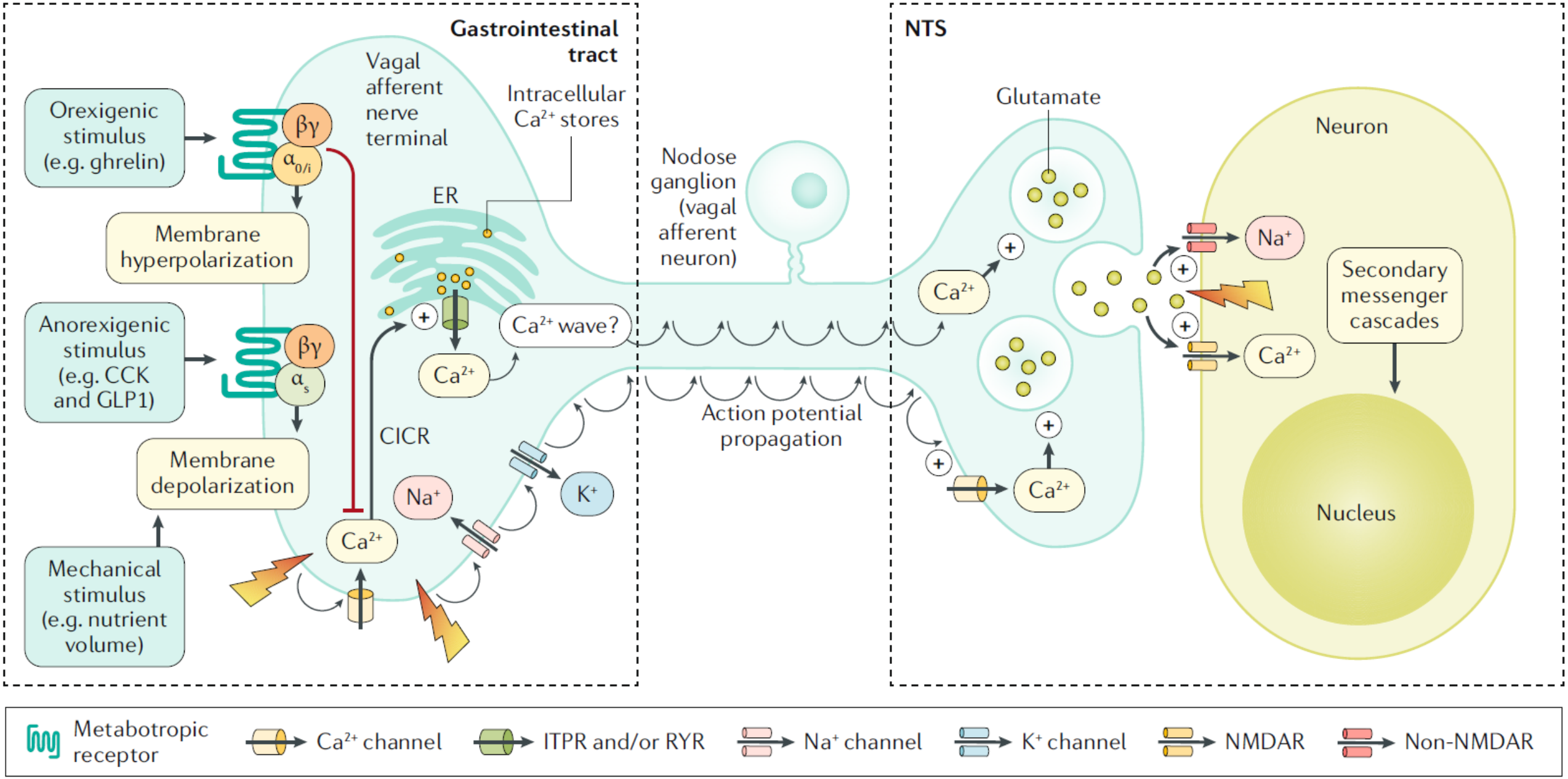
Microbiota Gut-Brain Axis: Action Potential of Afferent Vagus Nerve Simulation

Shannon Q Fernandes

LEHIGH
UNIVERSITY

Afferent Vagus Nerve



Action Potential

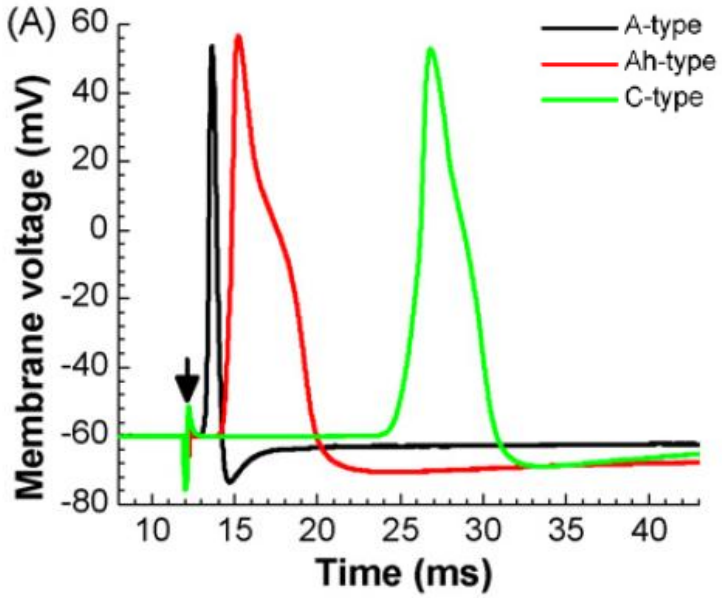
In the rat nodose ganglia, there neurons exists to be of the following types:

Myelinated A-type ~13%

Myelinated Ah-type ~12%

Unmyelinated C-type afferents ~75%

Action potential waveforms



Conduction velocity

A type ~10 m/s

Ah type: ~4 m/s

C type: ~ less than 1 m/s.

