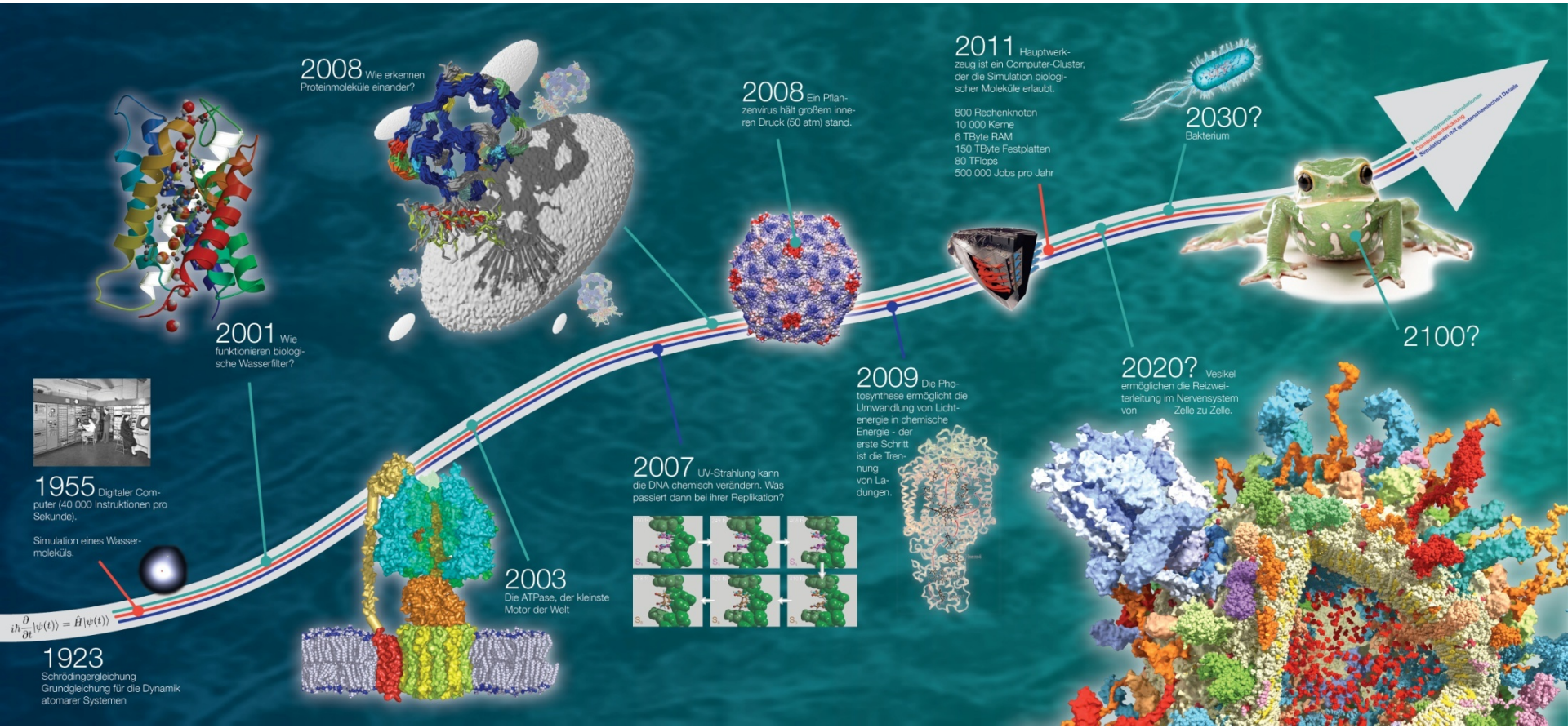
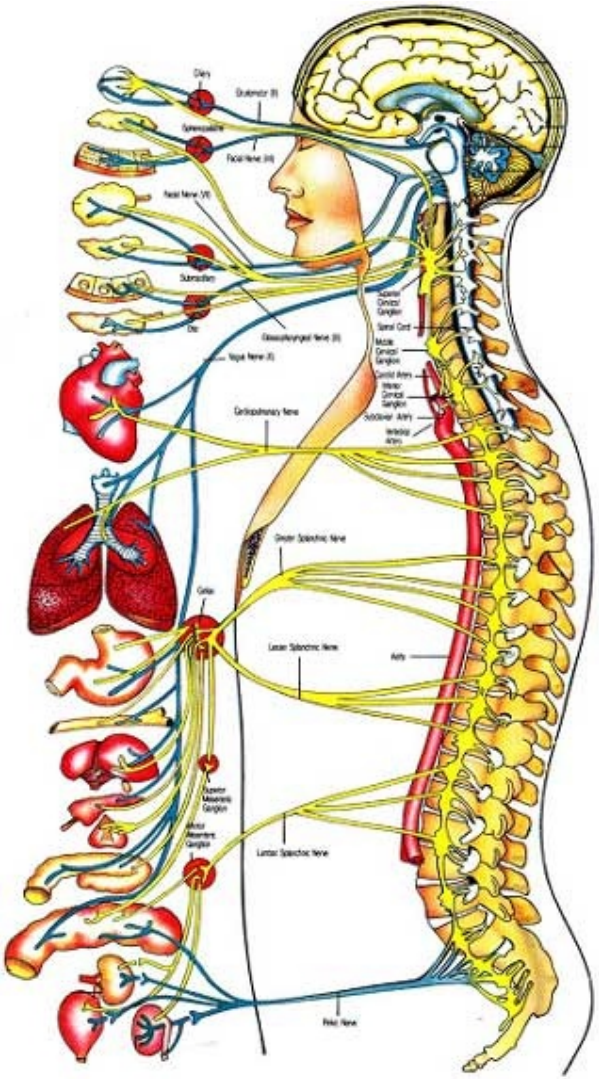
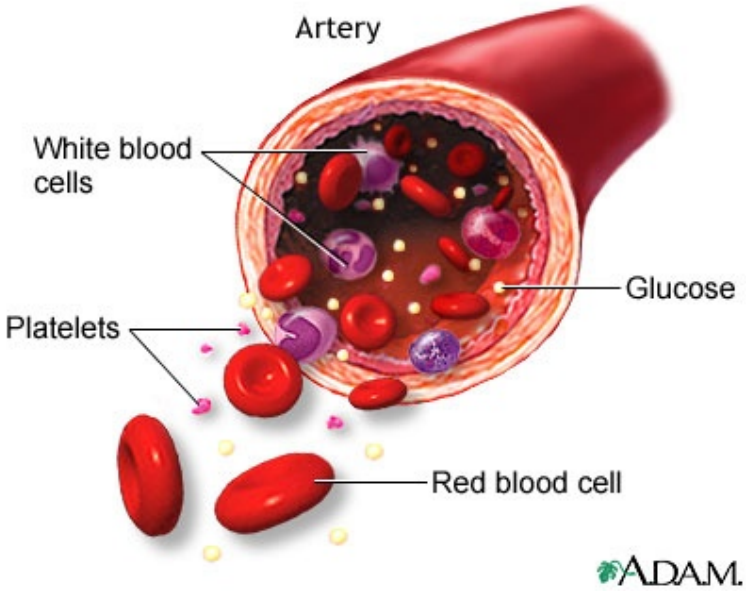
Exascale computing to explore the nanoscale

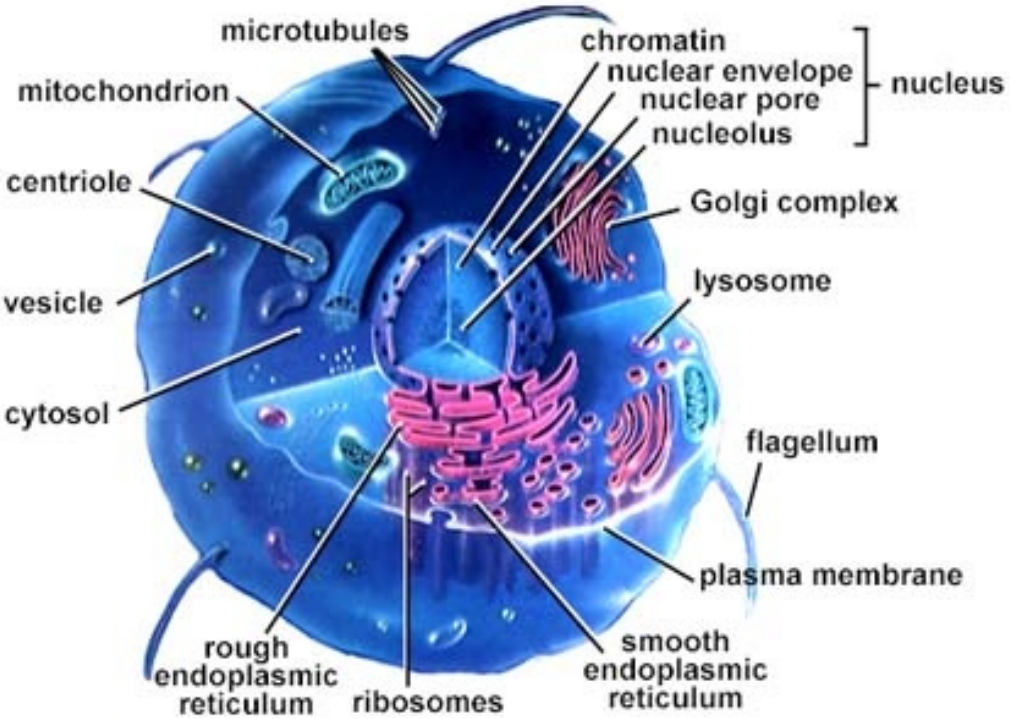


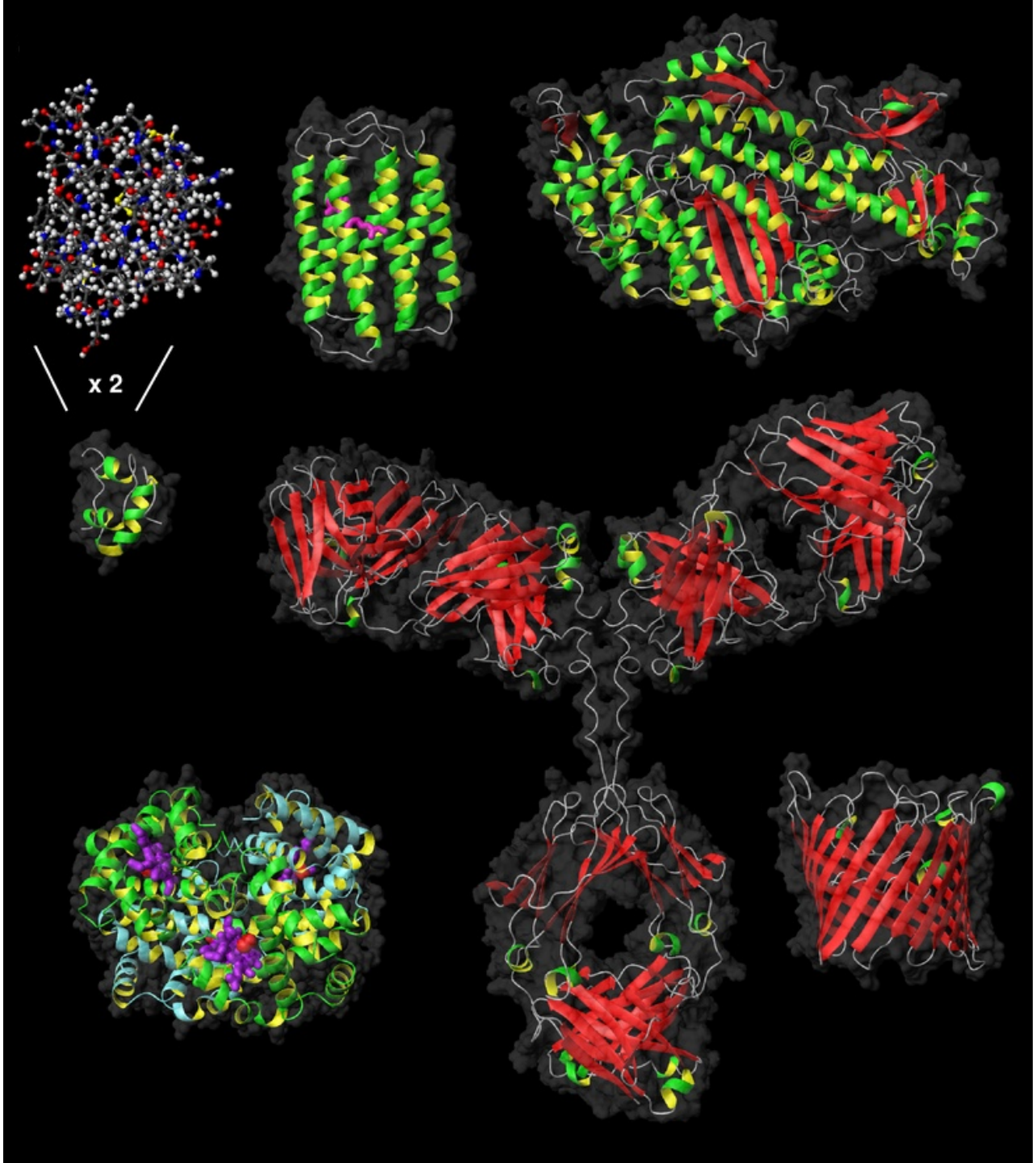
Bert de Groot, MPI for biophysical Chemistry, Göttingen

The Cell



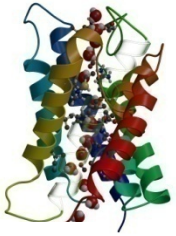

Artery
White blood cells
Glucose
Platelets
Red blood cell
A.D.A.M.


microtubules
chromatin
nuclear envelope
nuclear pore
nucleolus
nucleus
mitochondrion
centriole
Golgi complex
vesicle
lysosome
cytosol
flagellum
plasma membrane
rough endoplasmic reticulum
ribosomes
smooth endoplasmic reticulum



Proteins are nature‘s nanomachines

Aquaporin Water Channels



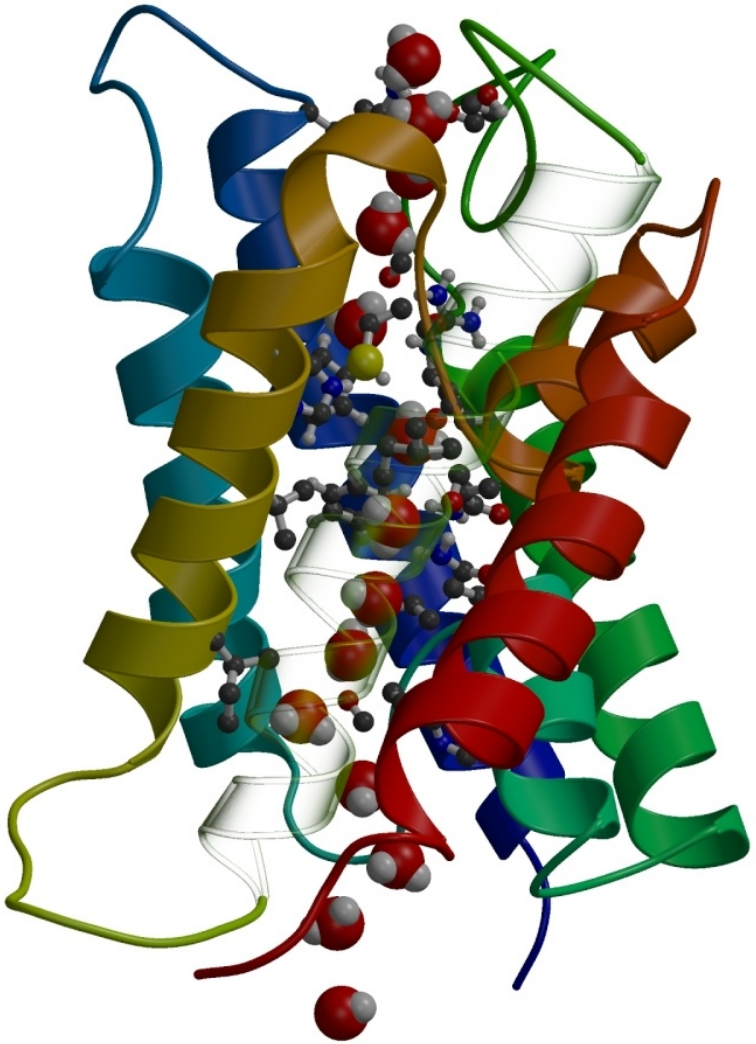
Aquaporins are highly selective, efficient water channels (10^9/s)

vital for water/solute balance in e.g. kidney, brain, eye

Malfunction associated with diabetes (AQP2), brain oedema (AQP4), glaucoma (AQP1), cell migration/cancer (AQP1/3).

