CHEM 436 / 630

Molecular modelling of proteins

Winter 2018 Term

Instructor:
Guillaume Lamoureux
Concordia University, Montréal, Canada

Molecular dynamics

"Putting the thermal fluctuations back into a protein structure"

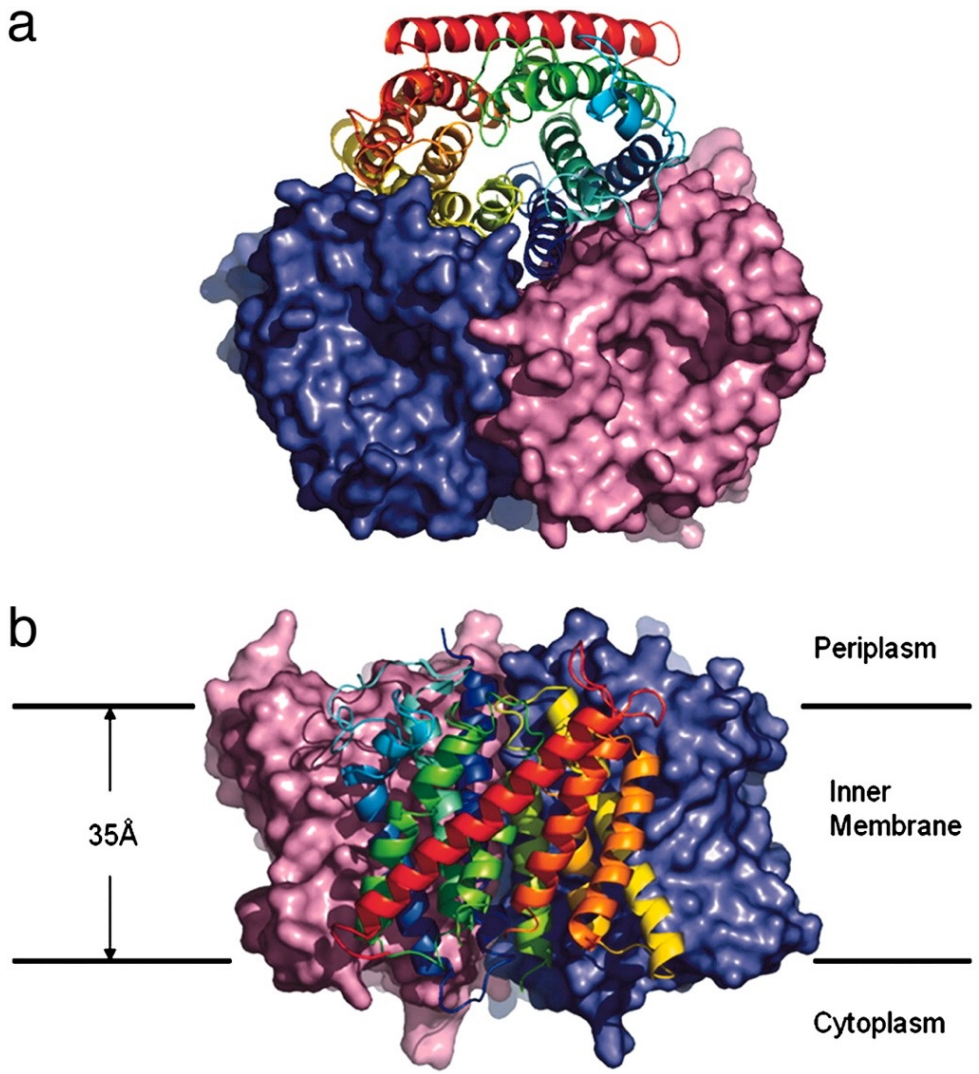
Basic techniques :
Simulation of a system undergoing thermal fluctuations

