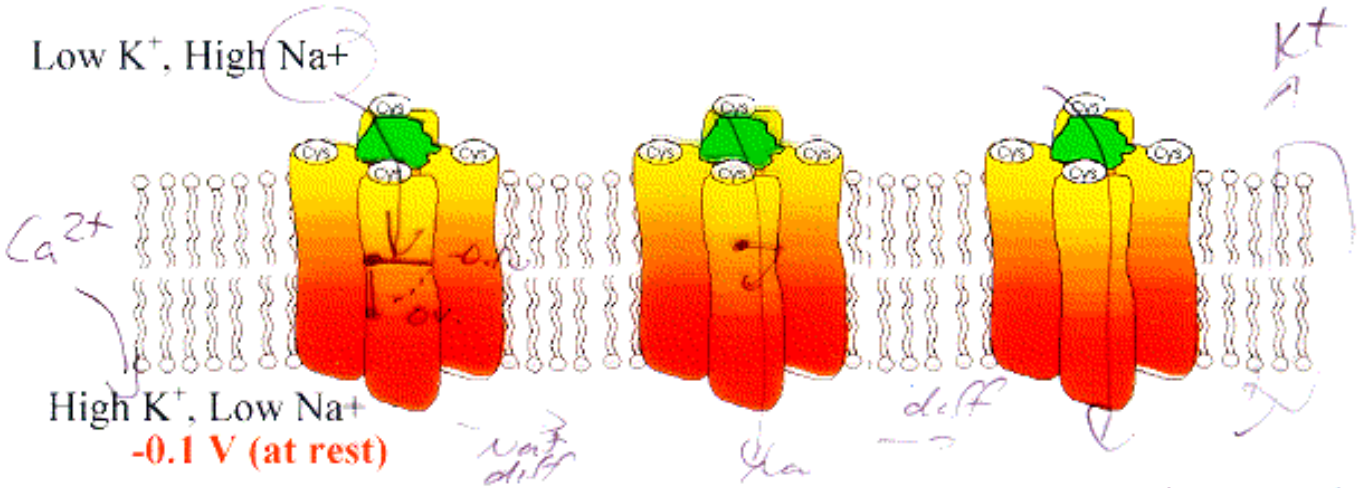
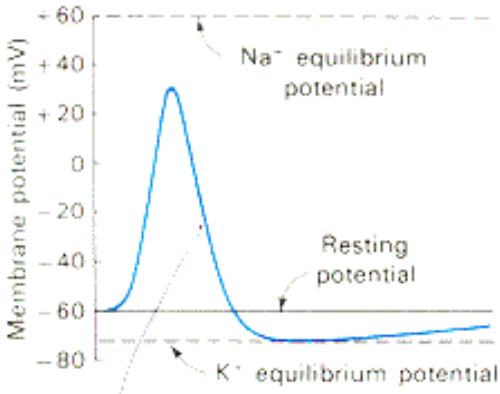
Action Potential

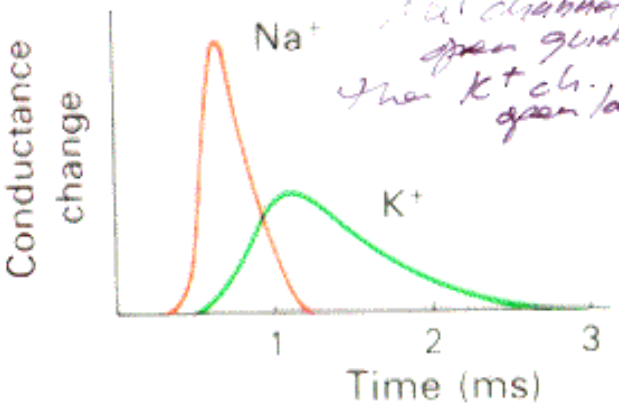
Rush of Na^+ in, followed by K^+ out.

At resting (negative) potential, channels closed.
At less negative potential (0mV), channels open.

At one end of neuron, some chemical released
→causes some charges (Ca^{2+}) injected/ depolarize membrane.





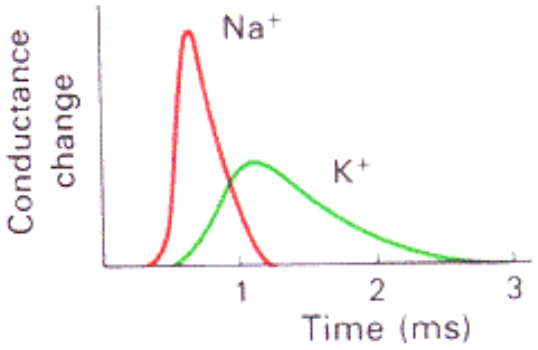


~10 million ions/sec go through single channel

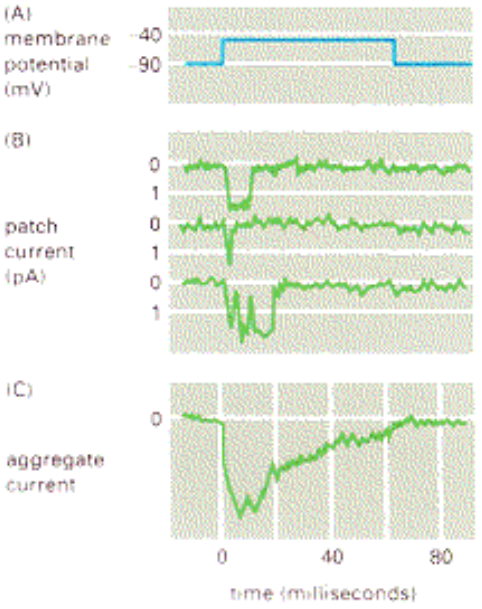
Na^+ channels spontaneously close after being open for a while.

