Mathematical Model of Neuron

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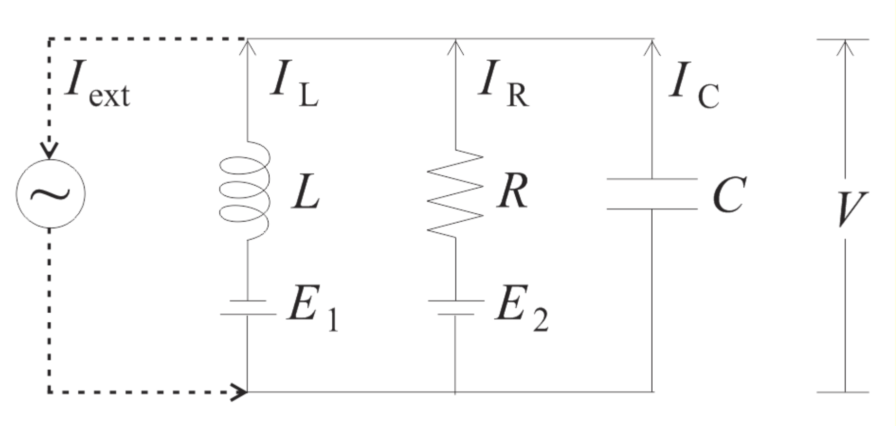
Review -- One Basic Circuit



By Kirchhoff's Current Law

$$0 = I_C + I_{\text{R}} + I_{\text{L}} - I_{\text{ext}}$$

By Kirchhoff's Voltage Law and device IV-characteristics

$$I_C = C\frac{dV}{dt}$$

$$I_{\text{R}} = \frac{1}{R}(V - E_2) = g\,(V - E_2)$$

$$\frac{dI_L}{dt} = L\,(V - E_1)$$

where C is the capacitance, R is the resistance (g is the conductance), and L is the inductance

Review -- Exponential Growth Model

Change of a variable P is proportional to itself and thechange of another variable t :

$$\Delta P \sim P\Delta t$$

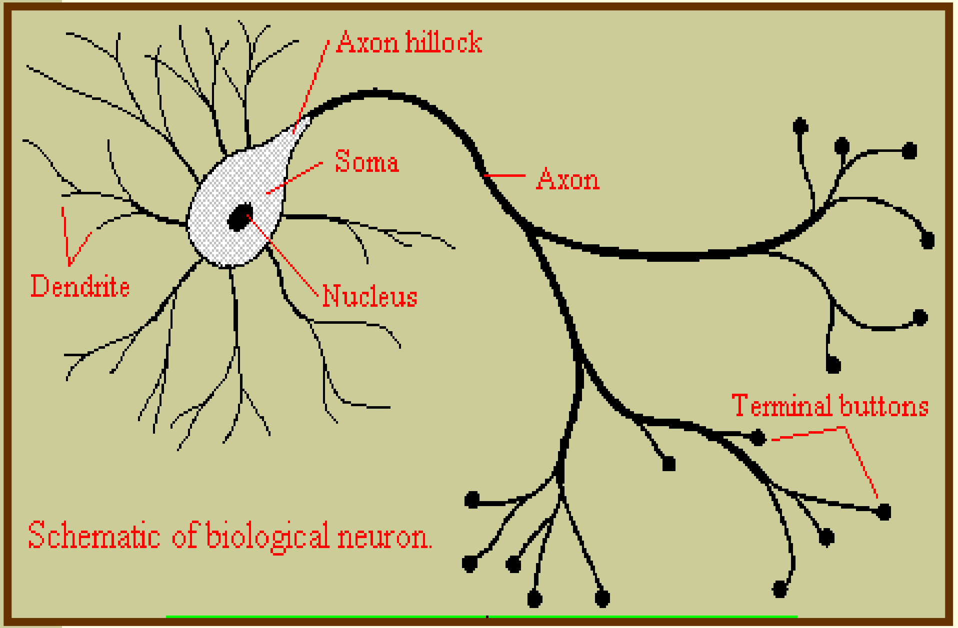
i.e. $$\frac{dP}{dt} = r\,P$$

$$\rightarrow \quad P(t) = P_0\, e^{rt}$$

where r is the growth or decay parameter, P_0 is the initial amount

Applications --- Population dynamics
--- Radioactive decay
--- Ion channel activation

