Introduction to Neural Computation

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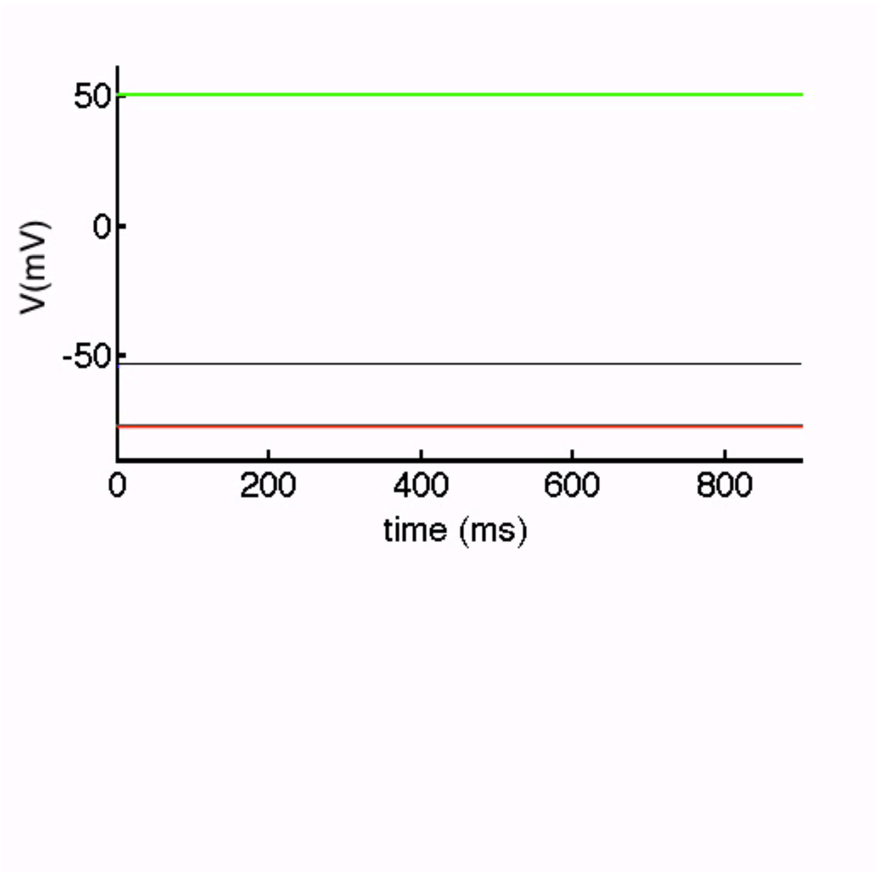
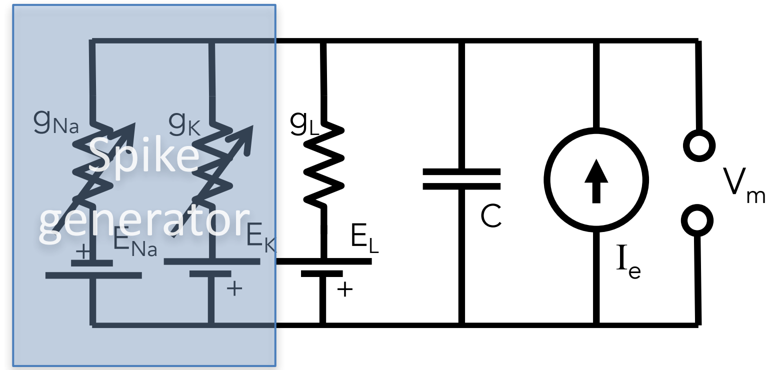
MIT BCS 9.40 — 2018

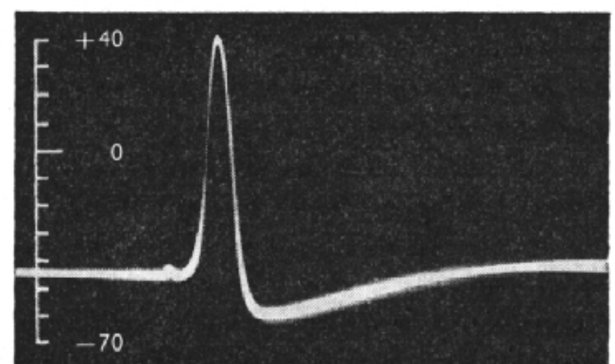
Lecture 5

Hodgkin-Huxley model of action potential generation

Voltage and time-dependent ion channels are the 'knobs' that control membrane potential.

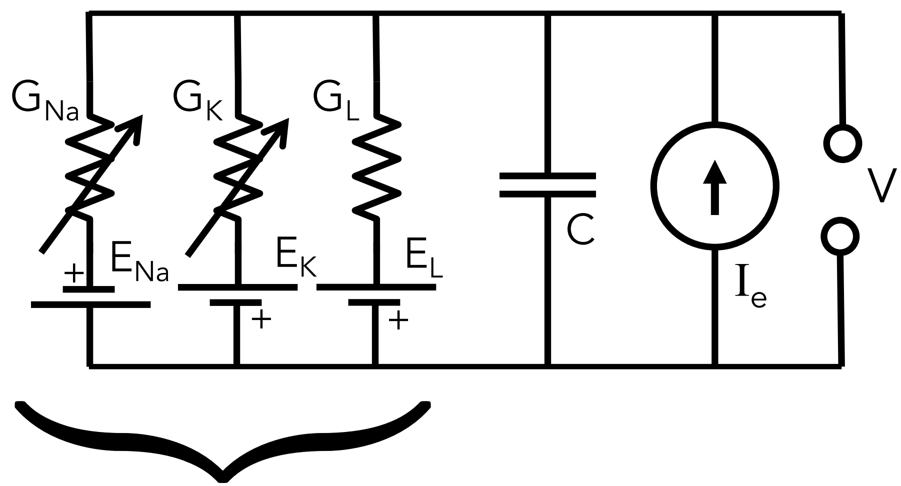






Hodgkin and Huxley, 1938

Hodgkin-Huxley model of action potential generation



$$I_m = I_{Na} + I_K + I_L$$

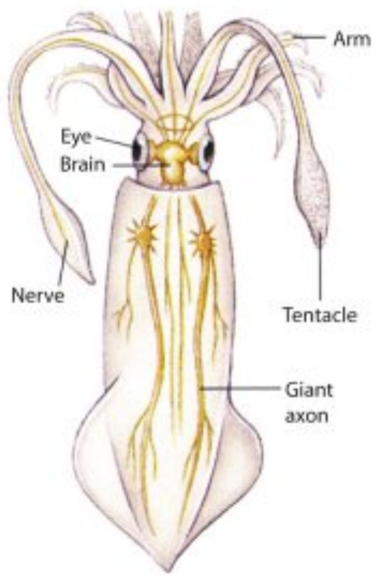
This is the total membrane ionic current, and it includes the contribution from —sodium channels, potassium channels and a 'leak' conductance.

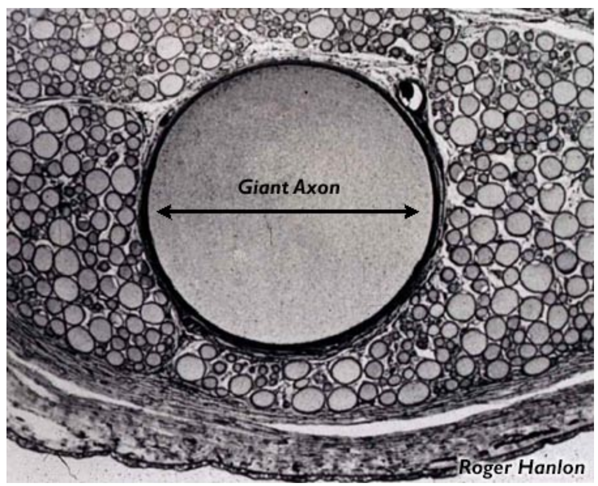
The equation for our HH model neuron is

$$I_m(t) + C\frac{dV(t)}{dt} = I_e(t)$$

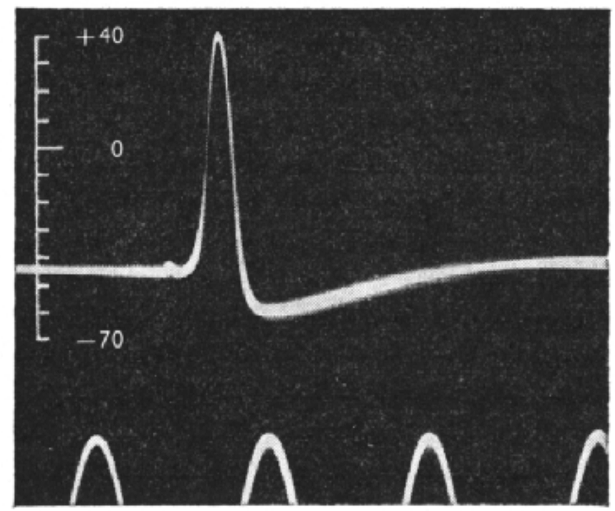
Voltage and Time dependence

- Voltage and time-dependent ion channels are the 'knobs' that control membrane potential.
- H&H studied the properties of K and Na channels in the squid giant axon. In particular they wanted to study the voltage and time dependence of the K and Na channels.