Do ion channels open gradually or all or nothing?

Ensemble



Single Ion Channel

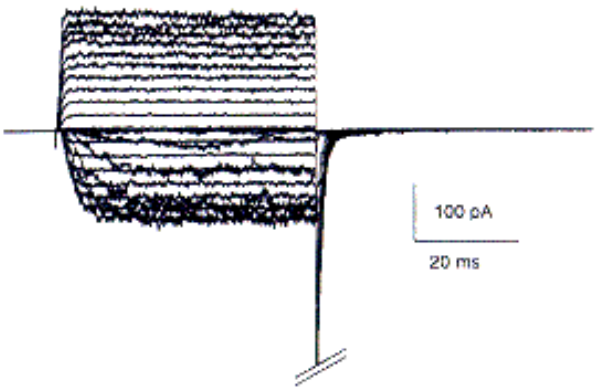


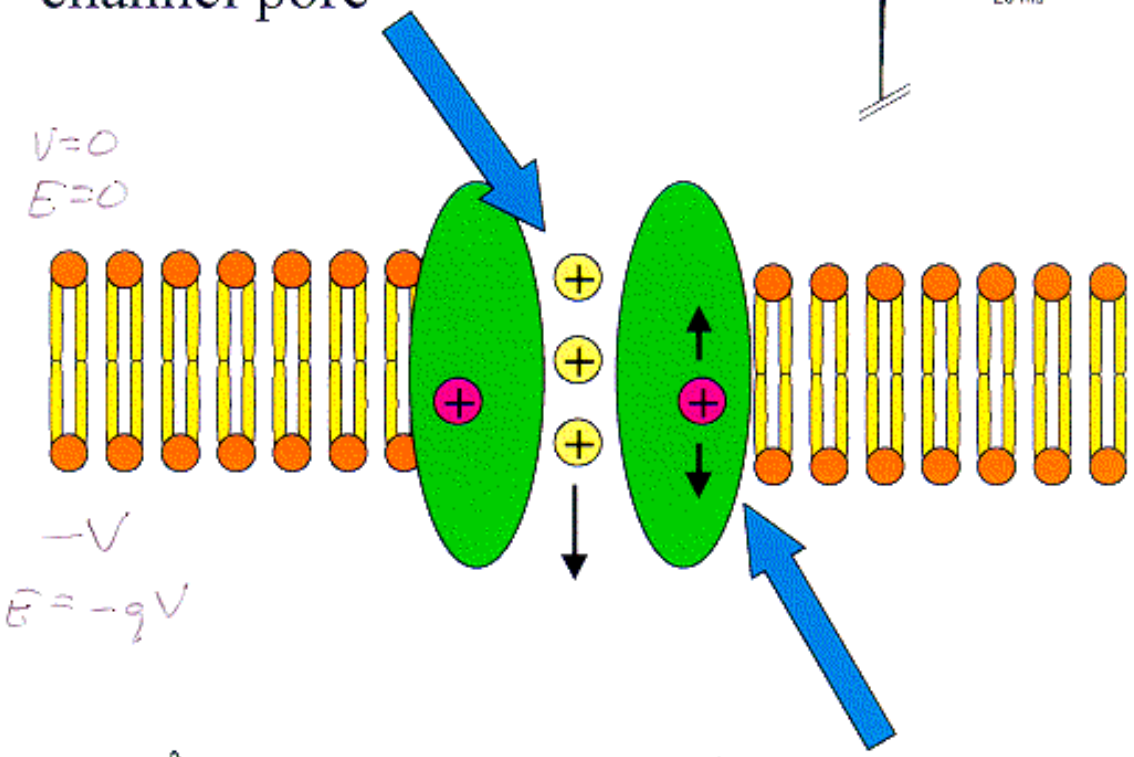
Patlack & Horn, 1982

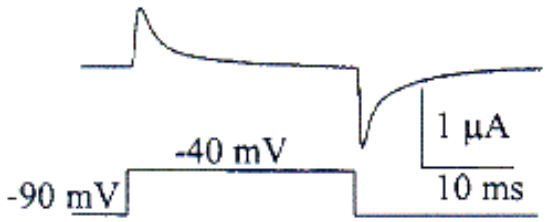
Note: Ion conduction (Na^+, K^+)

