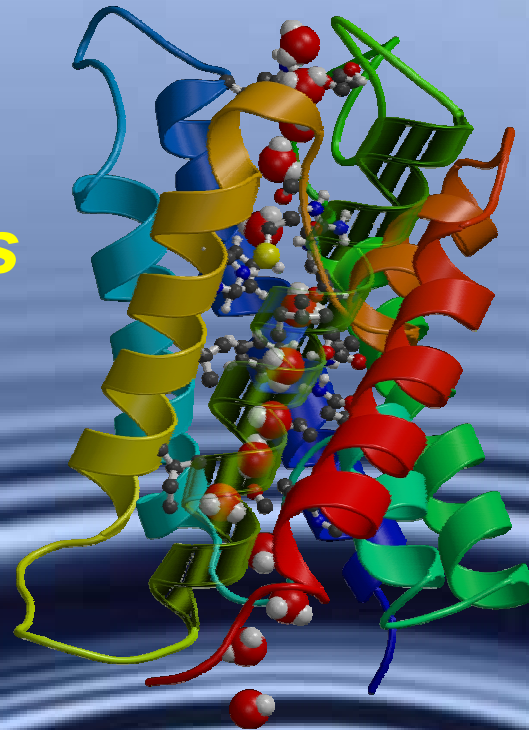


***Aquaporins:
Perfect Filters***



***Dynamics
Efficiency
Selectivity***

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Matthias Müller***

***Theoretical and Computational Biophysics Department
Max Planck Institute for Biophysical Chemistry
Göttingen, Germany***

www.mpibpc.gwdg.de/abteilungen/070

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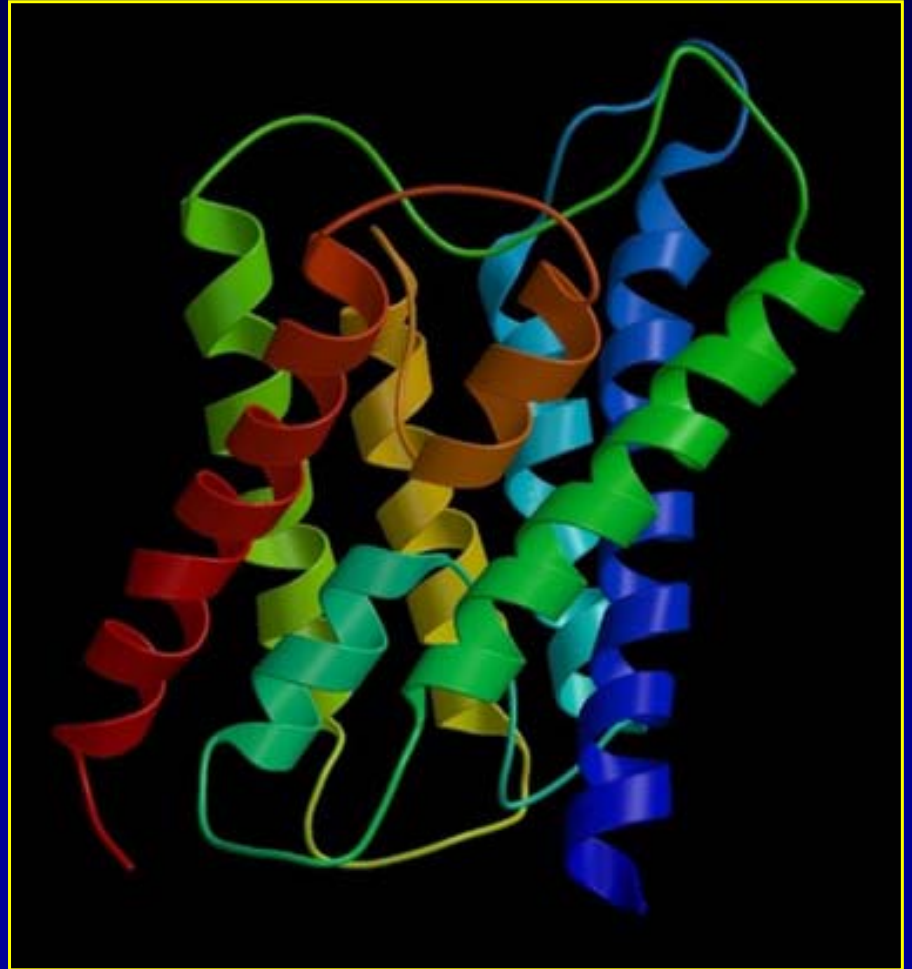
Aquaporin Water Channels

Aquaporins are highly selective, efficient water channels ($10^9/s$)

Expressed mainly in red blood cells, kidney, lung, brain, eye lens

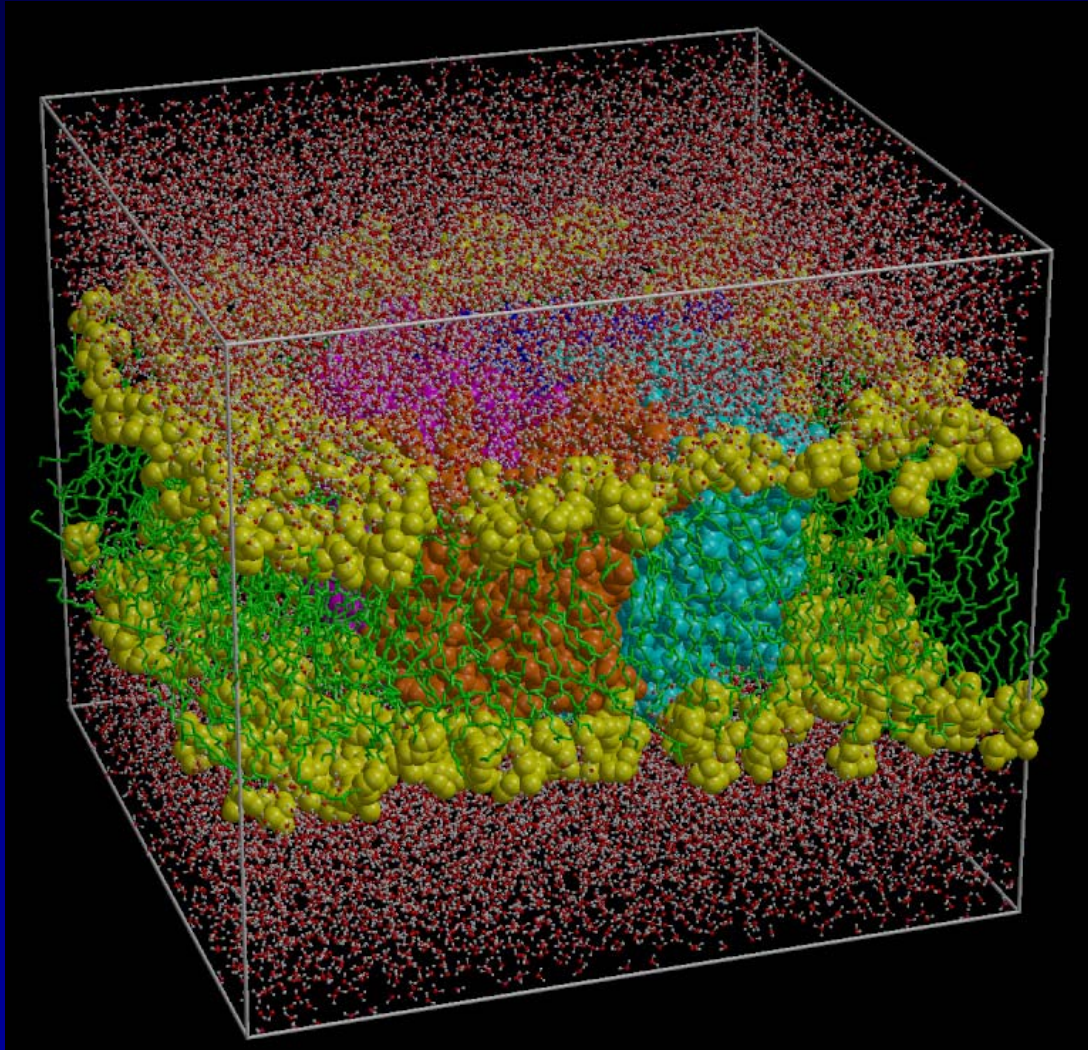
Question:

How can aquaporins be so selective and at the same time so efficient?

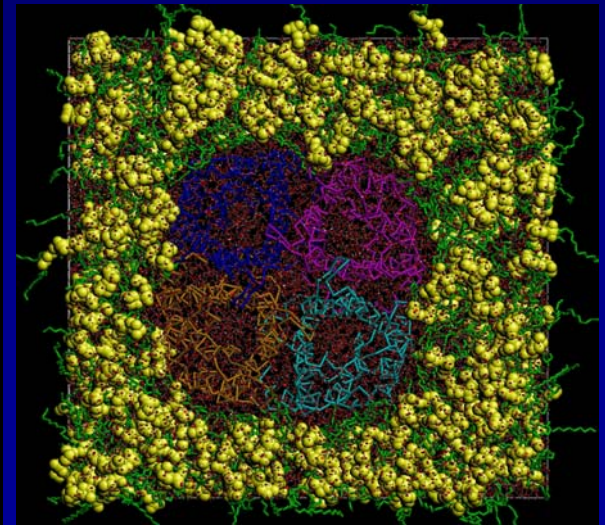


Aquaporin: Dynamics

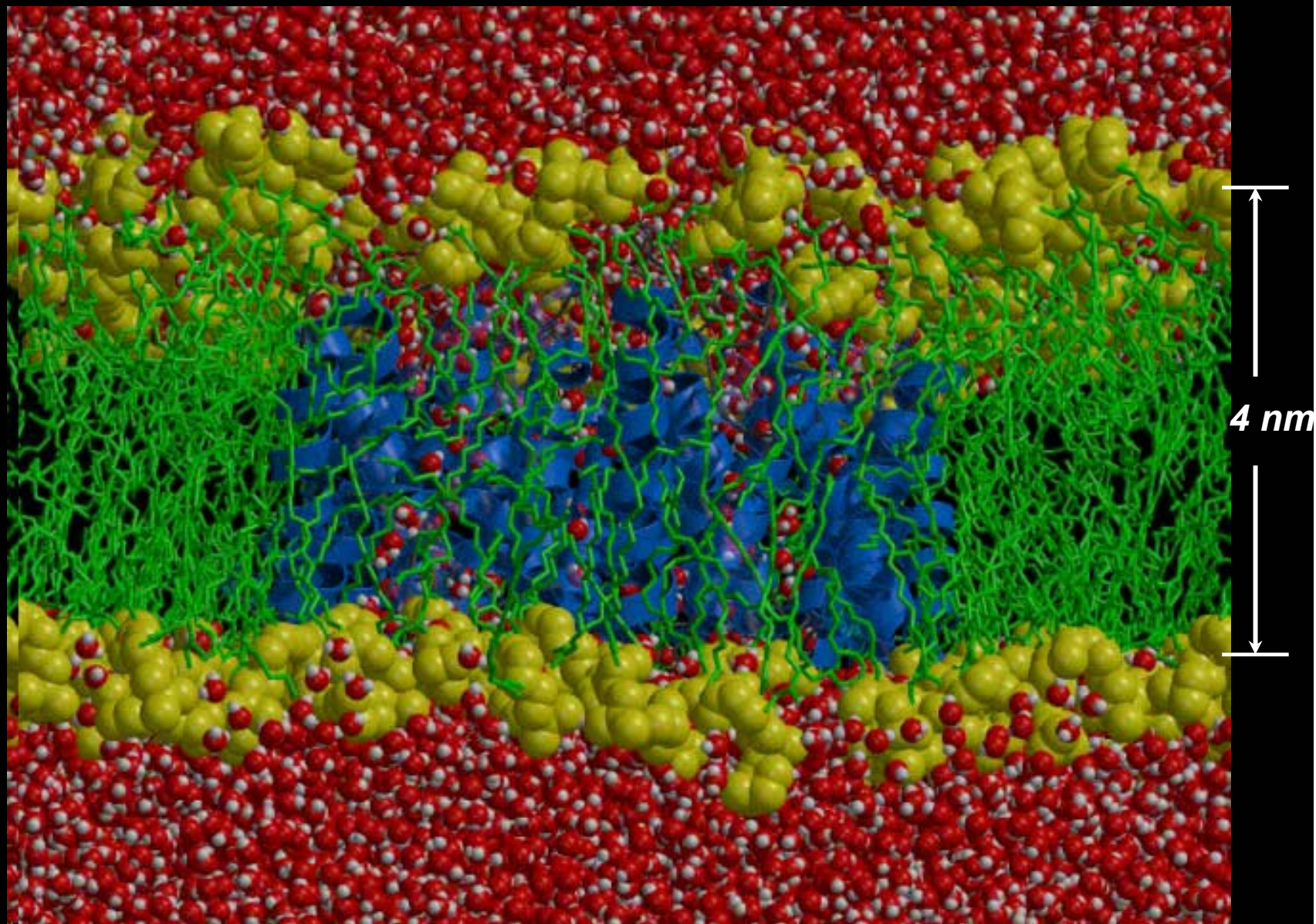
MD simulations of water transport



- *ca. 100 000 atoms*
- *full electrostatics, periodic boundary*
- *10 ns simulation time*



top view



Molecular dynamics simulation, $1\text{s} \hat{=} 2 \cdot 10^{-11}\text{s}$

Water Permeation proceeds in steps

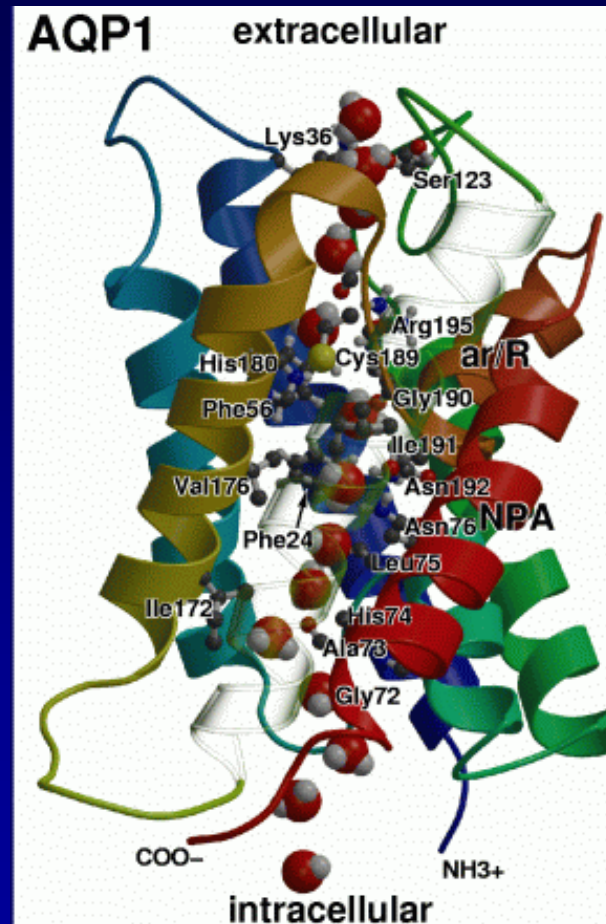
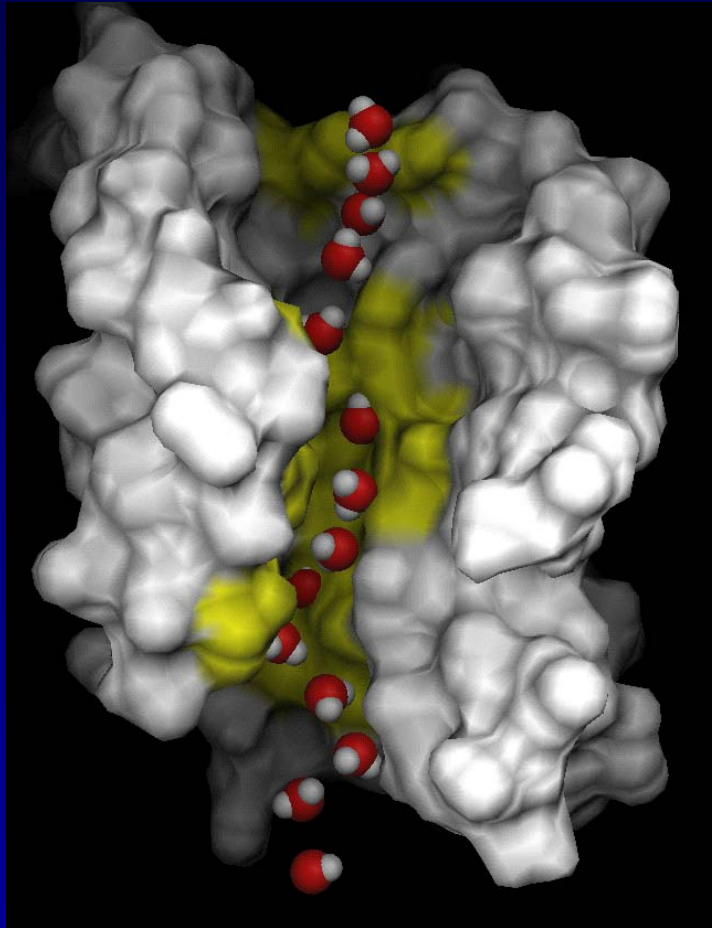
***one out of 16 full
spontaneous
permeation
events (2 ns)***

