Enhancing refinement with quantum mechanics in neutron protein crystallography

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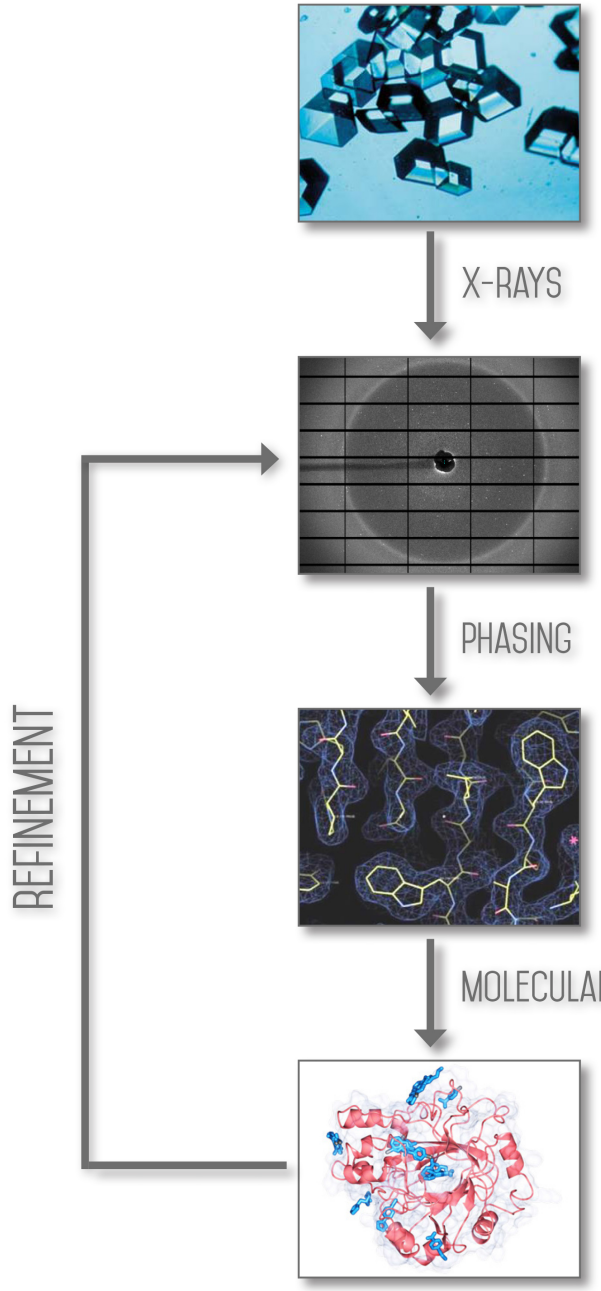


NUCLEAR DENSITY MAP

WITH INDIVIDUAL DEUTERIUM ATOMS

Courtesy of diamond.ac.uk

Crystallographic refinement

Structure refinement is a process of changing a model parameters in order to optimize a goal (target) function:

$$T = F\,(\textit{Experimental data}\ ,\ \textit{Model parameters},\ \textit{Restraints})$$

Experimental data – a set of diffraction amplitudes F_{obs}

Model parameters: coordinates, ADP, occupancies

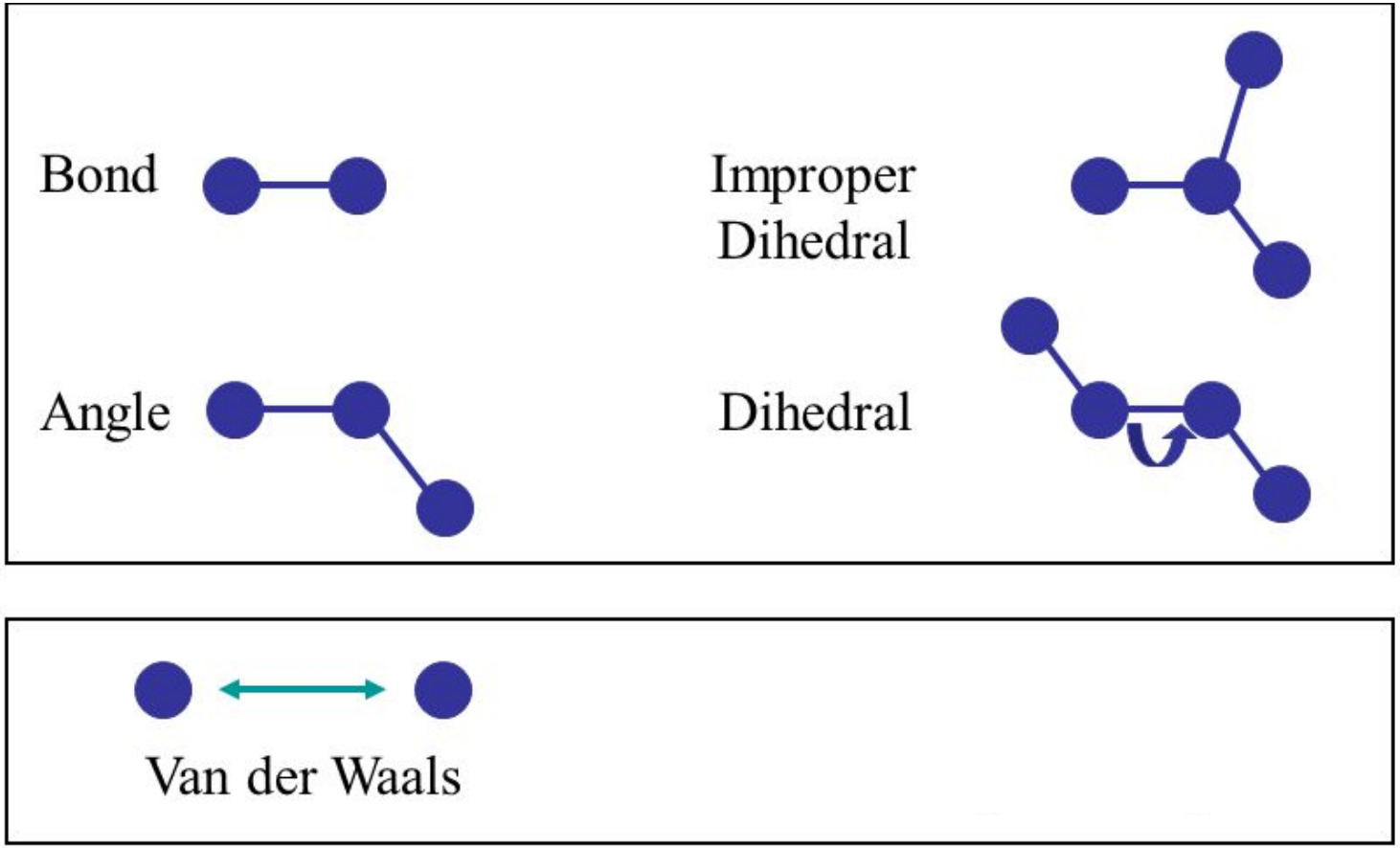
Restraints – additional information to compensate for the insufficiency of experimental data