Neuron -- Overview



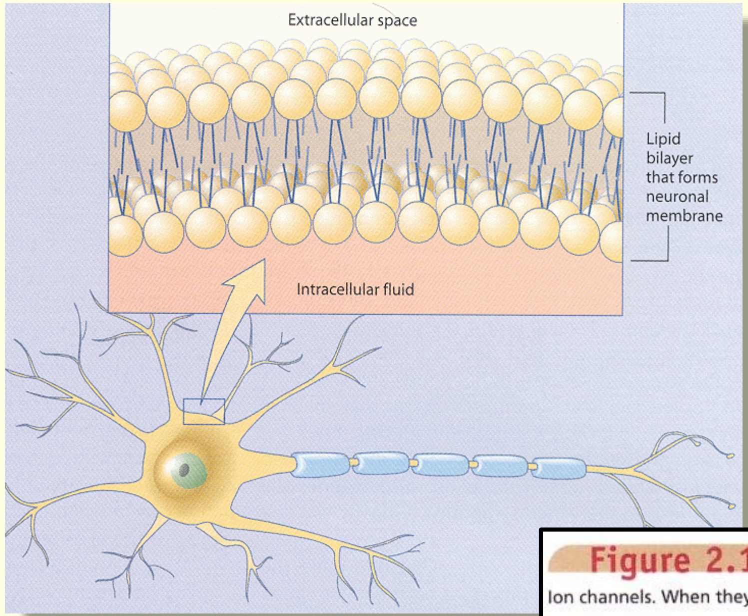
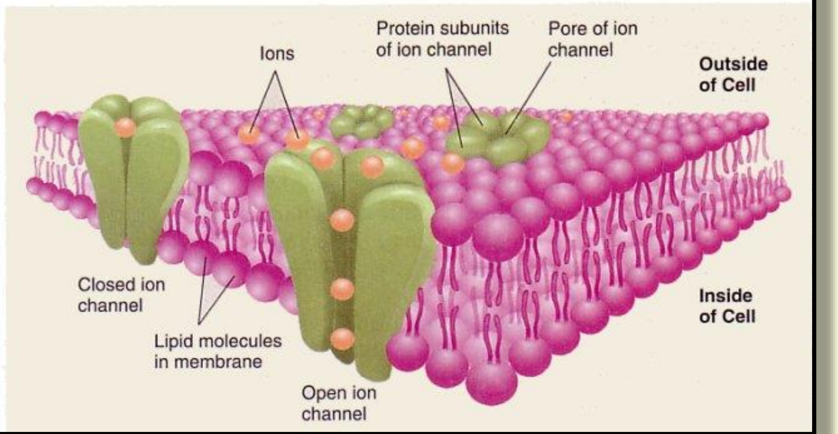


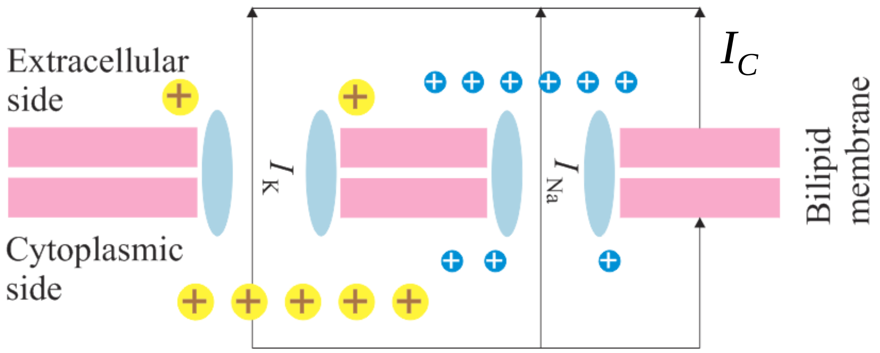
Figure 2.17

Ion channels. When they are open, ions can pass through them, entering or leaving the cell.



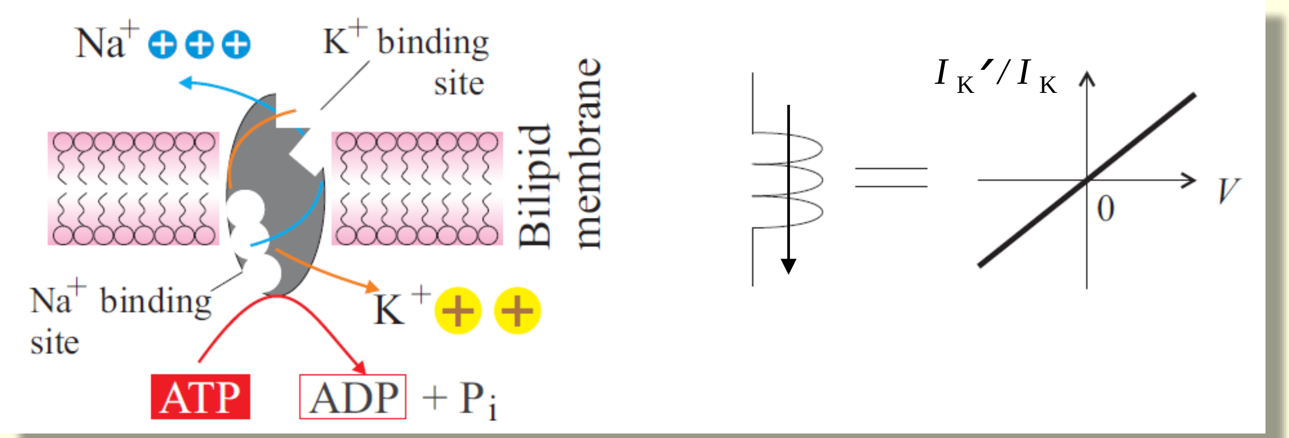
Neuron Circuit

- Kenneth Cole (1936-1941) determined that the bilipid membrane has a consistent capacitance around C = 1μF so that it can be modeled as a capacitor: $I_C = C\frac{dV}{dt}$
- Two ion currents: sodium ion (Na^+) current I_{Na}, and potassium ion (K^+) current I_{K}
- Each ion species has an electrical potential created by a biochemical pump $E_{\mathrm{Na}} \sim 70\ mV$ and $E_{\mathrm{K}} \sim -60\ mV$
- The early attempted conceptual model is



with $I_{\mathrm{Na}} = g_{\mathrm{Na}}(V - E_{\mathrm{Na}})$ and $I_{\mathrm{K}} = g_{\mathrm{K}}(V - E_{\mathrm{K}})$, where g_{Na}, g_{K} are the conductances

