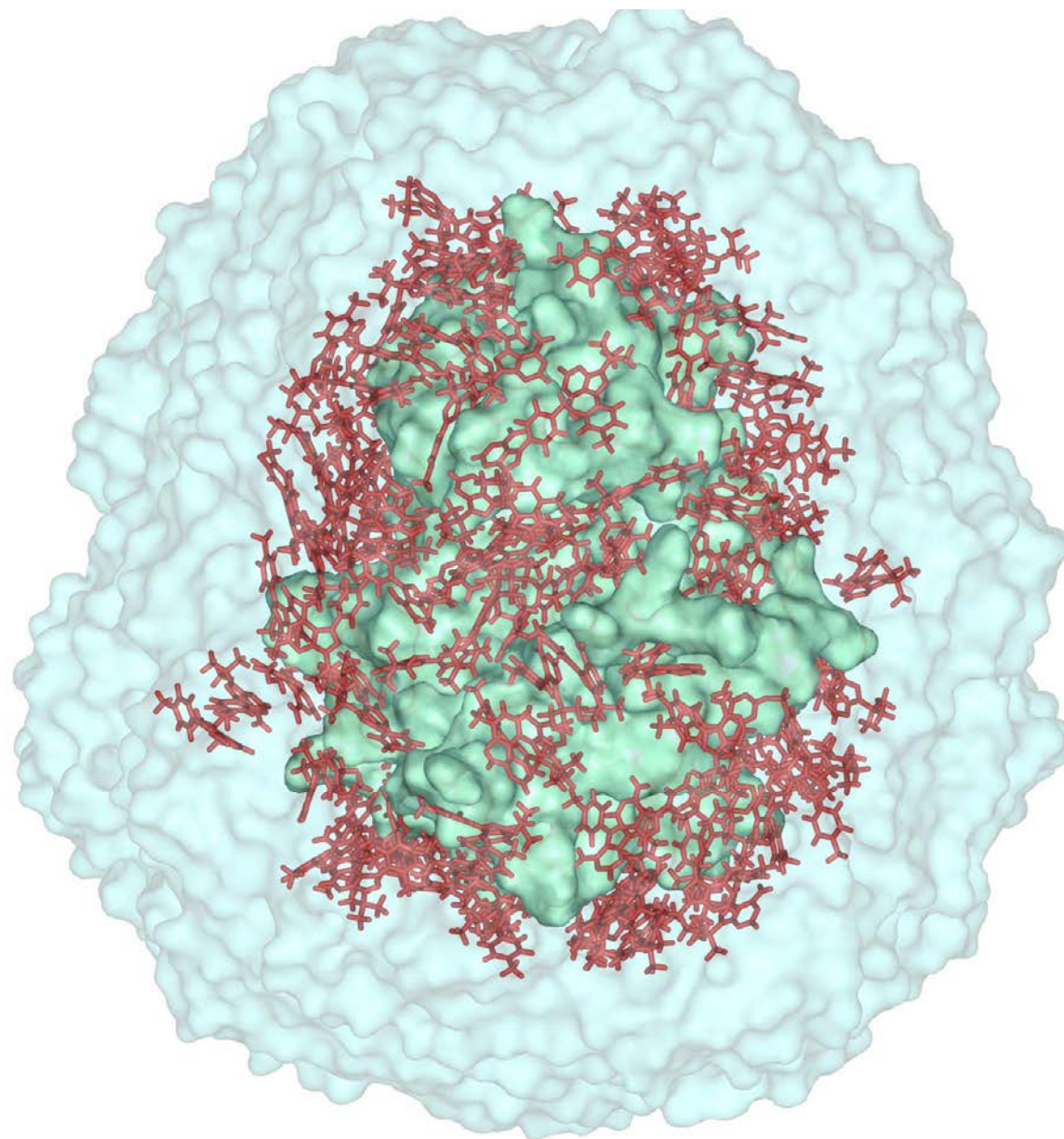
# Shaker

=

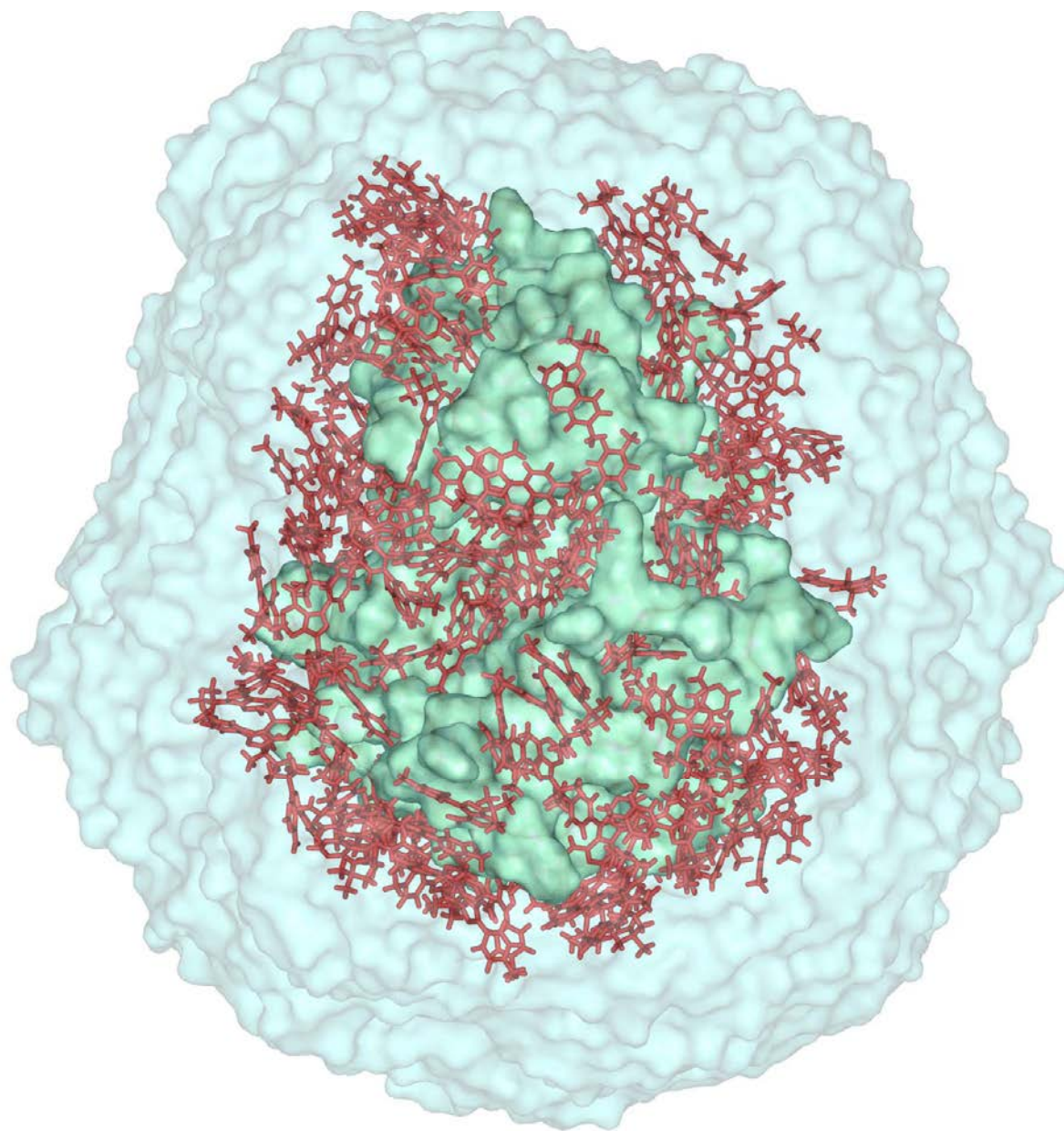
short molecular dynamics cycles  
in explicit water