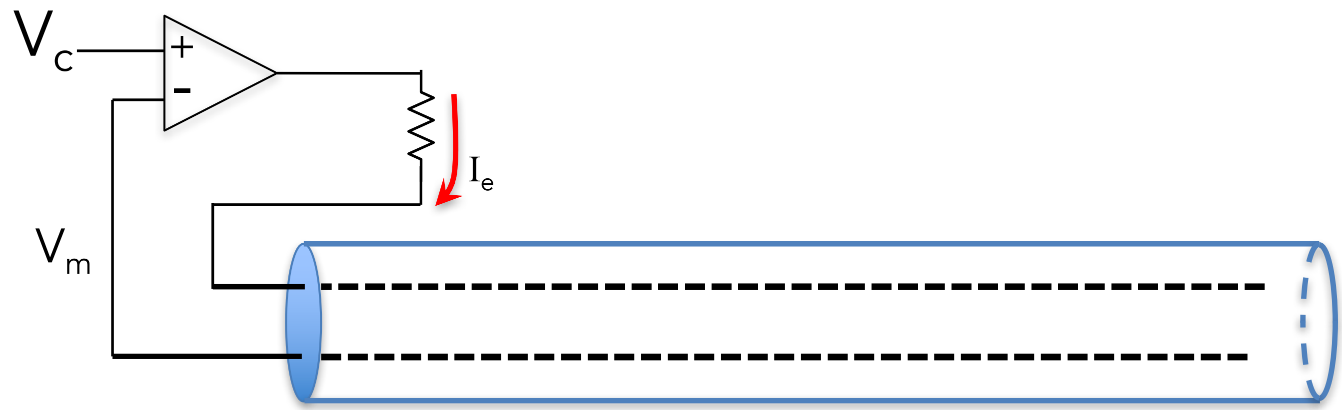


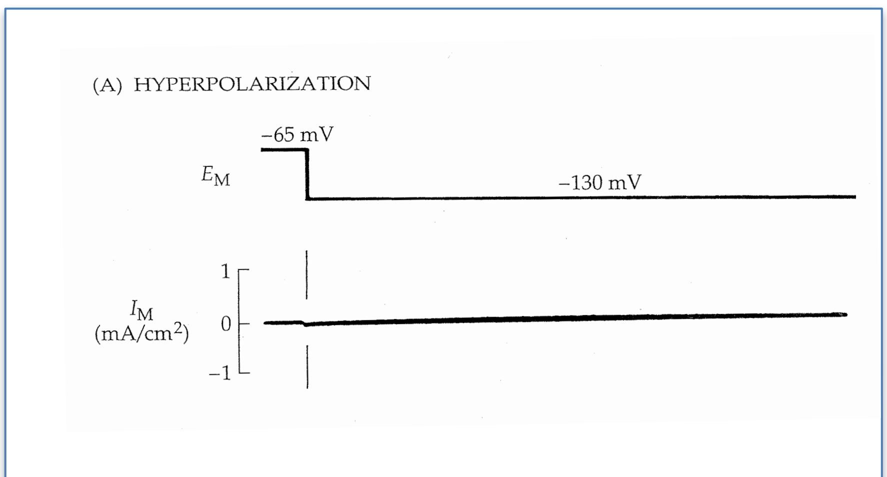
1mm diameter!

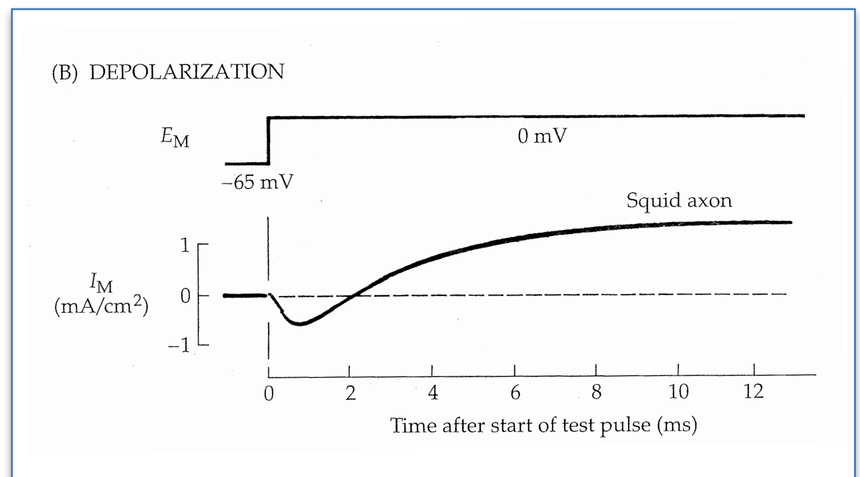


Hodgkin and Huxley, 1938

Ionic currents



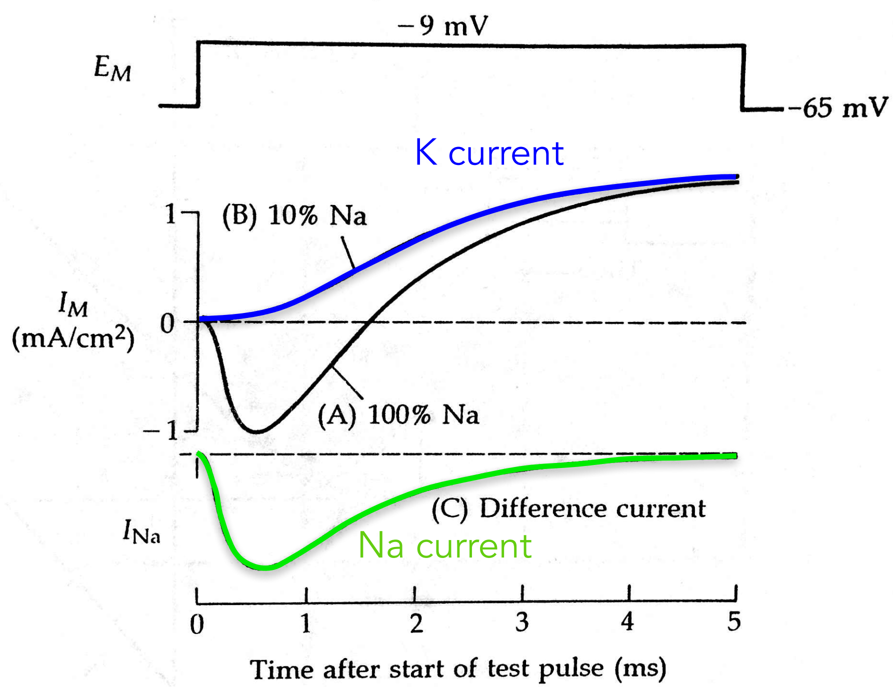




Ionic currents

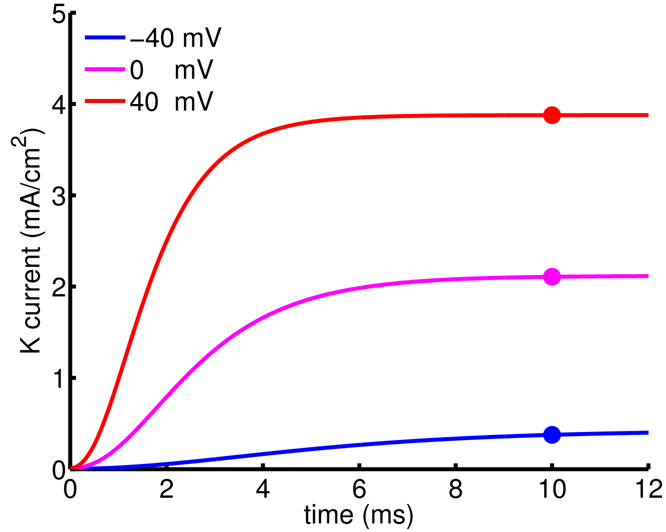
How do we figure out the contribution of Na and the contribution of K?