***(outside the channel,
only few water
molecules are shown)***

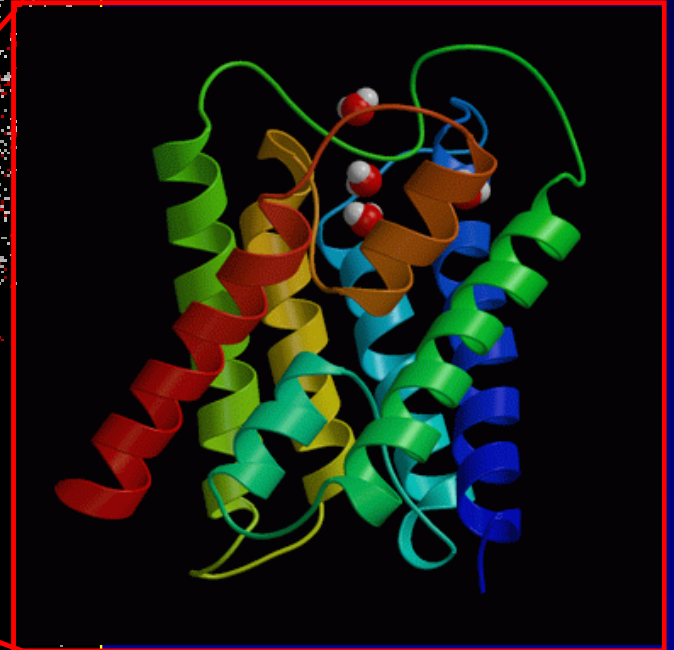
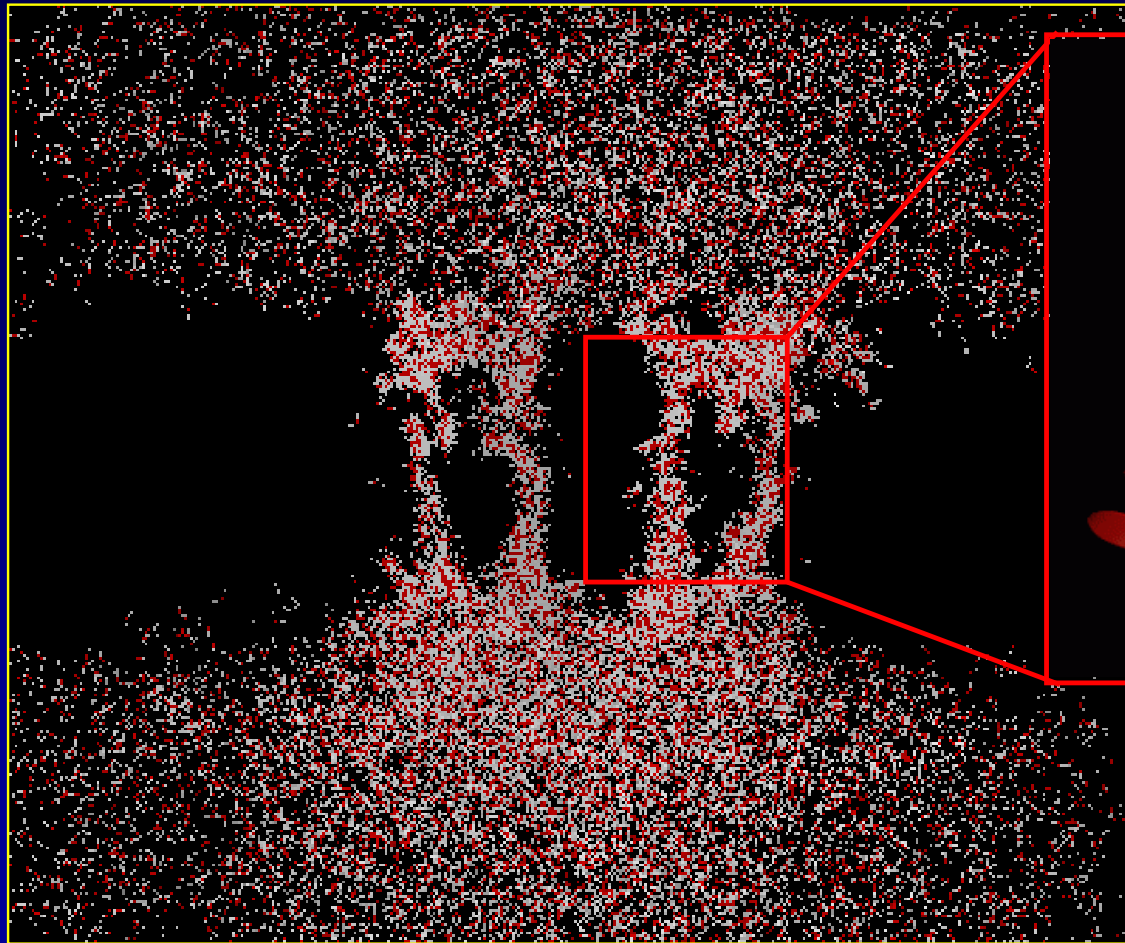


Efficiency

Water pathway and hydrogen bonding in Aquaporin-1



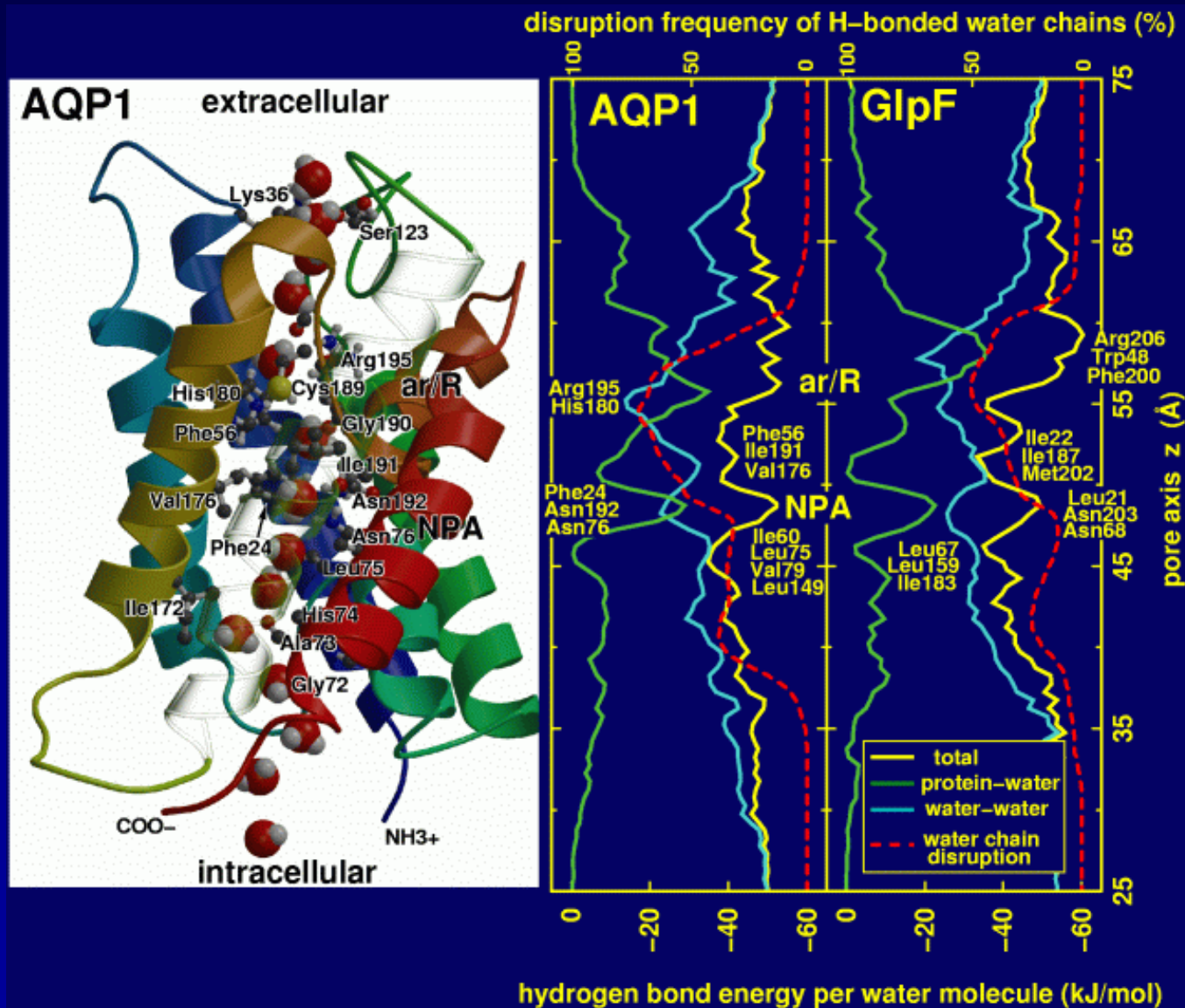
MD simulations of water transport (overlay)



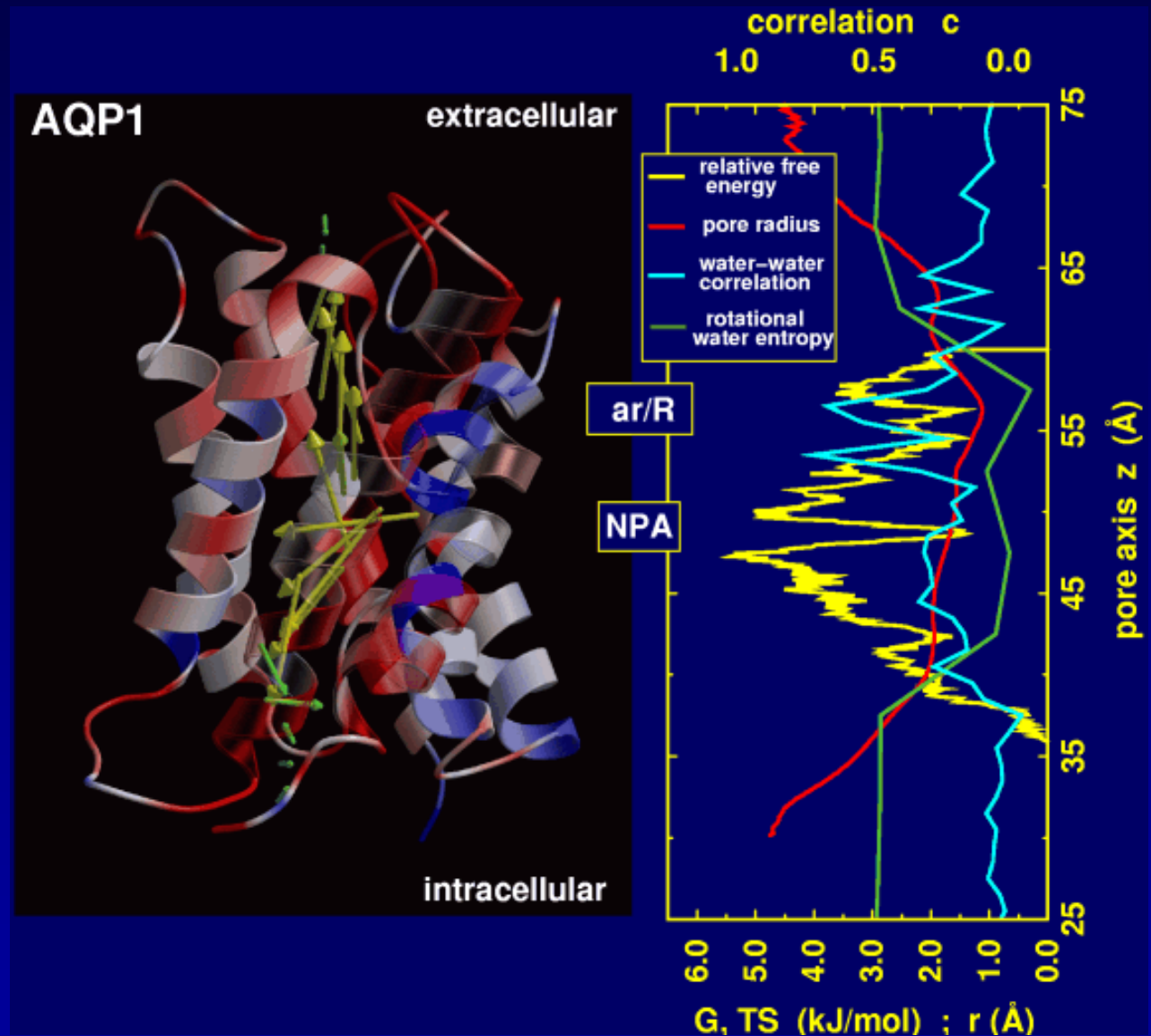
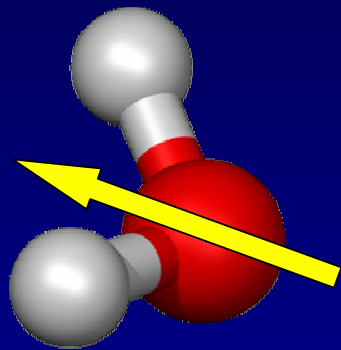
Water flow

Water mobility (Aquaporin-1)

Water pathway and hydrogen bonding in Aquaporin-1

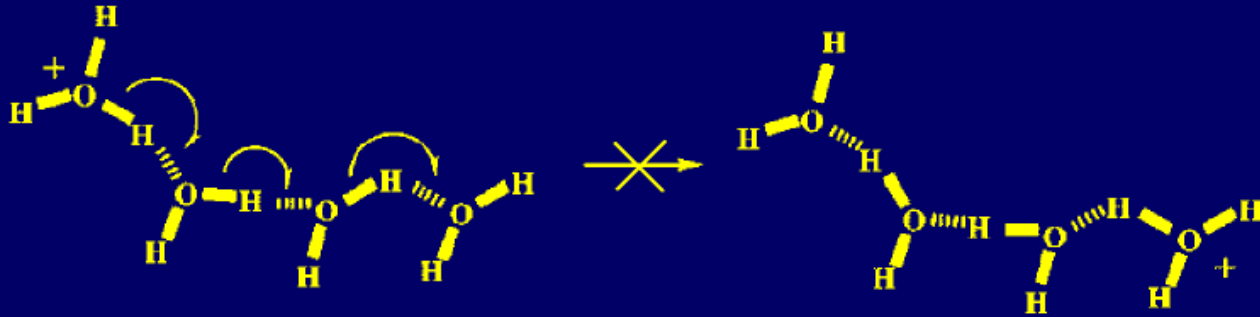


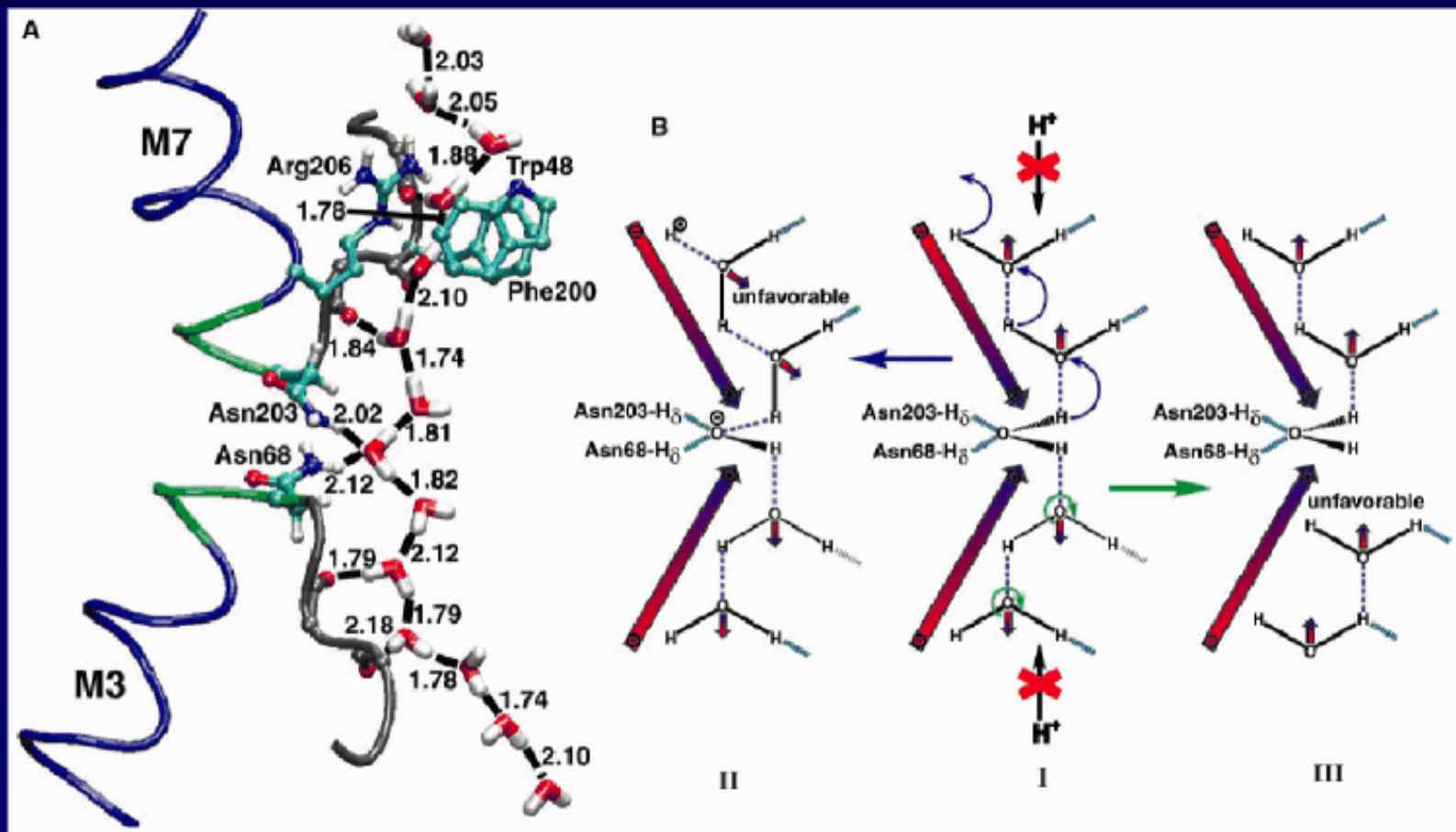
Choreography of water molecules in Aquaporin-1



Selectivity
against protons

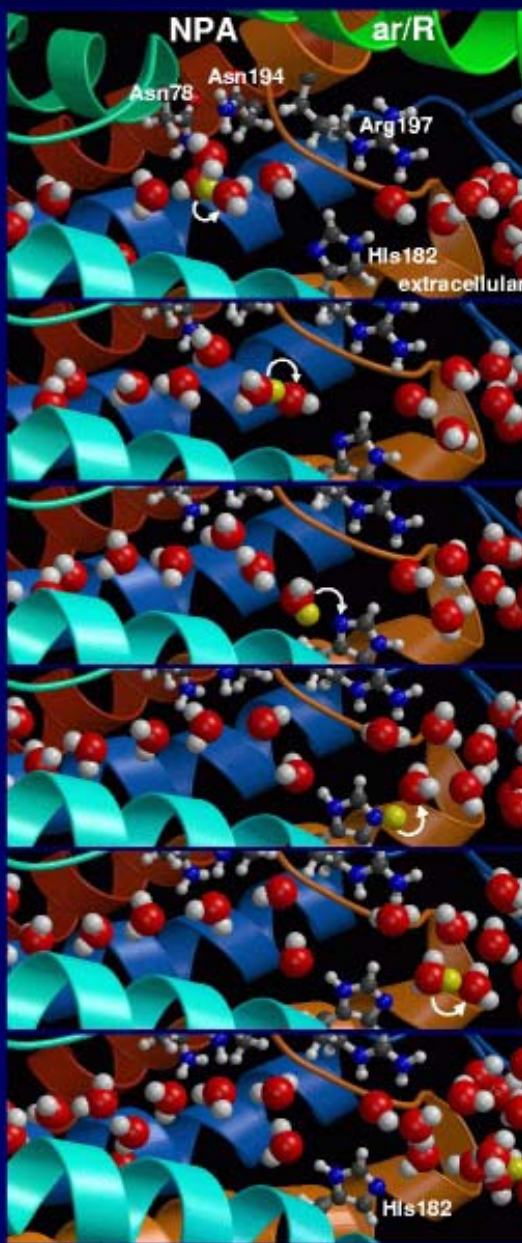
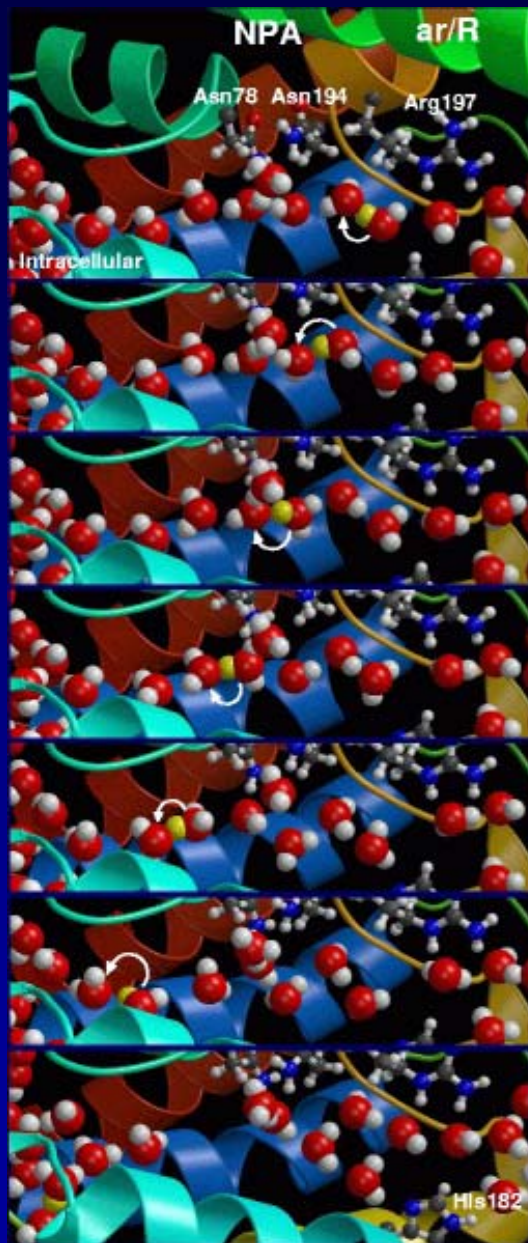
The Grotthuss mechanism of proton translocation