Ionic Current and Gating Current

Ionic current results from diffusion of ions through the channel pore



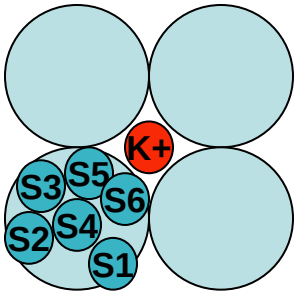


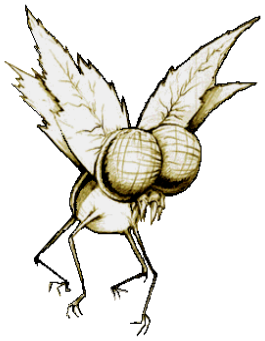


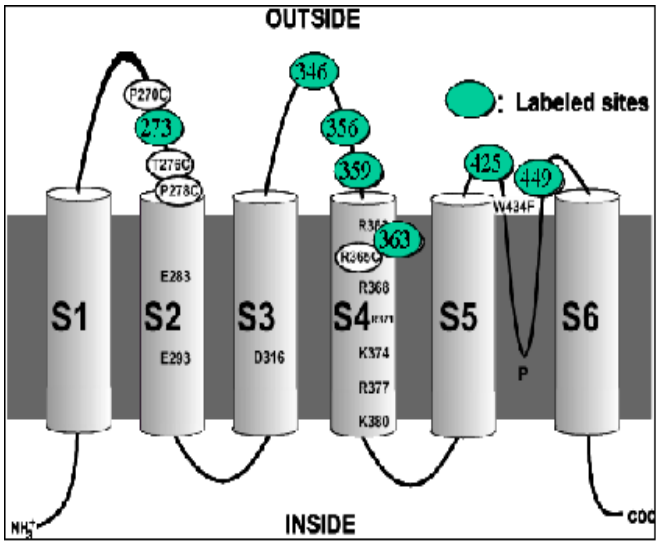
Gating current results from gating charge movement
~ 1 ms time scale

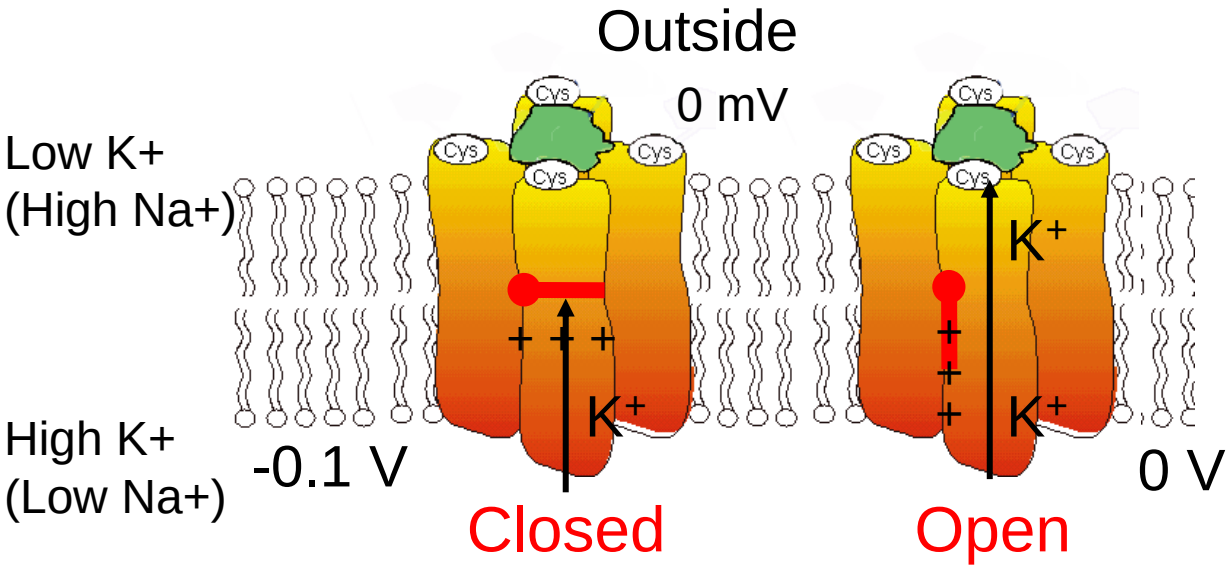
Charged amino acids (largely in the voltage sensor) move.

How does gate turn on/shut off?





