Molecular Basis of Neuronal Signaling

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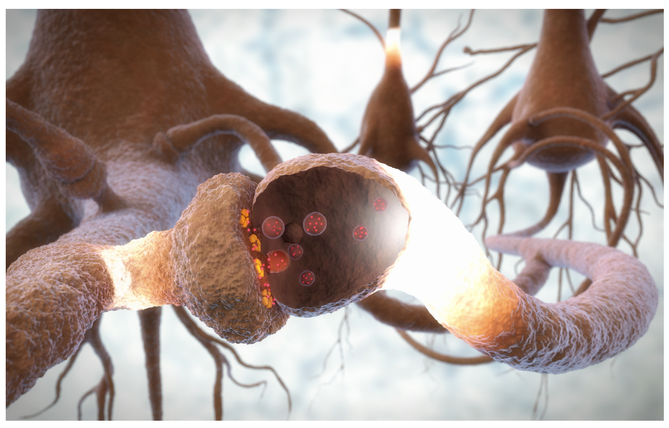
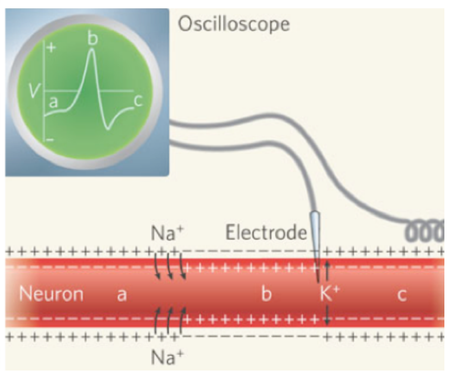
Abstract

A single-channel kinetic models were constructed for both voltage-gated sodium and potassium channels based on the kinetic rates of their voltage-sensor domains (VSDs). The modeling results indicate that neural signaling casted successfully in the form of Hodgkin-Huxley (HH) equations can arise from a single (fast) sodium / (slow) potassium channel pair. A sodium channel homology model together with sequence analysis and mutation studies indicate detailed polar residue pair interaction contribute to the kinetic difference between sodium and potassium channels . The results showed that cellular signaling behavior can arise from molecular details of individual channel.

Background





-Neural electrical signal is mainly propagated by voltage-gated ion channels: e.g. sodium/potassium channel

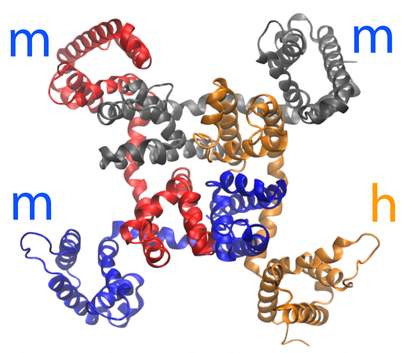
Hodgkin-Huxley (HH) Model:

$$C\frac{dV}{dt} = -[\underbrace{g_{\mathrm{Na}}m^3h(V-V_{\mathrm{Na}})}_{\mathrm{Na}} + \underbrace{g_{\mathrm{K}}n^4(V-V_{\mathrm{K}})}_{\mathrm{K}} + g_{\mathrm{L}}(V-V_{\mathrm{L}})] + I$$

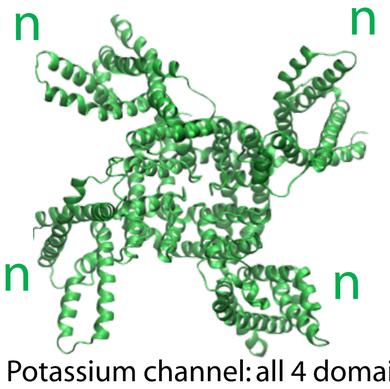
$$\frac{dx}{dt} = \alpha_x(V)(1-x) - \beta_x(V)x,\ x = m,\ h,\ n$$

- HH model was the first successful model to describe quantitatively the firing and thresholding behavior of a neuron

- Eukaryotic sodium channel is a hetrotetramer; potassium channel is a monotetramer. Is there a correspondence between molecular structure and the macroscopic HH model?



