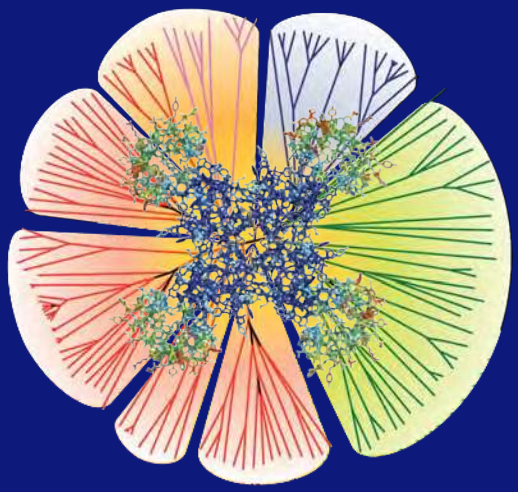
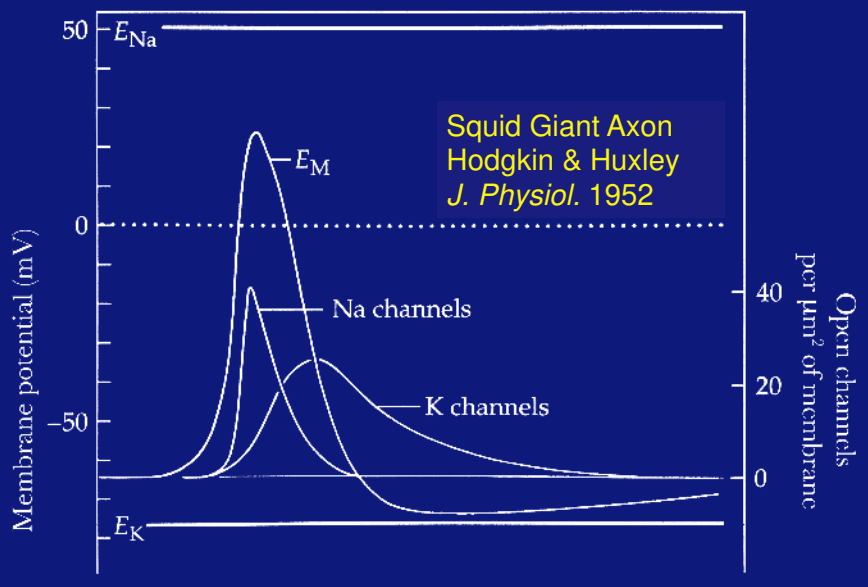
Structure and Function of Voltage-Gated Sodium Channels at Atomic Resolution



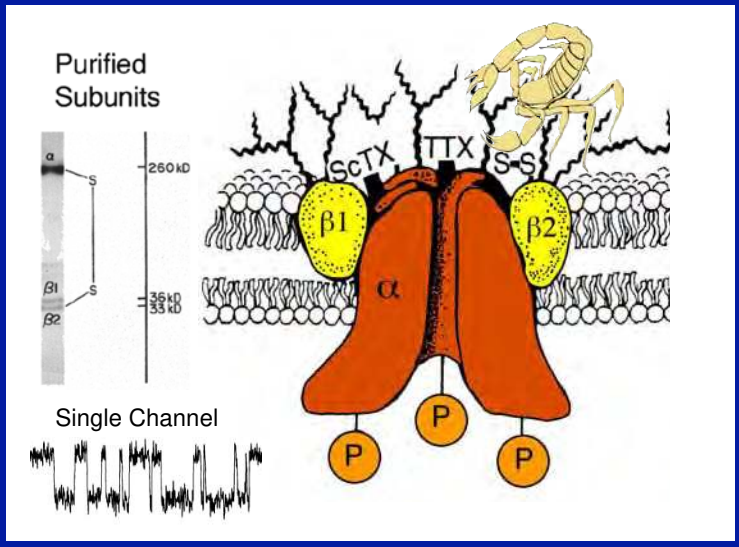
Royal Society of Chemistry
Cambridge UK, March 2013