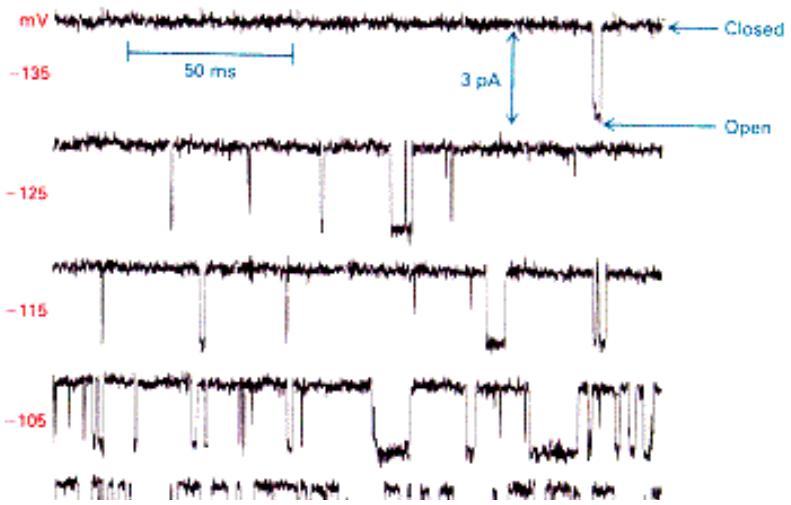




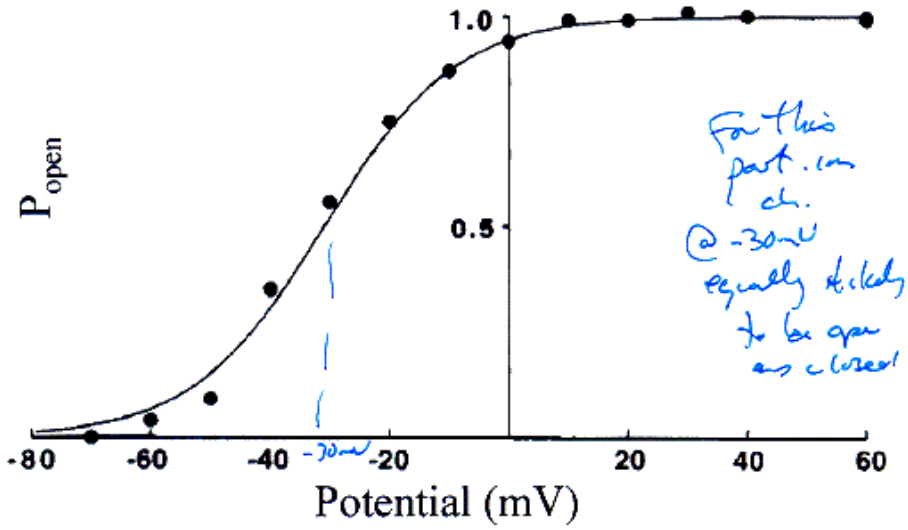
There is some charged amino acids, which feels the force of voltage.

Voltage dependence of on/off transitions.

(Can measure by ensemble or single-channels)



$$P_{open} = \frac{1}{e^{q_a (V_{50} - V)/kT} + 1}$$

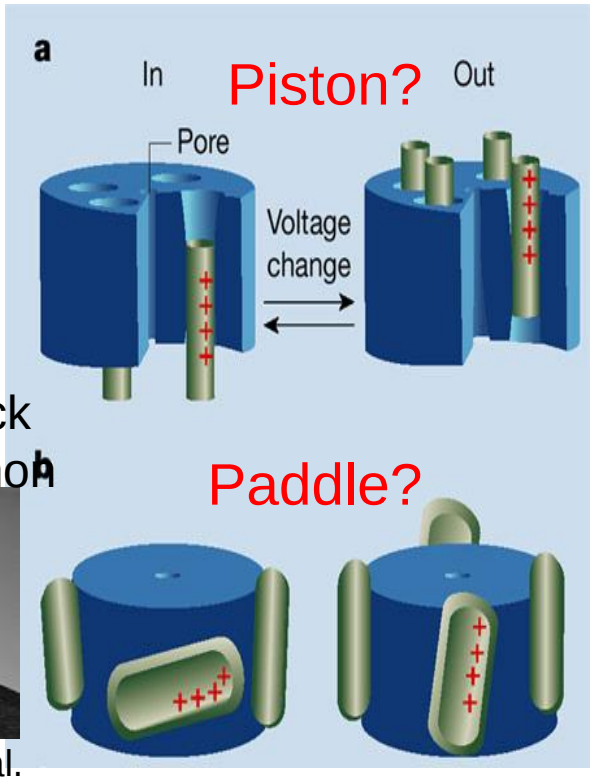


Suggests model where 2 states that differ in energy by qV

Where q is about 13e, or 13e/4 per S1-S4 sub-unit; V= -80mV.

q is part of channel—gating current, not ionic current!

How does gate (S4) move? General Models

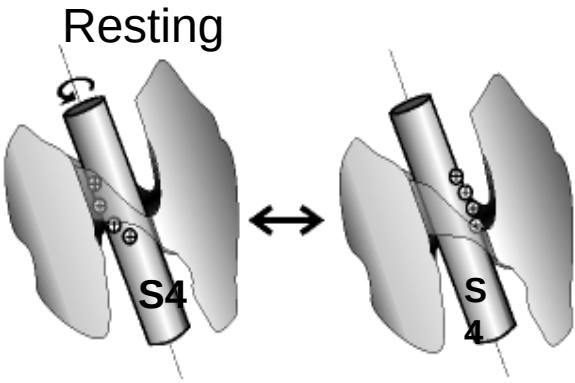


Roderick MacKinnon

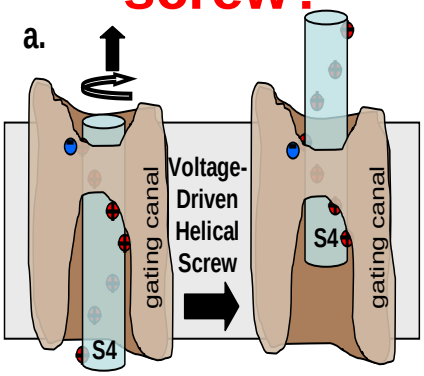
Jiang et al. *Nature*, 2003

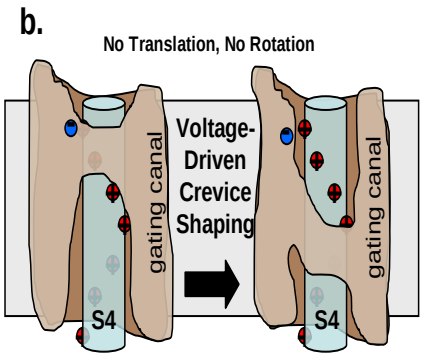
Blaustein and Miller, *Nature* **427**, 499-500. (2004).

