Modeling the sodium conductance

Selina Baeza-Loya

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Introduction

To clear up confusion and mollify any misunderstandings, I have typed up the modeling of sodium conductance using Hodgkin-Huxley (HH) formulations, as I understand them. I've included some inserts from the original HH papers (specifically, the 1952d paper, A QUANTITATIVE DESCRIPTION OF MEMBRANE CURRENT AND ITS APPLICATION TO CONDUCTION AND EXCITATION IN NERVE), as well as some other works that I've referenced over the years.

Sodium conductance modeled as a set of first order equations

To model a traditional, TTX-sensitive transient sodium current, as was recorded in the giant squid axon by Hodgkin and Huxley, we begin with:

$$g_{Na} = \bar{g}_{Na} m^3 h$$

where g_{Na} is the sodium conductance, $\bar{g}_{Na}$ is the fixed sodium conductance density of open Na channels, m is the activation rate and h is the inactivation rate.

Hodgkin and Huxley described the activation and inactivation with the following gating equations:

$$m' = \alpha_m(1 - m) - \beta_m m$$

$$h' = \alpha_h(1 - h) - \beta_h h$$

where α and β are rate constants. See page 512, Hodgkin and Huxley 1952d.

To characterize voltage-gated channels, equations are fit to voltage clamp data. Under voltage clamp conditions, where the voltage can be held constant, the nonlinear gating equations can be reduced to:

$$m = m_\infty - (m_\infty - m_0)\exp\left(-\frac{t}{\tau_m}\right); h = h_\infty - (h_\infty - h_0)\exp\left(-\frac{t}{\tau_h}\right)$$

Where $m_\infty$is the steady-state activation function, τ_m is the time constant of activation, h_∞ is the steady-state inactivation function, and τ_h is the time constant of inactivation. Steady state voltage-dependent time constants of activation and inactivation functions are as follows:

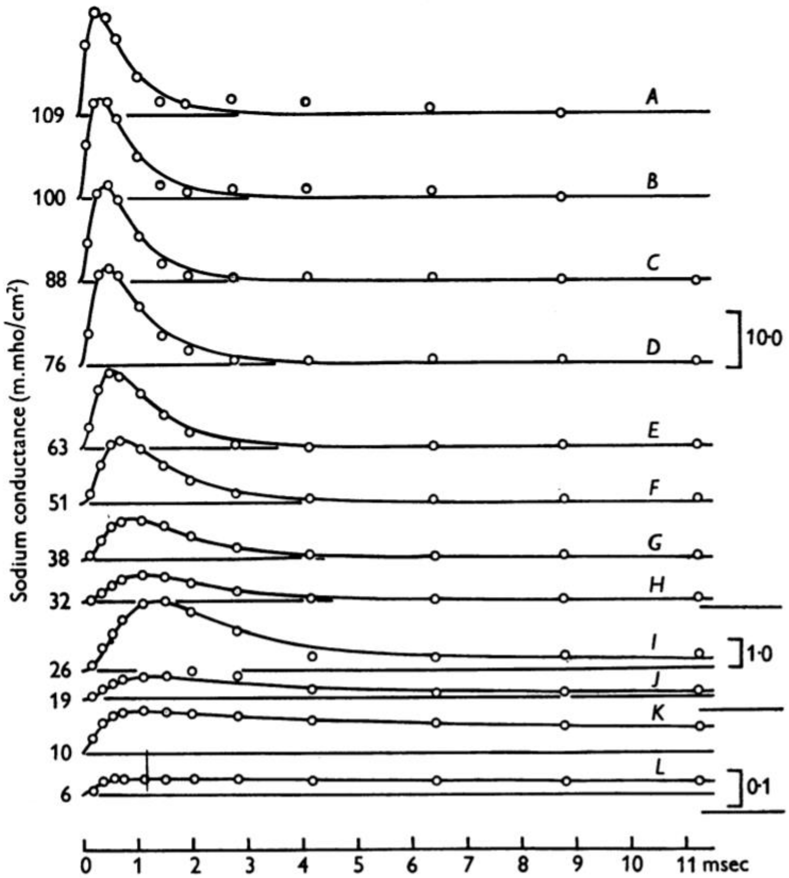
$$\tau_m = \frac{1}{\alpha_m + \beta_m}; \tau_h = \frac{1}{\alpha_h + \beta_h}$$

Ok, so given these steady-state equations, and the following two assumptions: At rest, the sodium conductance is small relative to the conductance during a large depolarization, (1) which therefore allows us (them) to neglect m_∞ if the depolarization is greater than 30 mV. Also, inactivation is "very nearly complete" is the V < -30 mV so that (2) h_∞ may also be neglected.

