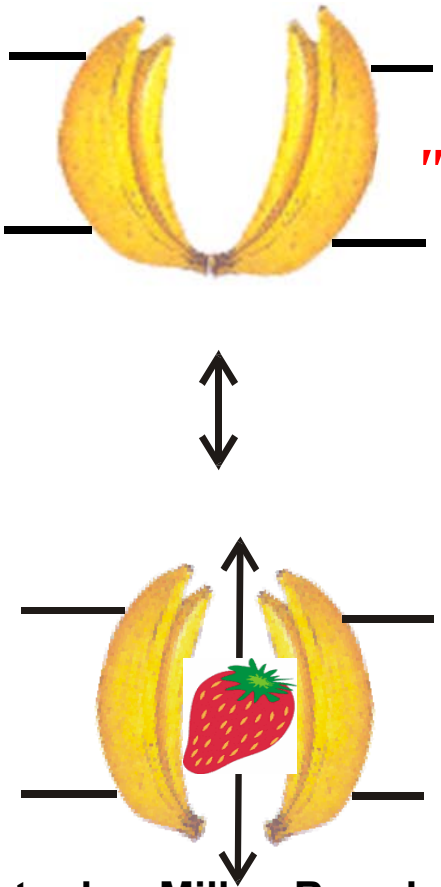
The yin and yang of membrane transport

Channels

diffusive, dissipative, fast

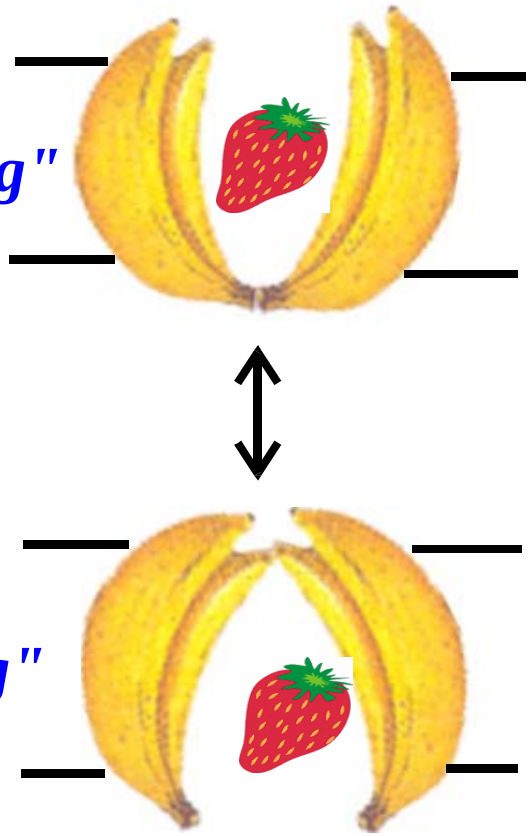


"closed"

"open"

Pumps

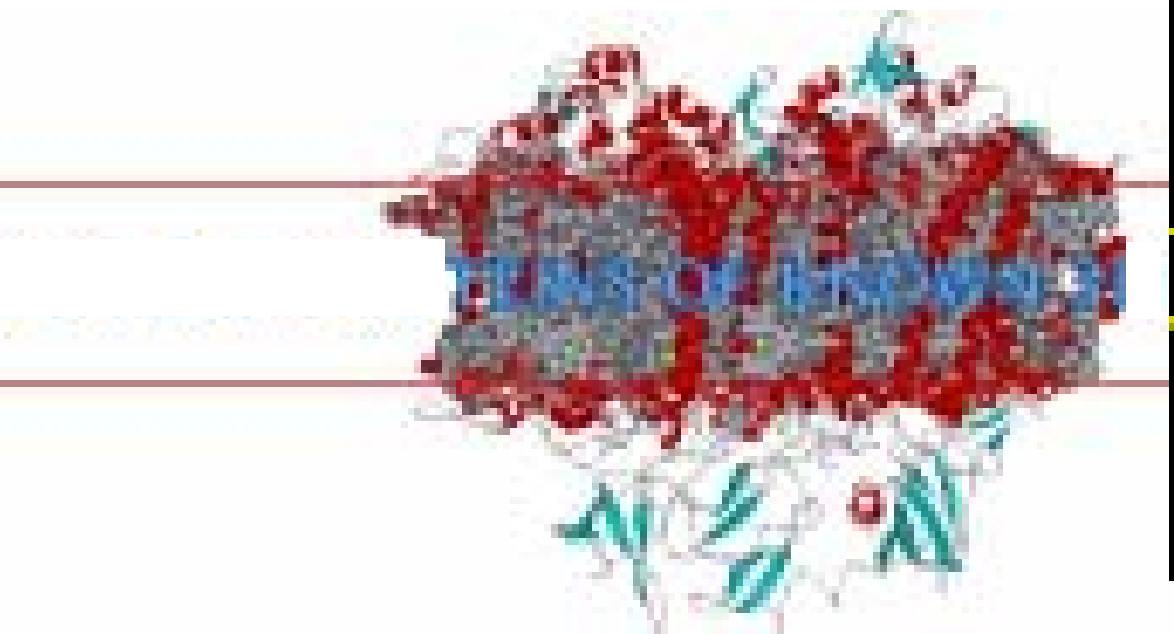
conformational, conservative, slow



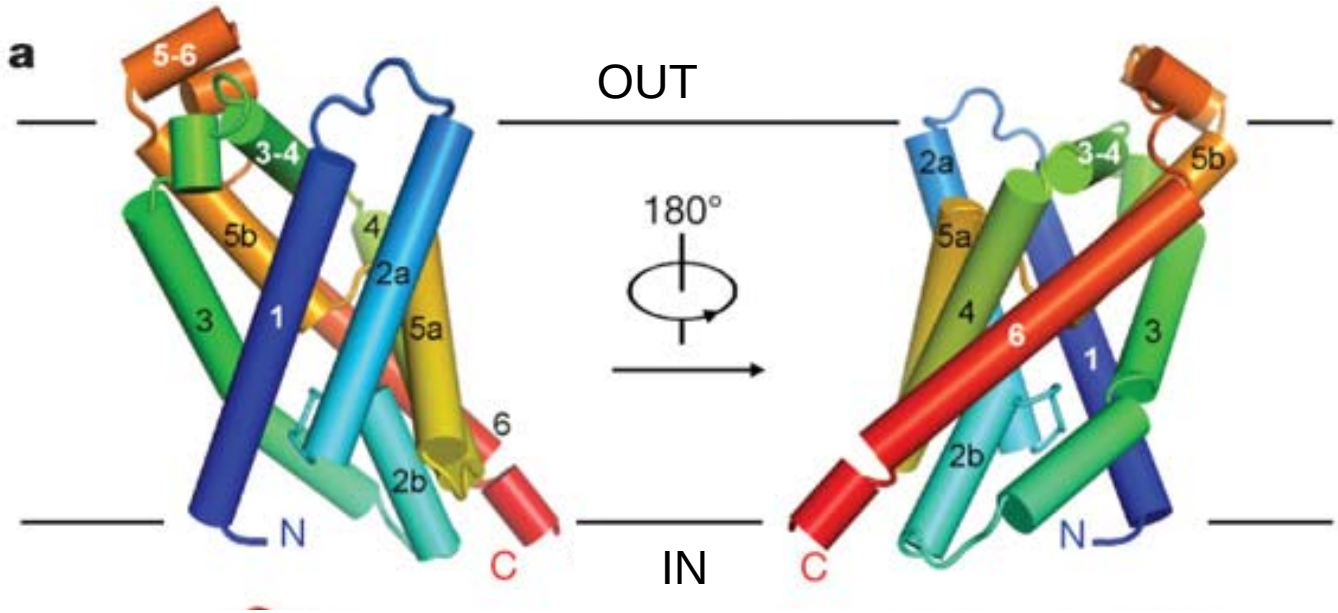
"out-facing"

"in-facing"

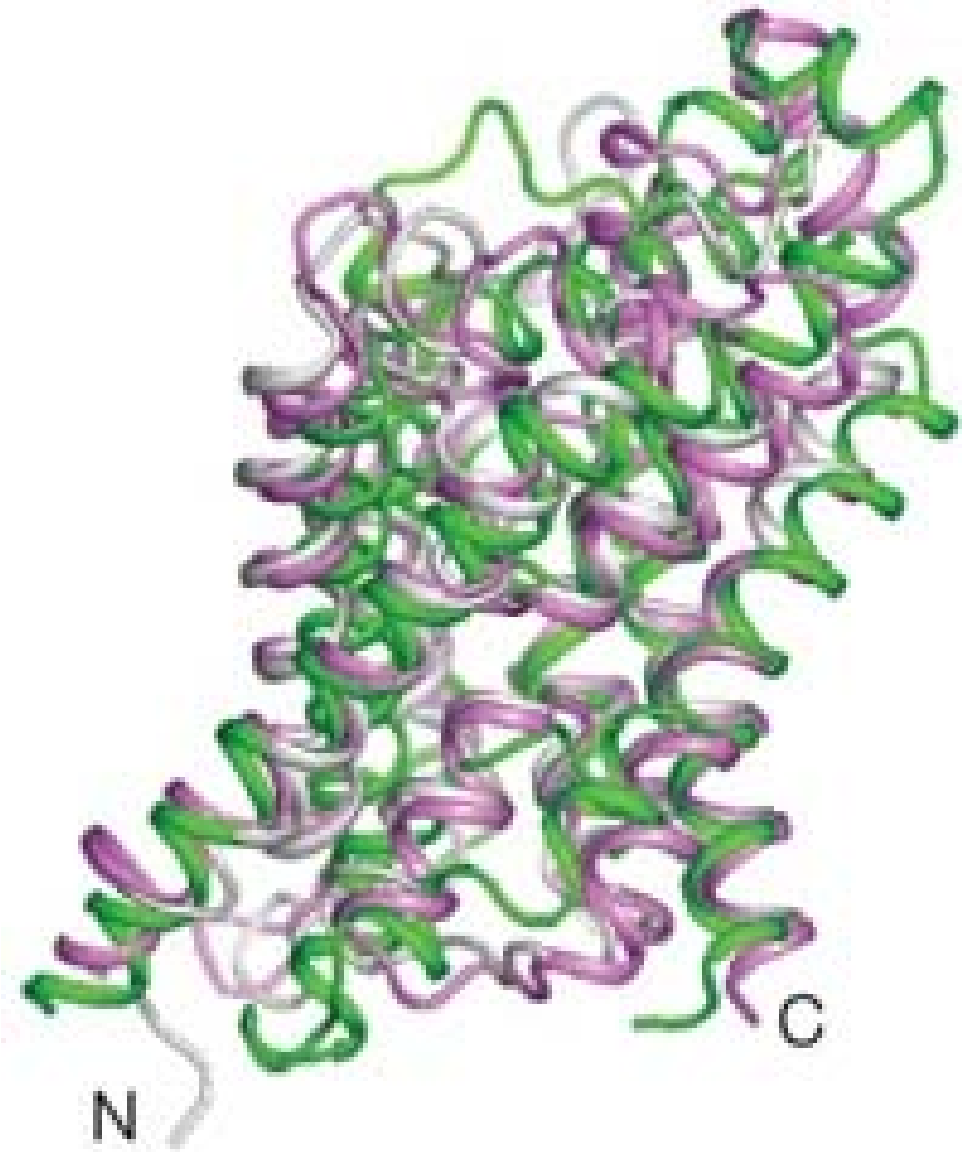
Story #1:
Evolutionary weirdness in membrane protein structures