Rotation?



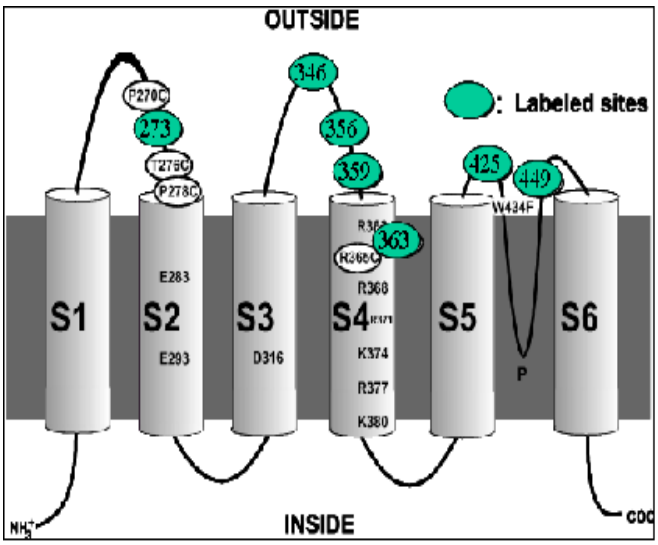
Cork-screw?





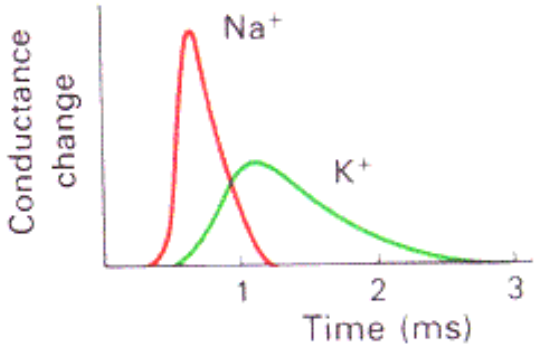
Crevice Reshaping?

FRET can (mostly) tell

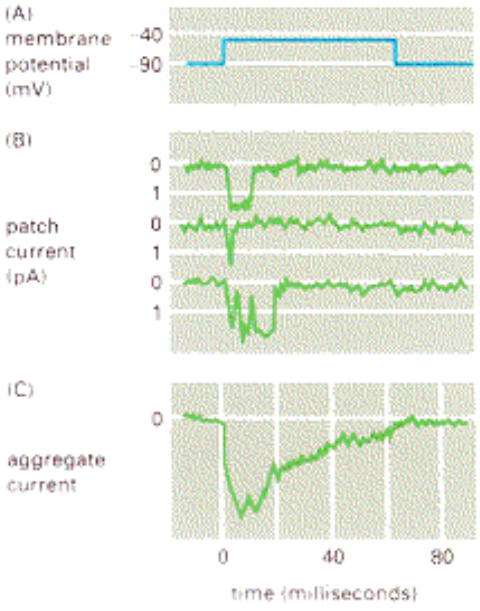


Do ion channels open gradually or all or nothing?

Ensemble



Single Ion Channel



Patlack & Horn, 1982

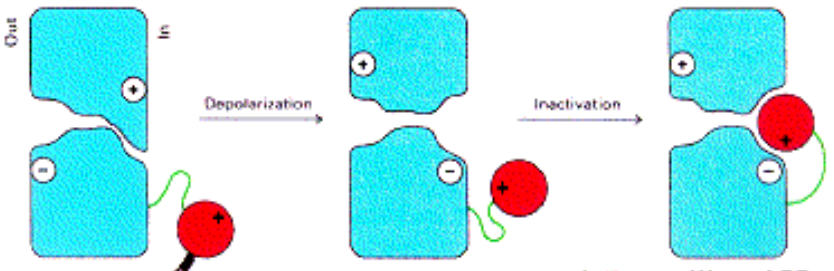
How does gate spontaneously shut-off?
How fast?

Nerve Impulse propagate, not spread, because Na^+ spontaneously shut-off.

What shuts off channel?

Na channels shut off in a msec
i.e. why you don't have spasms
i.e. why action potential travels rather than just spreads.
Why you can have repetitive firings of nerve.