William A. Catterall, Department of Pharmacology, University of Washington

Sodium Channels Initiate Action Potentials in Excitable Cells

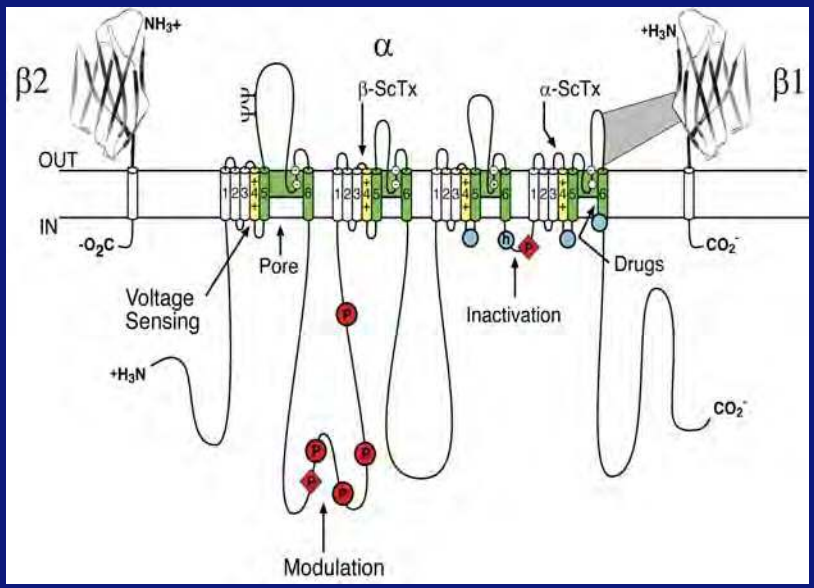


The Sodium Channel: A Molecular Machine for Electrical Signaling

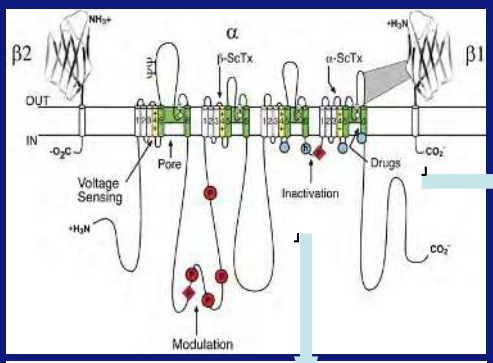


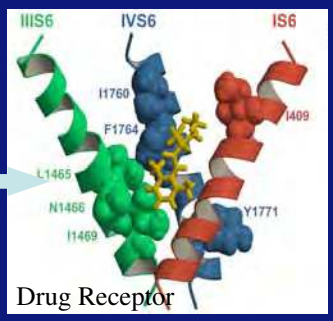
Beneski and Catterall, 1980; Hartshorne et al., 1981, 1982, 1984, 1985; Tamkun et al., 1984

Structure-Function Map of the Sodium Channel

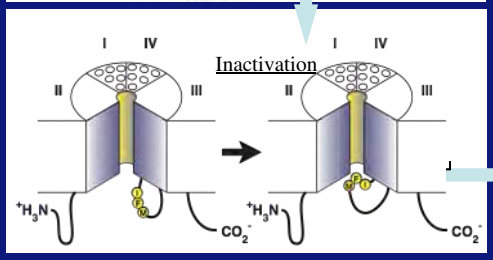


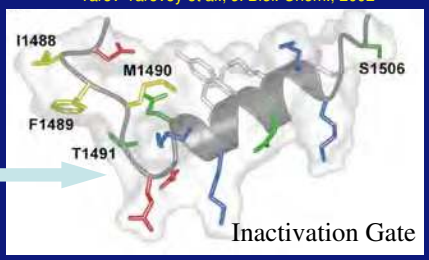
Structure-Function Map of Inactivation and Drug Block





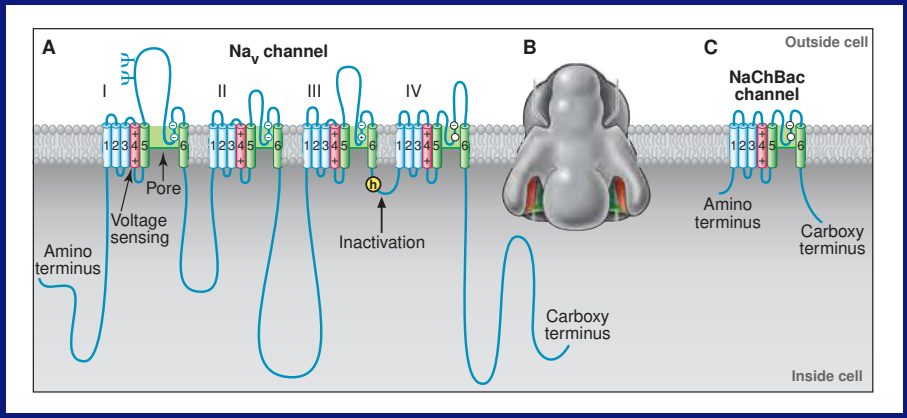
Ragsdale et al., *Science*, 1994, *PNAS*, 1996
Yarov-Yarovoy et al., *J. Biol. Chem.*, 2002