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

Advanced techniques :
Free energy calculations

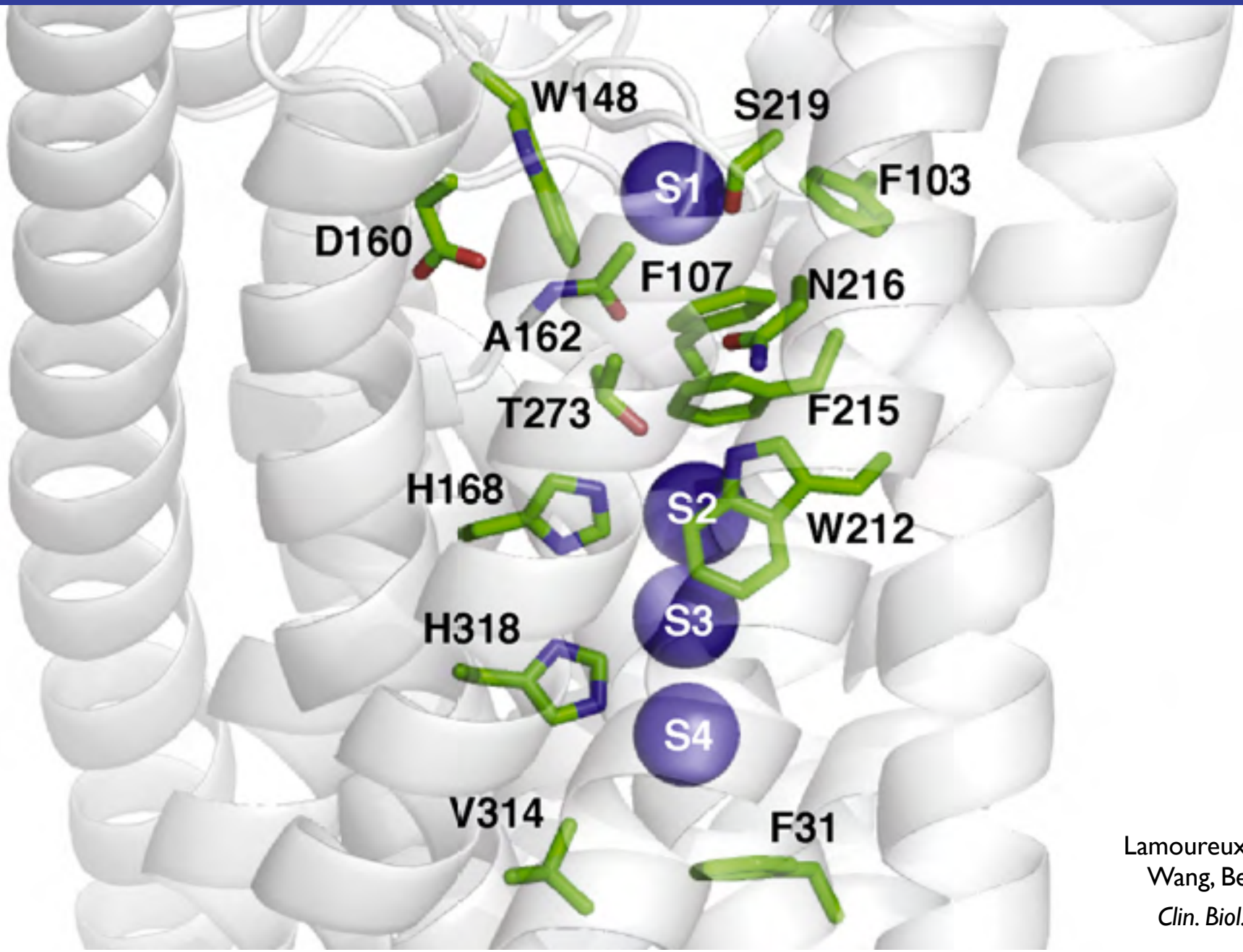
- Reaction profiles (conformational change, substrate permeation, etc.)
- Binding free energies of ligands
- Partition constants ("log *P*")
- Thermodynamic effects of a mutation
- pK_a calculations
- Rate constants / kinetics

