CHEM 498Q / 630Q

Molecular modelling of proteins

Fall 2015 Term

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Molecular dynamics

"Putting the thermal fluctuations back into a protein structure"

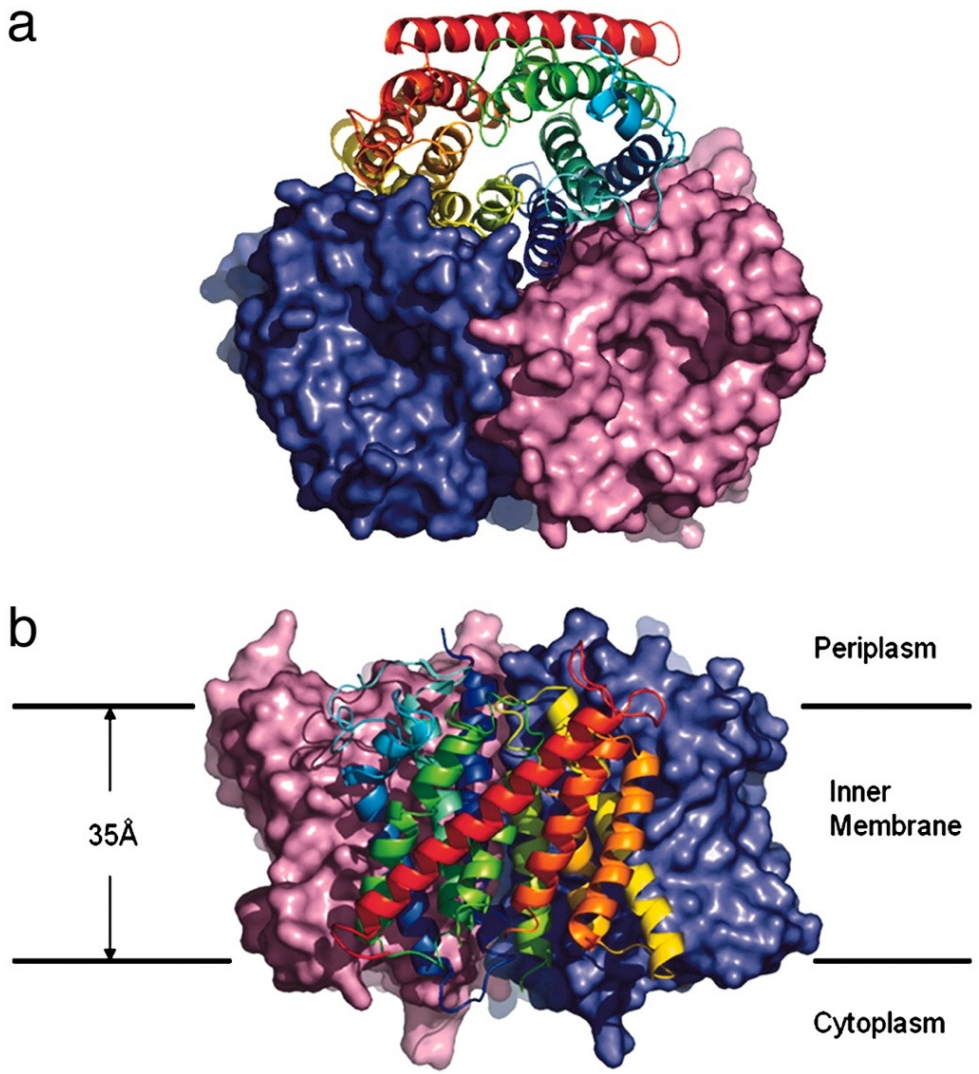
Basic techniques :
Simulation of a system undergoing thermal fluctuations

- Conformational sampling / searching
- Exploration of dynamics
- Debye–Waller factors (x-ray)
- Diffusion coefficients
- IR spectra
- NMR observables
- Raman spectra

