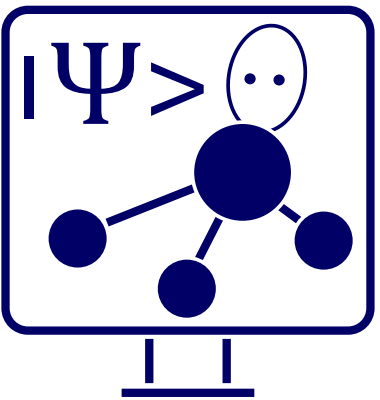
PITFALLS OF SARS-COV2 MAIN PROTEASE COVALENT INHIBITION MODELING WITH THE COMBINED QUANTUM AND MOLECULAR MECHANICS APPROACHES

Igor Polyakov[1,2], Maria Khrenova[1,2]

[1]*Lomonosov Moscow State University, Moscow, Russia*

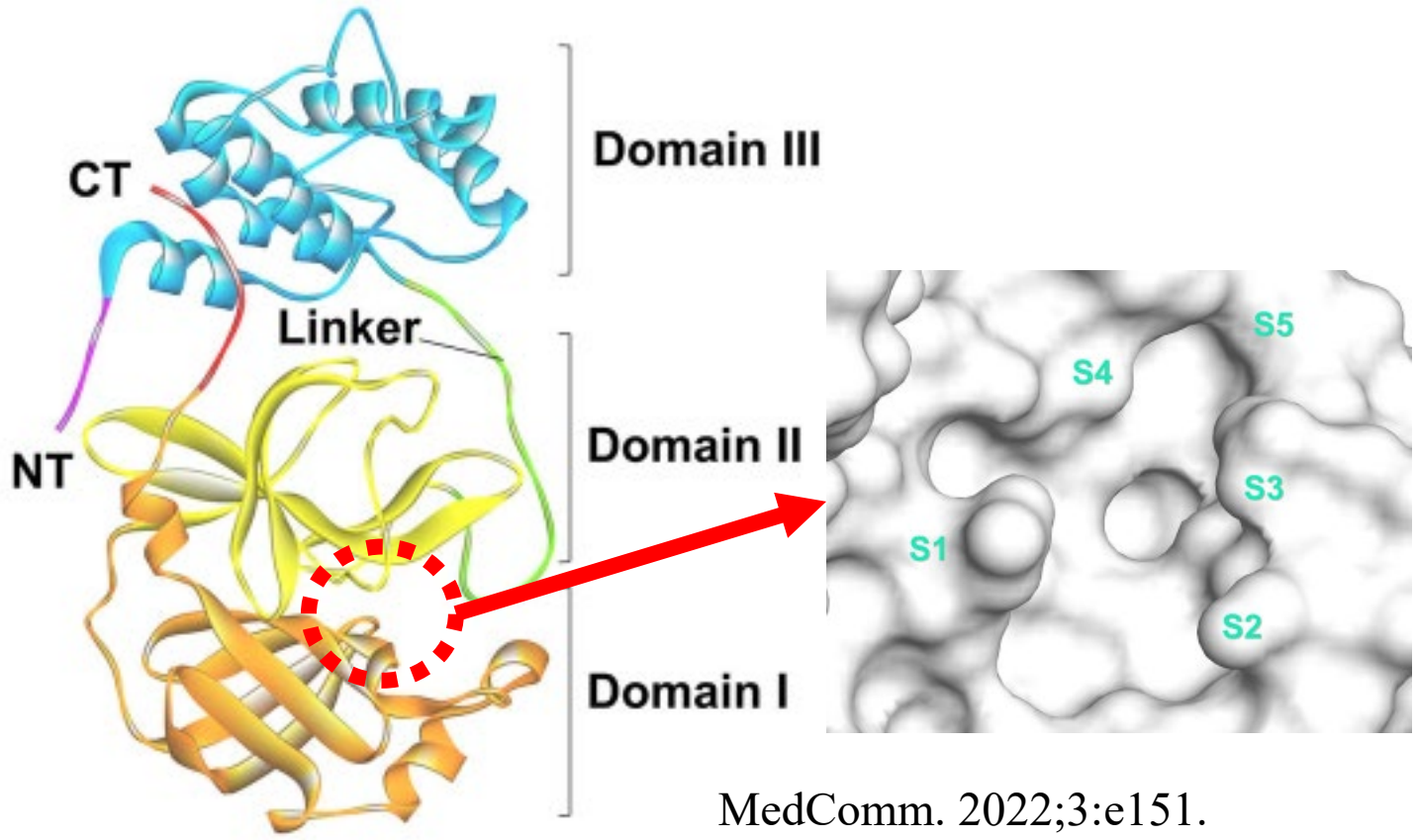
[2]*Emanuel Institute of Biochemical Physics RAS, Moscow, Russia*

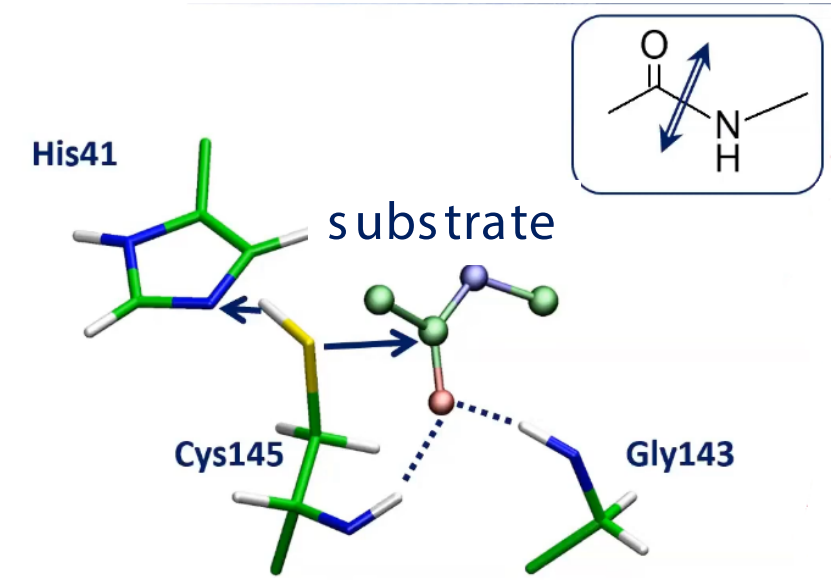


IBCP RAS

SARS-CoV-2 M^{pro} ($3CL^{pro}$) – cysteine hydrolase

- Hundreds of PDB structures with different ligands
- 306 residues, 34.21 kD monomer
- Catalytic dyad Cys145+His41.
- Cuts the polypeptide chain to produce the nsp4-16 proteins





Moiety	Surface	Specificity
S1	Phe140, Gly143, Ser144, Cys145, His163, Glu166, His172	Glutamine, lactam
S2	Thr25, His41, Cys145	Leu, Phe, Met, Val
S3	His41, Met49, Met165	None
S4	Met165, Glu166	Hydrophobic aa
S5	Glu166, Met165, Gln189	Hydrophilic aa

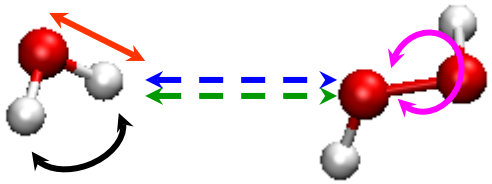
MedComm. 2022;3:e151.

Molecule as a stable system of nuclei and electrons

$$\hat{H}\Psi = E_{QM}\Psi, \quad \Psi = \Psi(r_i, R_j, t)$$

$$\hat{H} = \sum_i \left(-\frac{1}{2}\Delta_{r_i}\right) + \sum_w \left(-\frac{1}{2M_w}\Delta_{R_w}\right) + \sum_{i<j}\frac{1}{r_{ij}} + \sum_{w<v}\frac{Z_w Z_v}{R_{wv}} - \sum_{iw}\frac{Z_w}{|R_w - r_i|}$$