Vassilev et al., *Science*, 1988; *PNAS*, 1989; West et al., *PNAS*, 1992; Eaholtz et al., *Neuron*, 1995; Rohl et al., *Biochem.*, 1999

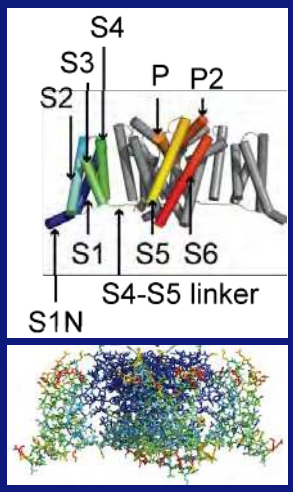
The NaChBac Family of Bacterial Sodium Channels

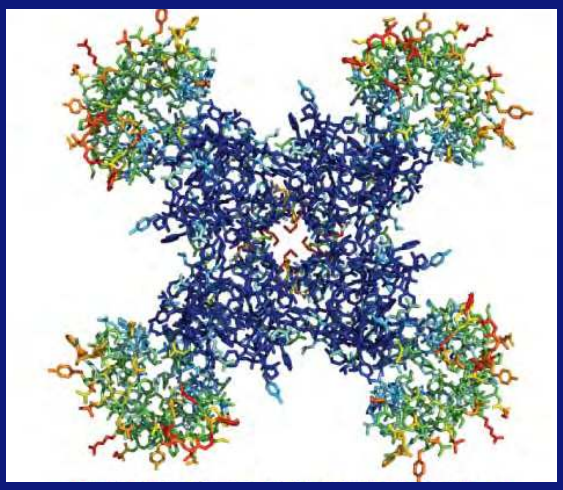


Ren D, Navarro B, Xu H, Yue L, Shi Q, Clapham DE. A prokaryotic voltage-gated sodium channel. *Science* 294:2372-2375 (2001).

Koishi R, Xu H, Ren D, Navarro B, Spiller BW, Shi Q, Clapham DE. A superfamily of voltage-gated sodium channels in bacteria. *J Biol Chem* 279:9532-9538.

Structure of NavAb/I217C at 2.7 Å

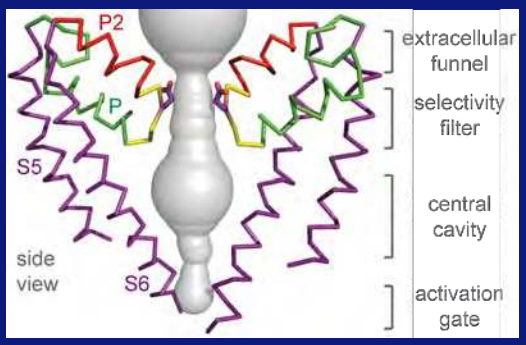


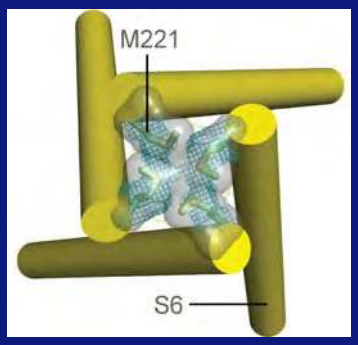


Temperature factors show dynamic character of the voltage sensor
Space Group: *I222*; 36,477 reflections; R Factors: 26.6/27.3