$$E = w * E_{DATA} + E_{RESTRAINTS}$$

$$E = w\,(w_X * E_{XRAY} + w_N * E_{NEUTRON}) + E_{EH}$$

Restraints used in crystallographic refinement

Engh & Huber restraints – statistical force-field

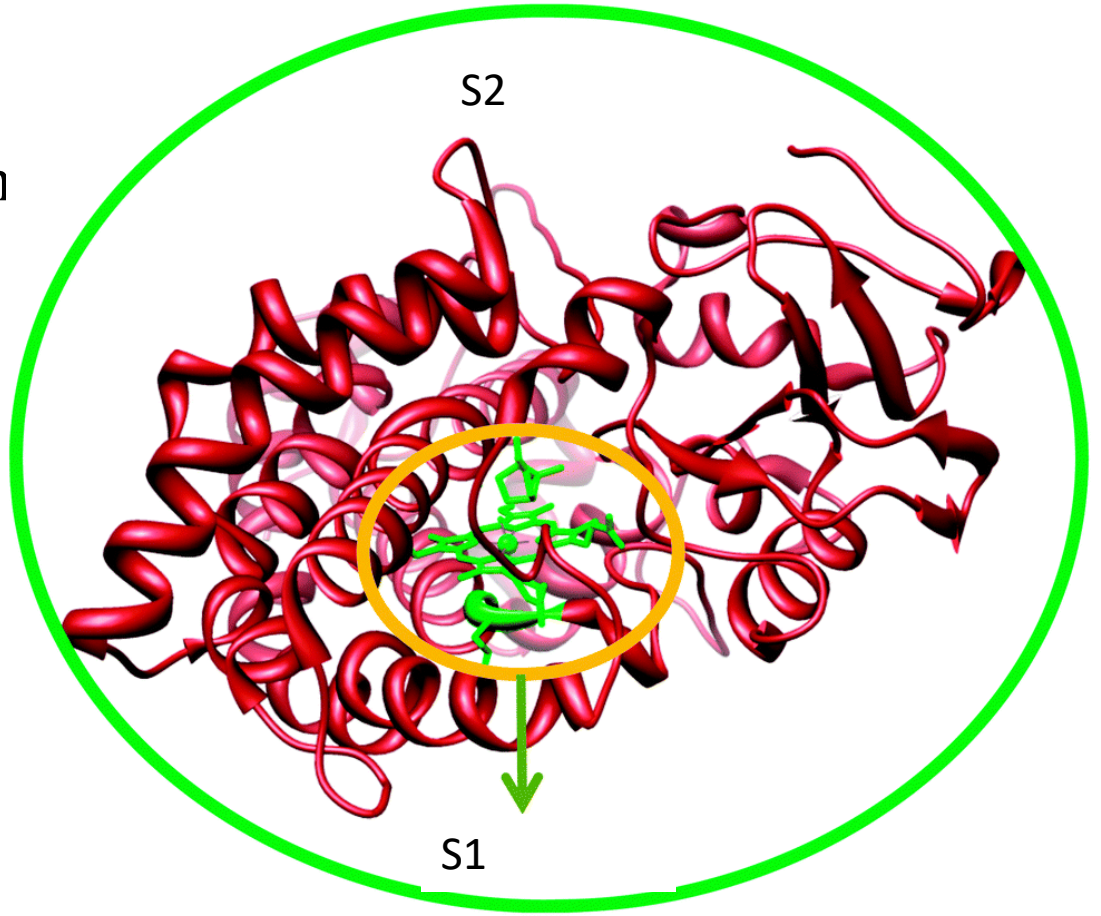


Quantum refinement – how does it work?