An example of strange similarity: FocA



Structural alignment: FNT and AqP-family proteins



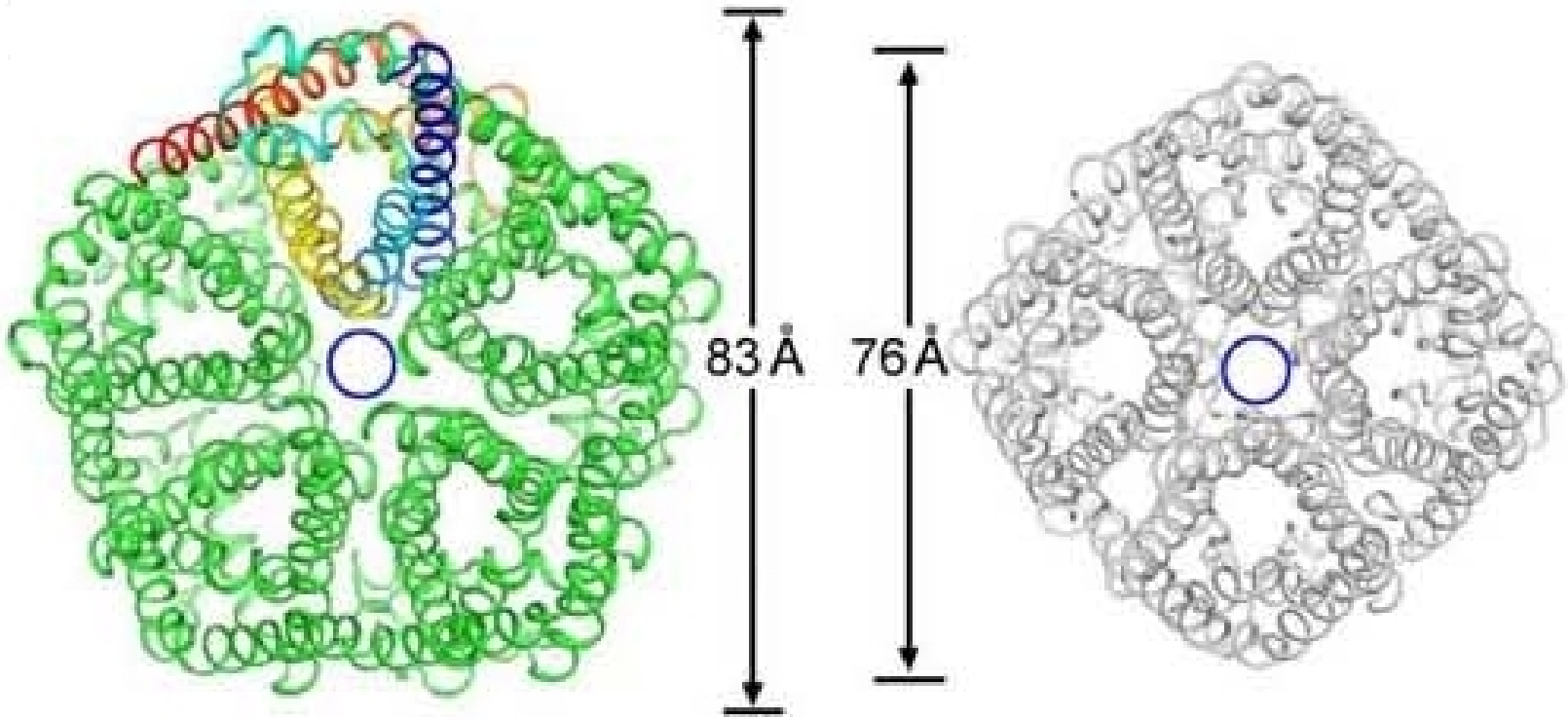
Same structure, different assembly

FocA

Pentamer

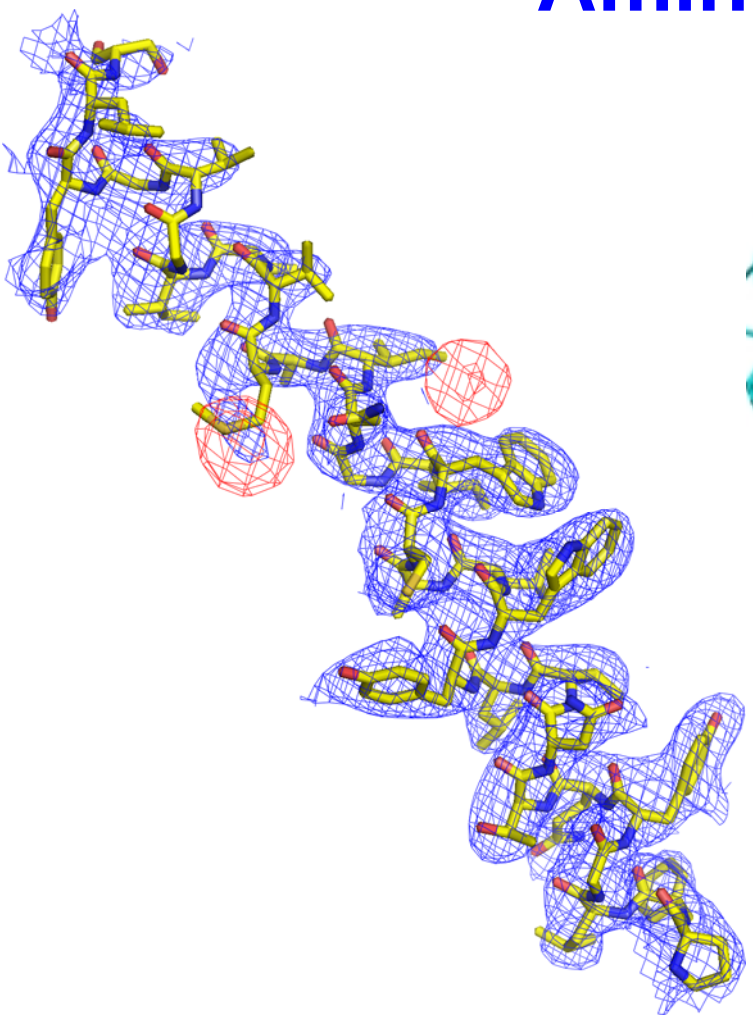
AqP

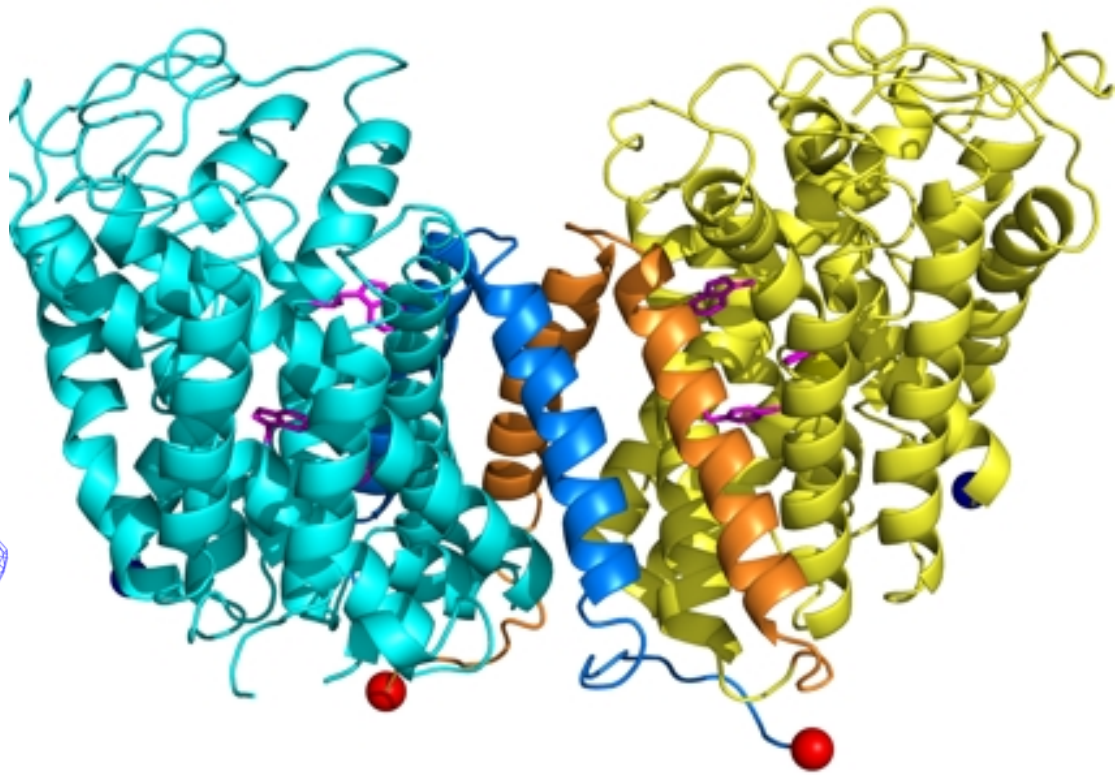
Tetramer



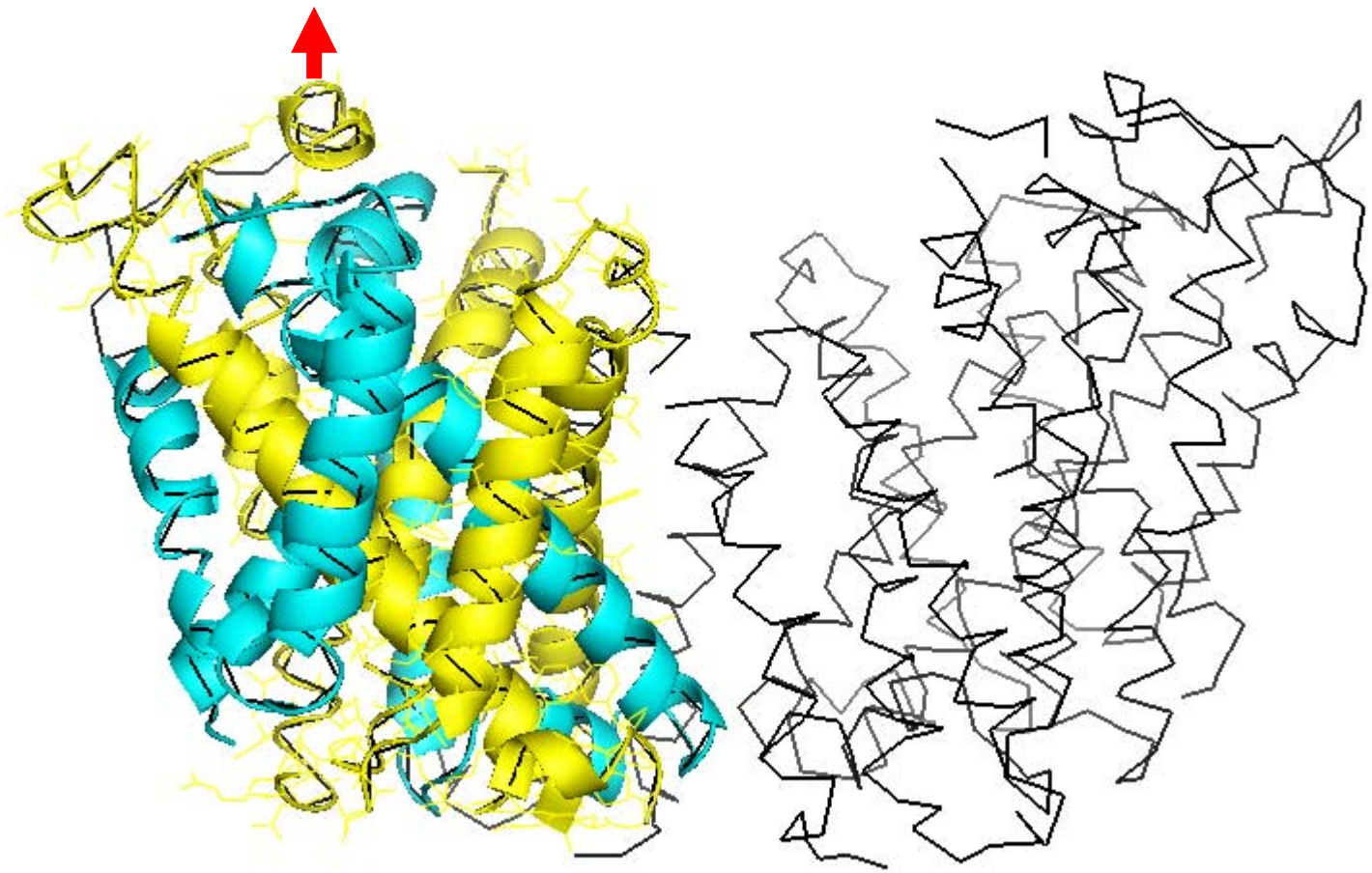
Even stranger - AdiC

Amino acid transporter

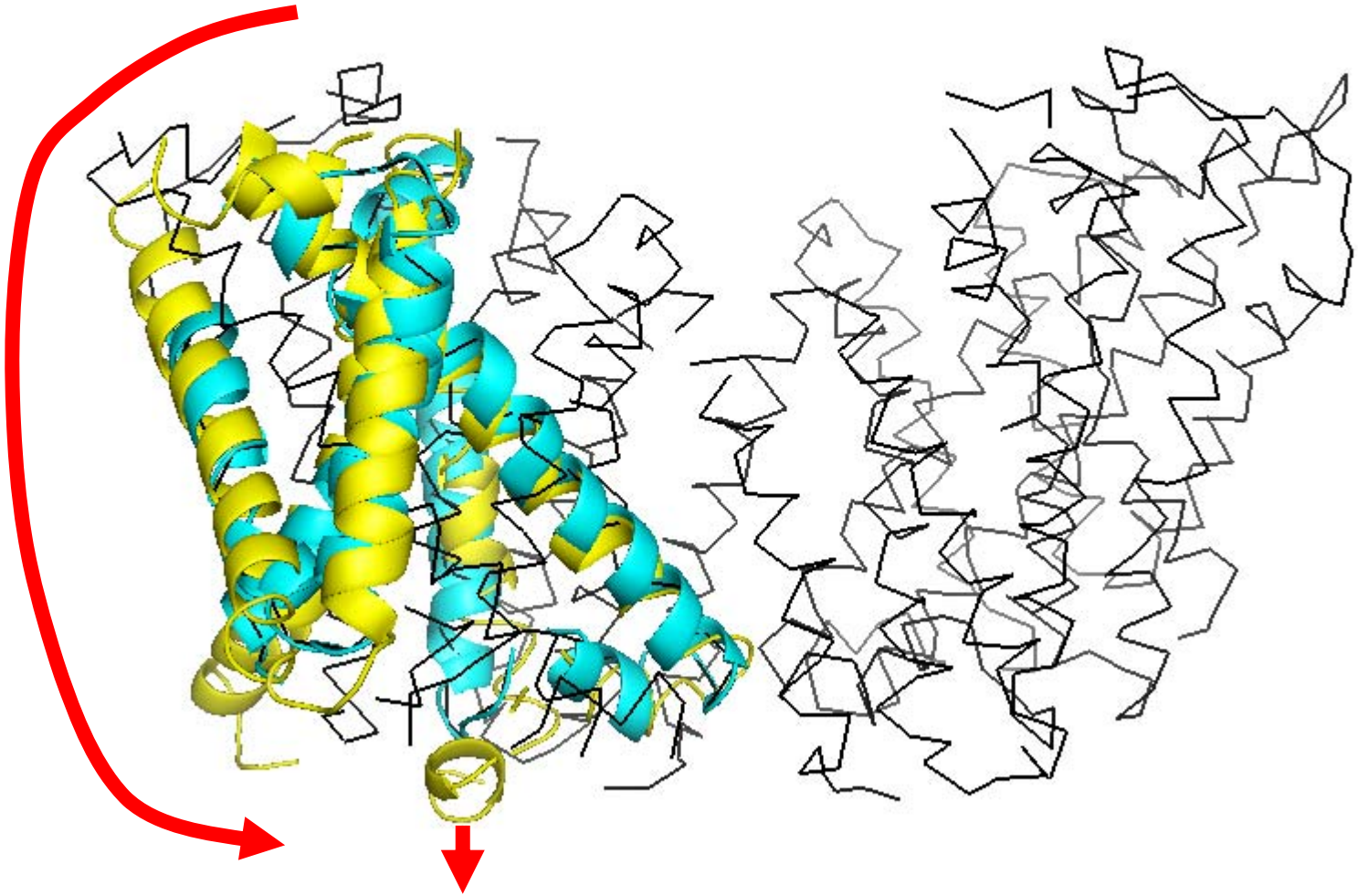




Inverted structural repeat in AdiC:
TM1- 5 / TM 6-10



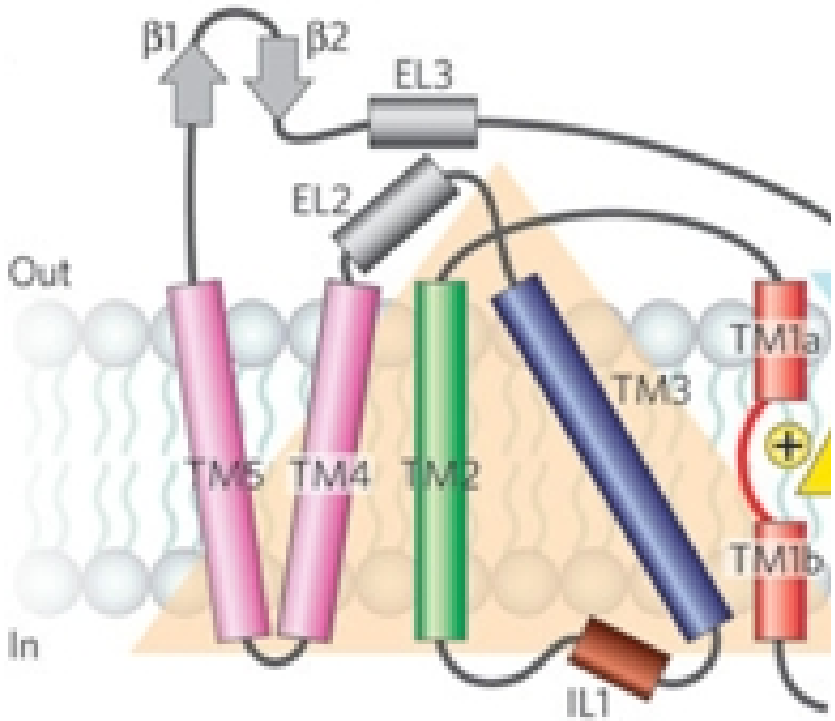
Inverted structural repeat in AdiC:
TM1- 5 / TM 6-10



The LeuT fold

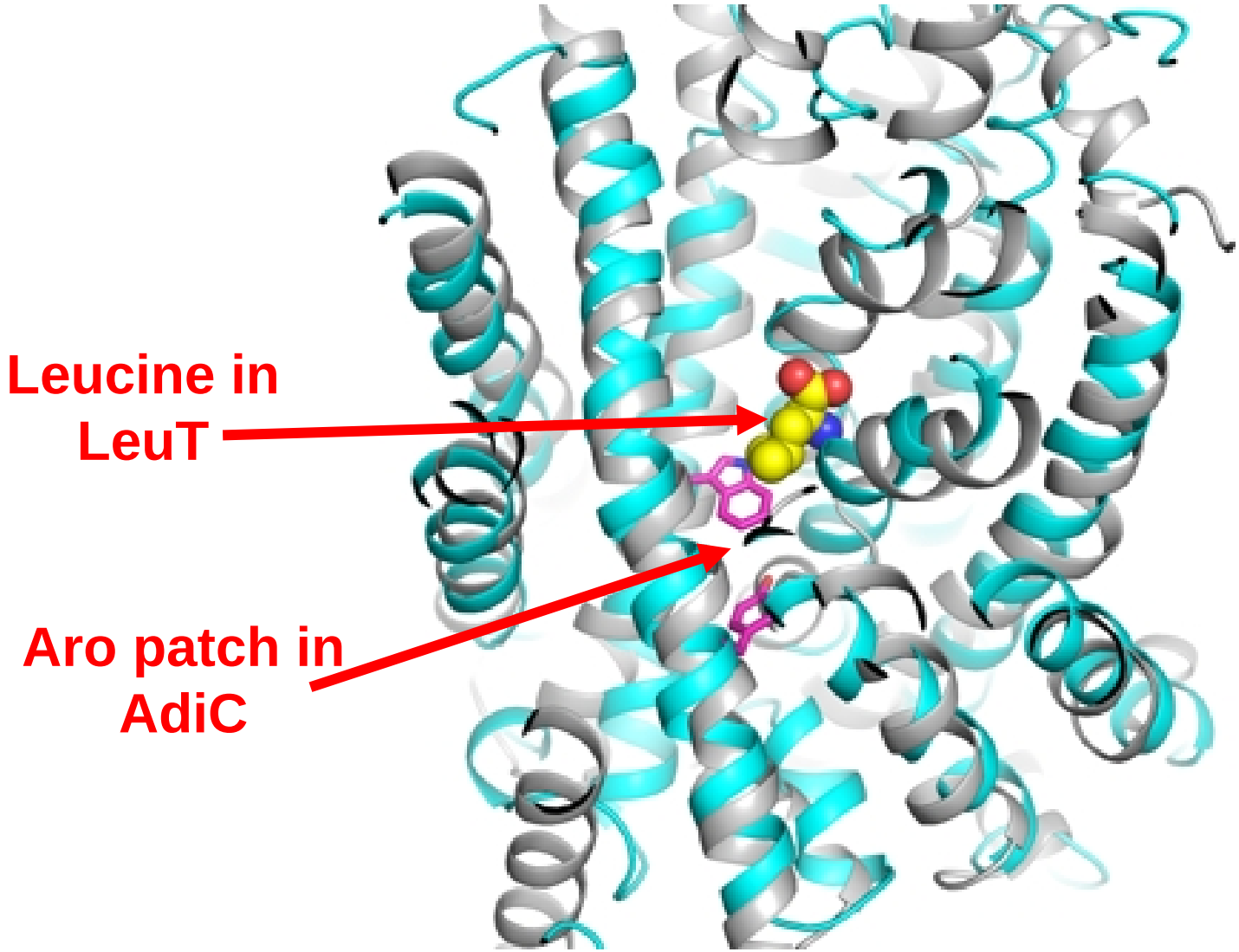
- Gouaux, 2005 - 2009

5 + 7 architecture



TM 1-5

AdiC aligns with LeuT (aerial view)

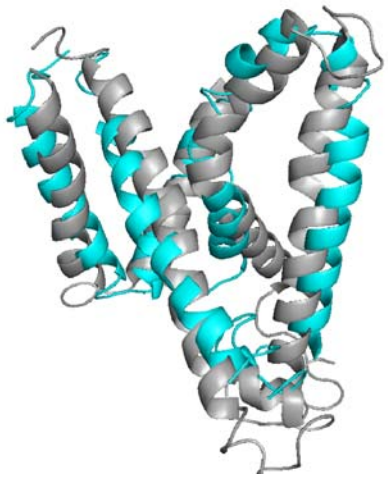