Payandeh, Scheuer, Zheng, and Catterall, *Nature*, 2011

The Architecture of the Pore

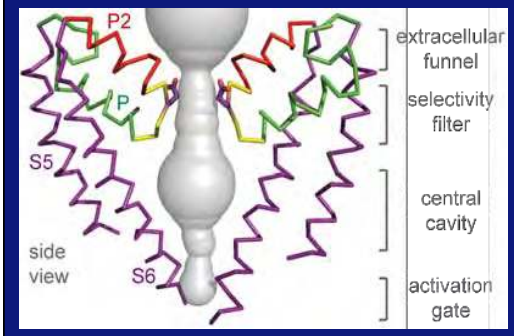


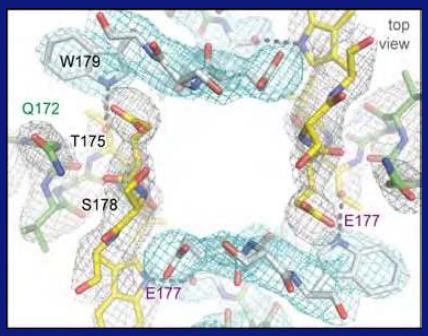


A conserved P-helix and a novel P2-helix flank the selectivity filter.
The central cavity is very large.

The activation gate is tightly closed

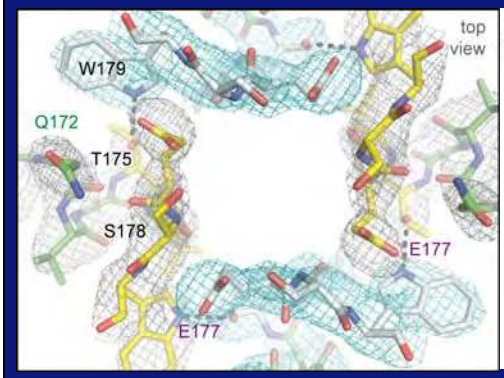
The Selectivity Filter Has An Outer Rectangle of Four Glutamates with a Central Opening of 4.6 Å

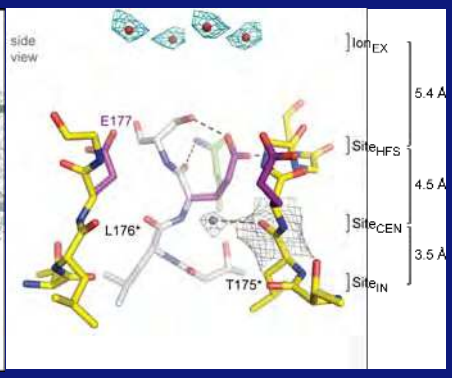




A hydrogen bond between T175 and W179 staples neighboring subunits.

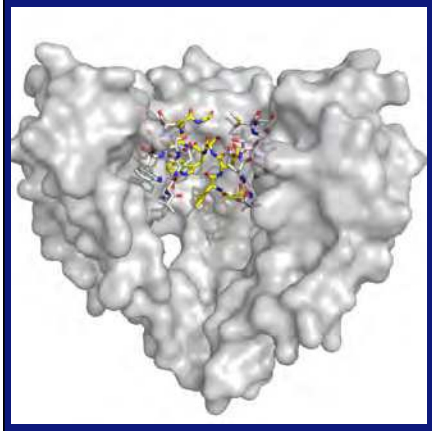
Three Sequential Interaction Sites in the Selectivity Filter

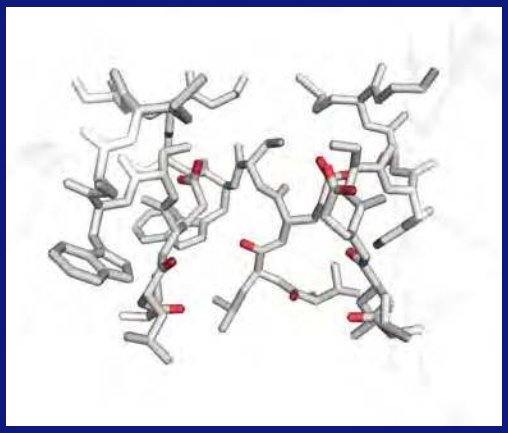




The Selectivity Filter is wide: 4.6 Å.
Na^+ is conducted with associated waters of hydration:
Two planar H_2O at $Site_{HFS}$ and four at $Site_{CEN}$ and $Site_{IN}$.
Backbone carbonyls of T175 and L176 bind square Na^+:$4H_2O$ complex.