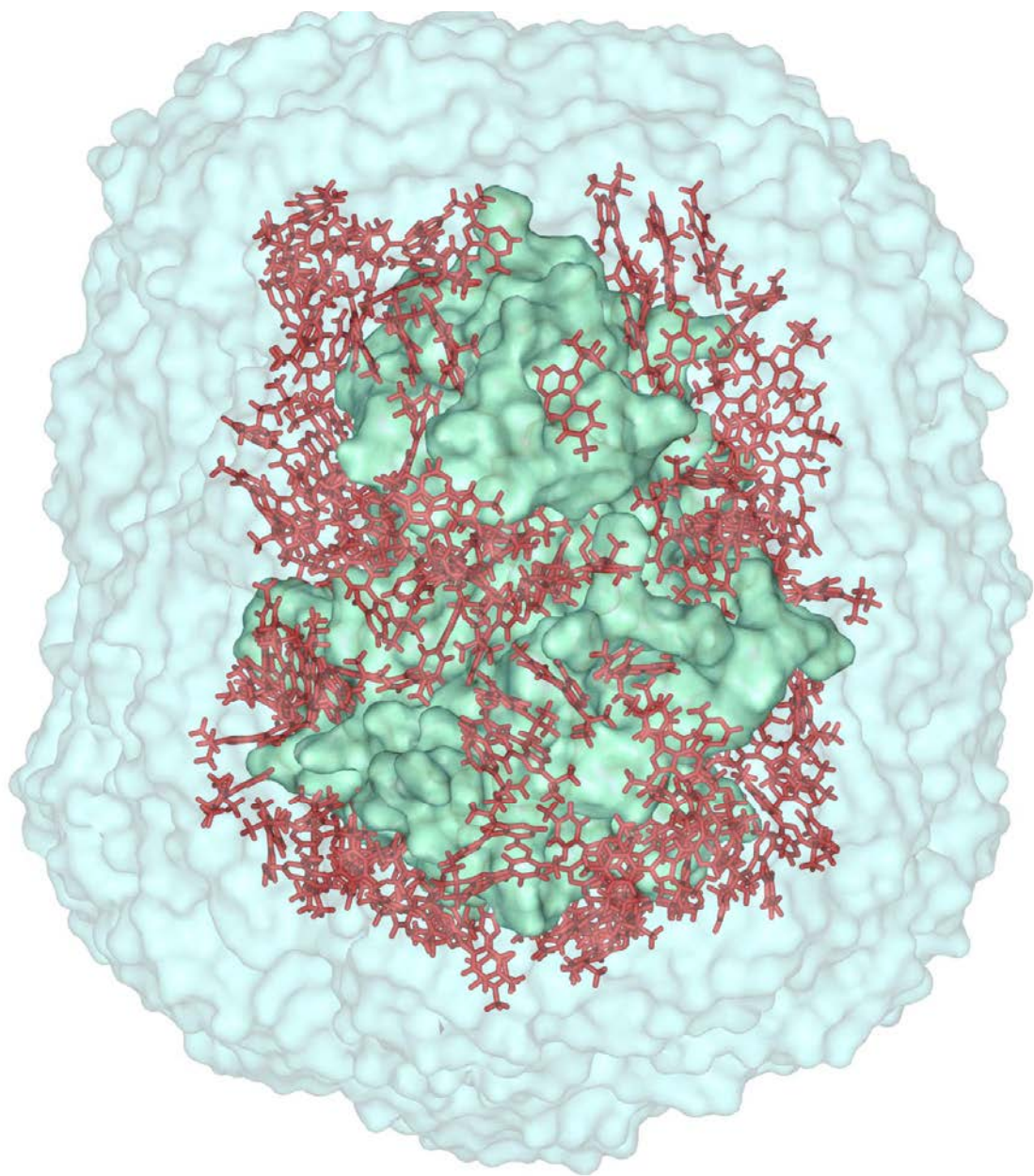




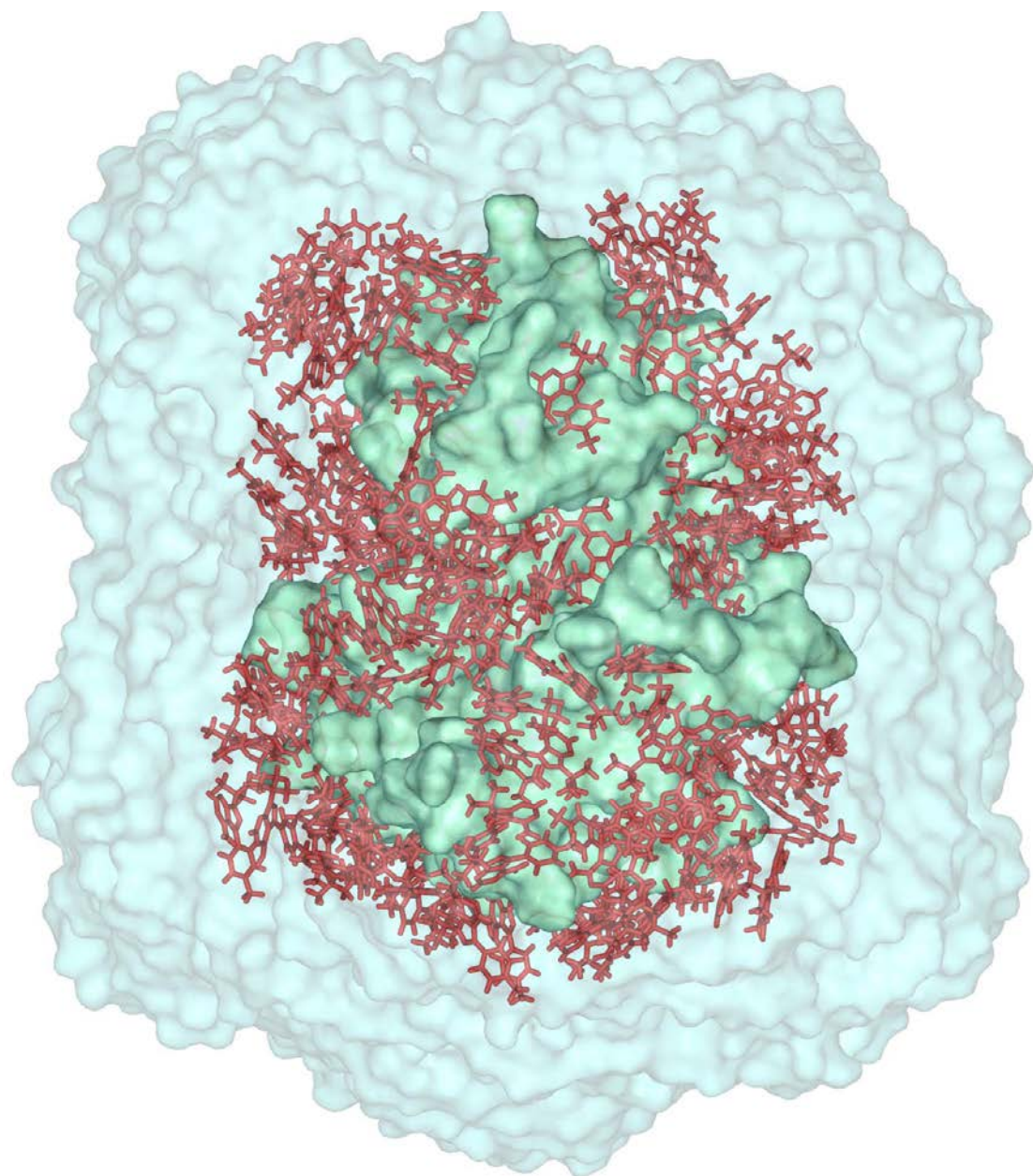