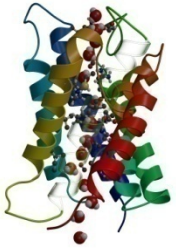
Plasmodium falciparum expresses one AQP

- ***water permeation***
- ***permeation of other solutes?***
- ***inhibition***



B.L. de Groot, A. Engel, H. Grubmüller, *FEBS Lett.* **504** (2001) 206

MD simulations of water permeation

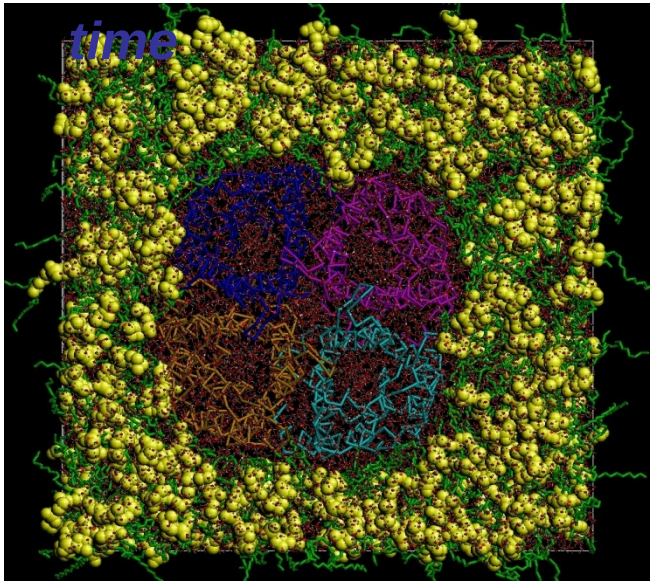


Gromacs:

- ca. 100 000 atoms

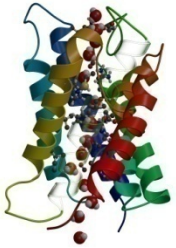
- full electrostatics, periodic boundary

-10-100 ns simulation



B.L. de Groot, H. Grubmüller, *Science* **294**, 2353 (2001)

MD simulations of water permeation



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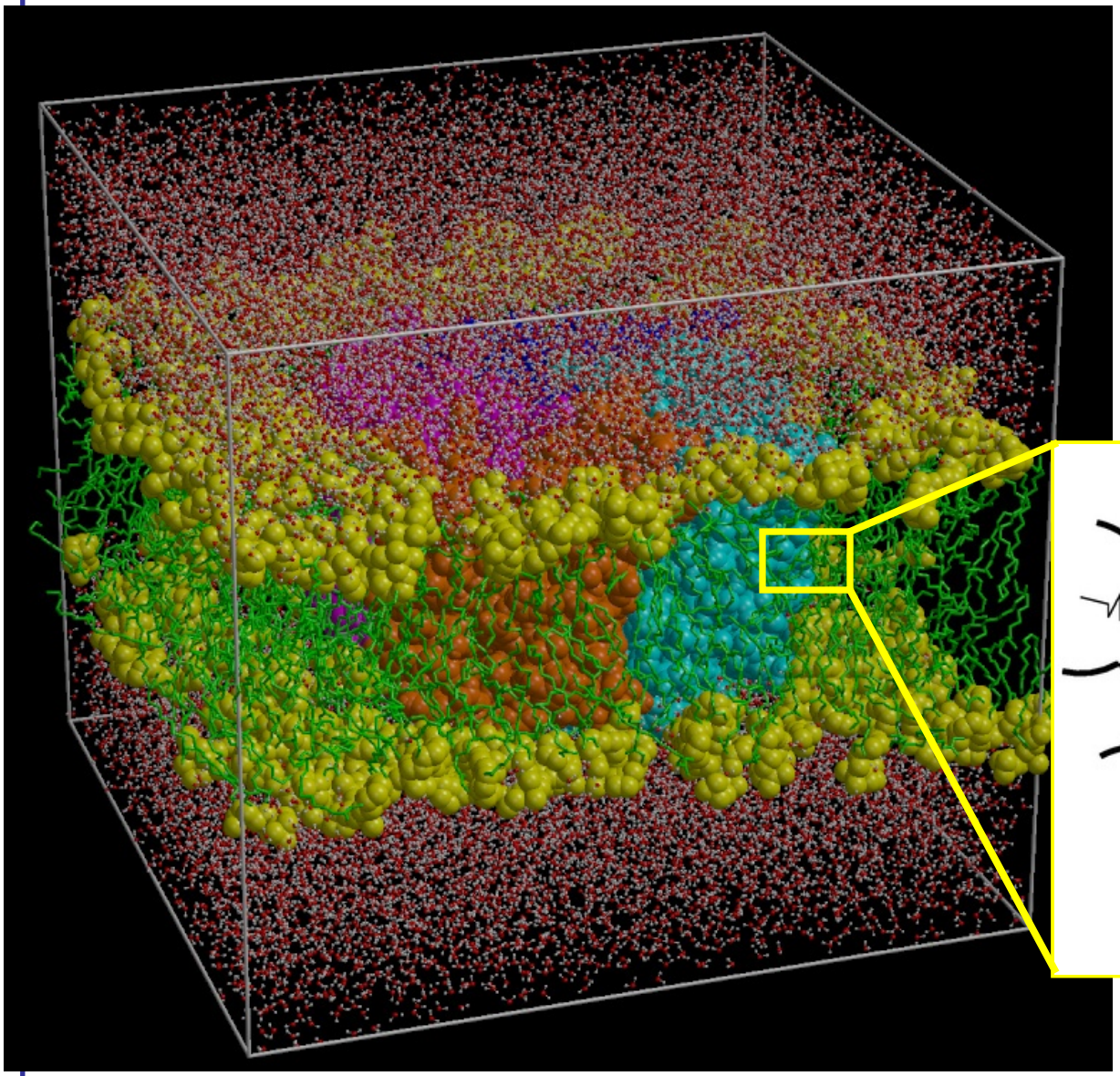
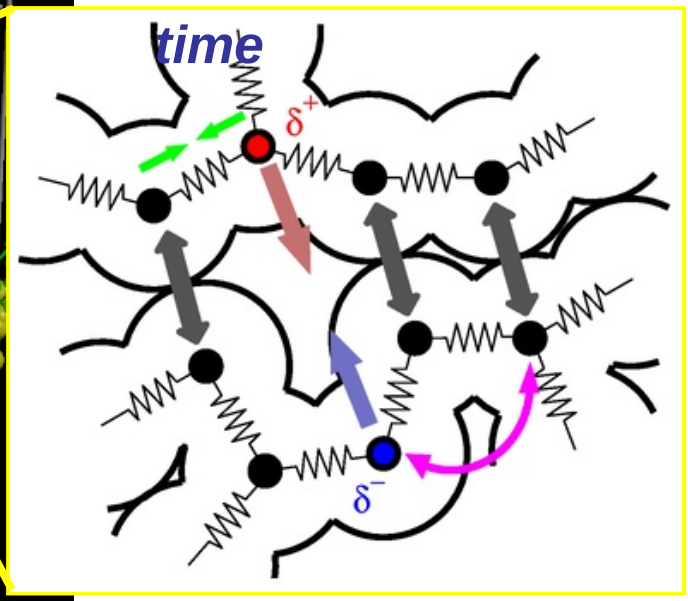
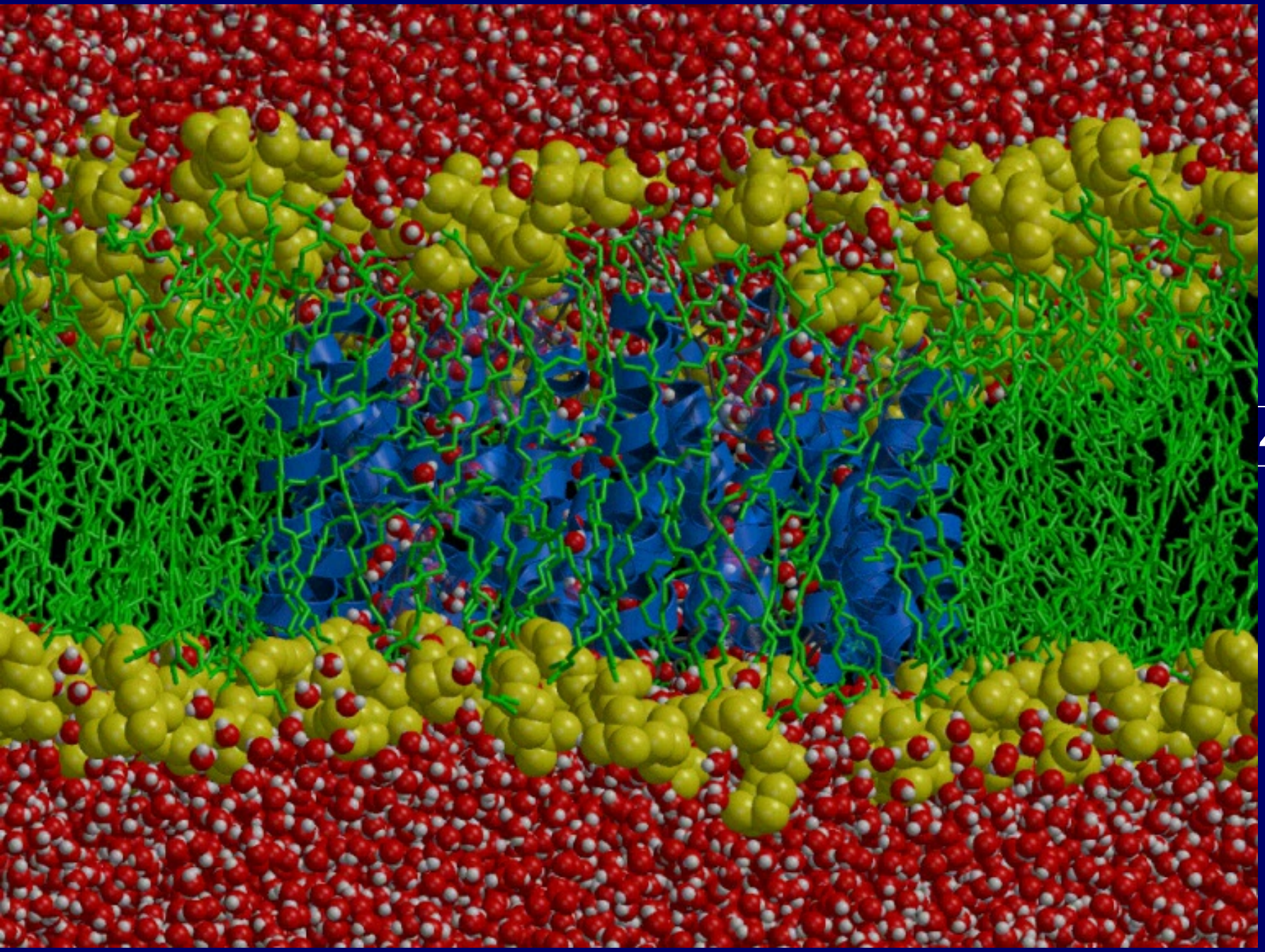




B.L. de Groot, H. Grubmüller, *Science* **294**, 2353 (2001)