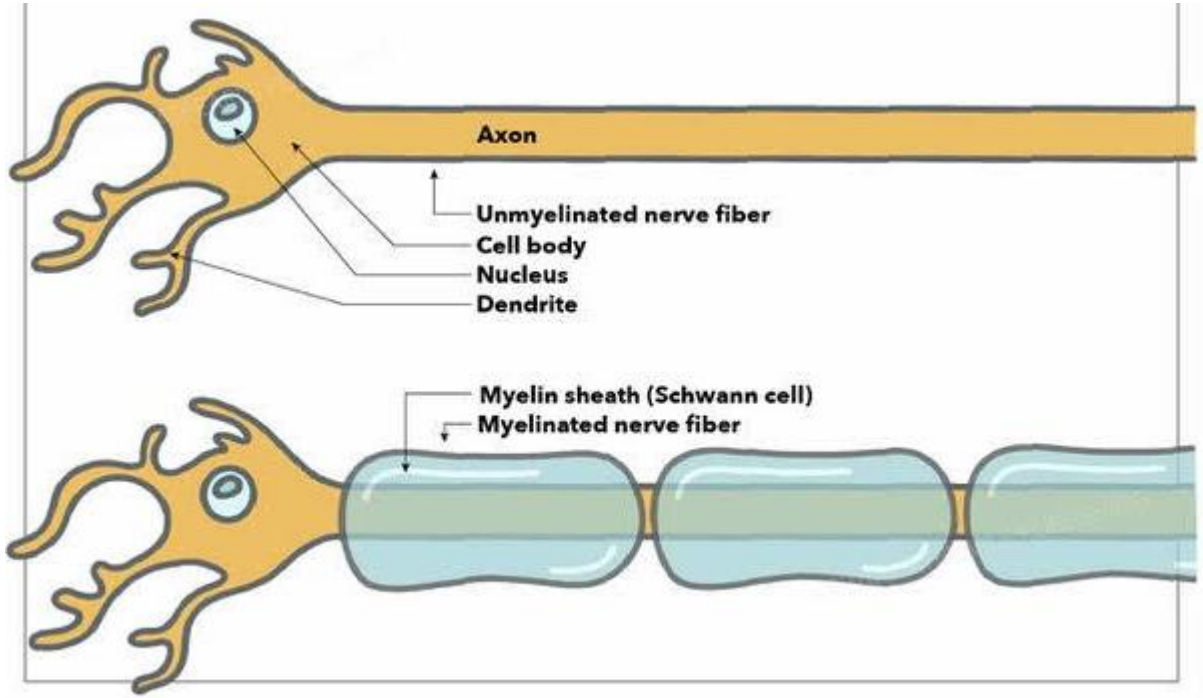
Electrophysiological and pharmacological validation of vagal afferent fiber type of neurons enzymatically isolated from rat nodose ganglia

Bai-Yan Li [a,b], John H. Schild [a,*]

[a] Department of Biomedical Engineering, Indiana University Purdue University Indianapolis, 723 W. Michigan St., Suite SL174, Indianapolis, IN 46202, United States

[b] Department of Pharmacology, Harbin Medical University, Harbin 150081, China

Received 18 January 2007; received in revised form 26 March 2007; accepted 2 April 2007



A- and C-Type Rat Nodose Sensory Neurons: Model Interpretations of Dynamic Discharge Characteristics

J. H. SCHILD, J. W. CLARK, M. HAY, D. MENDELOWITZ, M. C. ANDRESEN, AND D. L. KUNZE
Department of Electrical and Computer Engineering, Rice University, Houston 77251-1892; Department of Molecular Physiology and Biophysics, Baylor College of Medicine, Houston, 77030; and Department of Physiology and Biophysics, University of Texas Medical Branch, Galveston, Texas 77555