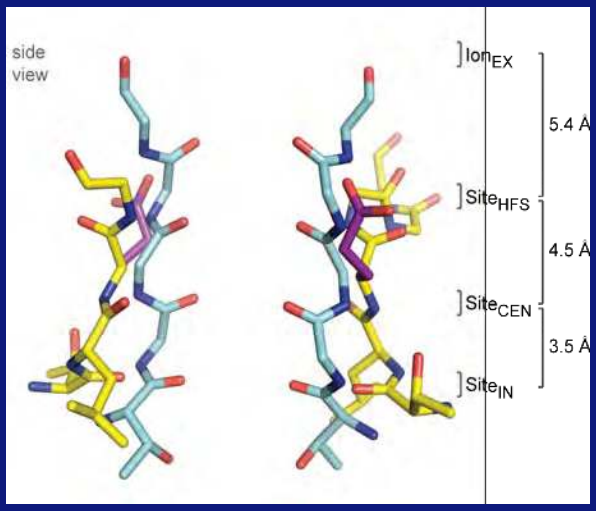
3D View of the NavAb Selectivity Filter





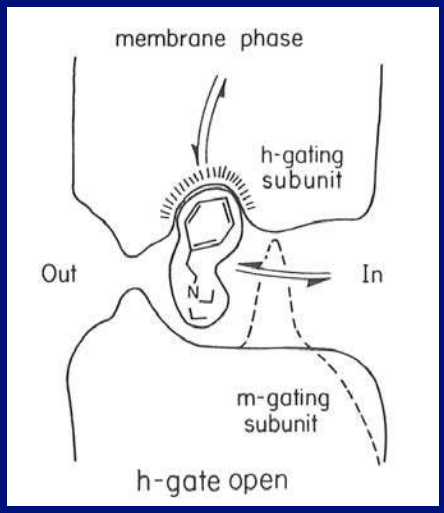
- Coordinating E177 carboxyls and T175/L176 carbonyls are highlighted in red.

K_V Selectivity Filter Fits Inside of the NavAb Selectivity Filter



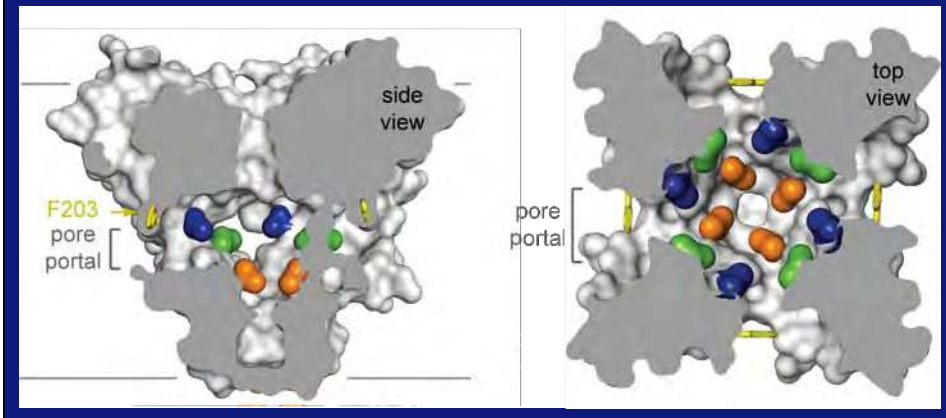
- K_V channels conduct dehydrated K^+; NavAb channel conducts hydrated Na^+.

The Modulated Receptor Hypothesis



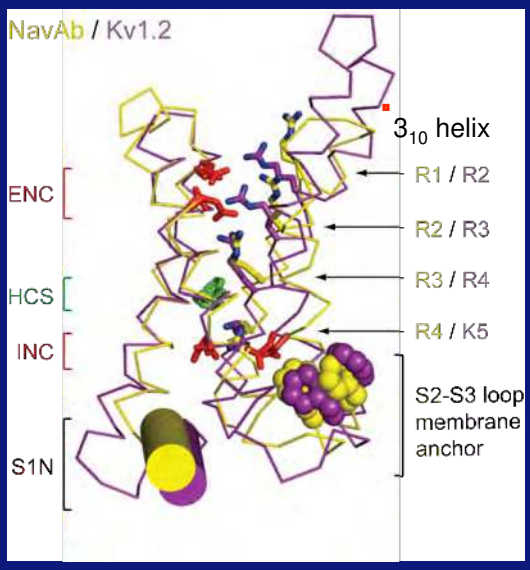
Small hydrophobic drugs may reach their receptor site in the pore through either the open activation gate or from the membrane phase.
Hille, *J Gen Physiol* 1977

