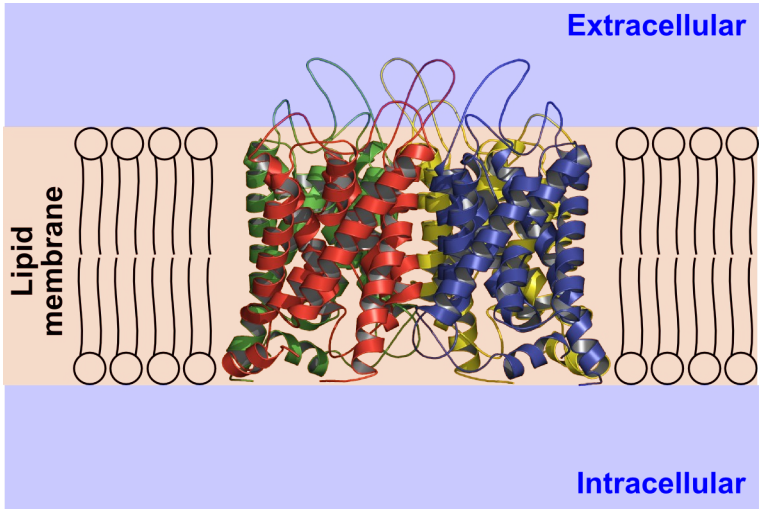
Membrane proteins



Carry out vital processes:

- Transport of substances (e.g. ions, water, solutes)
- Transmission of information (signaling)
- …

Potential drug targets
- 35% of proteins are MP

What can we learn from MD simulations?

- Energetics of permeation

- Calculation of permeabilities or conductances

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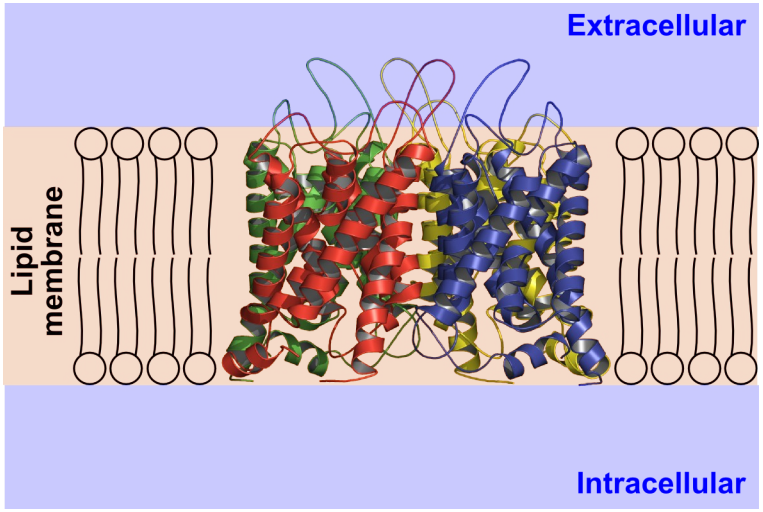
- Role of mechanical stress

-...

Membrane proteins



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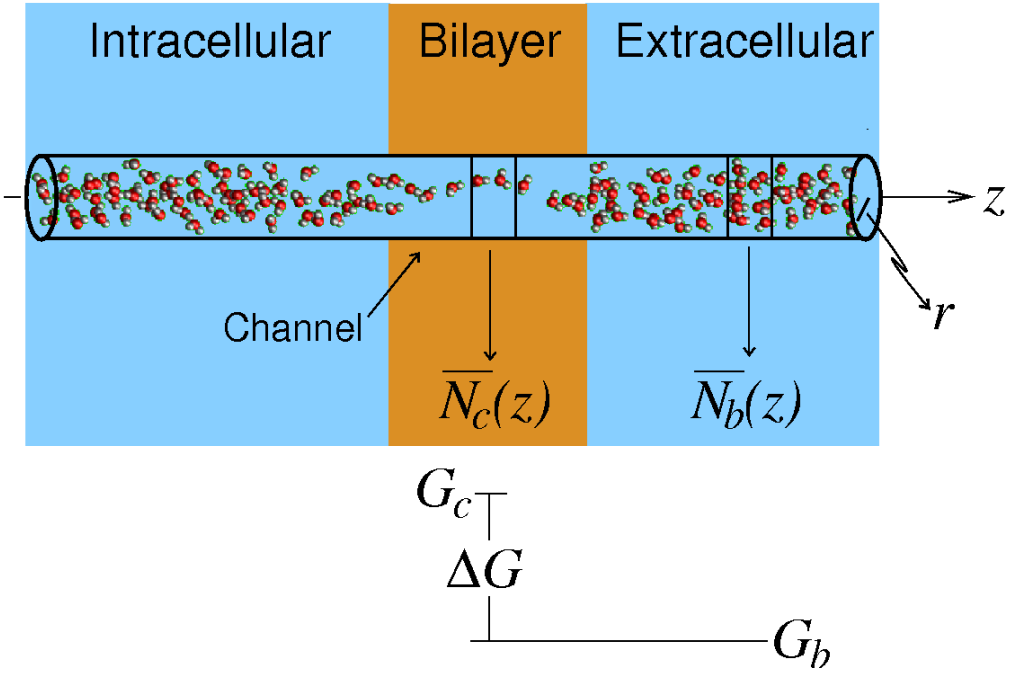
Free energy profiles for water permeation

- Detect relevant interactions:
  permeating water molecules - protein
- Energetic barriers and binding sites inside the channel
- More favourable permeation pathway:
  channel vs. lipid bilayer

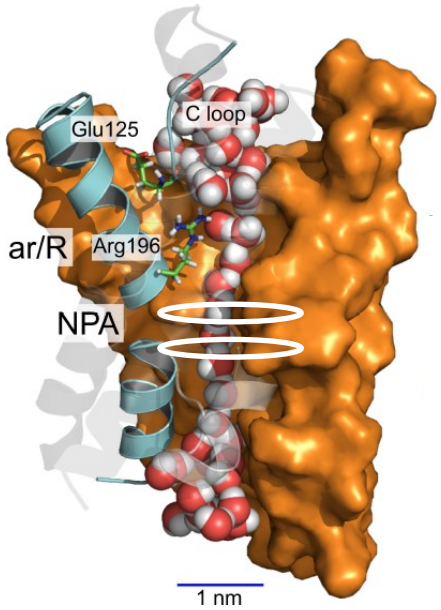
Boltzmann-factor related to the water occupancy,

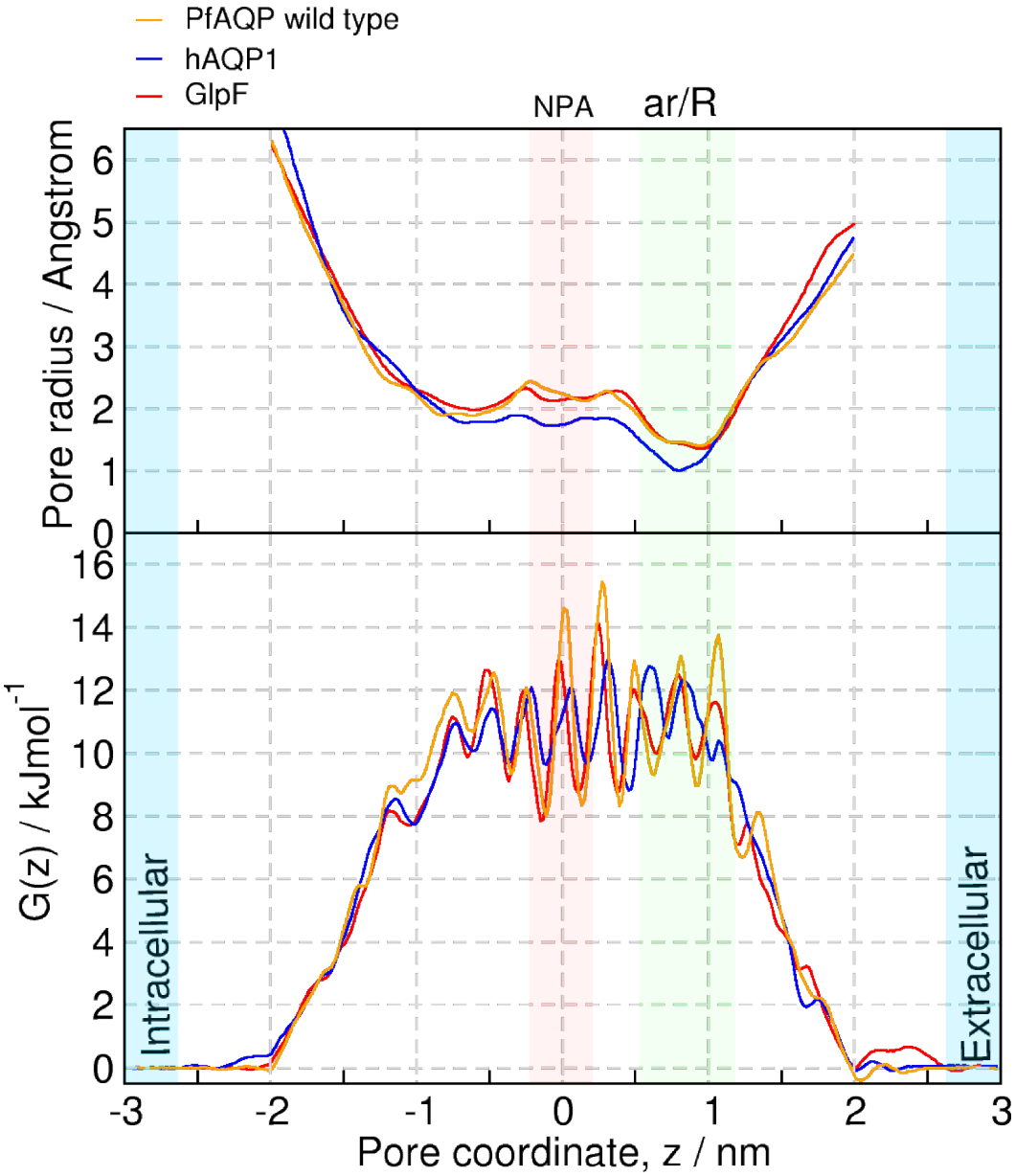
$$\frac{\langle N_c \rangle}{\langle N_b \rangle} = \exp\left(\frac{-\Delta G}{K_B T}\right)$$