Molecule as springs and charged balls



Bond deformation

Valence angles deformation

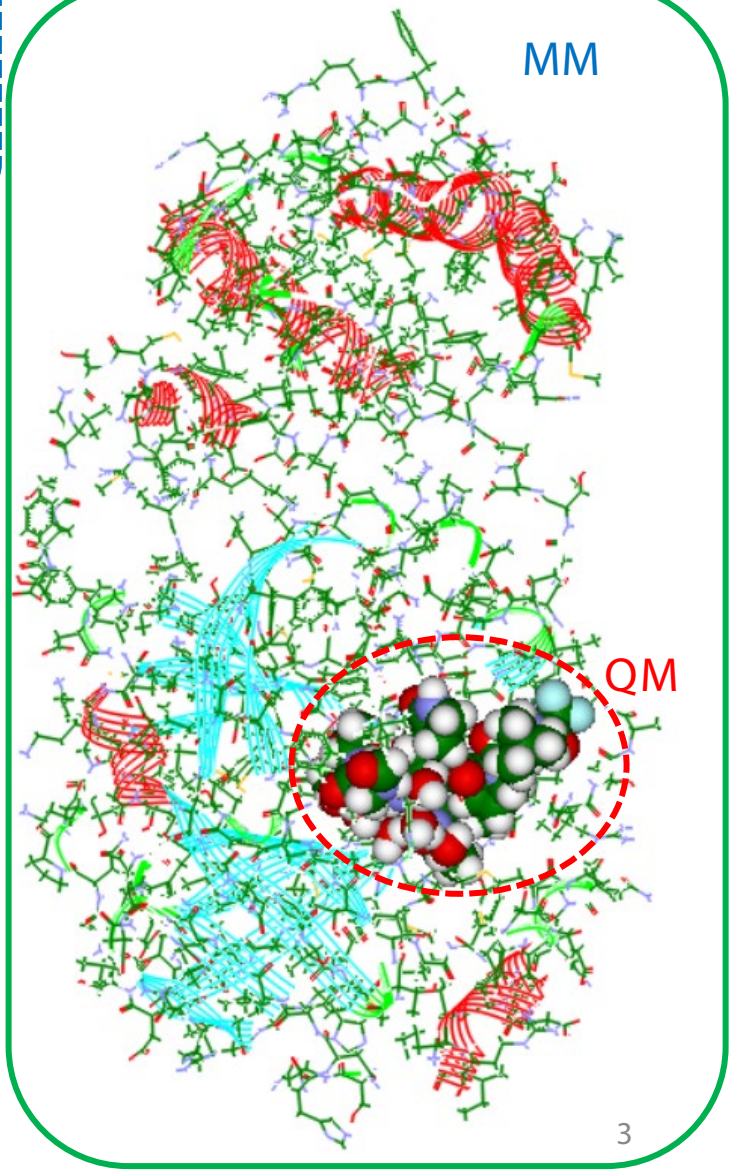
Torsion rotations

Electrostatic interaction

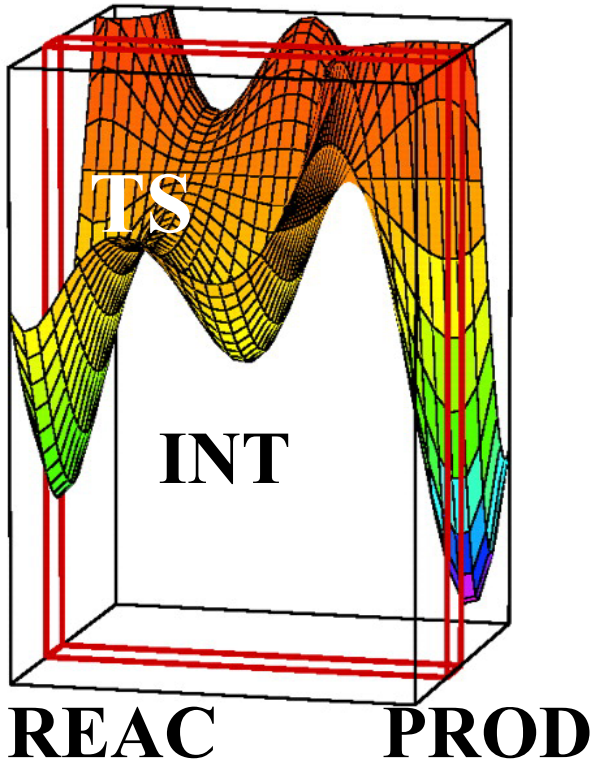
Van-der-Waals interactions

Full energy of the system:

E(QM/MM) = E(QM) + E(MM) + E(QM/MM)



Stationary points on the potential energy surface (PES)

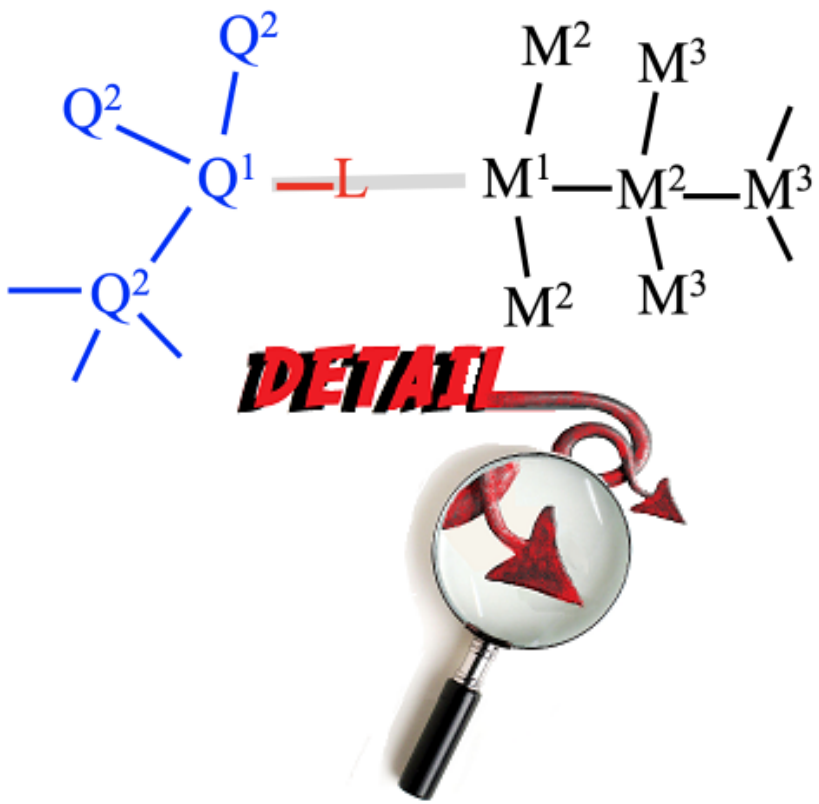


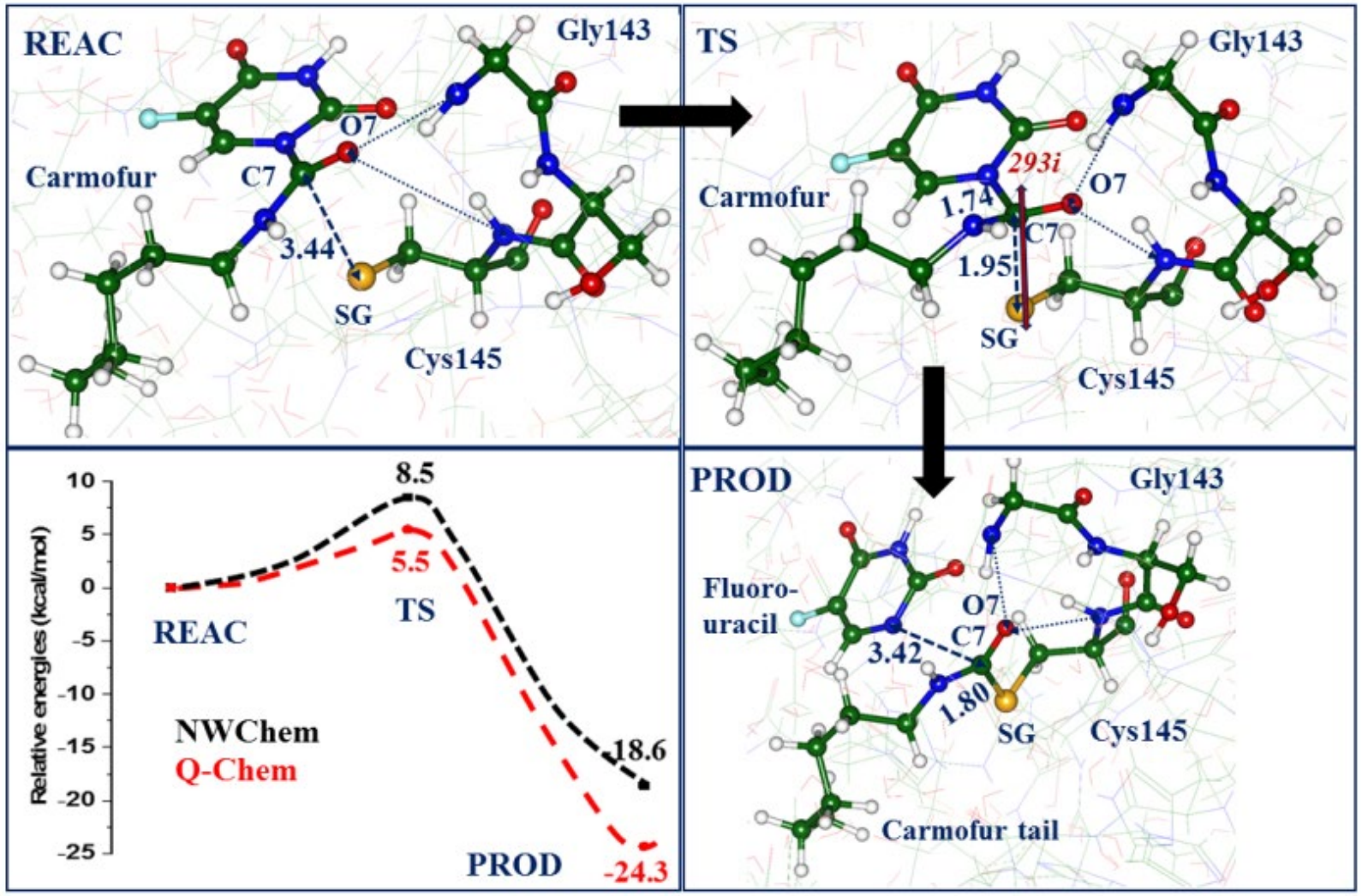
3

How Reproducible Are QM/MM Simulations? Lessons from Computational Studies of the Covalent Inhibition of the SARS-CoV-2 Main Protease by Carmofur