Resting Potentials -- Ion Pump

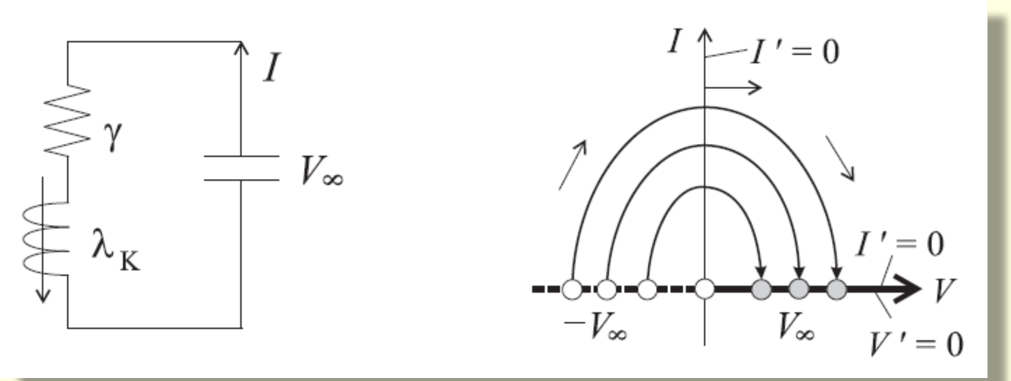


Differential equation (device IV-characteristics) for individual ion pump current

$$\frac{dI}{dt} = \lambda IV$$

Namely, the rate of change of pump current is proportional to the power across the pump

Resting Potentials -- Ion Pump Dynamics



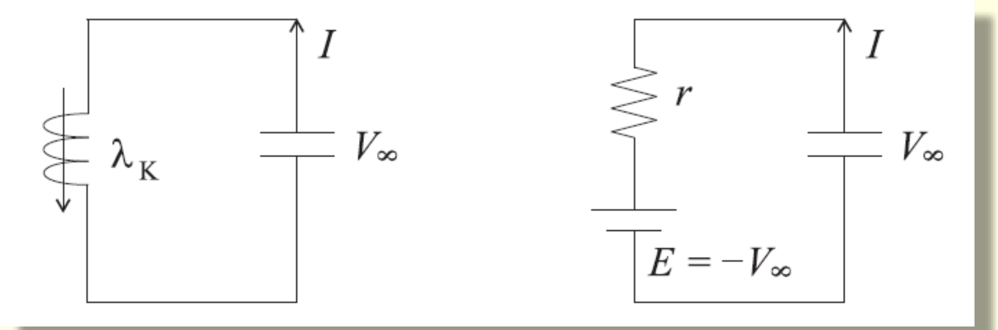
The differential equations for the circuit loop are

$$CV' = I, \qquad I' = -\lambda I(V + \gamma I)$$

Solve the system explicitly, and express the solution in term so the asymptotic steady-state potential as

$$V(t) = V_\infty \frac{1 - \exp(-\lambda V_\infty t)}{1 + \exp(-\lambda V_\infty t)} \sim V_\infty[1 - 2\exp(-\lambda V_\infty t)]$$

Resting Potentials -- Battery Equivalence of Ion Pump



Ion Pump

$$CV' = I, \qquad I' = -\lambda I(V + \gamma I)$$

Solution with initial $V(0) = 0$

$$V(t) = V_\infty \frac{1 - \exp(-\lambda V_\infty t)}{1 + \exp(-\lambda V_\infty t)} \sim V_\infty[1 - 2\exp(-\lambda V_\infty t)]$$

Battery Circuit

$$CV' = I = -(V + E)/r$$

Solution with initial $V(0) = 0$

$$V(t) = -E[1 - \exp(-t/(rC))] = V_\infty[1 - \exp(-t/(rC))]$$

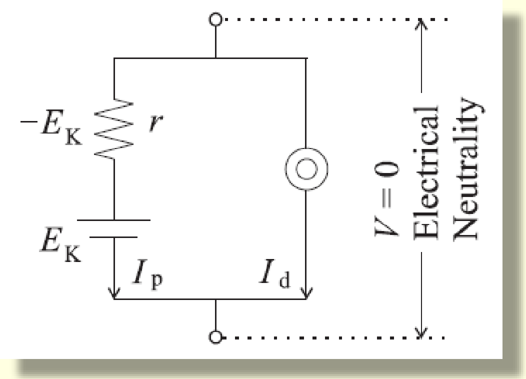
With

$$1/r = \lambda C V_\infty$$

These two circuits are exponentially equivalent to each other

Resting Potentials -- Nernst Potential with Ion Pump and Electrical Neutrality

As the potassium pump is capable of establishing any asymptotical potential $E = -V_\infty$, the question is what is the actual resting potential E_K under the action of across-membrane diffusion and electrical neutrality?