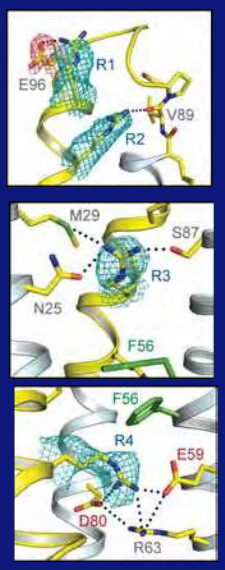
Fenestrations Lead to the Local Anesthetic Receptor Site



Ragsdale, McPhee, Scheuer, & Catterall, *Science* 1994; *PNAS*, 1996
Payandeh, Scheuer, Zheng, & Catterall, *Nature*, 2011

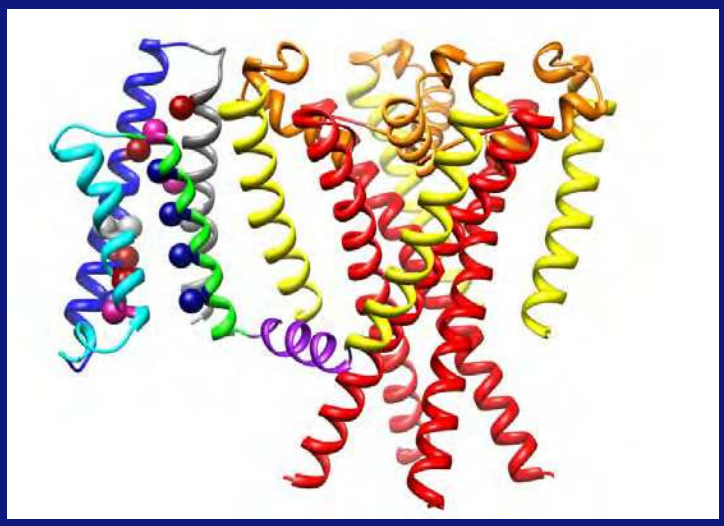
The NavAb Voltage Sensor





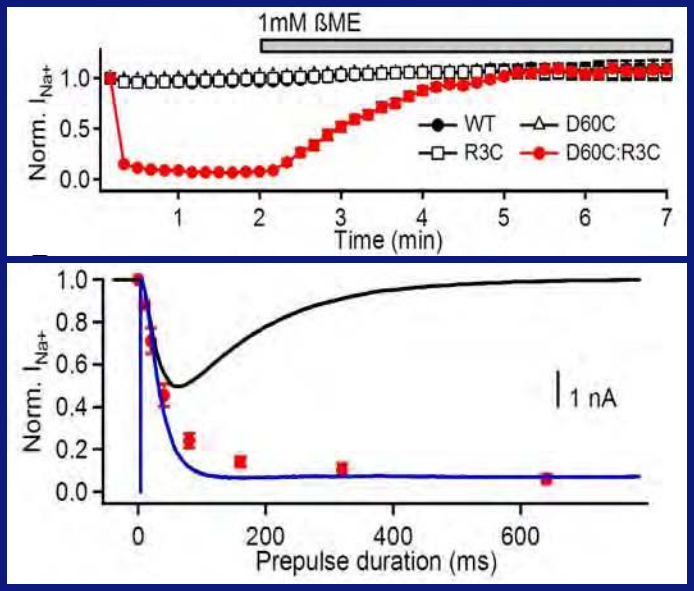
A pre-open state: voltage sensors activated but pore still closed.

Sliding Helix Model with Partial α-Helix to 3_{10}-Helix Transition in S4



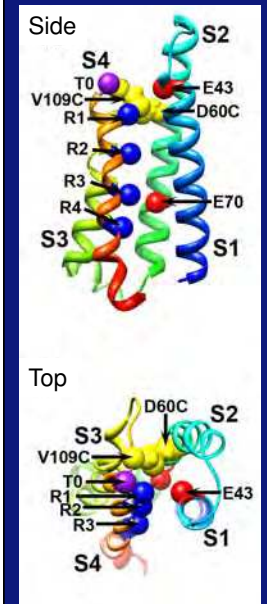
Yarov-Yarovoy, DeCaen, Westenbroek, Pan, Scheuer, Baker, & Catterall, *PNAS* 2011