Goran Giudetti, Igor Polyakov, Bella L. Grigorenko, Shirin Faraji, Alexander V. Nemukhin, and Anna I. Krylov*

Article Views 1601 | Altmetric 8 | Citations 5

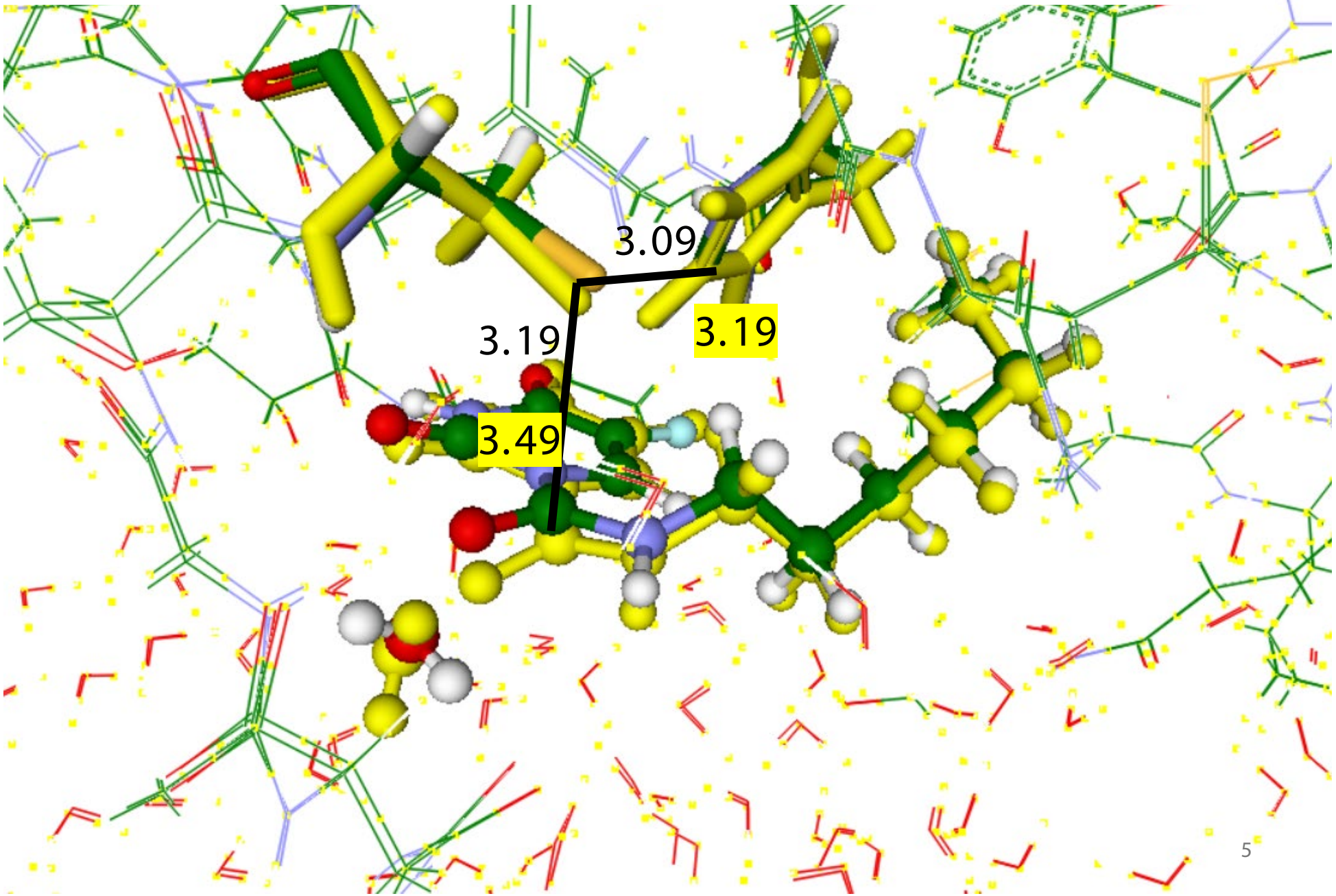




Stationary points located with different optimization algorithms!

Minimum
located by:

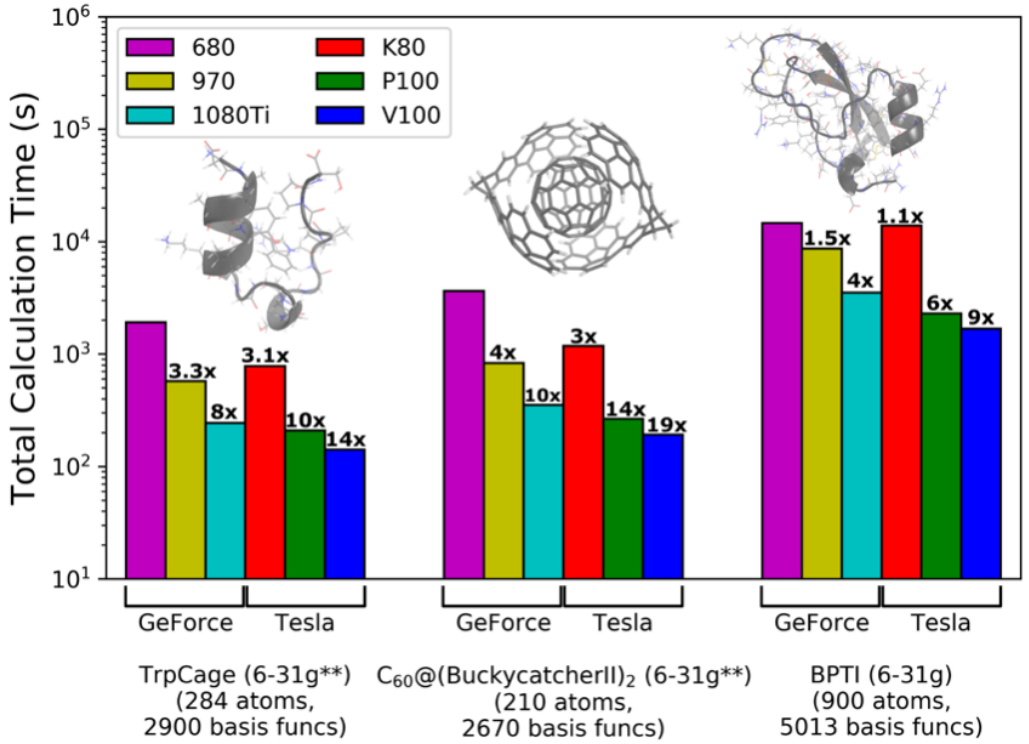
NWChem
or
Q-Chem



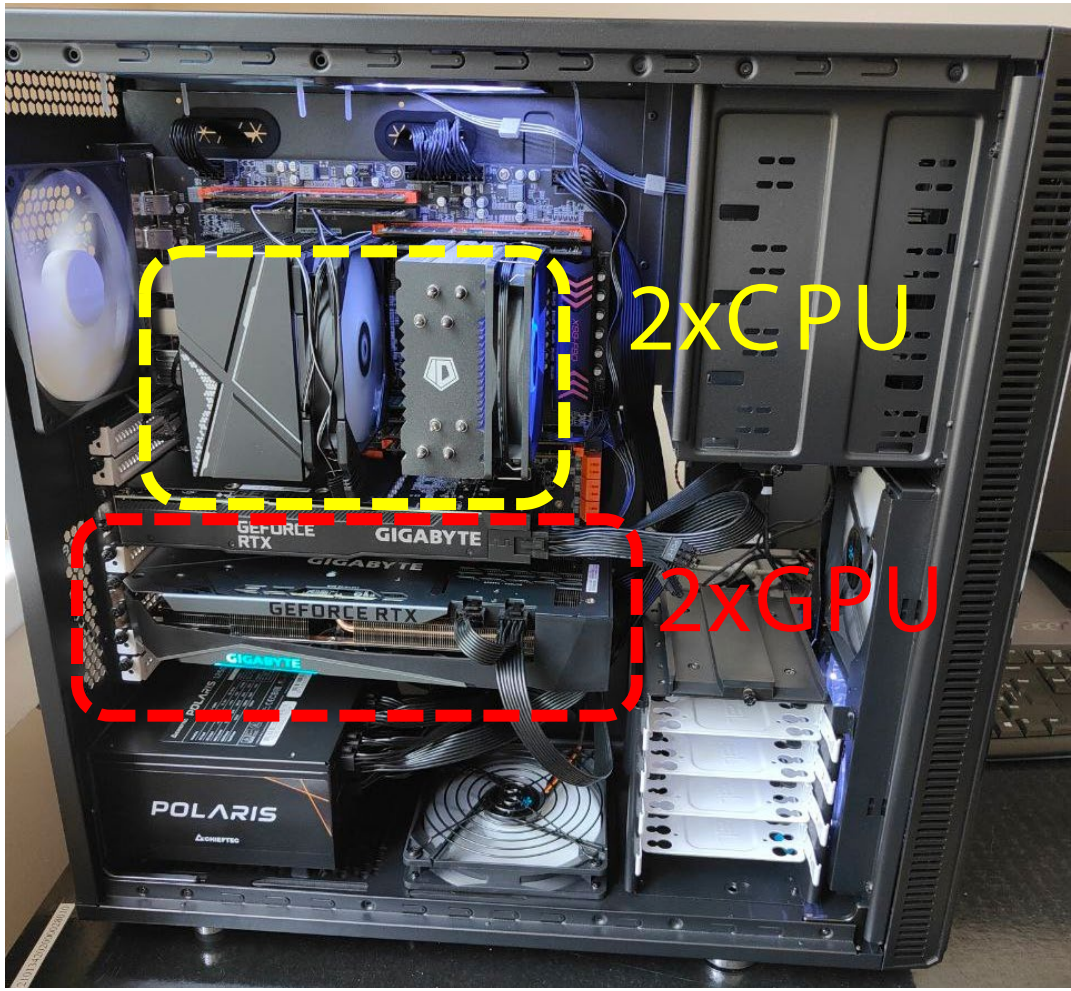
There is no one way to do the QM/MM..

..but there are more or less efficient ones!

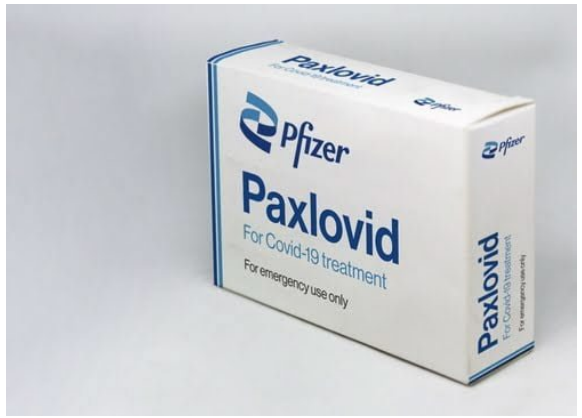
- TURBOMOLE+ChemShell PES QM/MM
- TeraChem+NAMD FES (QM/MM MD) with CUDA GPU



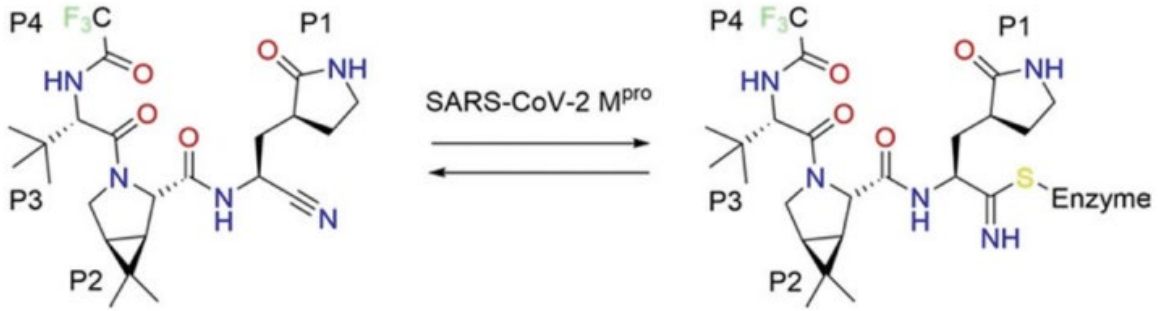
WIREs Comput Mol Sci. 2021; 11:e1494.

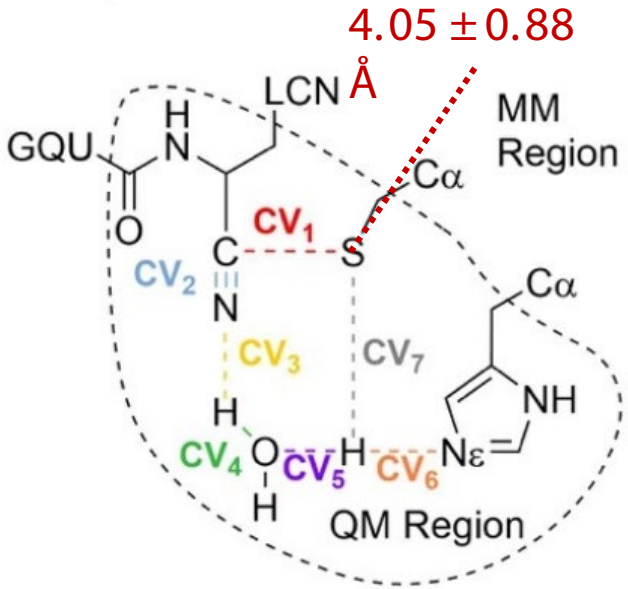


Used server+consumer grade hardware are available, inexpensive and powerful



PF-07321332
(nirmatrelvir)



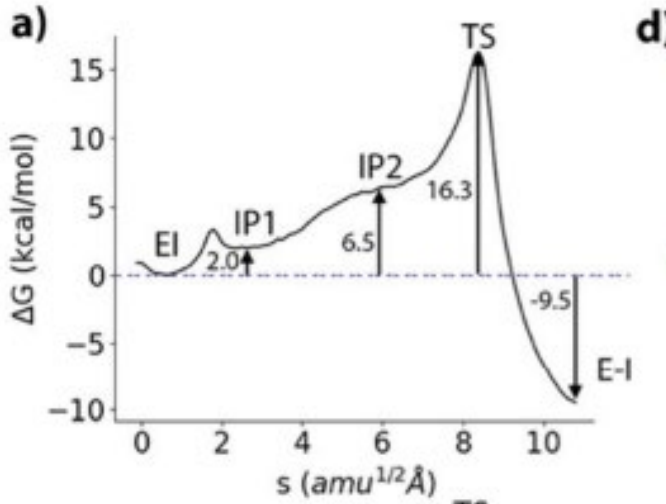


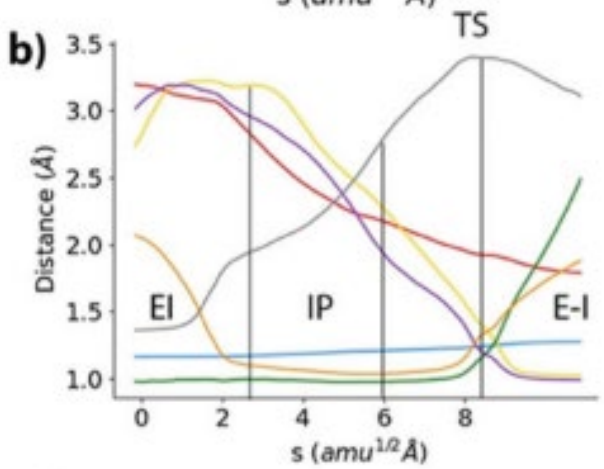
Gau16/AMBER18

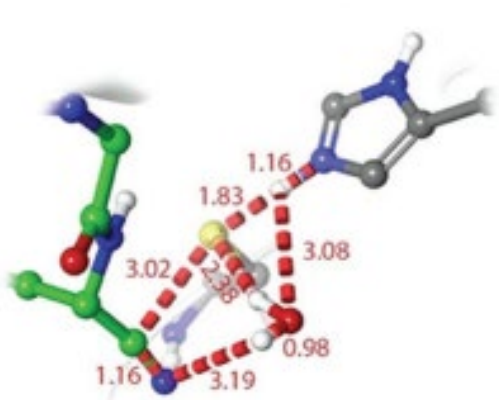
1 mln CPU hours
Intel Xeon Platinum!