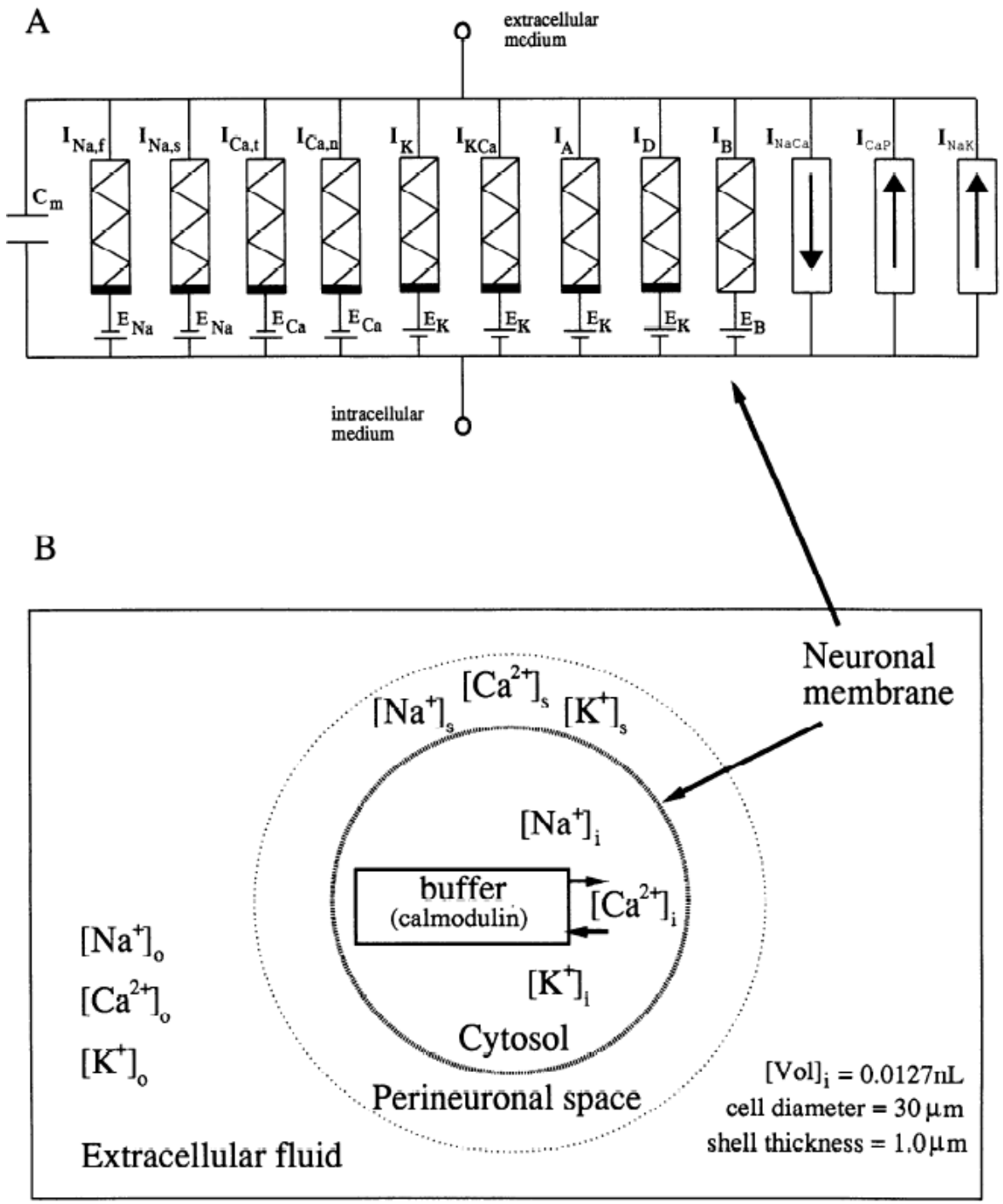
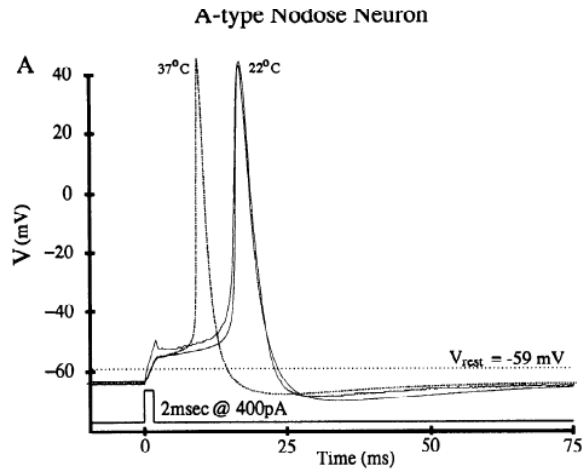
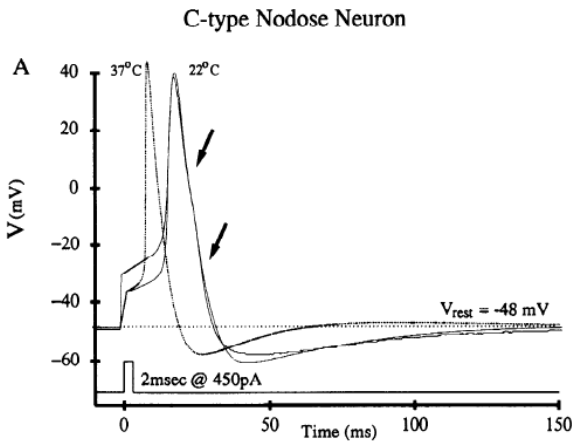


FIG. 2. Parallel conductance membrane model of a rat nodose neuron. *A*: equivalent circuit of the neuron where membrane capacitance C_m is shunted by time- and voltage-dependent sodium, calcium, and potassium channel-mediated currents (I_{Na_f}, I_{Na_s}, $I_{Ca,t}$, $I_{Ca,n}$, I_K), a Ca^{2+} activated potassium current ($I_{K,Ca}$), a transient outward current (I_A), a delay current (I_D), a linear leakage current (I_B), and electrogenic transporter-mediated currents (Na^+-Ca^{2+} exchanger, Na^+-K^+ pump, Ca^{2+} pump). E_{Na}, E_K, E_{Ca}, and E_B are the equilibrium potentials for the sodium, potassium, calcium, and background ion-mediated channels, respectively. *B*: lumped fluid compartmental model. This model consists of 3 separate well-stirred fluid compartments containing Na^+, K^+, and Ca^{2+} in different concentrations. The 3 compartments are *1*) an intracellular fluid space describing lumped ion concentrations ($[Ca^{2+}]_i$, $[Na^+]_i$, $[K^+]_i$) and protein binding sites for Ca^{2+} on a calmodulin type buffer, *2*) a 1.0 µm annular fluid space describing local ion concentrations ($[Ca^{2+}]_s$, $[Na^+]_s$, $[K^+]_s$) around the external surface of the neuron (not drawn to scale), and *3*) a large extracellular volume where all ionic concentrations ($[Ca^{2+}]_o$, $[Na^+]_o$, $[K^+]_o$) are assumed to be constant.