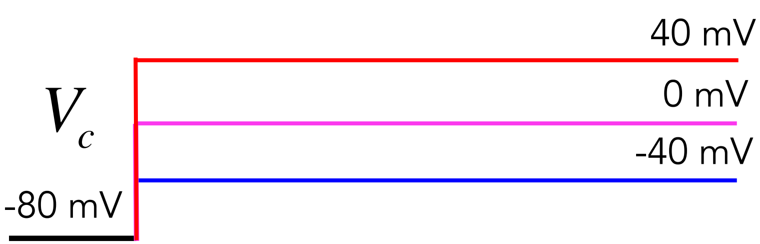
Ionic substitution (e.g. replace NaCl with choline chloride)



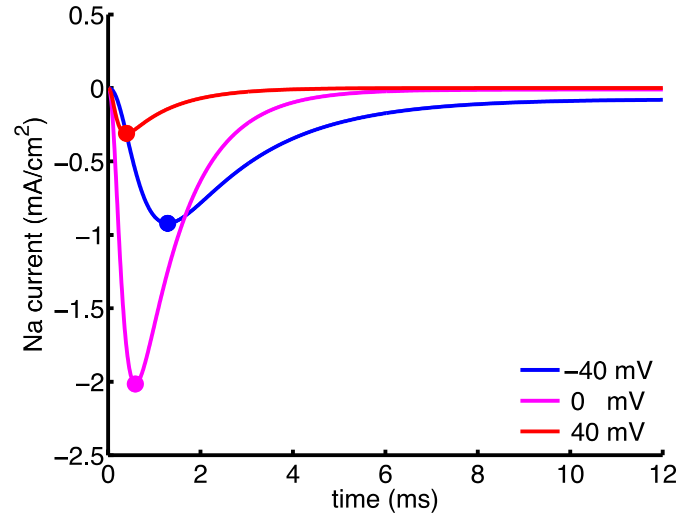
Ionic currents

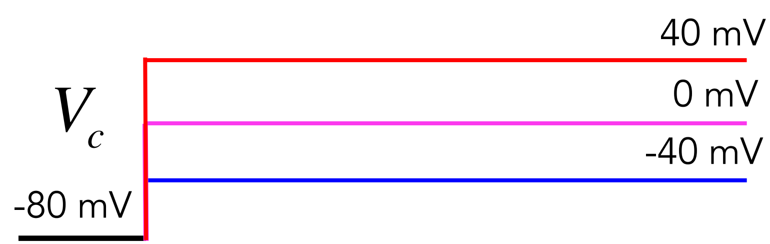
K current



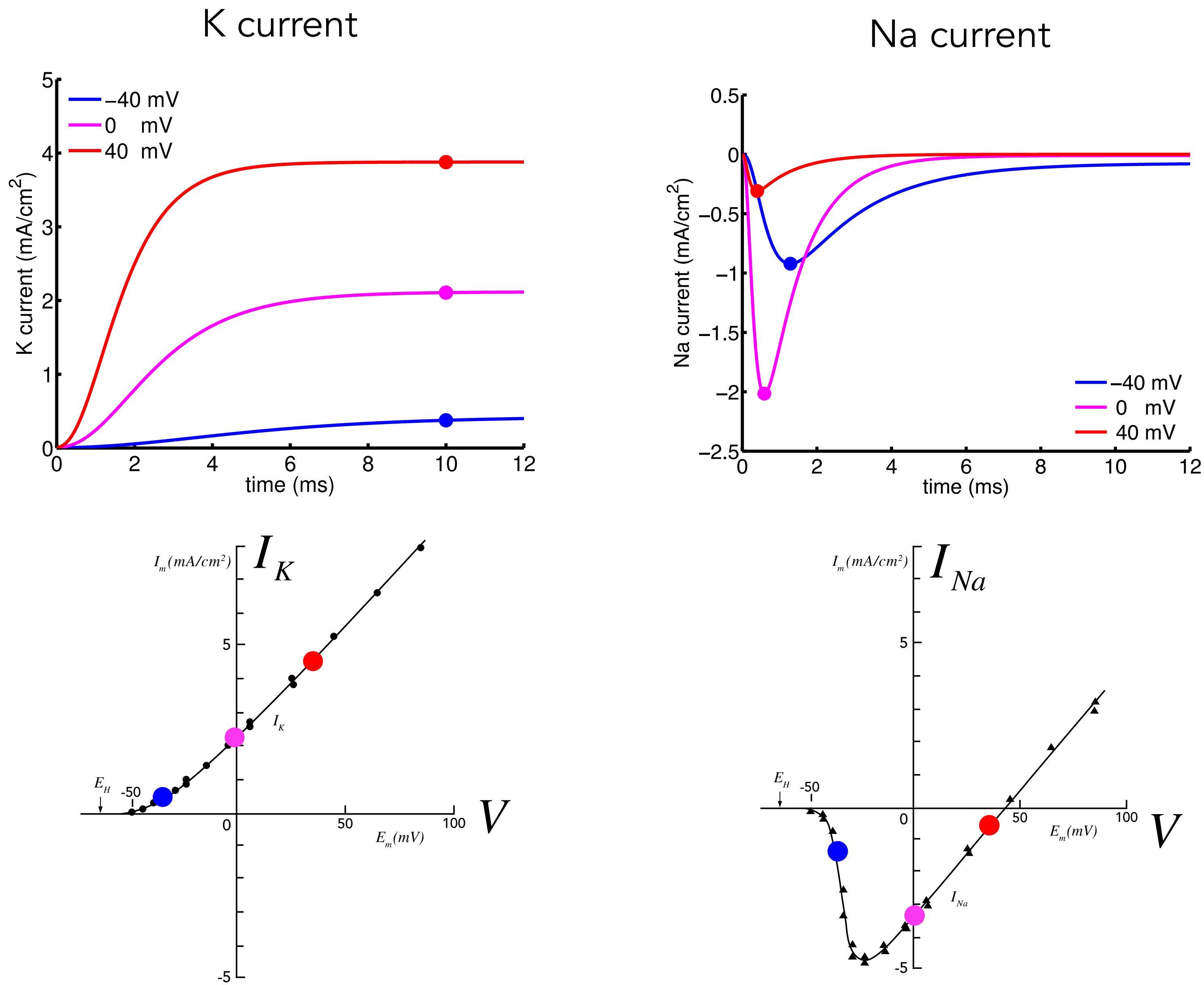


Na current

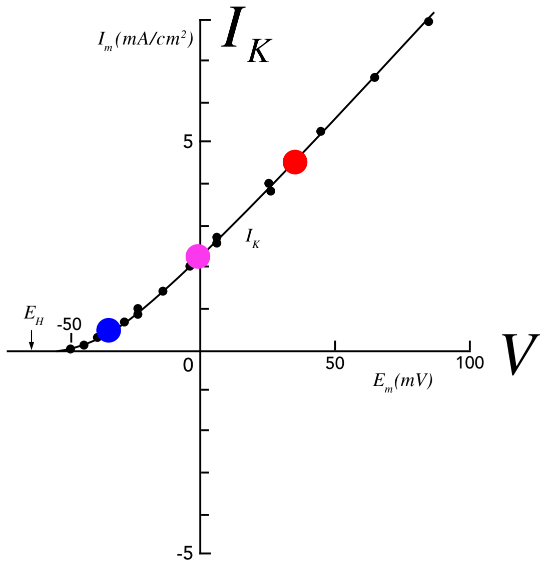


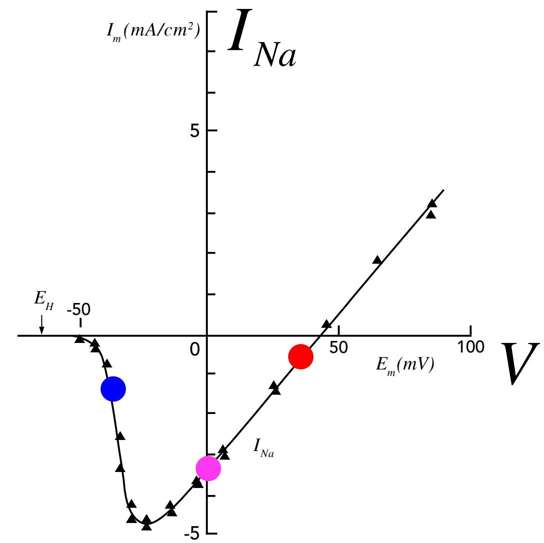