Molecular dynamics simulation, 1s $\triangleq$ 2 ·10 $^{-11}$s

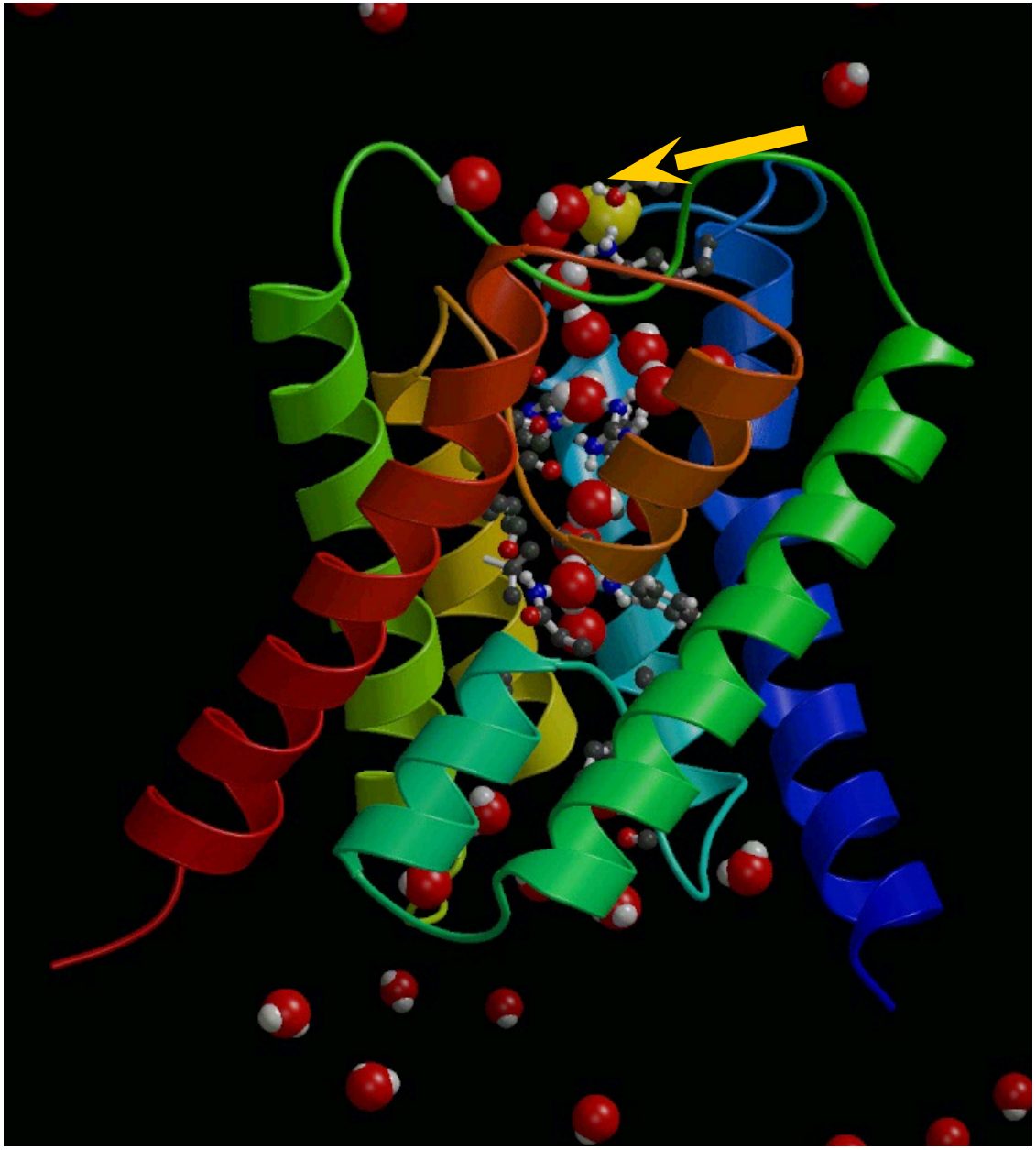
‚Real time' water permeation

one out of several spontaneous permeation events

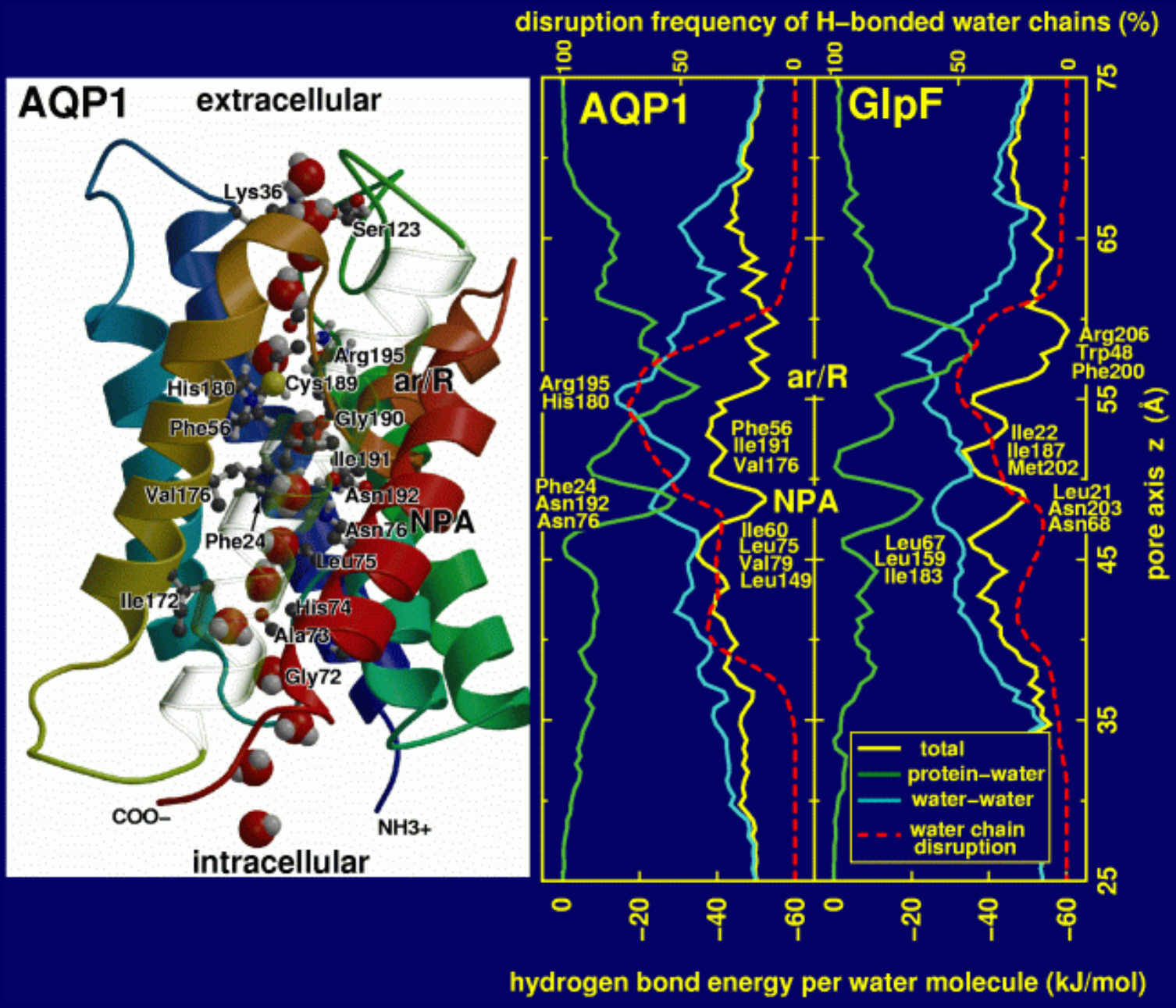
pf = 7.5 • 10^{-14} cm^3/s

(exp: 3.2 – 11.7 • 10^{-14} cm^3/s)

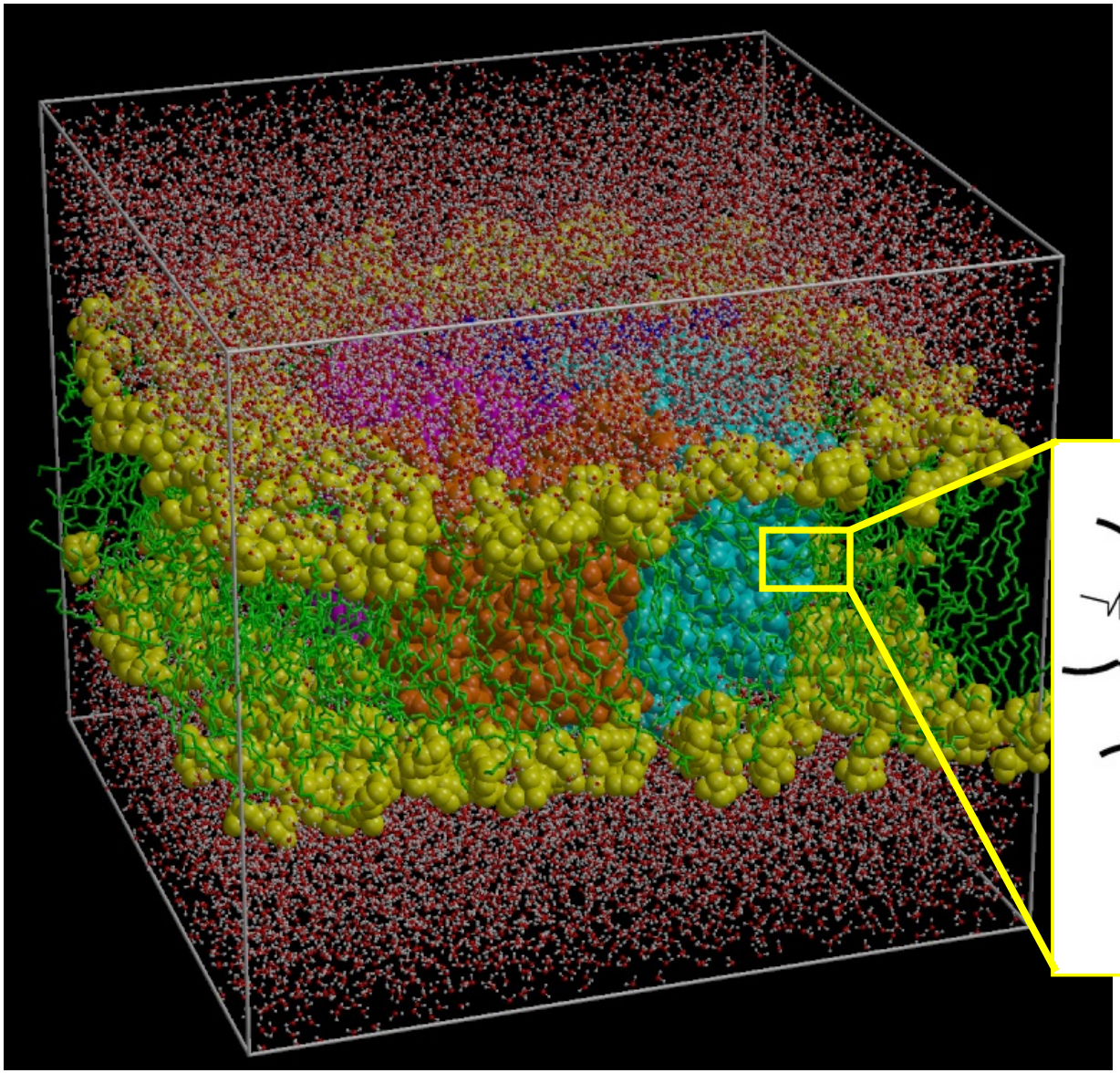
(outside the channel, only few water molecules are shown)



Water pathway and hydrogen bonding



Why are these calculations so expensive?

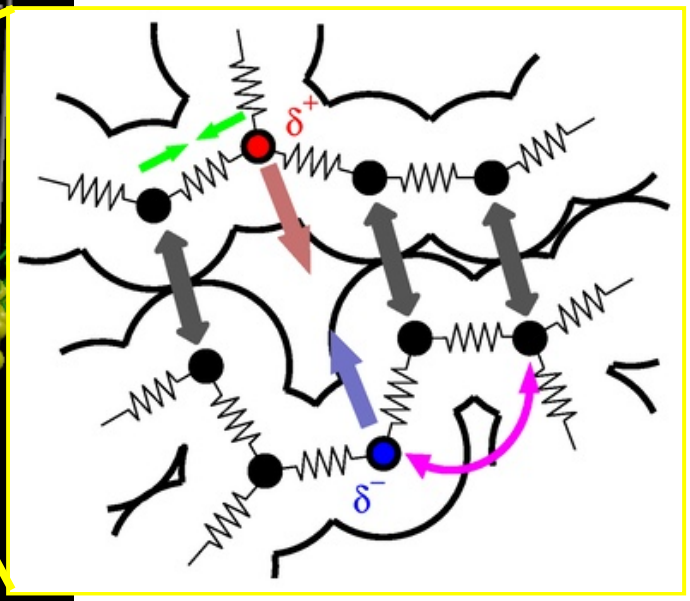


ca. 100 000 atoms

→in principle 10^{10} interactions

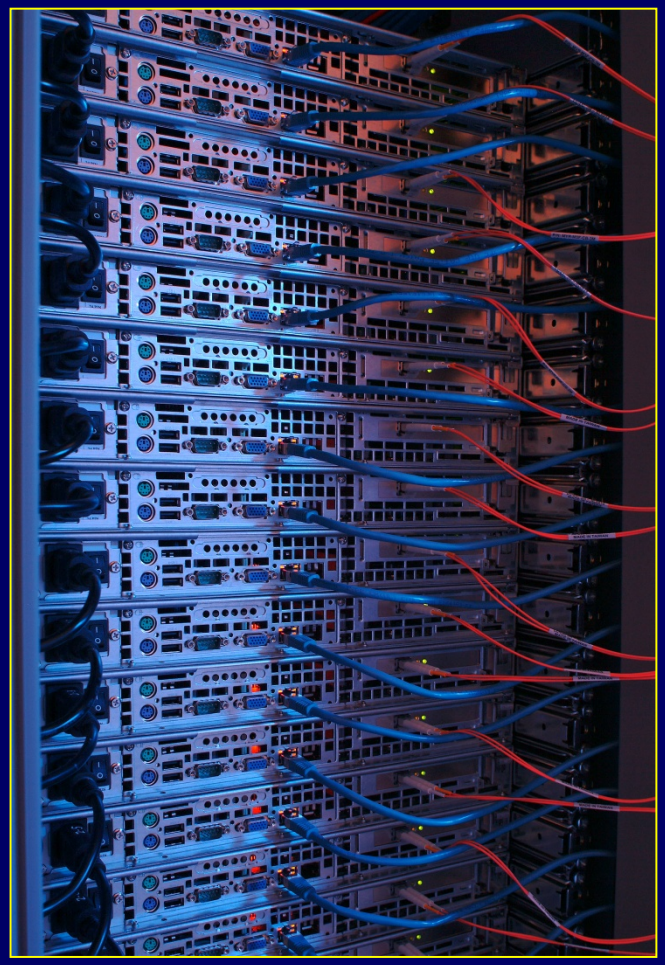
time step ~ 10^{-15} s

→ 10^{9} steps for 1µs



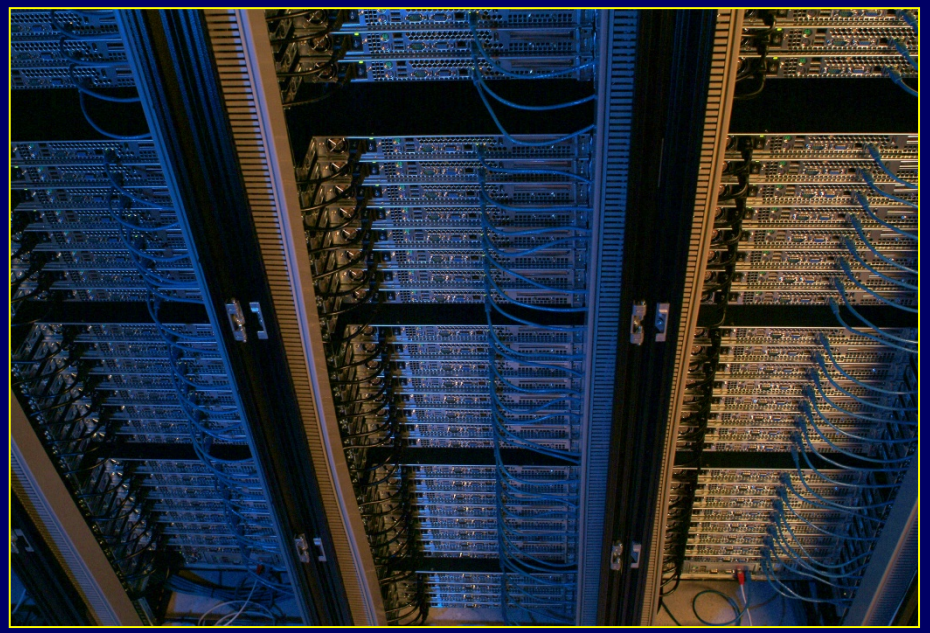
B.L. de Groot, H. Grubmüller, *Science* **294**, 2353 (2001)

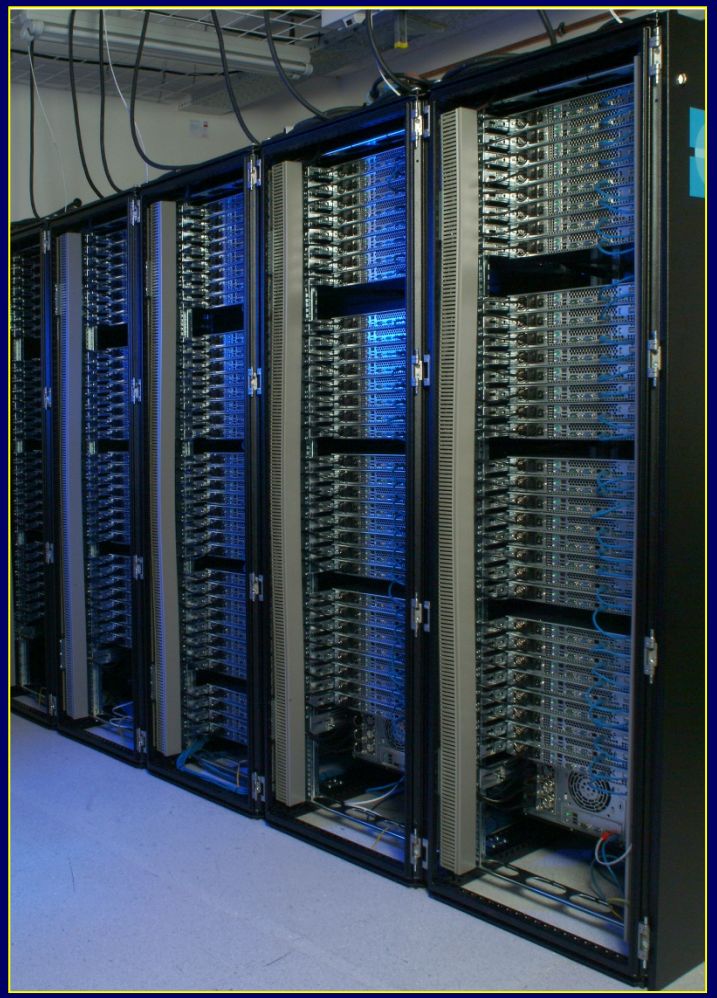
High performance parallel computing



Molecular dynamics simulations of biological processes requires huge computational resources.
Typical simulation: 1-10 exaflop