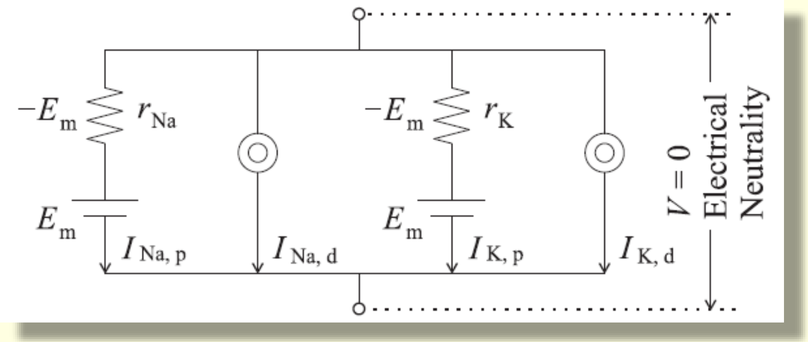
The equation for this setting is the Goldman equation (1943):

$$0 = I_d + I_p = D\left(-\frac{dn}{dx}\right) + \mu n\left(-\frac{E_K}{a}\right)$$

Solving this linear equation for the concentration $n(x)$ with the boundary conditions $n(0) = [K]_o$, $n(a) = [K]_i$ leads to the Nernst potential

$$E_K = \frac{RT}{F}\ln\frac{[K]_i}{[K]_o}$$

Resting Potentials -- Membrane Resting Potential E_{m} with Ion Pump and Electrical Neutrality



Equation for the steady state

$$0 = \sum \left[z_k D_k \left(-\frac{dn_k}{dx} \right) + \mu_k n_k \left(-\frac{E_m}{a} \right) \right]$$

with z_k =+1 we have

$$0 = \sum \left[D_k \left(-\frac{dn_k}{dx} \right) + \mu_k n_k \left(-\frac{E_m}{a} \right) \right]$$

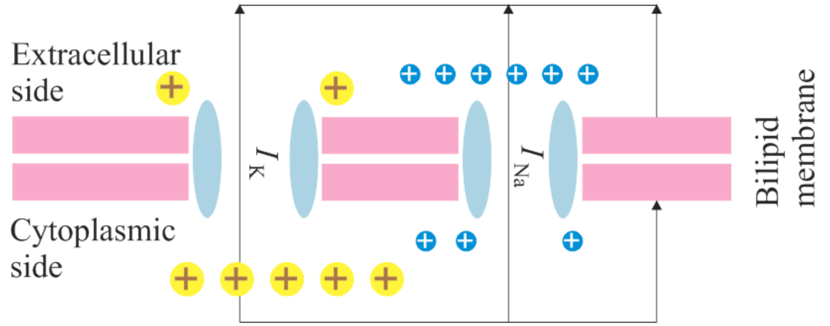
and

$$\frac{E_m}{a} dx = -\frac{RT}{F} \frac{d(\sum \mu_k n_k)}{\sum \mu_k n_k} \quad \Rightarrow \quad E_m = \frac{RT}{F} \ln \frac{\mu_{\mathrm{K}} [\mathrm{K}]_o + \mu_{\mathrm{Na}} [\mathrm{Na}]_o}{\mu_{\mathrm{K}} [\mathrm{K}]_i + \mu_{\mathrm{Na}} [\mathrm{Na}]_i}$$

~ – 55 mV

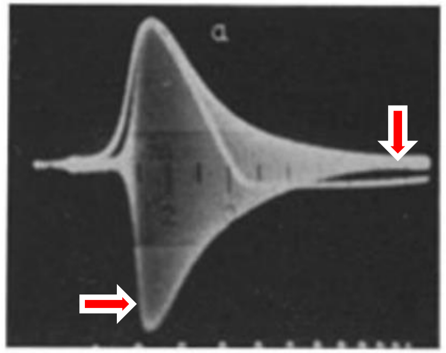
Hodgkin-Huxley Model (1952)

- Back to the conceptual circuit model, Cole and others soon realized that a neuronal circuit model could not be a linear circuit



$$C\frac{dV}{dt} = -[I_{Na} + I_K - I_{ext}] = -[g_{Na}(V - E_{Na}) + g_K(V - E_K) - I_{ext}]$$

with g_{Na}, g_K being constants. One reason is that g_{Na} must be near zero despite the potential difference $(E_m - E_{Na}) \sim -125$ mV at rest, and large during action potential depolarization



(Cole and Curtis (1939))

Anatomy of action potential pulse:
- membrane voltage arises as sodium ions rush inside
- membrane voltage falls as potassium ions rush outside
- membrane voltage returns to its resting potential as both ion currents fall to near zero.