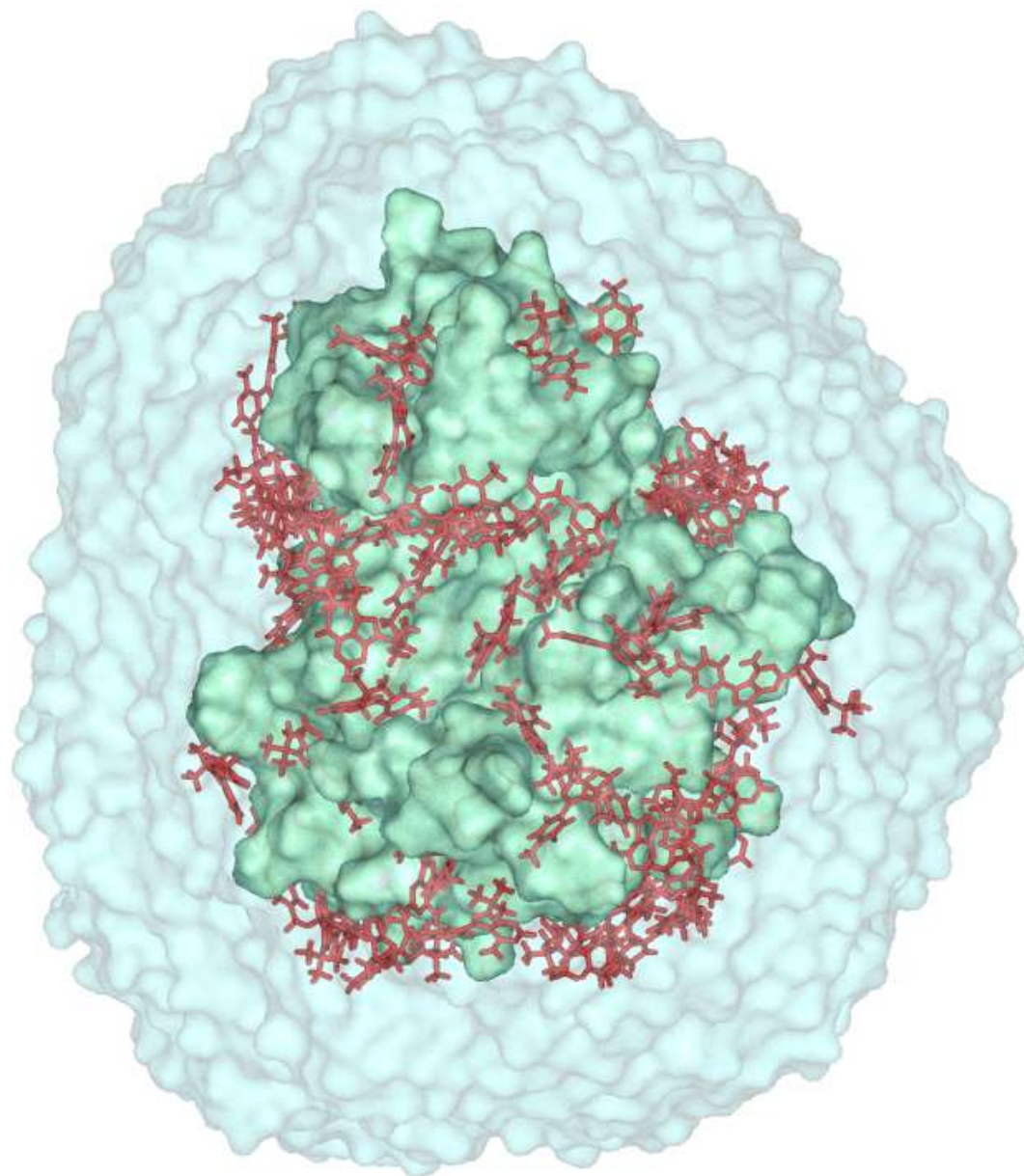