AmtB structure



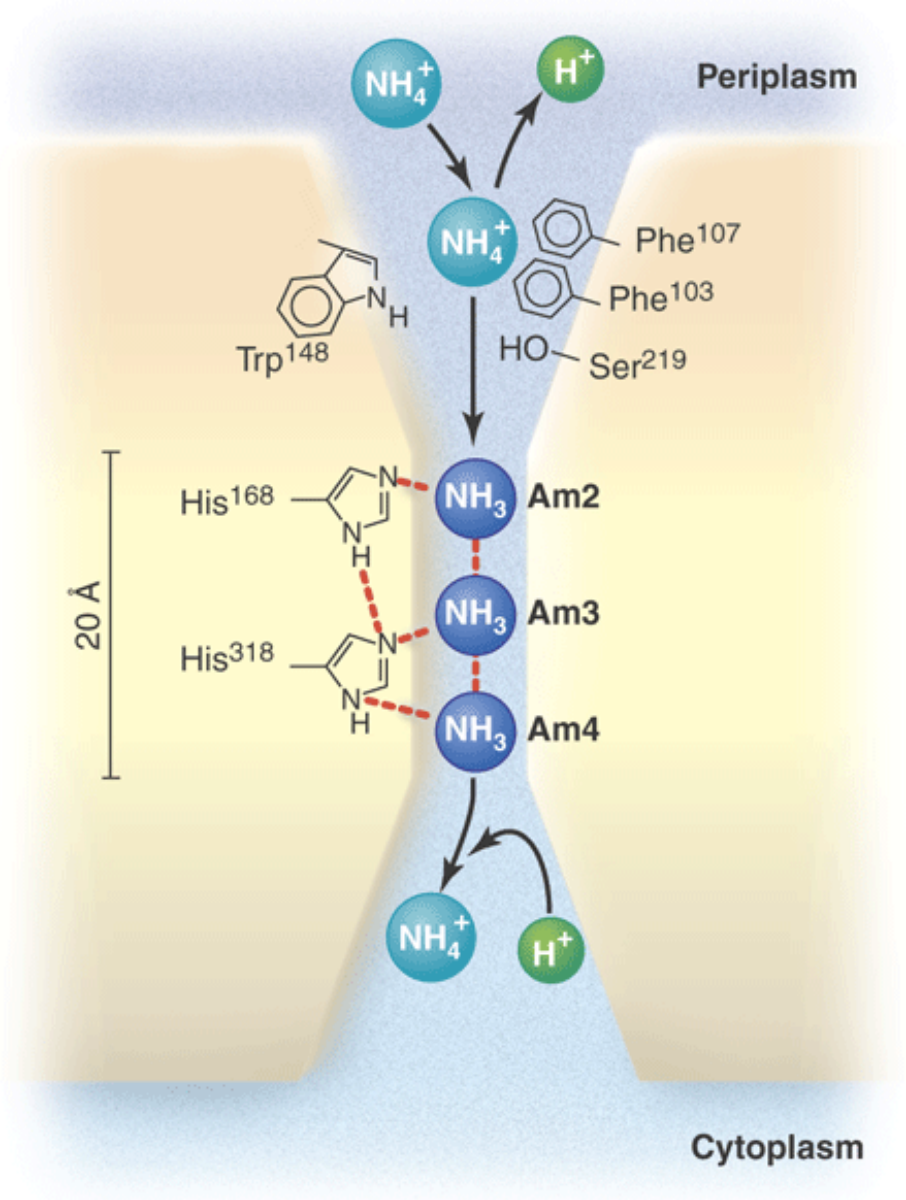
AmtB crystal structure
(Zheng et al., *PNAS* 2004, **101**, 17090)

AmtB structure



Lamoureux, Javelle, Baday, Wang, Bernèche, *Transf. Clin. Biol.* 2010, **17**, 168

Permeation mechanism?