- Researchers concluded that the conductances must be functions of the voltage

$$g_{\mathrm{Na}} = g_{\mathrm{Na}}(V) \quad \text{and} \quad g_{\mathrm{K}} = g_{\mathrm{K}}(V)$$

- Hodgkin and Huxley (1952) proposed the following model:

Membrane as a Capacitor

$$C_m \frac{dV}{dt} = I(t)$$

$$I(t) = I_{Na^+} + I_{K^+} - I_L$$

$$I_{K^+} = \bar{g}_K n^4 (V - V_K)$$

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

$$I_L = \bar{g}_L (V - V_L)$$

Probabilities of Channel Openning

$$\frac{dn}{dt} = \alpha_n (1-n) - \beta_n n$$

$$\frac{dm}{dt} = \alpha_m (1-m) - \beta_m m$$

$$\frac{dh}{dt} = \alpha_h (1-h) - \beta_h h$$

Voltage-dependence of Channel Kinetics (Hodgkin & Huxley, 1952)

$$\alpha_n = \frac{10 - V}{100\left(e^{1-0.1V} - 1\right)} \qquad \beta_n = 0.125 e^{-V/80}$$

$$\alpha_m = \frac{25 - V}{10\left(e^{0.1(25-V)} - 1\right)} \qquad \beta_m = 4 e^{-V/18}$$

$$\alpha_h = 0.07 e^{-V/20} \qquad \beta_h = \frac{1}{e^{0.1(30-V)} - 1}$$

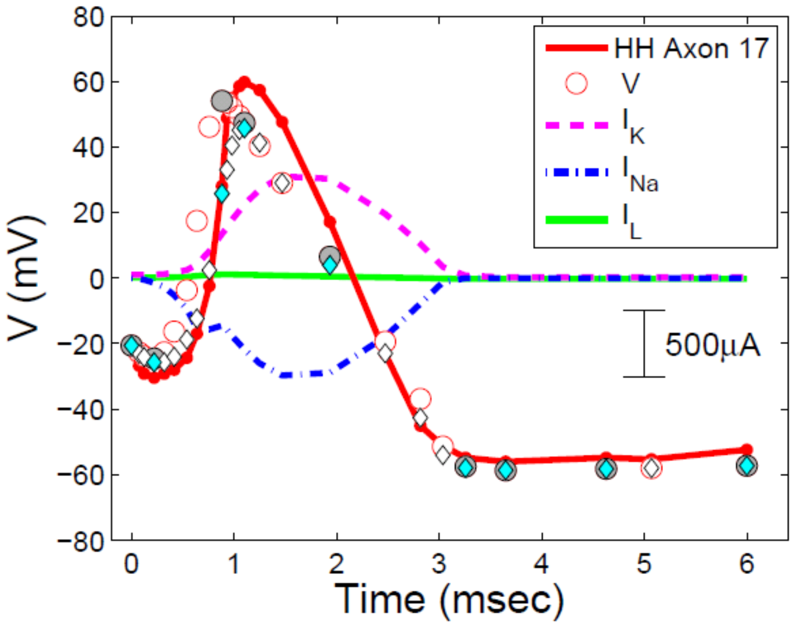
Constants in the Hodgkin-Huxley Model

$$\bar{g}_{Na^+} = 120 \mathrm{mS(cm)^{-2}} \qquad V_{Na} = 115 \mathrm{mV}$$

$$\bar{g}_{K^+} = 36 \mathrm{mS(cm)^{-2}} \qquad V_K = -12 \mathrm{mV}$$

$$\bar{g}_L = 0.3 \mathrm{mS(cm)^{-2}} \qquad V_L = 10.6 \mathrm{mV}$$

- Hodgkin-Huxley model fits experiments very well



- It has been the benchmark of excitable membranes in electrophysiology since 1952
- One fundamental drawback is the lack of a mechanistic basis for the voltage activated conductances
- It also fails to include the voltage gating current discovered later in the 1970s

Model Revision -- Channel Activation

- For the steady state IV-characteristics of the sodium current, $I_{\mathrm{Na}} = g_{\mathrm{Na}}(V - E_{\mathrm{Na}})$, we assume the conductance change is proportional to the conductance and the voltage change:

$$\Delta g_{\mathrm{Na}} \sim g_{\mathrm{Na}} \Delta V$$

i.e. $$\frac{dg_{\mathrm{Na}}}{dV} = \frac{g_{\mathrm{Na}}}{b_{\mathrm{Na}}}$$

$$\rightarrow \quad g_{\mathrm{Na}}(V) = \bar{g}_{\mathrm{Na}} e^{(V - E_{\mathrm{Na}})/b_{\mathrm{Na}}}$$

where b_{Na} is the sodium activation range parameter and $\bar{g}_{\mathrm{Na}}$ is the intrinsic conductance $\bar{g}_{\mathrm{Na}} = g_{\mathrm{Na}}(E_{\mathrm{Na}})$

- Similarly, we have the voltage activated potassium steady state conductance

$$g_{\mathrm{K}}(V) = \bar{g}_{\mathrm{K}} e^{(V - E_{\mathrm{K}})/b_{\mathrm{K}}}$$

where b_{K} is the potassium activation range parameter and $\bar{g}_{\mathrm{K}}$ is the intrinsic conductance