Combines nCNS (crystallographic refinement) with Turbomole (QM calculations)

Refinement steps:

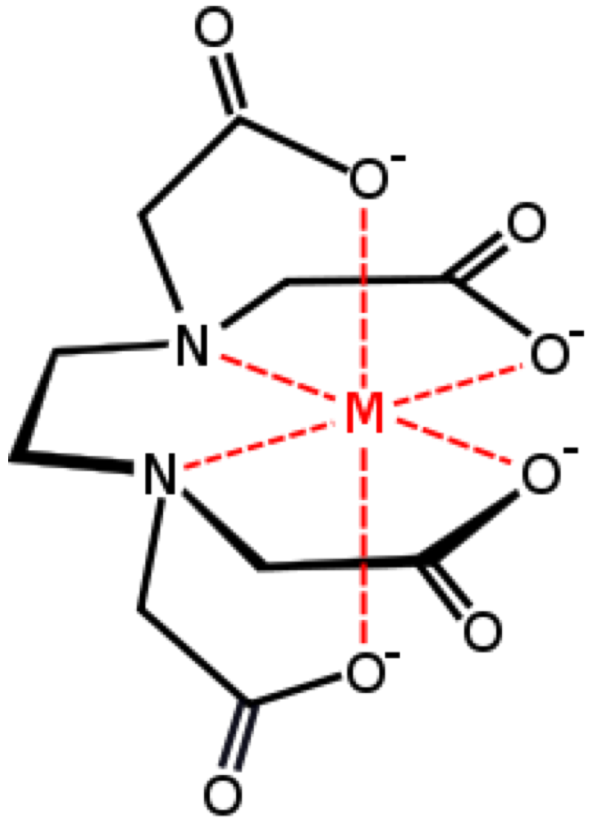
- Evaluate QM wavefunction
- Relax the geometry of S1
- Crystallographic refinement of S2 with S1 fixed
- ADP refinement



$$E = w\,(w_X * E_{X\text{-}RAY} + w_N * E_{NEUTRON}) + E_{QM1} + w_{EH}\,(E_{EH12} - E_{EH1})$$

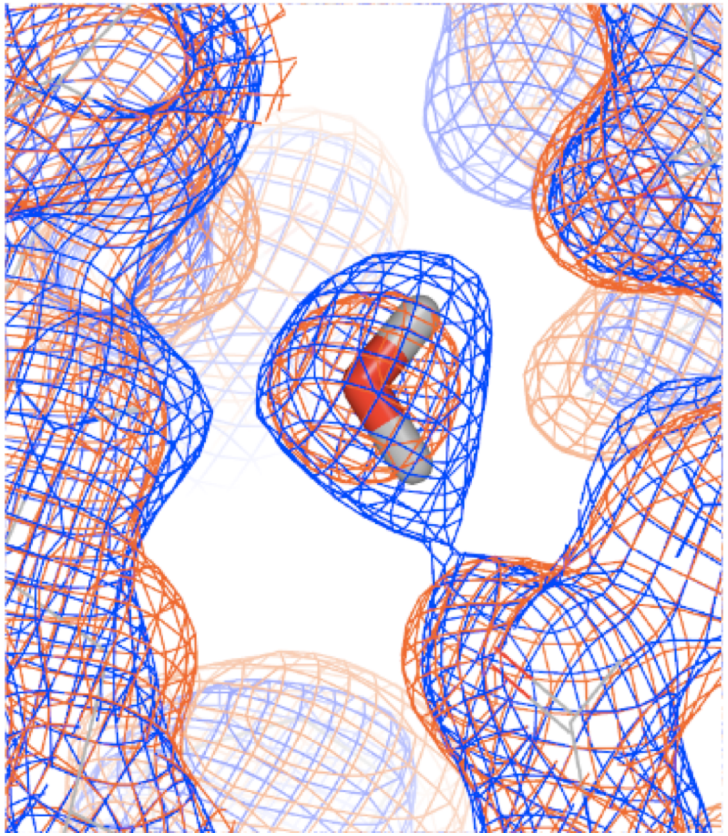
How can quantum chemistry help in neutron protein crystallography?

- Poor ligand parametrization
- Poor metal parametrization
- X-H/X-D distances not optimized
- Hydrogen bonding terms