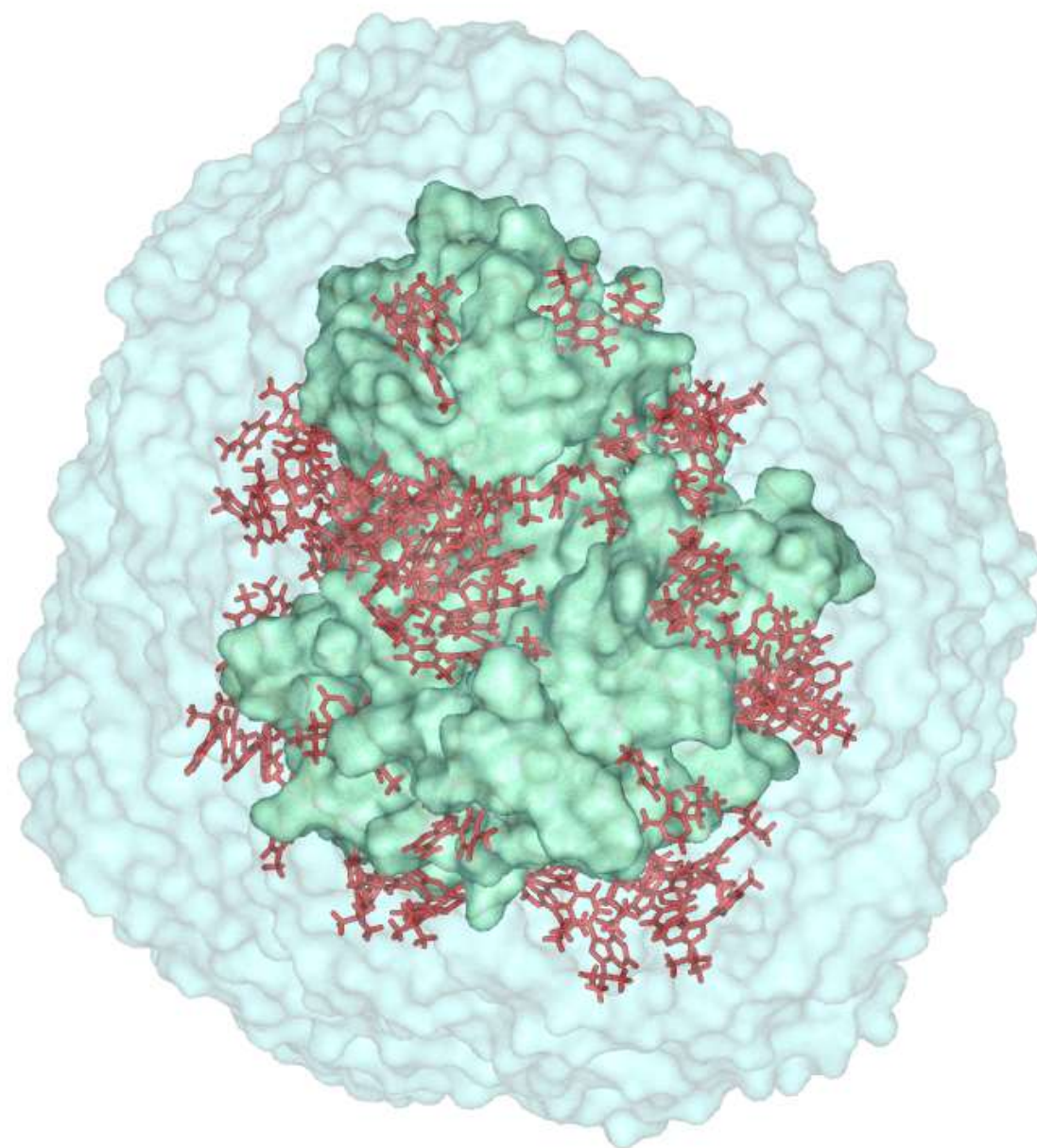




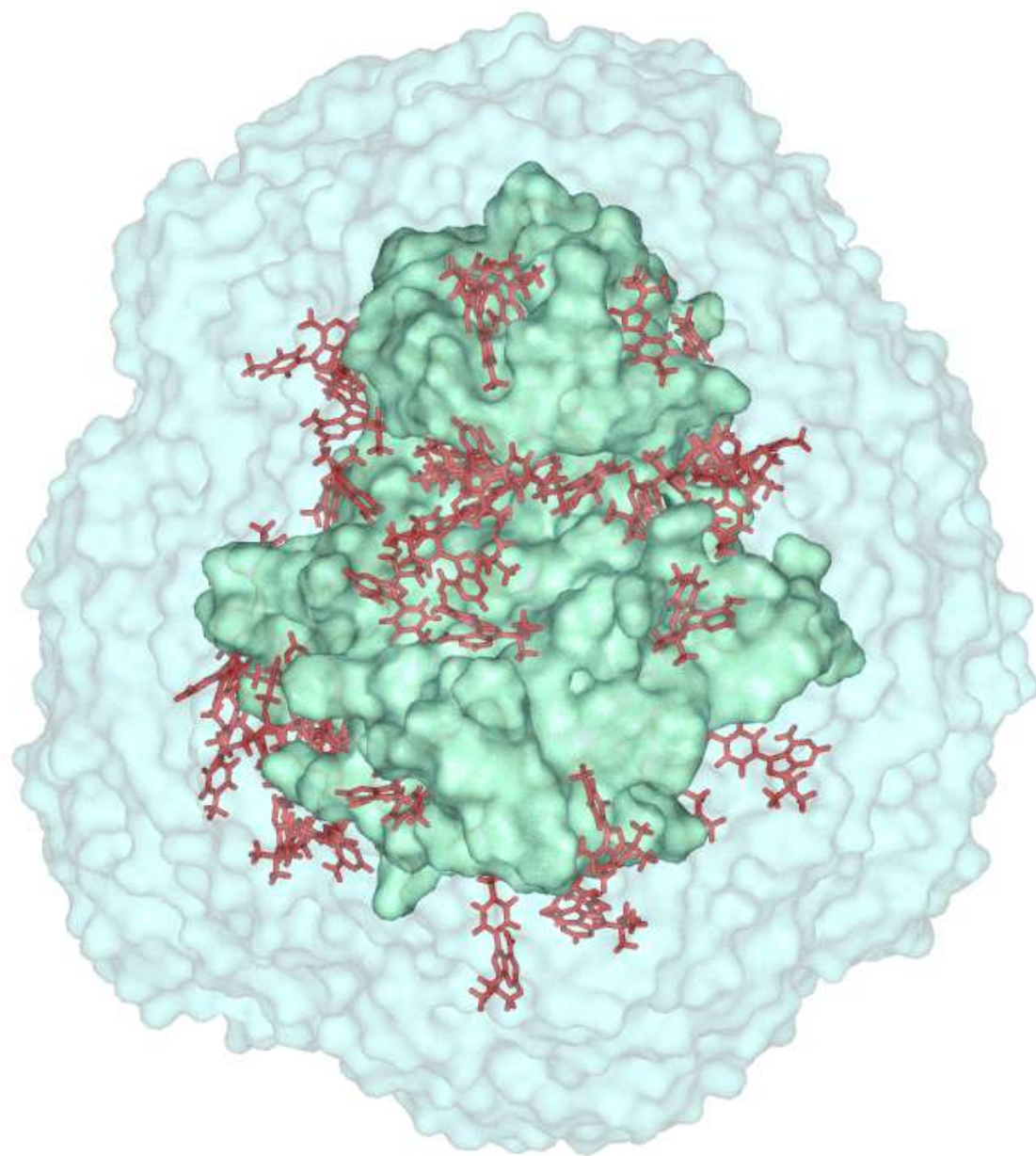