„High performance“ parallel computing





In-house linux cluster (~ 40 users):
~ 16000 CPU cores, 450 GTX GPUs

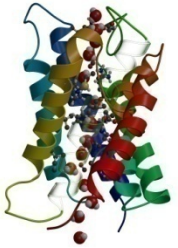
+ external sources, e.g. GWDG, Garching

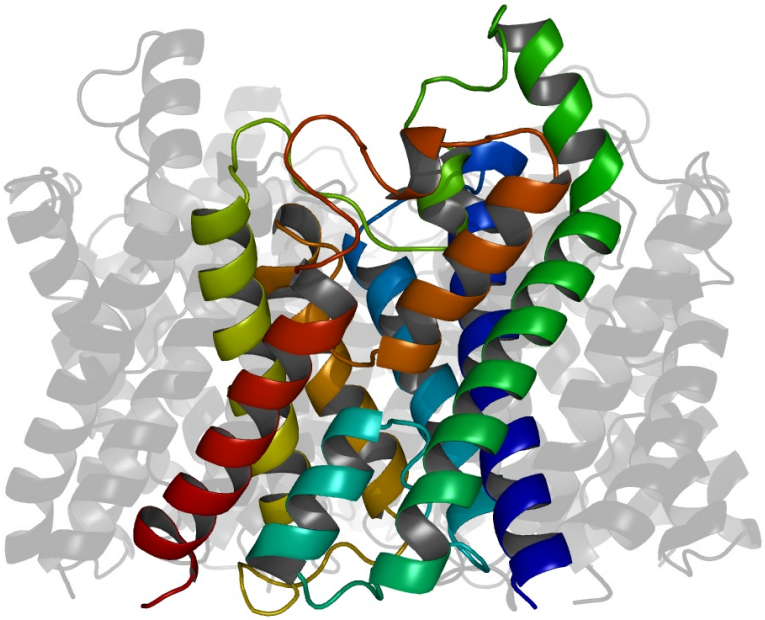
Backup traffic:
> 10 TB / week

Long term storage:
> 200 TB / year

Molecular dynamics in drug design

AQP9 inhibitor design

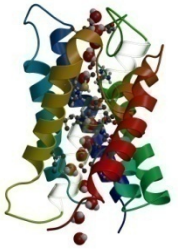


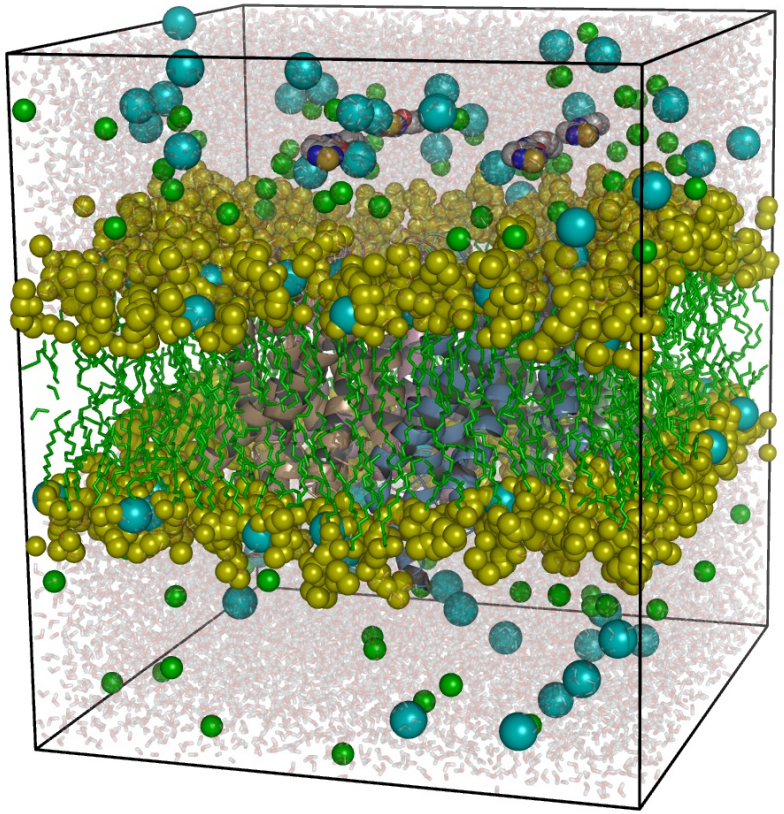


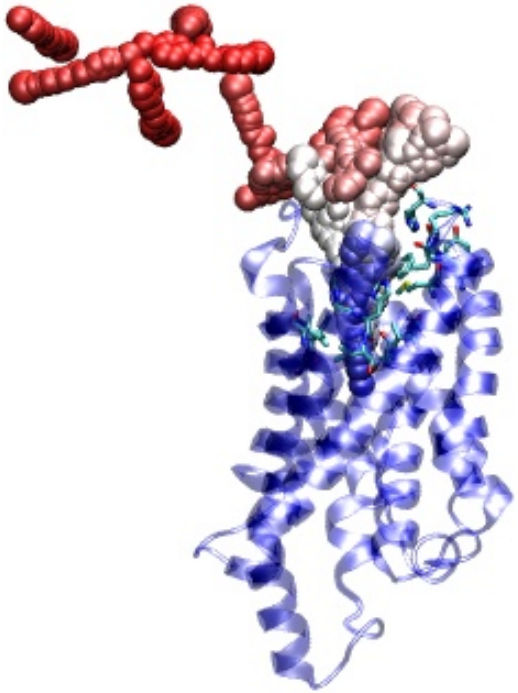
- aquaglyceroporin expressed mainly in the liver
- plays a major role in glycerol metabolism
- possible diabetes target
- structure unknown, homology model based on bacterial GlpF

Collaborations:
Michael Rützler (Aarhus)

Simulation of ligand binding to AQP9

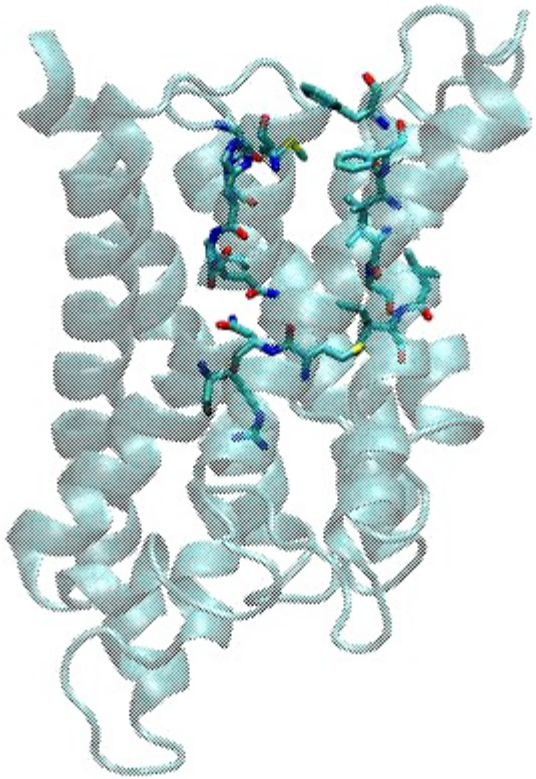






ID	EC50 [µM]	Max. inhibition [%]
HTS1	2.7	100
HTS2	0.4	90

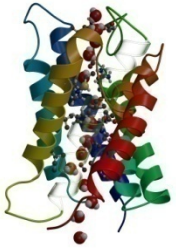
4x HTS2
20 simulations à 100ns
4 intracellular associations
1 extracellular association

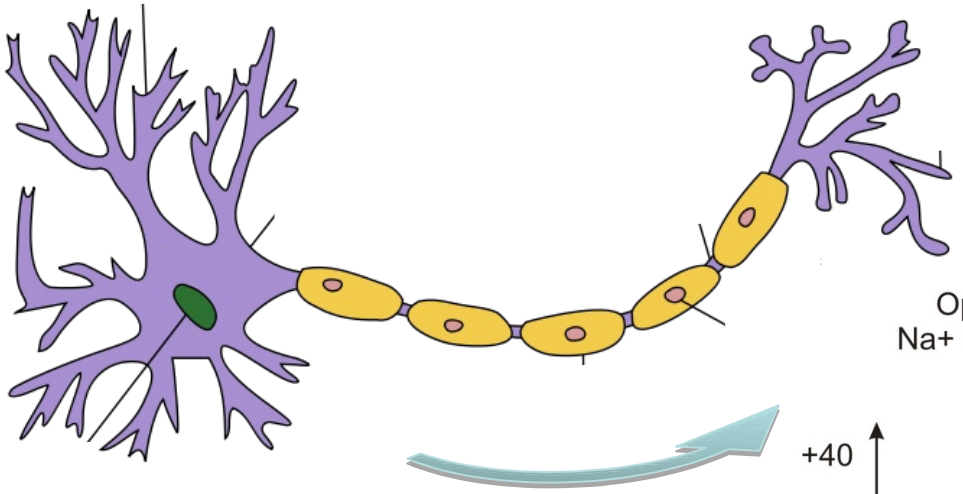


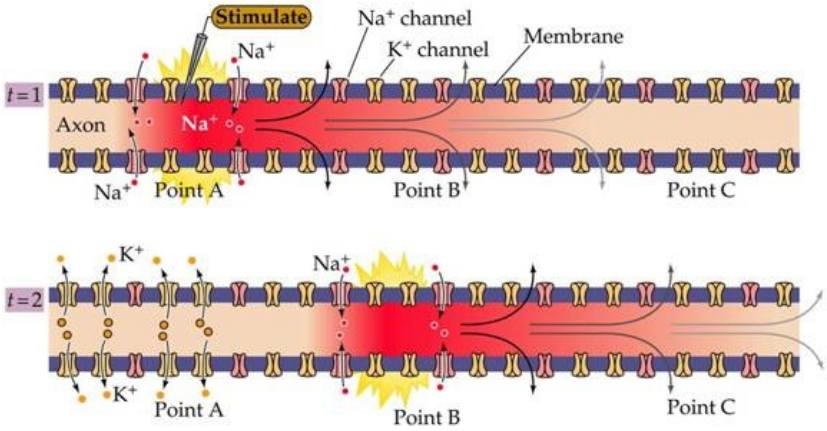
Wacker et al. Mol. Memb. Biol, 30 (2013)

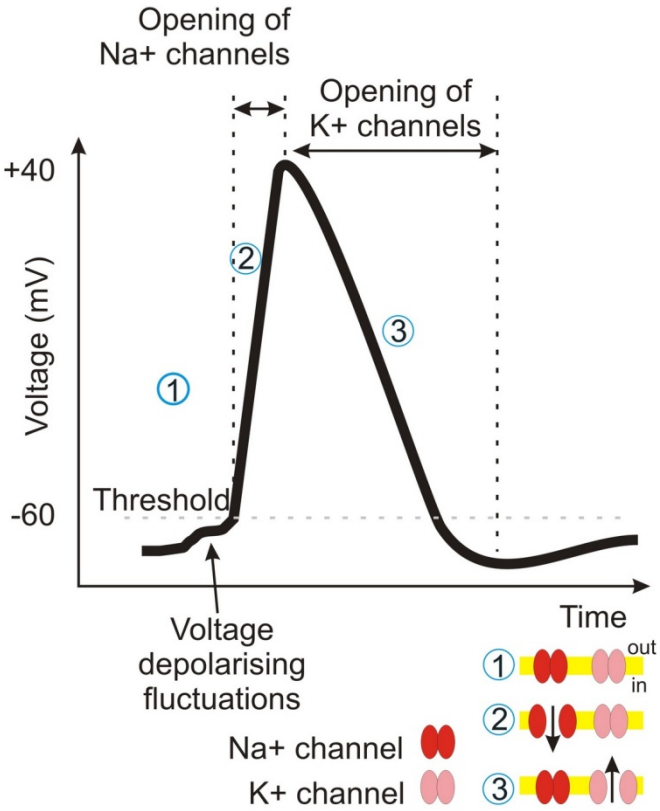
K^+ permeation through potassium channels

Ion Channels in Excitable Cells



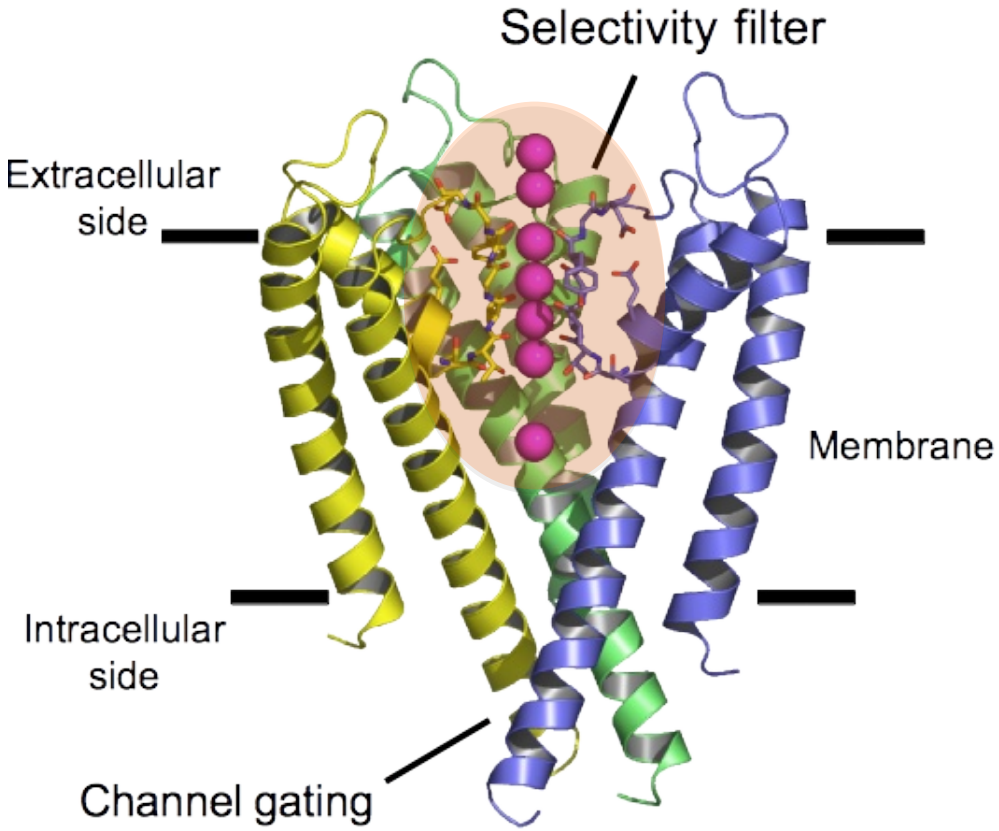






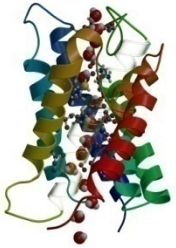
Images from US National Cancer Institute / McGill University

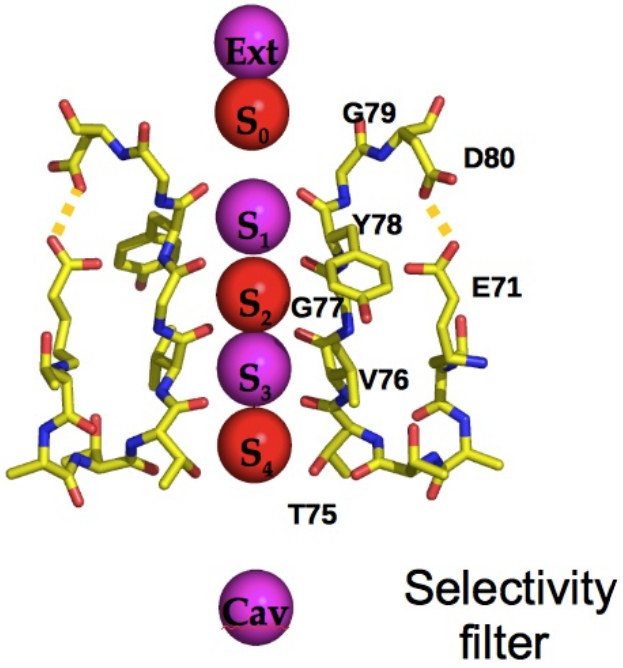
Mechanism of Selective Potassium Translocation across Membranes



Potassium channels

Mechanism of Selective Potassium Translocation across Membranes



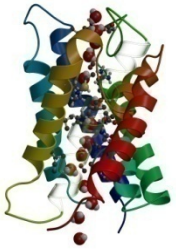


Potassium channel SF:

- combines strong selectivity for K^+ with impressive efficiency
- catalyses transmembrane ion transfer to ~ 10^8 ions per second

→ ~ diffusion limited ion conduction

Mechanism of Selective Potassium Translocation across Membranes



Chemistry of ion coordination and hydration revealed by a K^+ channel–Fab complex at 2.0 Å resolution