Example:
Plasmodium falciparum malaria aquaporin (PfAQP)

Water rate limiting region:
Hydrophobic rings
near NPA motifs

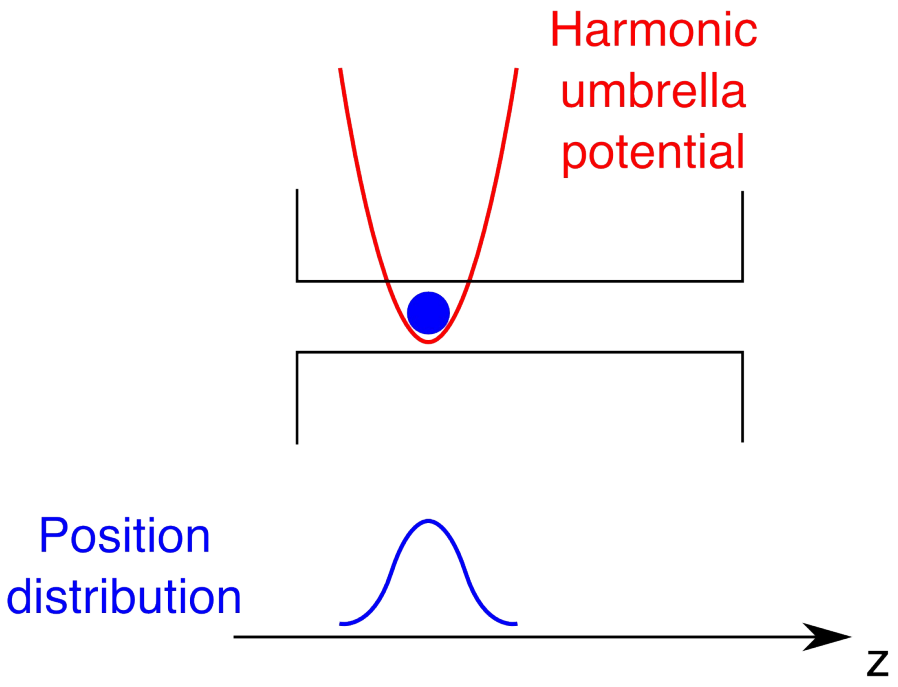




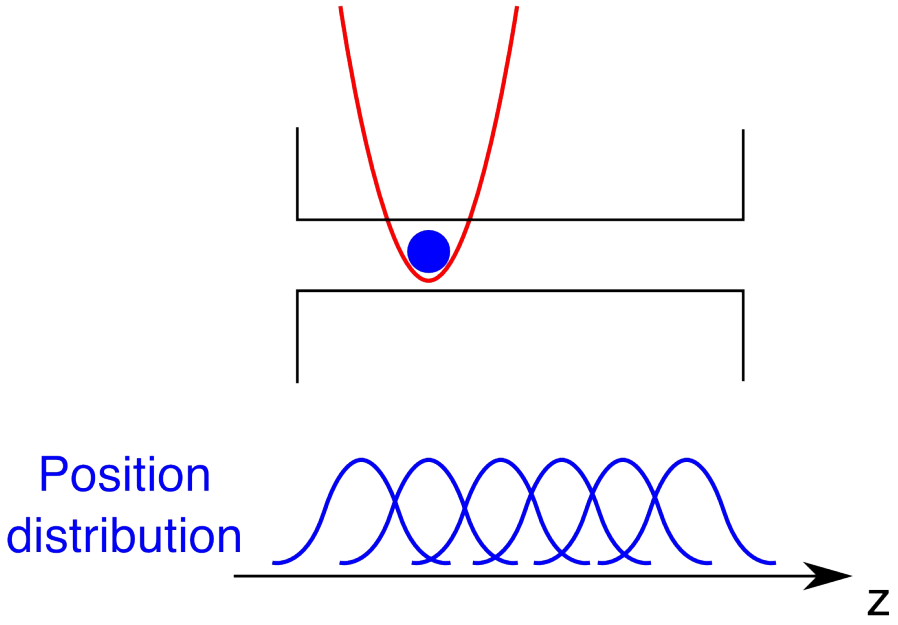
Aponte, Hub, de Groot, ***PCCP*** *12: 10246 (2010)*

Permeation of other solutes or ions: Umbrella sampling

[water] = 55.5 M >> [solutel] ~ 100 mM



Permeation of glycerol and urea: Umbrella sampling



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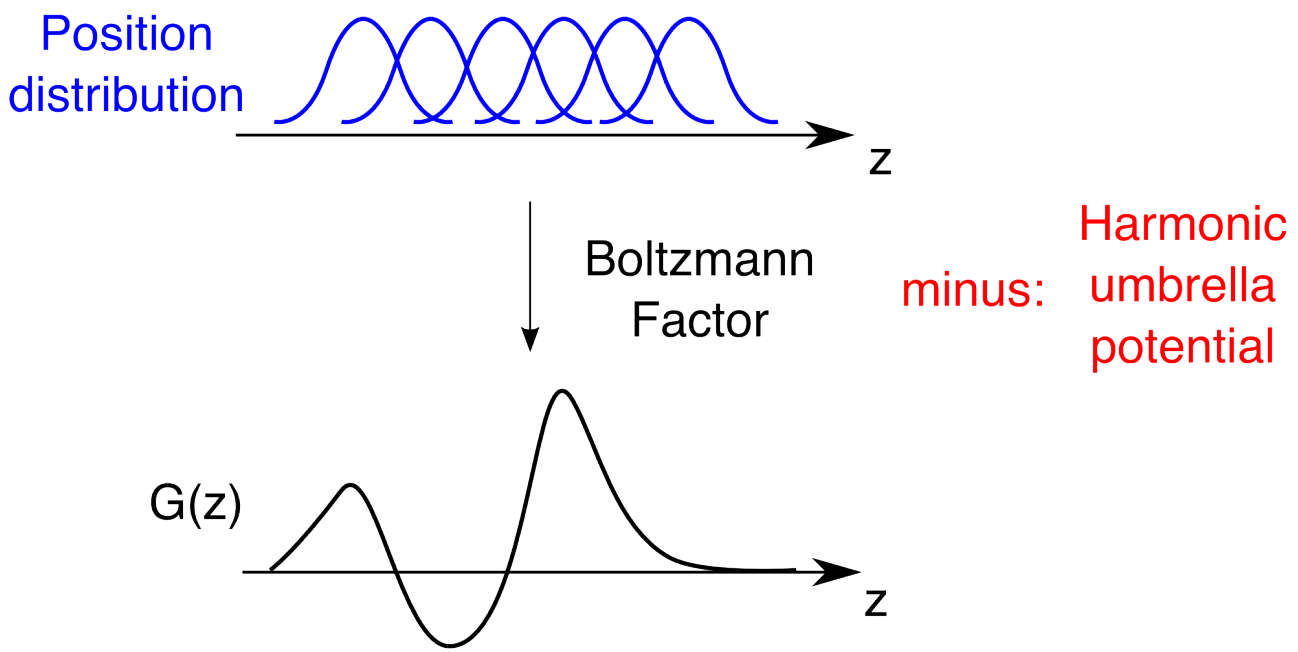


Example:
Permeation of glycerol and urea through PfAQP

Solute permeation through PfAQP:

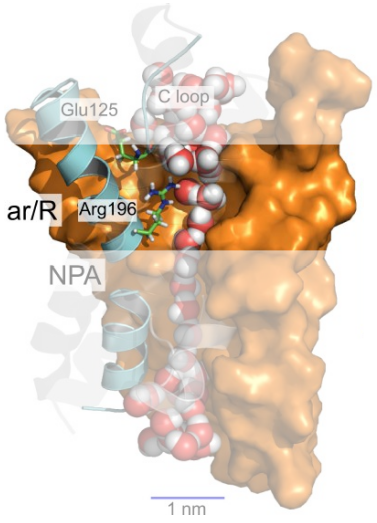
Glycerol > Urea

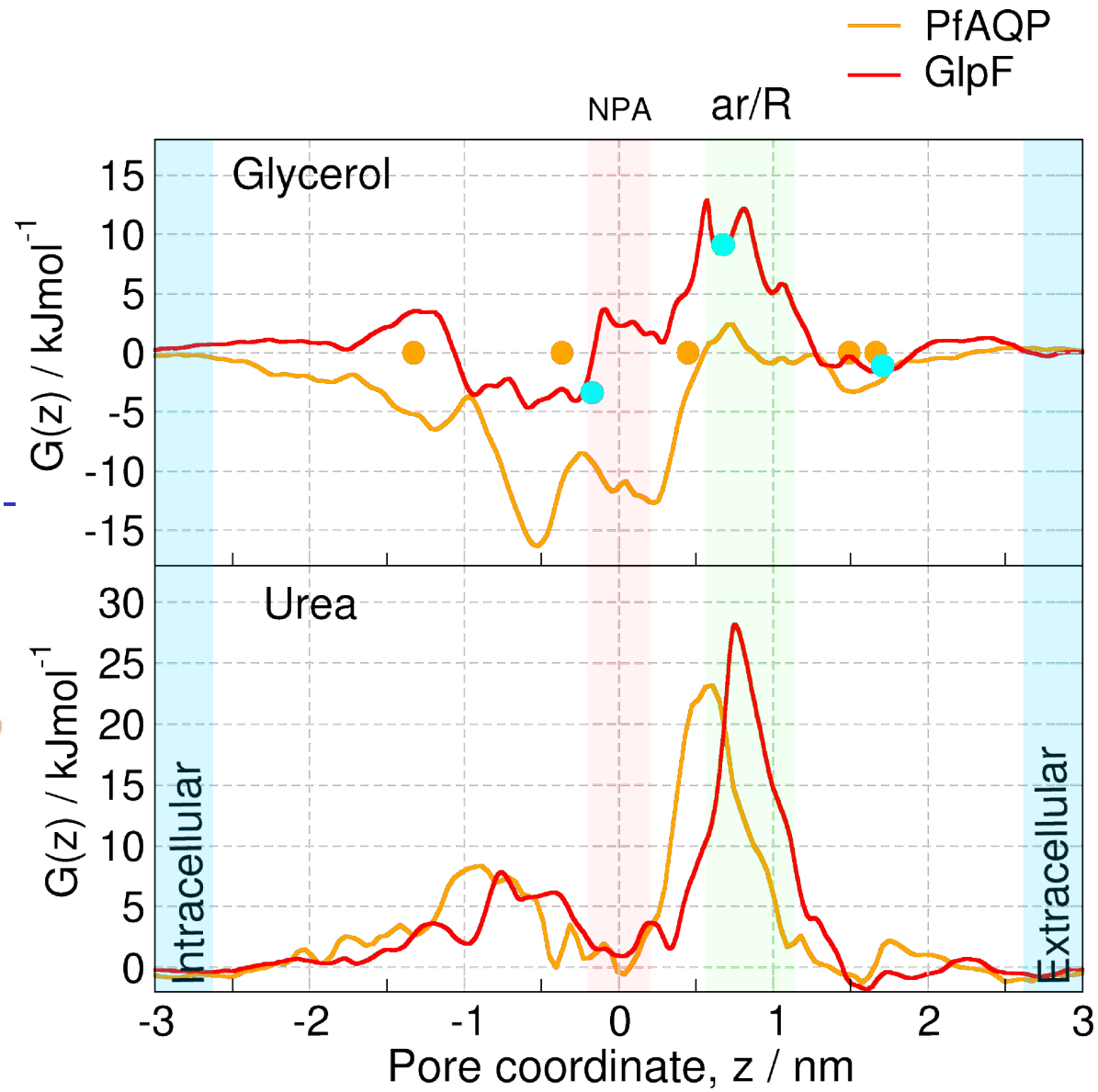
Compared to GlpF (E. Coli):