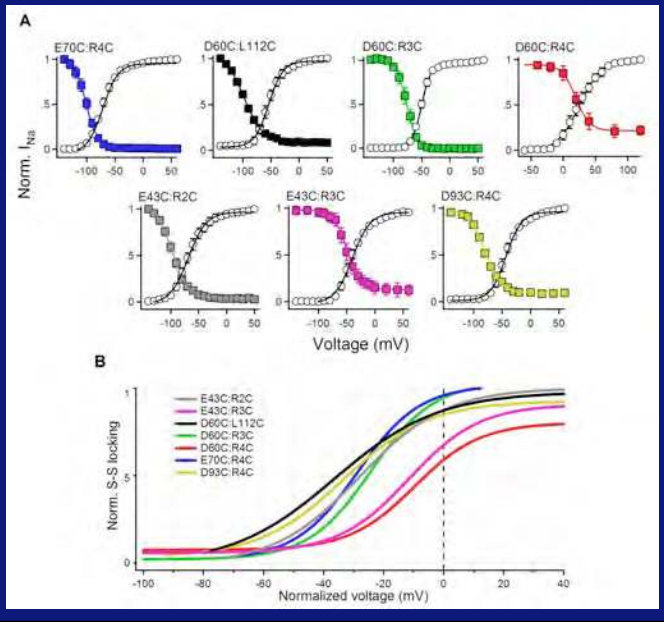
Disulfide Locking the NaChBac Voltage Sensor



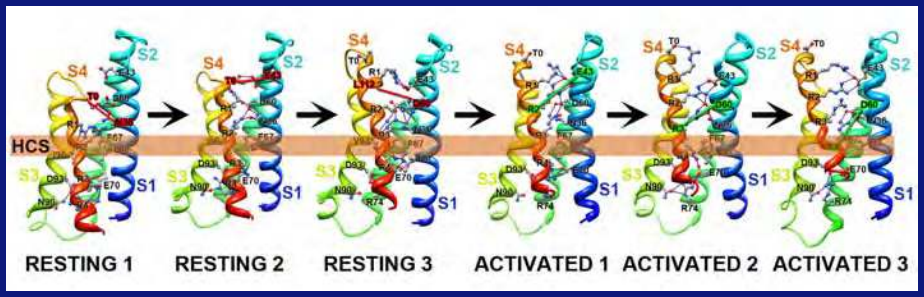
DeCaen, Zhao, Scheuer, and Catterall, *PNAS*, 2008

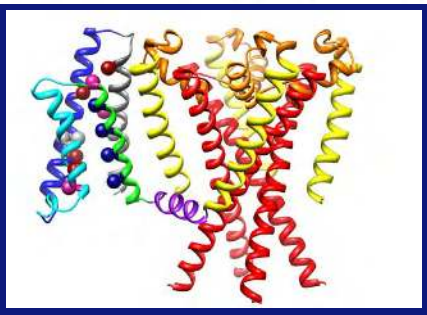
Sequence of Ion Pair Formation By Gating Charges