Structural repeat aligned to 4 “unrelated” families

AdiC core aligned with Na^+-coupled symporters:

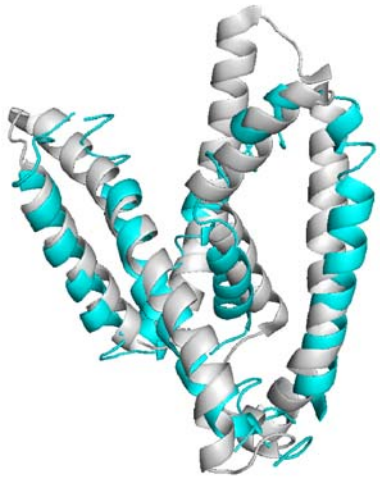
LeuT (NSS)

amino acids



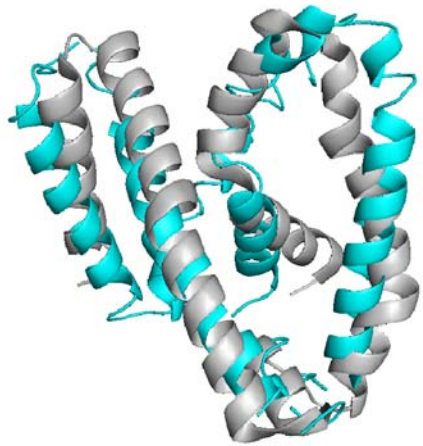
BetP (BCCT)

gly-betaine



Mhp1 (NCS1)

nucleobase



SGLT (SSS)

sugar

Question arising: Is this strange, or not?

Common ancestors or convergent structures?

Special considerations of membrane proteins:

*** More constraints on folding in quasi 2-D**

*** Reduced residue-set for lipid exposure**

*** Electrostatic biases at bilayer surfaces**

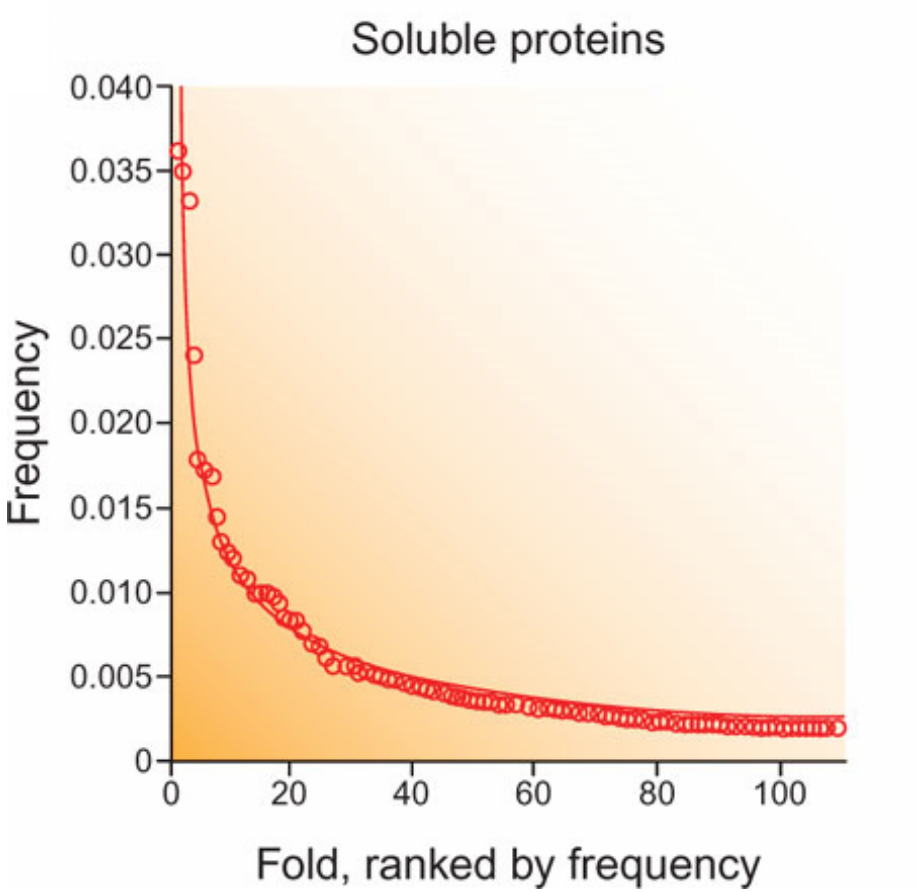
Ergo:

Membrane proteins should be

more susceptible to structural convergence

Structural similarities of non-homologous proteins:

Ranked fold-distribution



…but not so fast…..