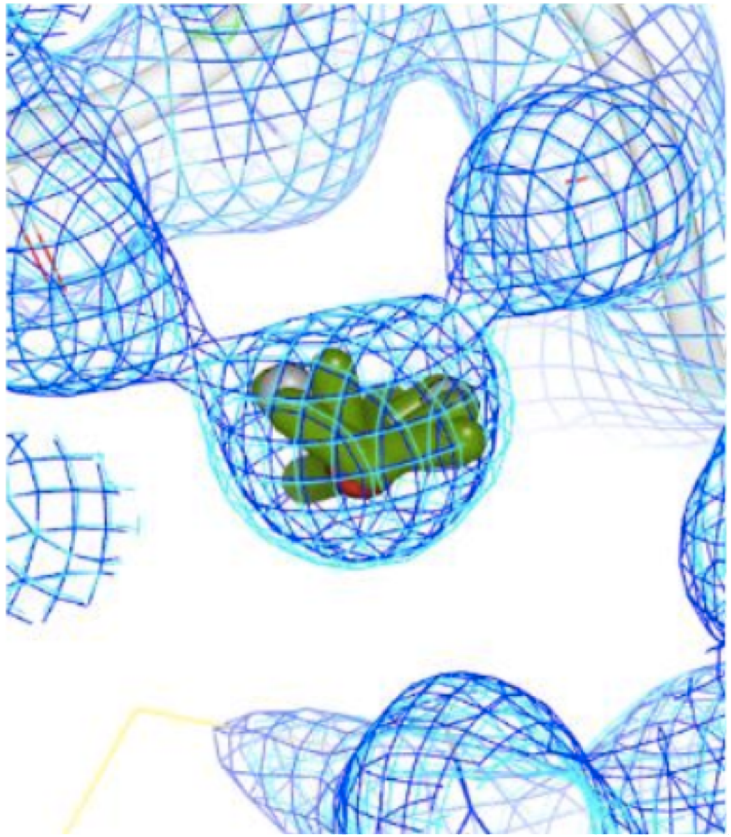


Applications

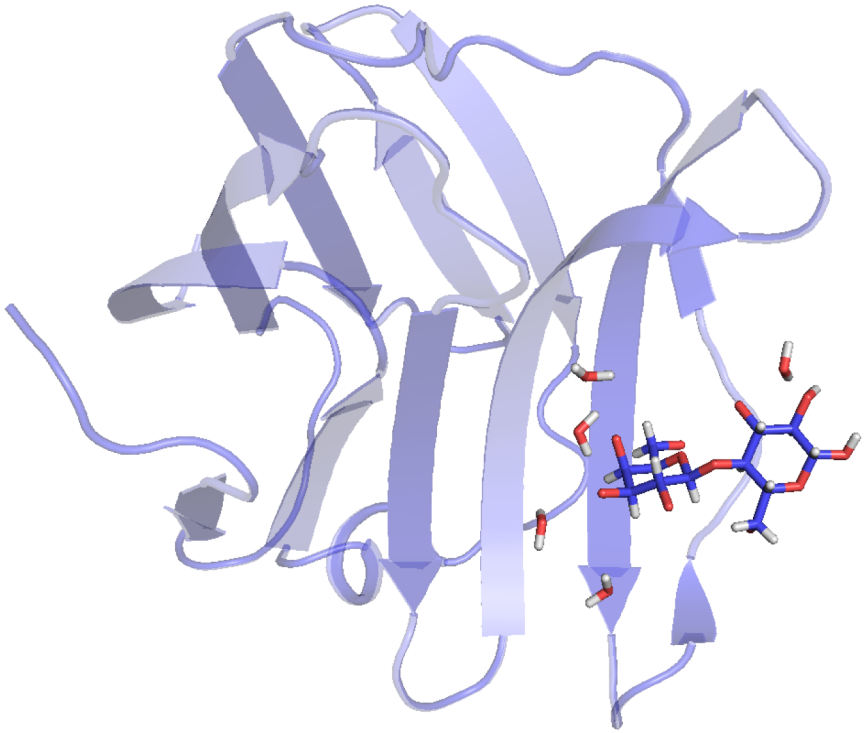
Orientation of water molecules



Orange – electron density