We can further reduce the equation for sodium conductance to:

$$g_{Na} = \bar{g}_{Na}[1 - \exp\left(-\frac{t}{\tau_m}\right)]^3 \exp\left(-\frac{t}{\tau_h}\right)$$

Then $\bar{g}_{Na}$, τ_m and τ_h values were calculated by fitting that equation to the following experimental data:



Using these, they were able to calculate α and β using: $\alpha_m = m_\infty/\tau_m$ and $\beta_m = (1 - m_\infty)/\tau_m$ as shown below:

TABLE 2. Analysis of curves in Fig. 6

Curve	V (mV)	g'_{Na} (m.mho/cm²)	m_∞	τ_m (msec)	α_m (msec⁻¹)	β_m (msec⁻¹)	τ_h (msec)	h_∞	α_h (msec⁻¹)	β_h (msec⁻¹)
—	(−∞)	(42·9)	(1·00)	—	—	—	—	—	—	—
A	−109	40·3	0·980	0·140	7·0	(0·14)	0·67	(0)	(0)	1·50
B	−100	42·6	0·997	0·160	6·2	(0·02)	0·67	(0)	(0)	1·50
C	− 88	46·8	1·029	0·200	5·15	(−0·14)	0·67	(0)	(0)	1·50
D	− 76	39·5	0·975	0·189	5·15	0·13	0·84	(0)	(0)	1·19
E	− 63	38·2	0·963	0·252	3·82	0·15	0·84	(0)	(0)	1·19
F	− 51	30·7	0·895	0·318	2·82	0·33	1·06	(0)	(0)	0·94
G	− 38	20·0	0·778	0·382	2·03	0·58	1·27	(0)	(0)	0·79
H	− 32	15·3	0·709	0·520	1·36	0·56	1·33	(0)	(0)	0·75
I	− 26	7·90	0·569	0·600	0·95	0·72	(1·50)	(0·029)	(0·02)	(0·65)
J	− 19	1·44	0·323	0·400	0·81	1·69	(2·30)	(0·069)	(0·03)	(0·40)
K	− 10	0·13	0·145	0·220	0·66	3·9	(5·52)	(0·263)	(0·05)	(0·13)
L	− 6	0·046	0·103	0·200	0·51	4·5	(6·73)	(0·388)	(0·06)	(0·09)
—	(0)	(0·0033)	(0·042)	—	—	—	—	(0·608)	—	—

Values enclosed in brackets were not plotted in Figs. 7–10 either because they were too small to be reliable or because they were not independent measurements obtained in this experiment.

α_h and β_h were derived in a similar manner, by plotting against data and solved using: $\alpha_h = h_\infty/\tau_h$ and $\beta_h = (1 - h_\infty)/\tau_h$.

Modeling sodium currents in vestibular ganglion neurons

We used a different but functionally equivalent formulation:

$$I_{Na} = \bar{g}_{Na}(m^3 h)(V - E_{Na})$$

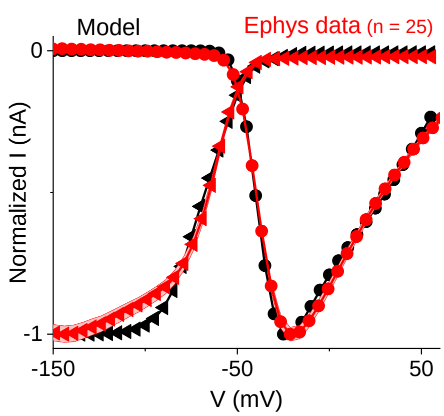
where

$$m' = \frac{m_\infty - m}{\tau_m}; \;\; h' = \frac{h_\infty - h}{\tau_h}$$

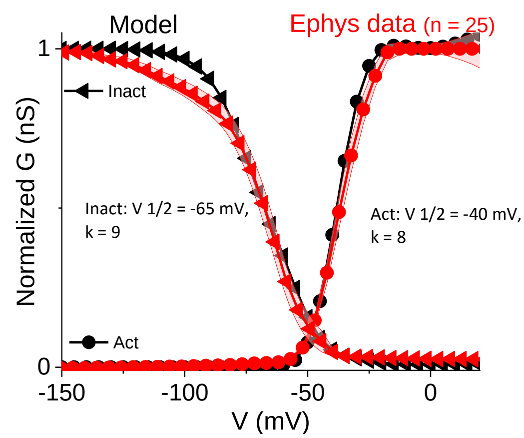
and

$$m_\infty = \left[1 + \exp\left(-\frac{V + V^{1/2}}{k}\right)\right]^{-1} \; ; \;\; h_\infty = \left[1 + \exp\left(-\frac{V + V^{1/2}}{k}\right)\right]^{-1}$$

$m_\infty$is still the steady-state activation function, $\tau_m$the time constant of activation, h_∞ the steady-state inactivation function, and τ_h the time constant of inactivation. Steady Conductance density ($\bar{g}$), reversal potential (E_{Na}), half activation ($V^{1/2}$), and slope factor (k) were based on experimentally derived values from this our study.



Current-Voltage curves comparison



Conductance-Voltage curves comparison

Our steady state equations are therefore:

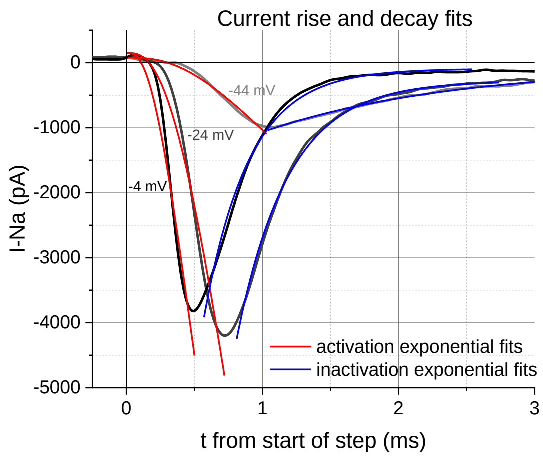
$$m_\infty = \left[1 + \exp\left(-\frac{V + 40}{8}\right)\right]^{-1} \; ; \;\; h_\infty = \left[1 + \exp\left(-\frac{V + 65}{9}\right)\right]^{-1}$$

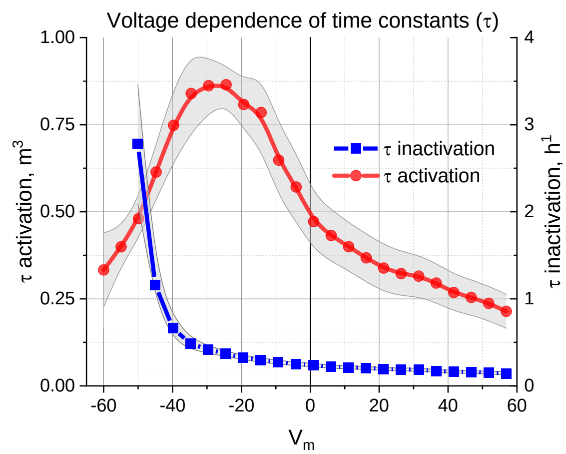
Our time constants of activation and inactivation were derived by fitting the rising and decay phase of sodium currents to determine the voltage-dependence of time constants. The time constant of activation (τ_m) was assessed by fitting the rising phase of a sodium current with the equation:

$$y = y_0 - A(1 - e^{-\frac{x}{\tau}})^3$$

The power (3) was used since it best fit the very fast rise of the sodium current. The time constant of inactivation (τ_h) was assessed by fitting the decaying phase of a sodium current with:

$$y = y_0 + A(e^{-\frac{x}{\tau}})$$





Using a similar methodology, Rothman and Manis (2003c) use the following equations for τ_m and τ_h, which were subsequently used in Hight and Kalluri 2016, and Ventura and Kalluri, 2019:

$$\tau_m = 10\left\{5\exp\left[\frac{V+60}{18}\right] + 36\exp\left[-\frac{V+60}{25}\right]\right\}^{-1} + 0.04$$