Advanced techniques :
Free energy calculations

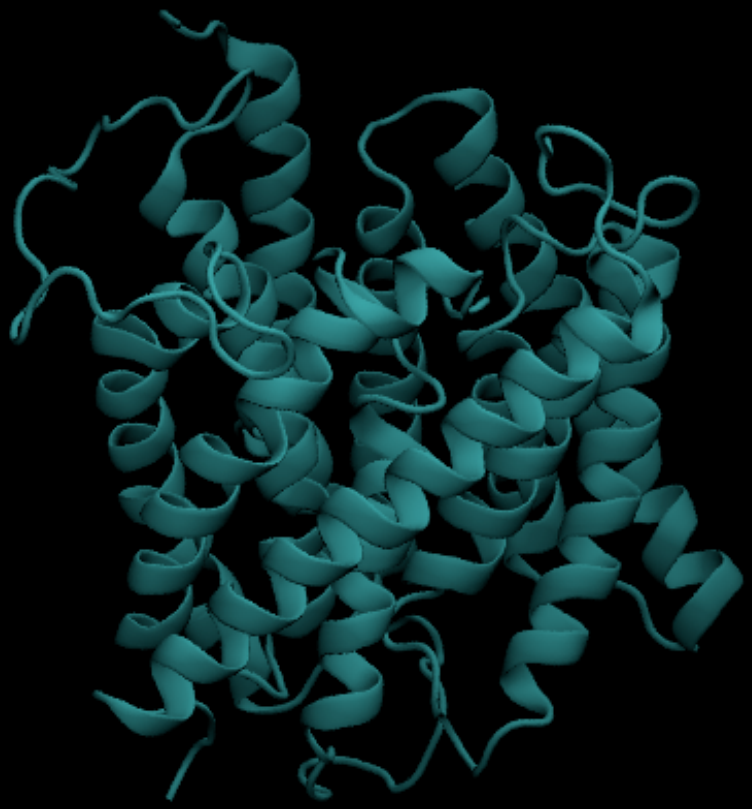
- Reaction profiles (conformational change, substrate permeation, etc.)
- Binding free energies of ligands
- Partition constants ("log *P*")
- Thermodynamic effects of a mutation
- pK_a calculations
- Rate constants / kinetics