Ionic currents



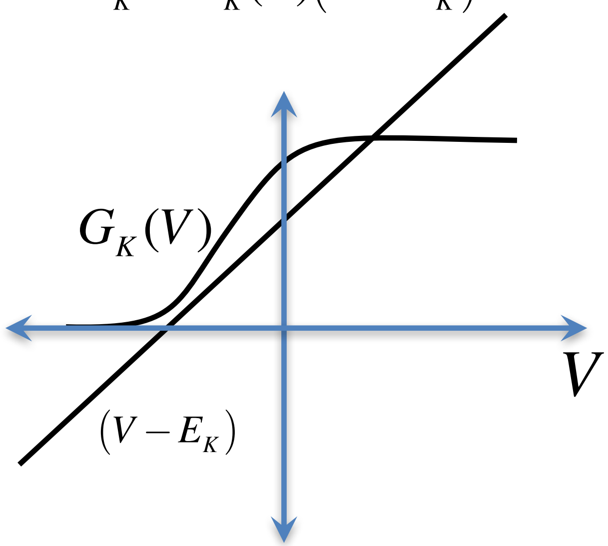
Ionic currents (Voltage dependence)

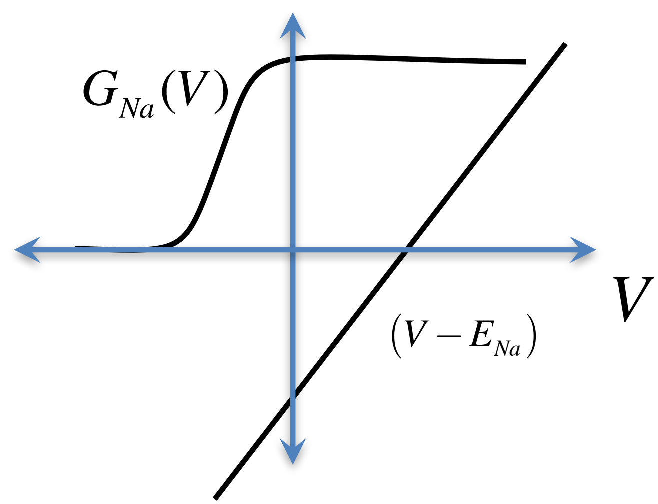




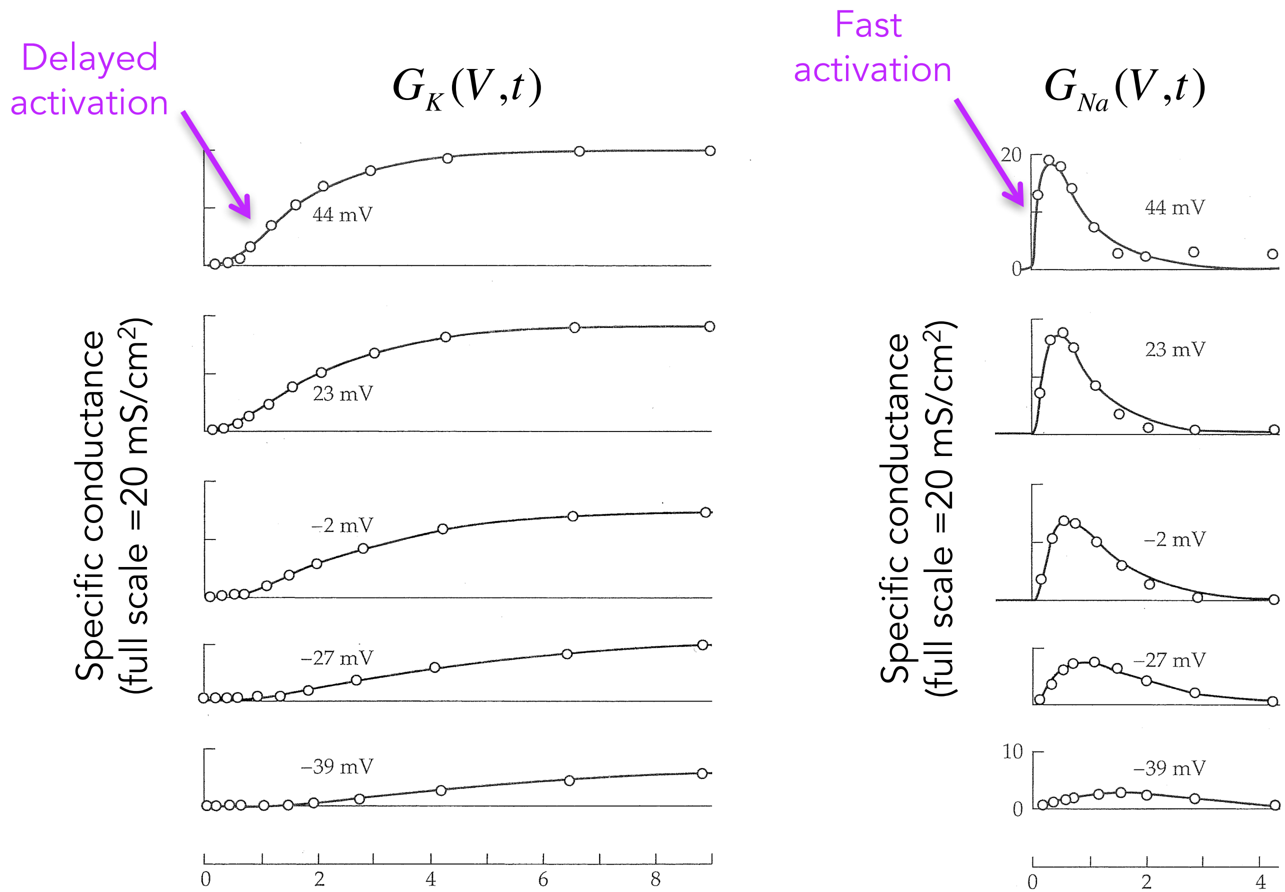
$$I_K = G_K(V)\left(V - E_K\right)$$

$$I_{Na} = G_{Na}(V)\left(V - E_{Na}\right)$$



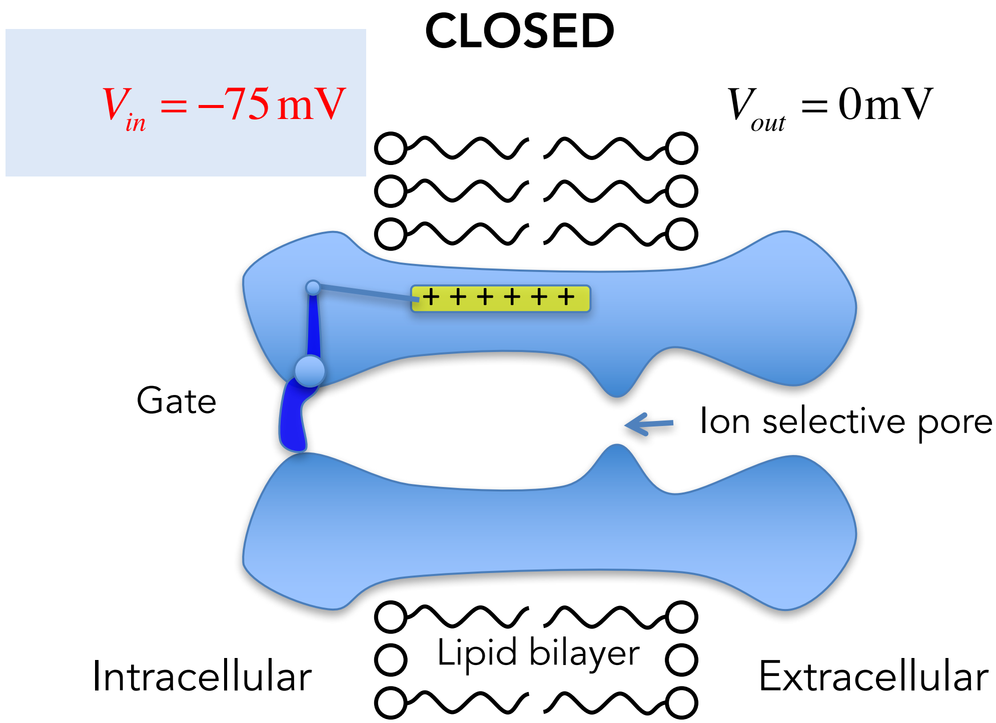


Ionic currents
(time and voltage dependence)