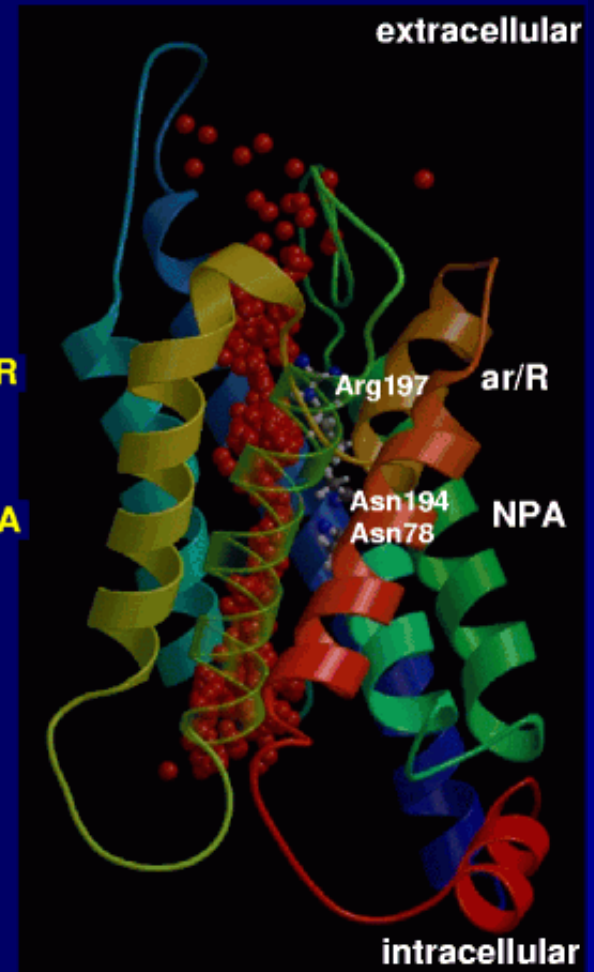
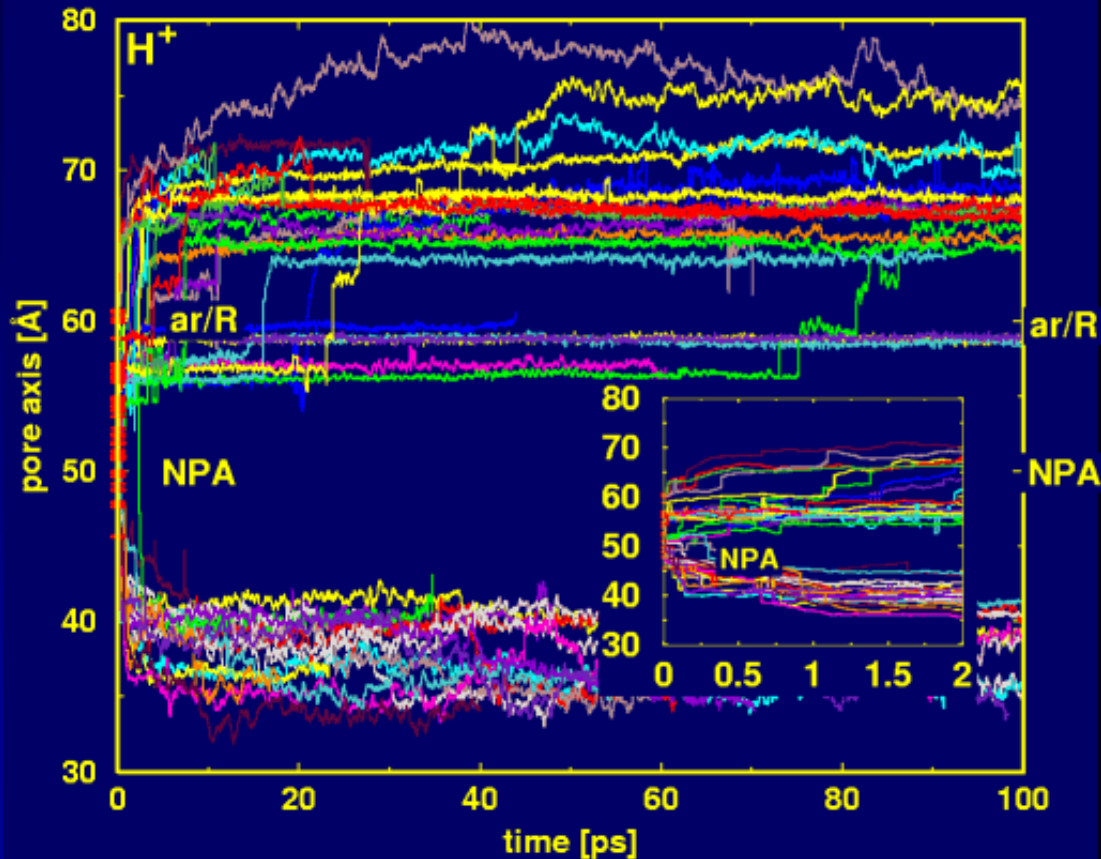


Tajkhorshid et al. (Science 296:525 (2002))

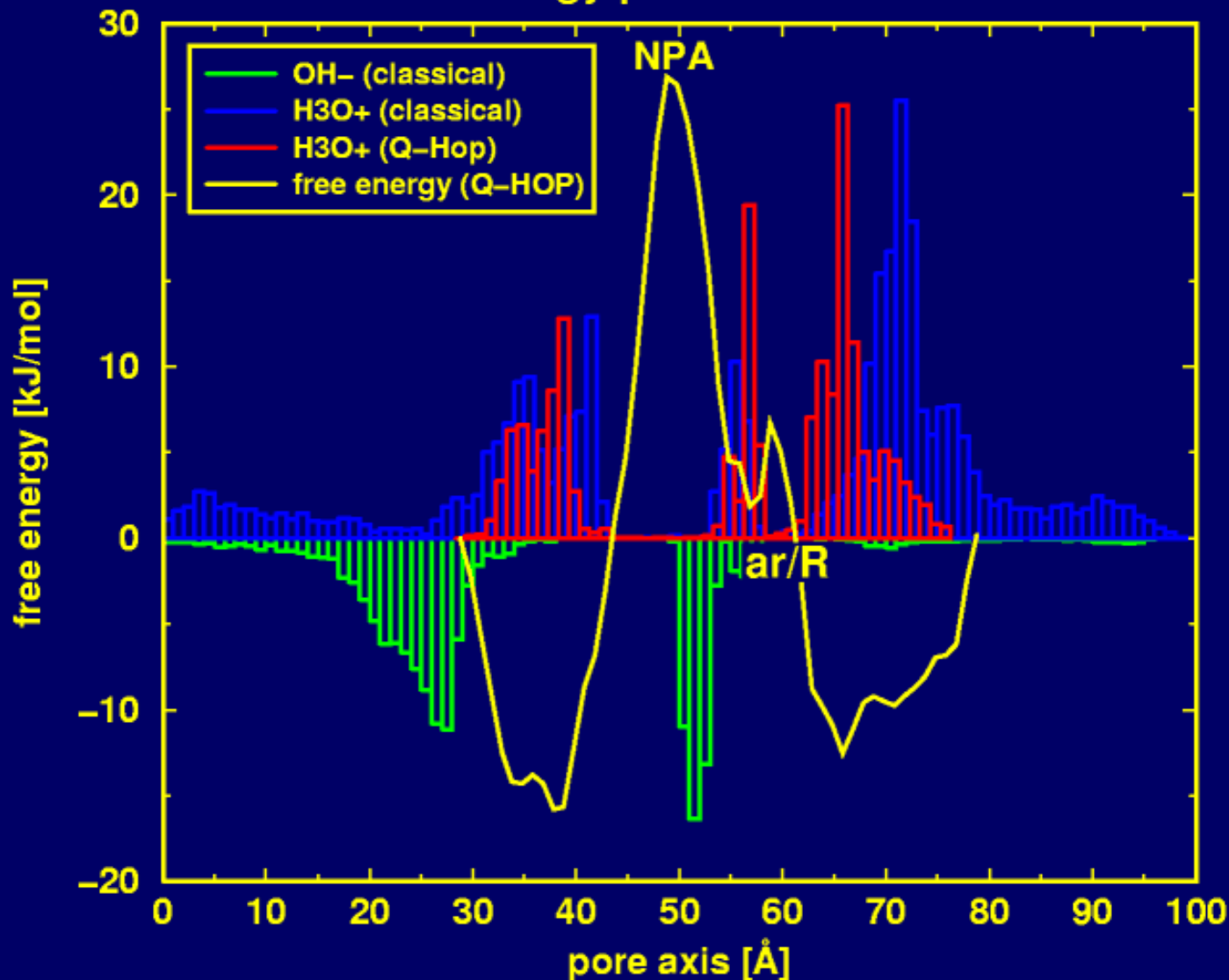
Two sample Q-hop simulations



Proton trajectories in Q-HOP simulations



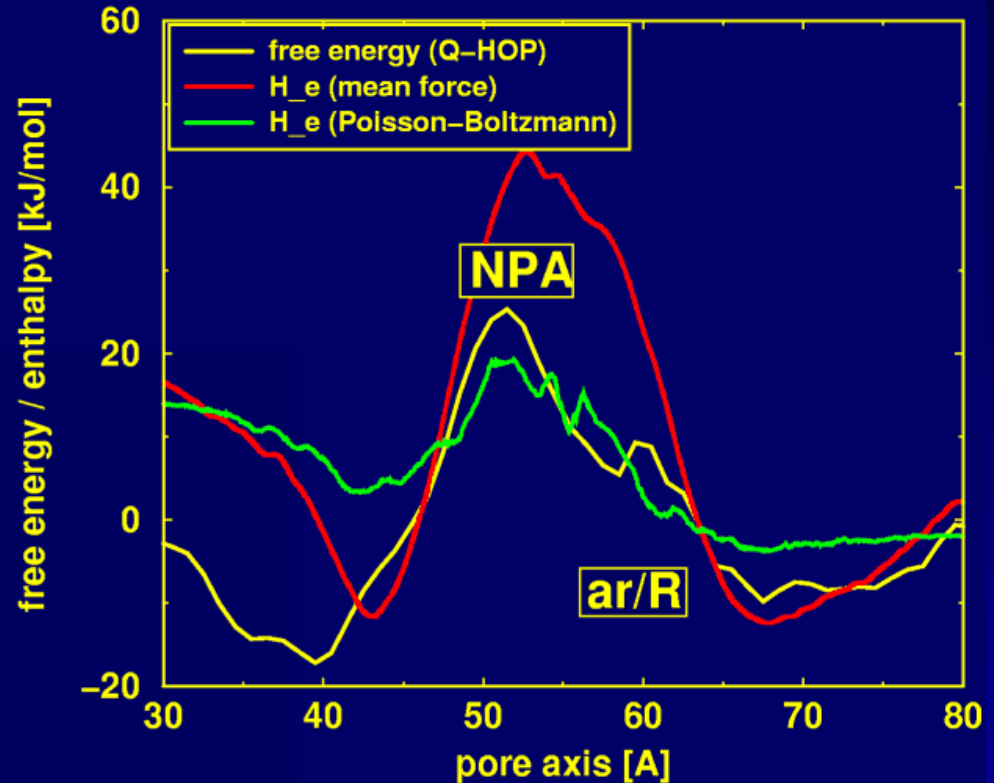
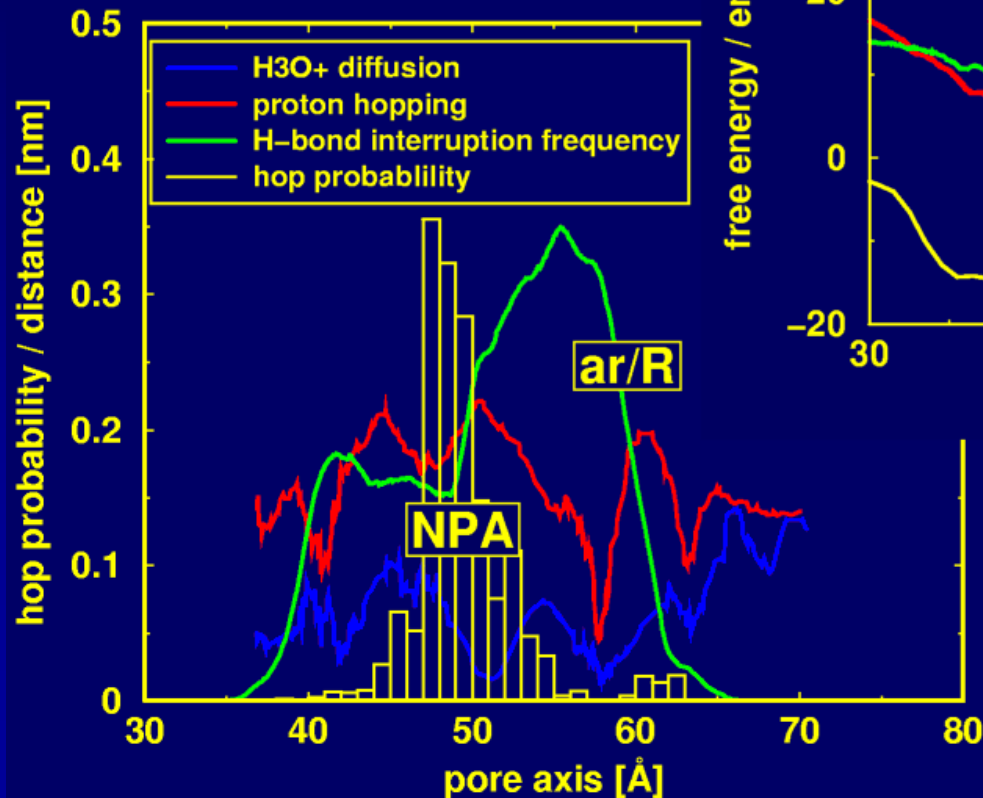
Proton free energy profile and distributions



Beware: no equilibrium!

Determinants of proton exclusion

(2) hydrogen bonds



(1) electrostatics

Timescales of Protein Motions

seconds

10^4
 10^3
 10^2
 10^1
 10^0
 10^{-1}
 10^{-2}
 10^{-3}
 10^{-4}
 10^{-5}
 10^{-6}
 10^{-7}
 10^{-8}
 10^{-9}
 10^{-10}
 10^{-11}
 10^{-12}
 10^{-13}
 10^{-14}

protein

folding

'BIOCHEMISTRY':

- *gating of channels*
- *enzymatic reactions*
- *molecular motors*
- *recognition*