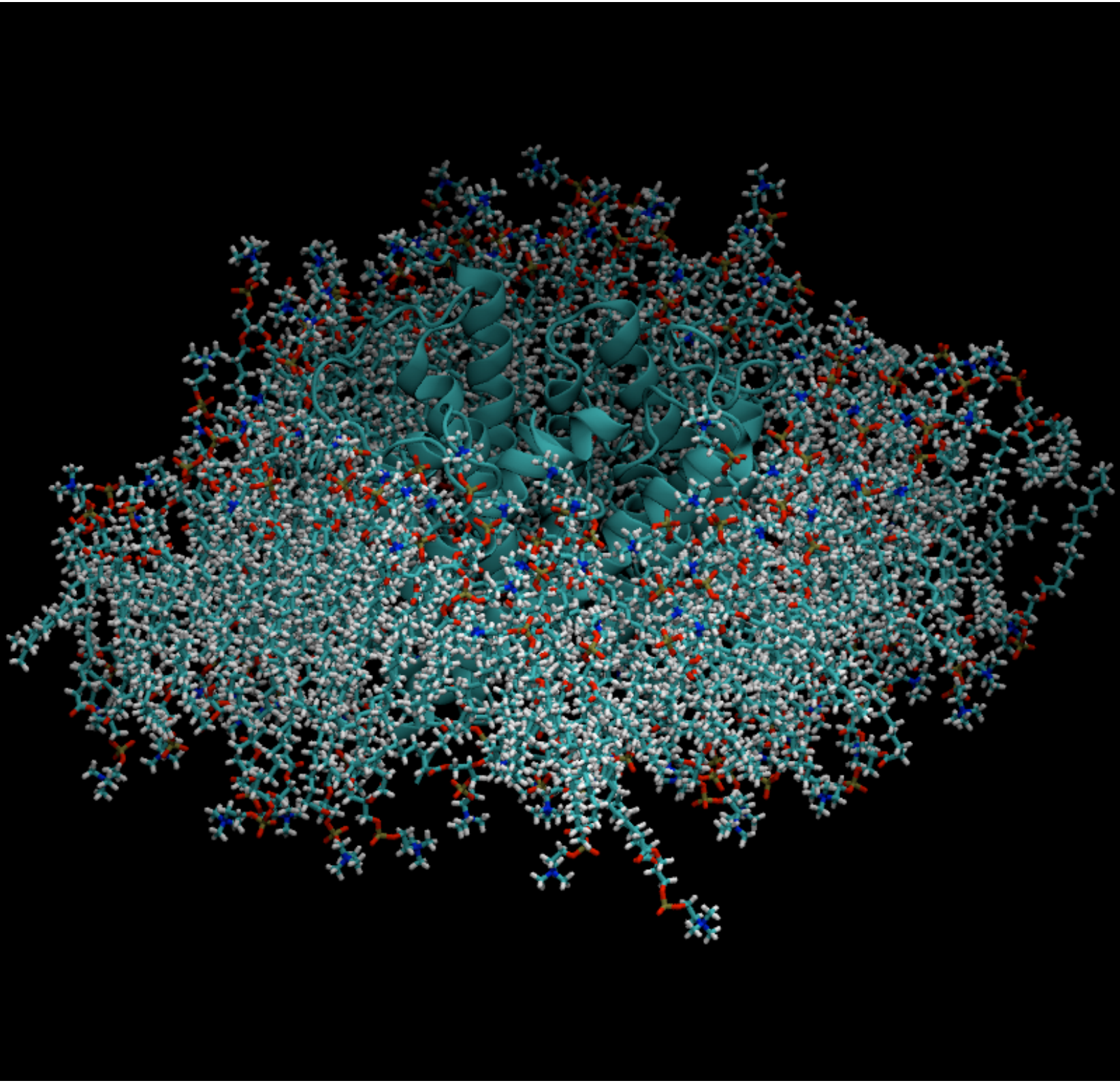
AmtB structure

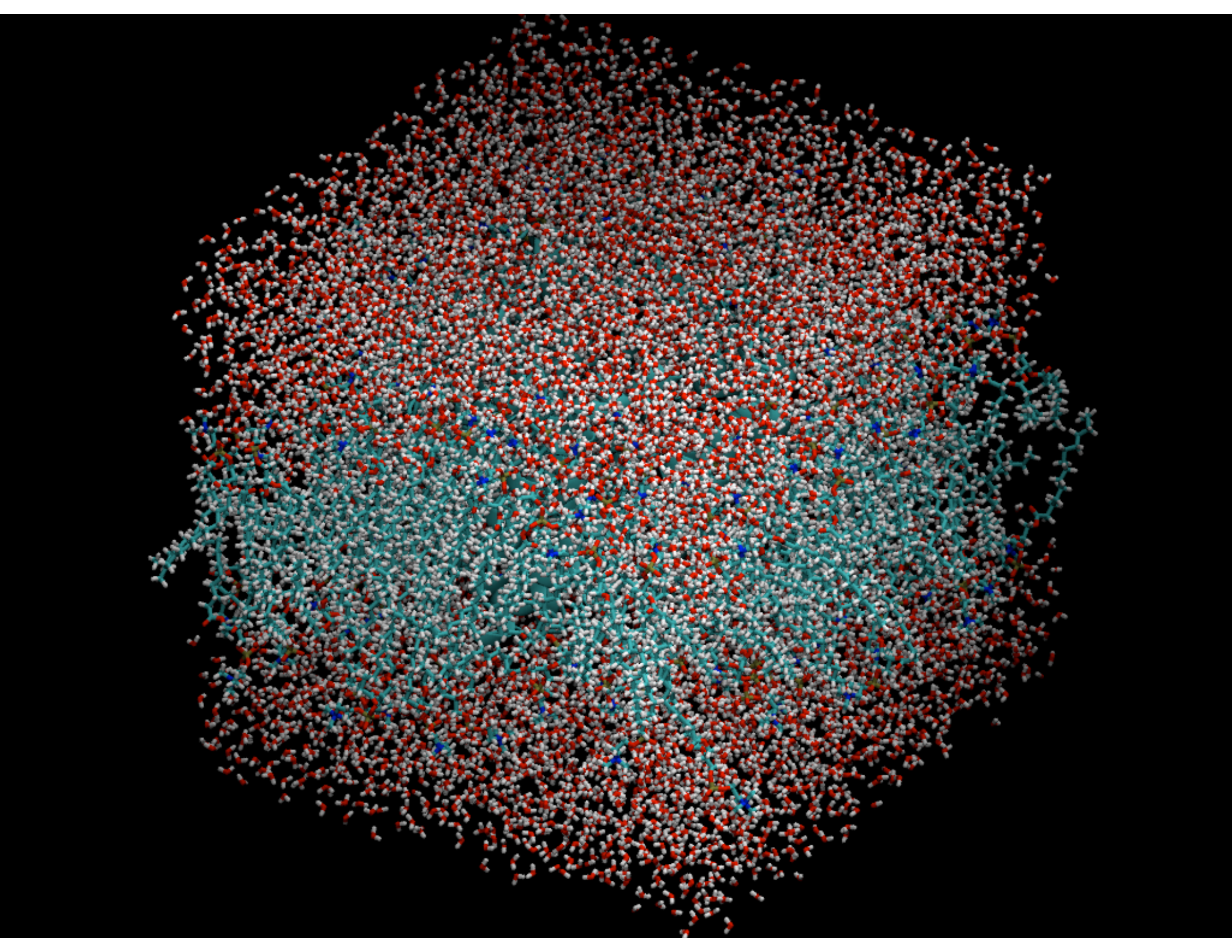