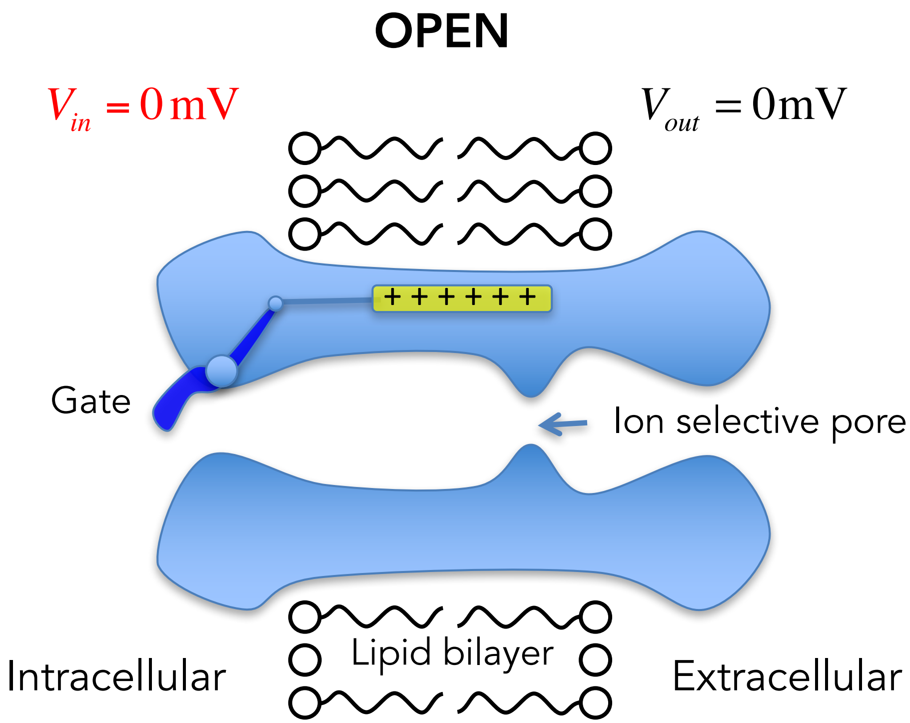


Time after start of pulse (ms)

Voltage-dependent conductance use voltage sensors



Voltage-dependent conductance use voltage sensors



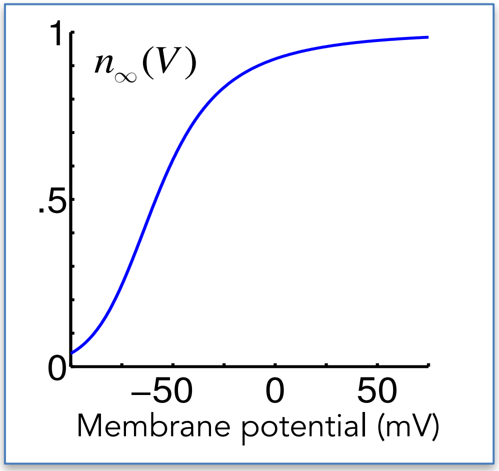
K and Na conductances

We modeled changes in conductance as transitions between 'closed' and 'open' states of ion channels.

K-conductance

$$\underset{1-n}{\text{'closed'}} \underset{\beta_n}{\overset{\alpha_n}{\rightleftharpoons}} \underset{n}{\text{'open'}}$$

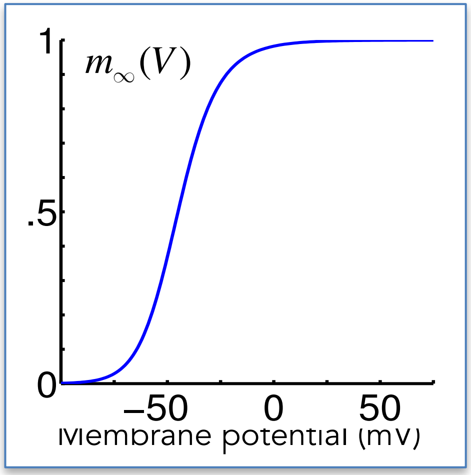
$$\tau_n \frac{dn}{dt} = n_\infty - n \qquad n_\infty = \frac{\alpha_n}{(\alpha_n + \beta_n)}$$



Na-conductance

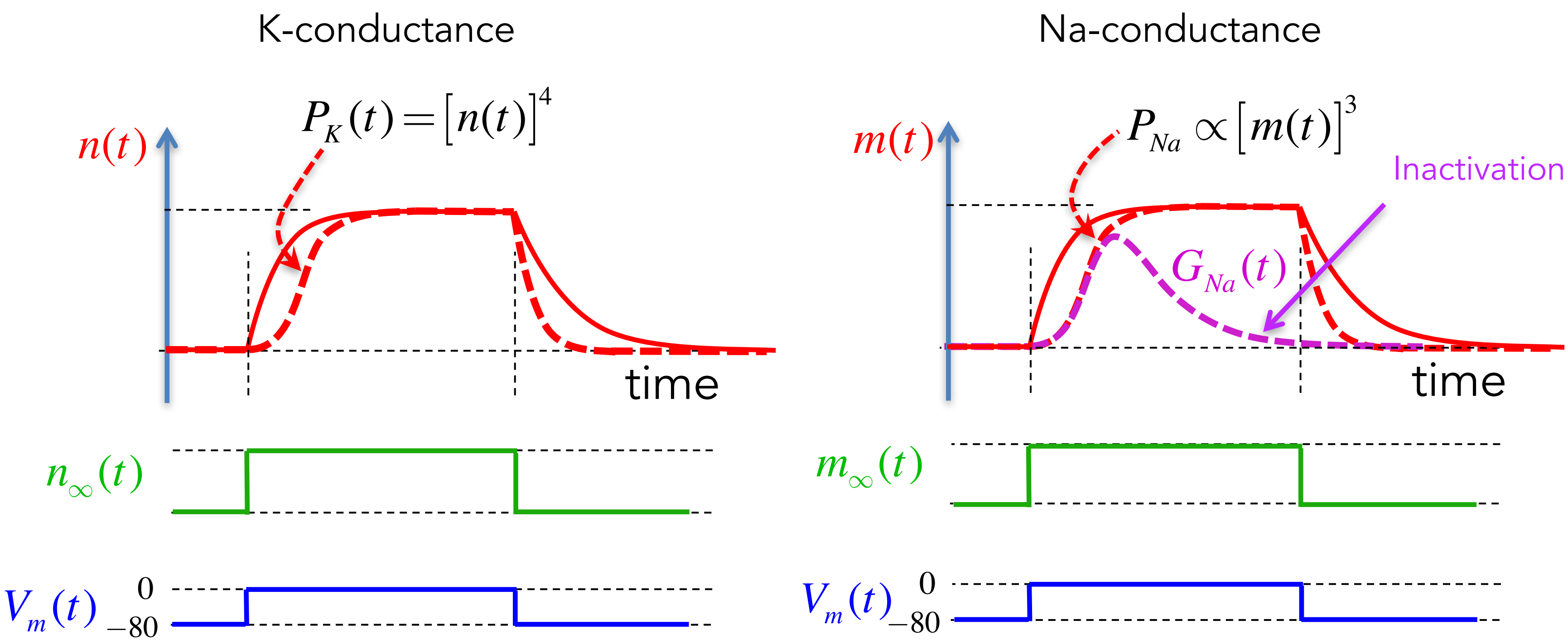
$$\underset{1-m}{\text{'closed'}} \underset{\beta_m}{\overset{\alpha_m}{\rightleftharpoons}} \underset{m}{\text{'open'}}$$

$$\tau_m \frac{dm}{dt} = m_\infty - m \qquad m_\infty = \frac{\alpha_m}{(\alpha_m + \beta_m)}$$