PfAQP > Glpf

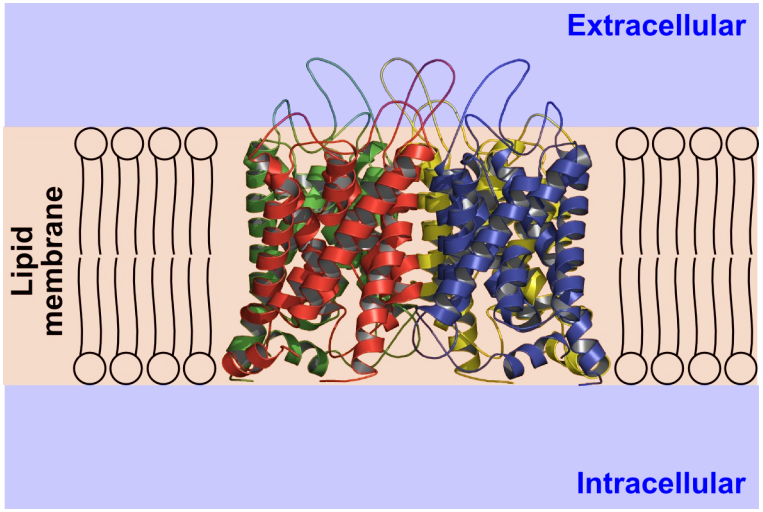
Glycerol binding site:

Prediction: Water permeability glycerol-concentration dependent





Membrane proteins



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Permeability coefficients from equilibrium MD simulations

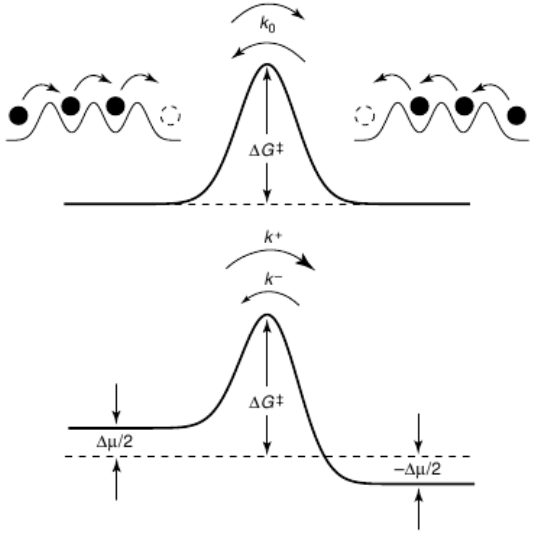
Osmotic permeability, p_f :

flux = p_f x Δ *solute concentration*

Efficient computation of p_f :

no hydrostatic pressure applied

Rate theory



From de Groot & Grubmüller, Curr Opin Struct Biol 2005

Collective diffusion

Based on Zhu, Tajkhorshid & Schulten PRL 2004

p_f related with

Concerted motion of waters inside the channel

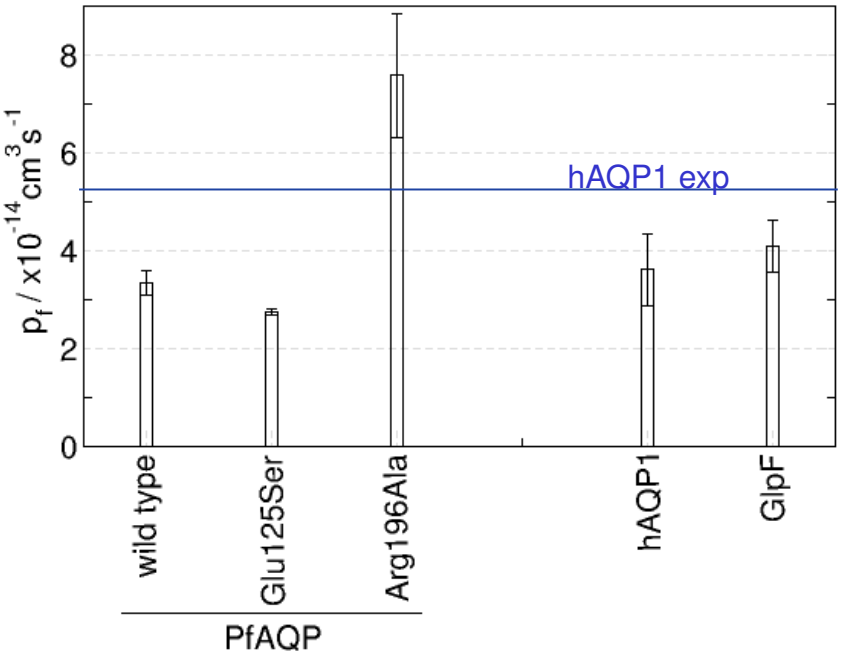
• Non-equilibrium:

Not efficient:

High hydrostatic pressures needed

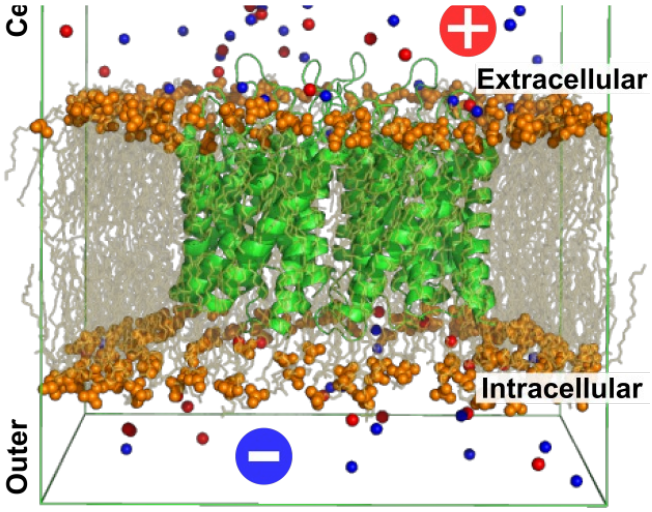
Example:

Malaria AQP (PfAQP) is a highly efficient water channel



Aponte, Hub & de Groot, ***PCCP*** *2010*

Ion permeation: computational electrophysiology



Kutzner C, Grubmüller H, de Groot BL, Zachariae U. Biophys J. 101: 809-817 (2011)

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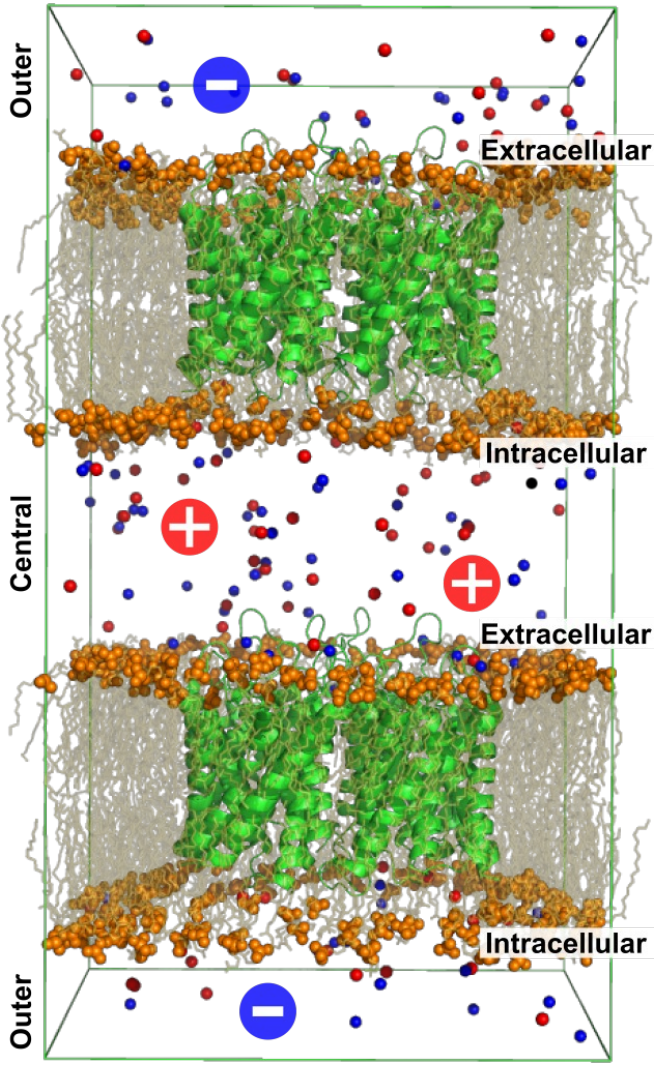