Mathematical model

Action potential

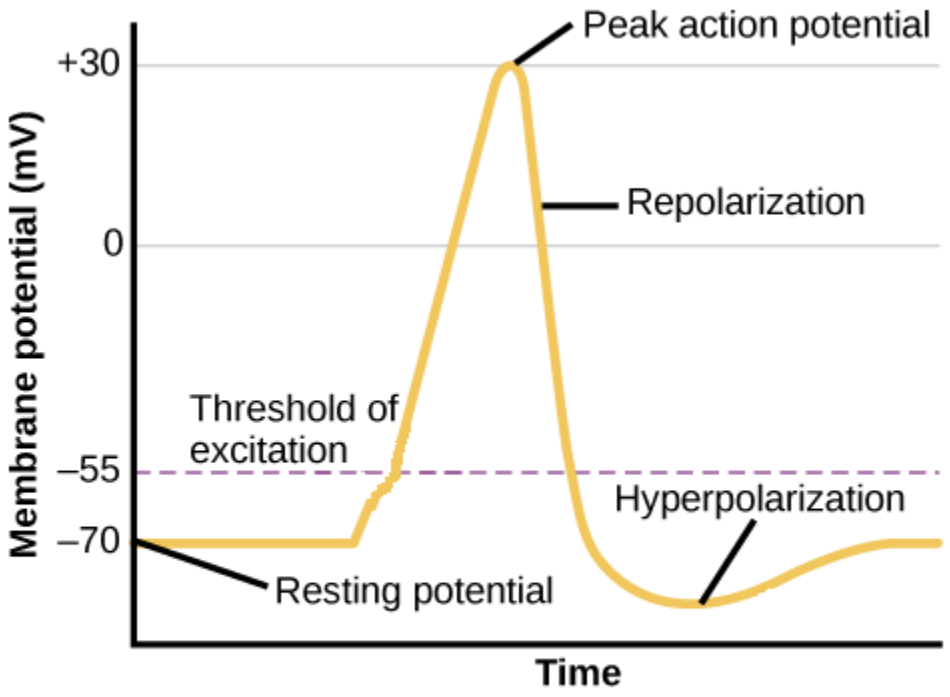
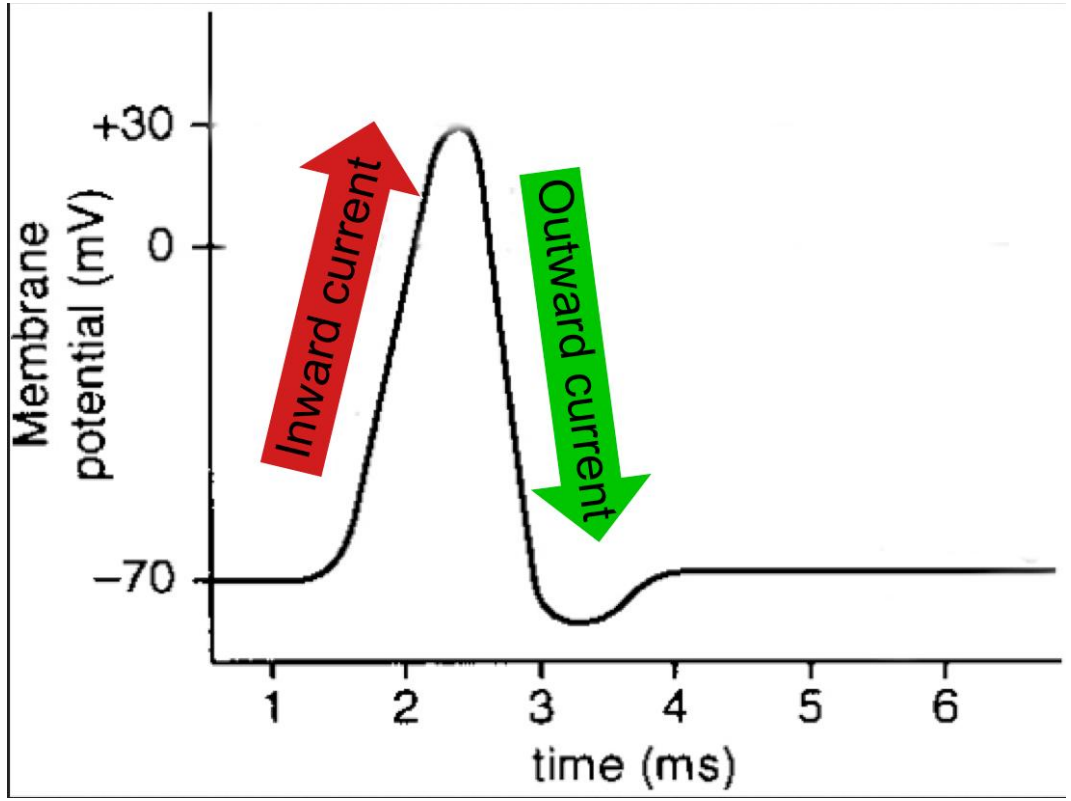


Image modified from "How neurons communicate: Figure 3," by OpenStax College, Biology (CC BY 3.0).



Inward Ca^{2+} channels

$I_{Ca,t}$: Low Threshold, Transient Calcium Current

$$I_{Ca,t} = \bar{g}_{Ca,t} d_t f_t (V - E_{Ca})$$

$$\dot{d}_t = \frac{d_{t\infty} - d_t}{\tau_{dt}} \qquad \dot{f}_t = \frac{f_{t\infty} - f_t}{\tau_{ft}} \qquad E_{Ca} = \frac{RT}{Z_{Ca}F} ln \frac{[Ca^{2+}]_s}{[Ca^{2+}]_i} - 78.7$$

$$\tau_{dt} = 22.0 \exp(-(0.052)^2 (V + 68.0)^2) + 2.5 \qquad \tau_{ft} = 103.0 \exp(-(0.050)^2 (V + 58.0)^2) + 12.5$$

$$d_{t\infty} = \frac{1.0}{1.0 + \exp((V + 54.00)/-5.75)} \qquad f_{t\infty} = \frac{1.0}{1.0 + \exp((V + 68.00)/6.0)}$$

$I_{Ca,n}$: High Threshold, Long-Lasting Calcium Current

$$I_{Ca,n} = \bar{g}_{Ca,n} d_n (0.55 f_{n_1} + 0.45 f_{n_2})(V - E_{Ca})$$

$$\dot{d}_n = \frac{d_{n\infty} - d_n}{\tau_{dn}} \qquad \dot{f}_{n_1} = \frac{f_{n_1\infty} - f_{n_1}}{\tau_{f_{n_1}}} \qquad \dot{f}_{n_2} = \frac{f_{n_2\infty} - f_{n_2}}{\tau_{f_{n_2}}}$$

$$\tau_{dn} = 3.25 \exp(-(0.042)^2 (V + 31.0)^2) + 0.395 \qquad \tau_{f_{n_1}} = 33.5 \exp(-(0.0395)^2 (V + 30.0)^2) + 5.0$$

$$\tau_{f_{n_2}} = 225.0 \exp(-(0.0275)^2 (V + 40.0)^2) + 75.00 \qquad d_{n\infty} = \frac{1.0}{1.0 + \exp((V + 20.0)/-4.5)}$$

$$f_{n_1\infty} = \frac{1.0}{1.0 + \exp((V + 20.0)/25.0)} \qquad f_{n_2\infty} = r_n + \frac{1.0}{1.0 + \exp((V + 40.0)/10.0)} \qquad r_n = \frac{0.2}{1.0 + \exp(\frac{V + 5.0}{-10.0})}$$

Inward Na^+ channels

Tetrodotoxin (TTX) is a sodium channel blocker.