Gating variables

The activation of both Na and K conductances is represented by 'gating variables' m and n



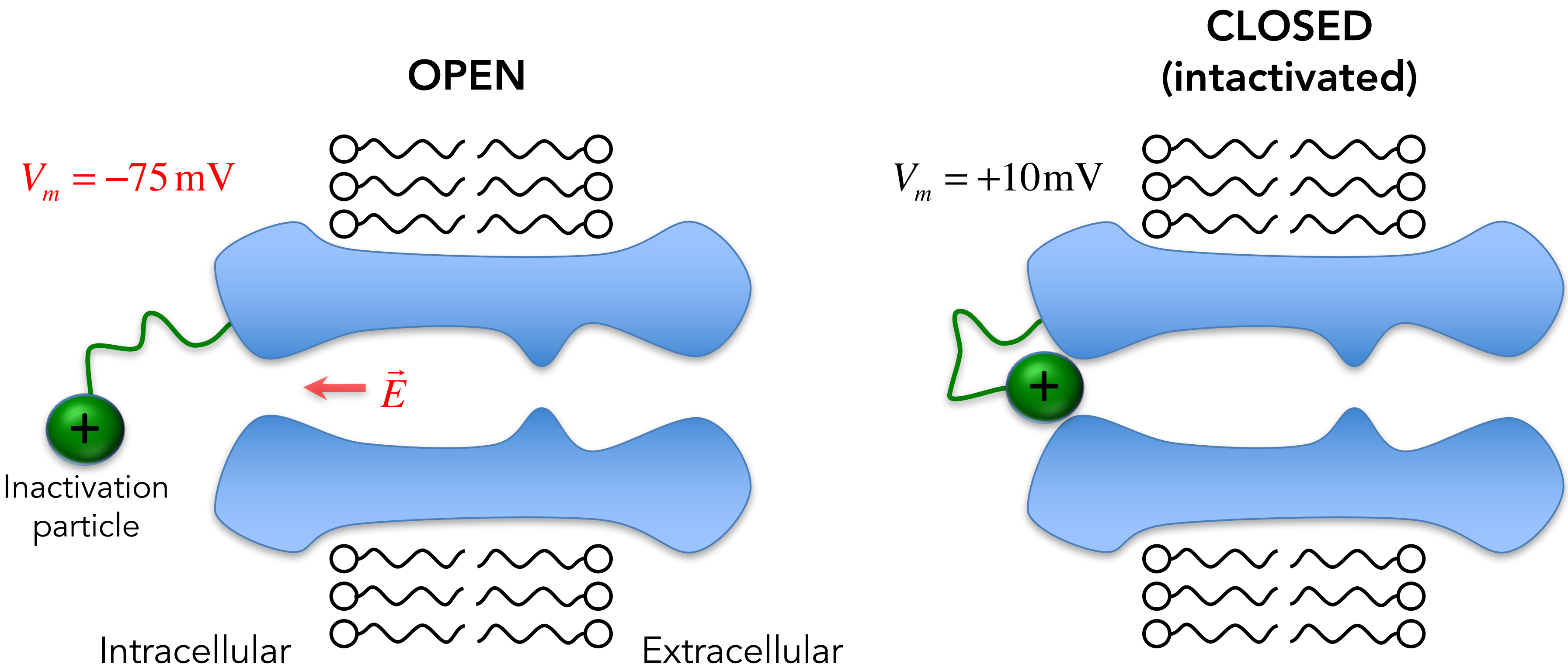
Activation gating variable

Inactivation gating variable

$$P_{Na} = m^3 h$$

Sodium channel inactivation

HH postulated an additional voltage-dependent inactivation gate.

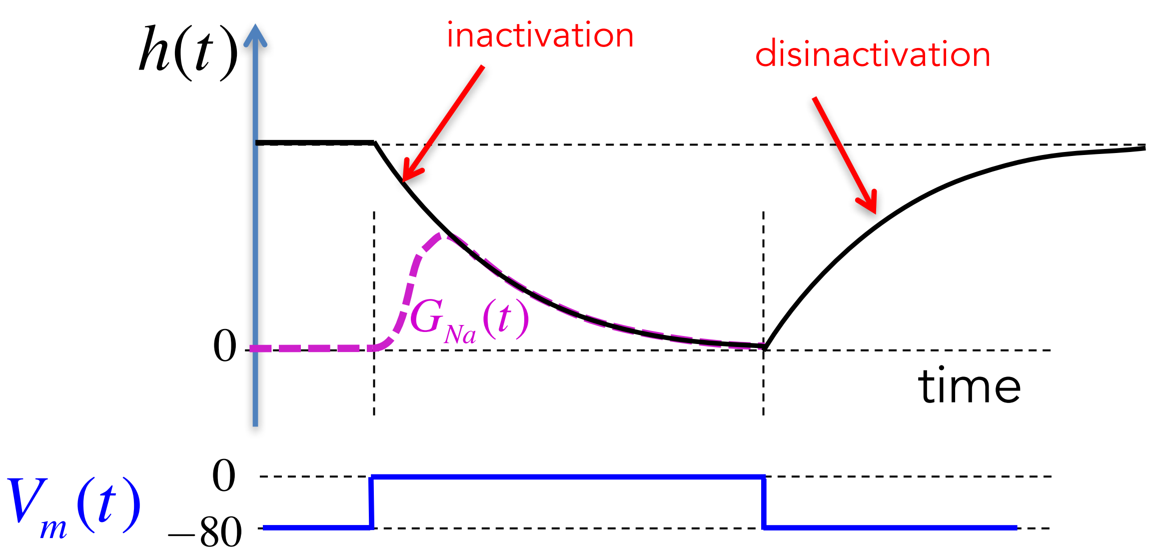


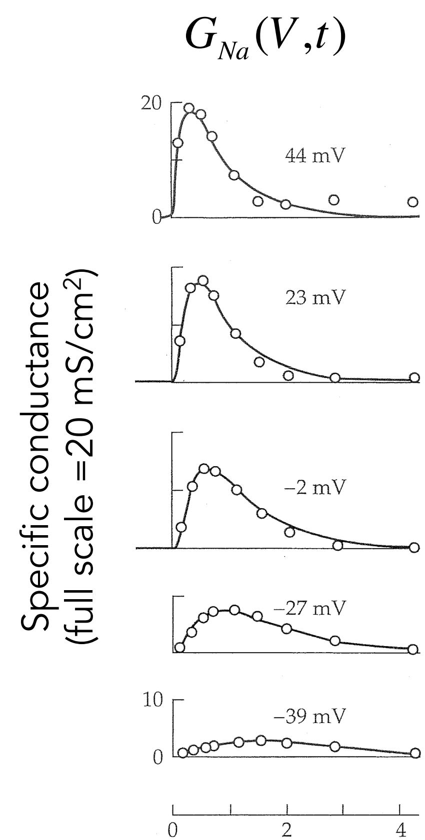
$$\underset{1-h}{\text{'closed'}} \underset{\beta_h}{\overset{\alpha_h}{\rightleftharpoons}} \underset{h}{\text{'open'}} \qquad \tau_h \frac{dh}{dt} = h_\infty - h$$

Sodium channel inactivation

Dynamics of inactivation are captured by a new gating variable ‘h’.