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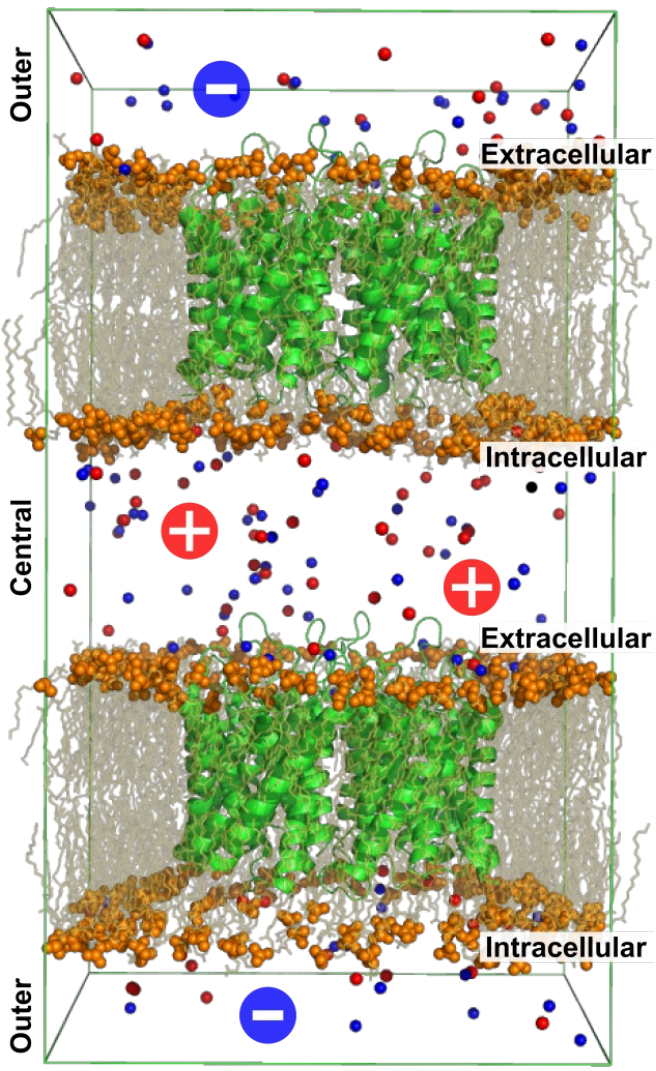
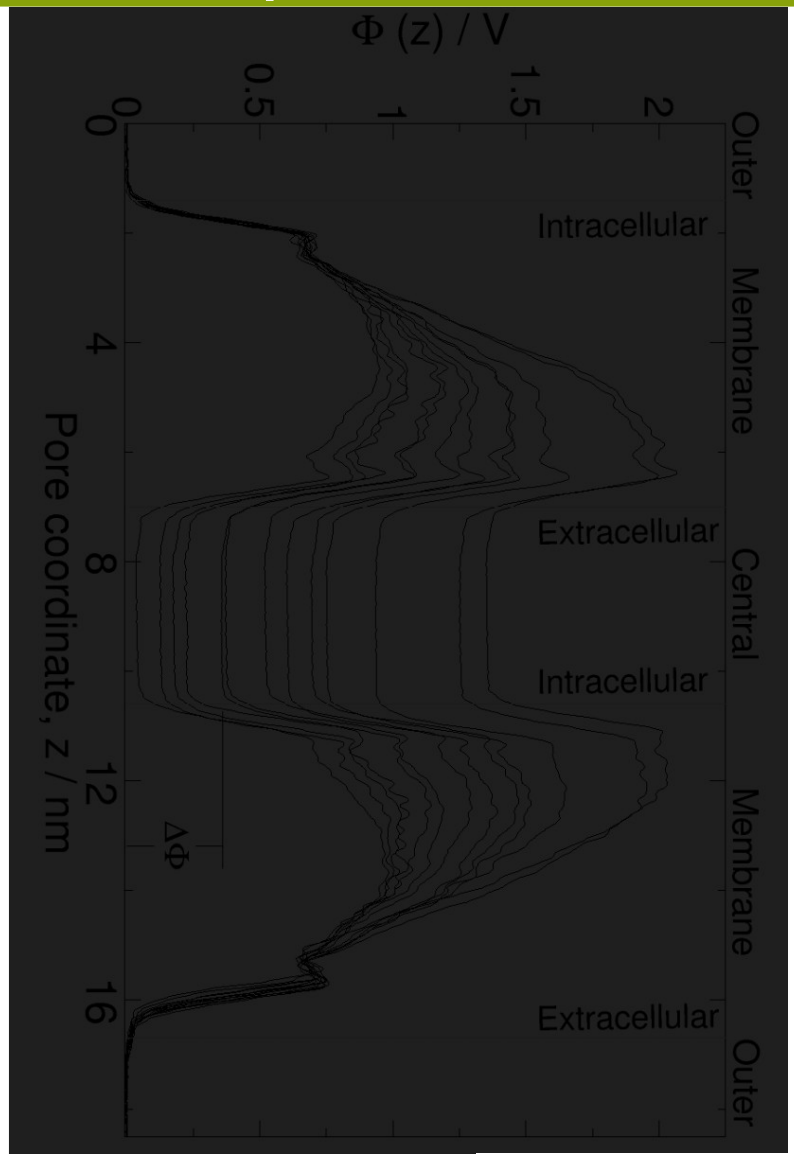




Electrostatic potential: numerical solution of Poisson equation:

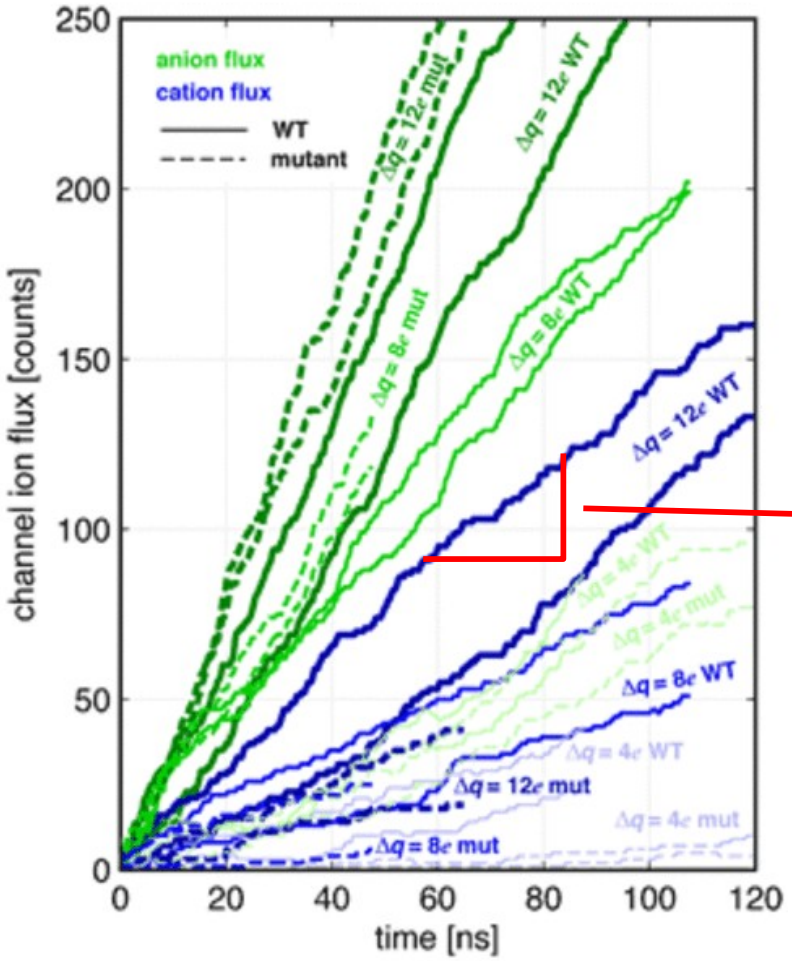
Double membrane system & Ion swapping to maintain electrostatic gradient

$$\Delta\Phi(\mathbf{x}) = -\rho(\mathbf{x})/\epsilon_0$$

Kutzner C, Grubmüller H, de Groot BL, Zachariae U. Biophys J. 101: 809-817 (2011)

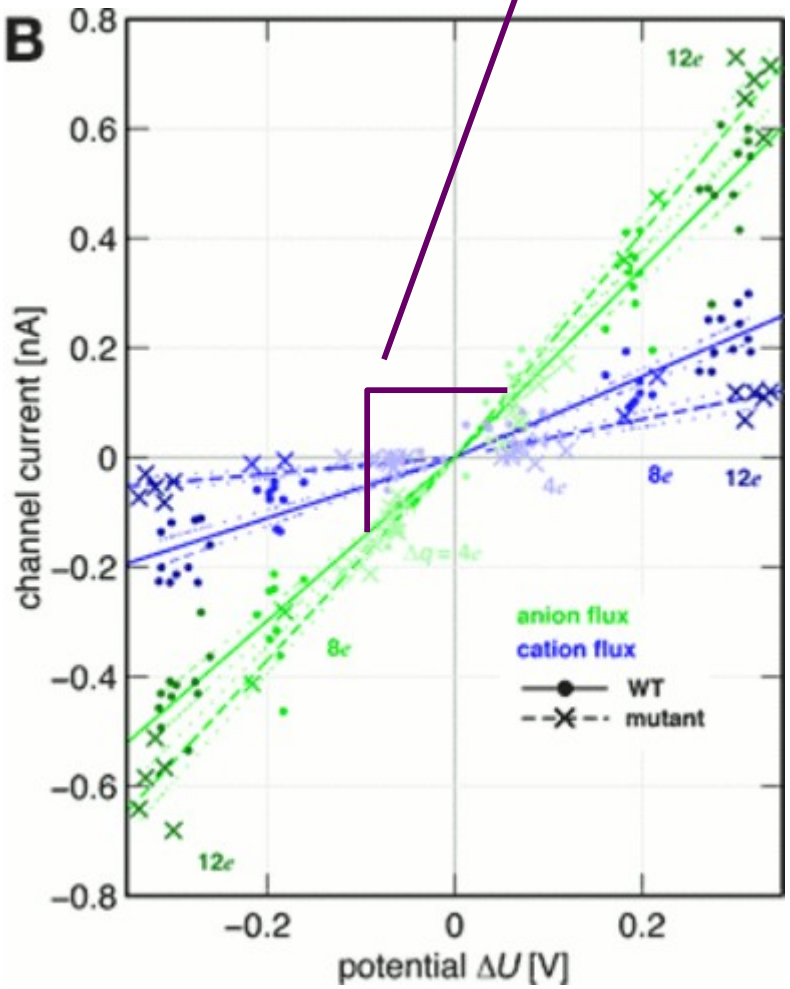
Ion permeation: computational electrophysiology

For one applied voltage:



Current

Conductance



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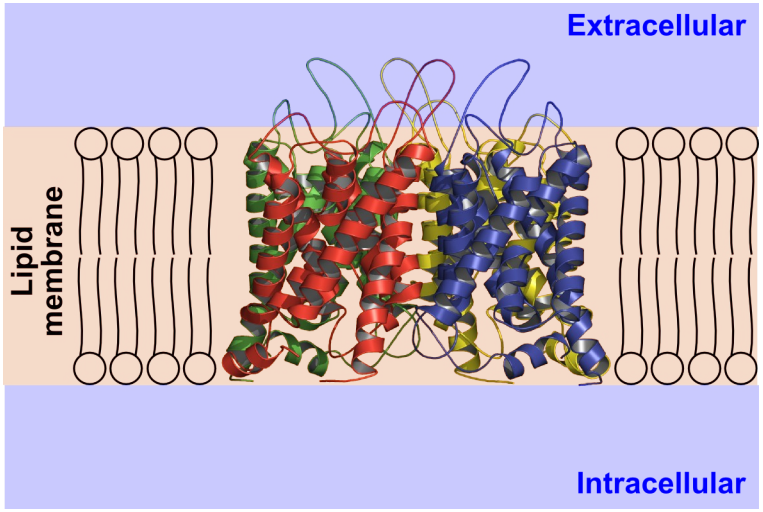

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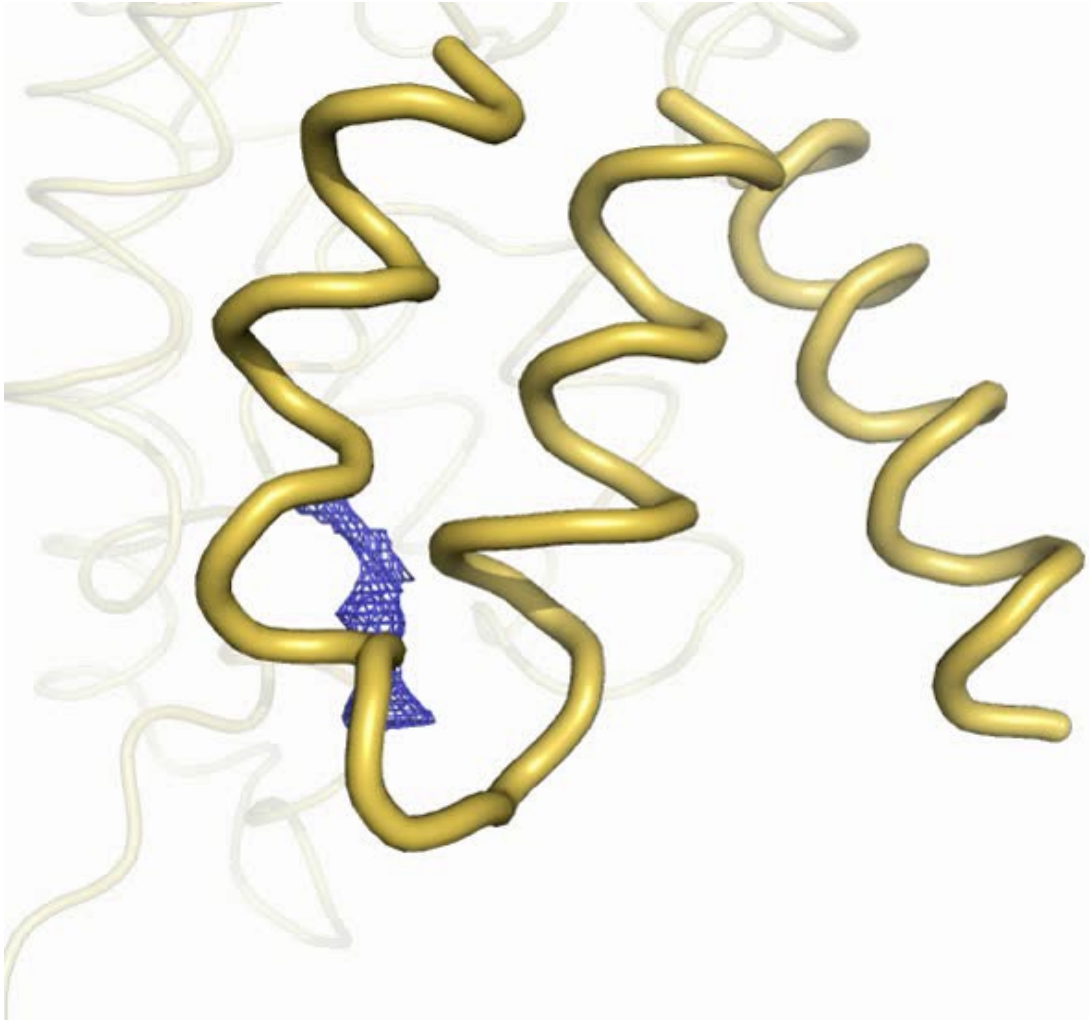
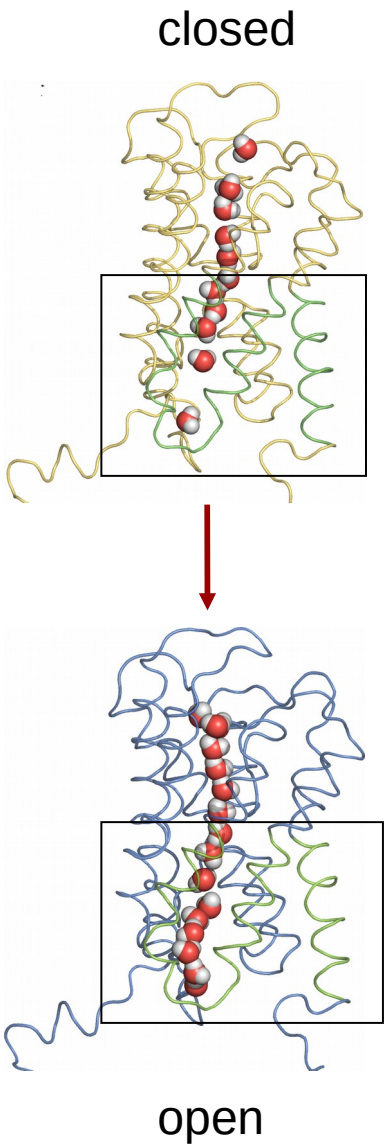
Gating collective motions of yeast aquaporin

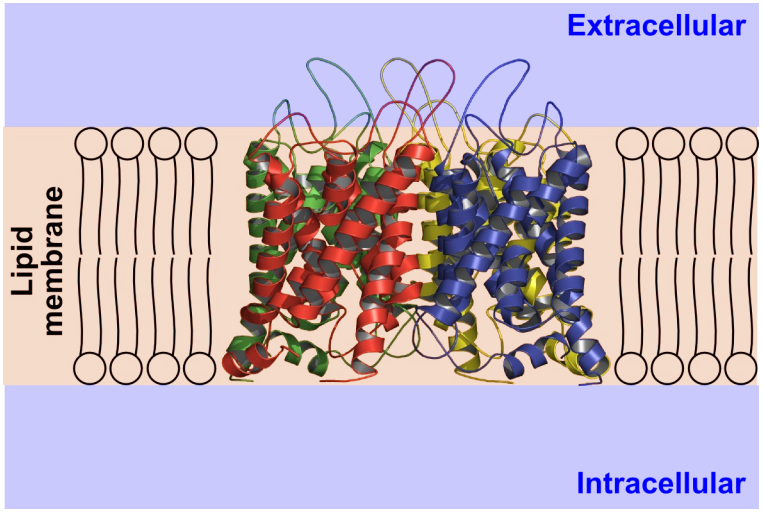
Gate





Fischer, Kosinska-Eriksson, Aponte, et. al. ***PLoS Biol.*** *7: e10000130 (2009)*

Membrane proteins



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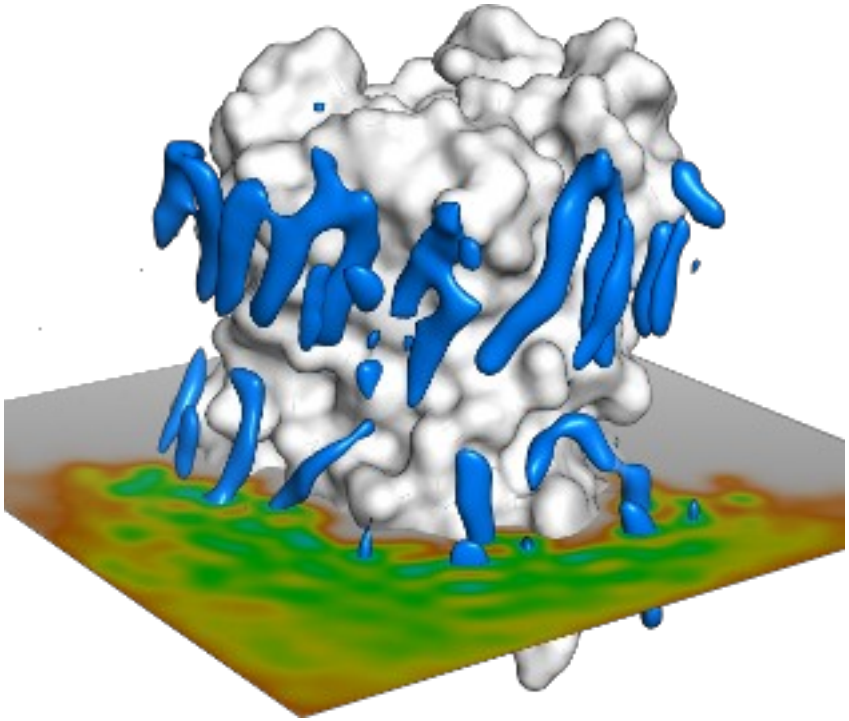
Lipid localization around aquaporin 0



AQP0 (white)

DMPC annular lipids (blue)

DMPC bulk lipids (green)

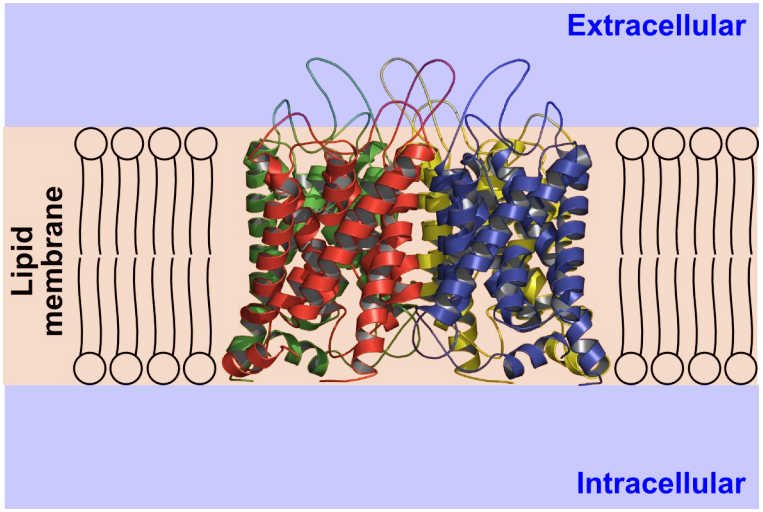
- Localization: acyl chains and not head-groups
- Protein mobility: distorting role
- Protein surface: modulating role
- hydrogen bonds: secondary role

membrane proteins:

laterally diffuse solvated by several layers of localized lipids

Aponte-Santamaria, Briones, Schenk, Walz, de Groot. PNAS 109: 9887-9892 (2012).