I_{Na_f}: Fast, TTX Sensitive Sodium Current

Nav1.3, Nav1.7

$$I_{Na_f} = \bar{g}_{Na_f} m_f^3 h_f j (V - E_{Na})$$

$$\dot{m_f} = \frac{m_{f\infty} - m_f}{\tau_{m_f}} \qquad \dot{h_f} = \frac{h_{f\infty} - h_f}{\tau_{h_f}} \qquad \dot{j} = \frac{j_\infty - j}{\tau_j}$$

$$\tau_{m_f} = 0.75 \exp(-(0.0635)^2 (V + 40.35)^2) + 0.12 \qquad \tau_{h_f} = 6.5 \exp(-(0.0295)^2 (V + 75.00)^2) + 0.55$$

$$m_{f\infty} = \frac{1.0}{1.0 + \exp((V + 41.35)/-4.75)} \qquad h_{f\infty} = \frac{1.0}{1.0 + \exp((V + 62.00)/4.50)}$$

$$j_\infty = \frac{1.0}{1.0 + \exp((V + 40.00)/1.50)} \qquad \tau_j = \frac{25.0}{1.0 + \exp((V - 20.00)/4.50)} + 0.01$$

I_{Na_s}: Slower, TTX Insensitive Sodium Current

Nav1.8,Nav1.9

$$I_{Na_s} = \bar{g}_{Na_s} m_s^3 h_s (V - E_{Na})$$

$$\dot{m_s} = \frac{m_{s\infty} - m_s}{\tau_{m_s}} \qquad \dot{h_s} = \frac{h_{s\infty} - h_s}{\tau_{h_s}}$$

$$\tau_{m_s} = 1.50 \exp(-(0.0595)^2 (V + 20.35)^2) + 0.15 \qquad \tau_{h_s} = 4.95 \exp(-(0.0335)^2 (V + 20.00)^2) + 0.75$$

$$m_{s\infty} = \frac{1.0}{1.0 + \exp((V + 20.35)/-4.45)} \qquad h_{s\infty} = \frac{1.0}{1.0 + \exp((V + 18.00)/4.50)} .$$

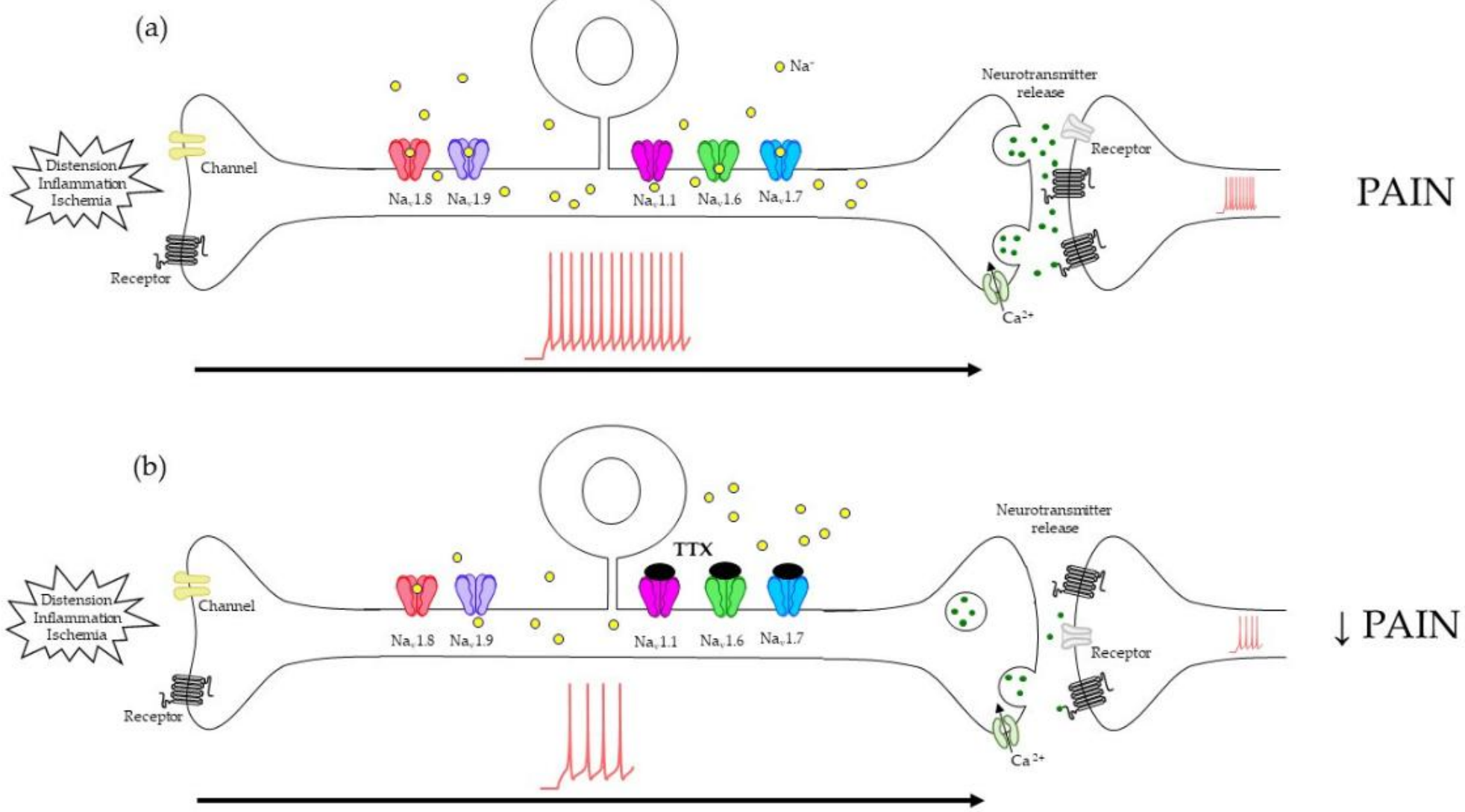
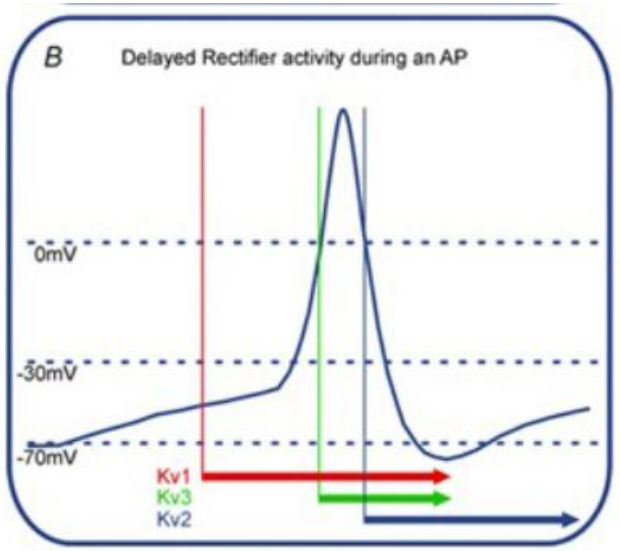