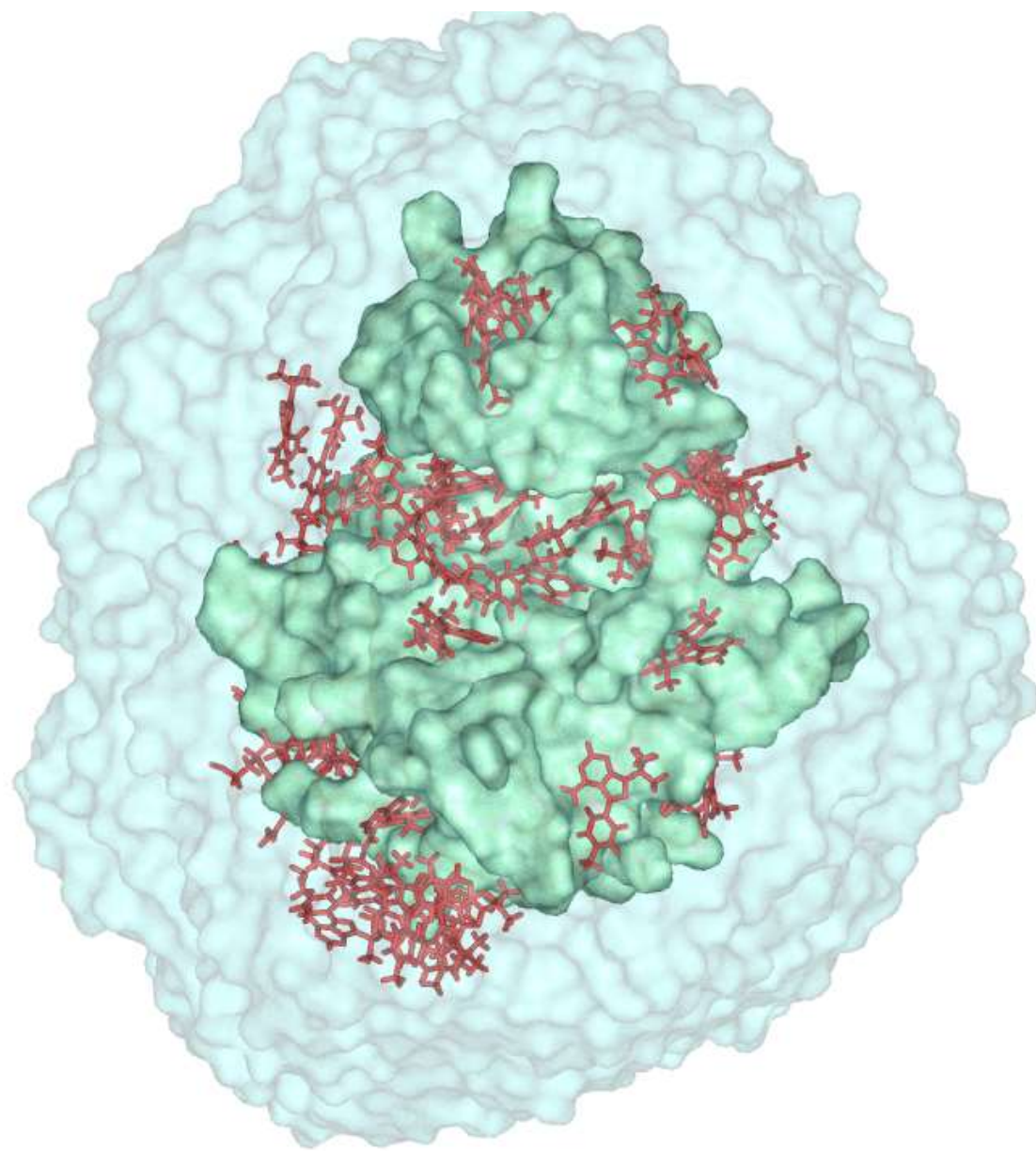






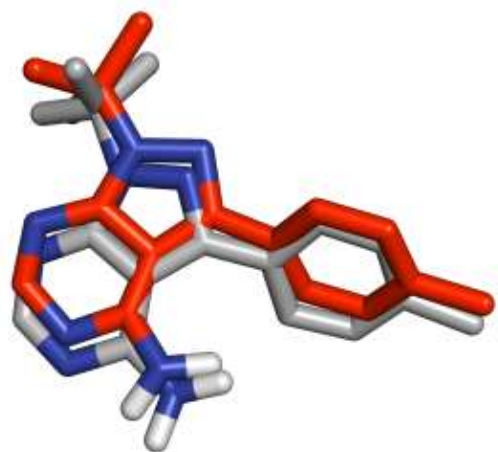