Yufeng Zhou, João H. Morais-Cabral*, Amelia Kaufman & Roderick MacKinnon

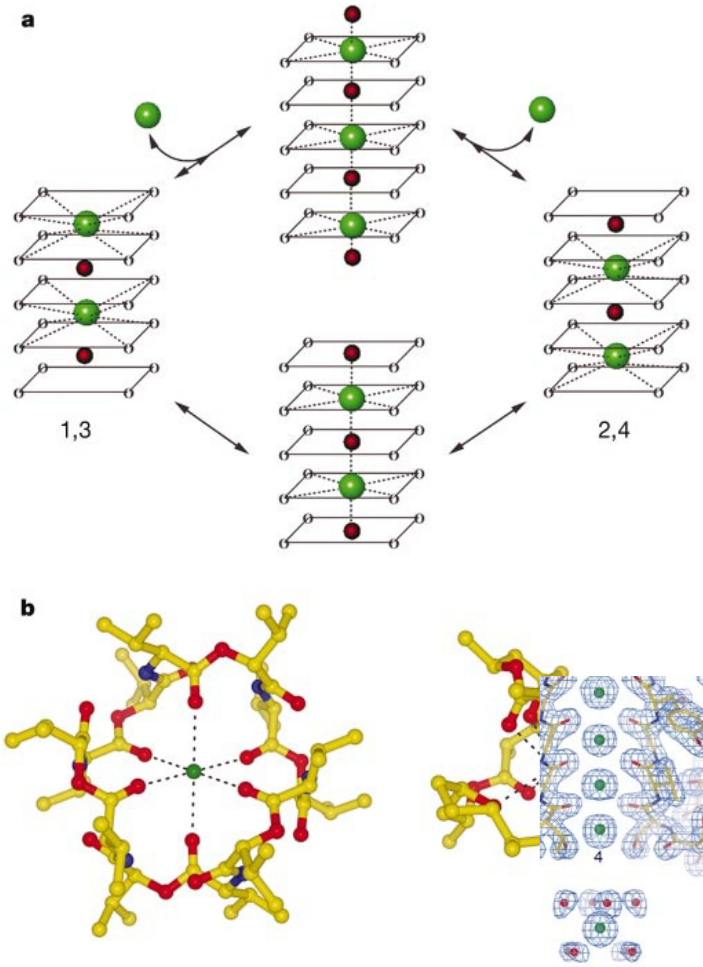
Howard Hughes Medical Institute, Laboratory of Molecular Neurobiology and Biophysics, Rockefeller University, 1230 York Avenue, New York, New York 10021, USA

Energetic optimization of ion conduction rate by the K^+ selectivity filter

João H. Morais-Cabral*, Yufeng Zhou & Roderick MacKinnon

Howard Hughes Medical Institute, Laboratory of Molecular Neurobiology and Biophysics, Rockefeller University, 1230 York Avenue, New York, New York 10021, USA

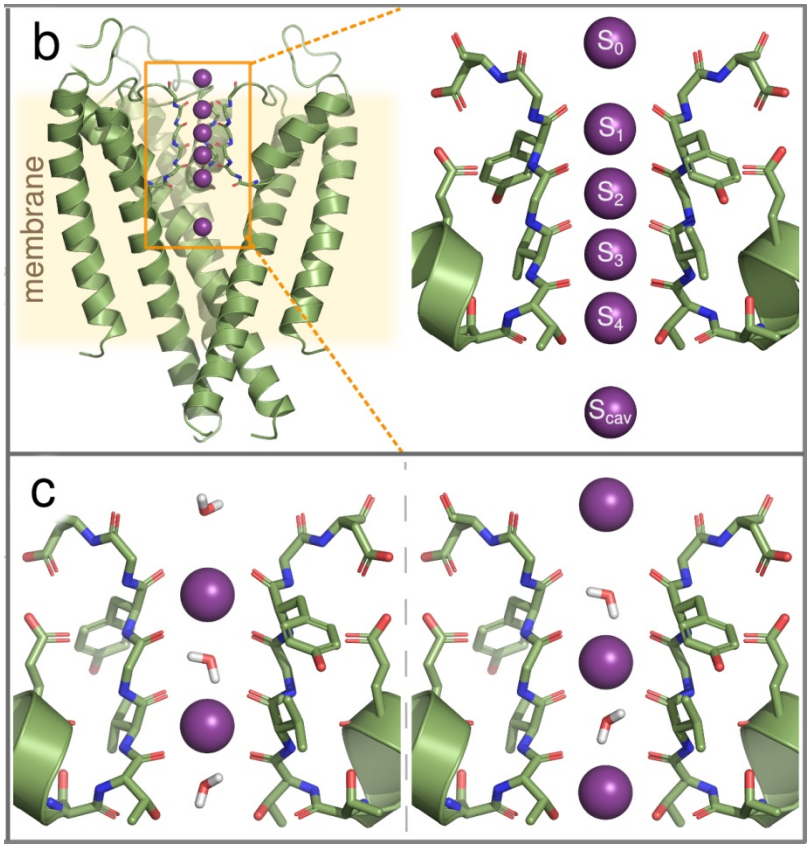
Adjacent peaks in the K^+ electron density profile are separated by about 3.2 Å (Fig. 3b). Potassium ions have a diameter of 2.7 Å, so they could, in principle, fit in the filter side by side, but this would seem to be an unstable binding configuration for electrostatic reasons. A survey of a database of small-molecule structure (Cambridge Crystallographic Data Centre, http://www.ccdc.cam.ac.uk) showed us that two K^+ ions only very rarely occur with a separation distance of less than 3.5 Å. Therefore, although K^+ ions

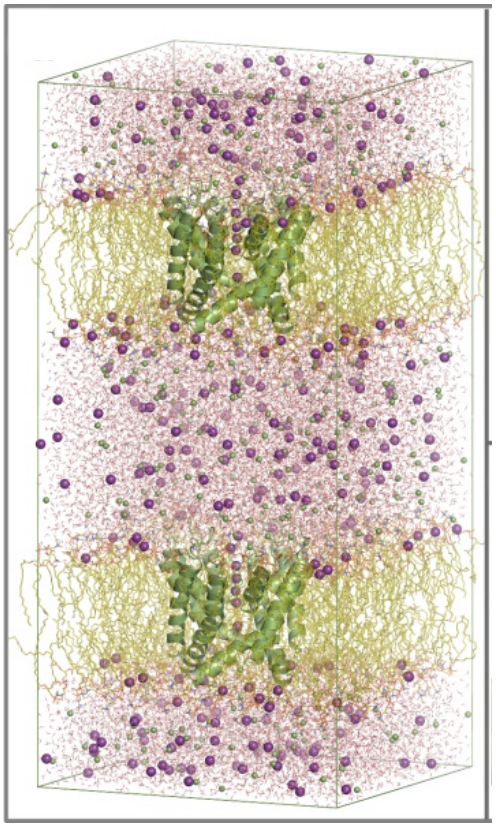


Nature, 2001; R. MacKinnon Nobel lecture, 2003

prokaryotic K^+ channel KcsA

Molecular mechanism of Potassium Permeation

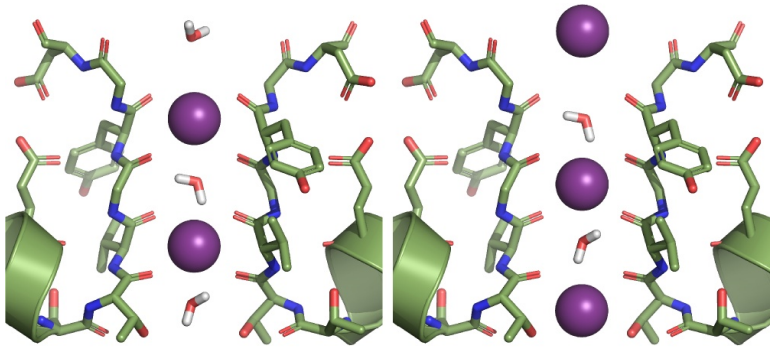




Open state structures of KcsA have recently become available

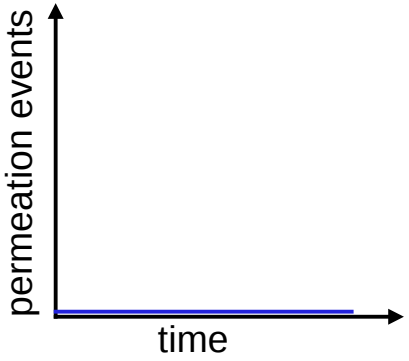
Computational electrophysiology Molecular Dynamics

How does the Selectivity Filter Conduct Ions?

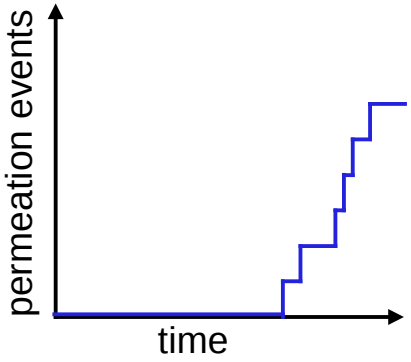


Simulation

most of the time

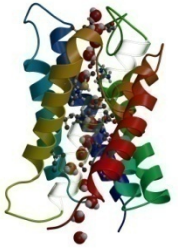


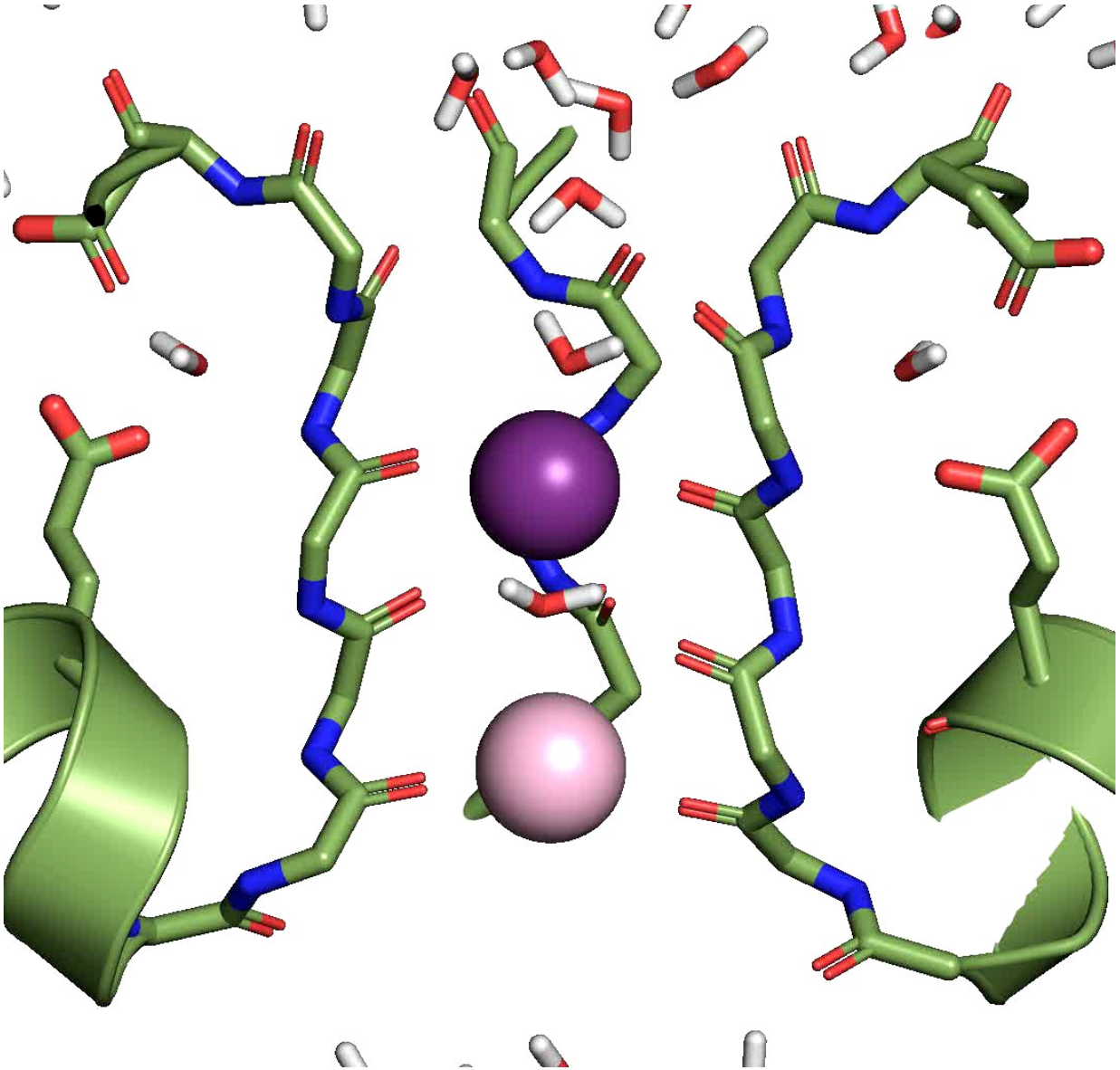
rarely



Köpfer et al. Science, 346 (2014)

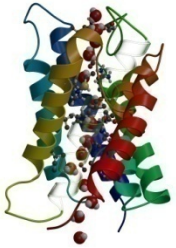
Potassium Permeation Through Open State KcsA

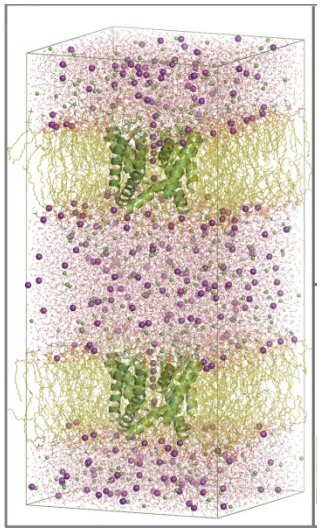




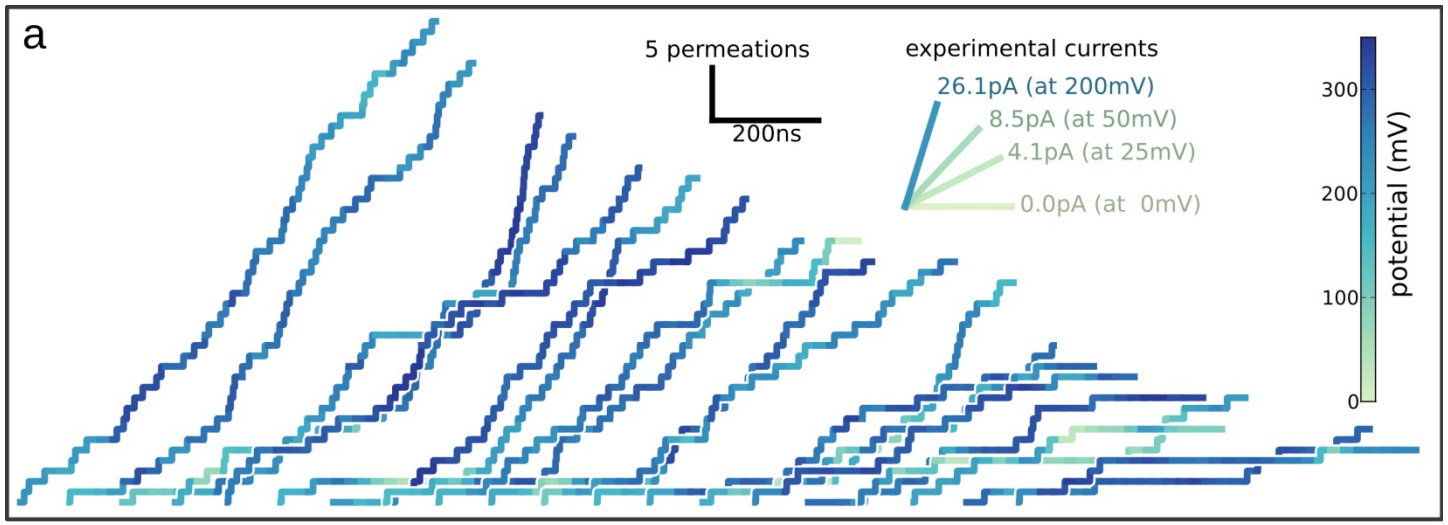
Köpfer et al. Science, 346 (2014)