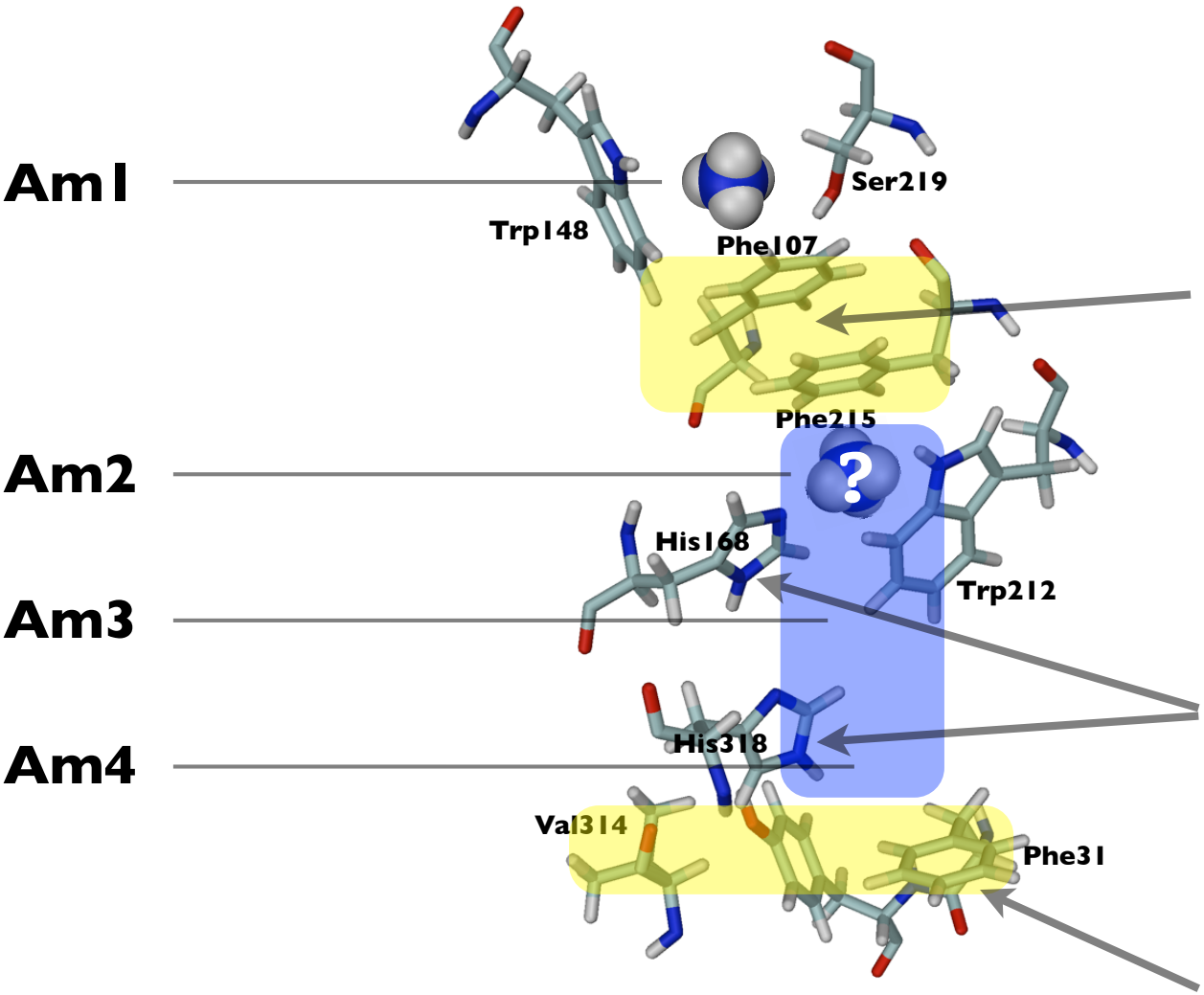


Deprotonation

"Single-file" mechanism

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

Permeation mechanism?