Blue – nuclear density

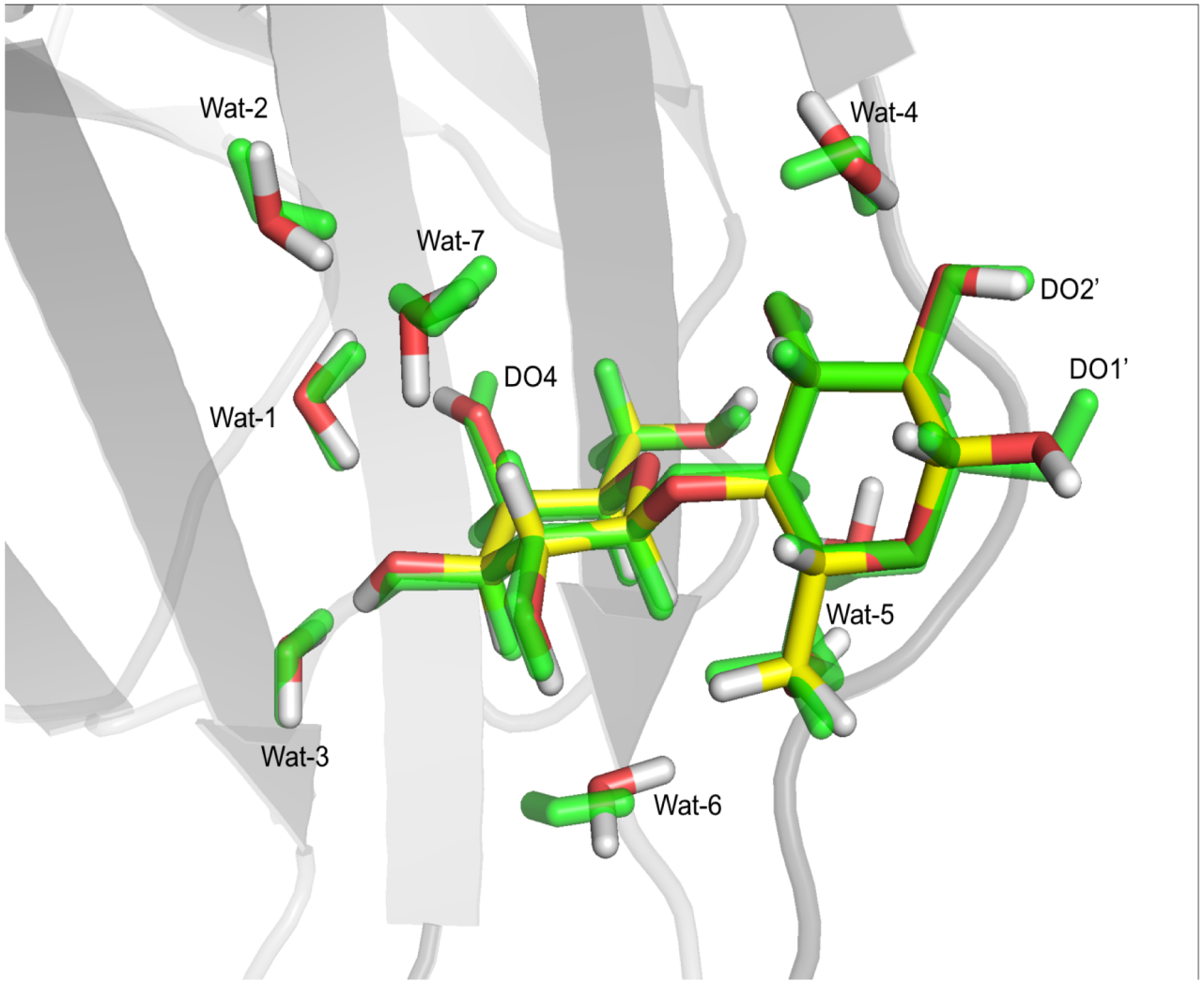


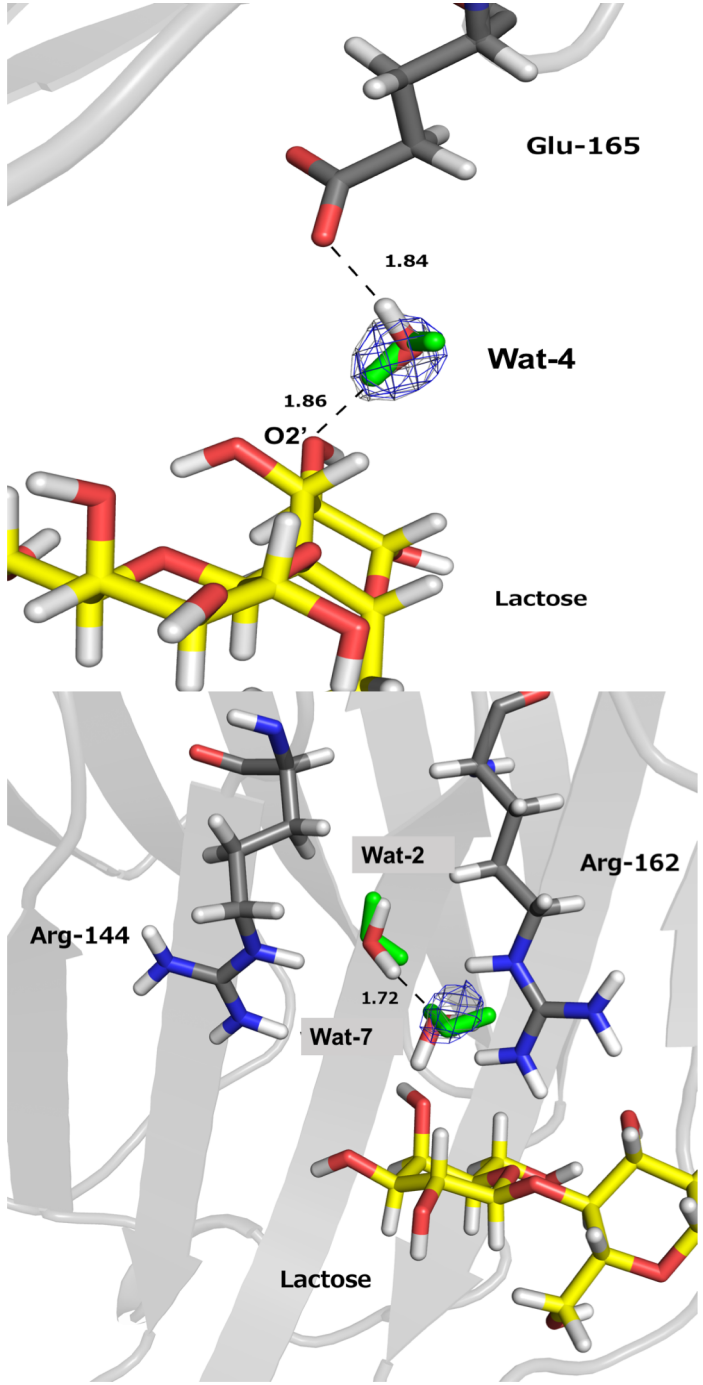
Teal – electron density
Blue – nuclear density