Potassium Permeation Through Open State KcsA





Ion current elicited by K^+ gradient

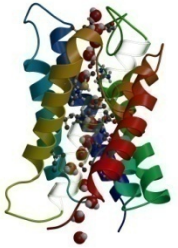


Accumulated ion permeation events on a microsecond timescale (>1500 individual permeation events)

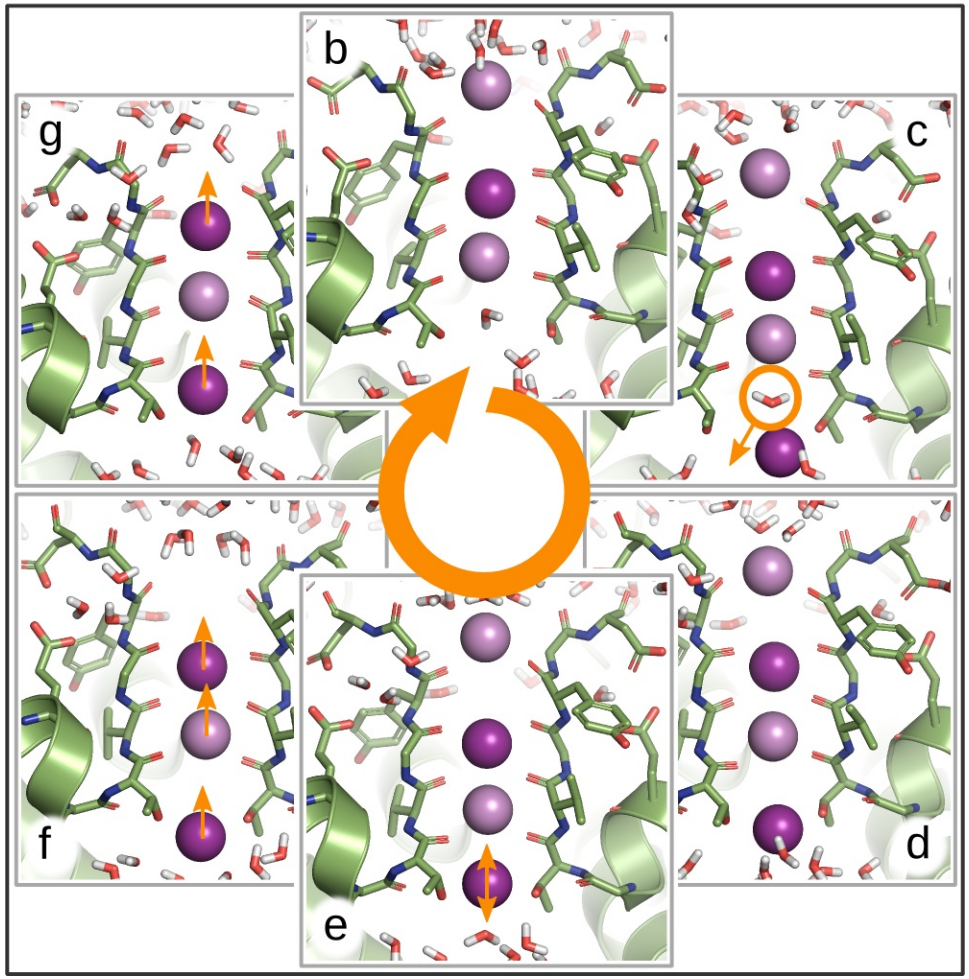
Conductance agrees with experiment within experimental error

Köpfer et al. Science, 346 (2014)

Mechanism of Diffusion-controlled Potassium Permeation



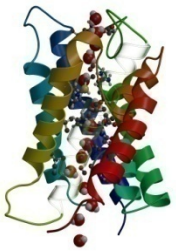
Detailed analysis of ion conduction mechanism



Same mechanism is seen in MthK and Kv1.2 channels

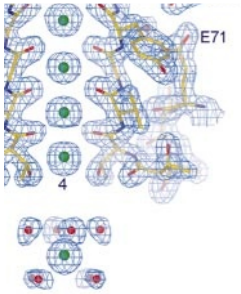
Köpfer et al. Science, 346 (2014)

Experimental Insights



Crystallography: Tim Gruene/George Sheldrick, Göttingen

		KcsA, PDB ID: 1r3j refinement of Tl^+			MthK, PDB ID: 3ldc refinement of K^+	
		res. id	abs. occ.	rel. occ.	res. id	abs. occ.
Binding site	S_1	C401	1.02 ± 0.04	1.0	A1	0.92 ± 0.07
	S_2	C402	0.93 ± 0.03	0.9	A2	0.80 ± 0.07
	S_3	C403	0.92 ± 0.04	0.9	A3	1.00 ± 0.09
	S_4	C404	0.99 ± 0.04	1.0	A4	1.00 ± 0.09



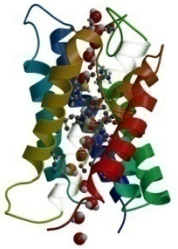
Occupancies refined against anomalous data

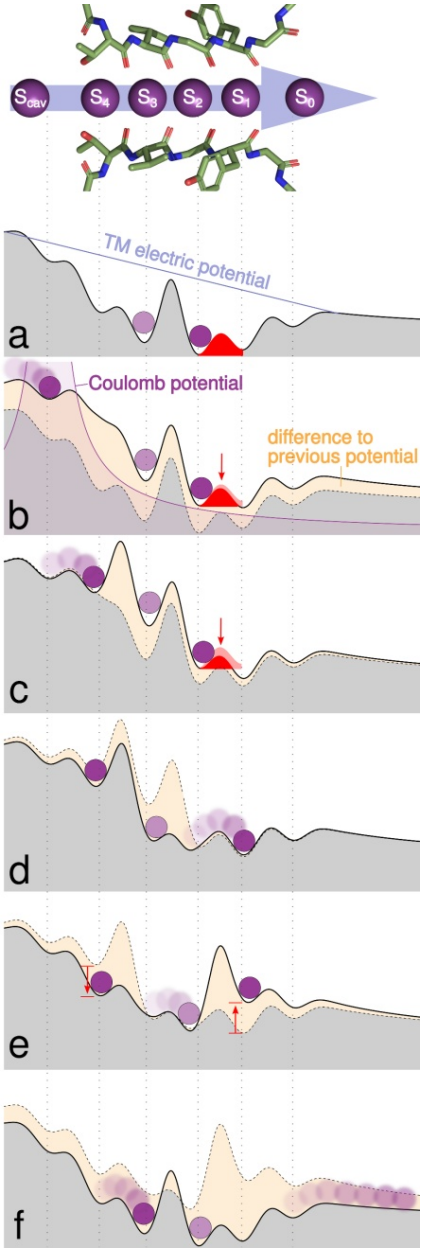
PDB IDs 1R3J (KcsA, Tl^+), 3LDC (MthK, K^+), 2QKS (Kir3.1, K^+) :

Tl^+, K^+: 4x ~full occupancy

Köpfer et al. Science, 346 (2014)

Mechanism of Selective Potassium Translocation across Membranes





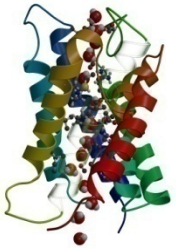
Köpfer et al. Science, 346 (2014)

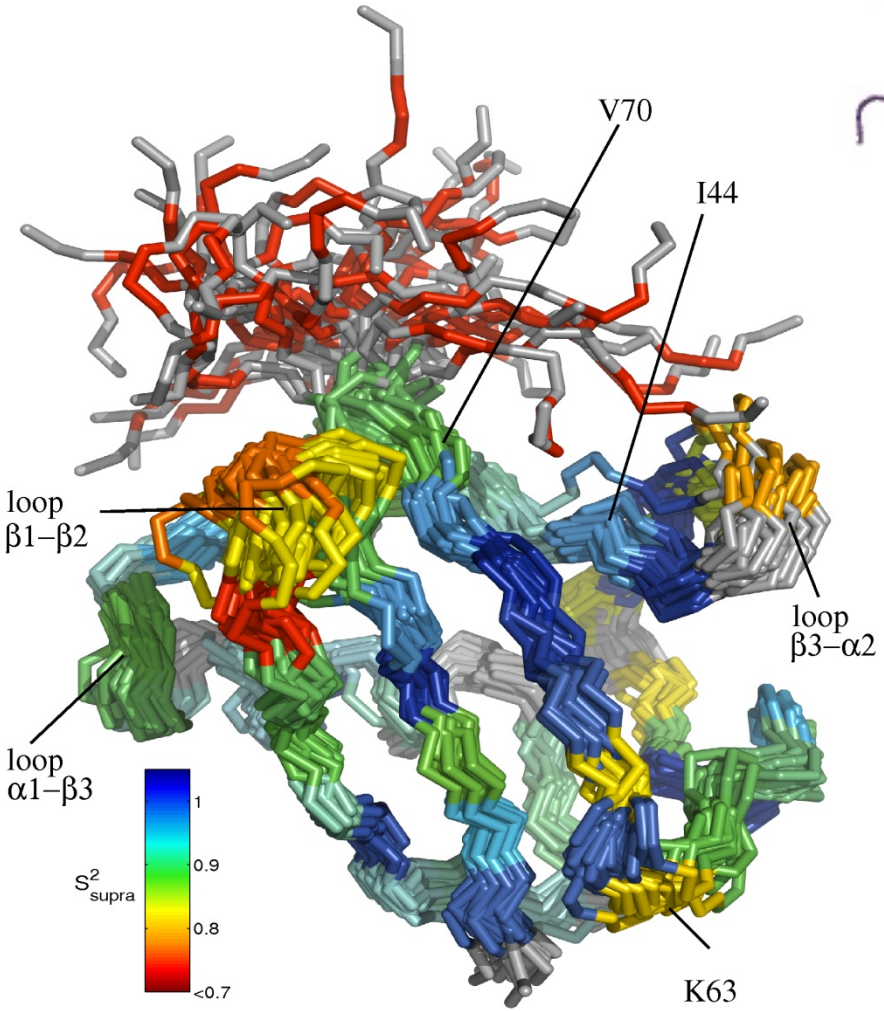
Molecular dynamics in protein recognition and design

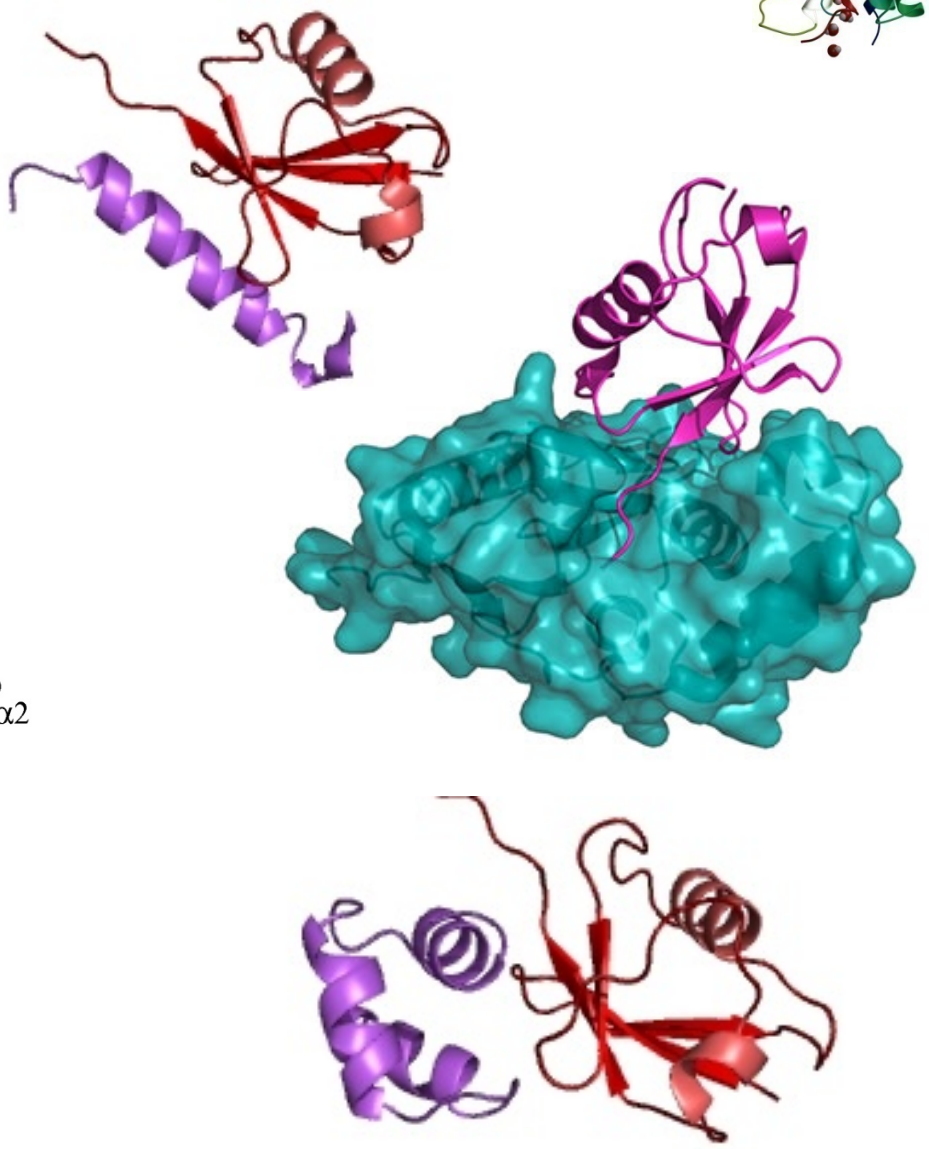
Molecular dynamics in protein recognition and design: The case of ubiquitin

gcq#401: "Ubiquitin's just a rock" (Berk Hess).