$$\tau_h \frac{dh}{dt} = h_\infty - h$$





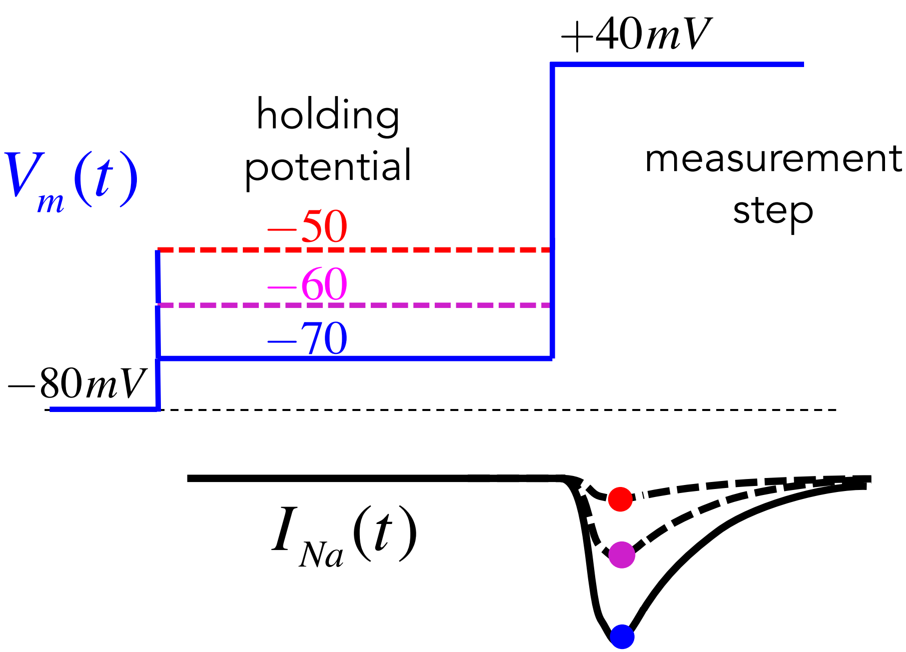
$$P_{Na} = m^3 h$$

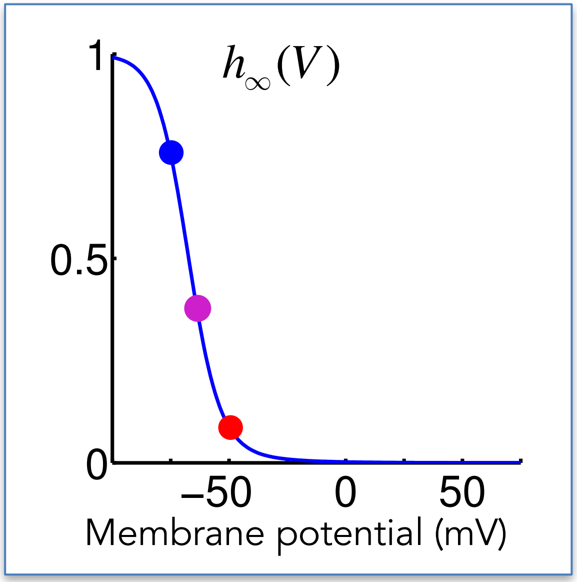
Measuring the parameters

How do we measure inactivation and recovery from inactivation?

1. Hold V_m at different values
2. Let the Na channels inactivate
3. Then measure the Na current!

$$\tau_h \frac{dh}{dt} = h_\infty - h$$





The sodium conductance

Putting our two Na-channel gating variables together, we get:

The probability of having a Na channel open is:

$$P_{Na} = m^3 h$$

Note independence

NOT !

But it's not so bad

The sodium conductance is:

$$G_{Na} = \bar{G}_{Na} m^3 h$$

And the sodium current is:

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

Putting it all together!

Start with initial contition $V_m = V_0$ at time step t_0

Compute:

$n_\infty(V)$ and $\tau_n(V)$ $m_\infty(V)$ and $\tau_m(V)$ $h_\infty(V)$ and $\tau_h(V)$

$$n(t) = n(t-1) + \frac{dn}{dt}\Delta t \quad m(t) = m(t-1) + \frac{dm}{dt}\Delta t \quad h(t) = h(t-1) + \frac{dh}{dt}\Delta t$$

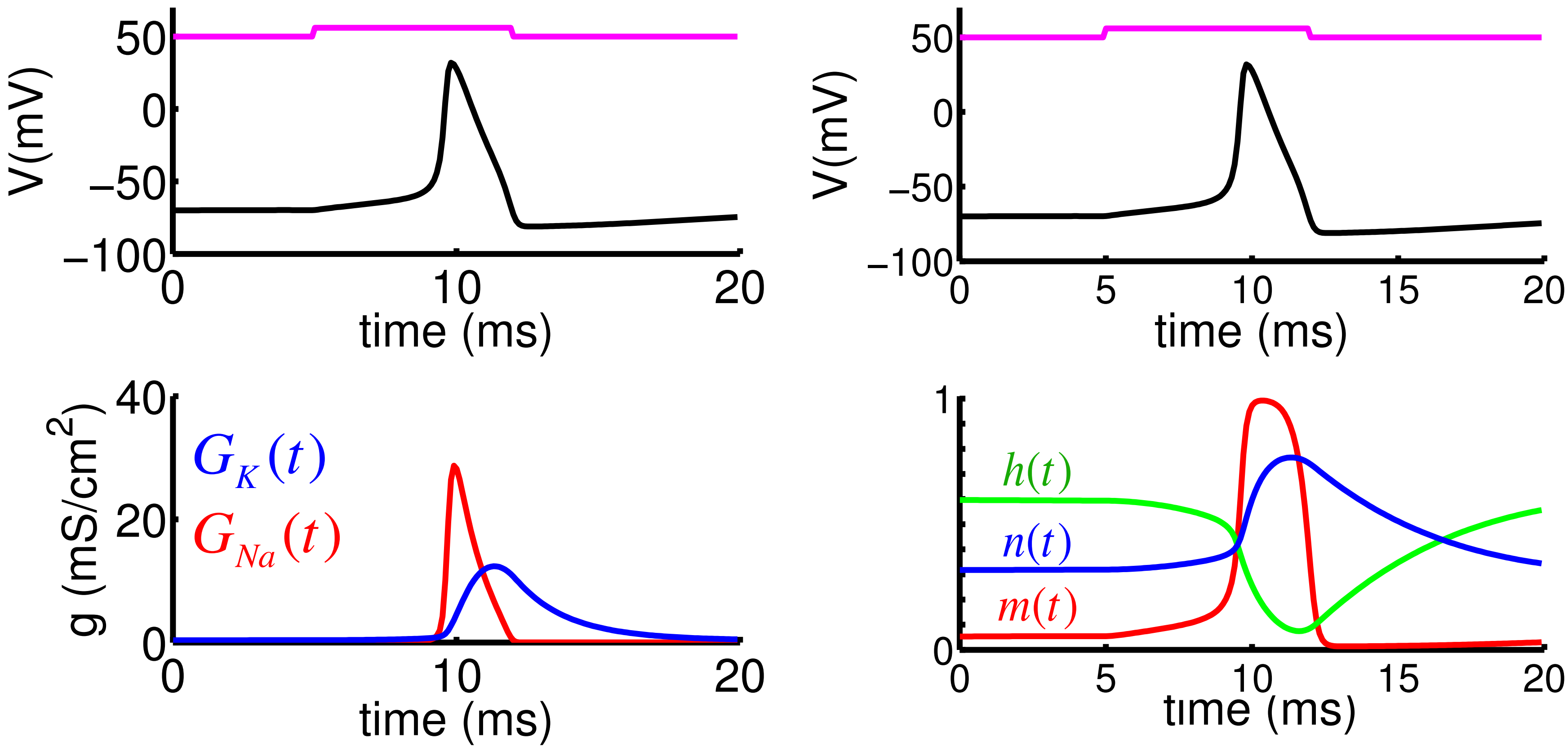
$$I_K = \bar{G}_K n^4 (V - E_K) \quad I_{Na} = \bar{G}_{Na} m^3 h (V - E_{Na}) \quad I_L = \bar{G}_L (V - E_L)$$