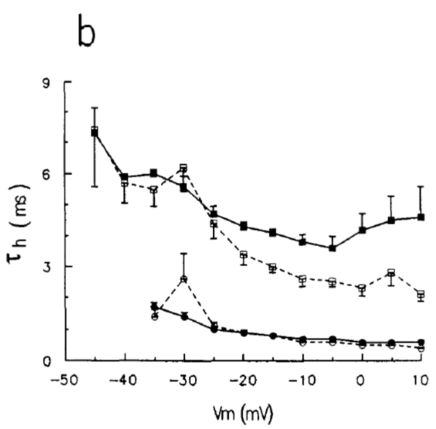
$$\tau_h = 100\left\{7\exp\left[\frac{V+60}{11}\right] + 10\exp\left[-\frac{V+60}{25}\right]\right\}^{-1} + 0.6$$

where presumably

$$\alpha_m = 5\exp\left[\frac{V+60}{18}\right]; \beta_m = 36\exp\left[-\frac{V+60}{25}\right]$$

$$\alpha_h = 7\exp\left[\frac{V+60}{11}\right]; \beta_m = 10\exp\left[-\frac{V+60}{25}\right]$$

These were putatively derived from data in Costa (1996):



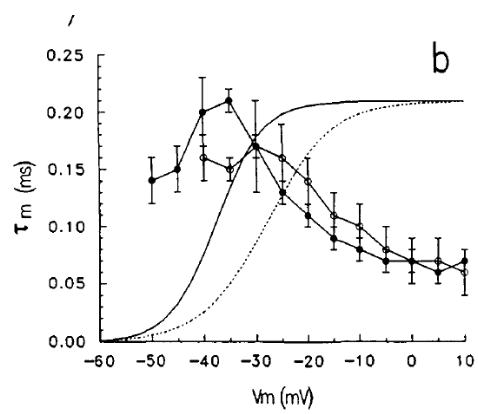


Fig. 4. Time-constant of activation (τ_m). A: illustration of the measurements (i_t and i_c) to calculate the time-constant of activation (τ_m, Eq. 3). Two exponentials were fit to the falling phase of the signal and extrapolated to the time of the start of the pulse; i_t and i_c as in Eq. (3). B: voltage-dependence of activation τ_m (mean values) in older (P > 25, filled circles) and immature cells (P_{3-5}, open circles); error bars are ± S.E.M. Corresponding representative activation (m_∞) curves obtained with the mean values in Table 1 ($V_{1/2}$ and V_s) were superimposed (solid line: P > 25; doted line: P_{3-5}).

Left: voltage-dependence of the time-constants of inactivation measured in activation protocols

Citations:

Costa PF. The kinetic parameters of sodium currents in maturing acutely isolated rat hippocampal CA1 neurones. *Developmental Brain Research* 91: 29–40, 1996.

Hight AE, **Kalluri R**. A biophysical model examining the role of low-voltage-activated potassium currents in shaping the responses of vestibular ganglion neurons. *Journal of Neurophysiology* 116: 503–521, 2016.

Hodgkin AL, **Huxley AF**. A quantitative description of membrane current and its application to conduction and excitation in nerve. *The Journal of Physiology* 117: 500–544, 1952.

Rothman JS, **Manis PB**. The Roles Potassium Currents Play in Regulating the Electrical Activity of Ventral Cochlear Nucleus Neurons. *Journal of Neurophysiology* 89: 3097–3113, 2003.

Ventura CM, **Kalluri R**. Enhanced Activation of HCN Channels Reduces Excitability and Spike-Timing Regularity in Maturing Vestibular Afferent Neurons. *J Neurosci* 39: 2860–2876, 2019.