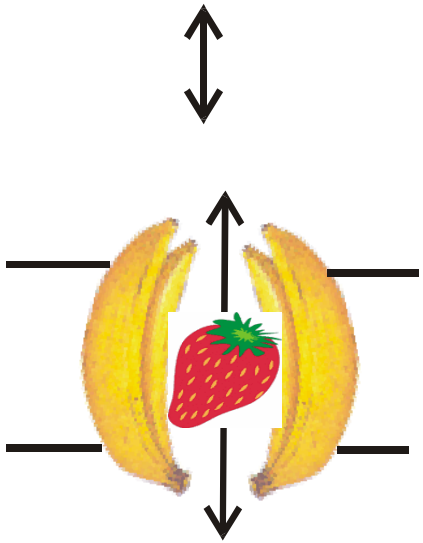
Story #2:
Break a pump – make a channel

The yin and yang of membrane transport

Channels

diffusive, dissipative, fast

"closed"

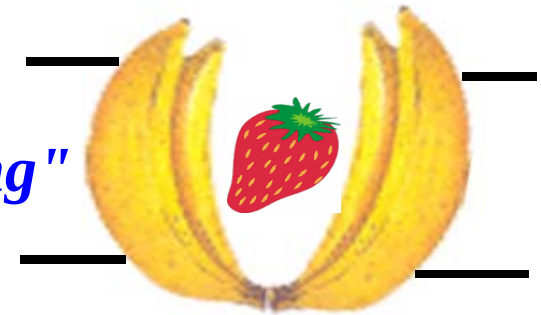


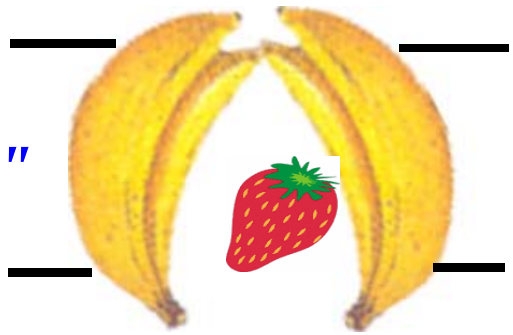
"open"

Pumps

conformational, conservative, slow

"out-facing"

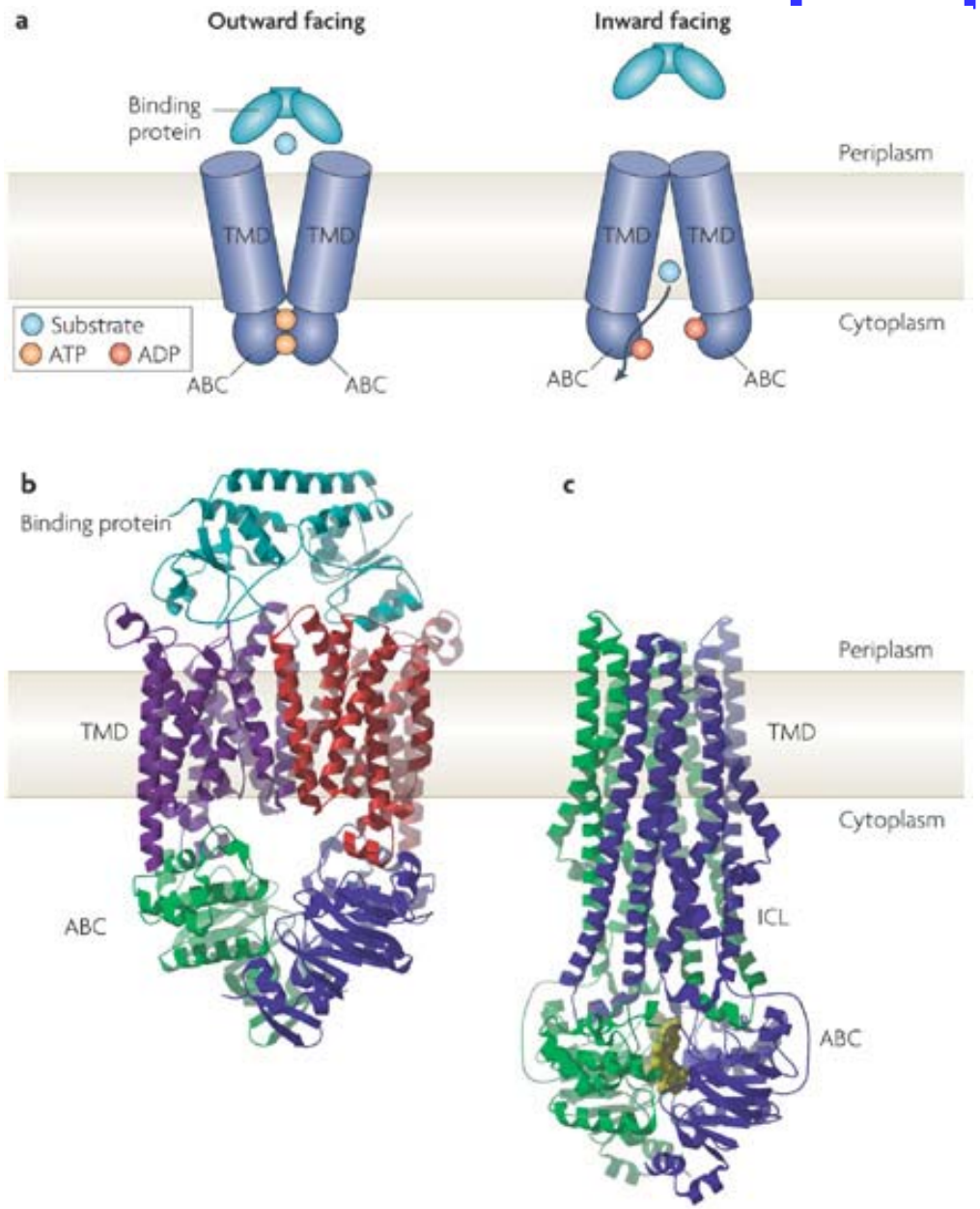




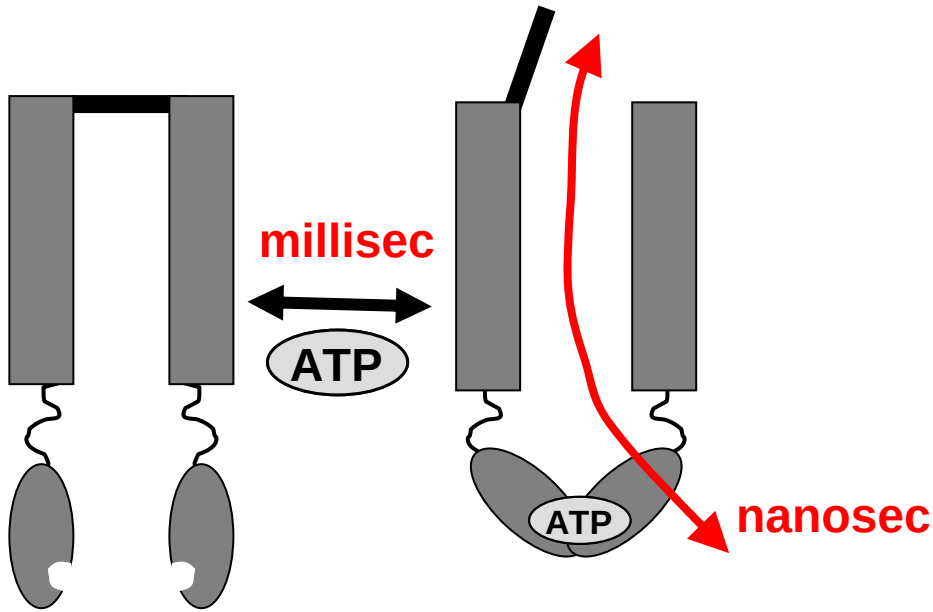
"in-facing"