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?

Molecular dynamics

System

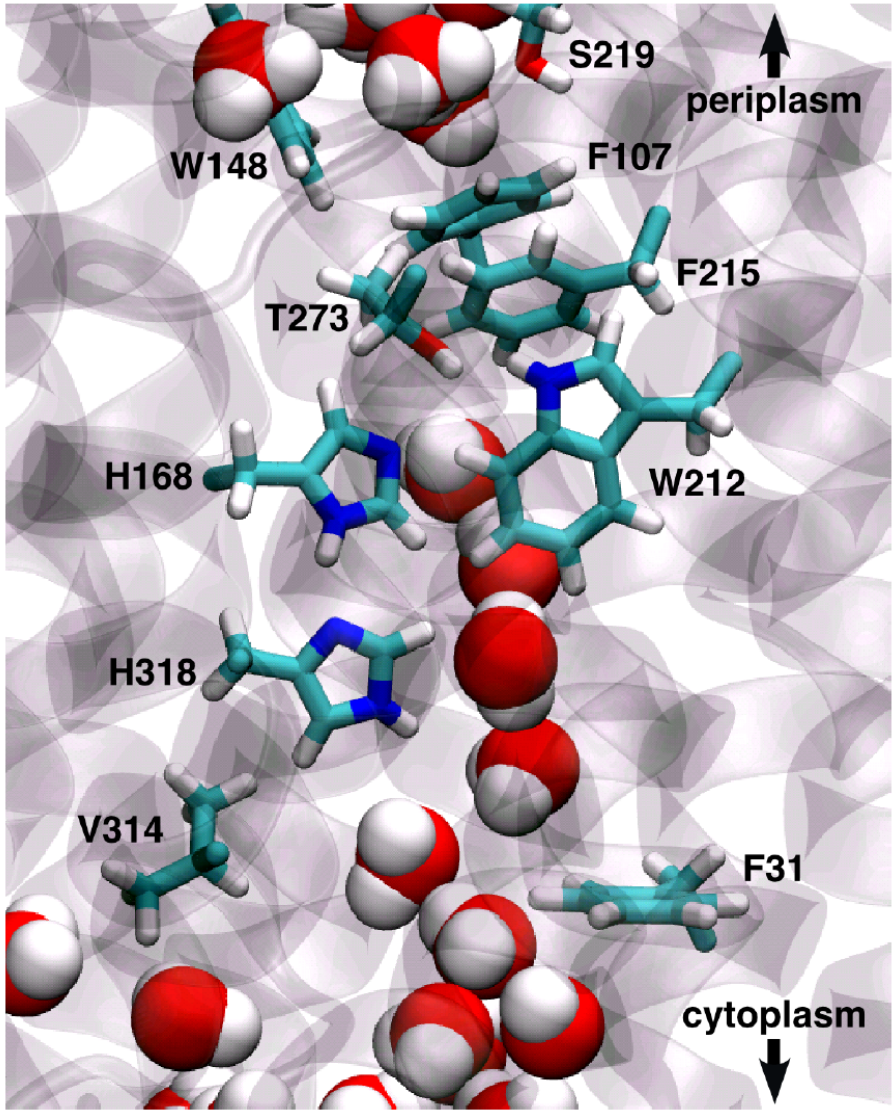
- PDB entry 1XQE ("open" structure)
- Unresolved loops modeled onto those of 1U7G
- AmtB monomer in DMPC membrane
- 0.1 M potassium chloride solution
- No ammonia, no ammonium

Two protonation states

- "His168 donor" (His318 acceptor)
- "His168 acceptor" (His318 donor)