Membrane proteins



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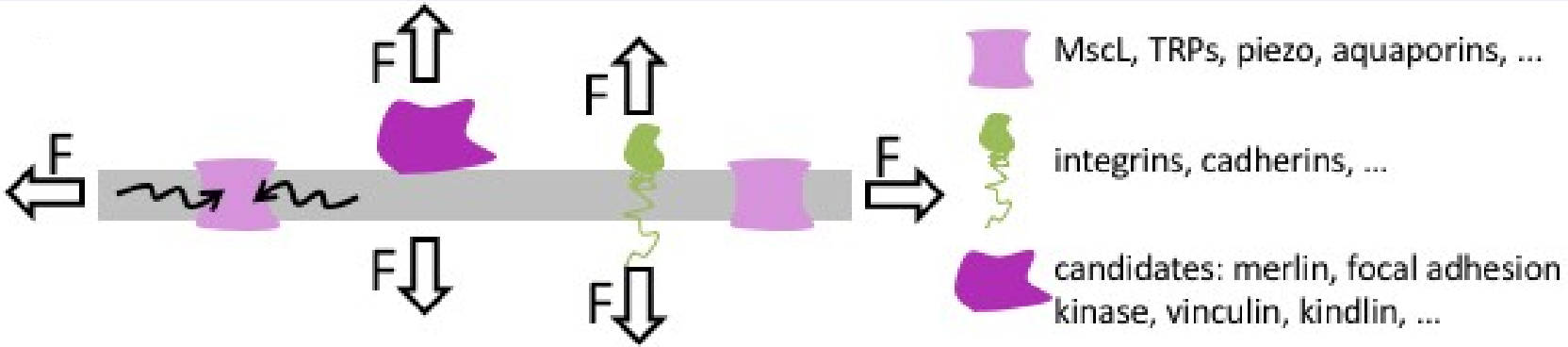
Mechanical stress plays key roles in biological membranes



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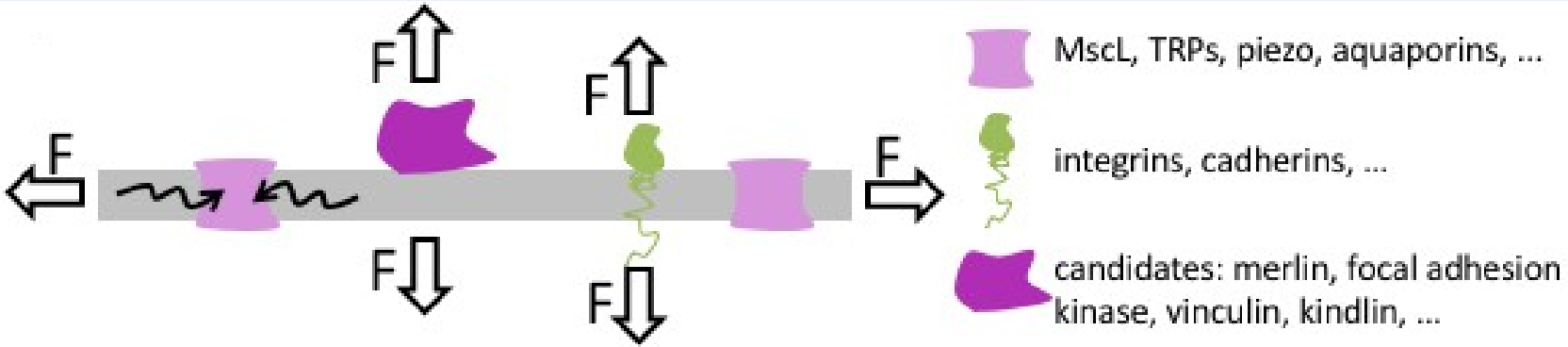
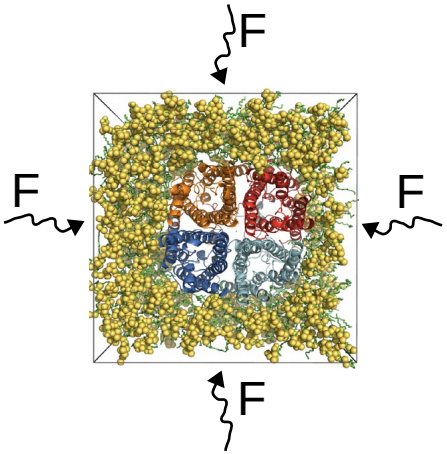


Mechanosensitive gating of aquaporins

Fischer, Kosinska, **CA-S**, et al. PLoS Biol. 2009



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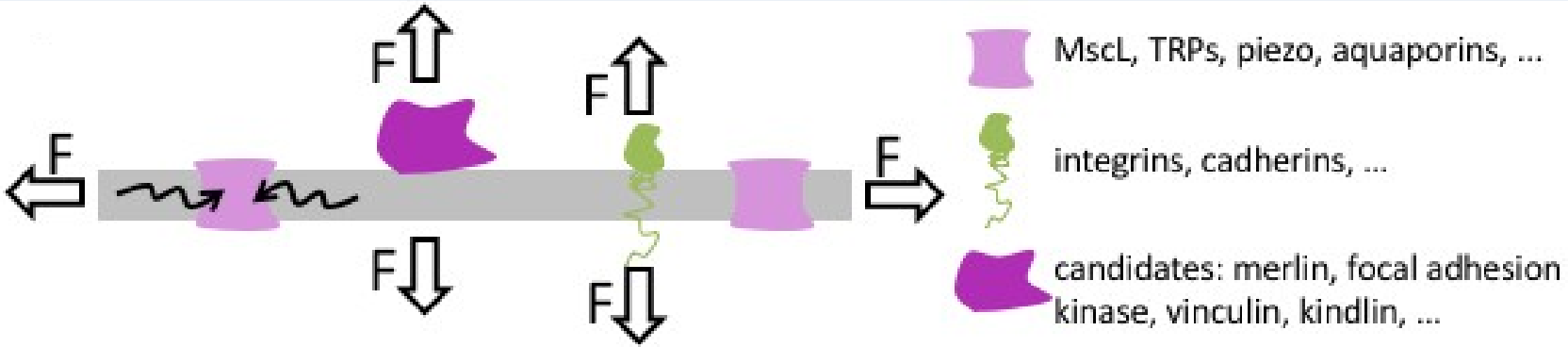

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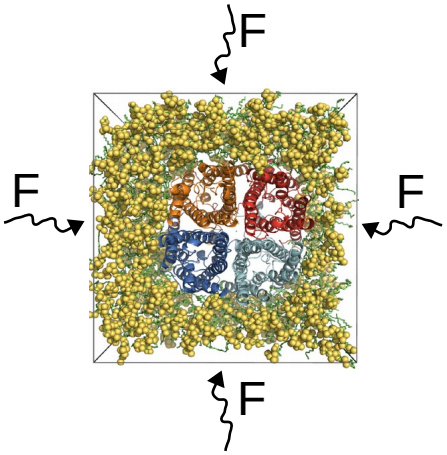
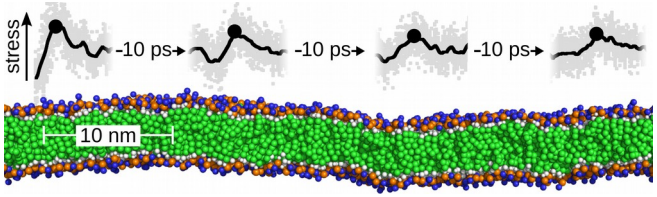


Stress propagation through lipid bilayers

CA-S, Brunken, Gräter. JACS. 2017



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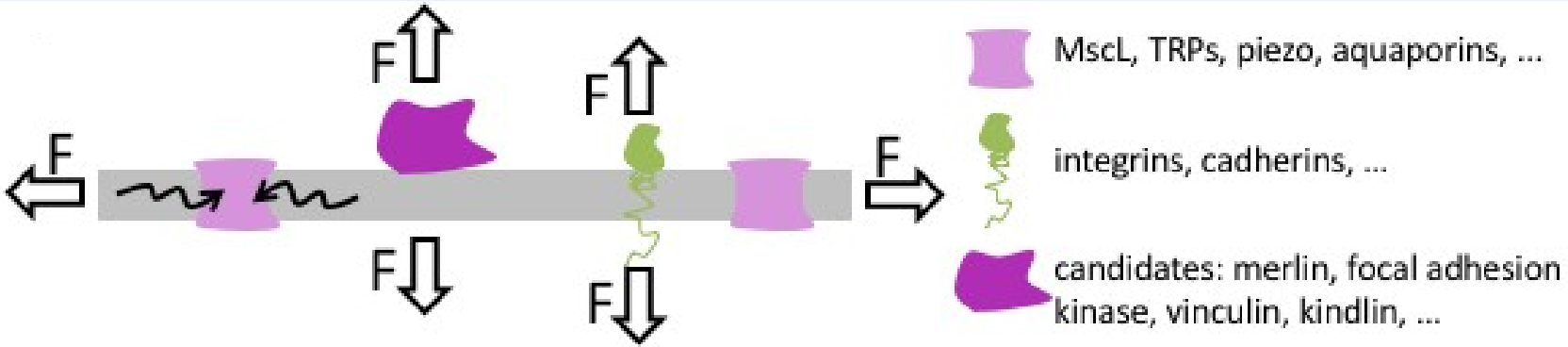