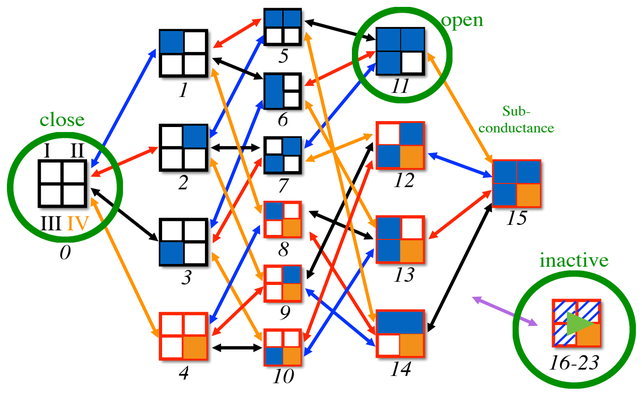
Sodium channel: distinct domains are shown in different colors



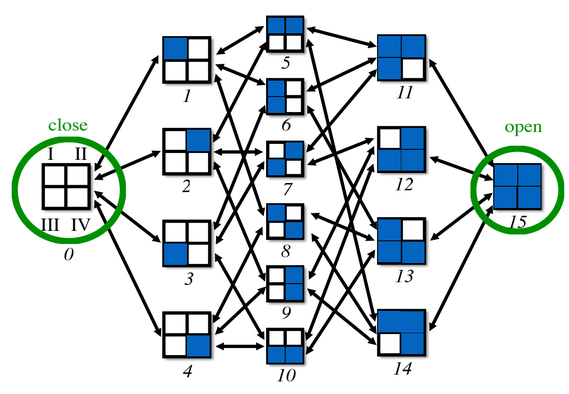
Potassium channel: all 4 domains are identical

VSD Motion Correspondence in HH Model

Sodium Channel



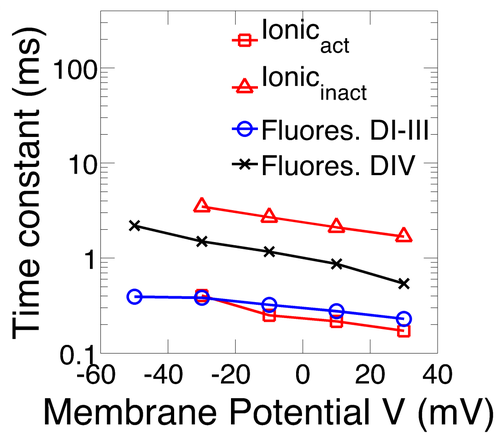
Potassium Channel



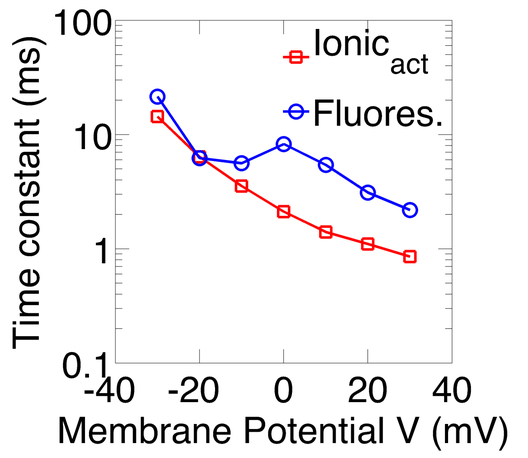
-Individual domain of the homotetramer K channel and hetrotetramer Na channel is represented by colored boxes. The state of the channels is described by probability P(state i)

-Time constant for each transition obtained from single-channel experimental fluorescence time scales of VSD motion (2-state model)

Na



K



Comparison between fluorescence (blue/black) time scales for VSD motion and ionic current (red) time scales in channel activation/inactivation.

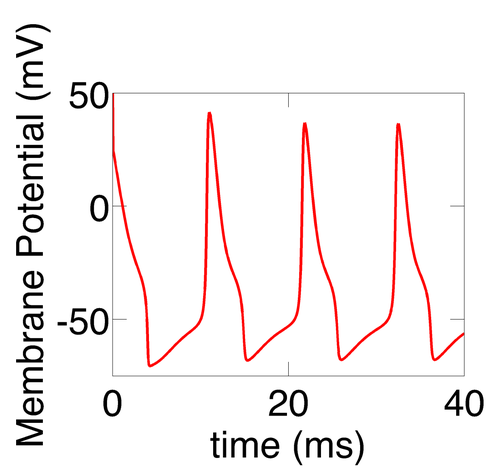
- DI-III in sodium channel and all identical domains in potassium channel correspond to channel **activation** (m, n)