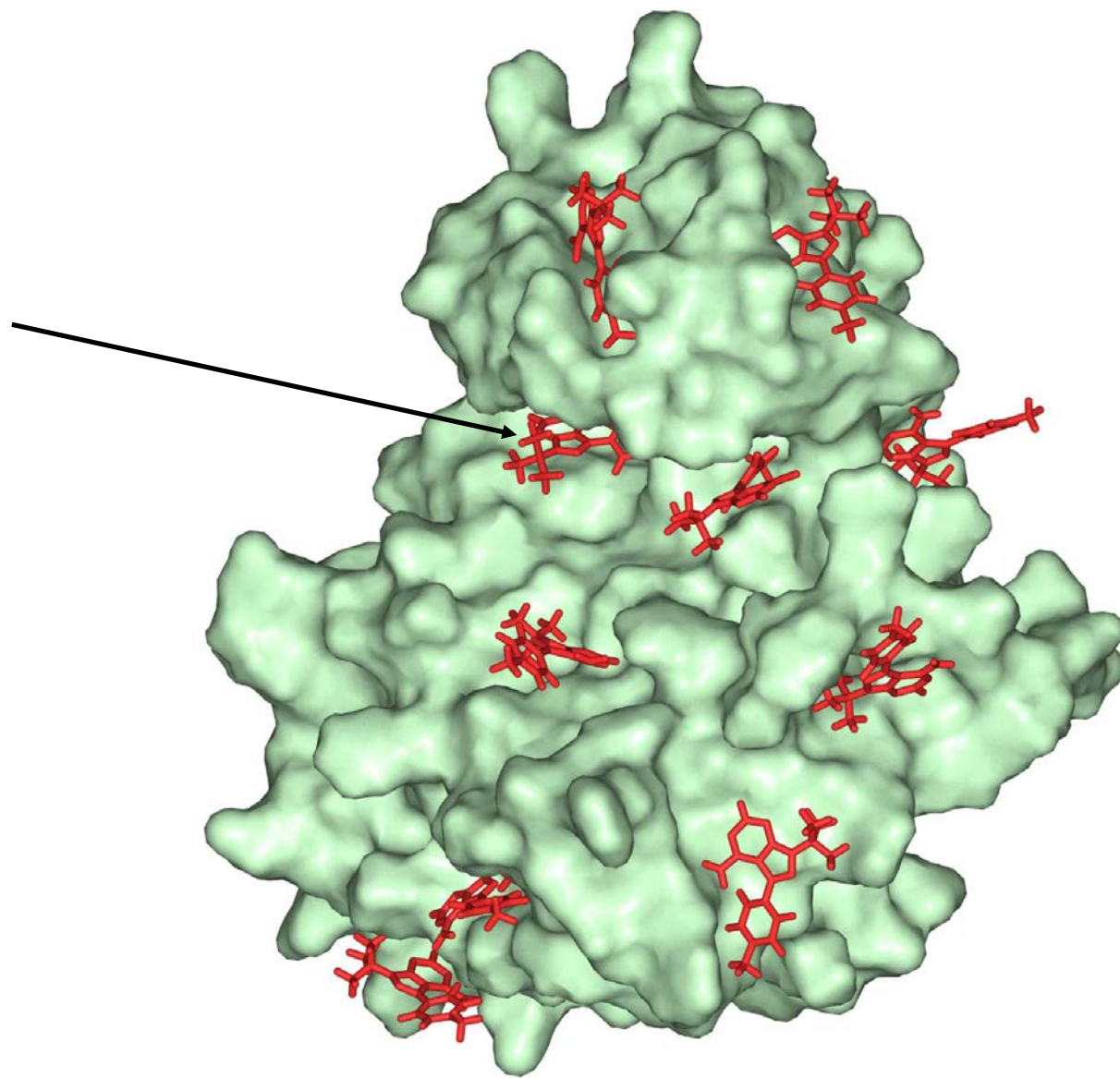