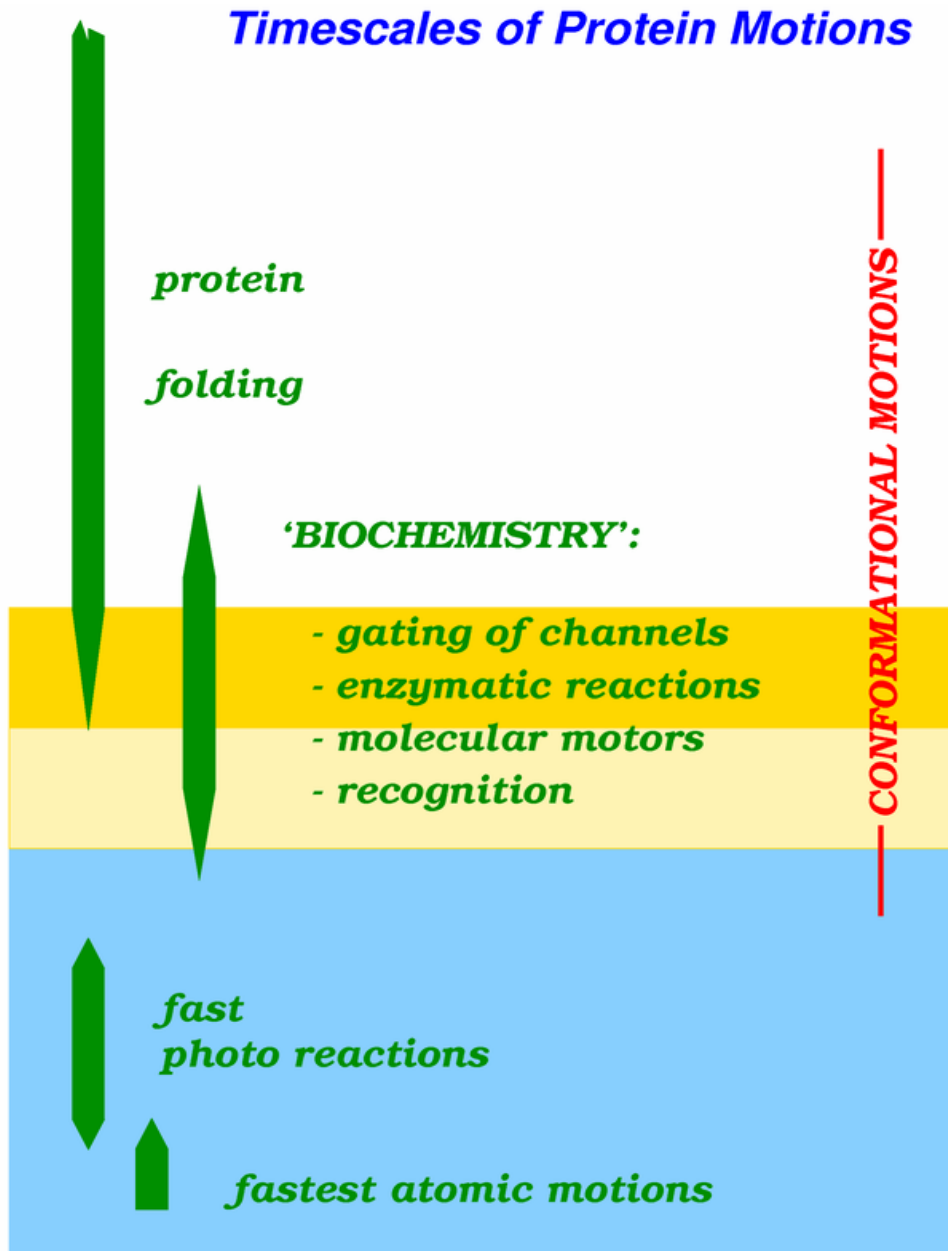
CONFORMATIONAL MOTIONS

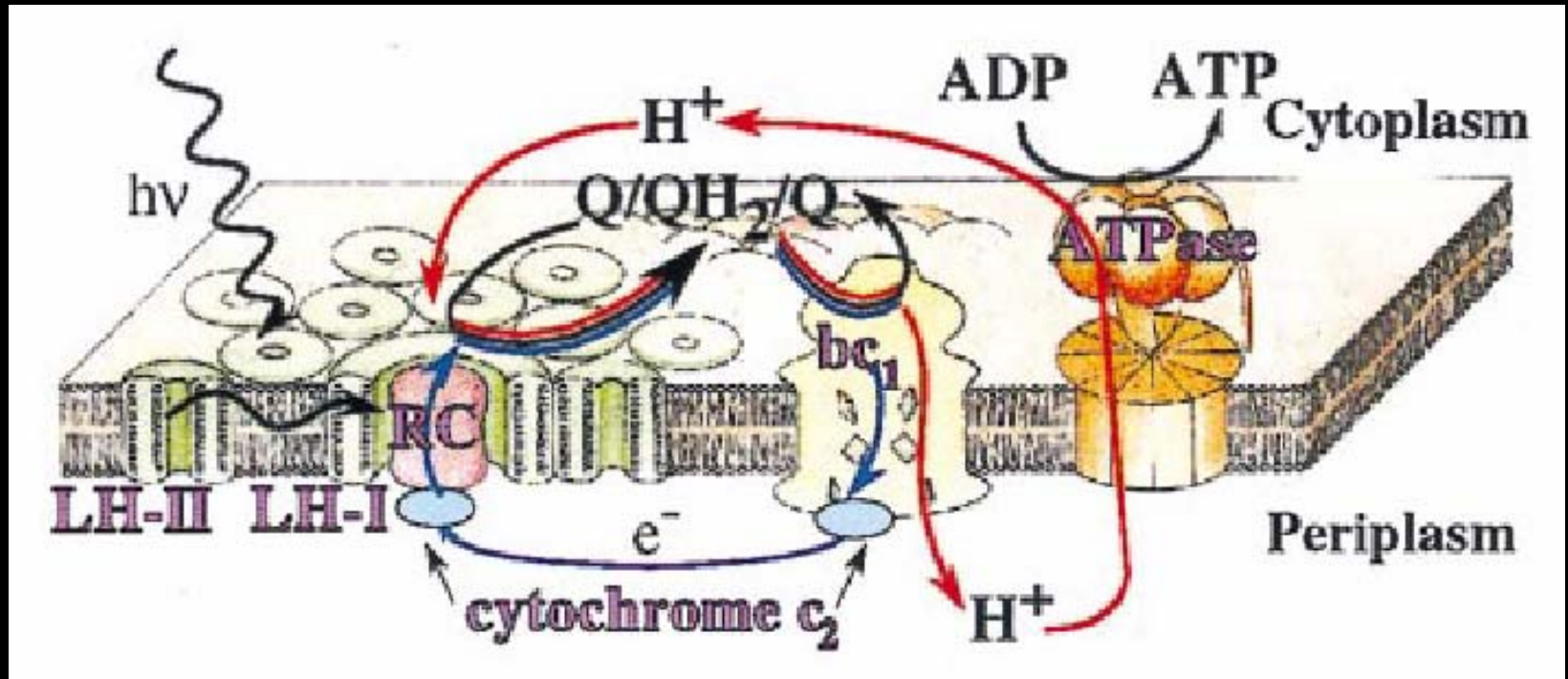
TeraFlop

Today

*fast
photo reactions*

fastest atomic motions



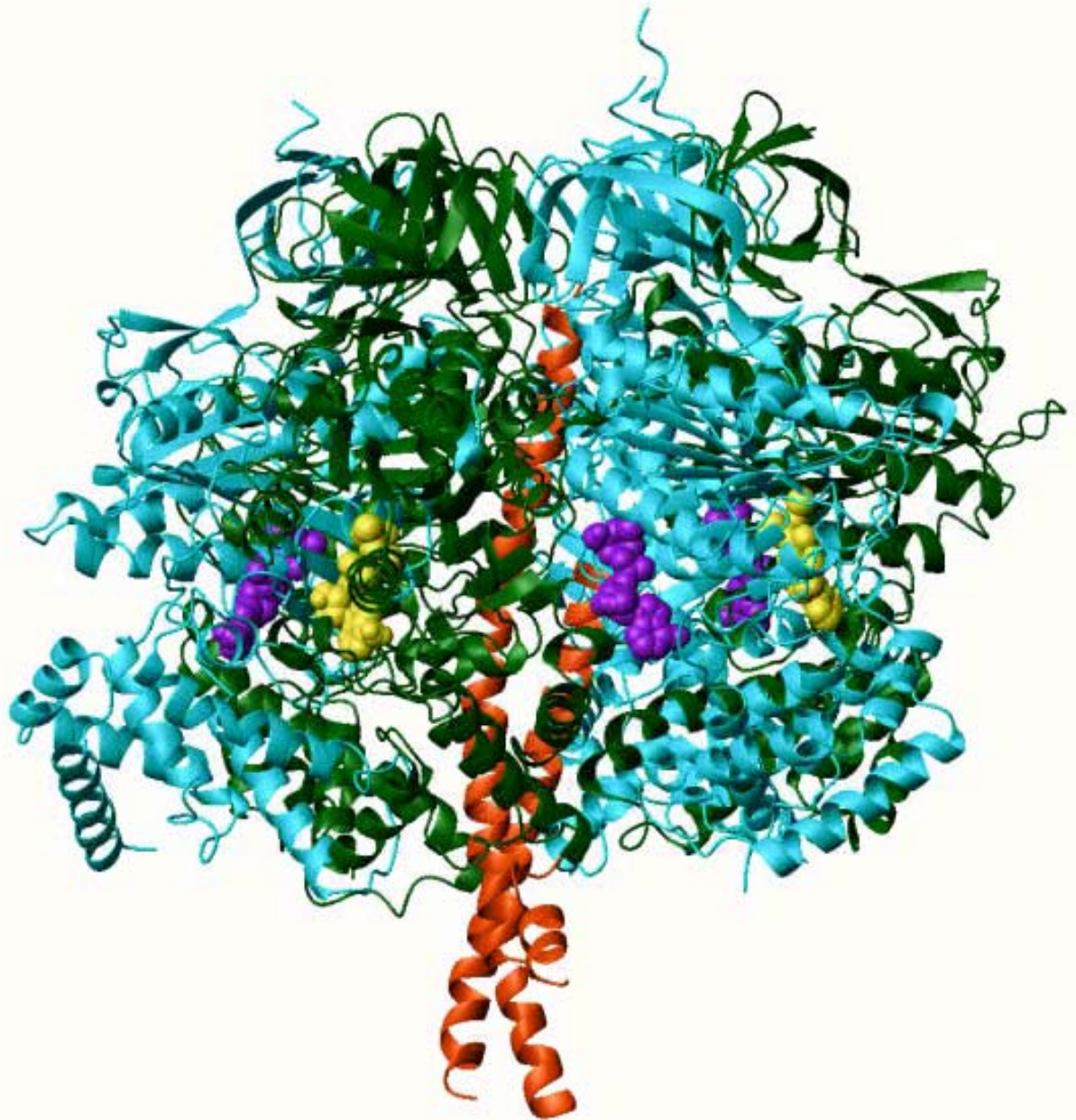


From: X. Hu et al., PNAS 95 (1998) 5935

Primary steps in photosynthesis

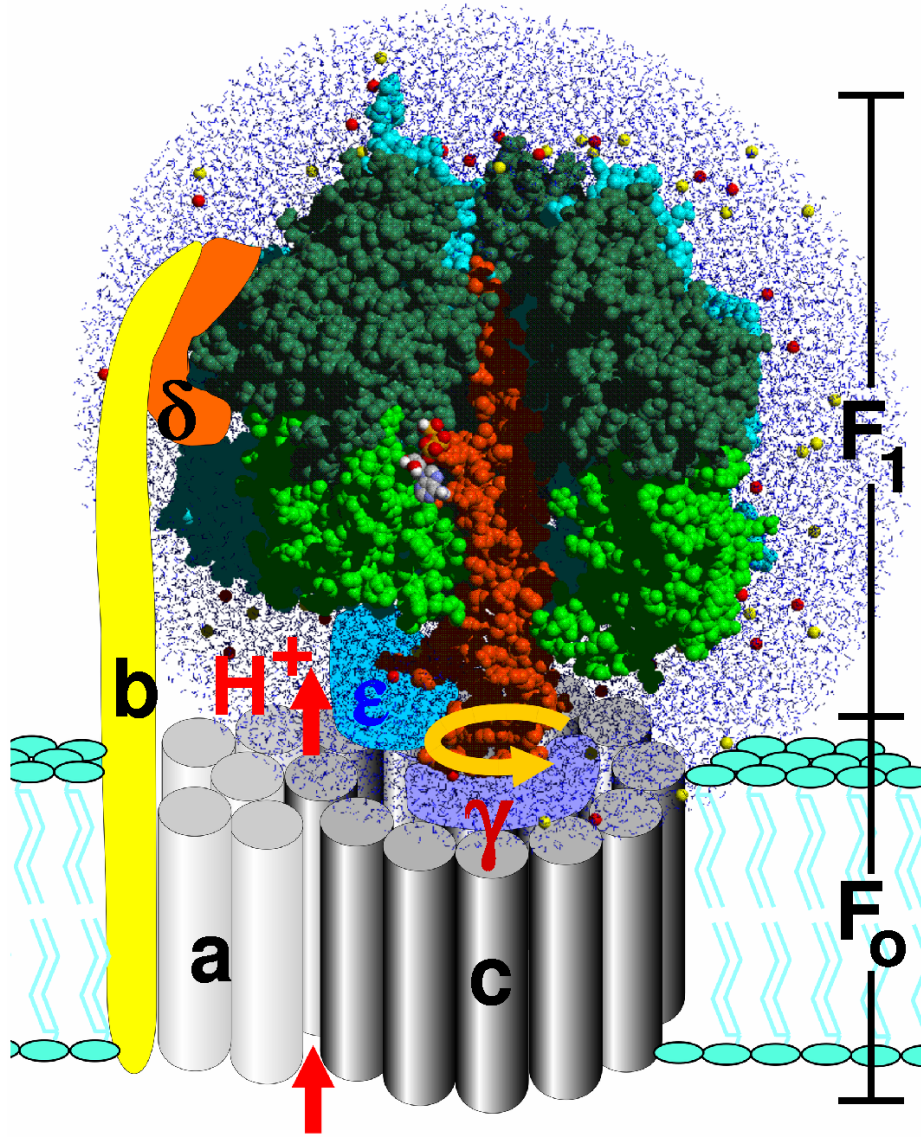
***F₁ ATP
Synthase:***

***Driving
a molecular
nano-machine***

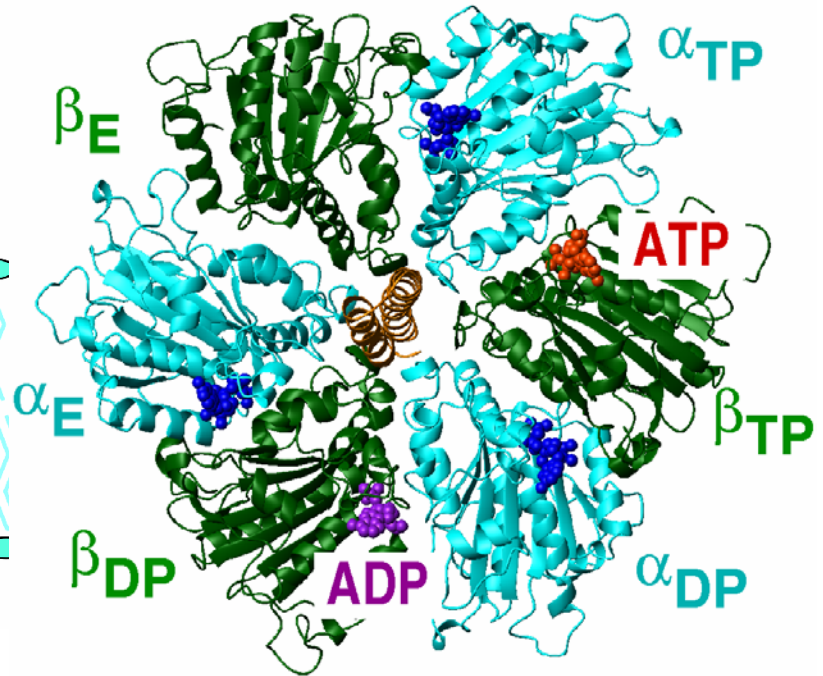
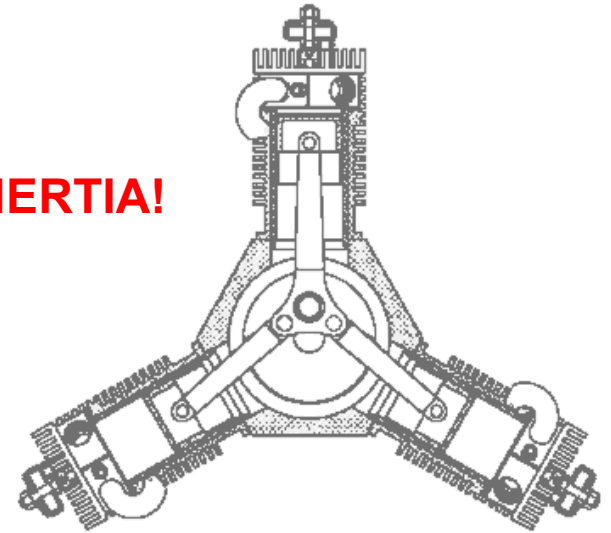


Rainer Böckmann

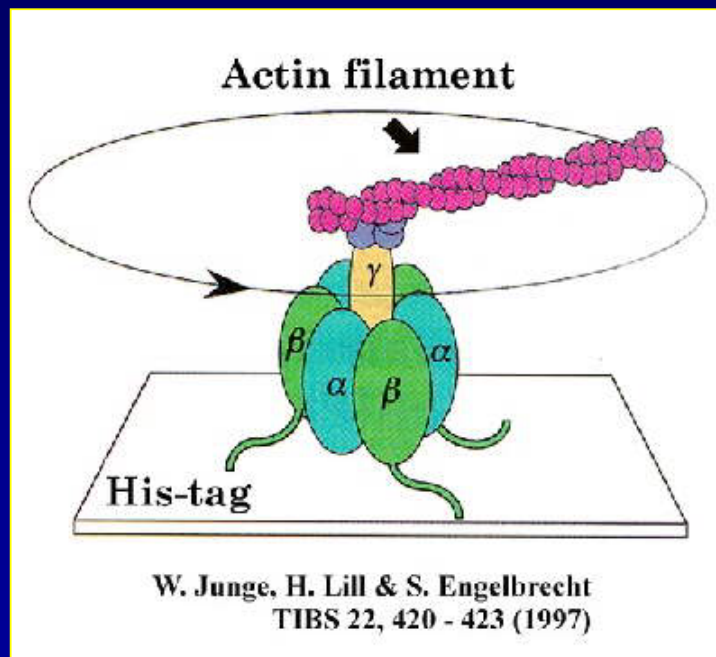
F_1 -ATP(synth)ase



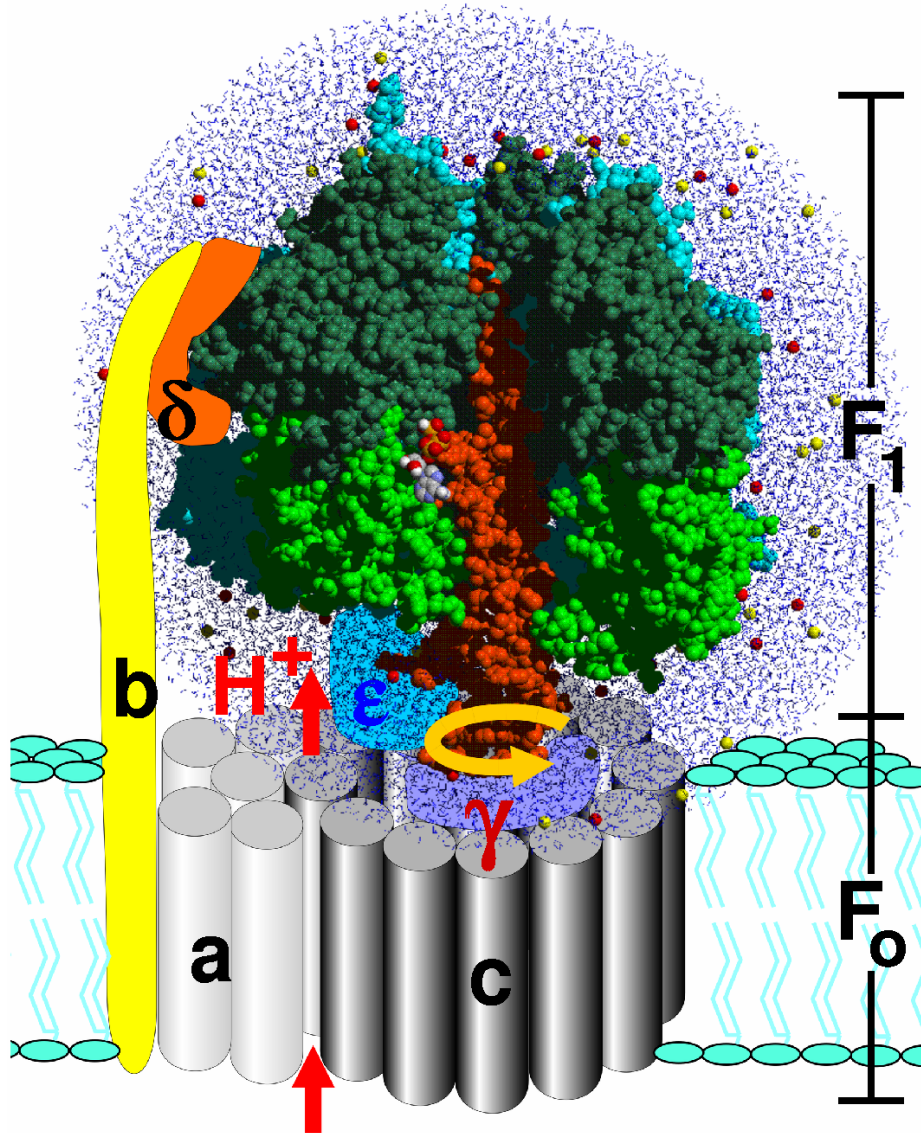
NO INERTIA!