Simulation protocol

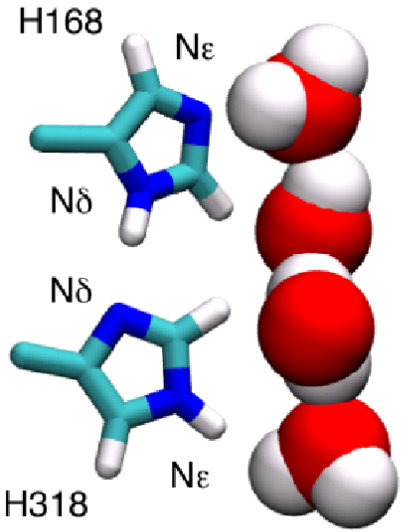
- CHARMM22 force field (TIP3P water)
- Constant-pressure and temperature
- NH_3 model calibrated relative to ΔG_{hydr} of water
- NH_4^+ model calibrated relative to ΔG_{hydr} of K^+

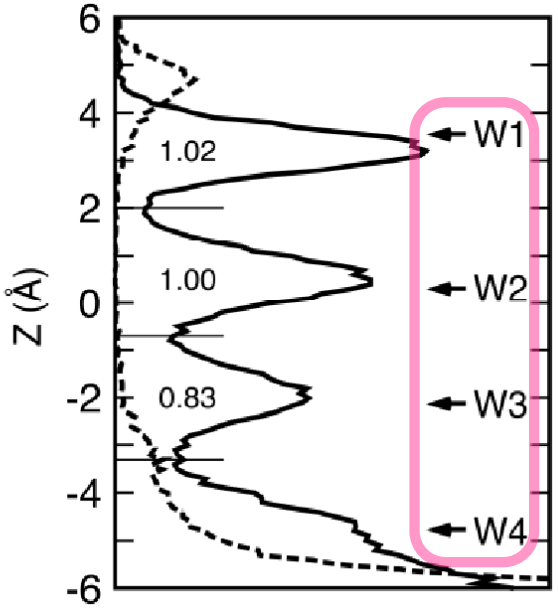


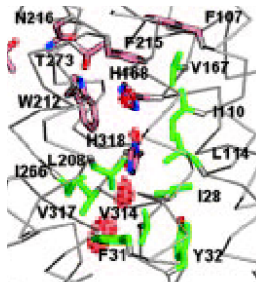
A stable water chain in the pore

The "His168 donor" state stabilizes a water chain.

(The "His168 acceptor" state does not.)