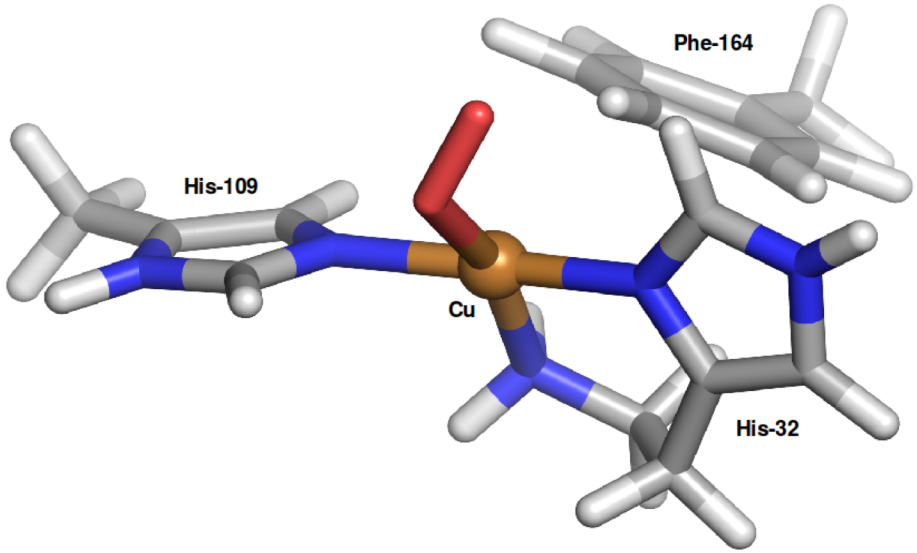
Lactose bound to Galectin-3C

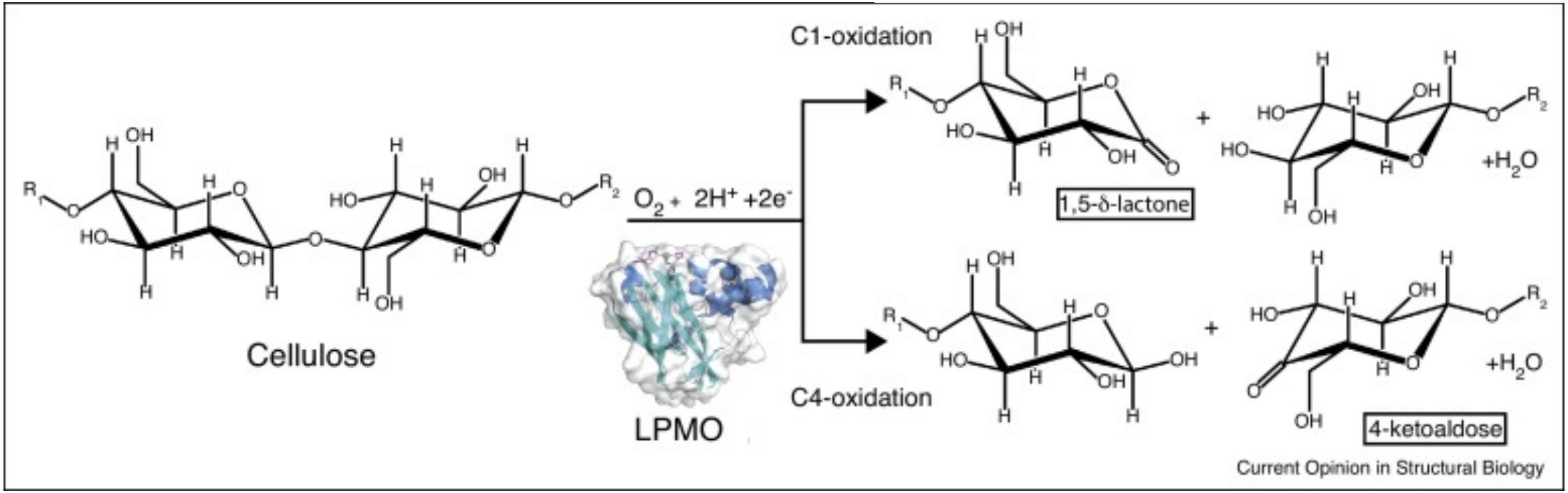
Structure before (green) and after (yellow) the QM refinement