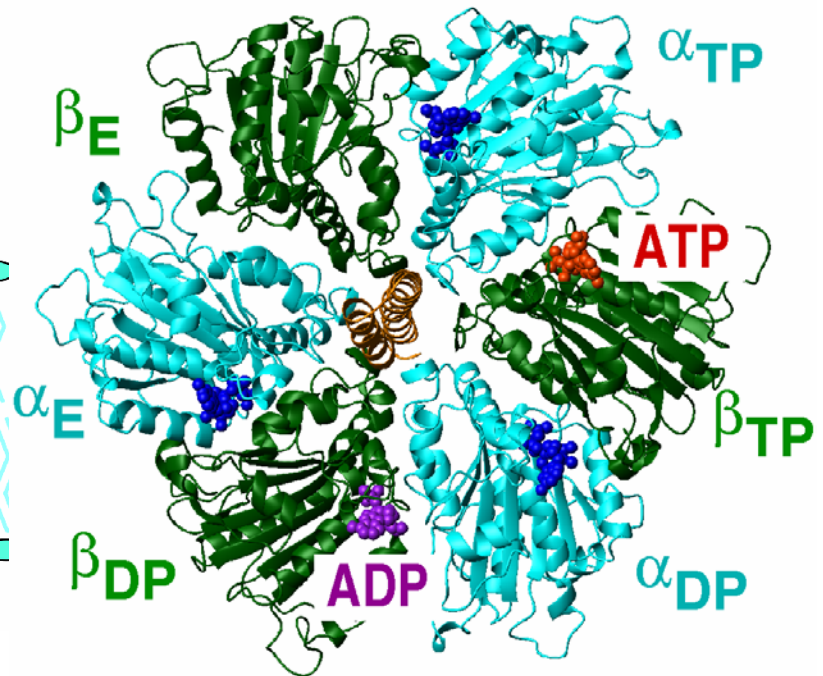
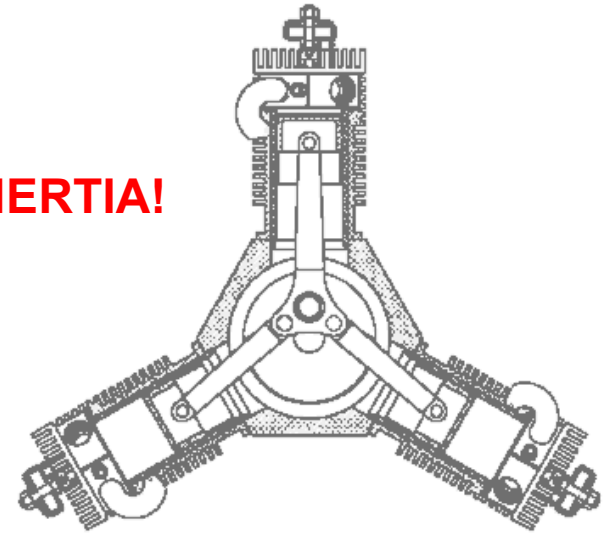
ATP hydrolysis drives rotation of γ subunit and attached actin filament



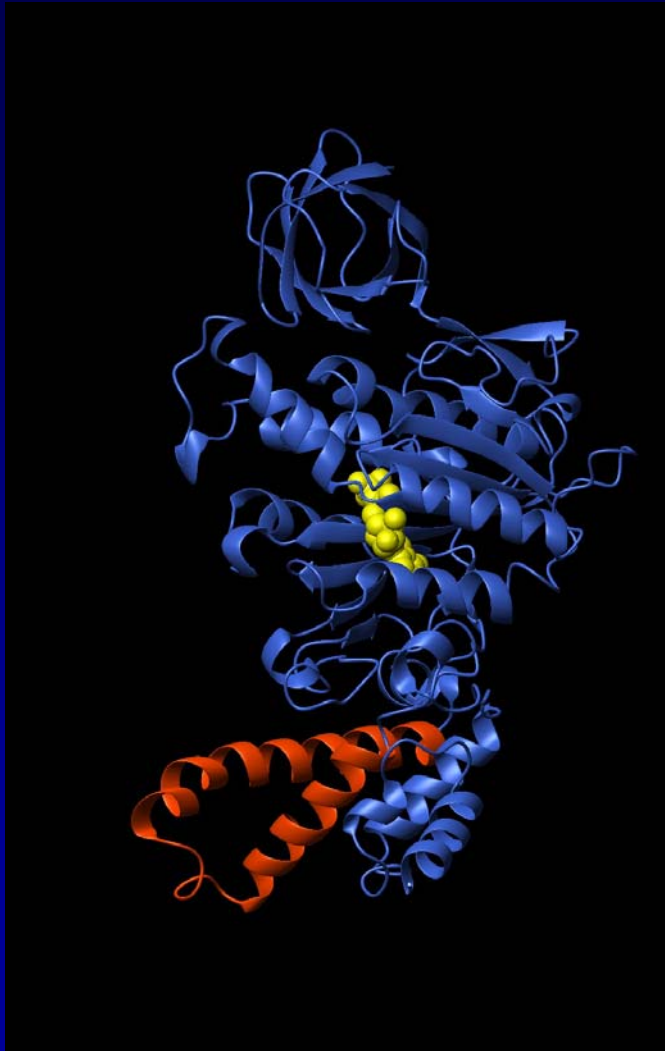
F_1 -ATP(synth)ase



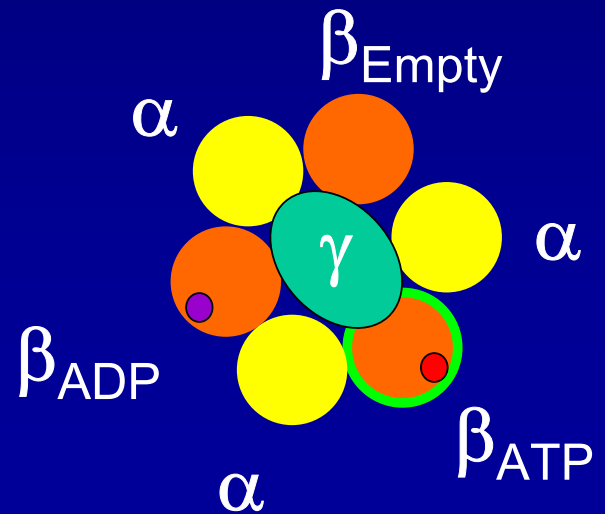
NO INERTIA!



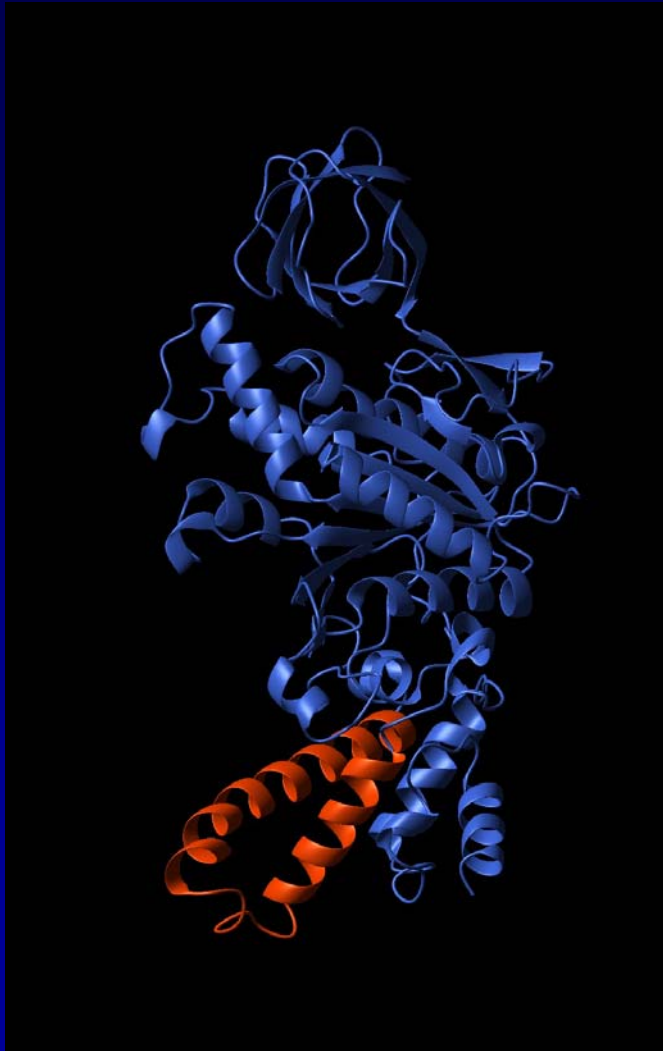
Conformational changes in the β -subunits



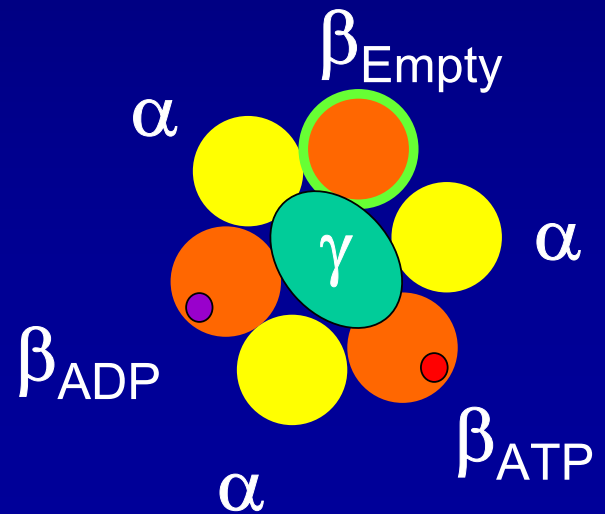
β_{ATP}



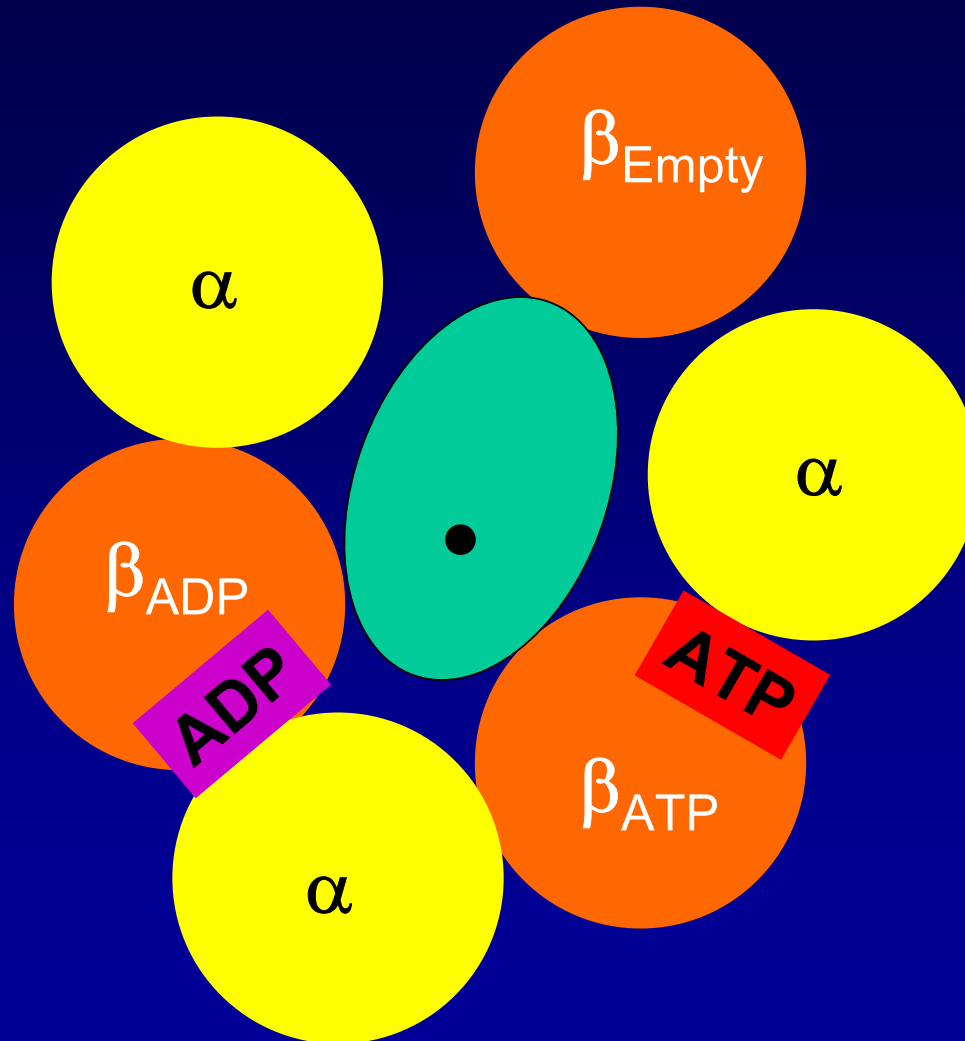
Conformational changes in the β -subunits



β_{Empty}

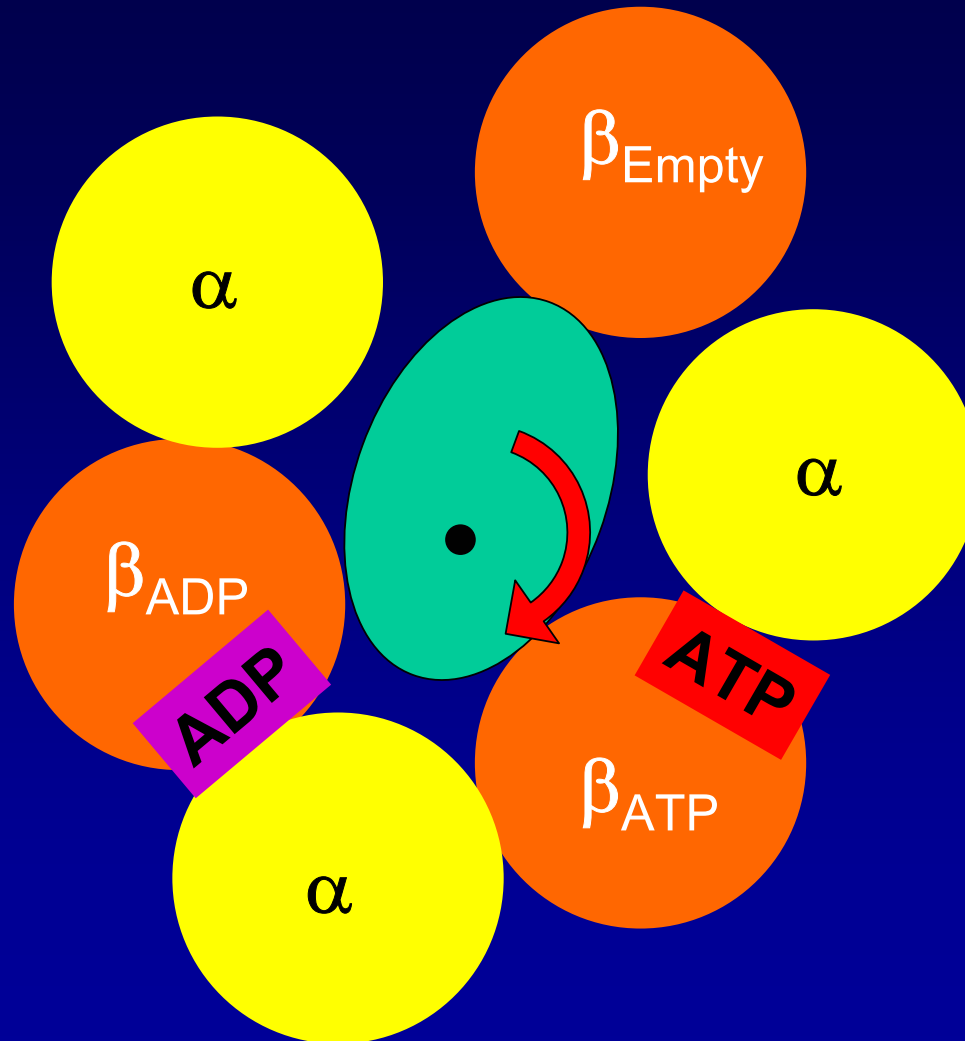


Binding change mechanism (ATP synthesis)