Ubiquitin binds to many partners in different conformations

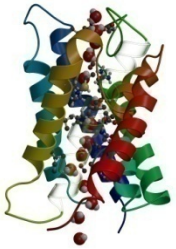


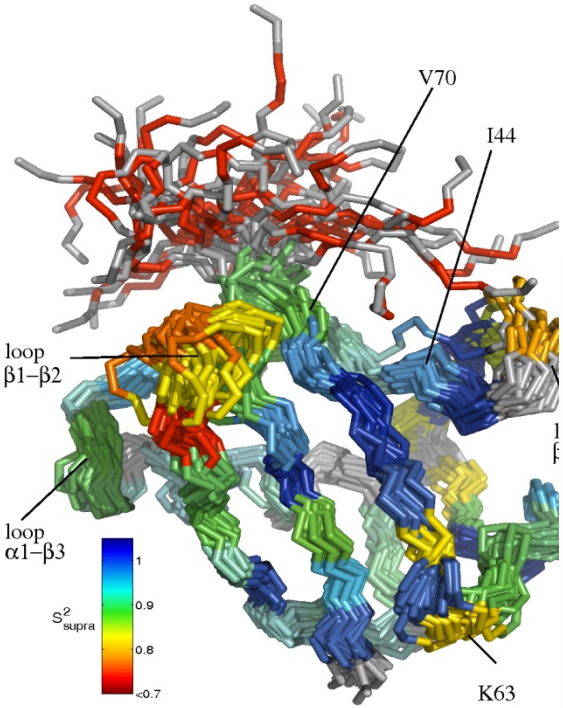


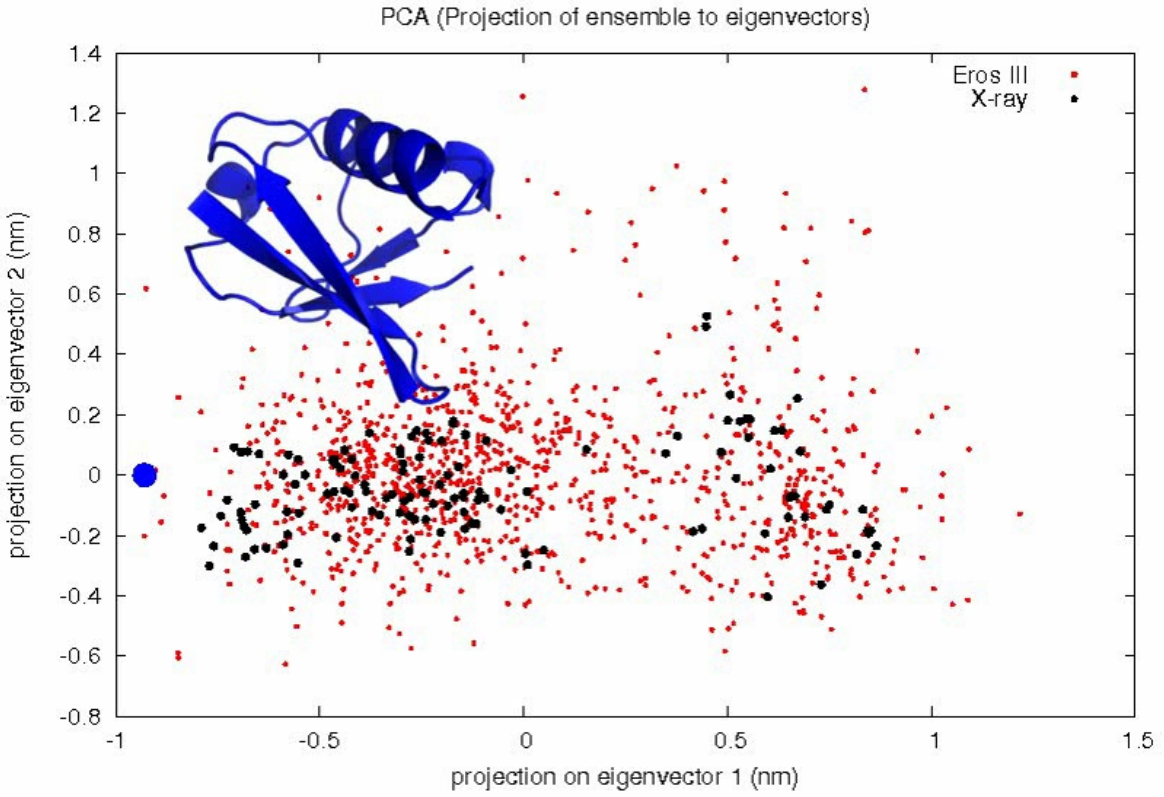


O. F. Lange, N.A. Lakomek, et al., *Science*, **320**, 1471-1475 (2008)

Ubiquitin complexed and free in solution

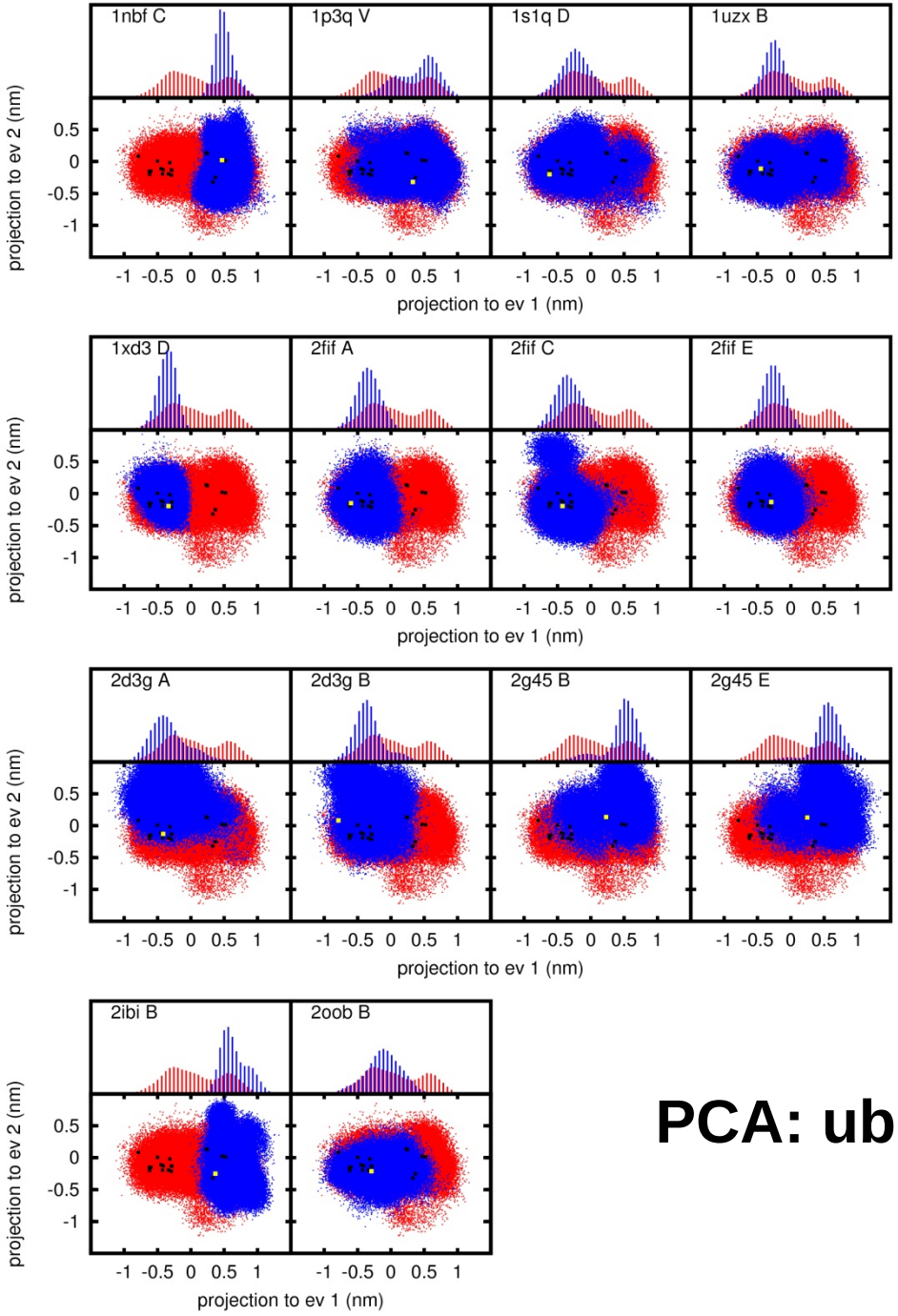






Overlap of bound and unbound ubiquitin ensembles suggests conformational selection

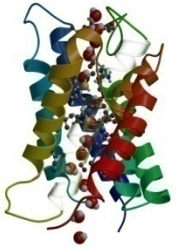
O. F. Lange, N.A. Lakomek, et al., *Science*, **320**, 1471-1475 (2008)

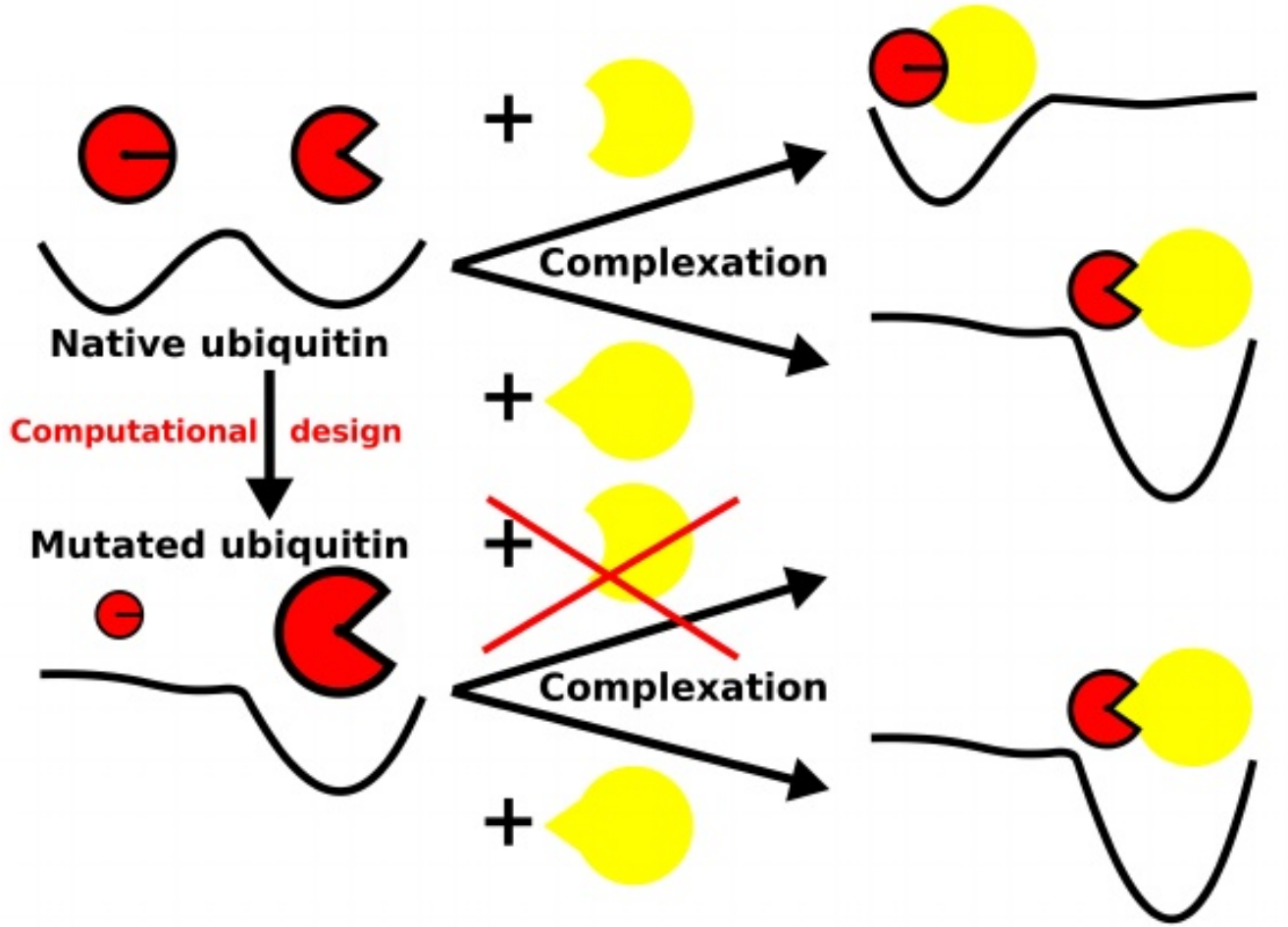


PCA: ubiquitin free vs complexed

Peters and de Groot. PLoS Comp. Biol (2012)

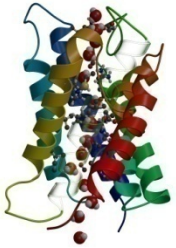
Ubiquitin mutants with altered affnity

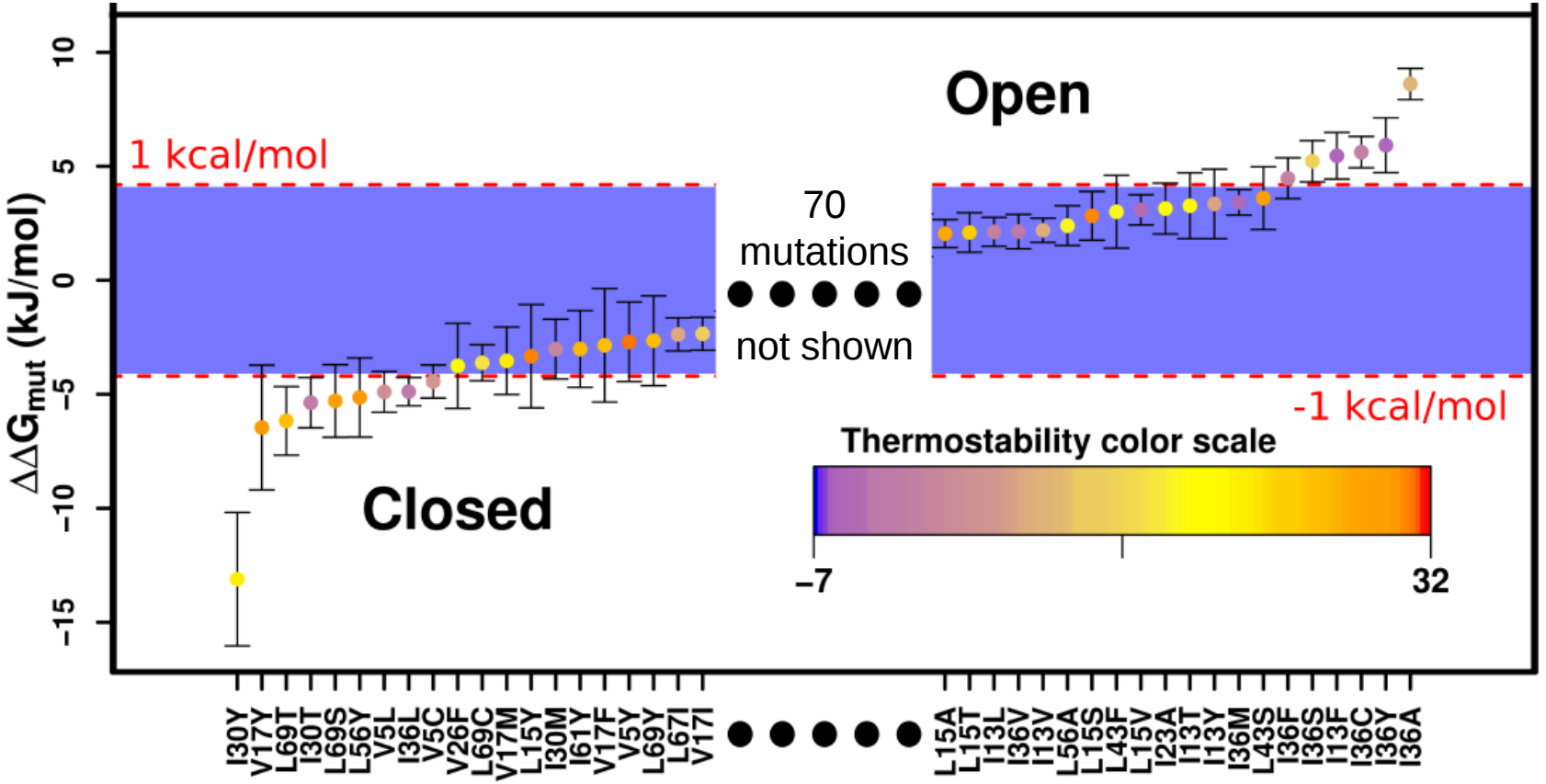




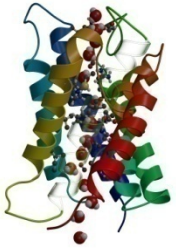
Peters et al. Angewandte Chemie (2014)