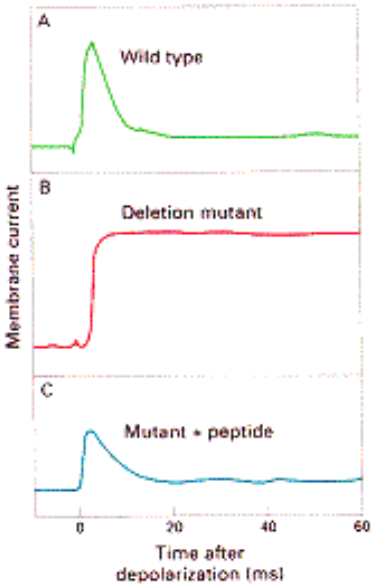
The Ball and Chain model



Armstrong & Bezanilla, 1977

protein segment (ball)

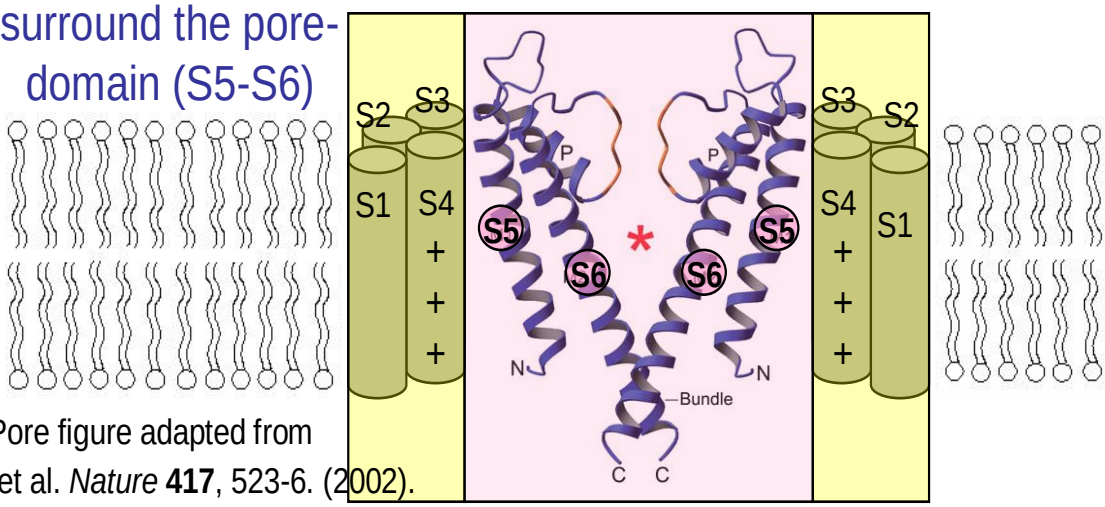
Cut off ball and chain,
and no (fast) inactivation.



Zagotta, Hoshi, Aldrich, 1990

Structure of Pore-Domain (S5-S6) is known (KvAP, Kv1.2… all yield the same structure)

b Voltage-sensing domains (S1-S4) surround the pore-domain (S5-S6)



Pore figure adapted from Jiang, Y. et al. *Nature* **417**, 523-6. (2002).

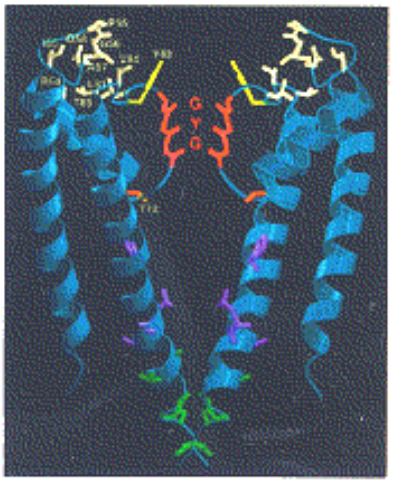
Explains ion selectivity ($K^+ > Na^+$) and rapid ion flux.

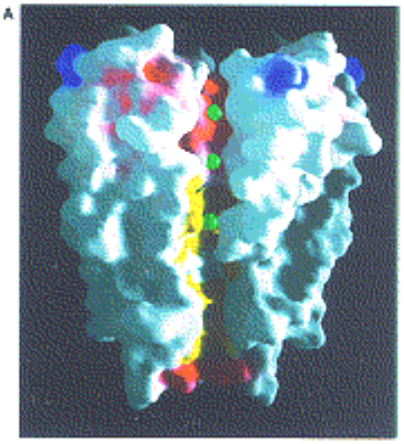
Excellent agreement between LRET/FRET and Crystallography

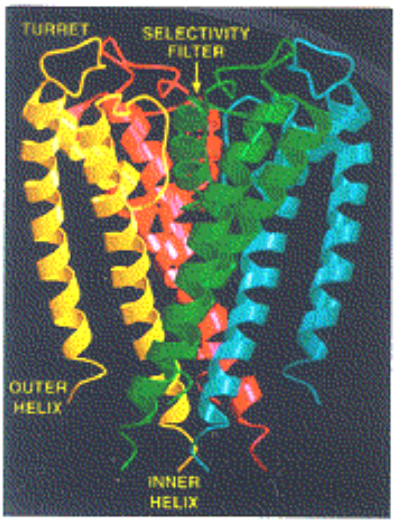
But how S4 (and S1-S3) move, remain controversial.