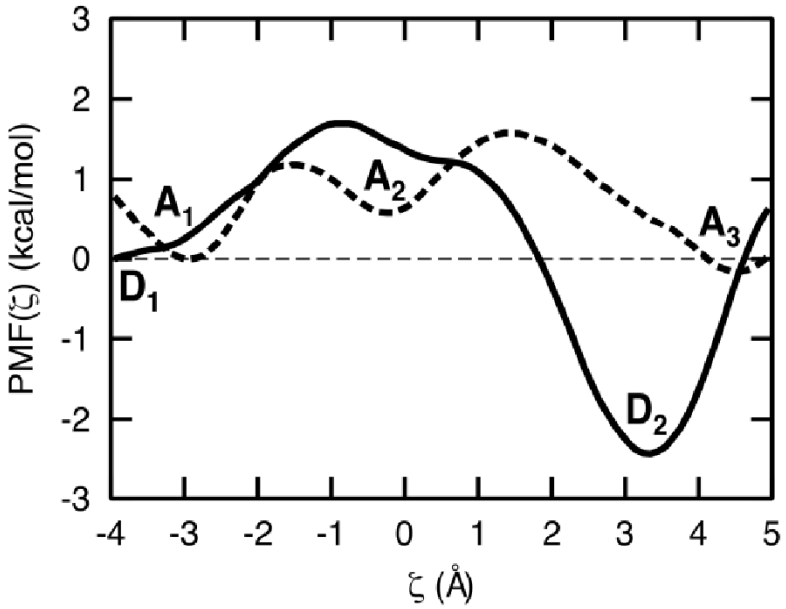


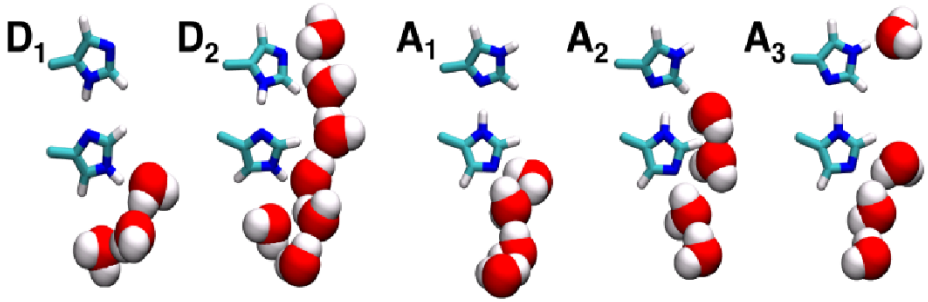


Equilibrium positions in concordance with the electron density maxima from "closed" structure 1XQF

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

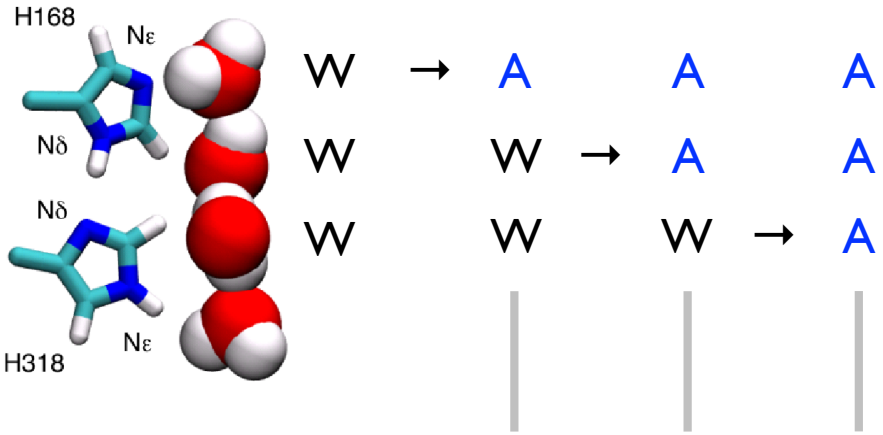
Potential of mean force (PMF) of cytoplasmic water going into the empty pore





Lamoureux, Klein, Bernèche, *Biophys. J.* 2007, **106**, L82

NH_3 *versus* H_2O in the pore



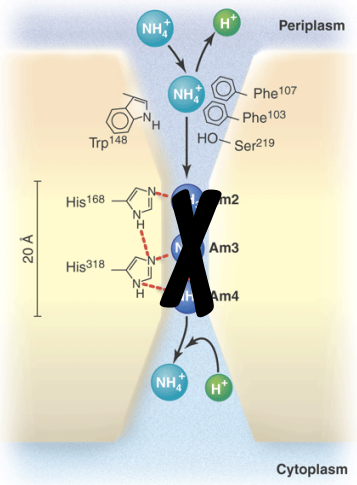


Figure adapted from: Khademi *et al.*, *Science* 2004, **305**, 1587

ΔG (kcal/mol)	-1.28	-2.39	-2.02
$\Delta\Delta G$ (kcal/mol)	-3.23	-4.34	-3.97
$T\Delta S$ [A] = 1 μM	10.6	10.6	10.6
$T\Delta S$ [A] = 1 mM	6.5	6.5	6.5

-1.95 kcal/mol from desolvation

Entropic cost of bringing NH_3 from a dilute solution to the binding site

Entropy "wins"

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.)