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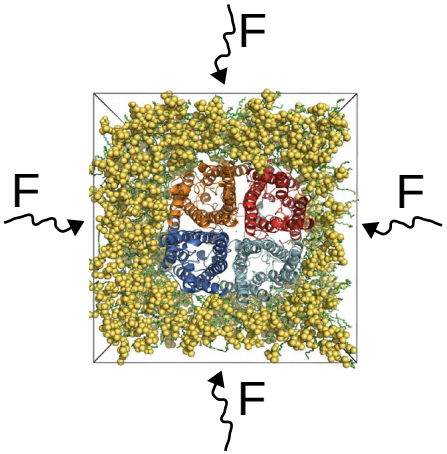

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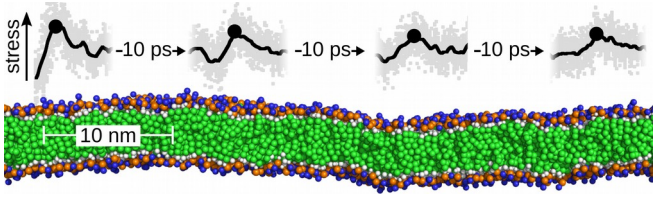
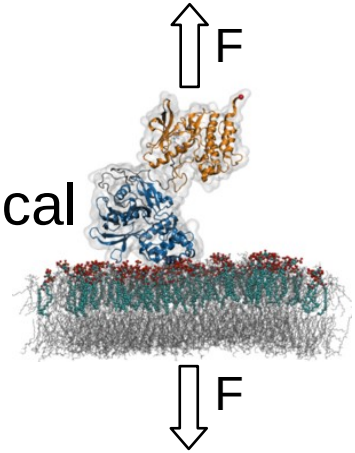


Mechanoactivation of focal adhesion kinase

Zhou*, **CA-S***,…, Gräter. PLoS Comp. Biol. 2015



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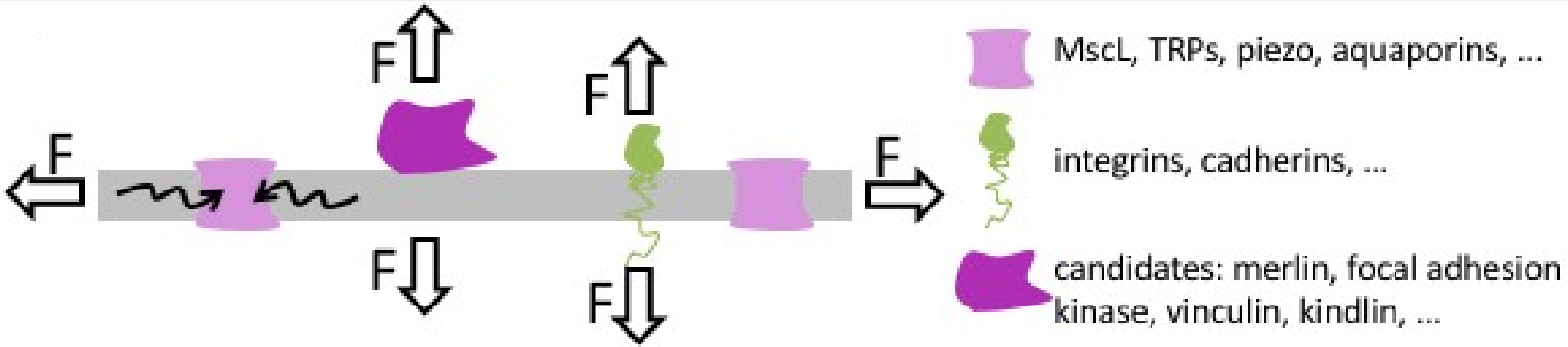

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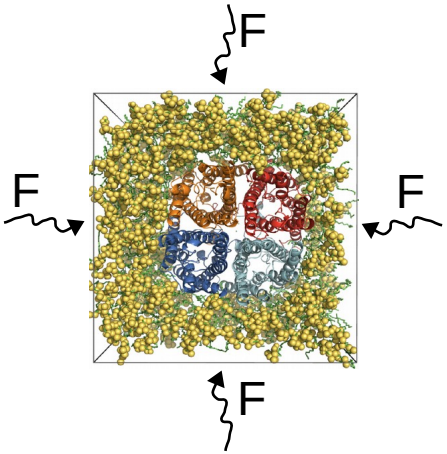

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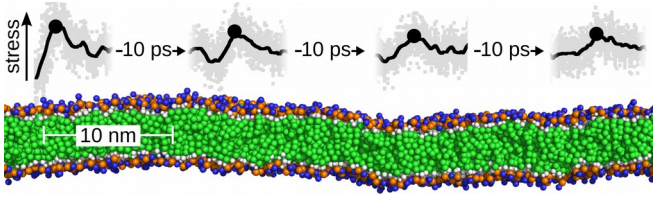

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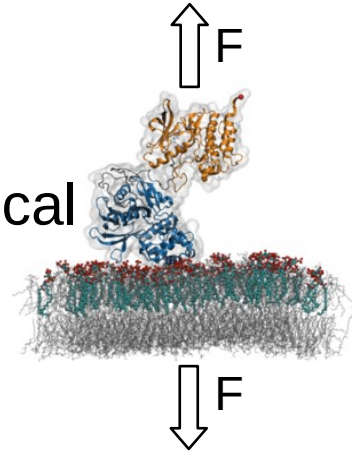
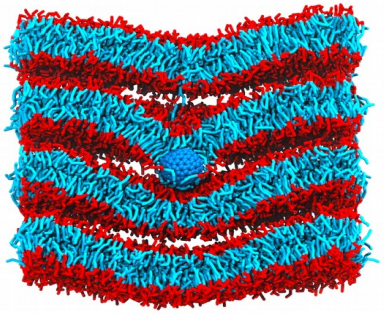
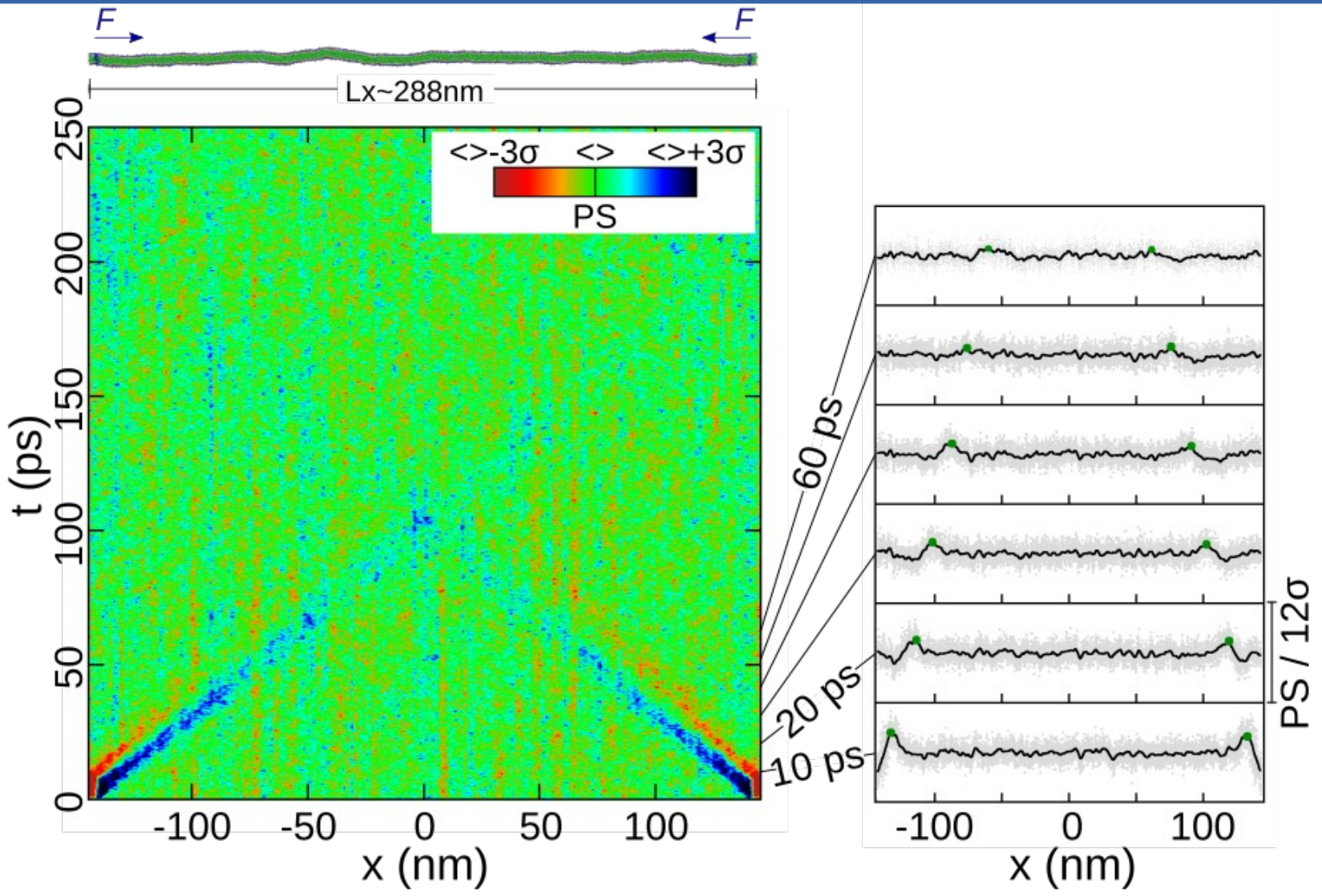