Model Revision -- Voltage Gating

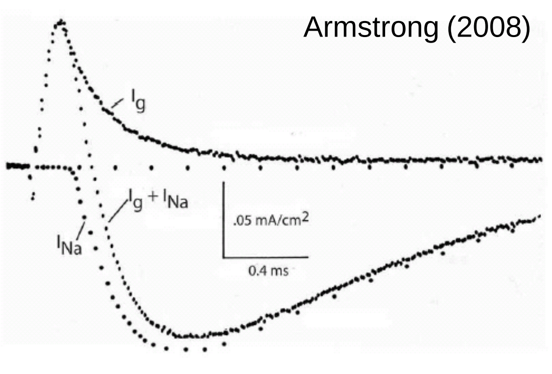
- Voltage gating is the phenomenon that when the membrane potential V is perturbed away from and above its resting potential E_{m} , the sodium channel undergoes some conformal changes which in turn release some positively charged particles to the outside for the effect of cancelling out the perturbation (depolarization)
- This so-called gating current is modeled similarly but with a conductance which is exponentially deactivated by the voltage:

$$I_{\mathrm{G}} = g_{\mathrm{G}}\,(V - E_{\mathrm{G}})$$

$$\Delta g_{\mathrm{G}} \sim -g_{\mathrm{G}}\Delta V$$

i.e. $$\frac{d g_{\mathrm{G}}}{dV} = -\frac{g_{\mathrm{G}}}{b_{\mathrm{G}}}$$

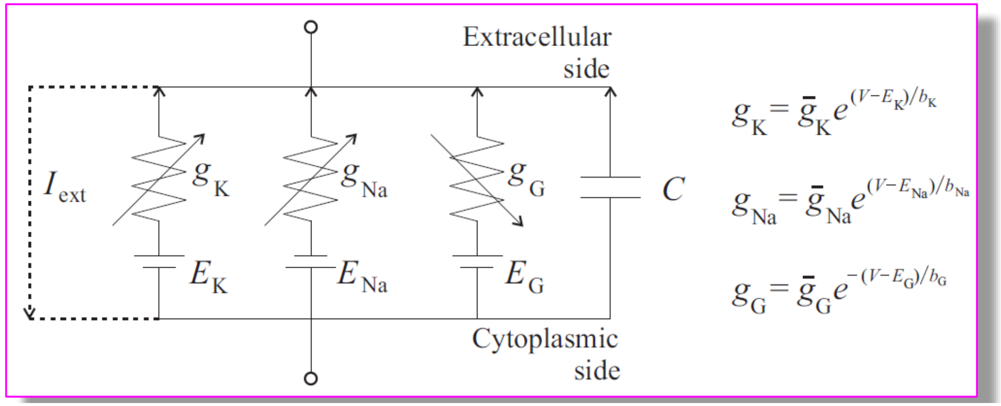
$$\rightarrow \quad g_{\mathrm{G}}(V) = \bar{g}_{\mathrm{G}} e^{-(V - E_{\mathrm{G}})/b_{\mathrm{G}}}$$



where b_{G} is the voltage-gating range parameter and $\bar{g}_{\mathrm{G}}$ is the intrinsic gating conductance

Model Revision -- At Last

- Assume there is a time delay (adaptation) of the electrical dynamics to the activation and gating conductances, the full model for the membrane is



$$\begin{cases} CV' = -[\bar{g}_K n(V - E_K) + \bar{g}_{Na} m(V - E_{Na}) + \bar{g}_G h(V - E_G) - I_{ext}] \\ n' = \tau_K (e^{(V-E_K)/b_K} - n) \\ m' = \tau_{NaG} (e^{(V-E_{Na})/b_{Na}} - m) \\ h' = \tau_{NaG} (e^{-(V-E_G)/b_G} - h) \end{cases}$$

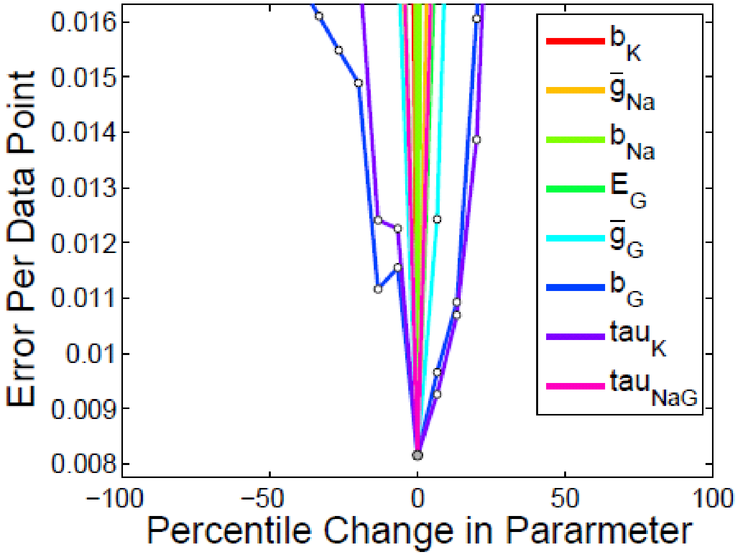
where τ_i are the time adaptation parameters.