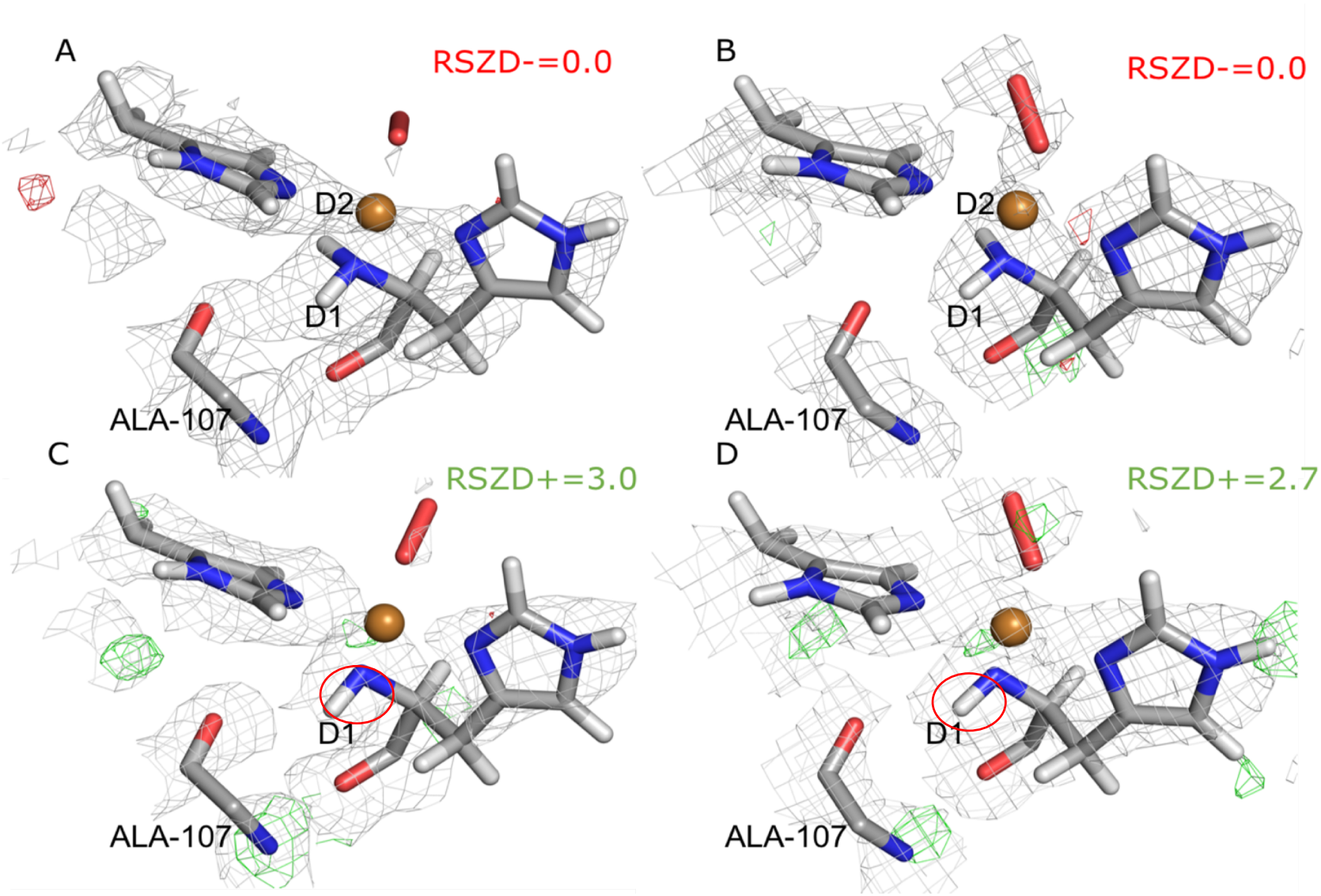


Interpretation of difficult data - Lytic polysaccharide monooxygenase

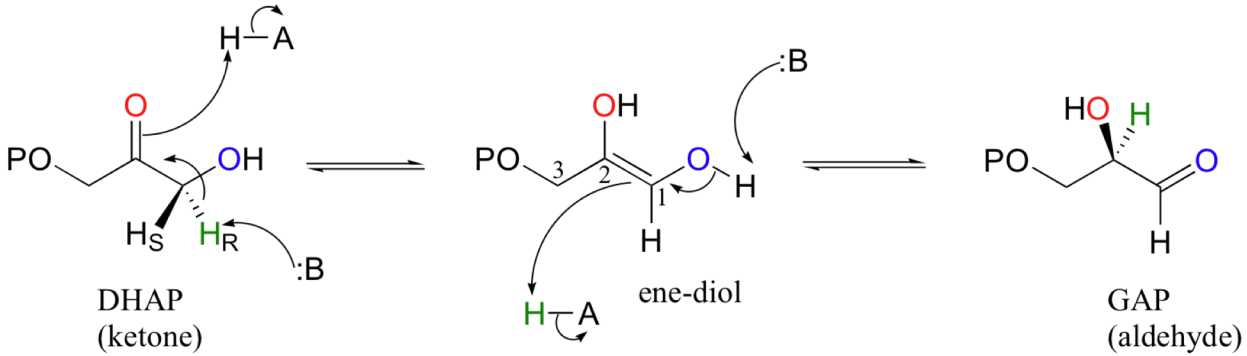




Subunit A **Subunit B**

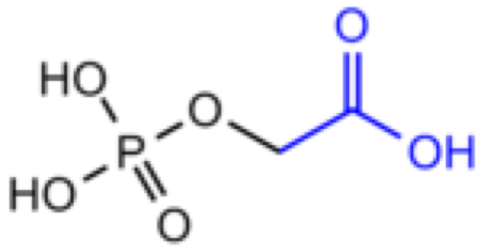