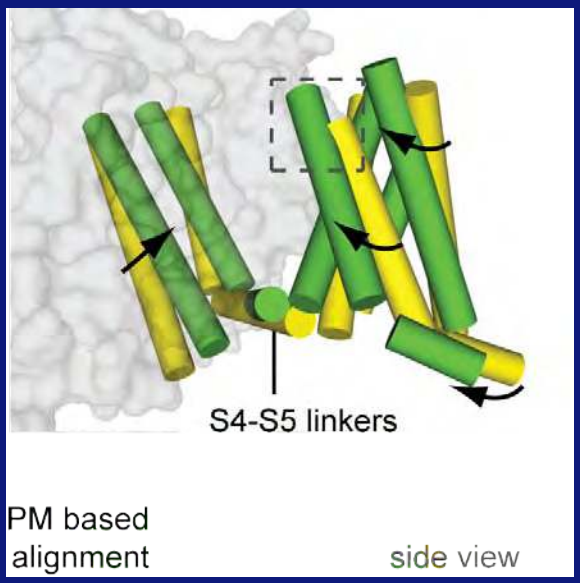


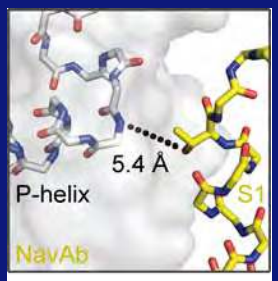
Stepwise Activation of a Voltage Sensor



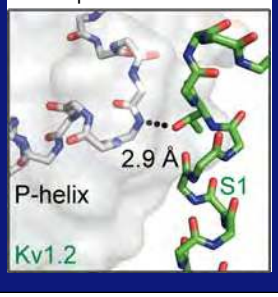


A Rolling Movement of the Voltage Sensor Opens the Pore

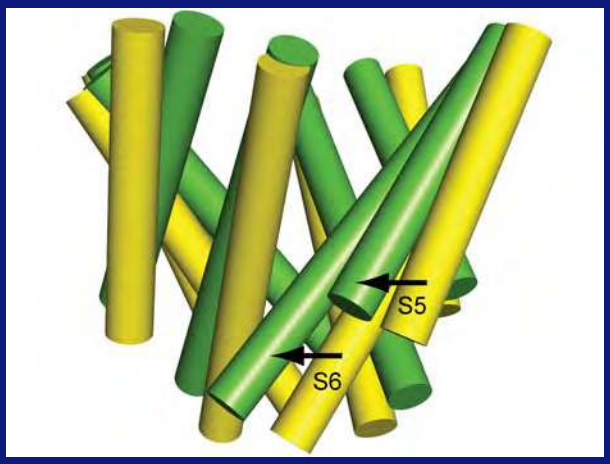


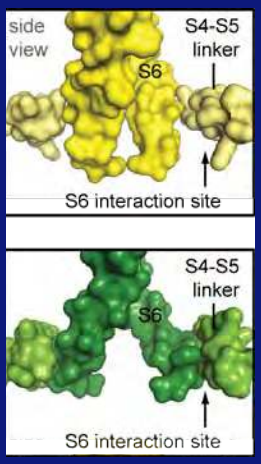


New open-state interaction



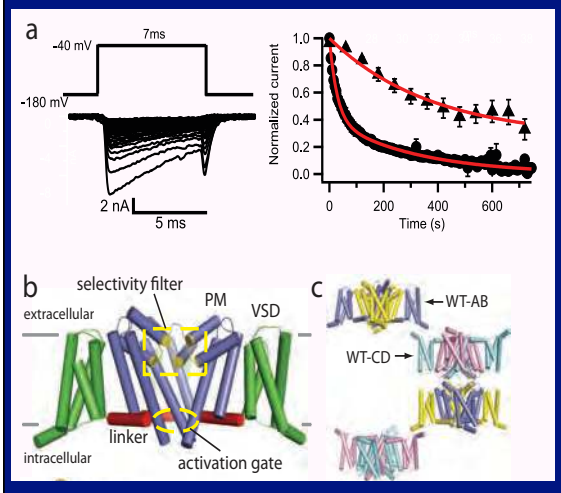
The Pore Opens with an Iris-like Motion

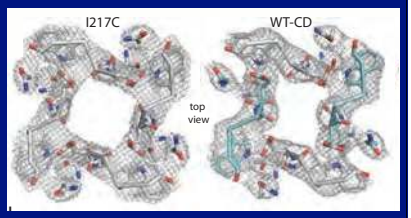


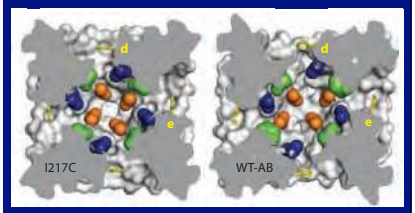


A new interaction is formed between S6 and the S4-S5 linker.

Asymmetric Pore Collapse During Slow Inactivation







Payandeh, Gamal El-Din, Scheuer, Zheng, and Catterall, *Nature,* 2012

New Structure-Based Conclusions

- Selectivity filter has three coordination sites:
  - One high field strength site composed of E177 carboxyls
  - Two sites composed of T175/L176 backbone carbonyls
- Na^+ is transported in partially hydrated form
- S4 moves gating charge by a sliding helix mechanism
  - Catalyzed by exchange of ion pair partners
- Rolling motion of voltage sensor opens the pore
  - Iris-like movement of activation gate
- Slow inactivation causes asymmetric pore collapse
- Drug receptor site is in the central cavity of the pore
- Fenestrations provide drug access from membrane phase
  - Slow inactivation changes conformation of drug receptor site

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Rachel Klevit, David Baker, Biochemistry

Regis Pomès, University of Toronto
Molecular Dynamics

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