Figure 2. Mechanism proposed for the blockade of tetrodotoxin (TTX) sensitive voltage-gated sodium channels (VGSCs) to diminish pain transduction in primary sensory neurons. (**a**) After a noxious stimulus reaches the depolarization threshold, TTX-sensitive and -resistant VGSCs are activated, generating action potentials (APs) along the axon to the presynaptic terminal. Here, neurotransmitter release activates the postsynaptic neuron, and the stimulus is transmitted to the central nervous system, evoking pain sensations. (**b**) By blocking TTX-sensitive VGSCs with TTX, AP transmission is dampened and consequently, painful sensations decrease.

Outward K^+ channels



I_K: Delayed Rectifier

$$I_K = \bar{g}_K n(V - E_K)$$

$$\dot{n} = \frac{n_\infty - n}{\tau_n}$$

$$\tau_n = \frac{1.0}{(\alpha_n + \beta_n)} + 1.0$$

$$n_\infty = \frac{1.0}{1.0 + \exp((V + 14.62)/-18.38)}$$

$$\alpha_n = \frac{0.001265(V + 14.273)}{1.0 - \exp((V + 14.273)/-10.0)}$$

$$\beta_n = 0.125 \exp\left(\frac{V + 55.0}{-2.5}\right)$$

I_A: Early Transient Outward Current

$$I_A = \bar{g}_A p^3 q (V - E_K)$$

$$\dot{p} = \frac{p_\infty - p}{\tau_p}$$

$$\dot{q} = \frac{q_\infty - q}{\tau_q}$$

$$\tau_p = 5.0 exp(-(0.022)^2 (V + 65.0)^2) + 2.5$$

$$\tau_q = 100.0 exp(-(0.035)^2 (V + 30.0)^2) + 10.5$$

$$p_\infty = \frac{1.0}{1.0 + \exp((V + 28.0)/-28.0)}$$

$$q_\infty = \frac{1.0}{1.0 + \exp((V + 58.0)/7.0)}$$

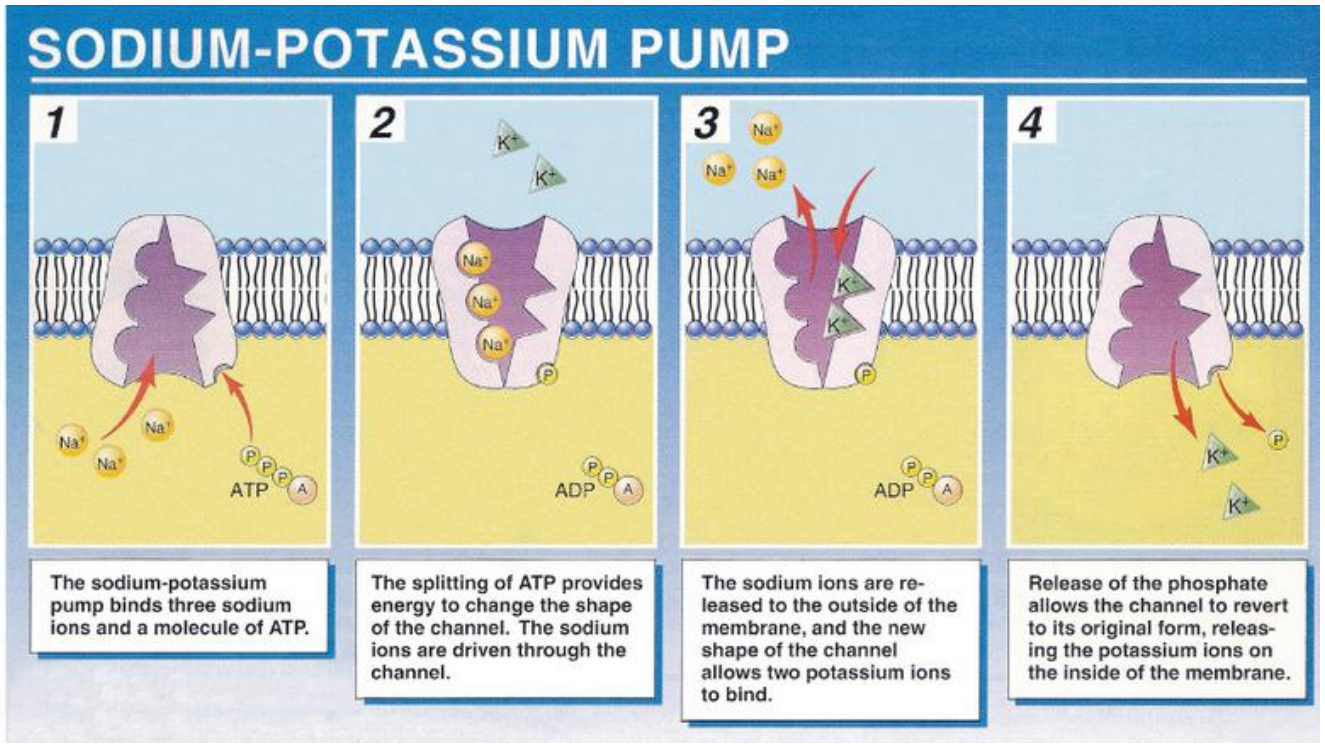
Pumps

I_{CaP} : Calcium Pump Current

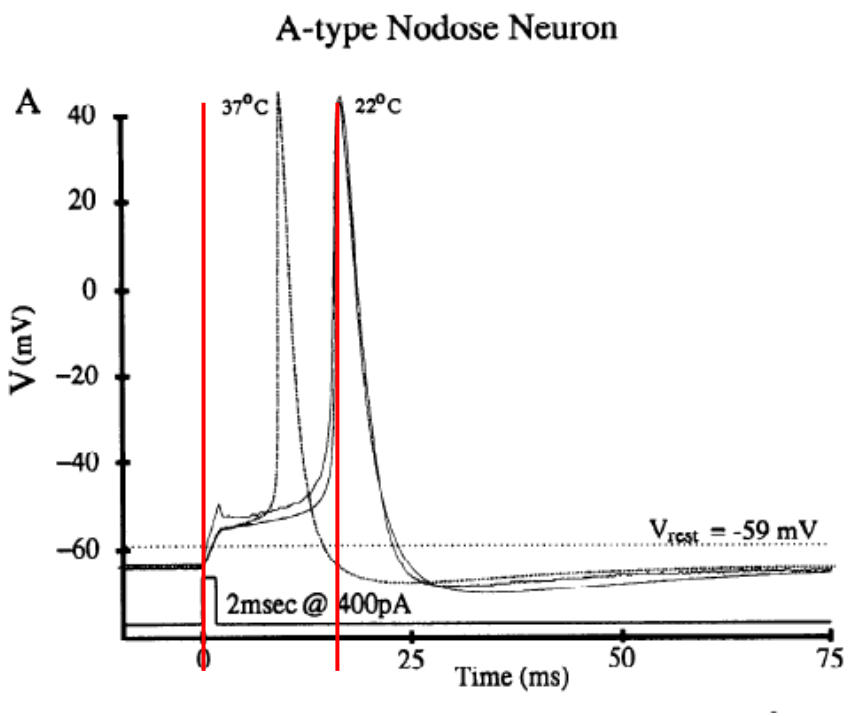
$$I_{CaP} = \bar{I}_{CaP} \left(\frac{[Ca^{2+}]_i}{[Ca^{2+}]_i + K_{M,CaP}} \right)$$

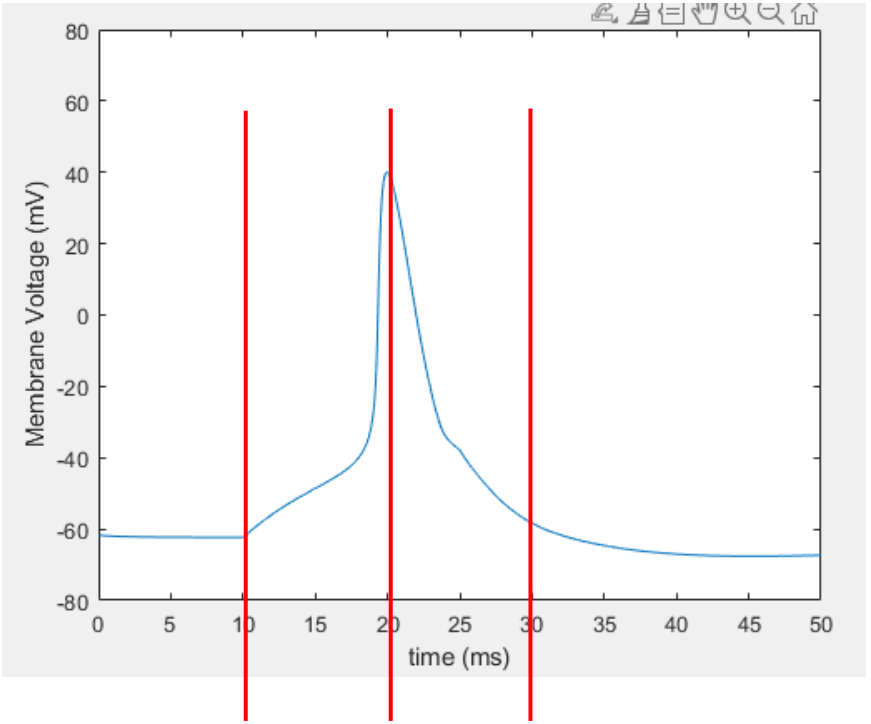
I_{NaK} : Sodium-Potassium Pump Current

$$I_{NaK} = \bar{I}_{NaK} \left(\frac{[Na^{+}]_i}{[Na^{+}]_i + K_{M,Na}} \right)^3 \left(\frac{[K^{+}]_o}{[K^{+}]_o + K_{M,K}} \right)^2 \left(\frac{V+150}{V+200} \right)$$