CFTR: A channel that “should” be a pump

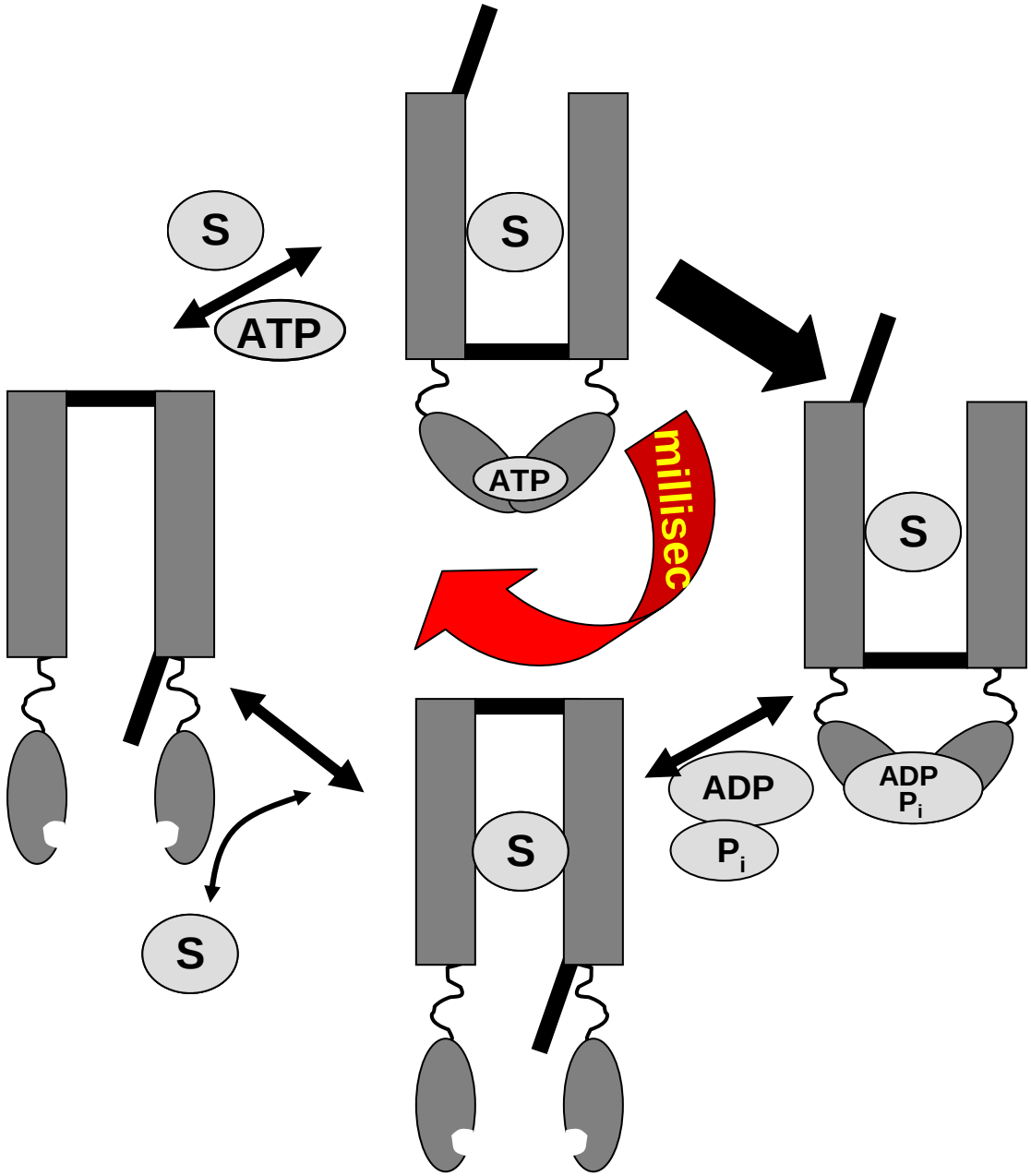
The “ABC” transporter family



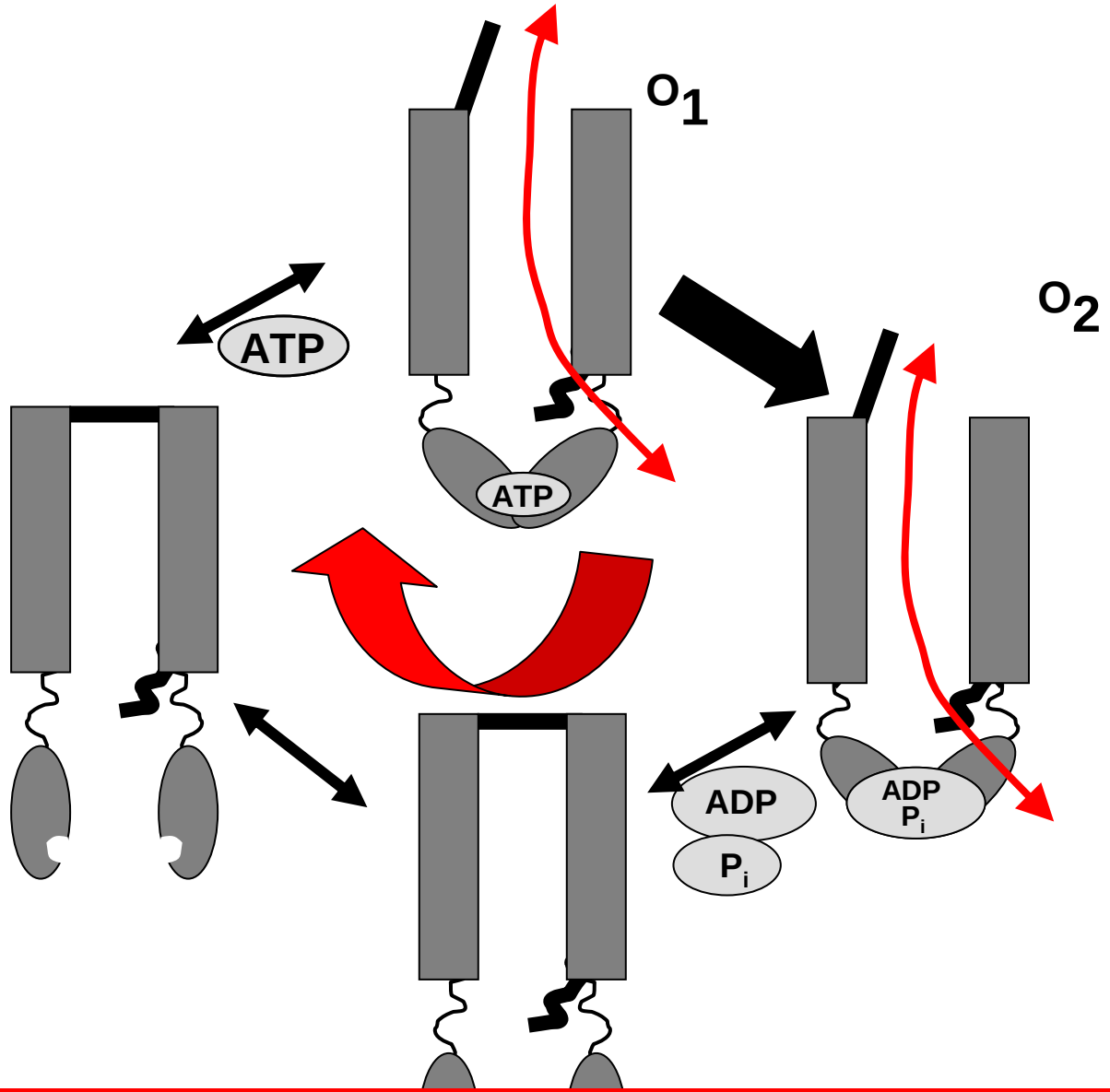
Bare-bones ligand-activated ion channel



Bare-bones ATP-driven pump

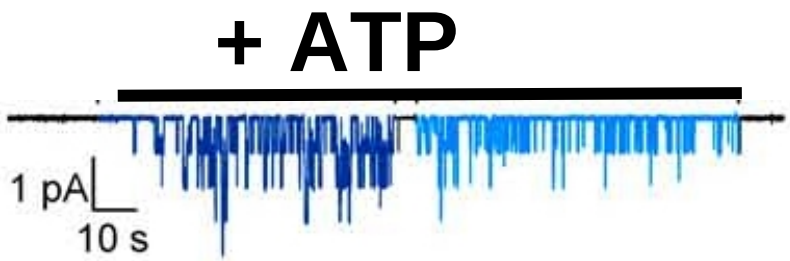


CFTR: a channelized pump



Prediction: Violation of microscopic reversibility!

Result: CFTR violates microscopic reversibility!



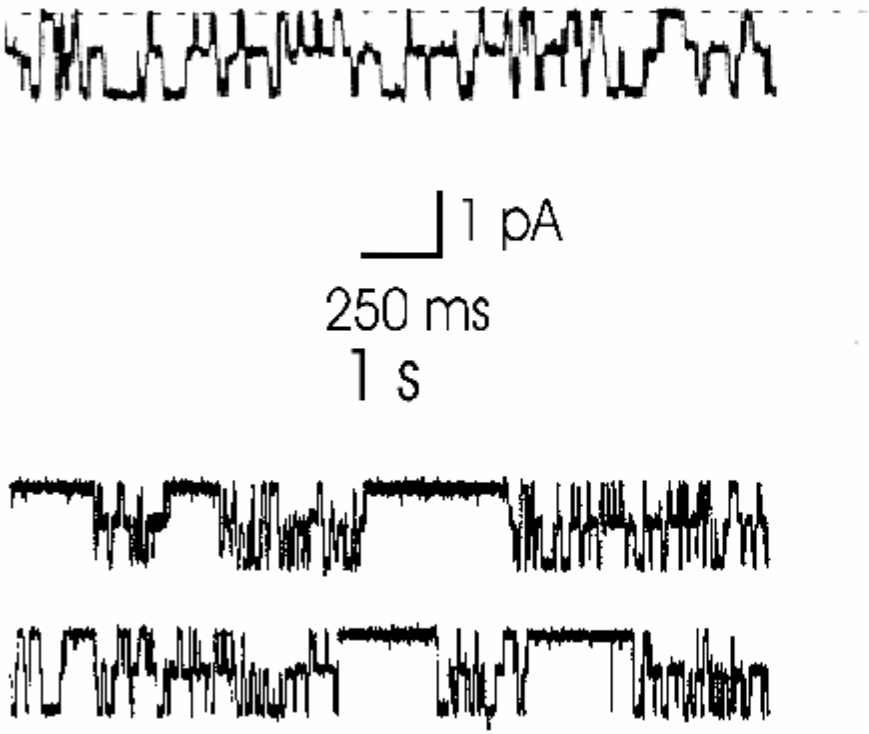
Prob density function

with *rising phase*

Story #3:
Whoa, baby – it’s a pump!