Action Potentials -- Best-fit of Model to Data

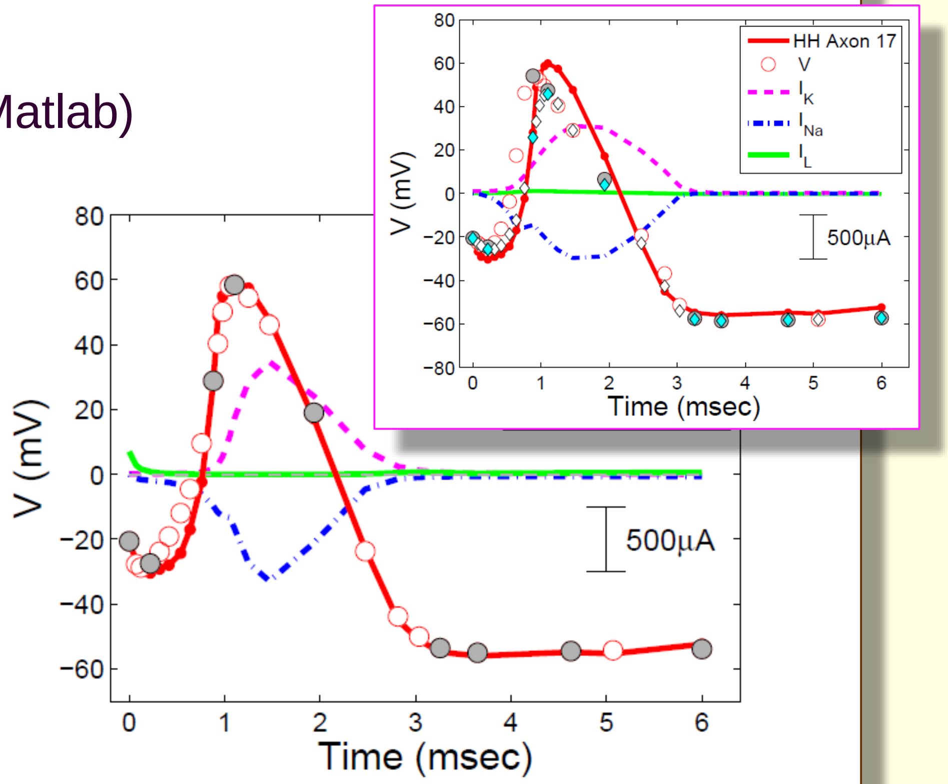
- Find parameter values so that the error between the predicted and the observed

$$\mathcal{E} = \frac{1}{N}\sqrt{\sum_{j=1}^{N}\left[\frac{|V(t_i)-V_i|}{\bar{V}}\right]^2}$$

is minimal. (This is done by Newton's line search method in Matlab)

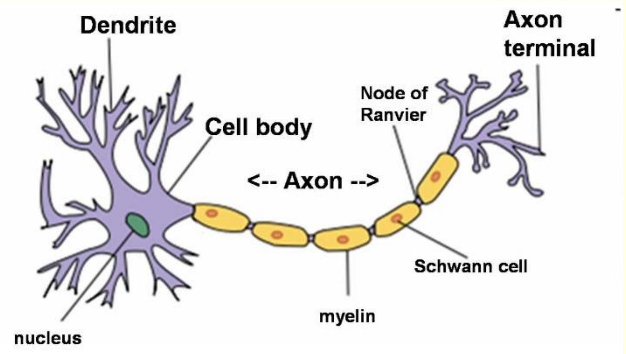


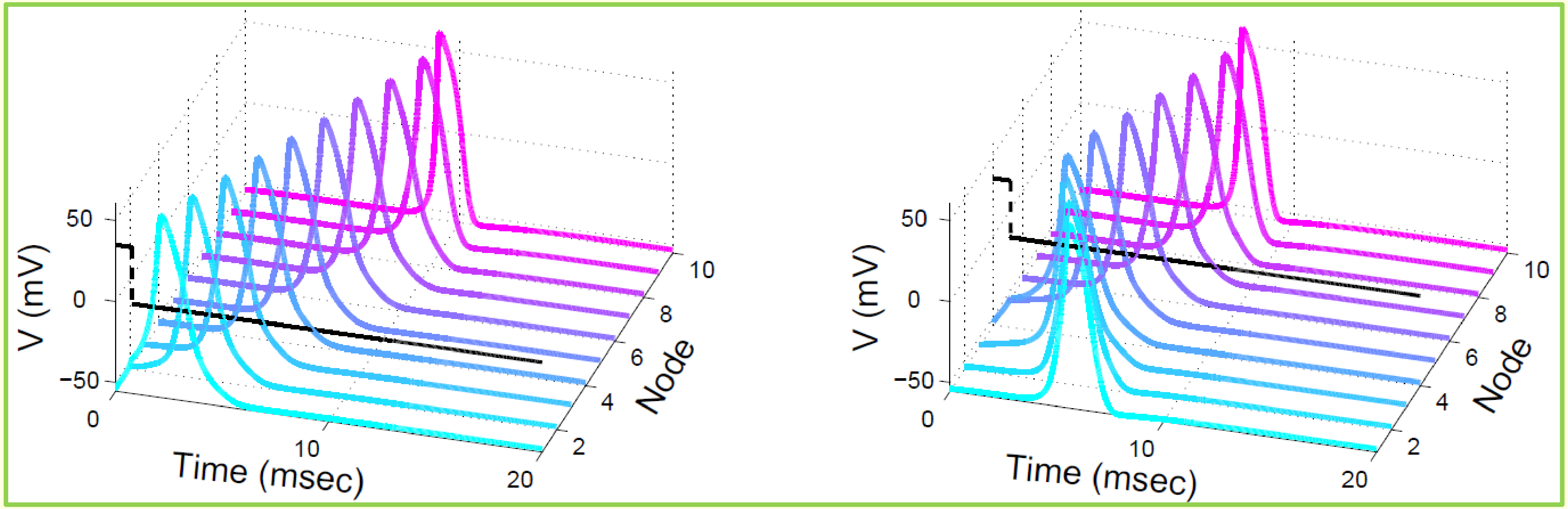
Fixed Exp. Value	Best-fit Value
$C = 1$	$b_K = 16.6$
$E_K = -59.5$	$\bar{g}_{Na} = 100$
$E_{Na} = 67.5$	$b_{Na} = 18.4$
$\bar{g}_K = 0.0229$	$E_G = -56$
	$\bar{g}_G = 9.3333$
	$b_G = 7.0667$
	$\tau_K = 0.8667$
	$\tau_{NaG} = 10$