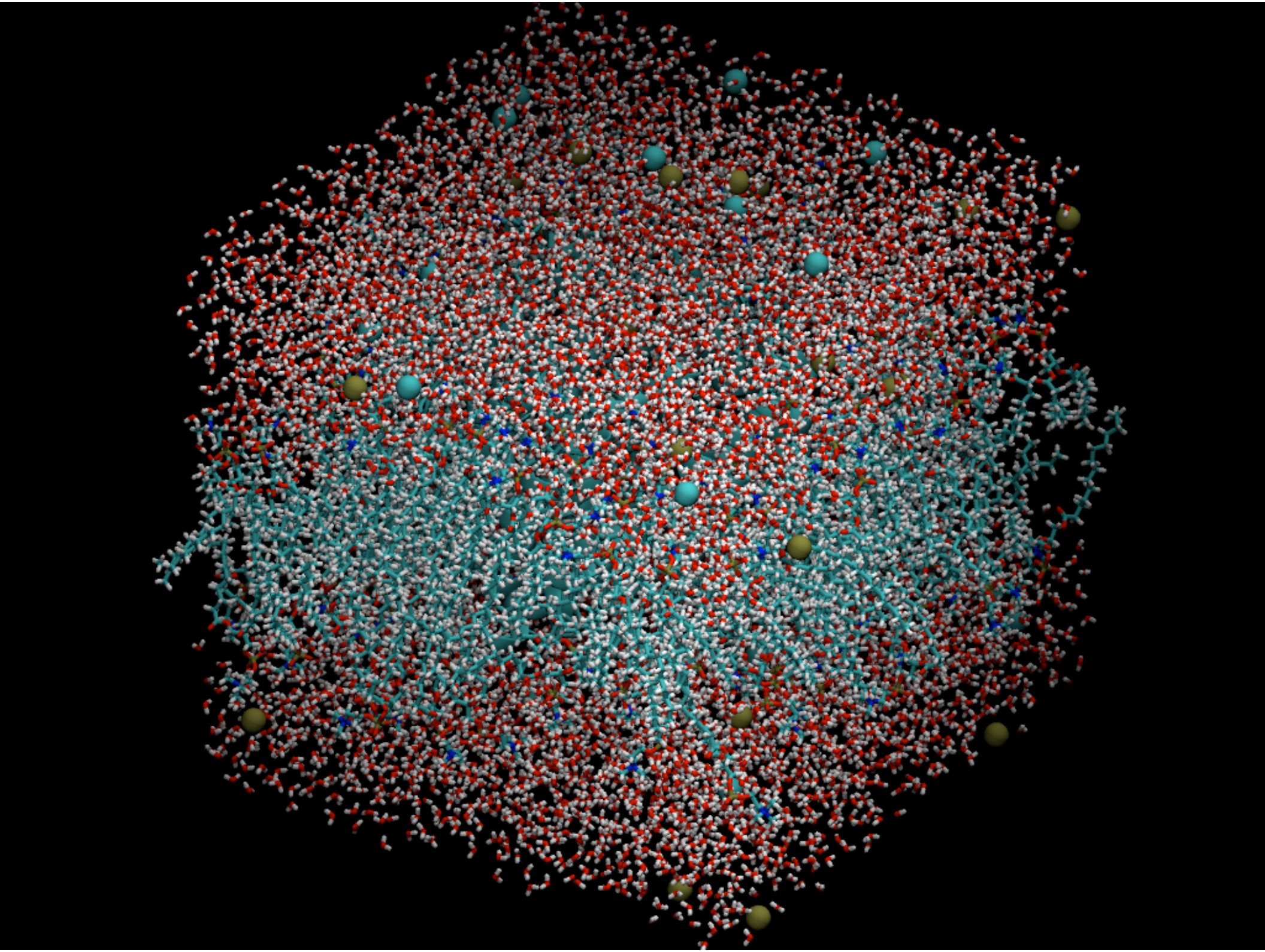
AmtB crystal structure