Indentation of stacked lipid bilayers

Franz, **CA-S**, Daday, Miletic, Gräter. JPCB. 2018



Mechanical pulses in action



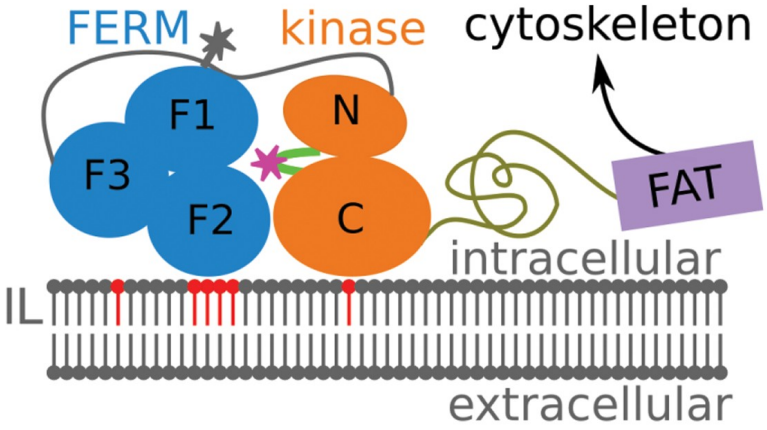
Propagation of ultra-short nm-wide pulses revealed

from time-resolved punctual stress (PS) calculations

Force Distribution Analysis, Costescu & Gräter, BMC 2013

$$PS(x,t) = \frac{1}{12}\sum_{i=1}^{i=12} PS_i(x,t)$$

Focal Adhesion Kinase (FAK) mechanoactivation



- key
  signal transductor
  at focal adhesions

Zhou*, **CA-S***, Sturm, Bullerjahn, Bronowska, Gräter.
PLoS Comp Biol. 11: e1004593 (2015)

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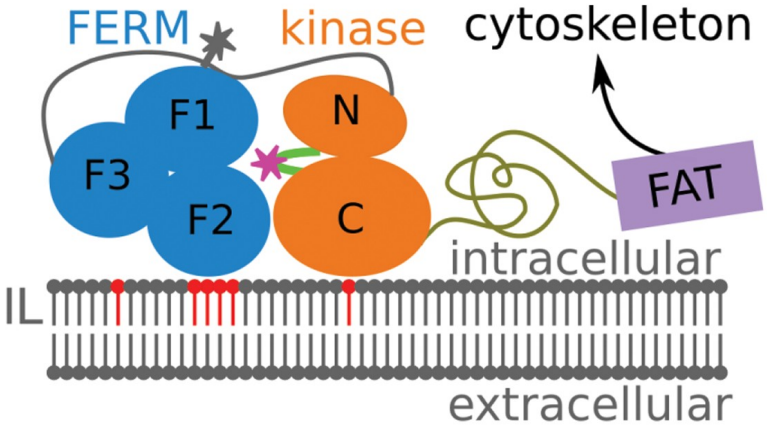

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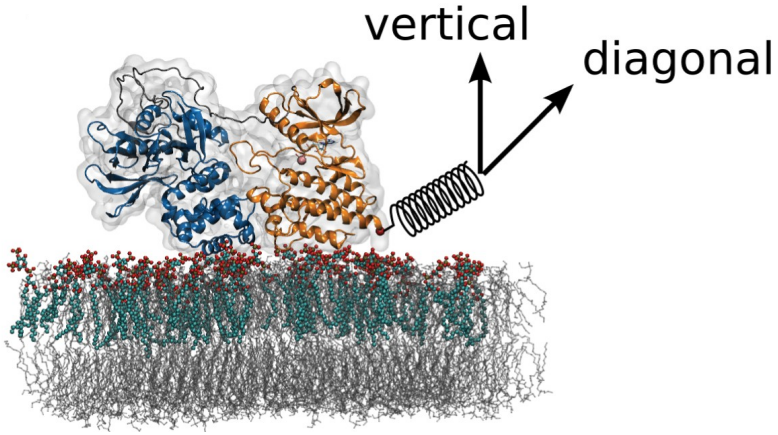

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  also
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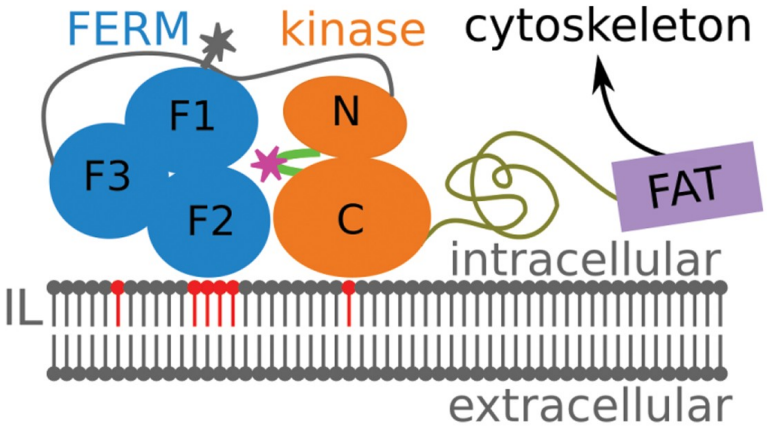

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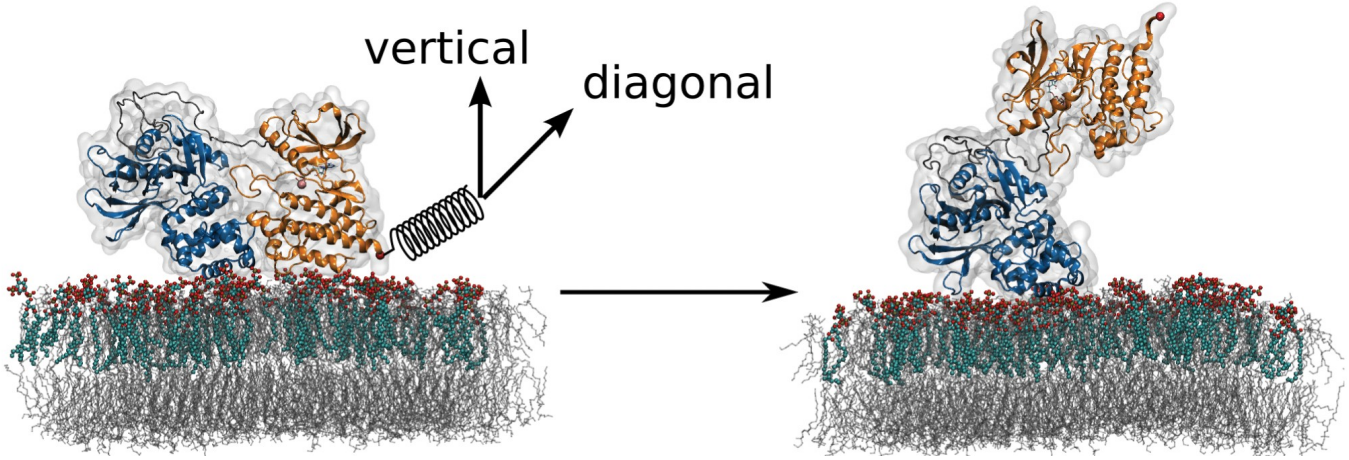
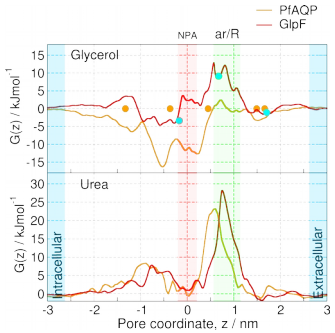


- Force-induced
  exposure
  of active sites
  previous to
  domain unfolding

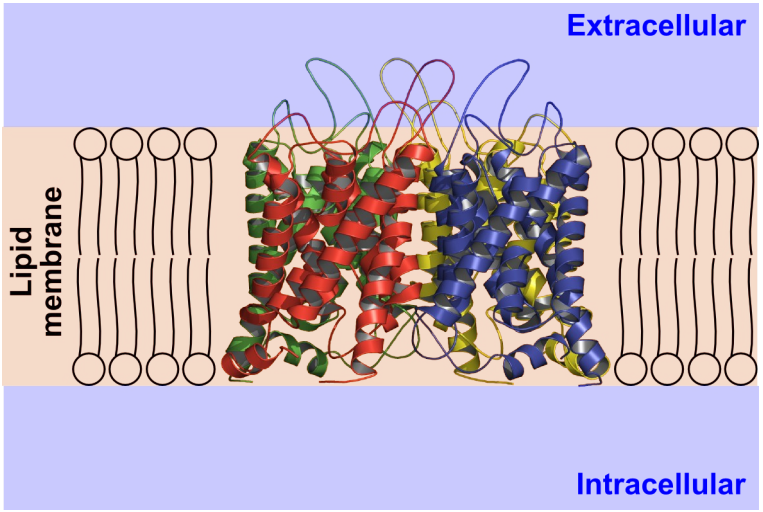
Zhou*, **CA-S***, Sturm, Bullerjahn, Bronowska, Gräter.
PLoS Comp Biol. 11: e1004593 (2015)

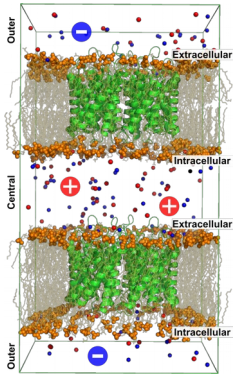
Summary: membrane proteins

What can we learn from MD simulations?

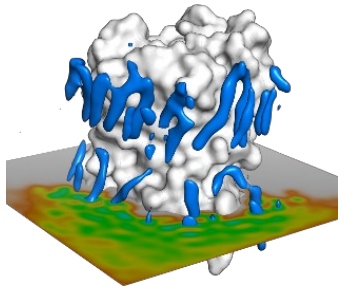


Energetics of permeation

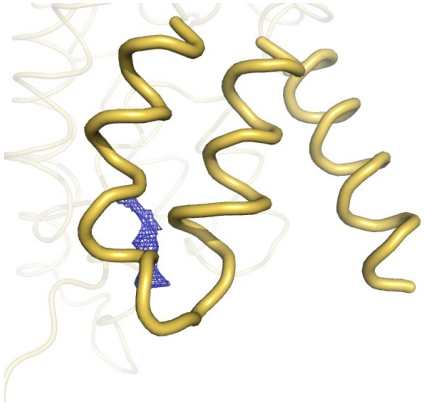




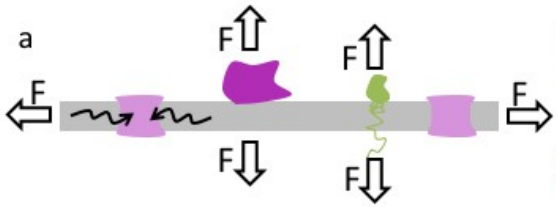
Calculation of permeabilities or conductances



Interactions with surrounding environment (lipid-protein interactions)



Relevant conformational changes



mechanical stress