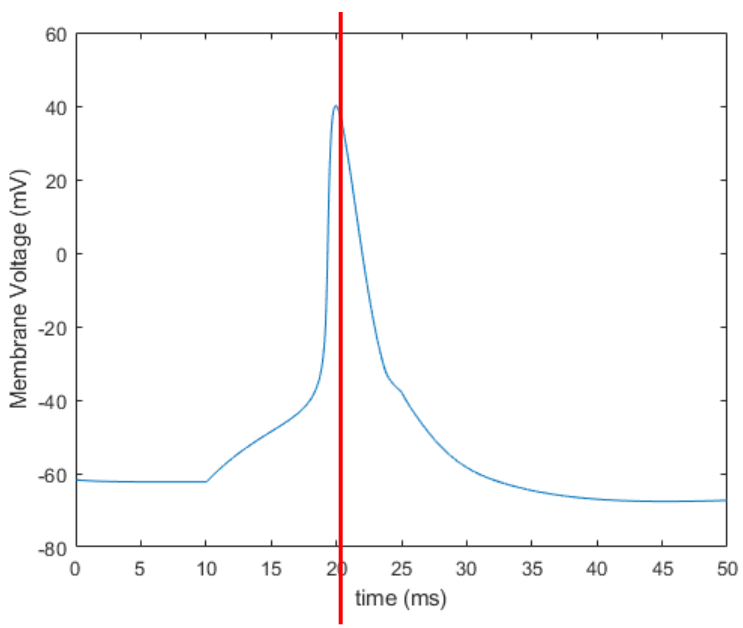


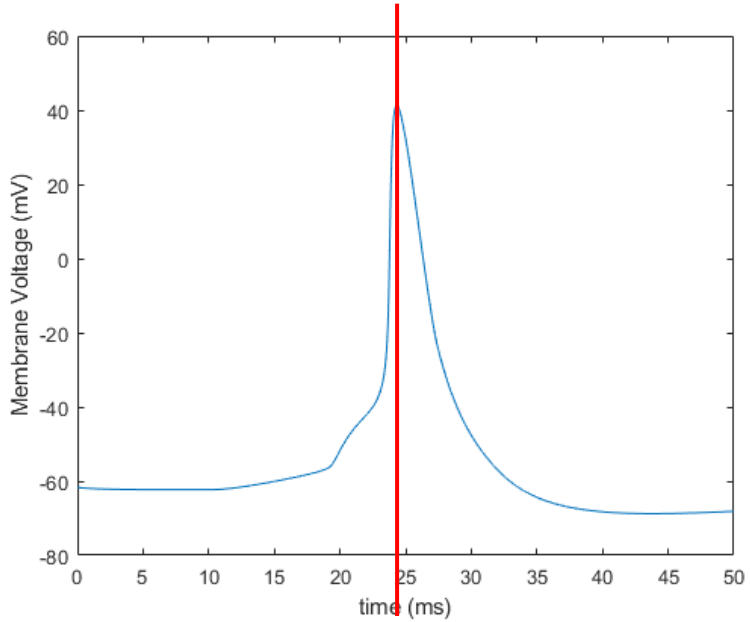
Action potential: A- type Nodose Neuron (37^0C)

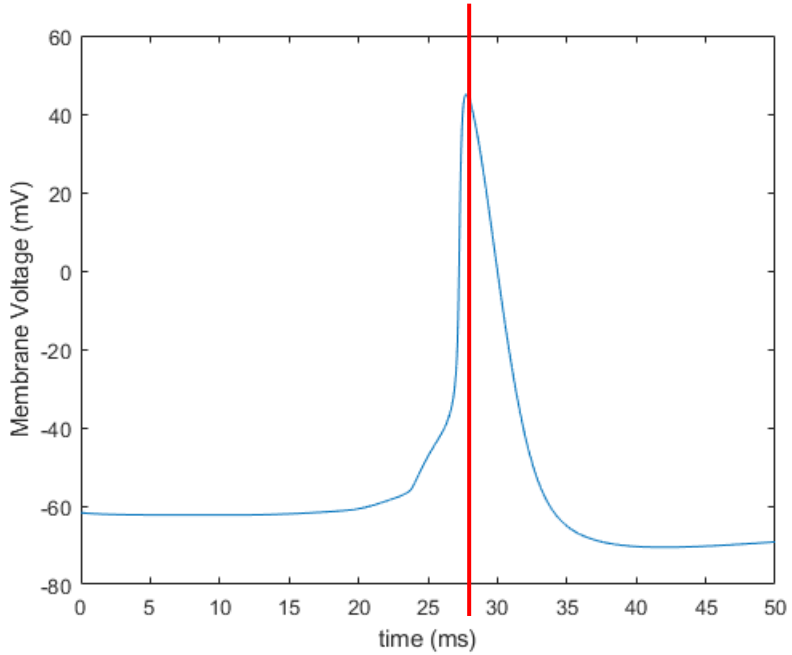




Action potential Propagation: Cable theory







Stimulation current in 1st compartment

Axon: 3 compartments

$a/(2r_L) = 0.7 cm^2/s$

➔ Cable equation: $c_m \frac{\partial V}{\partial t} = \frac{1}{2ar_L} \frac{\partial}{\partial x}\left(a^2 \frac{\partial V}{\partial x}\right) - i_m + i_e$

Thank you & Questions

References

- https://neuwritesd.files.wordpress.com/2015/12/actionpotential2.png
- https://www.guidetopharmacology.org/GRAC/FamilyIntroductionForward?familyId=81
- https://socratic.org/questions/how-does-the-sodium-potassium-pump-work
- https://slideplayer.com/slide/5752764/
- Campos-Ríos, A., Rueda-Ruzafa, L., Herrera-Pérez, S., Rivas-Ramírez, P., & Lamas, J. A. (2021). Tetrodotoxin: A new strategy to treat visceral pain?. *Toxins*, *13*(7), 496.
- Waise, T. M., Dranse, H. J., & Lam, T. K. (2018). The metabolic role of Vagal Afferent Innervation. *Nature Reviews Gastroenterology & Hepatology, 15*(10), 625-636. doi:10.1038/s41575-018-0062-1
- Arcilla, C. K., & Tadi, P. (2020). Neuroanatomy, unmyelinated nerve fibers.
- Schild, J. H., Clark, J. W., Hay, M., Mendelowitz, D., Andresen, M. C., & Kunze, D. L. (1994). A-and C-type rat nodose sensory neurons: model interpretations of dynamic discharge characteristics. *Journal of neurophysiology*, *71*(6), 2338-2358.
- Li, B. Y., & Schild, J. H. (2007). Electrophysiological and pharmacological validation of vagal afferent fiber type of neurons enzymatically isolated from rat nodose ganglia. *Journal of neuroscience methods*, *164*(1), 75-85.