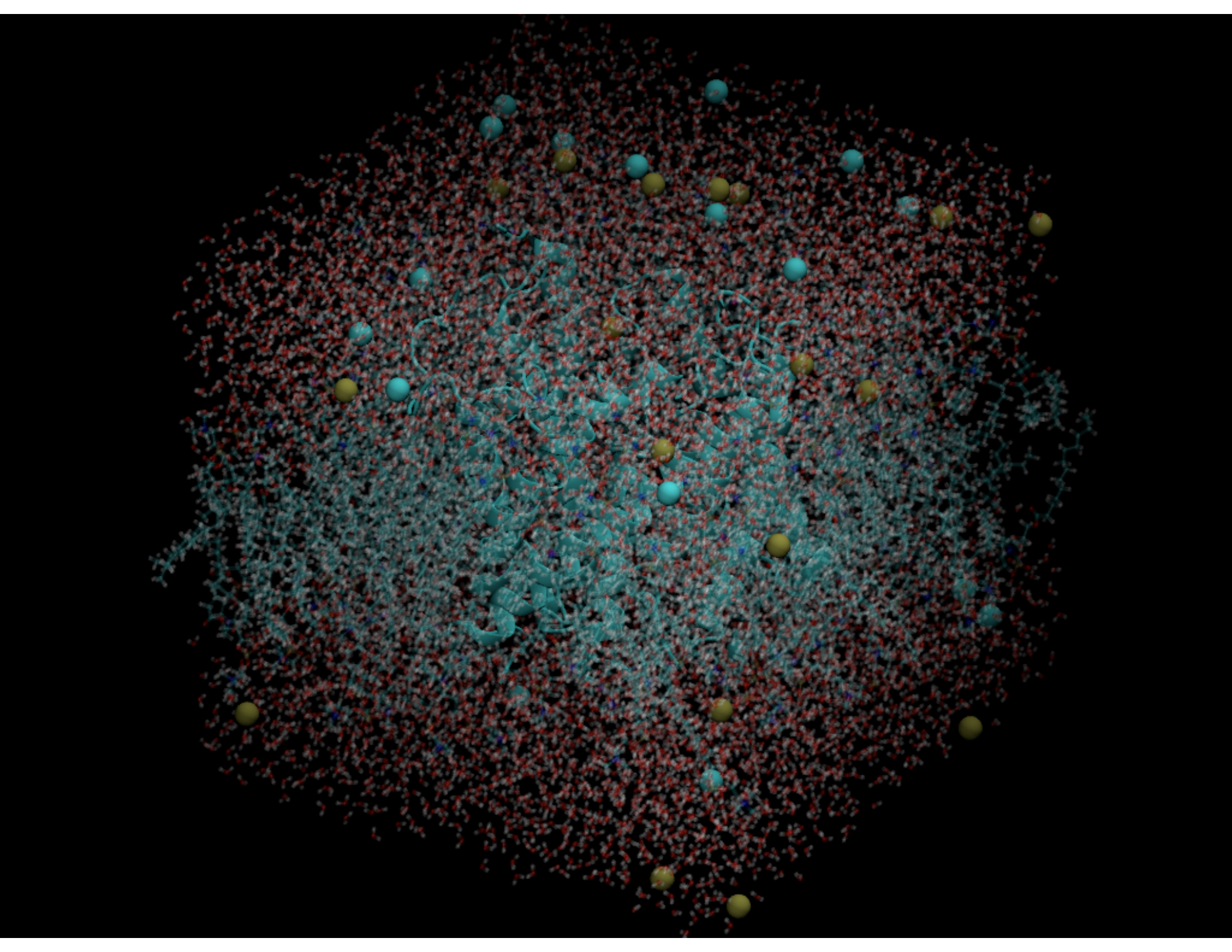
(Zheng et al., *PNAS* 2004, **101**, 17090)