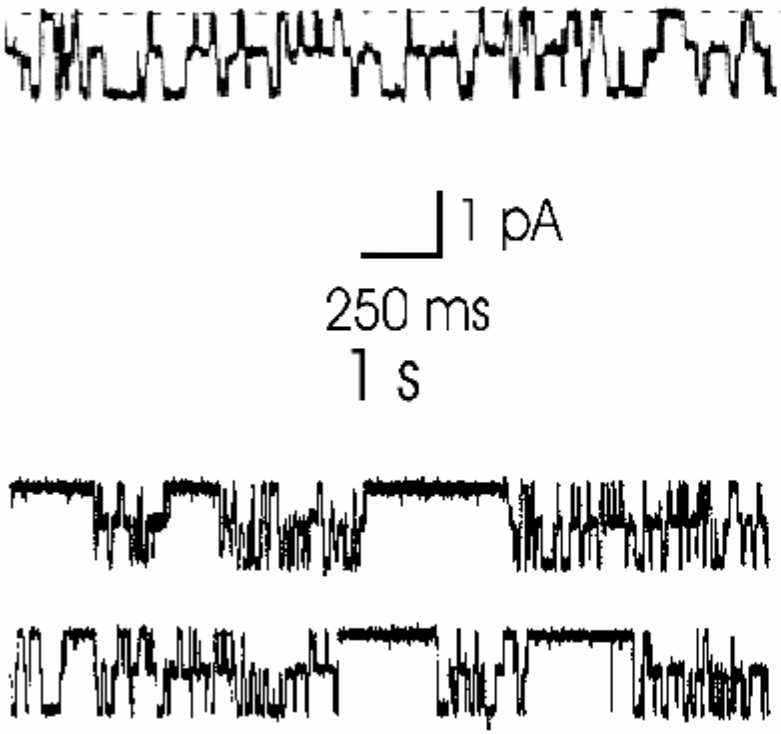
The CLC channel family

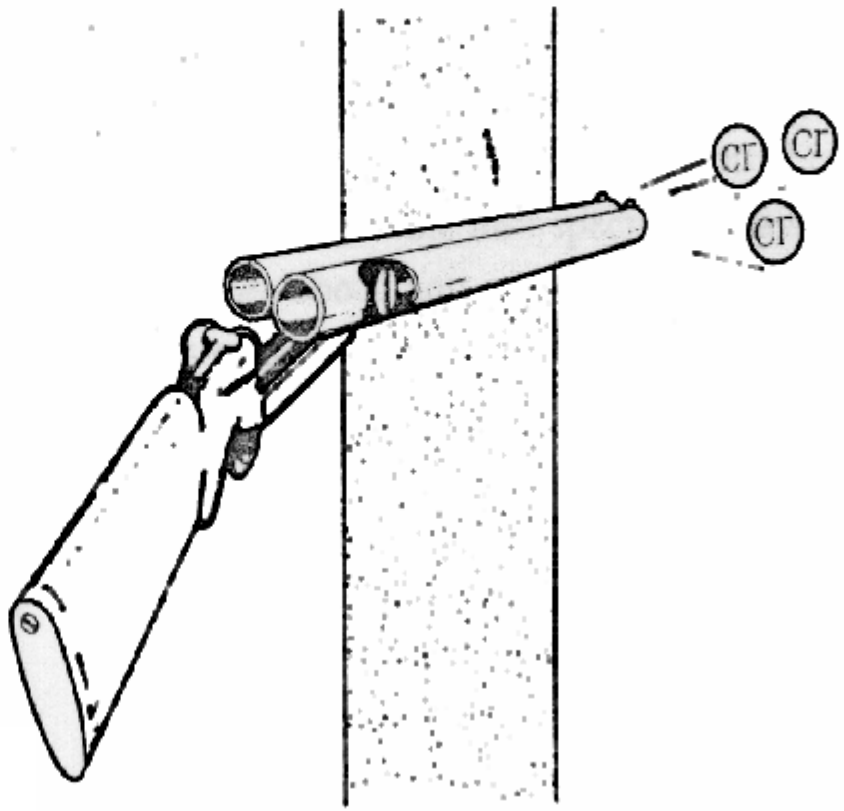
1979-2004



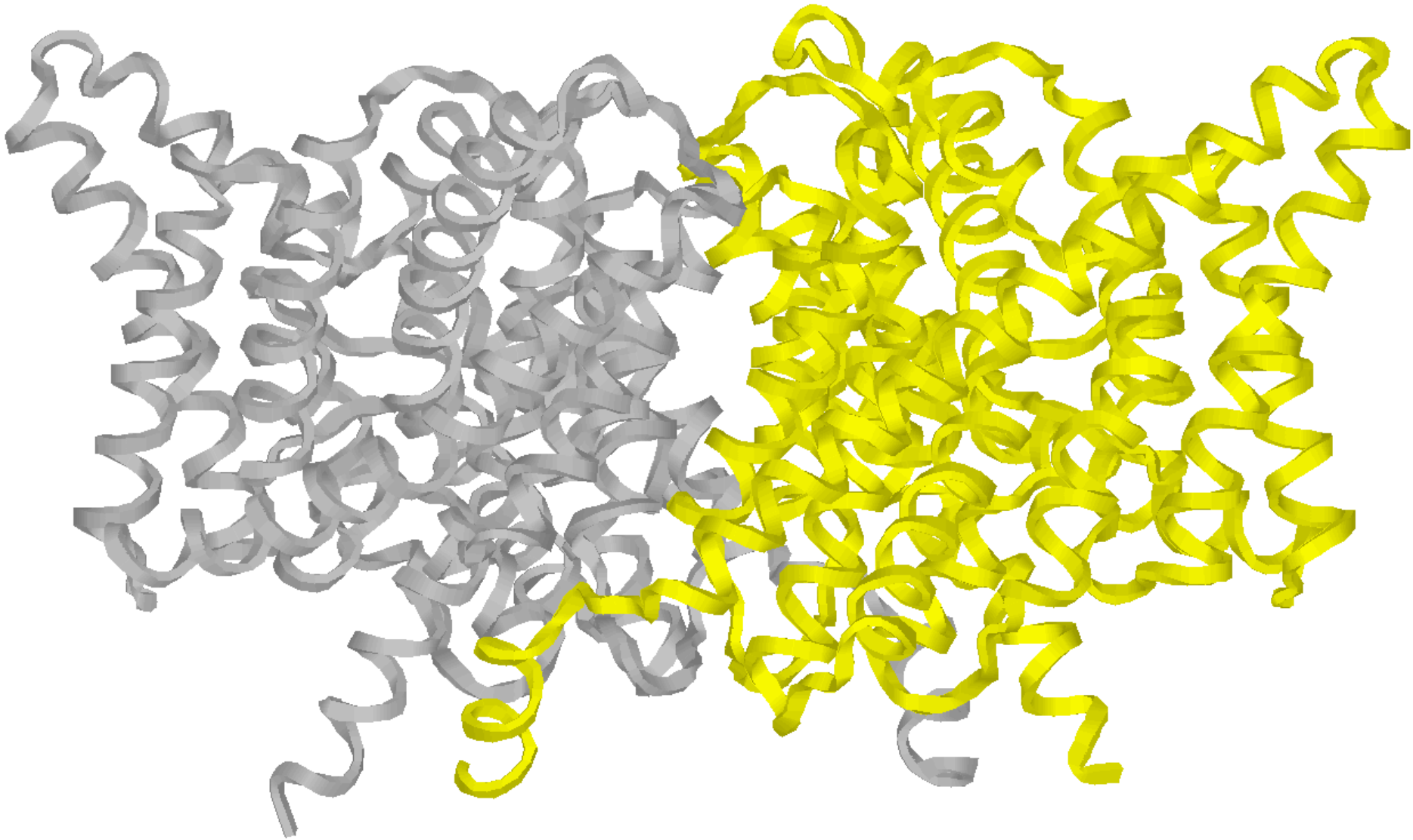
The CLC channel family

1979-2004

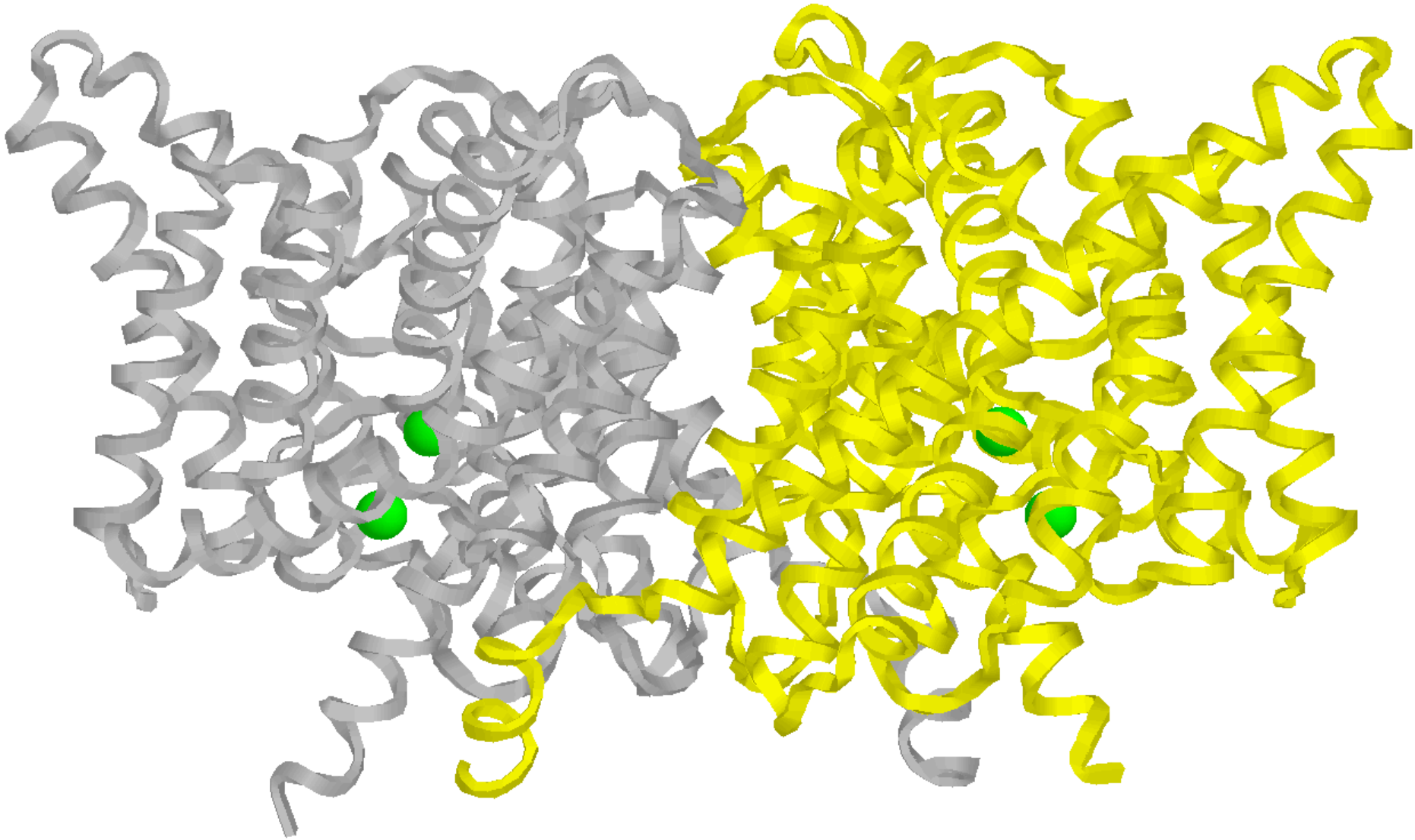




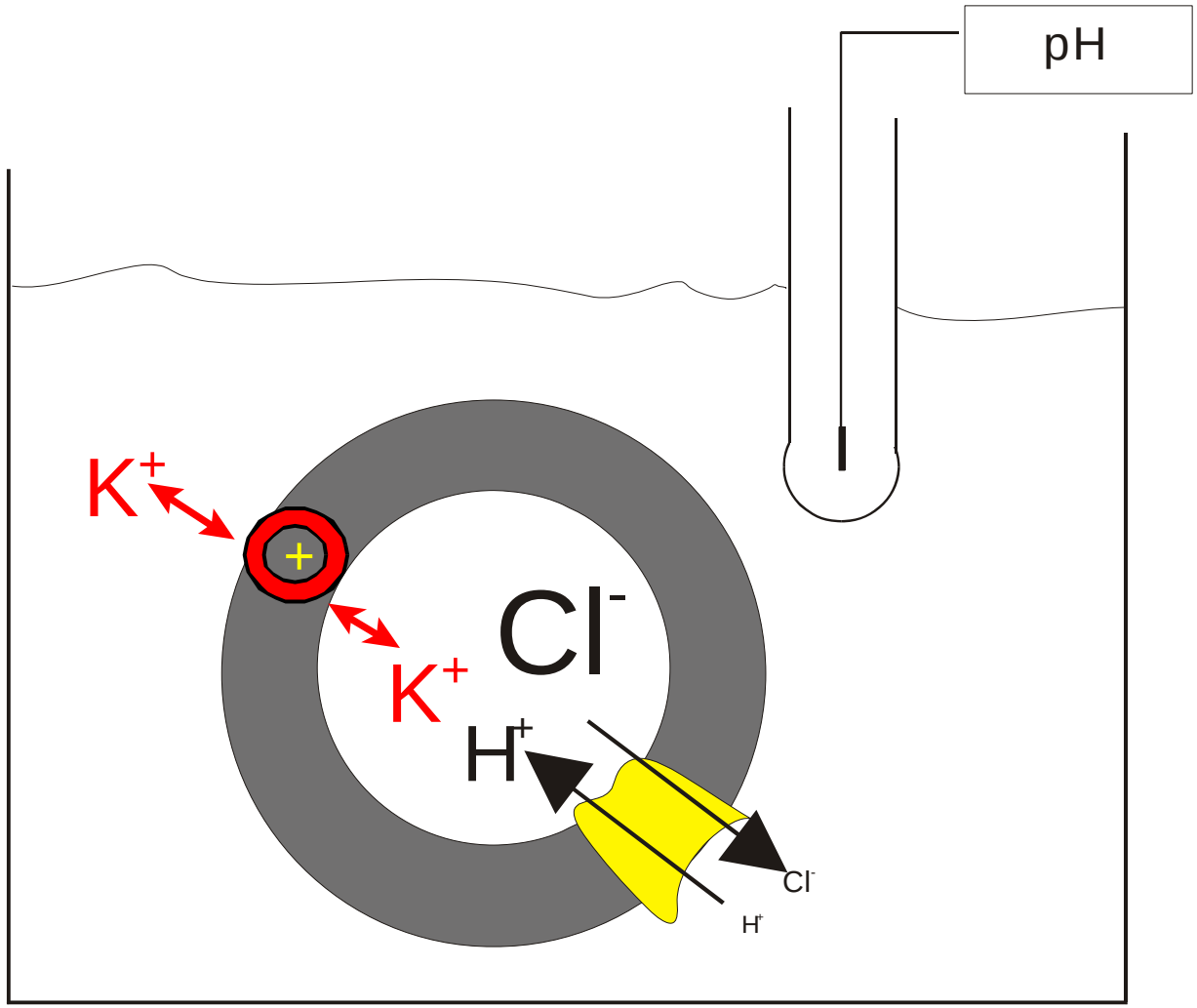
But where's the pore?



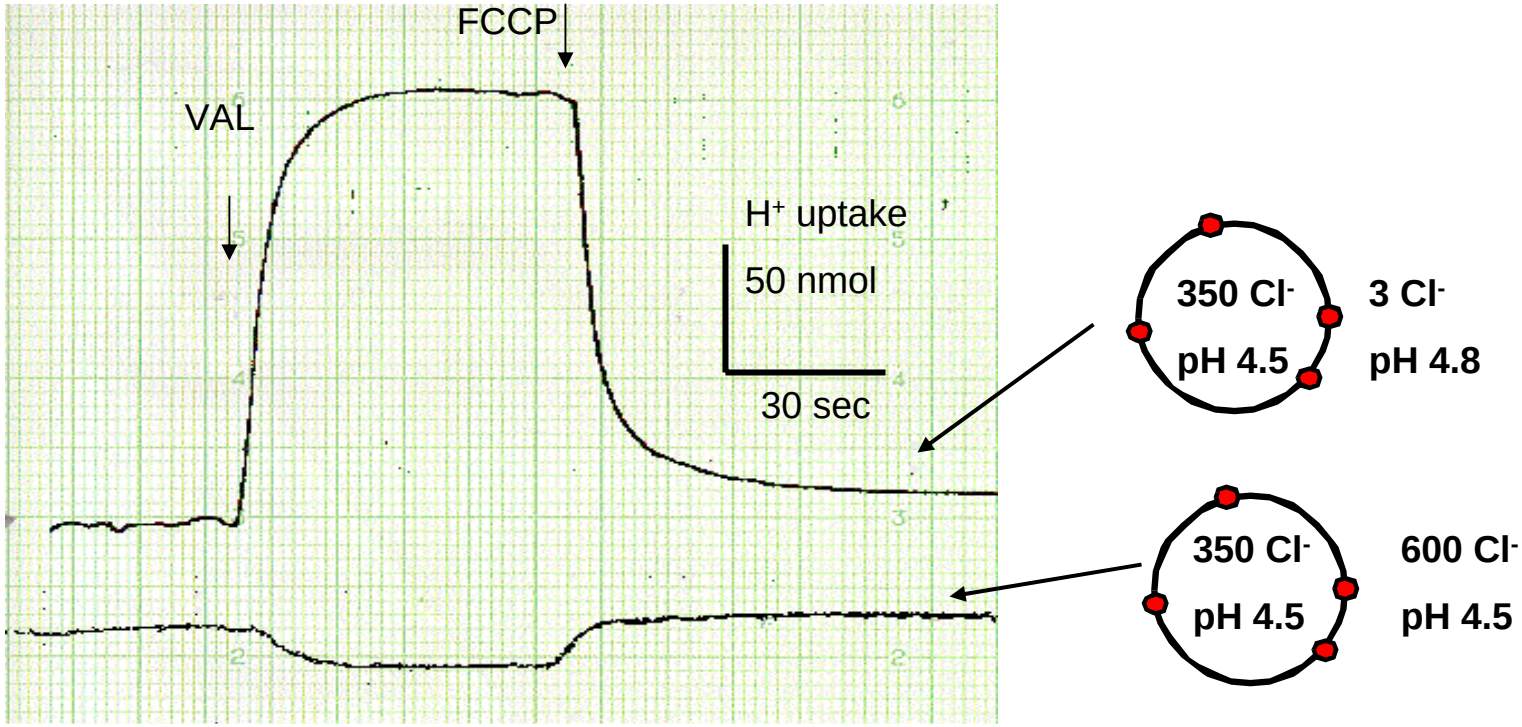
But where's the pore?



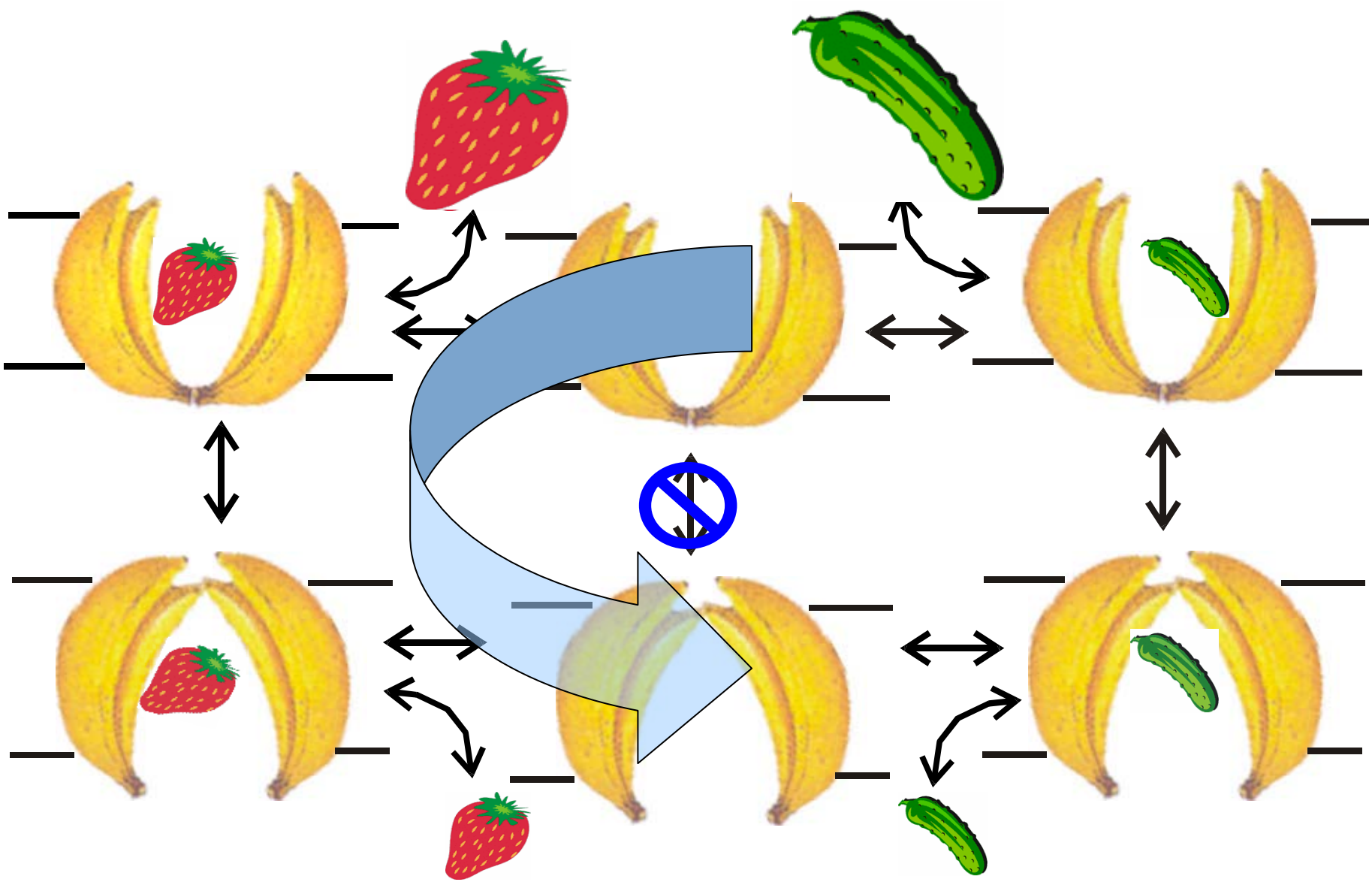
Cl^-–driven proton pumping: the direct demo