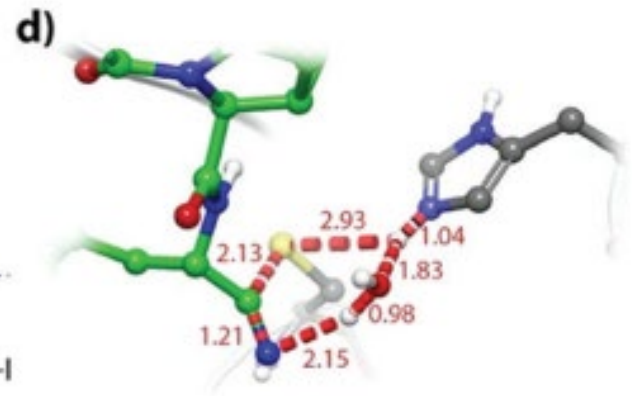
B3LYP-D3/6-31 +G*/MM

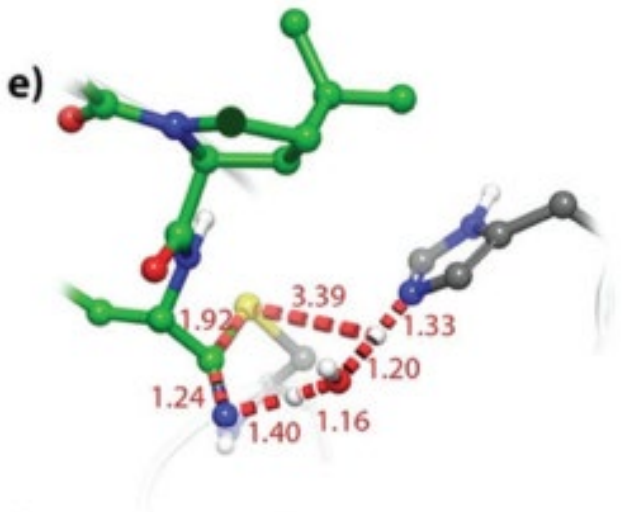
Chem. Commun., 2021, 57, 9096

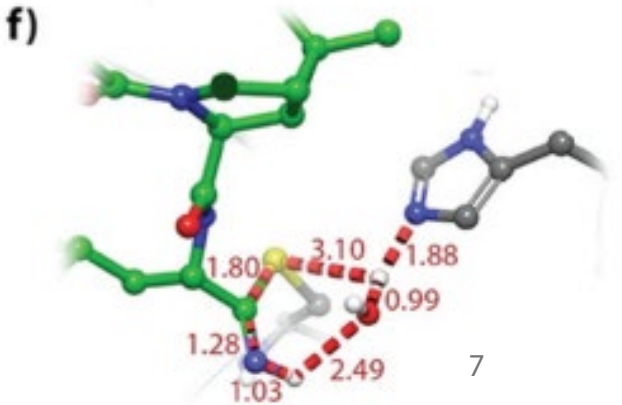












The intermediate structure

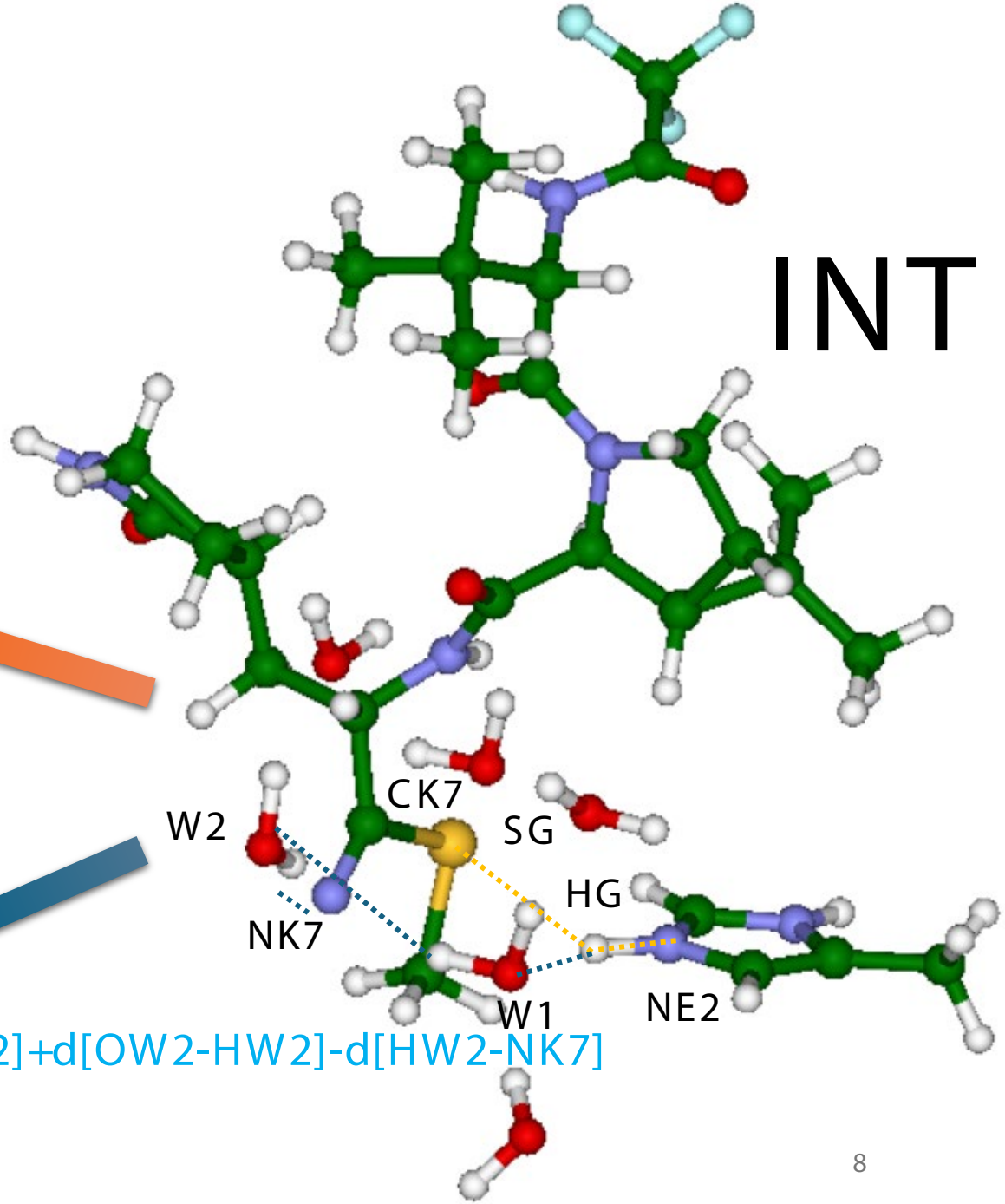
INT

CV1 = d[SG-CK7] -d[HG-SG]+d[NE2-HG]

To reactants

To products

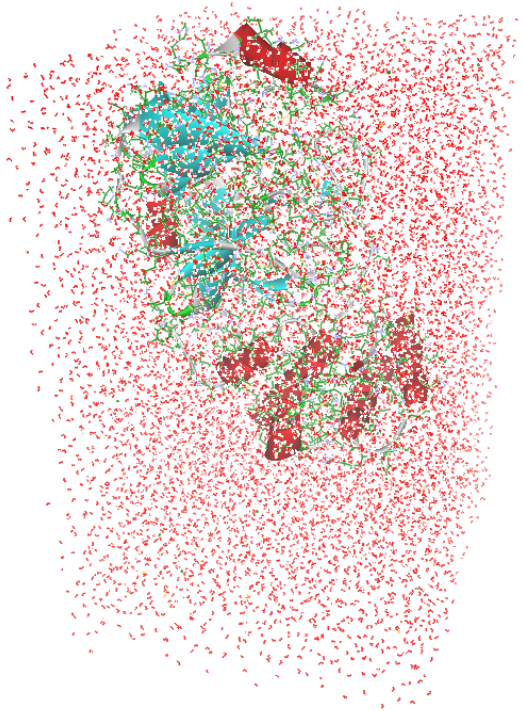
CV2 = d[NE+HG]-d[HG-OW1]+d[OW1-HW1]-d[HW1-OW2]+d[OW2-HW2]-d[HW2-NK7]