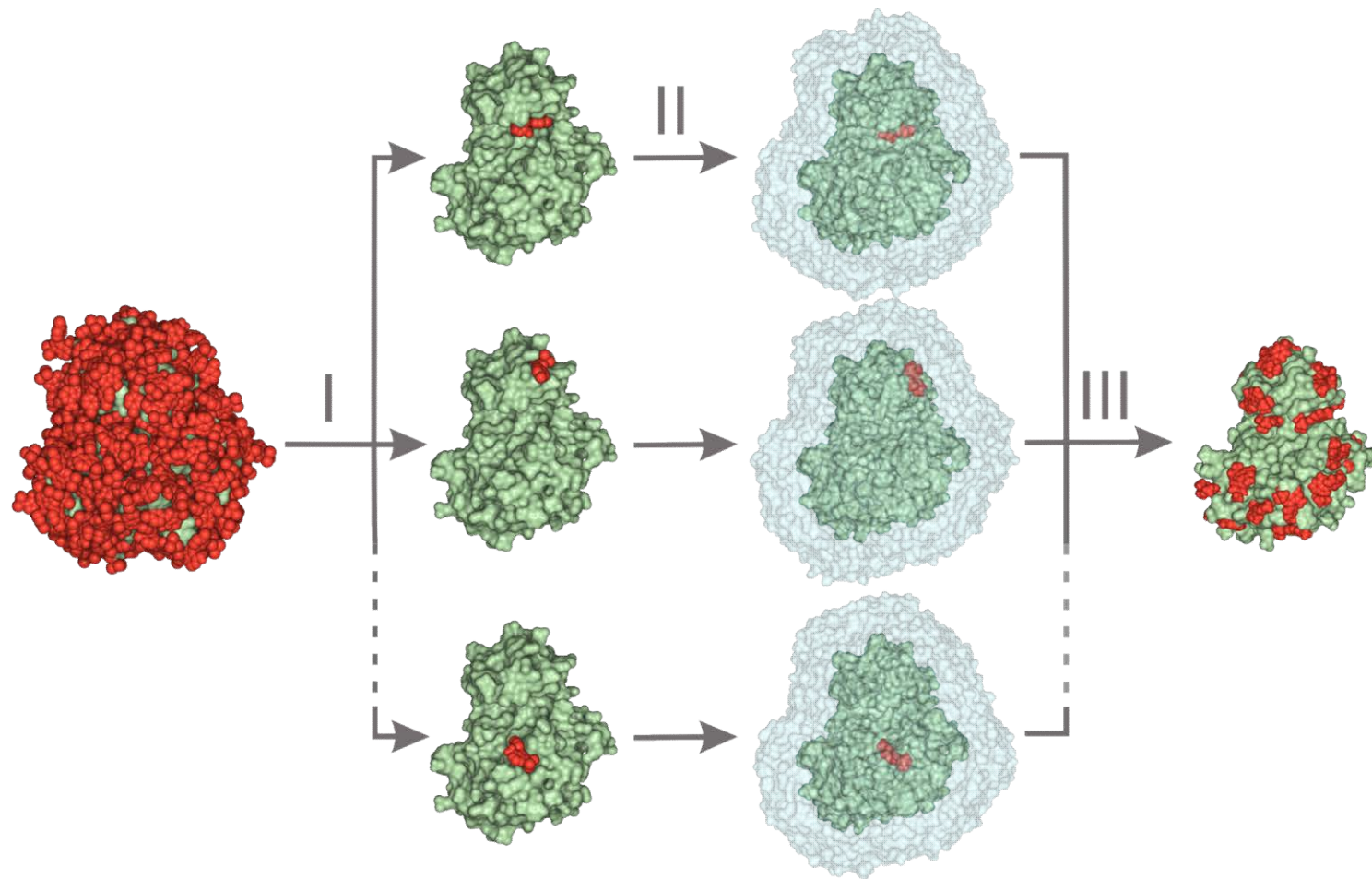


After some filtering, etc.  
the result:



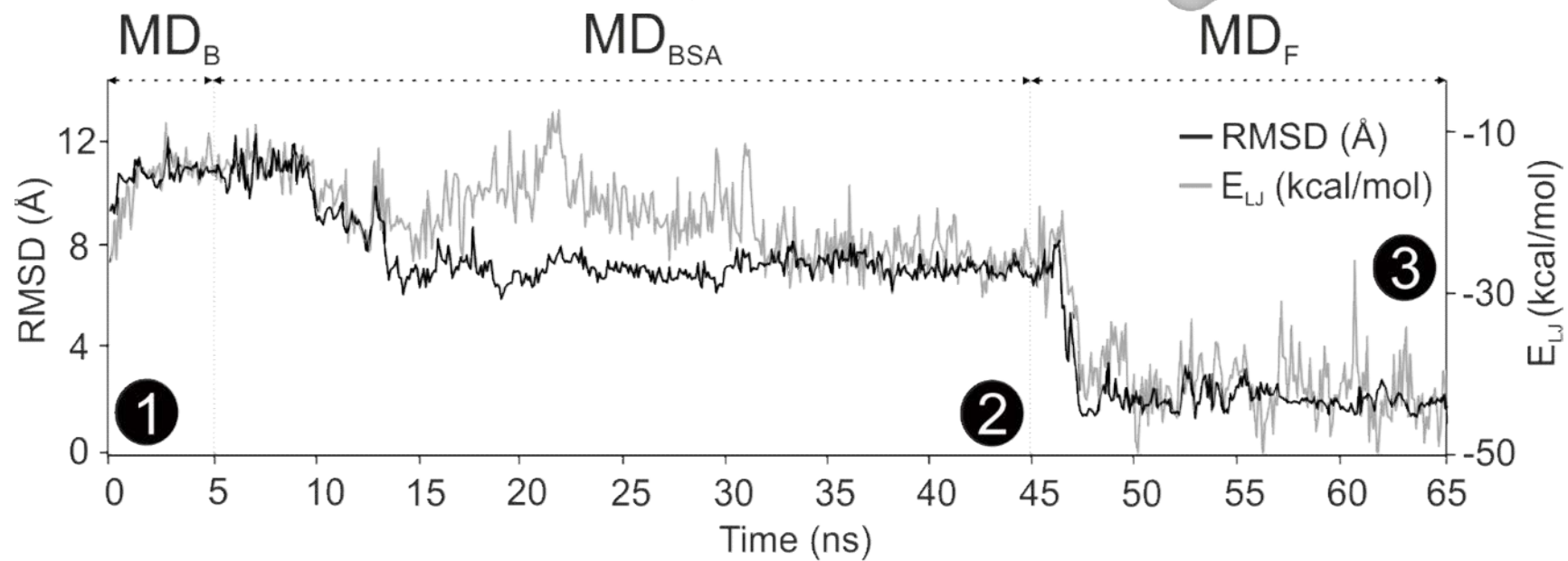
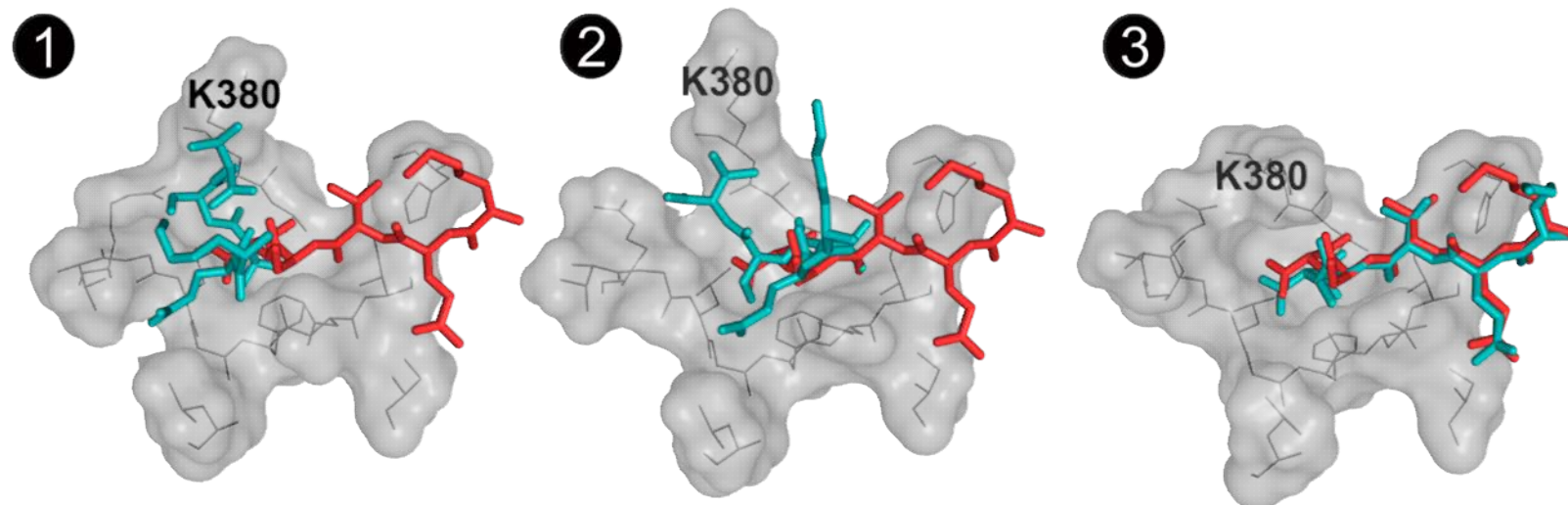
1.4 Å





Parallelization at both Shaker and MD levels

# Refinements with molecular dynamics





# Acknowledgements

National Research, Development, and Innovation  
Office, Hungary

University of Pécs

PRACE Partnership for Advanced Computing in  
Europe

CSCS Swiss National Supercomputing Centre

NIIF Hungarian National Information  
Infrastructure Development Institute

Gedeon Richter Pharmaceutical Plc.



# Thank You!



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