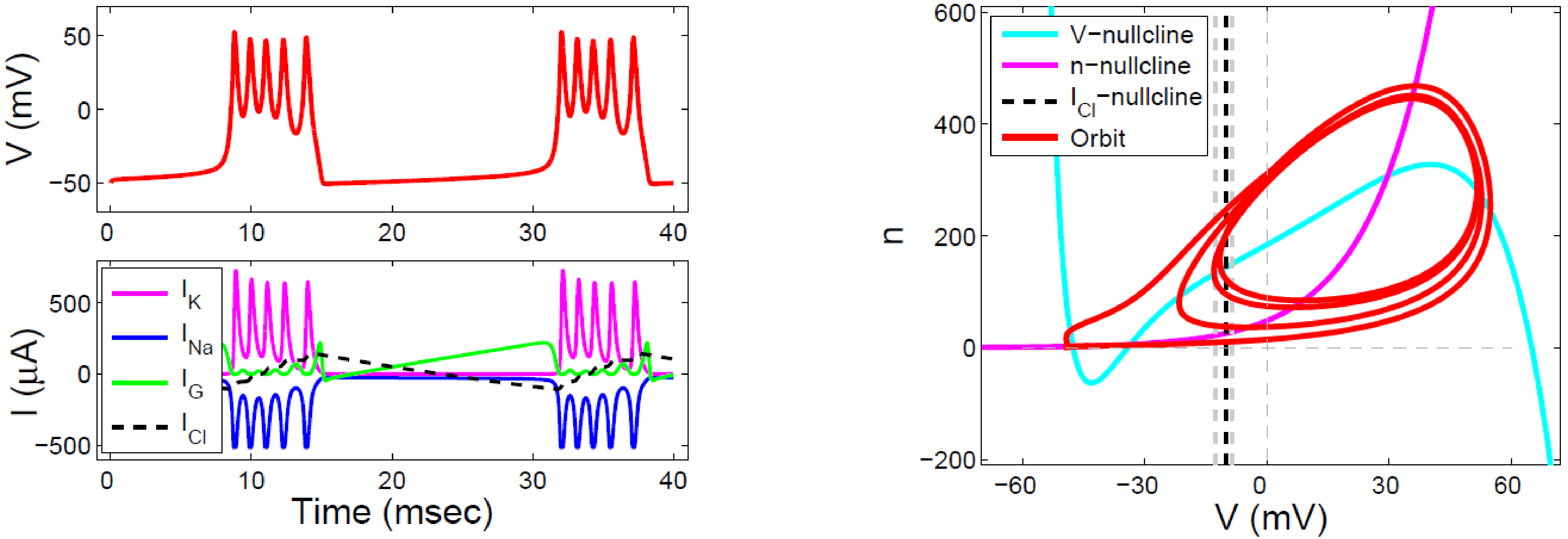
- It has a better best-fit than the HH model does, and with 13 fewer parameters

Action Potentials -- Nerve Impulse Propagation Along Axon





Action Potentials -- Bursting Spikes on Cell Body



Closing Remarks

- Neuron model can be constructed mechanistically
- Ion channel activation follows an exponential growth law,
  voltage gating follows an exponential decay law
- We can now teach undergraduate students the model with little arbitrariness
- It is hugely important to have a more accurate and simpler model when
  a large number of individual neuron models are connected in networks

Speaker: Bo Deng

Title: Mathematical Model of Neuron

Abstract: All information processed by animal brain is done by electrical pulses of neurons. Modeling neurons as electrical circuits is extremely important for the field of electrophysiology. In this talk we will talk about the benchmark neuron model which have been around for over sixty years and our recent effort to improve it. Only basic theory of circuit and elementary differential equation knowledge will be assumed.