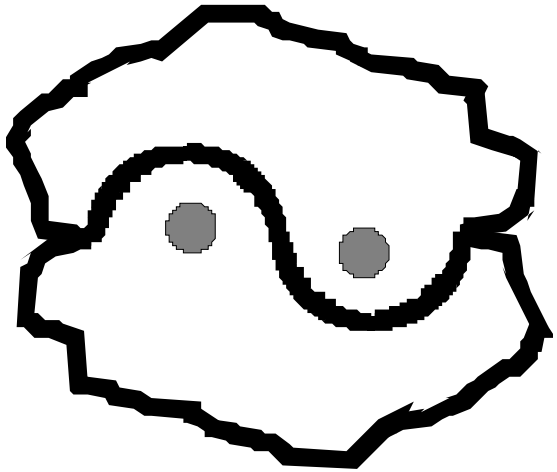
H^+ pumping driven by a Cl^- gradient



Classical alternating-site antiporter mechanism



2004: Yin and Yang in the CLC Family



Ur-CLC?

Cl^- channels

plasma membranes

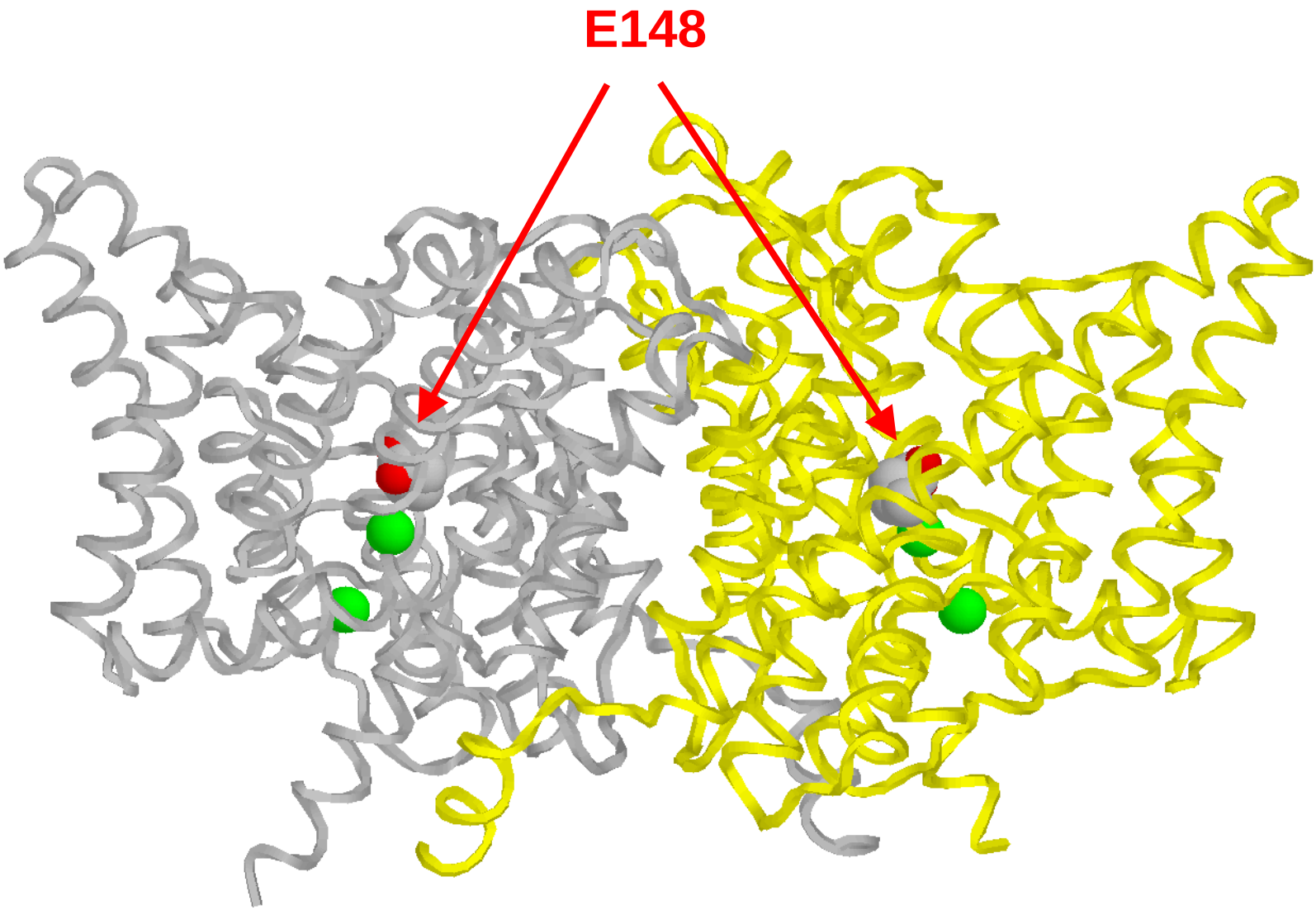
(CLC-0)

Cl^-/H^+ exchangers

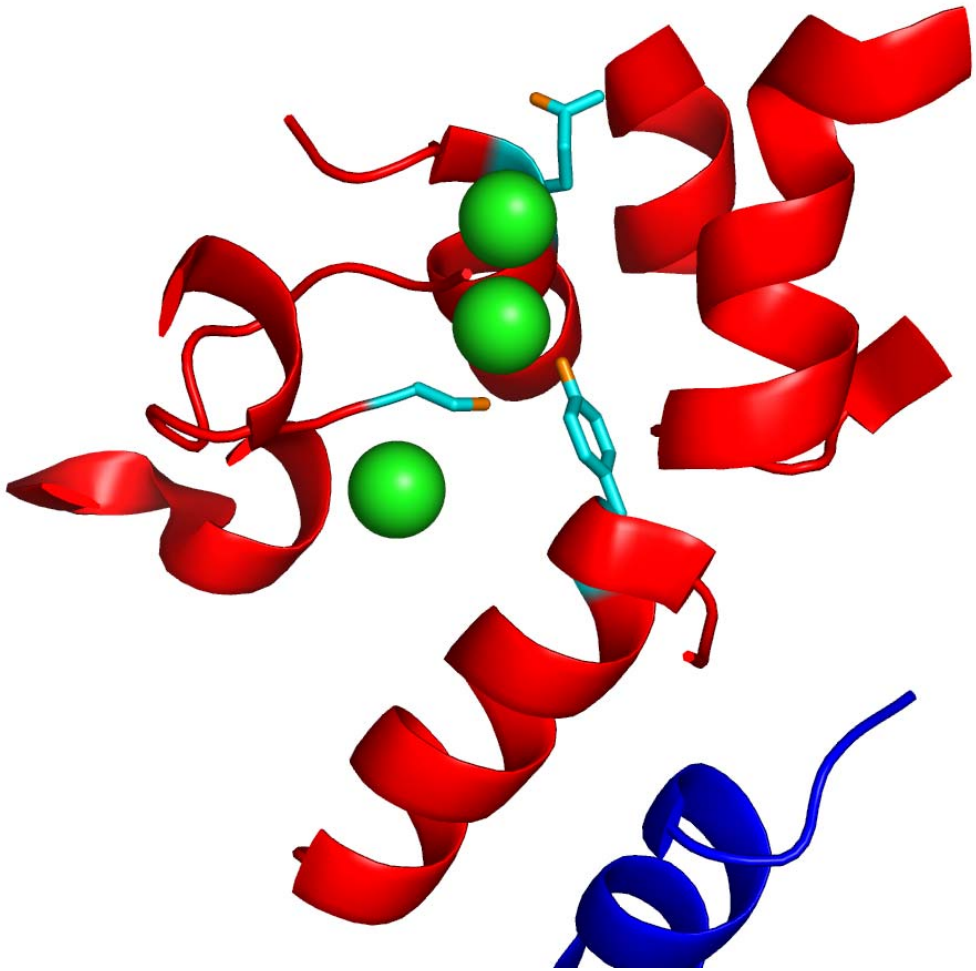
intracellular acidifying membranes

(CLC-ec1)

Extracellular H^+ transfer

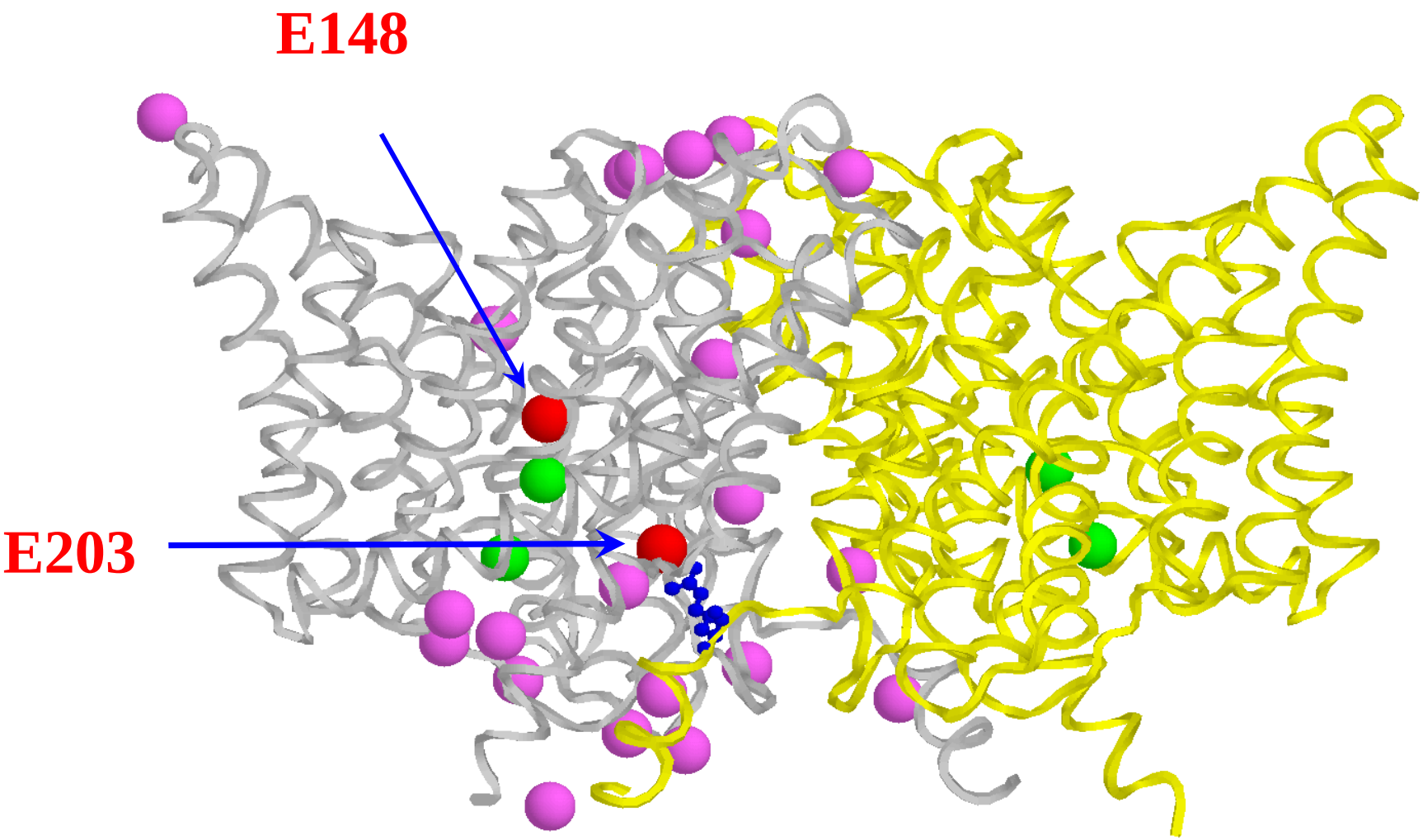


E148: extracellular H^+ “gating”