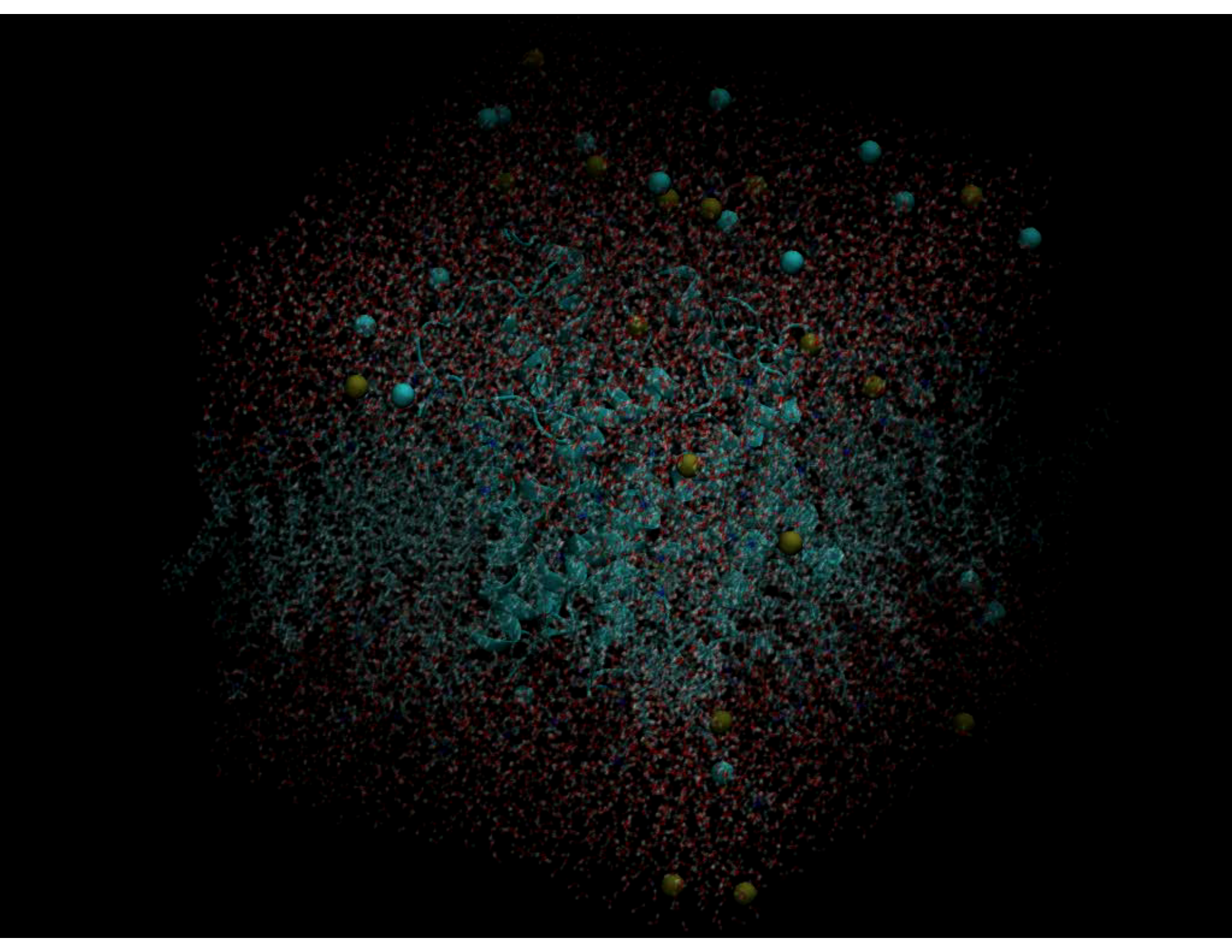












AmtB structure

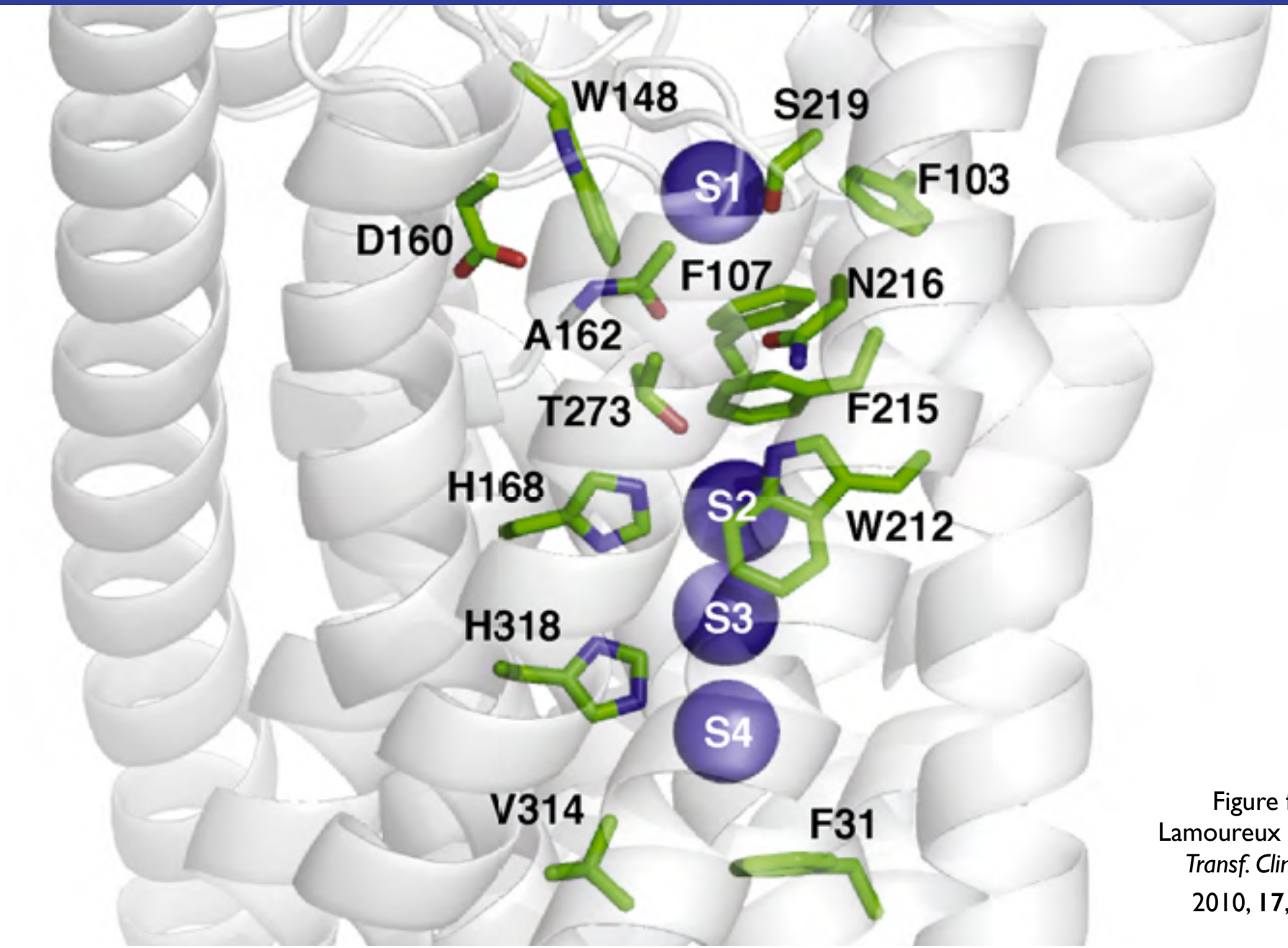