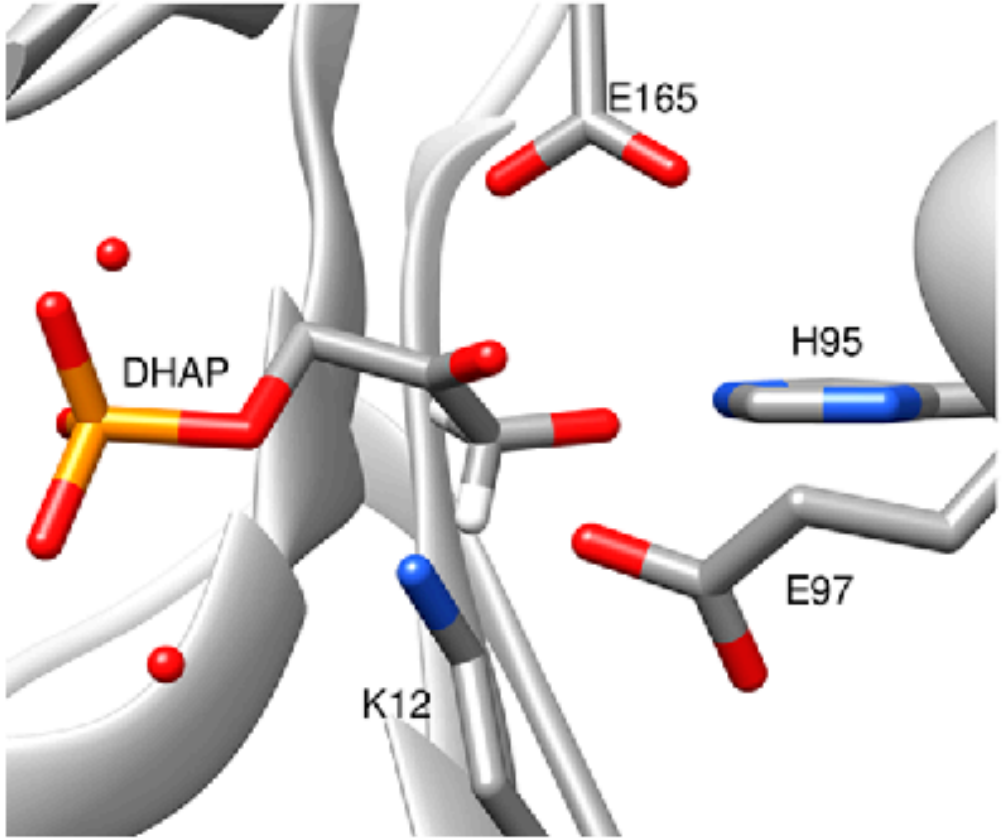
Proton transfer – TIM



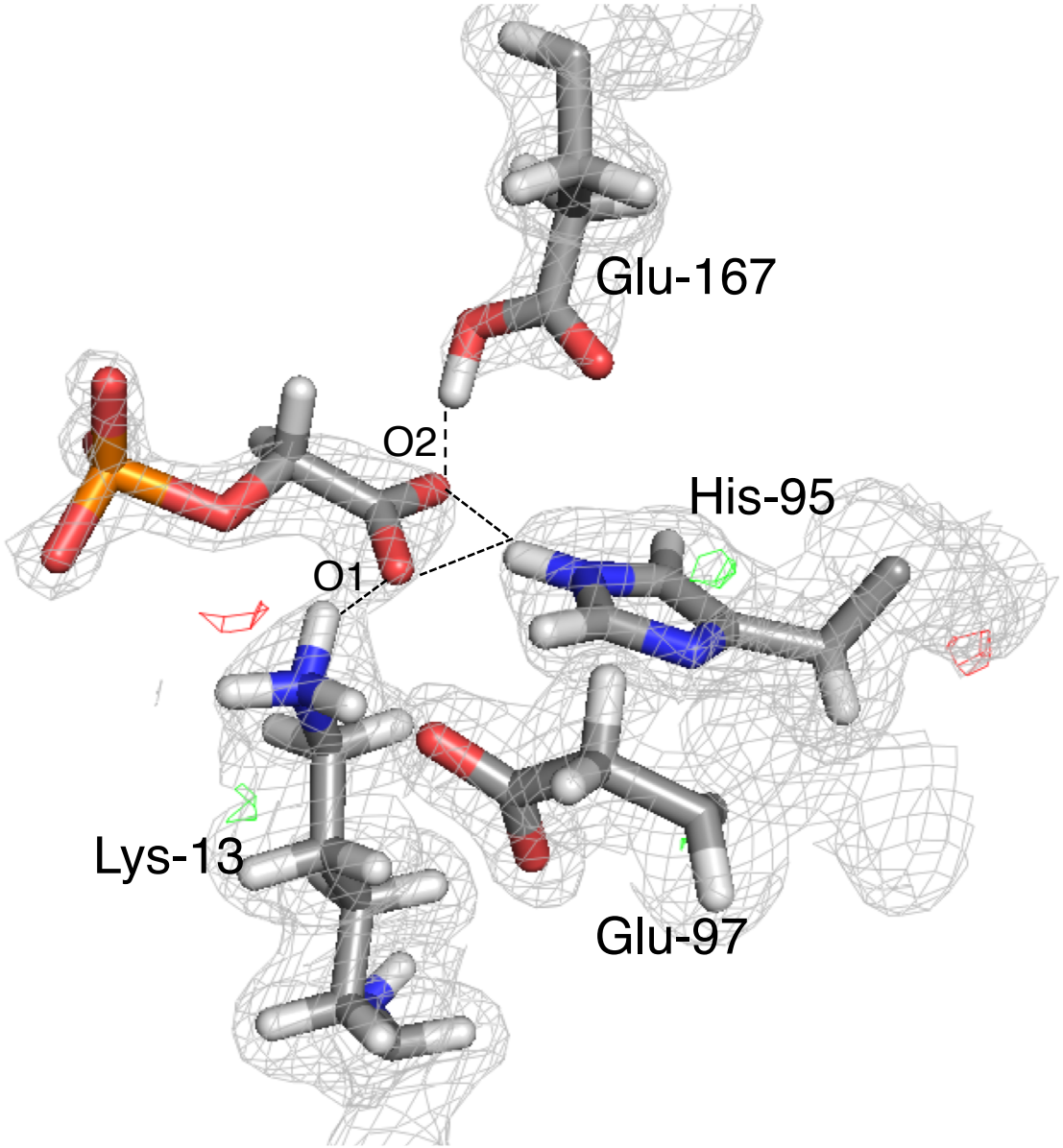
2-Phosphoglycolate

Transition state analog





PGA-TIM active site after quantum refinement



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