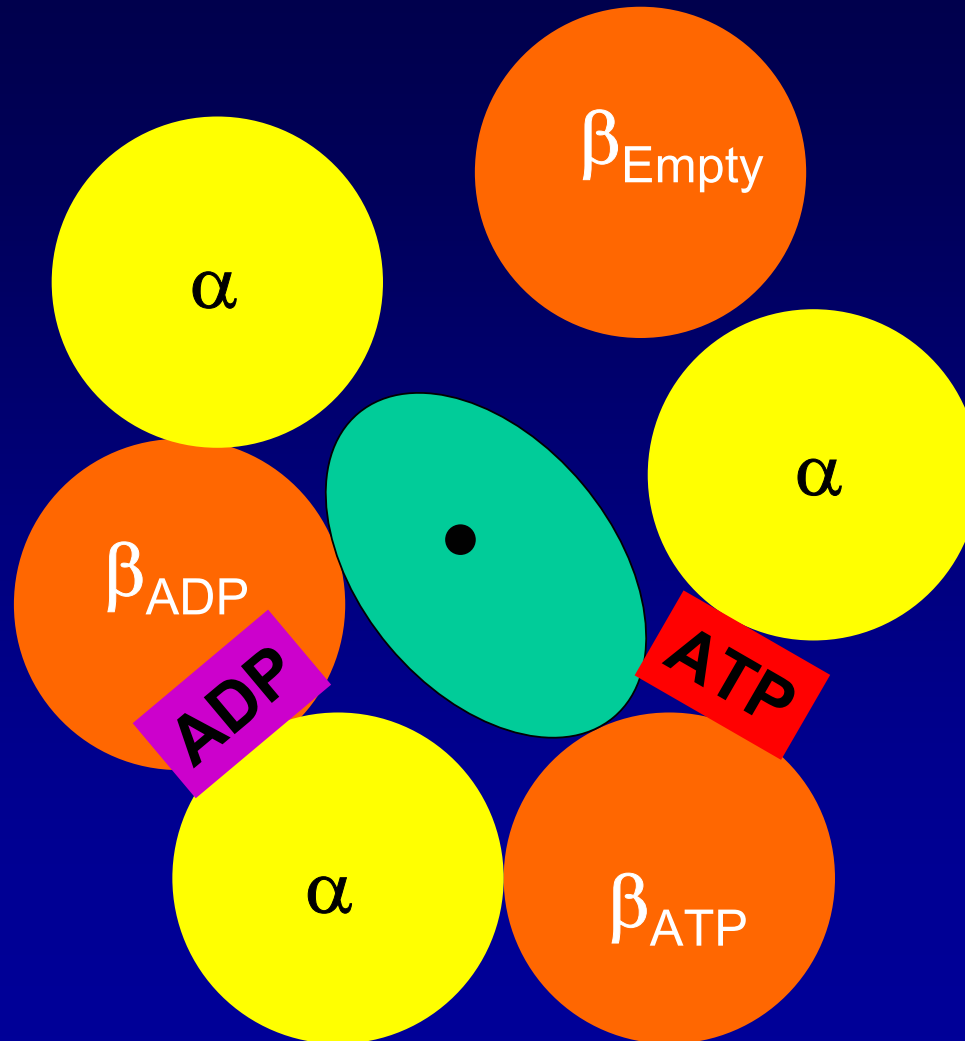


e.g., J.E. Walker, P.D. Boyer, A.E. Senior, G. Oster & H.Y. Wang

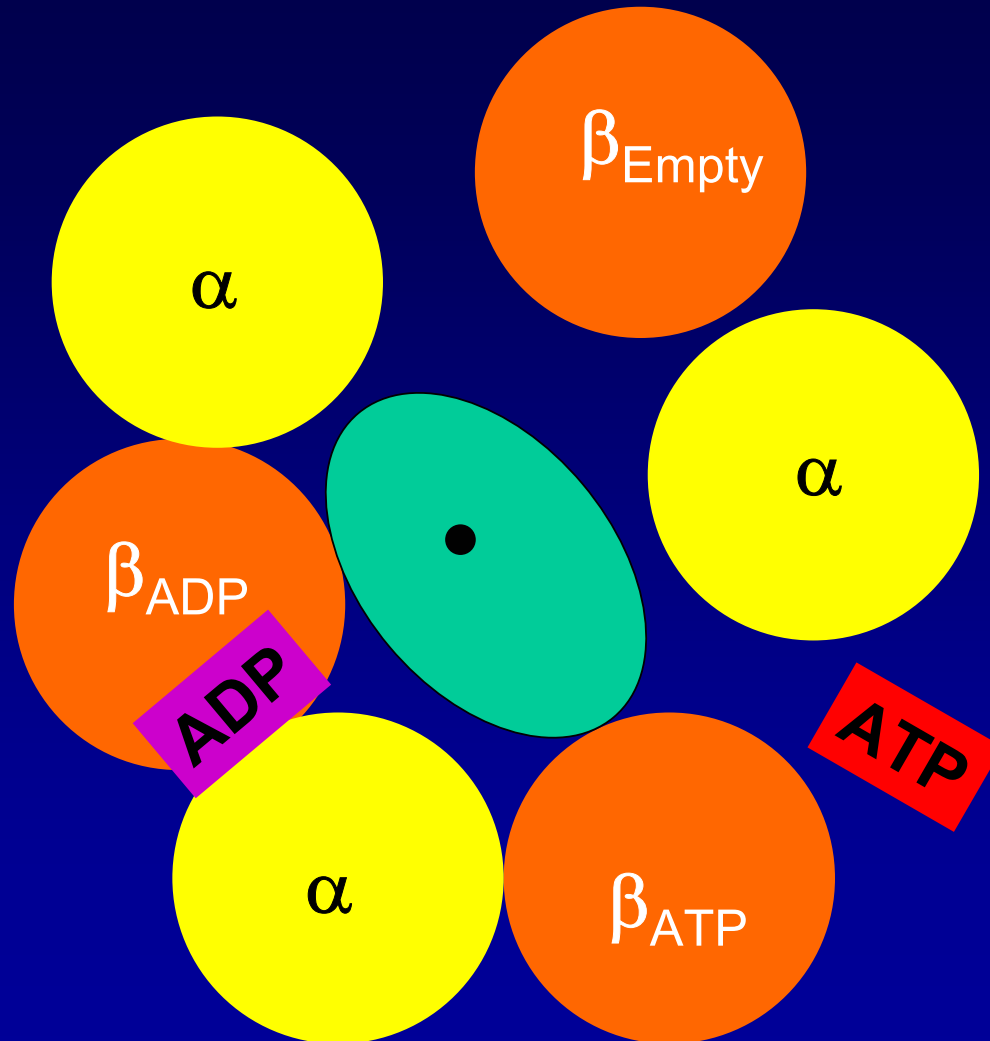
Binding change mechanism (ATP synthesis)



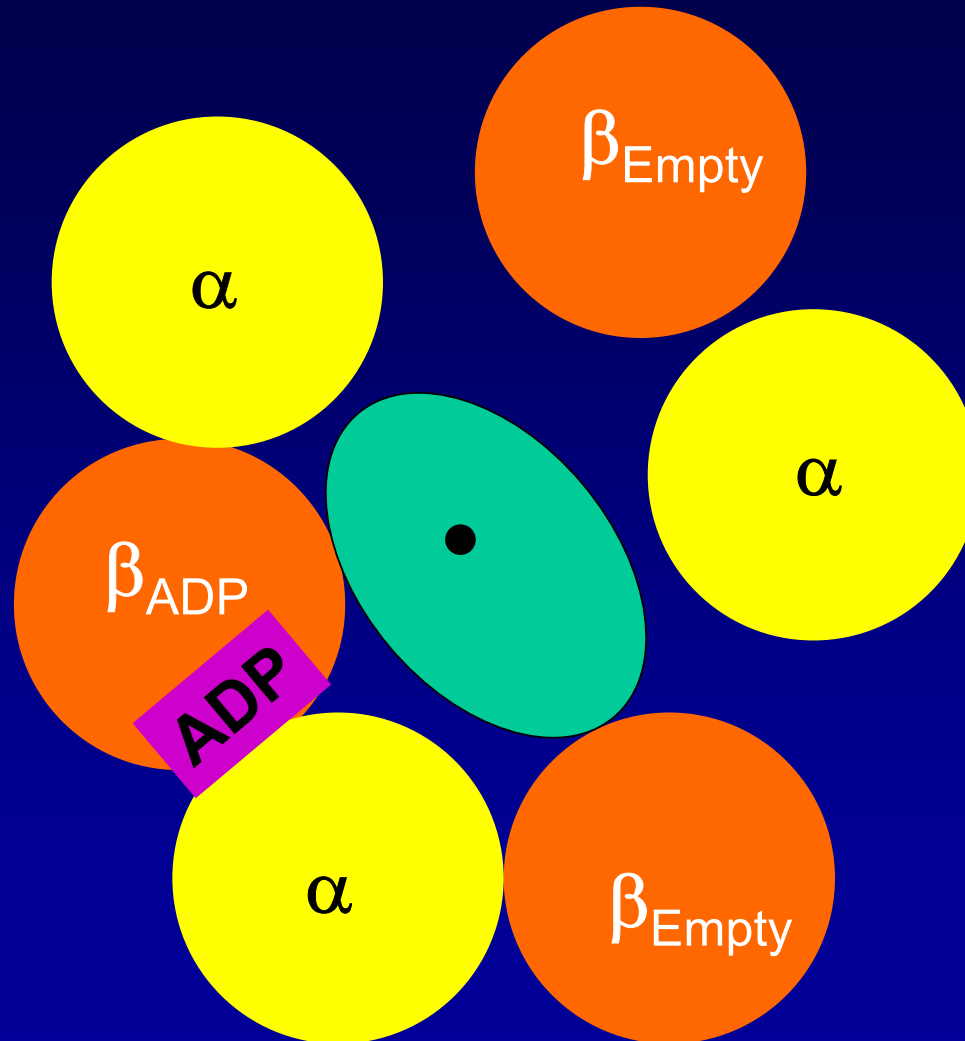
Binding change mechanism (ATP synthesis)



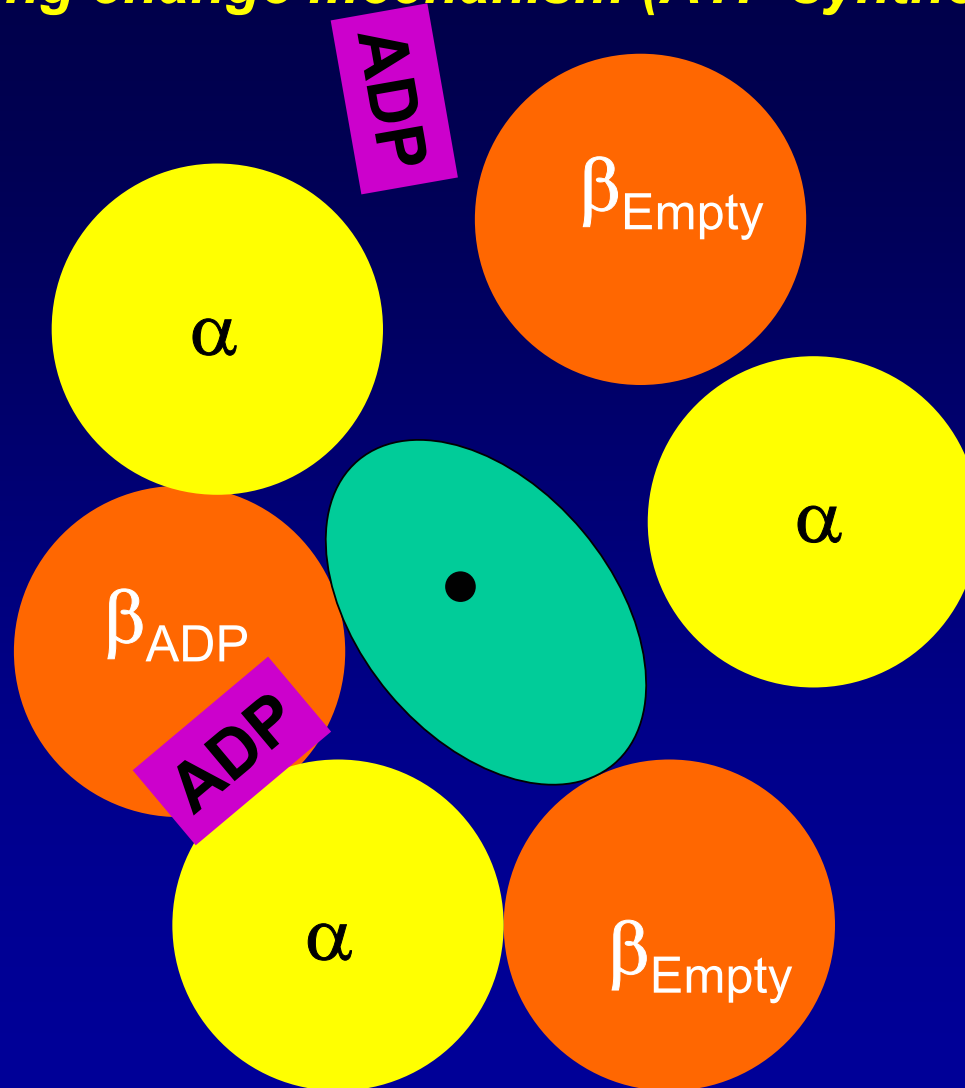
Binding change mechanism (ATP synthesis)



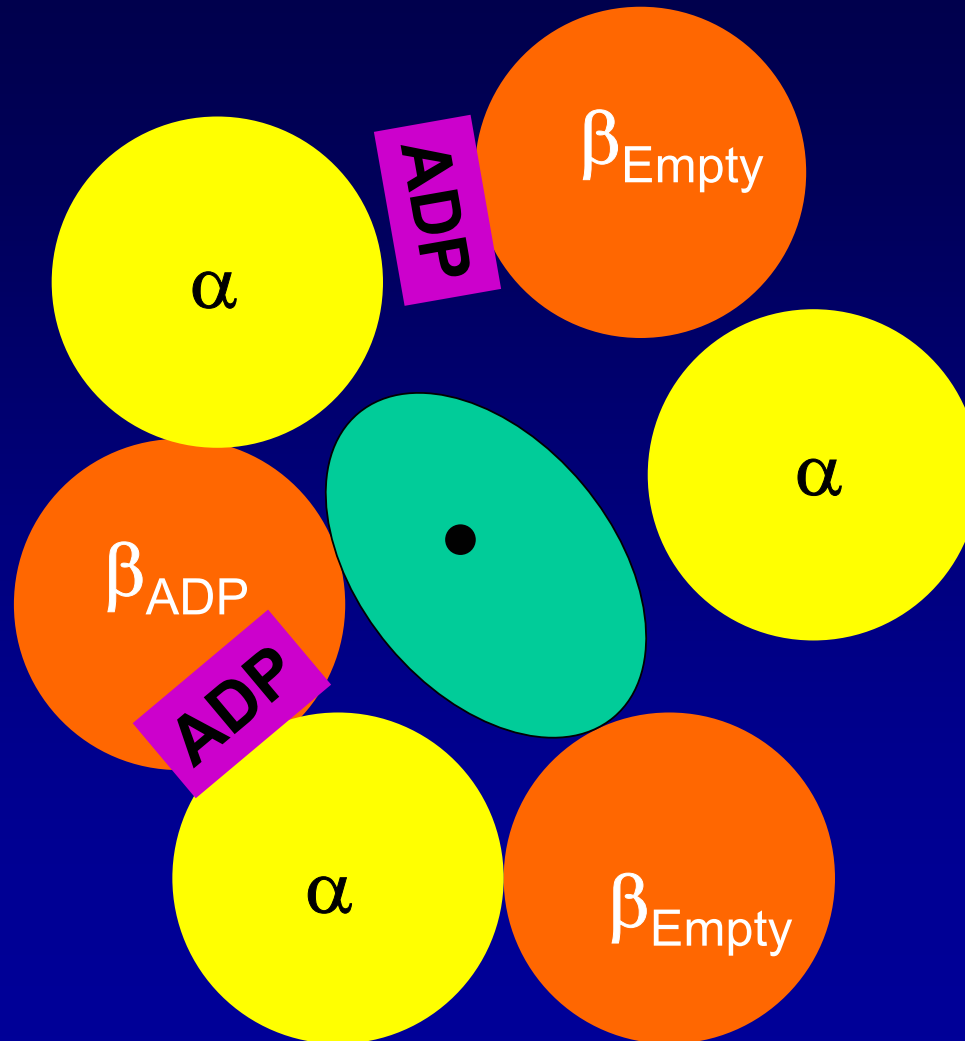
Binding change mechanism (ATP synthesis)



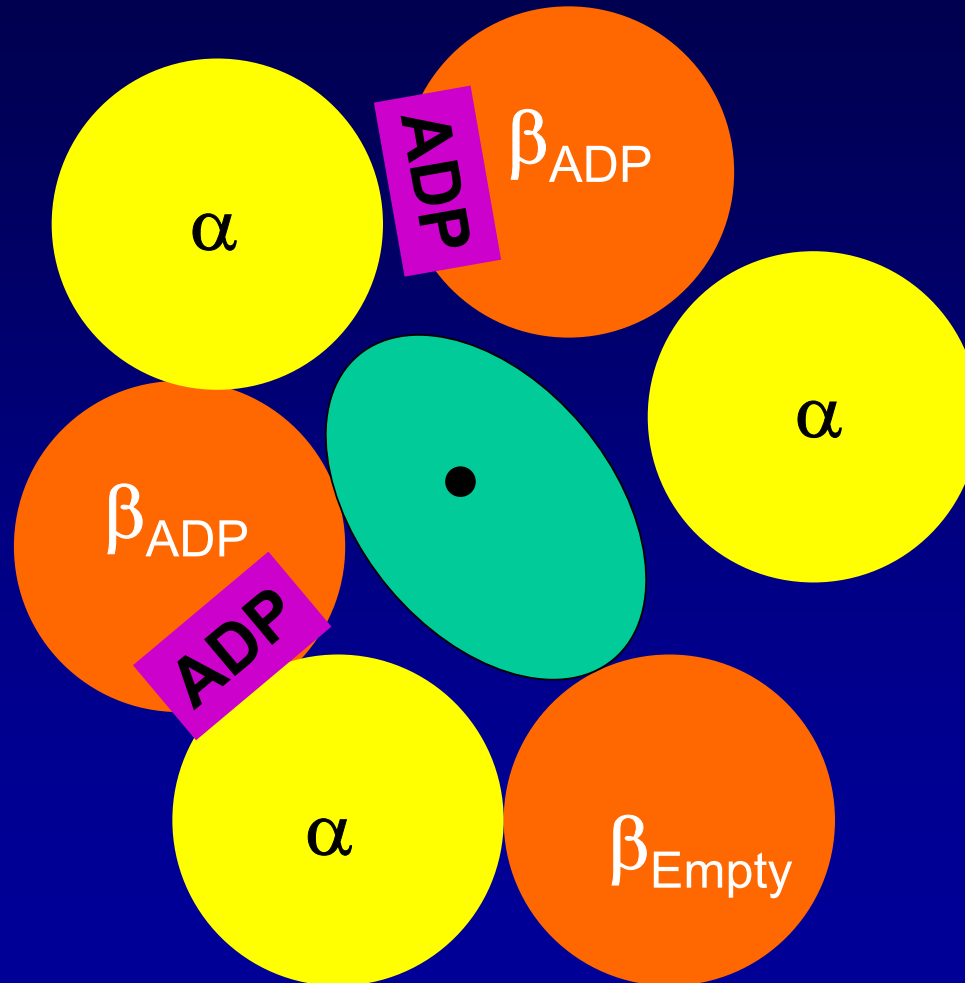
Binding change mechanism (ATP synthesis)



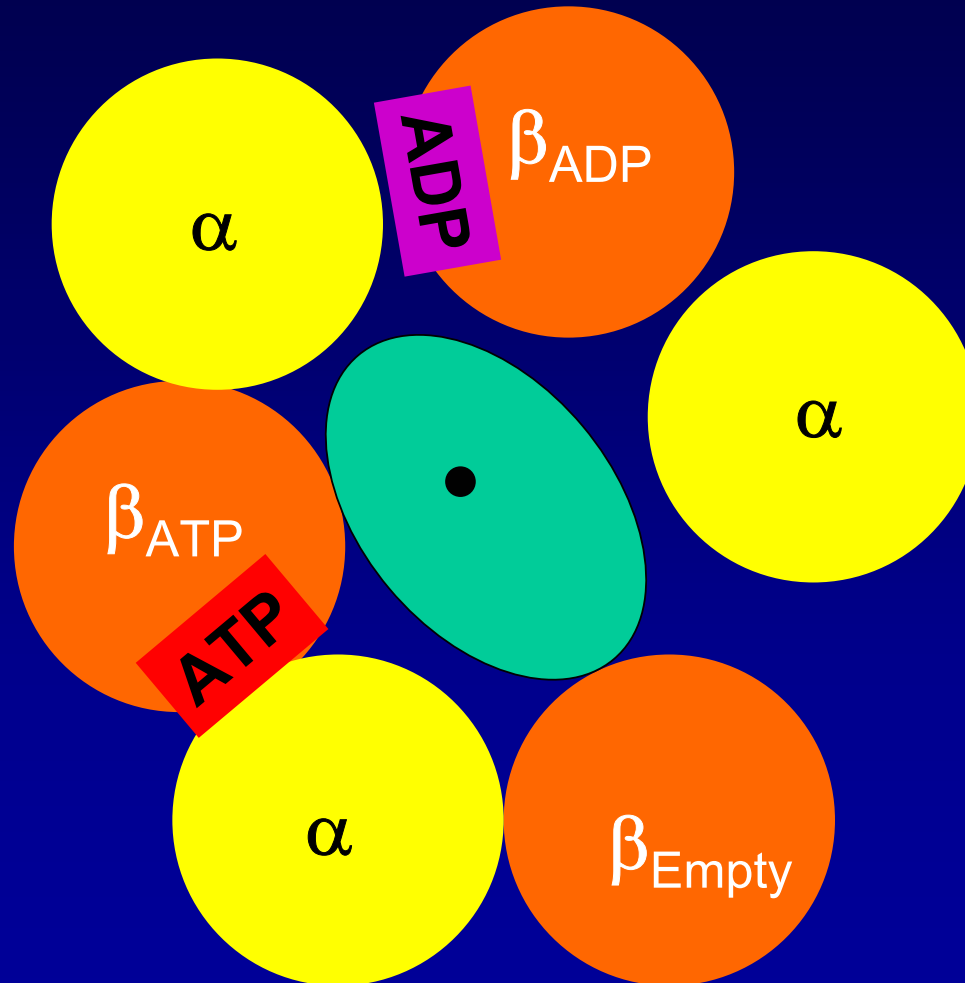
Binding change mechanism (ATP synthesis)