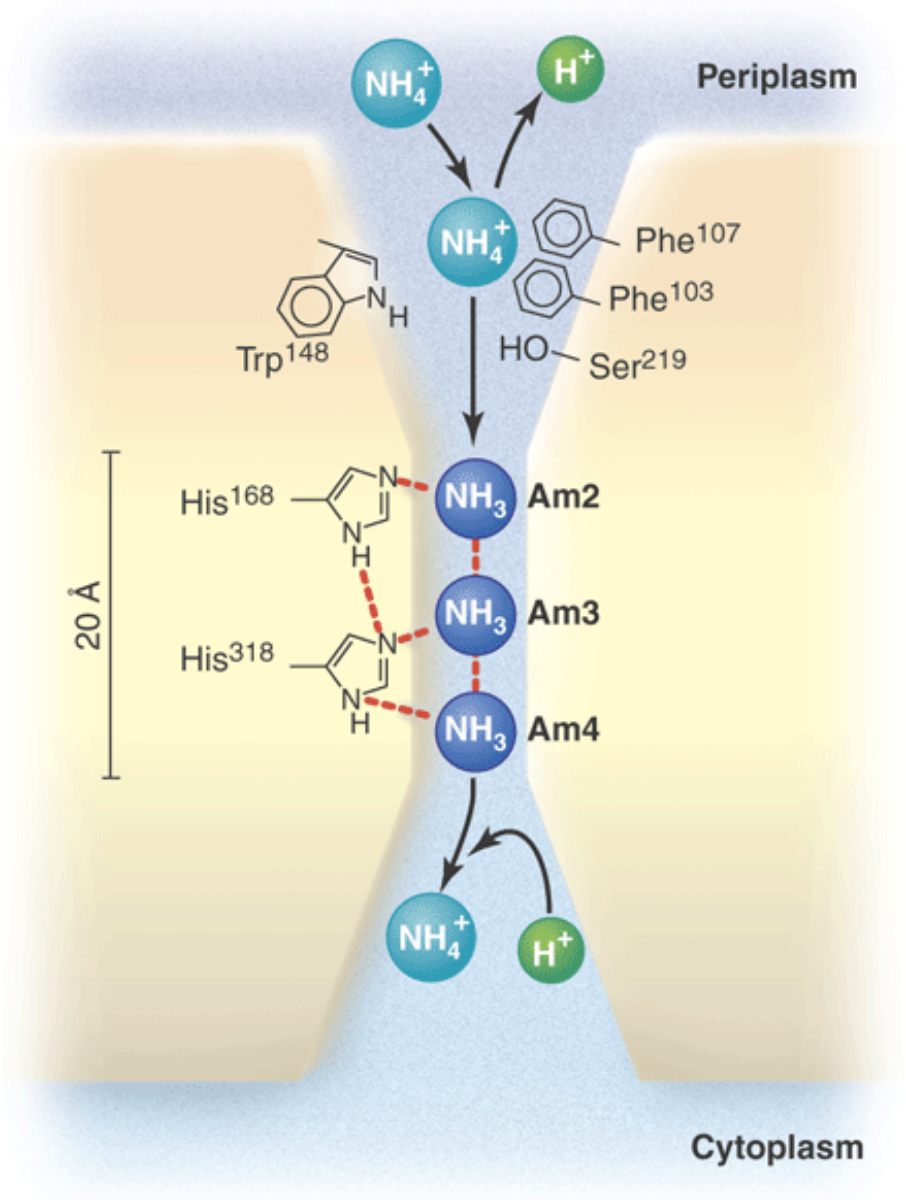


Figure from:
Lamoureux et al.,
Transf. Clin. Biol.
2010, **17**, 168)

Permeation mechanism?