Rod MacKinnon won Nobel Prize

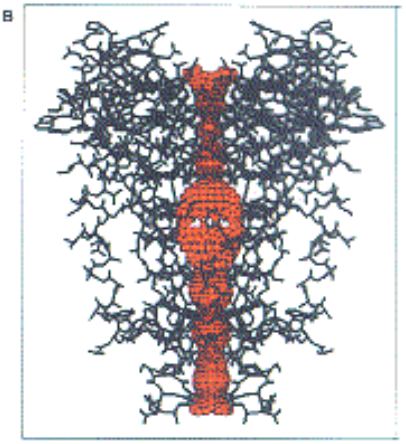
KcsA Selectivity Filter [Mackinnon, et al]

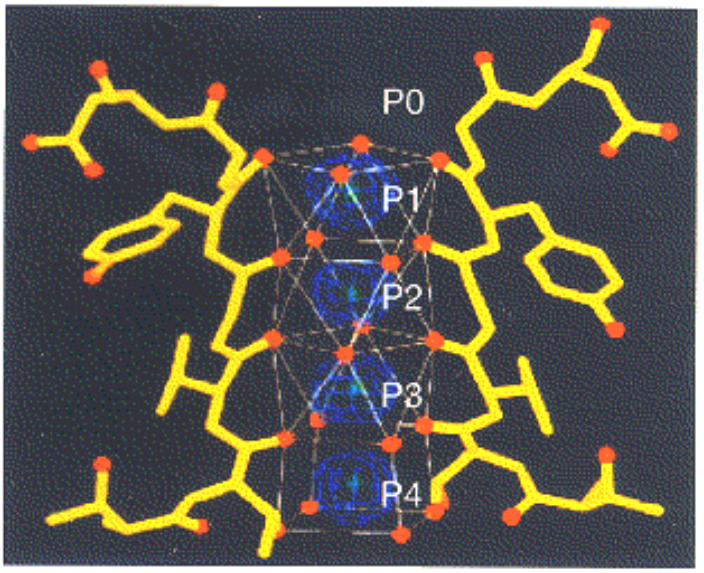






Notice Selectivity Filter (GYG)





Choe, Nature Reviews, Neuroscience, 2002

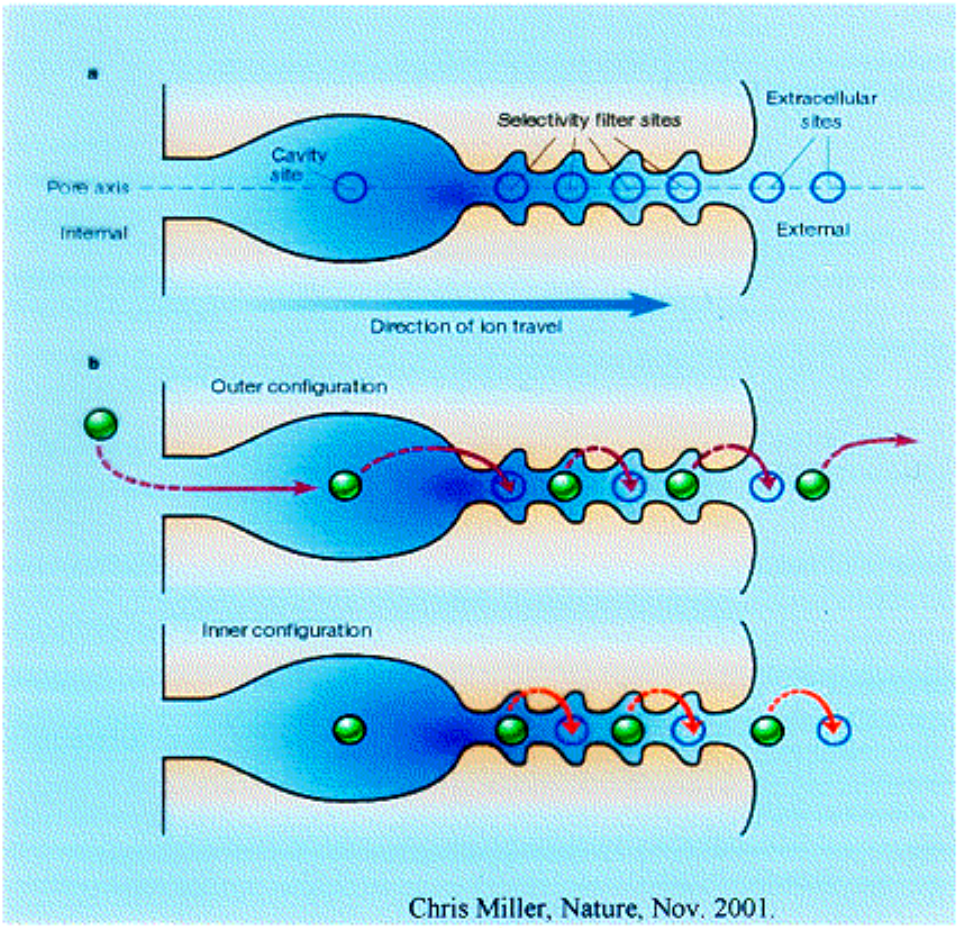
Ion channels contains an Aqueous Channel. & Selectivity Filter

In KcsA channel, filter accommodates 4 ions.

Fast throughput, low (no) energy-barrier to proper ions: 10^8 ions/sec.