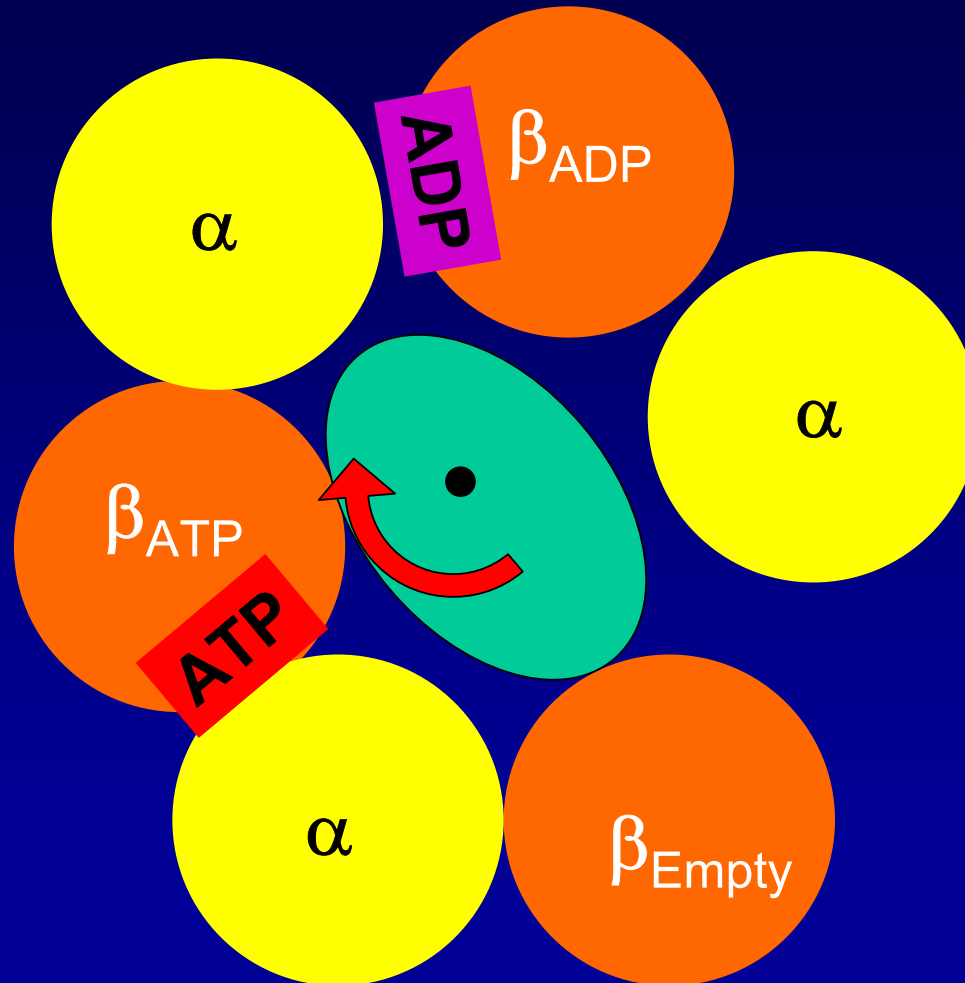
Binding change mechanism (ATP synthesis)



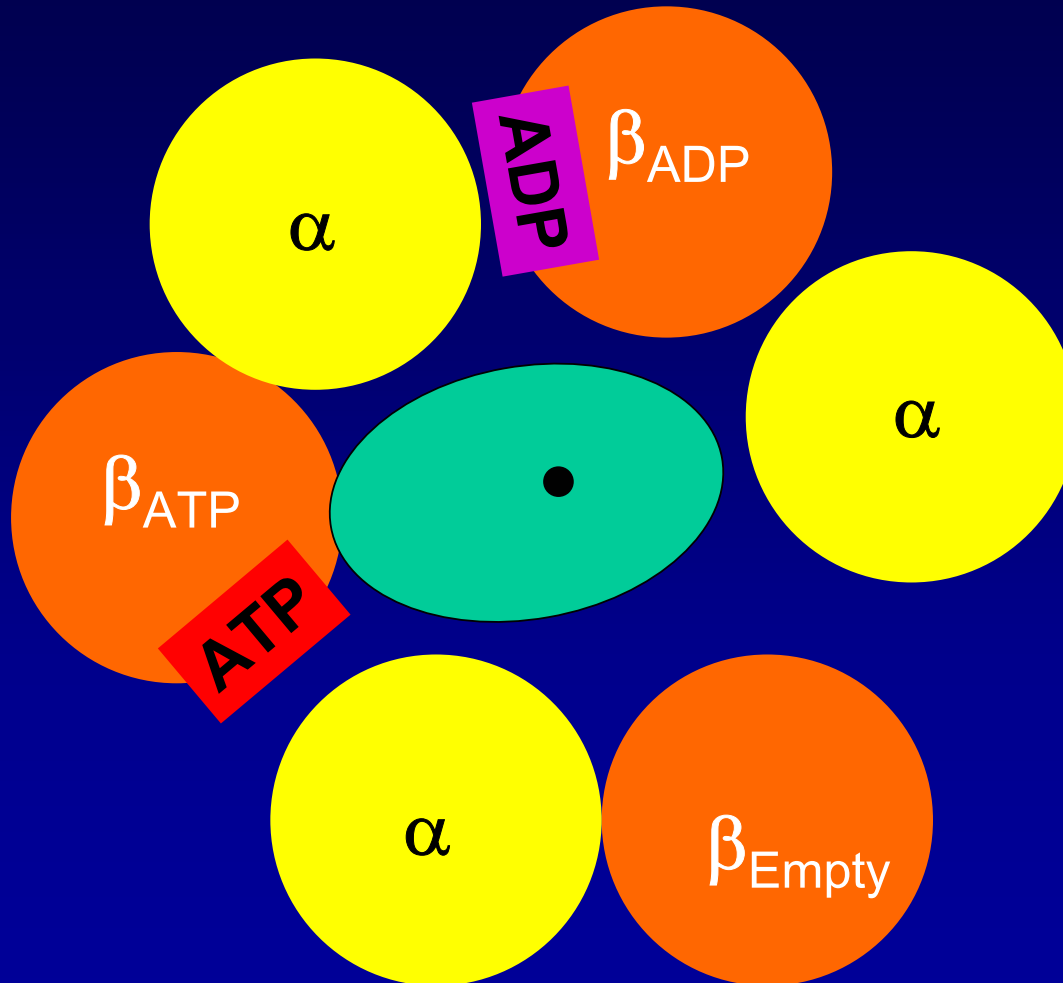
Binding change mechanism (ATP synthesis)



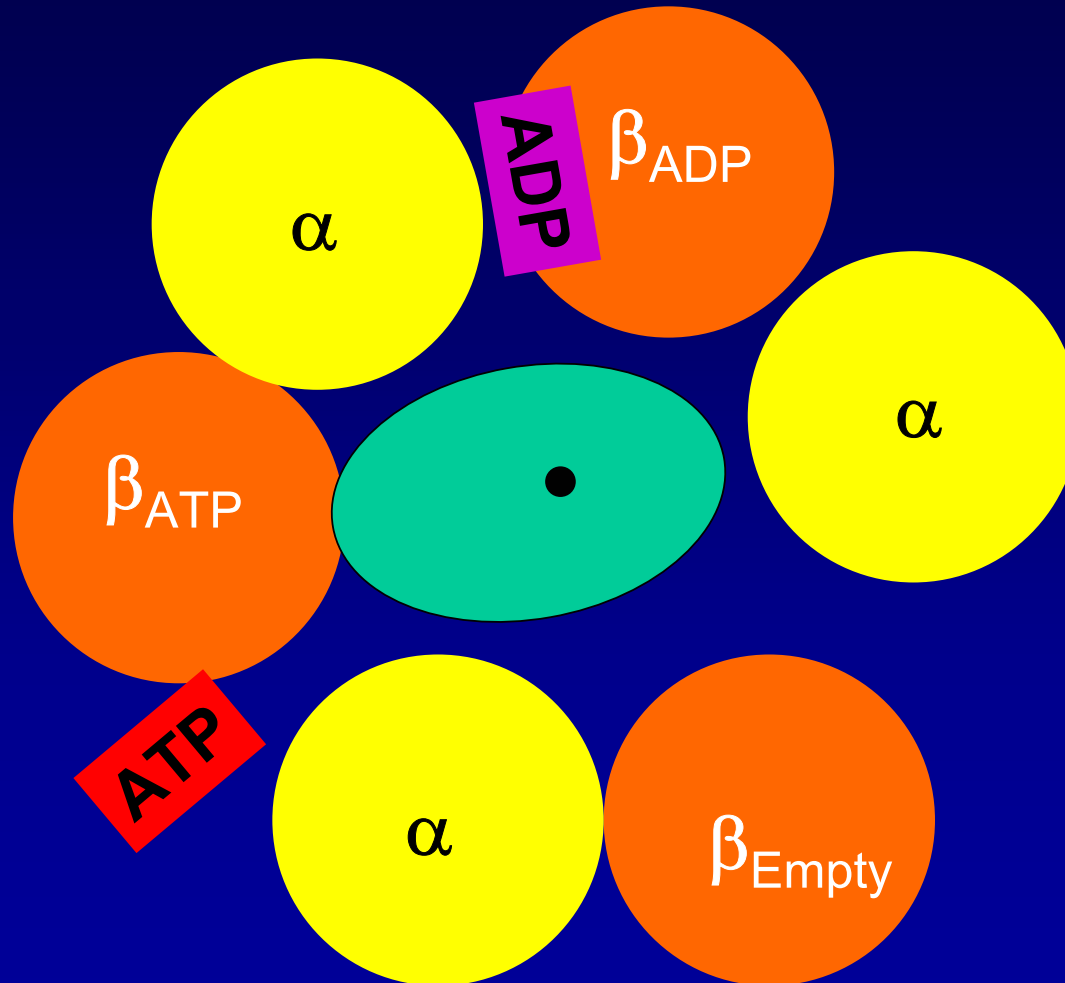
Binding change mechanism (ATP synthesis)



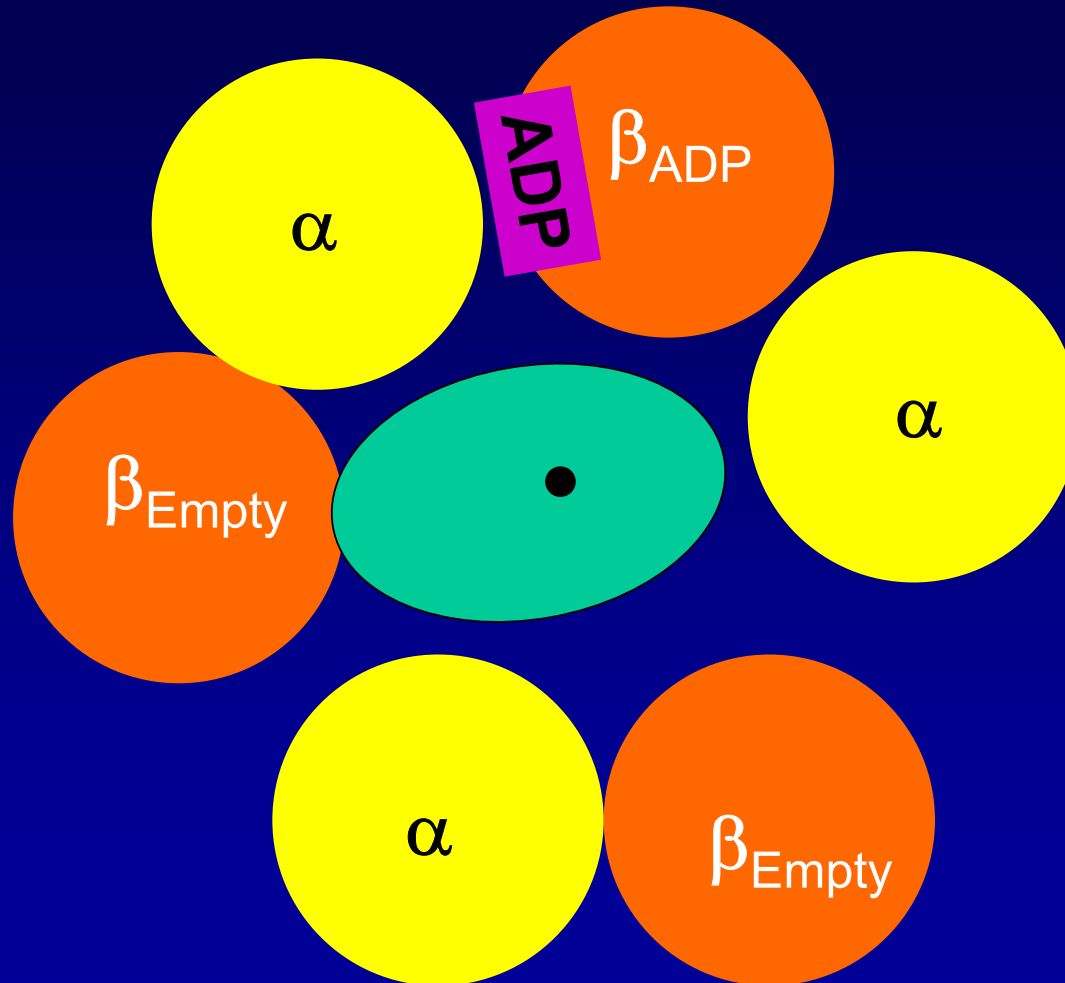
Binding change mechanism (ATP synthesis)



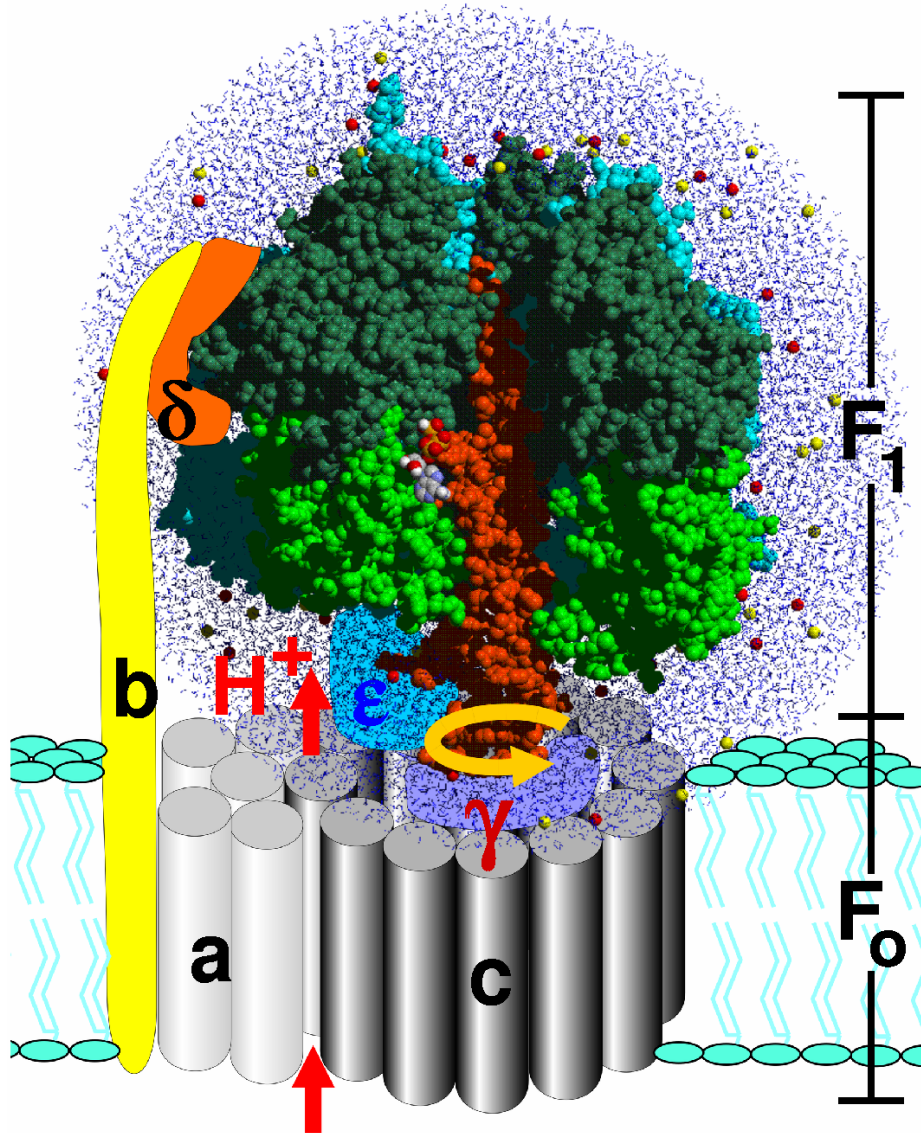
Binding change mechanism (ATP synthesis)