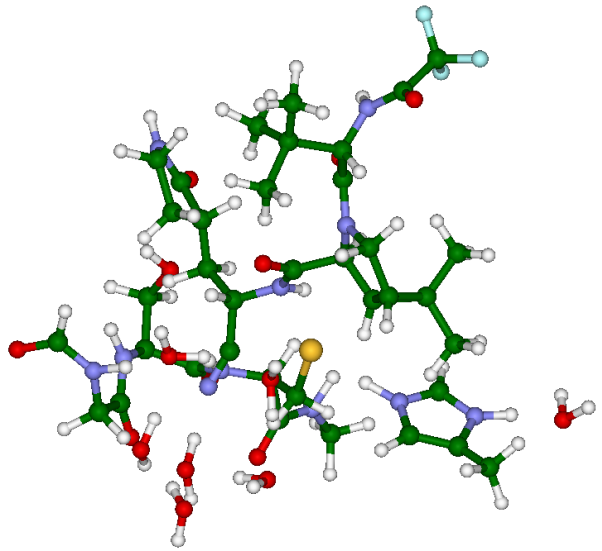
Free energy surfaces

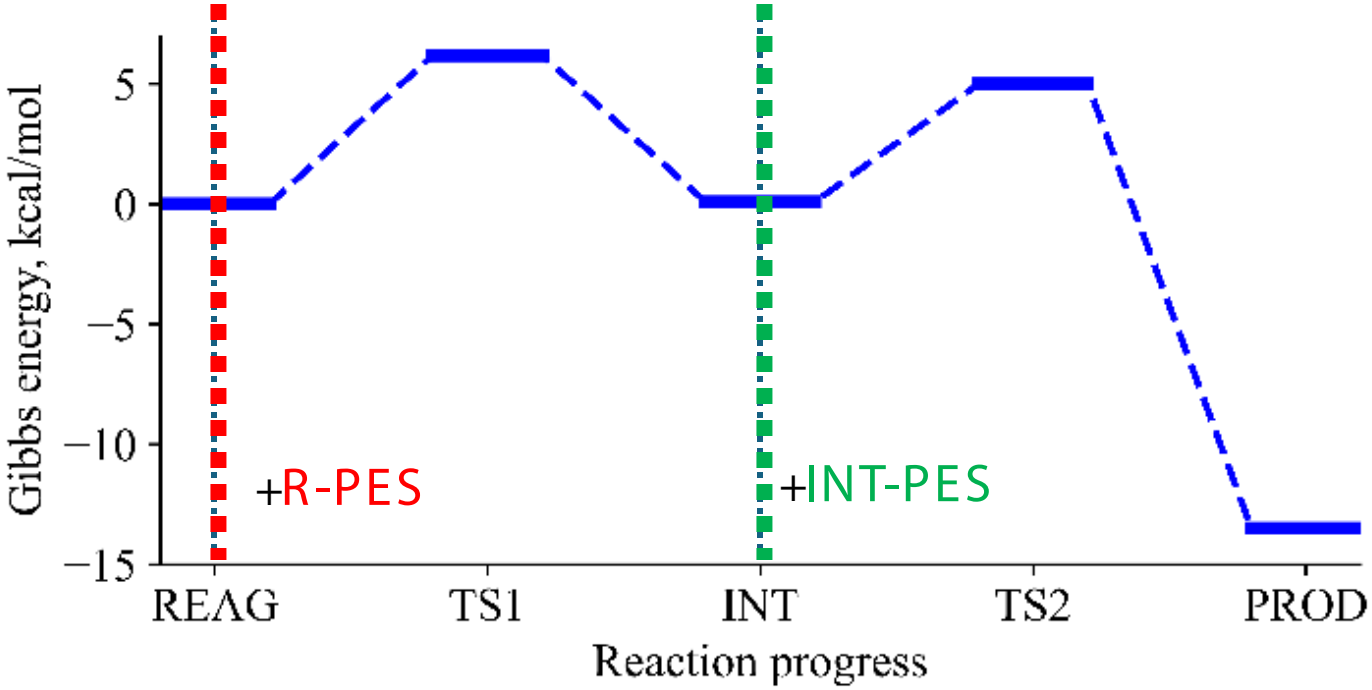
7BUY starting structure
TeraChem/NAMD
PBE0-D3/6-31G**/CHARMM36
T=300K P=1atm step=1fs
Umbrella sampling -> UI/WHAM
15ps per window!