50-10,000 fold **selectivity** of K over Na, e.g.

Inside



Outside

Chris Miller, Nature, Nov. 2001.
Review of Mackinnon, Nature, Nov. 2001

Important features

1. **Aqueous cavity/channel.**
   No energetic barrier of going from aqueous (water) to low dielectric membrane.

2. **Dehydrated K^+ is bound to eight oxygen atoms** formed from carbonyl (C=O backbone) of amino acids from selectivity filter.
   No energetic barrier to dehydration for K^+.
   Large cost for ions such as Na^+ (which is dehydrated slightly smaller; hydrated slightly bigger.)

3. **Multiple ions can be in cavity at same time.**
   High throughput. (10^8 ions/sec).

Diffusion-limited passive transport of K^+ while acting like a brick wall to Na^+.

Hydration Energy

To dehydrate H_2O from K^+ (or Na^+) takes ~100 kT!

If passage of ion through channel requires dehydration – extremely high energy barrier

Selectivity filter is arranged so that C=O carbacylate groups of a.a. are exactly in the right position so O of H_2O is replaced by O of C=O w/o any energetic difference. for K^+ in KcSA.

However, for smaller Na^+ ion (dehydrated), the C=O are too far apart to easily replace H_2O of Na^+-hydrated ion.

If 10,000 fold selectivity, what is E_{Na} vs. E_K ?

Ans: 9.2kT

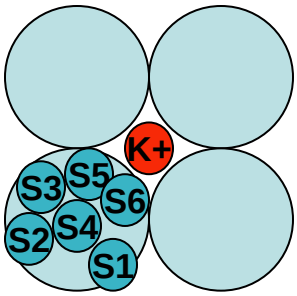
Sodium channel been crystallized. C=O just right for Na^+.

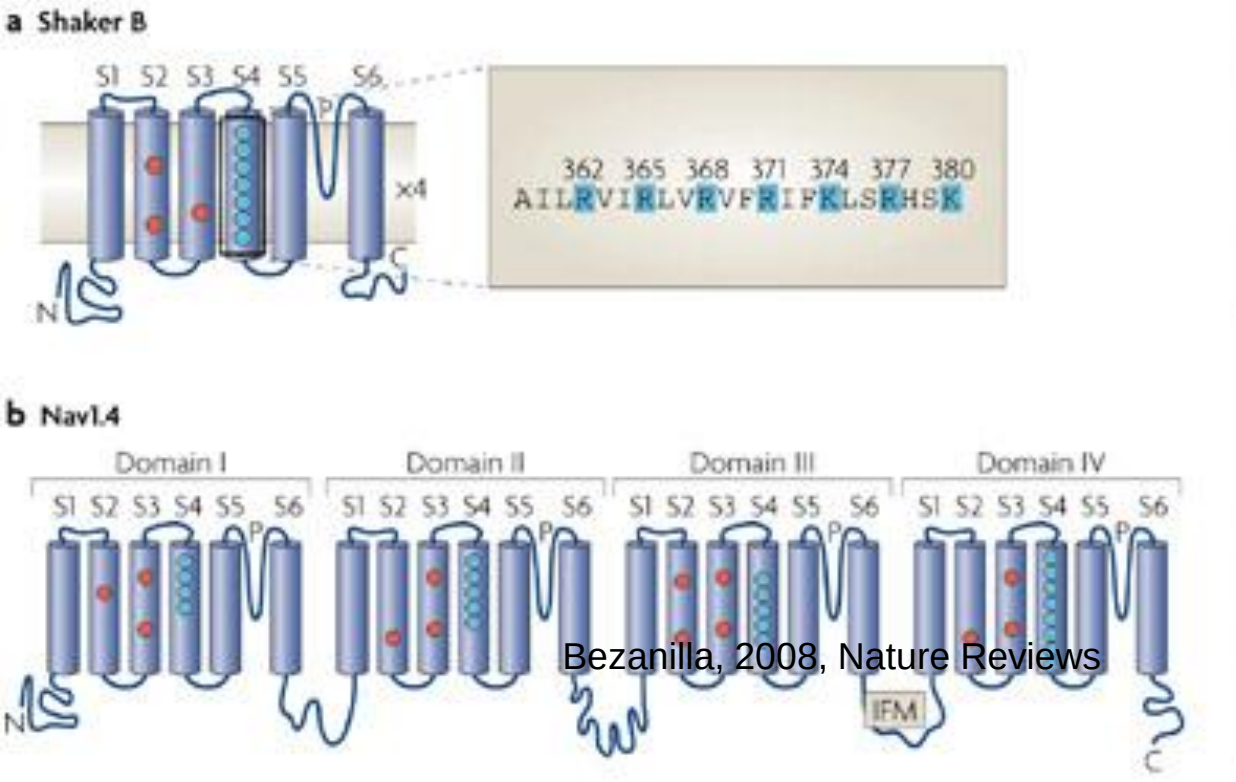
Potassium & Sodium Channel Similar

K^+ Channel: homotetramer S1-S6

Na^+ Channel heterotetramer S1-S6:

with each sub-unit havingslight variations)





Bezanilla, 2008, Nature Reviews