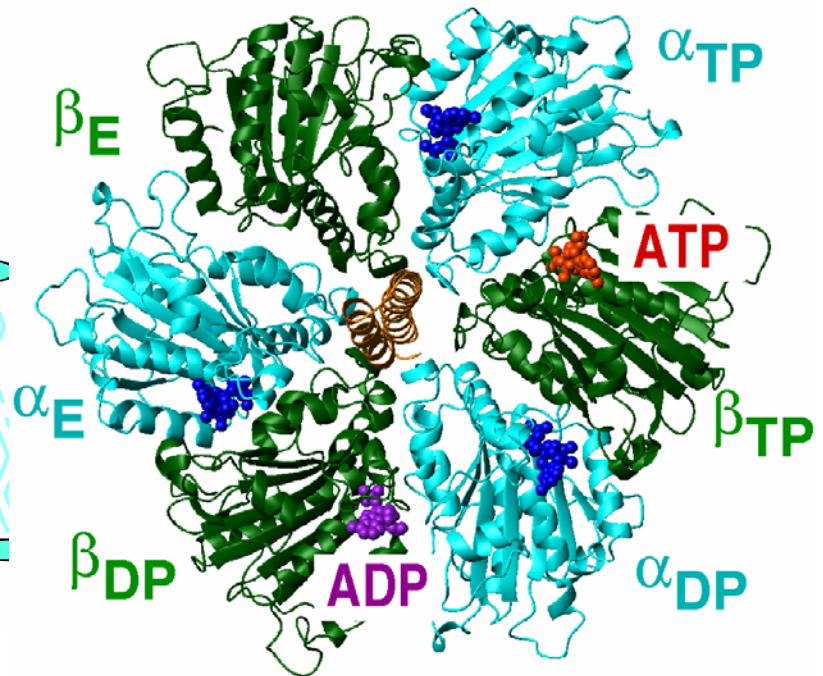
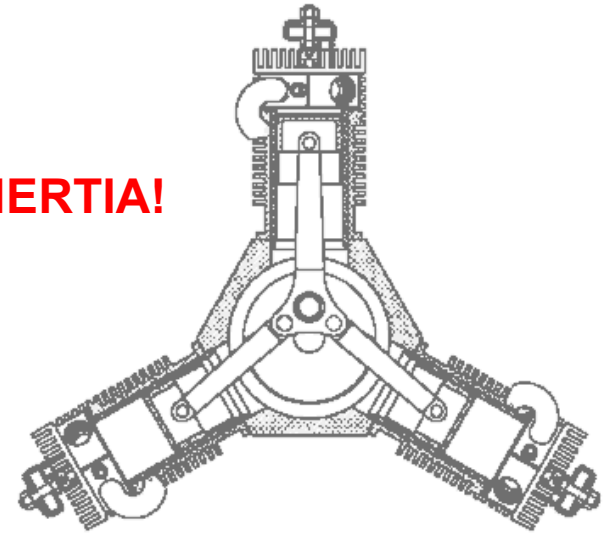
Binding change mechanism (ATP synthesis)



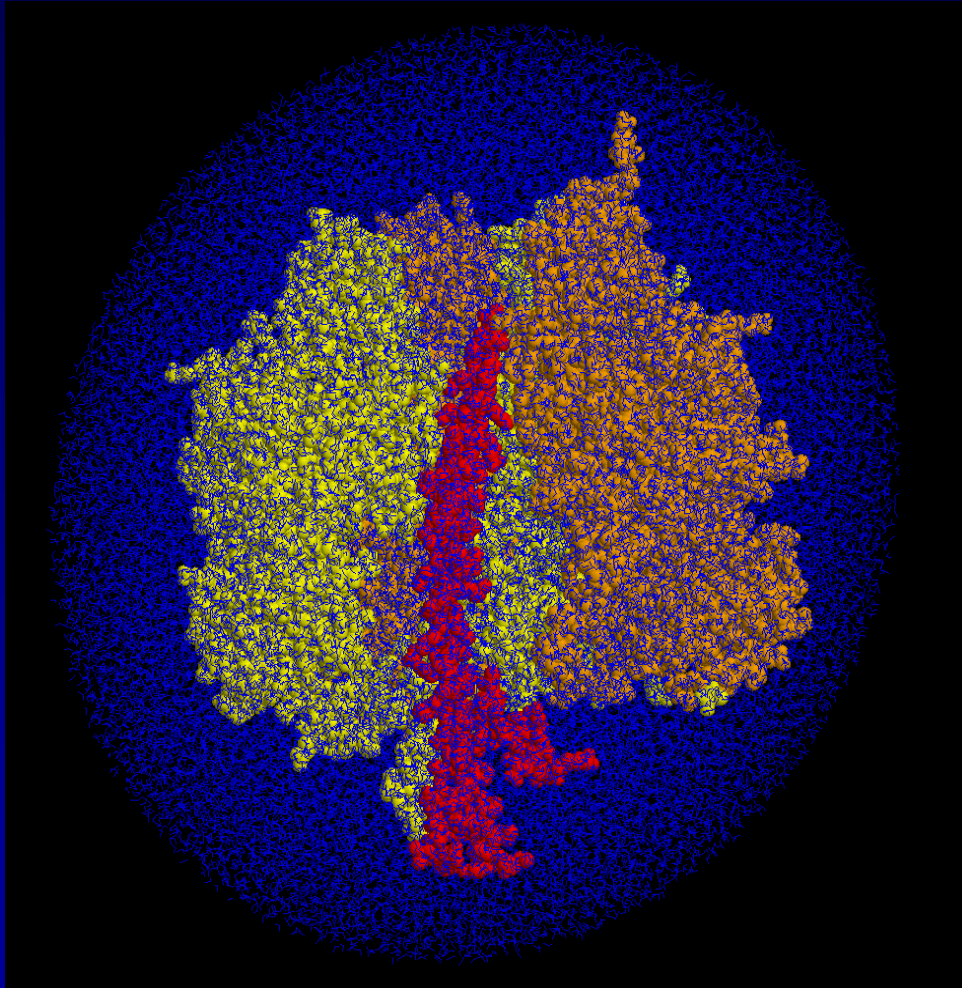
F_1 -ATP(synth)ase



NO INERTIA!



F₁-ATPase: Simulation System



Bovine mitochondrial
F₁-ATPase

51 788 water molecules

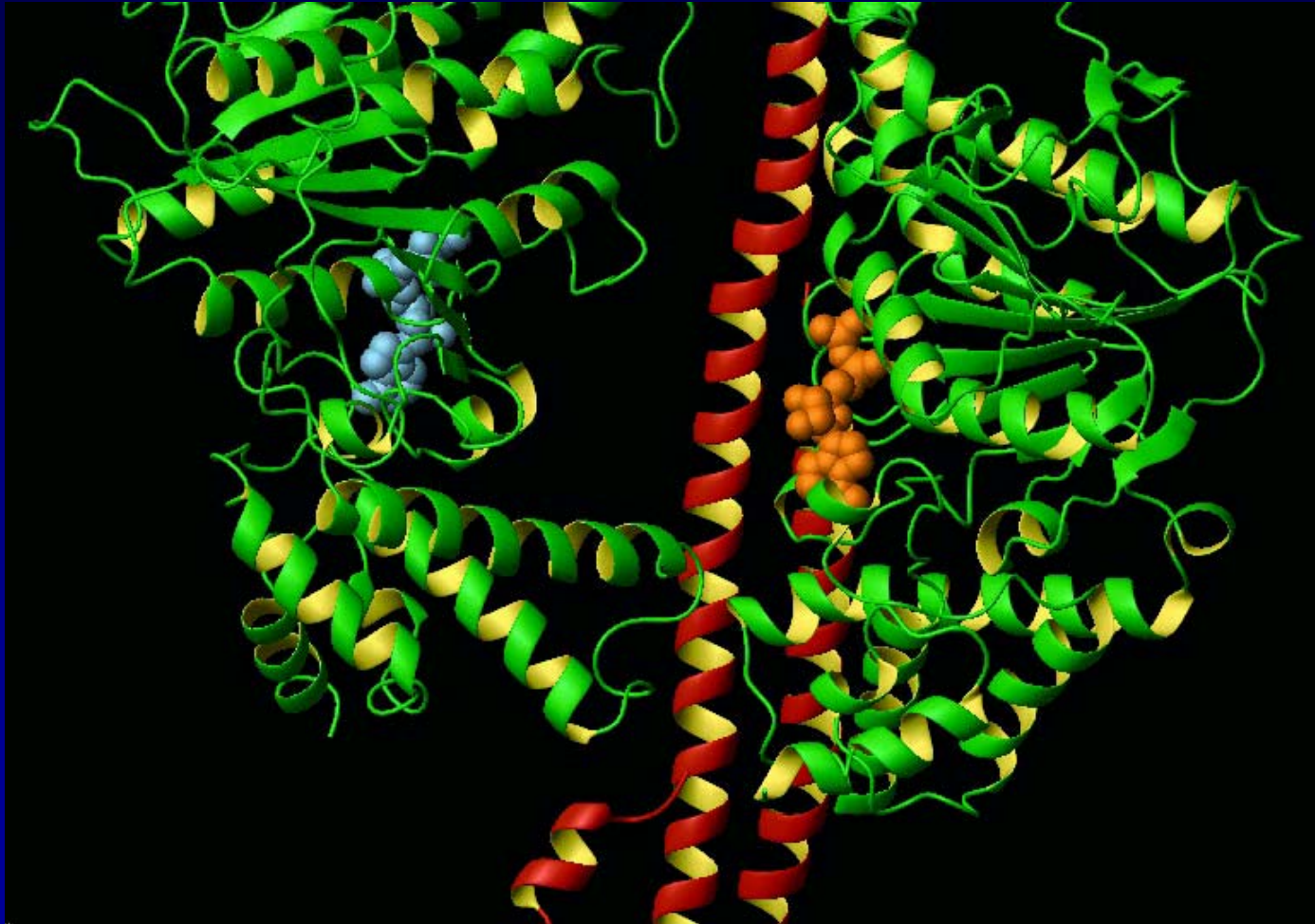
ions in physiological
concentration

183 674 atoms

full electrostatics, S-bound

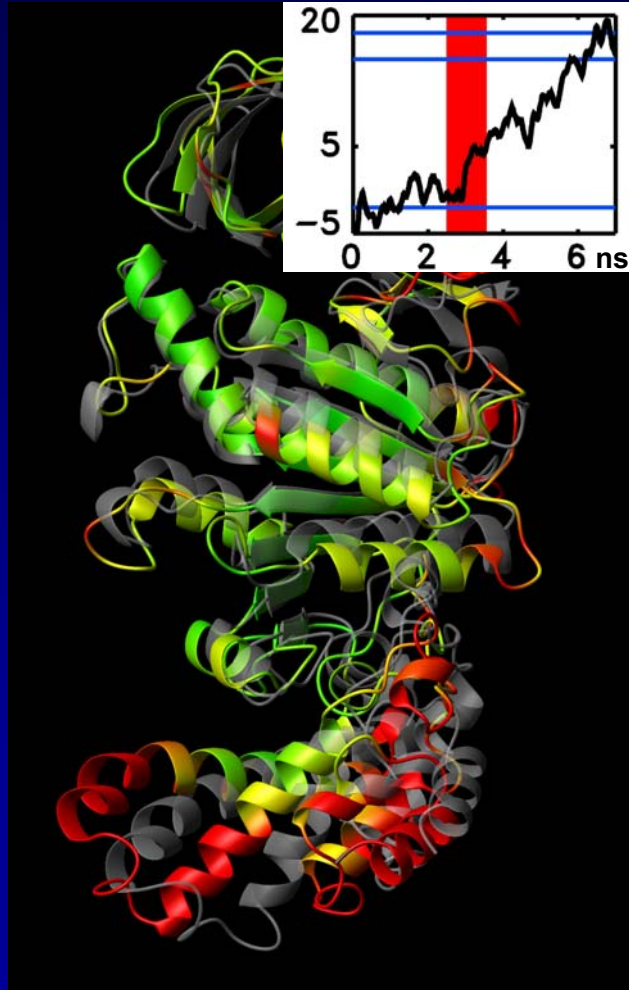
7 ns simulation time

Enforced γ -stalk rotation in F_1 -ATPase



spontaneous closure of β_{empty} subunit $\rightarrow \beta_{\text{ADP}}$

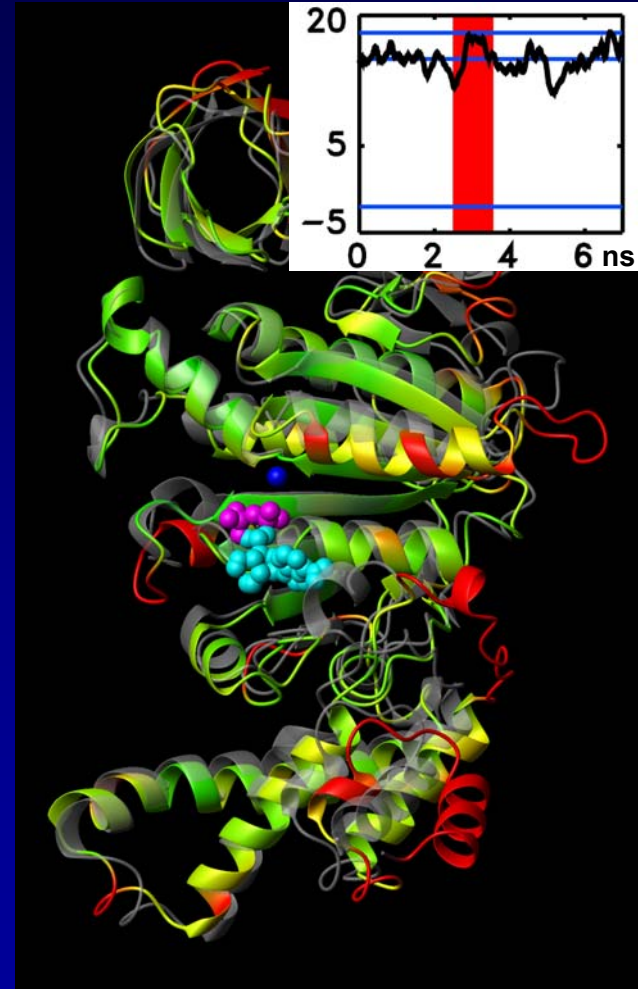
β_{empty} : before after



ATP
ADP

E

β_{ADP} : before after



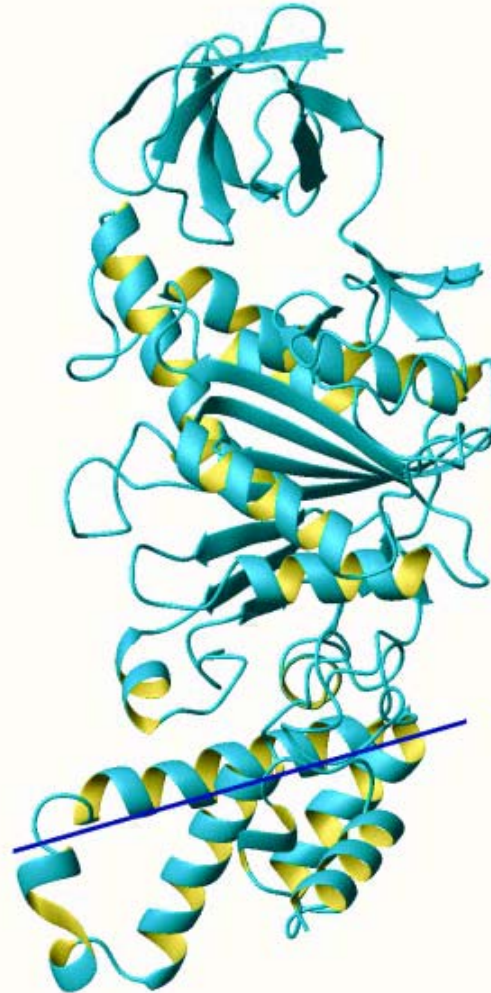
ATP
ADP

E

Enforced γ -stalk rotation in F_1 -ATPase

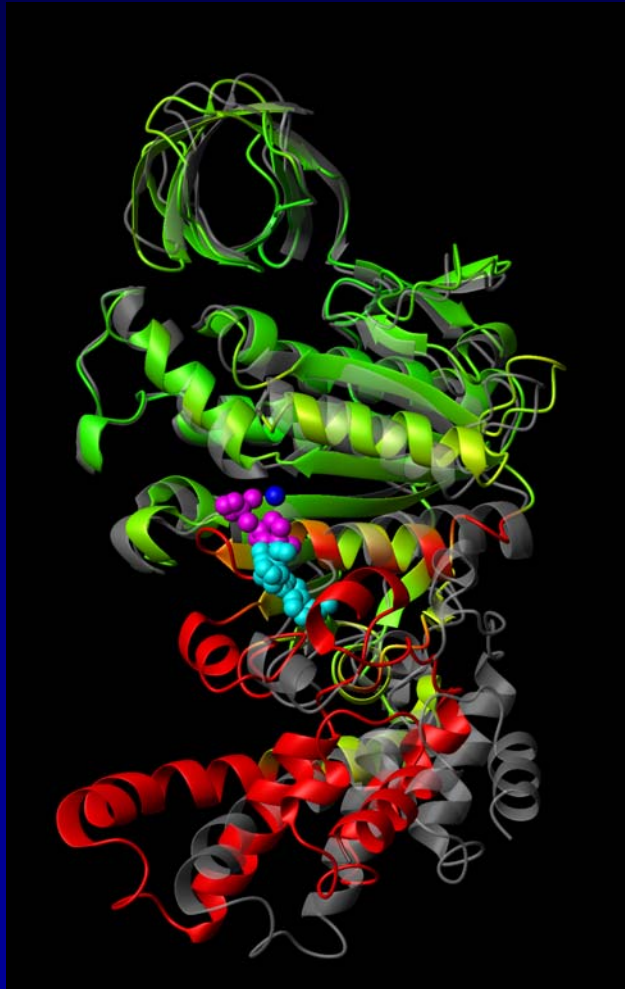
β -Empty subunit:

30° closure motion of
C-terminal domain

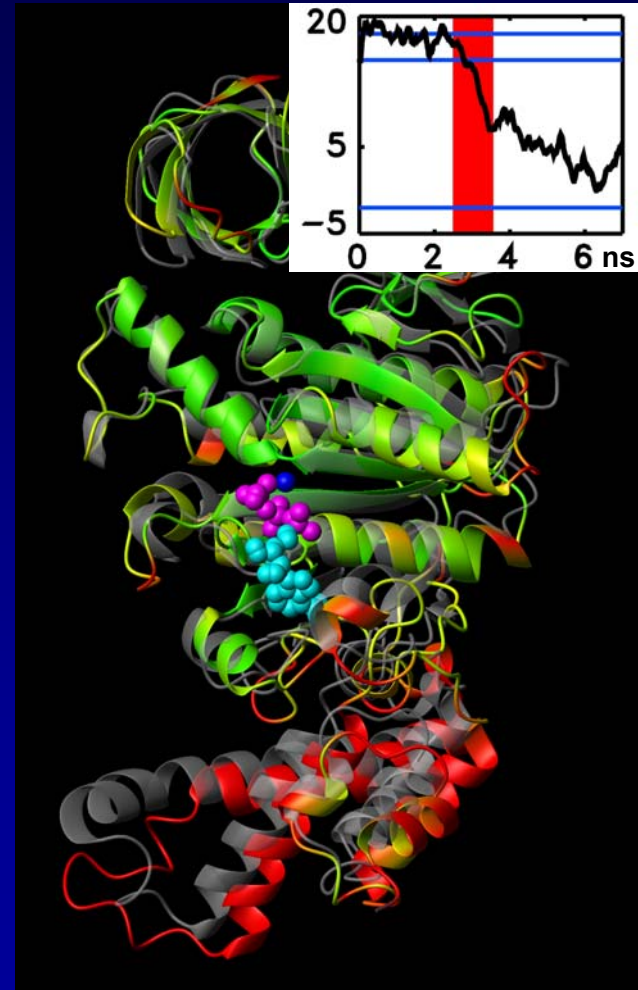


γ -induced opening of β_{ATP} subunit $\rightarrow \beta_{empty}$

X-ray: β_{ATP} β_{empty}



β_{ATP} : before after



ATP
ADP

E

Conformational changes in the binding pocket

sequential retraction
of charged arginines

→ interaction energy
is raised

→ ATP affinity
decreases