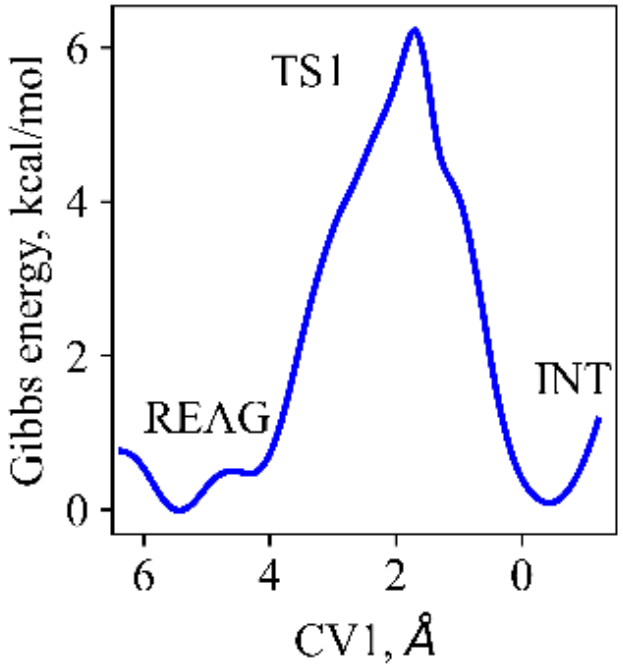
36679 atoms, PBC/PME

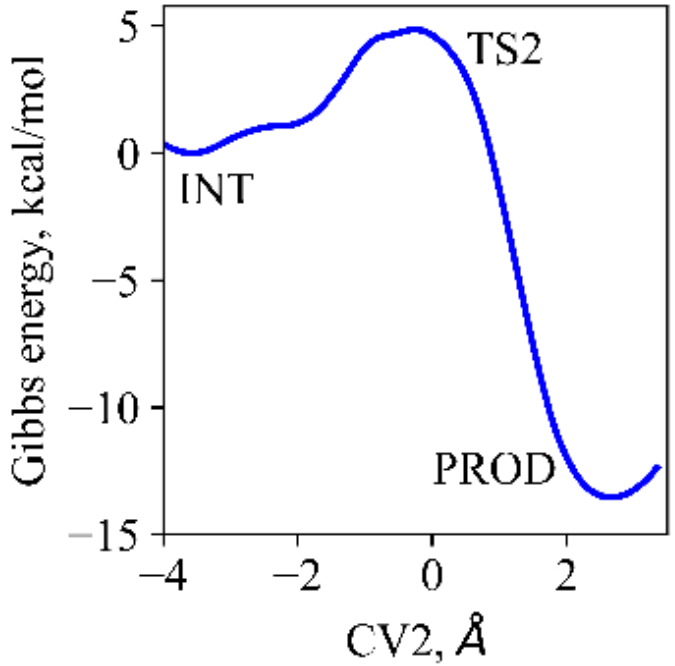


138 QM atoms

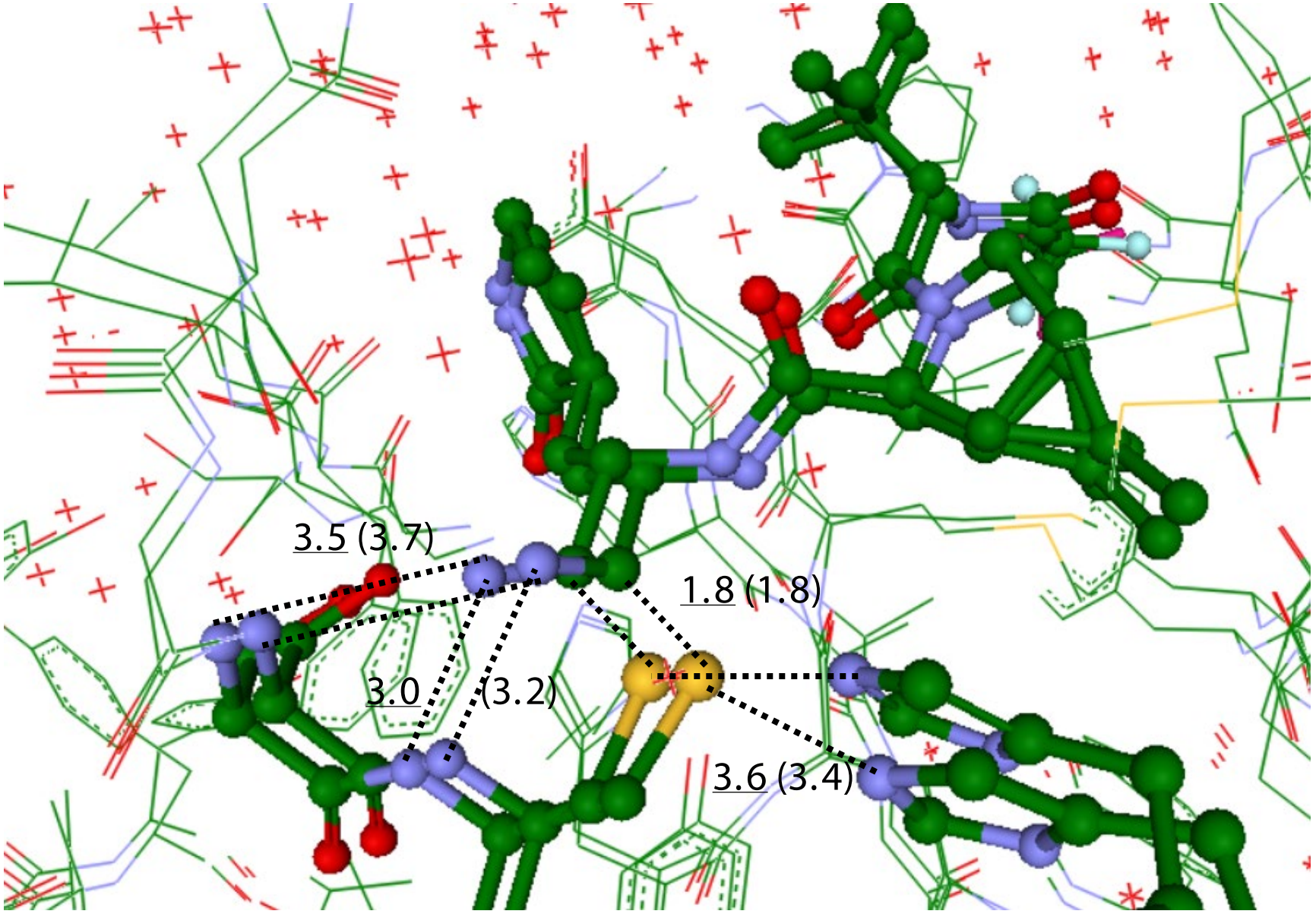






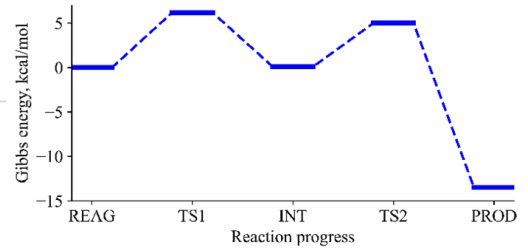


Computed structure of PROD vs 7VH8 crystal structure



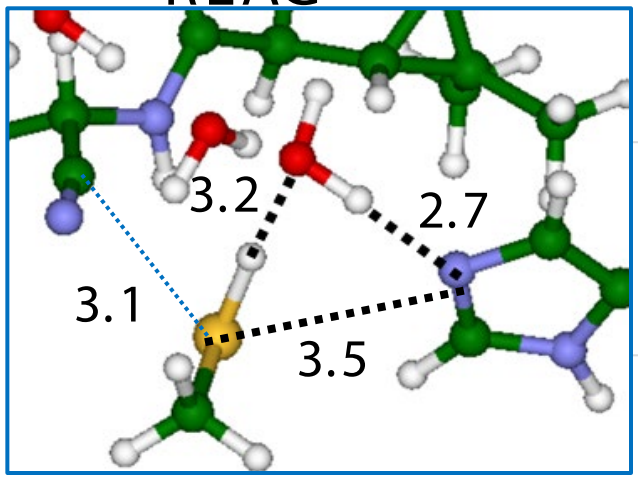
RMSD=1.0 Å
for 2026 heavy atoms of protein
(PyMol super procedure)

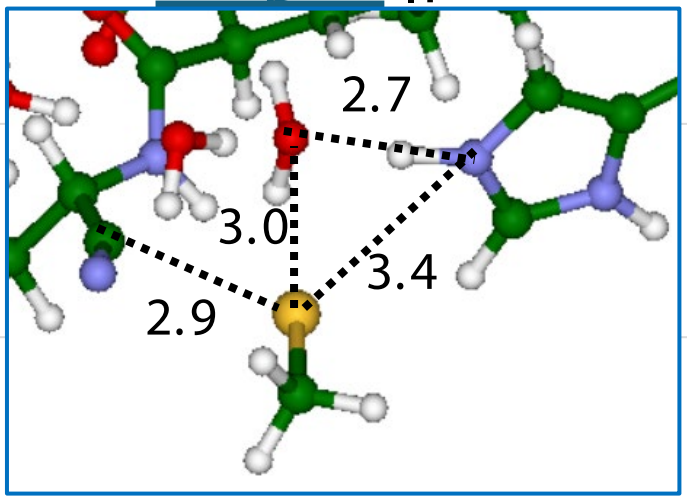
INT-PES

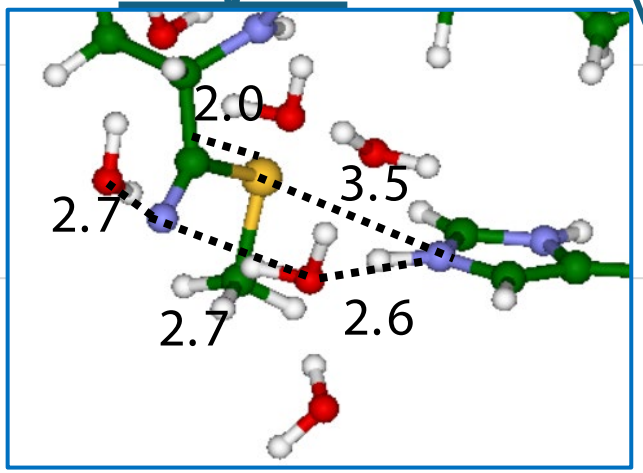


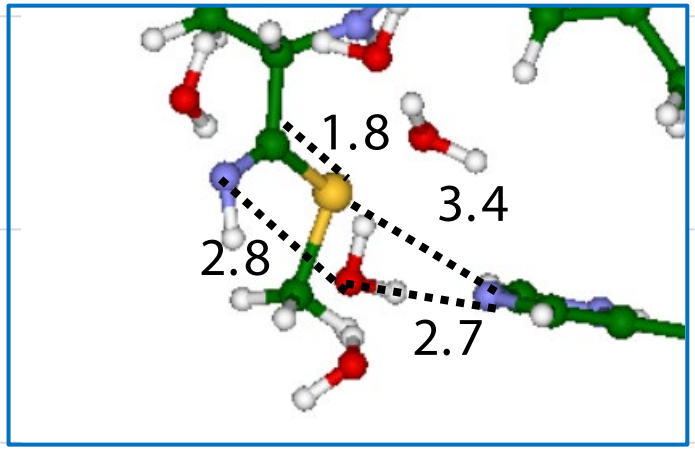
10
5
0
-15
-20

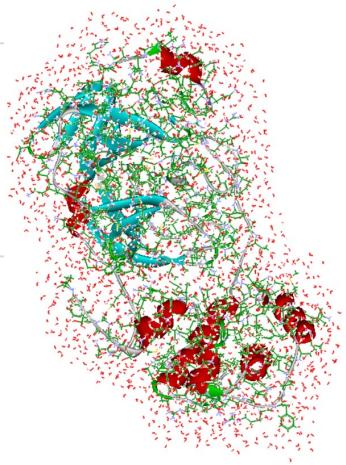
7
TS1
0
REAG
3
IP
5
TS2
1
INT
5
TS3
-16
PROD