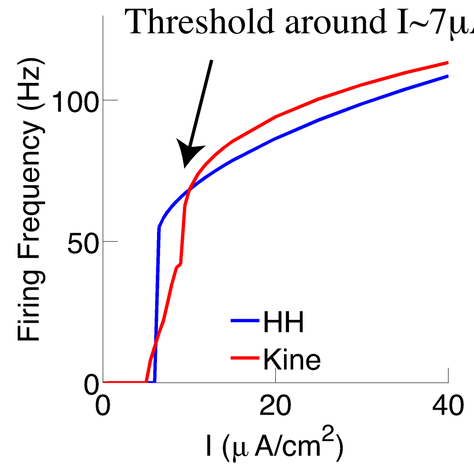
- DIV in sodium channel corresponds to channel **inactivaton** (h)

Neural Firing and Thresholding

$$C\frac{dV}{dt} = -[g_{\mathrm{Na}}P_{\mathrm{Na}}(\mathrm{Open})(V-V_{\mathrm{Na}}) + g_{\mathrm{K}}P_{\mathrm{K}}(\mathrm{Open})(V-V_{\mathrm{K}}) + g_{\mathrm{L}}(V-V_{\mathrm{L}})] + I$$

- The kinetic models were incorporated in a HH-like equation



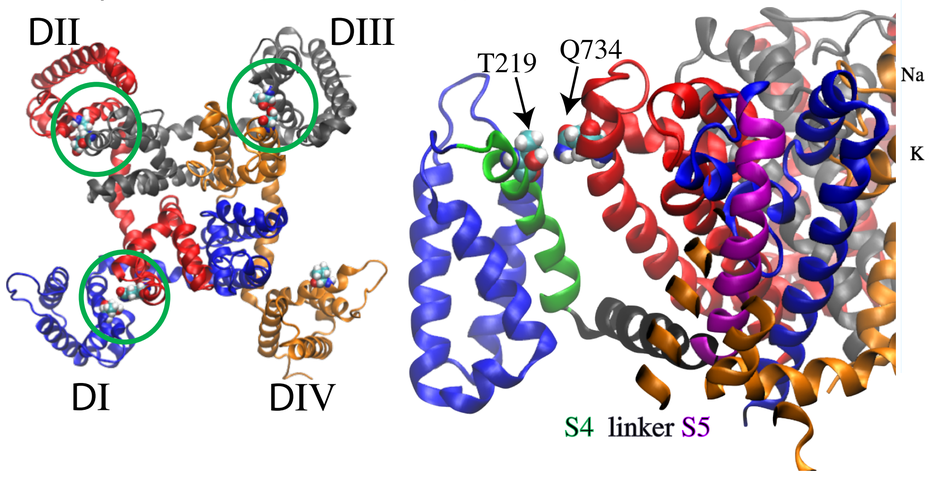


- Neural firing was simulated by the kinetic model, the firing frequency is comparable to HH model

- Nonlinear threshold behavior was captured

Polar Pair Interaction for Kinetic Difference

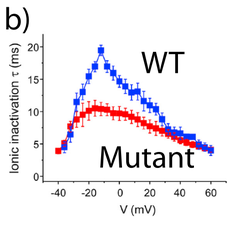
Homology atomistic model of an eukaryotic Na channel
Template: Navab (PDB code: 3RVY)



a)

		helix S4	helix S5
Na channel	Domain I	RTFRVLRALK	IFALIGMQLY
	Domain II	RSFRLLRVGK	IFAVMGQQLF
	Domain III	RSMRTLRALR	IFSIMGVQLF
	Domain IV	RVFRVGRVLR	IYSMFGMSFF
K channel	domains	RLVRVFRIFK	SSAVYFAEVD
		polar/hydrophobic	polar

b)



a) Dipole-dipole interaction between S4 and S5 helices of neighboring domains exists only in DI to DIII, not in DIV and K channel

b) Mutation experiment showed that by mutating the hydrophobic residue to a polar residue on S4 helix in DIV speed up the inactivation by 2-fold

Conclusion

- Single channel dynamics can be well-represented by VSD conformational rearrangement motion

- The molecular motion of Na/K VSD corresponds to the variables m, h and n in Hodgkin-Huxley model

- The dipole-dipole residue pairs in three of the VSDs of Na channel could account for the dynamical difference in activation time scales between Na and K

References

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