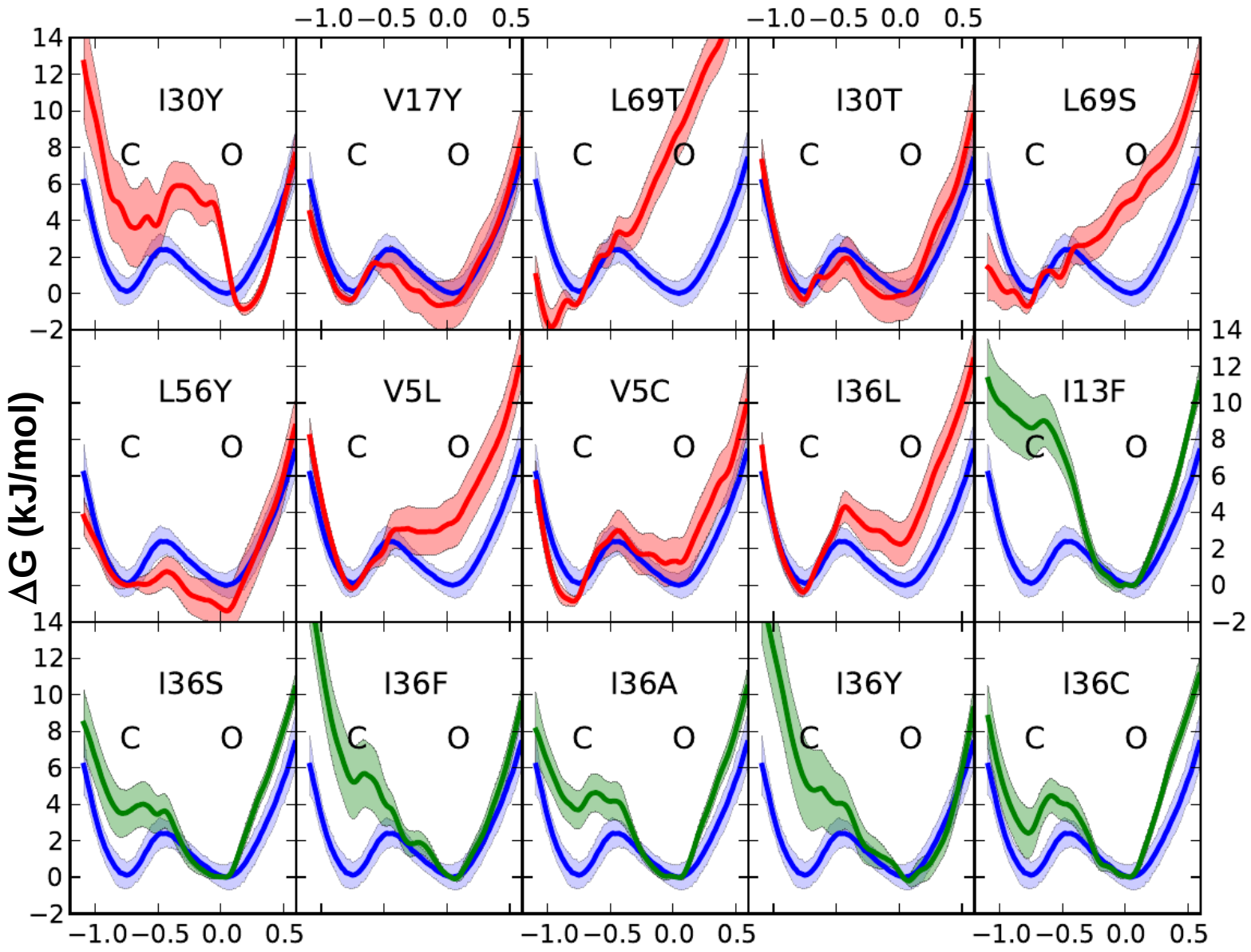
Alchemical screening of 112 mutants





Validation of ubiquitin mutants by umbrella sampling





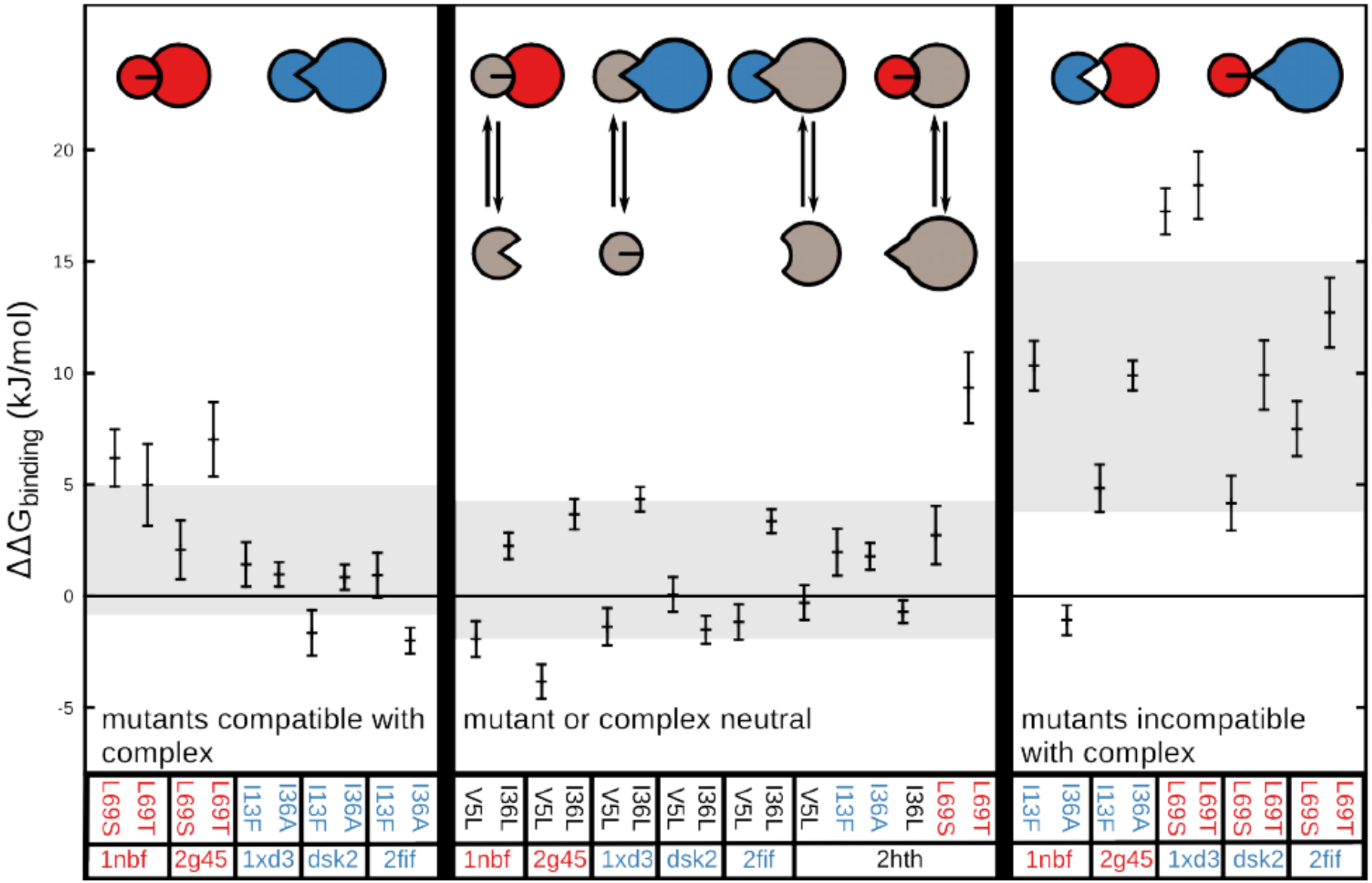
WT

closed stabilising

open stabilising

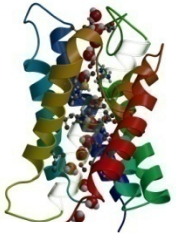
Peters et al. Angewandte Chemie (2014)

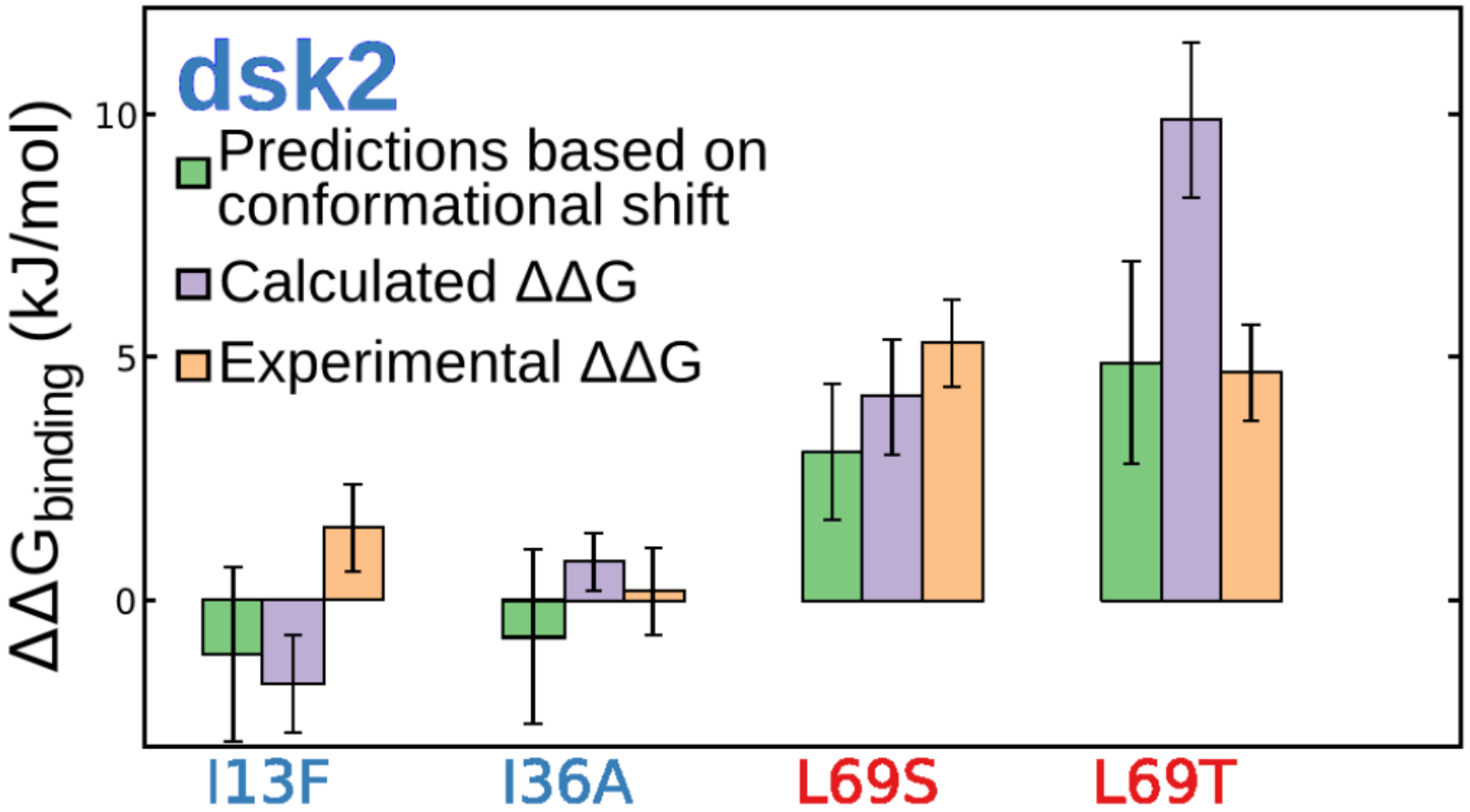
Complex formation of ubiquitin mutants



Peters et al. Angewandte Chemie (2014)

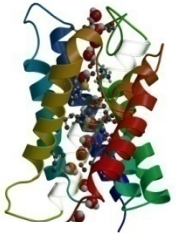
Complex formation of ubiquitin mutants

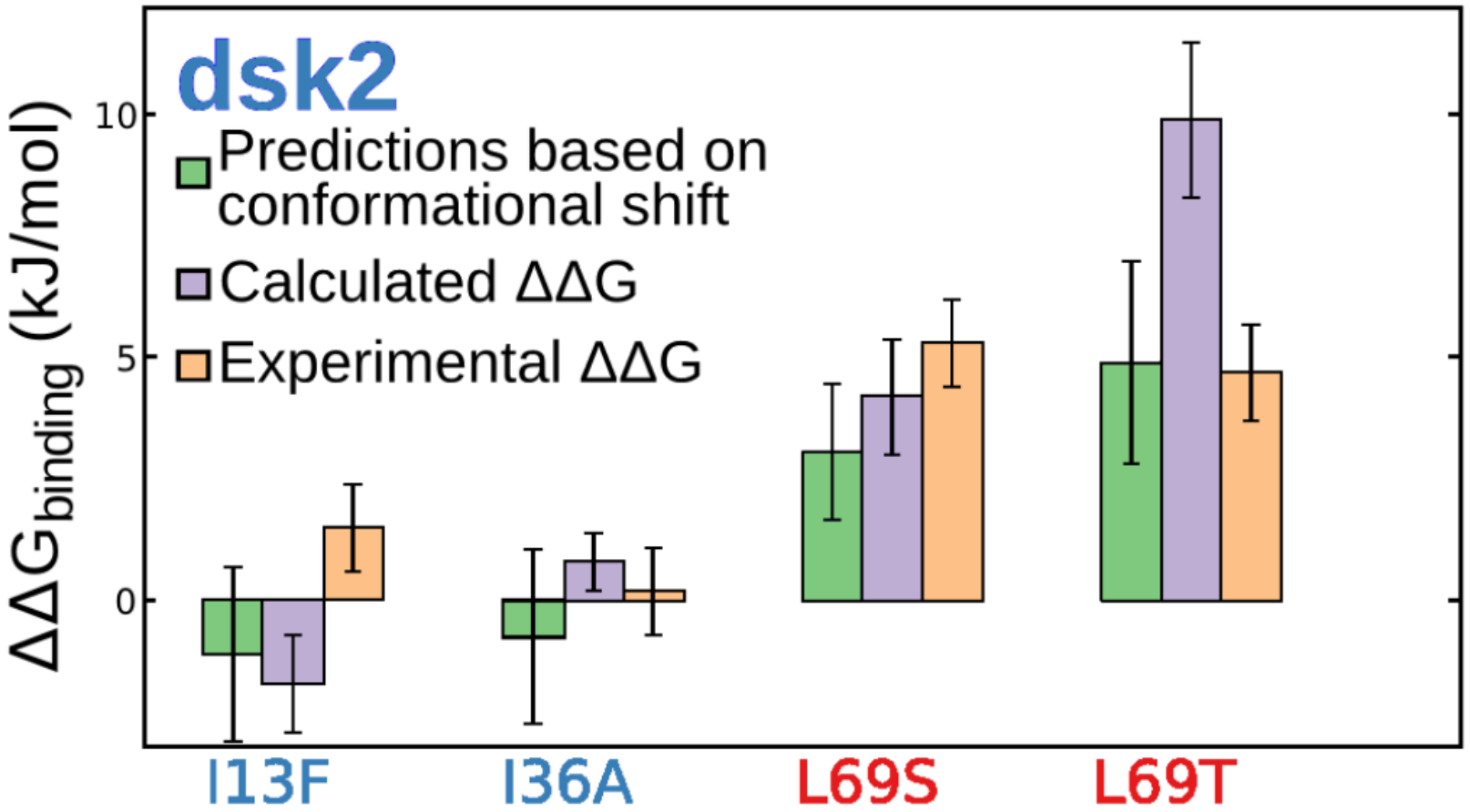




Peters et al. Angewandte Chemie (2014)

Complex formation of ubiquitin mutants





→ **Conformational shift induces change in function**

Peters et al. Angewandte Chemie (2014)

Team:

Water channels:

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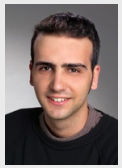
Rodolfo Briones

Guillem Portella (Barcelona)



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Marina Benatti
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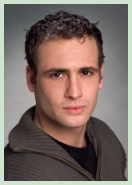

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Sabine Flitsch
Eric Beitz
Peter Johnson
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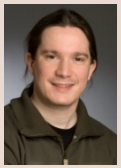
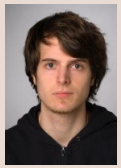
Deutsche Forschungsgemeinschaft DFG

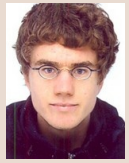
Molecular recognition:



Jan Peters



Dirk Matthes



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Oliver Lange
Christian Griesinger
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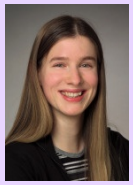
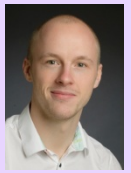
Physical & Chemical Graduate School Göttingen

Ion channels:

Anna Stary (Vienna)



Ulrich Zachariae (Dundee)



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Kornelius Zeth
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Claudia Steinem
Markus Zweckstetter

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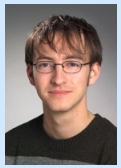
Hadas Leonov

Colin Smith

Martin Vesper



Axel Munk
Robert Tampe
Christian Griesinger

Alexander von Humboldt Stiftung/Foundation

IMPRS

Positions available!