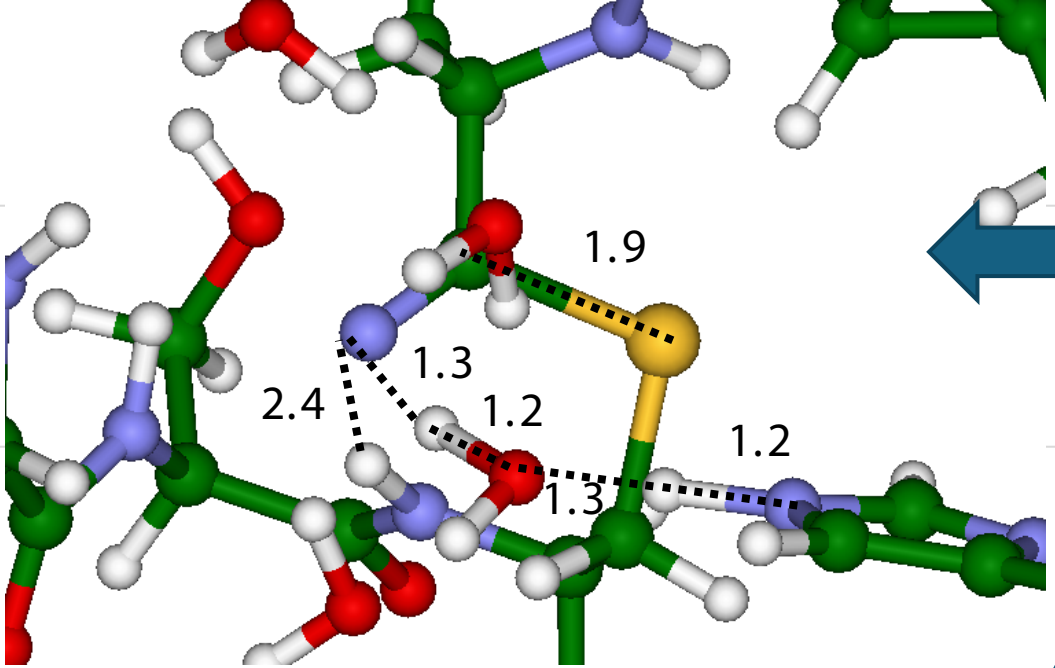


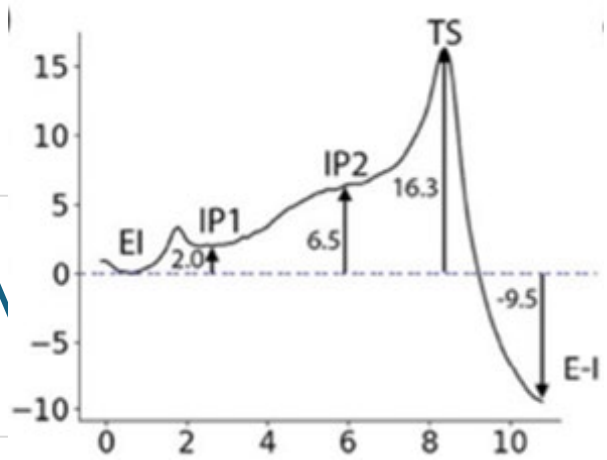




TURBOMOLE/ChemShell
PBE0-D3/6-31G**/CHARMM36
132 QM atoms

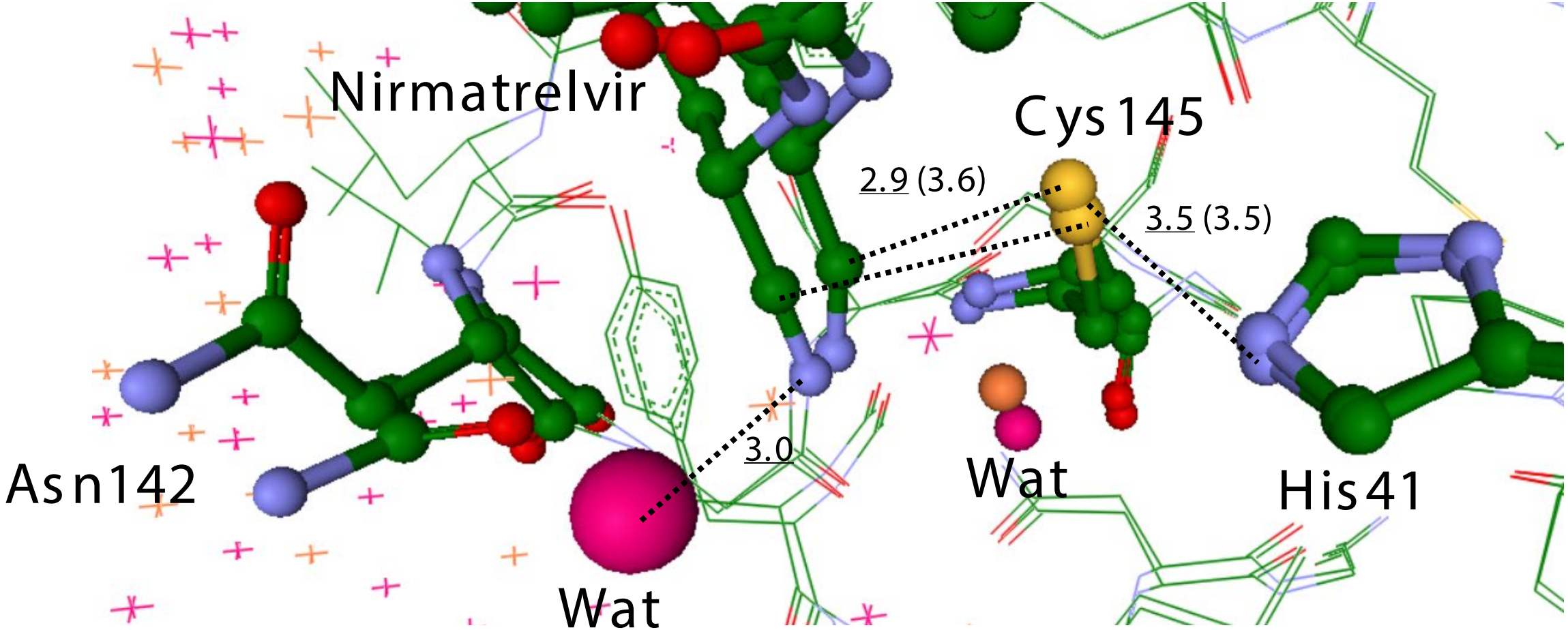
R-PES


1.9
1.3
2.4
1.2
1.2
1.3


TS
IP2
IP1
EI
16.3
6.5
2.0
-9.5
E-I
15
10
5
0
-5
-10
0
2
4
6
8
10

17
12
7
2
-3
-8
16
TS2
5
TS1
0,0
REAG
-2
IP
-7
PROD
12

IP structures from the R-PES and INT-PES

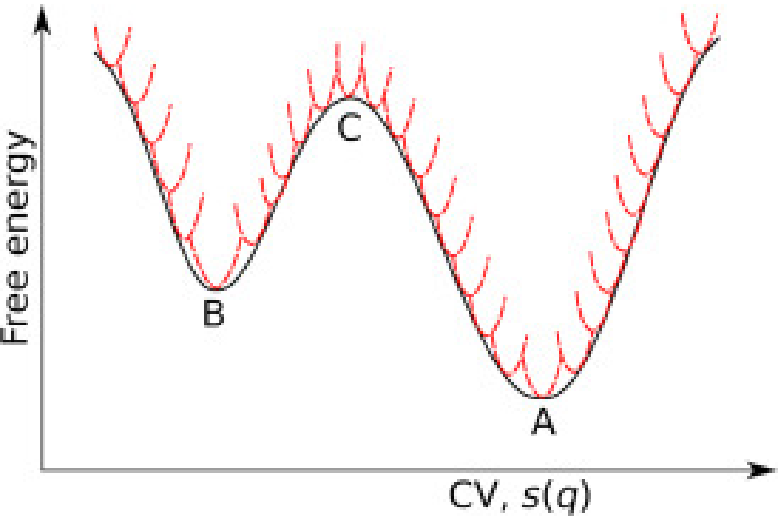


Thank you for your attention!

This work was supported by the RSF project # 19-73-20032

Calculations were carried out with the resources of supercomputer facilities at Lomonosov MSU

Umbrella integration/WHAM



$$E_{bias} = E_{unbias} + \omega_i(\xi)$$

$$\omega_i(\xi) = \frac{1}{2}K(\xi - \xi_i)^2$$

$$P_i^u(\xi) = \frac{\int \exp[-\beta E(r)]\delta[\xi^r(r) - \xi]d^{Nr}}{\int exp[-\beta E(r)]d^{Nr}}$$

$$P_i^u(\xi) = P_i^b(\xi)exp[\beta\omega_i(\xi)]exp[-\beta\omega_i(\xi)]$$

$$E_{unbias} = -\left(\frac{1}{\beta}\right)\ln P_i^b(\xi) - \omega_i(\xi) + F_i$$

J. Chem. Phys. 123, 144104 (2005)

doi:**10.1063/1.2052648**

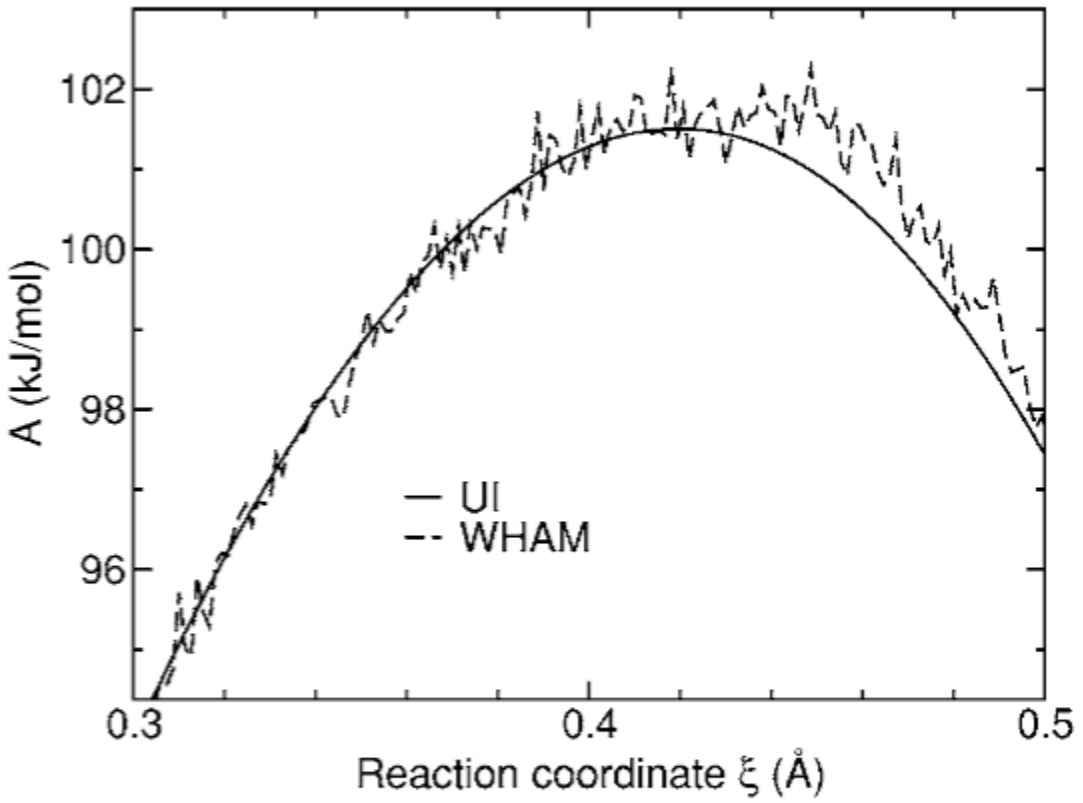


FIG. 5. Comparison between umbrella integration (UI) and WHAM for the example of PHBH. $A(\xi)$ around the transition state is shown using 3000 bins.