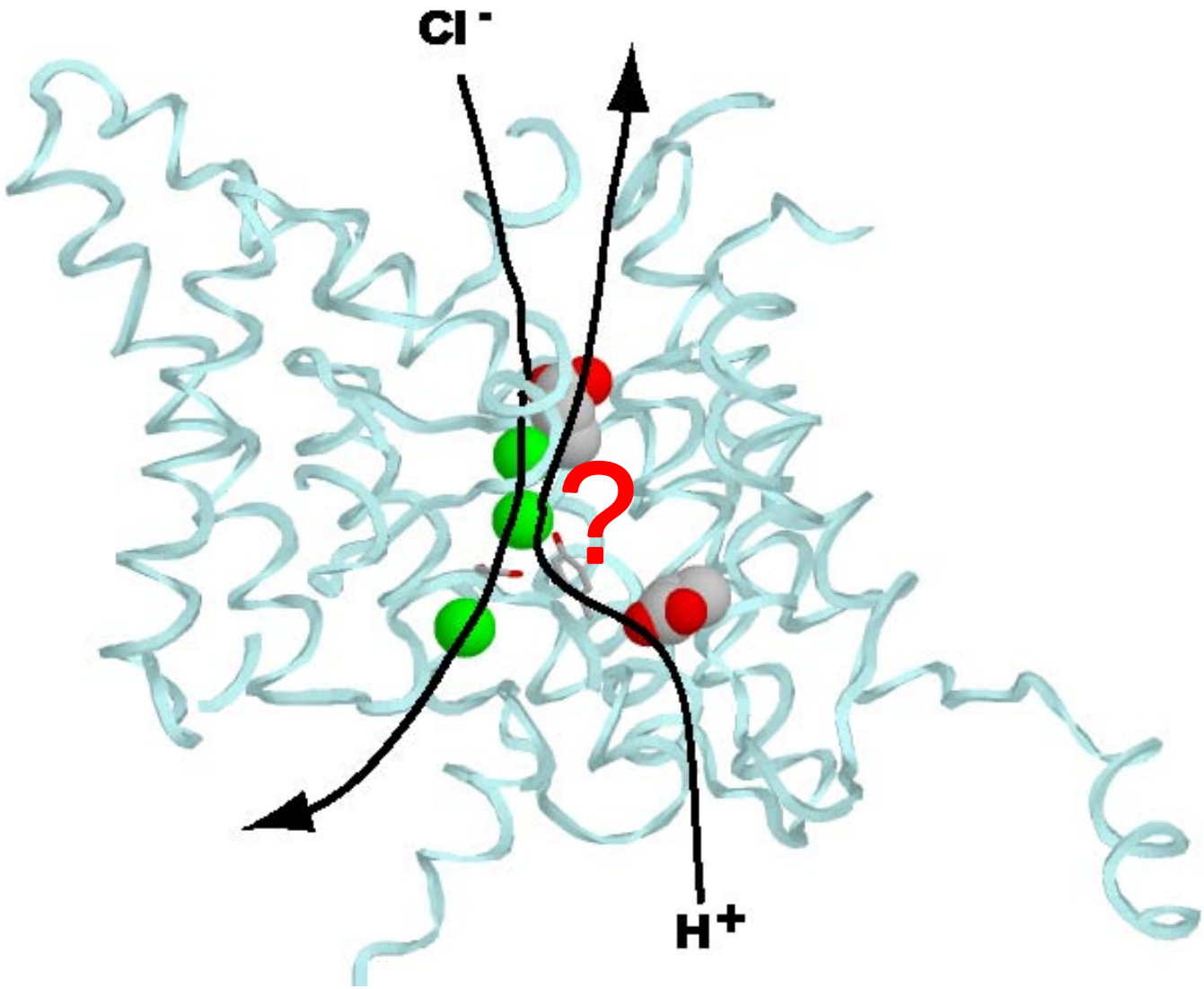


(Dutzler et al., Science 2003)

E203: Intracellular H^+ transfer

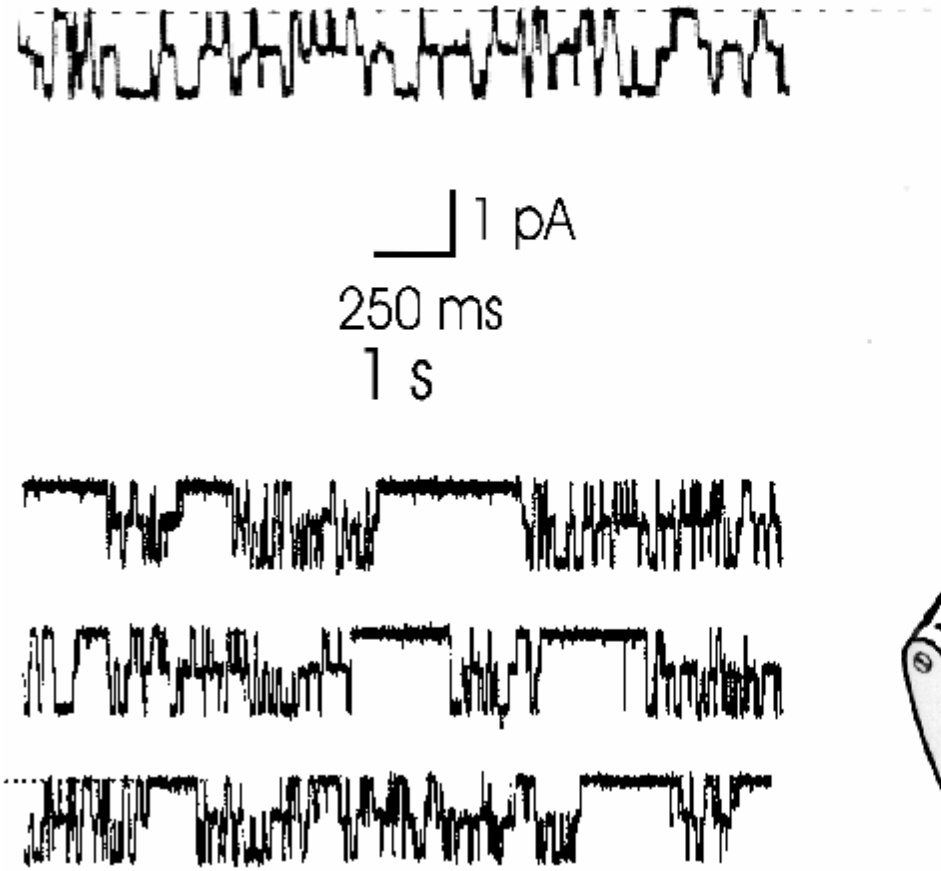


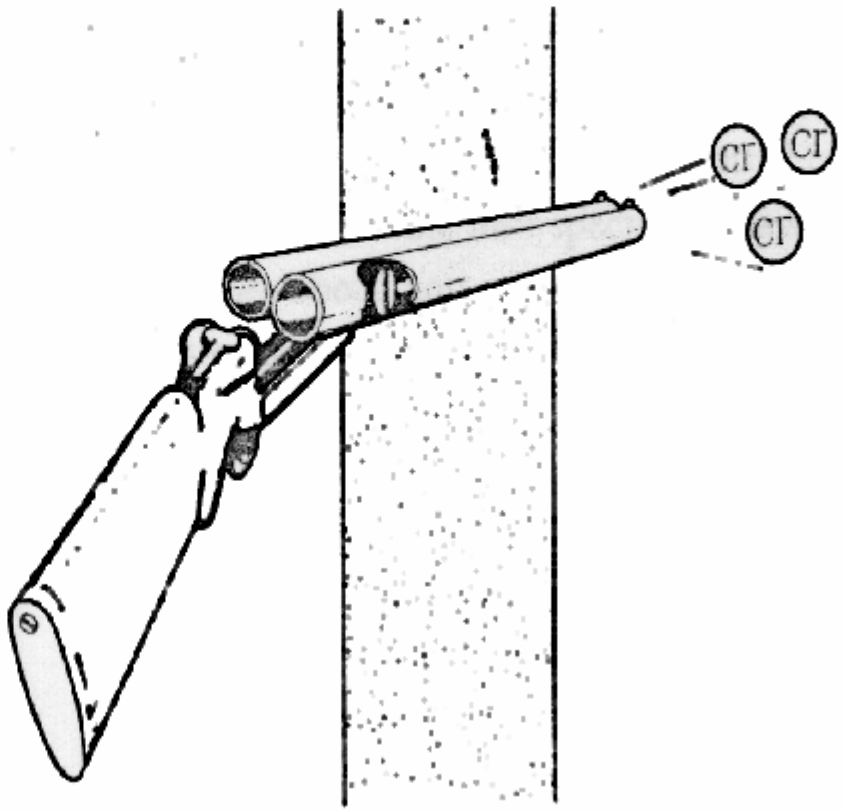
Bifurcated pathways for Cl^- and H^+



Back to the CLC *channels* :

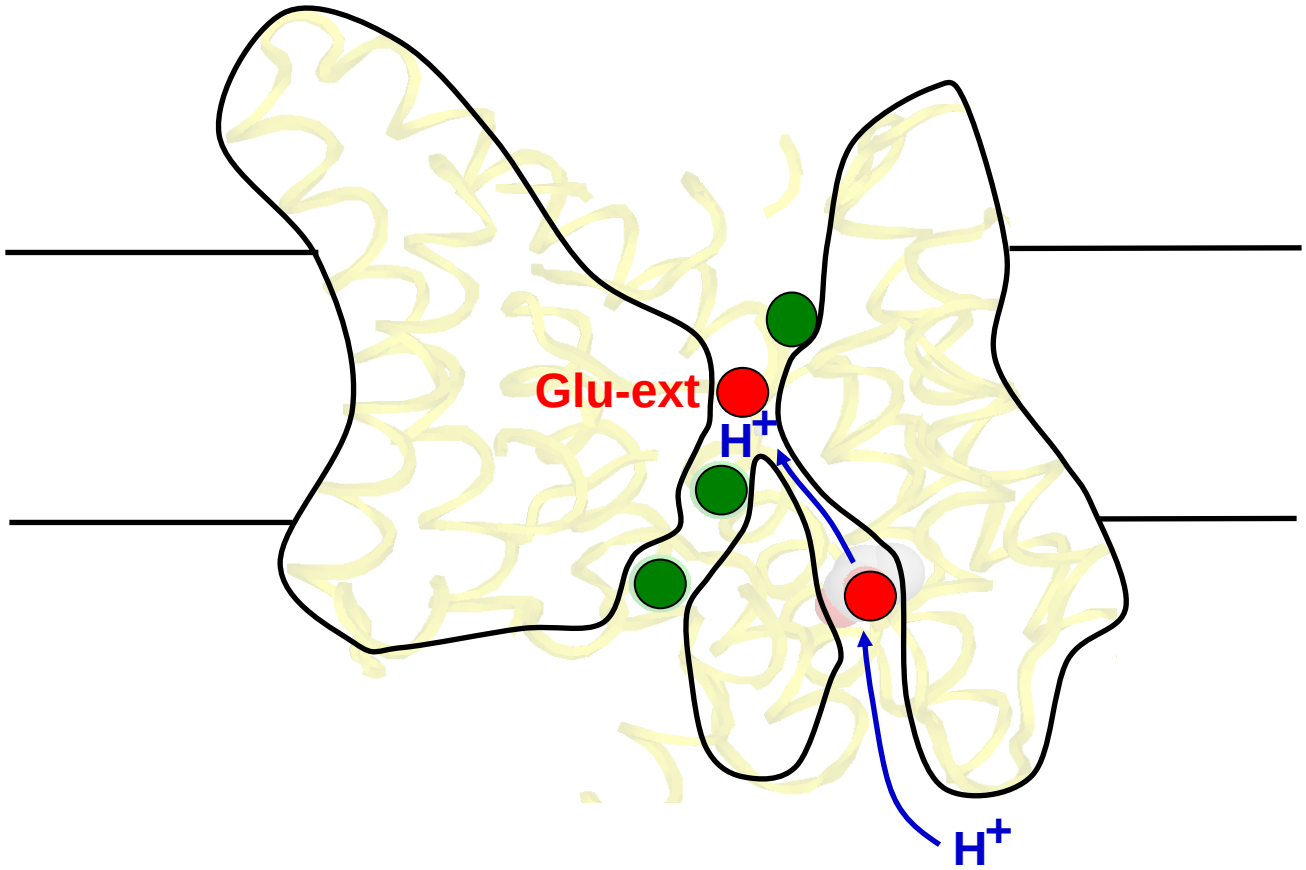
Do the pumps tell us anything?





Fast gating in the channels:

Degraded-transporter mechanism of V-dependence



Fast gating in the channels:

Degraded-transporter mechanism of V-dependence