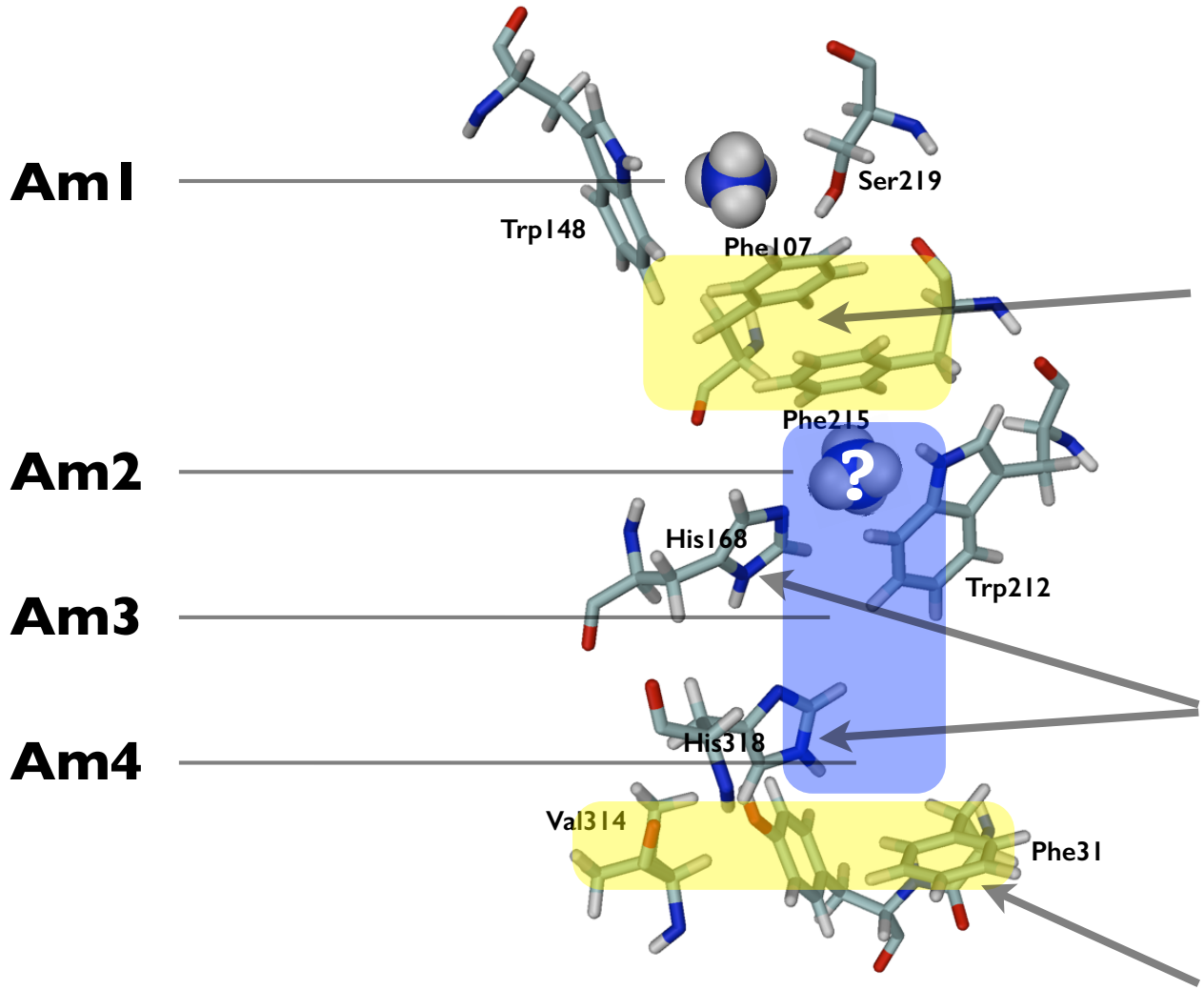


Deprotonation

"Single-file" mechanism

(adapted from Khademi et al., *Science* 2004, **305**, 1587)

Key questions



What is in the pore? (H_2O vs NH_3)

Can NH_4^+ cross the upper gate?

Is a proton being cotransported? (NH_3 vs NH_3/H^+)

What is the role of the two His?

What is the function of the Phe31/Val314 lower gate?

What are *your* questions?

Are the functionally important residues staying in place?
Are they moving?

What about the hydrogen bonds and salt bridges involving these residues?

What about metals and cofactors?

Is the secondary structure of the protein changing?

Are some loops opening or closing?

etc.

Two VMD tricks…

Once you have created a bond label (by typing "2" and clicking on two atoms) you can monitor the distance over time using the "Graphics > Labels… > Bonds > Graph" function.

To create a VMD Representation showing all residues within 3.0 Å of protein residue 123, use selection: "same residue as within 3.0 of (protein and resid 123)".

The same way, you could use "(resname ZN2)".

(Make sure you update the selection every frame.)