Total membrane current $I_m = I_K + I_{Na} + I_L$

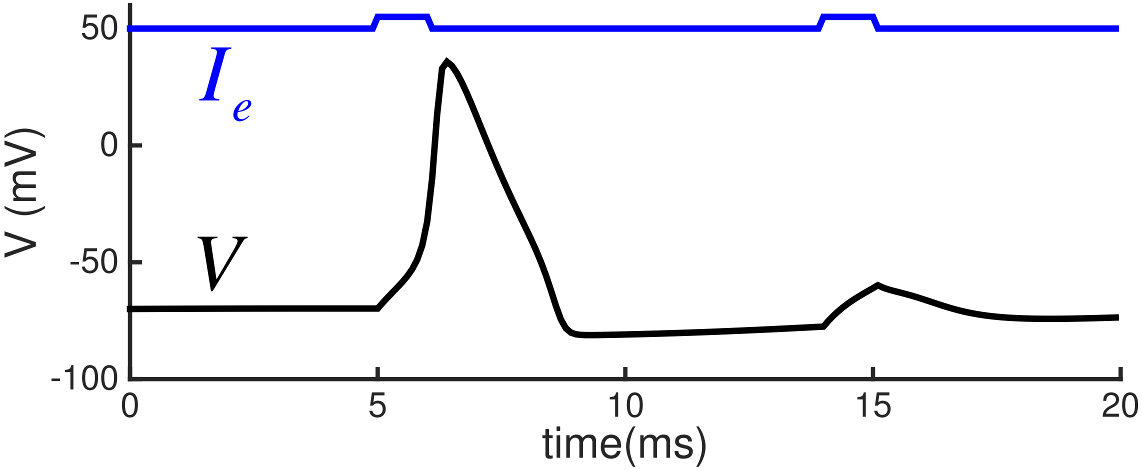
Compute τ_{mem} *and* V_∞

$$V_m(t) = V_m(t-1) + \frac{dV_m}{dt}\Delta t$$

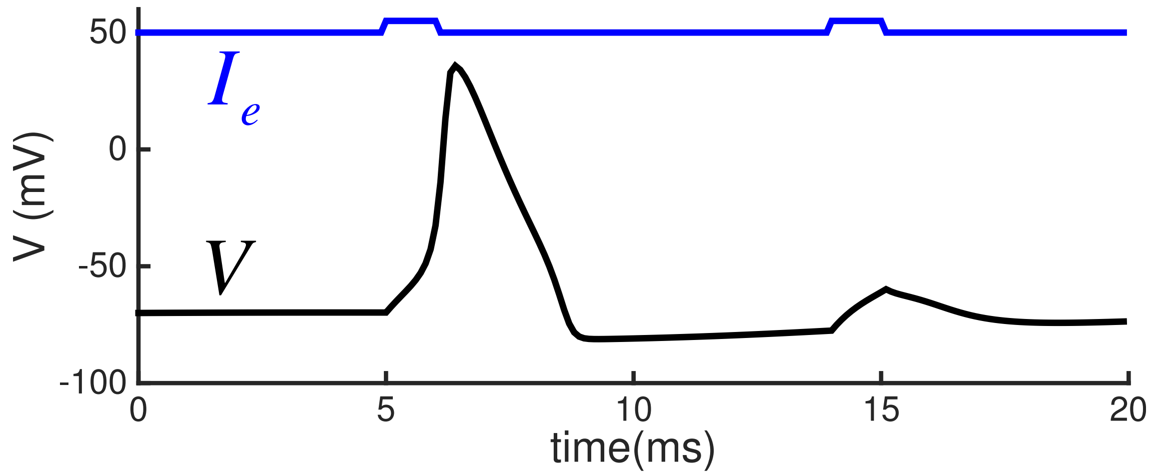
Putting it all together!

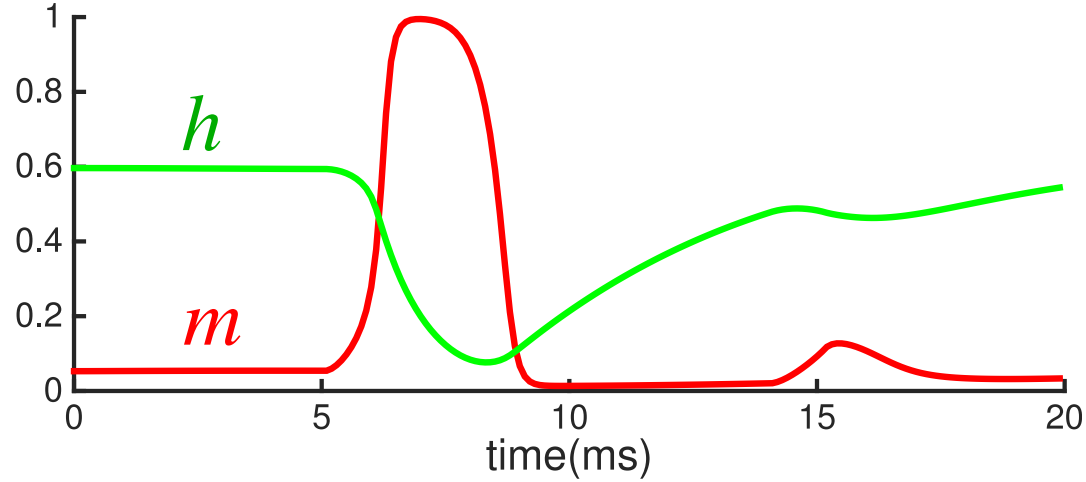


Spike refractory period



Spike refractory period due to sodium channel inactivation

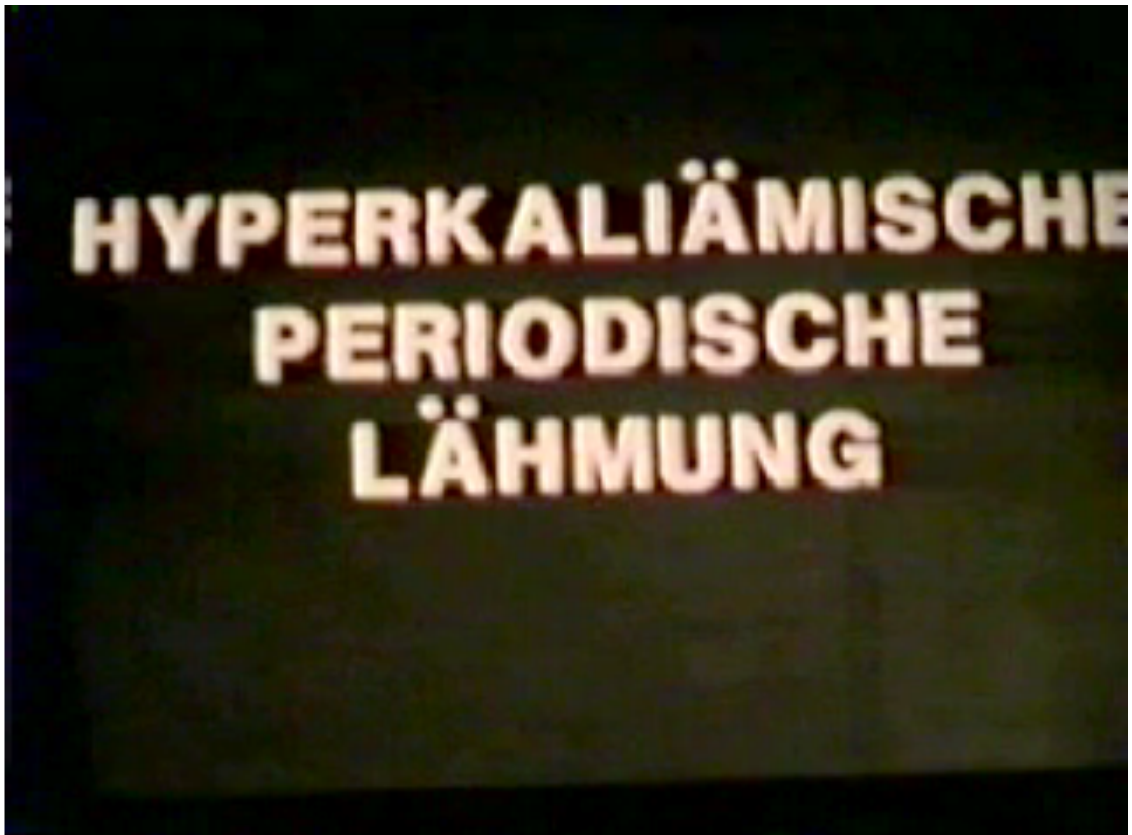




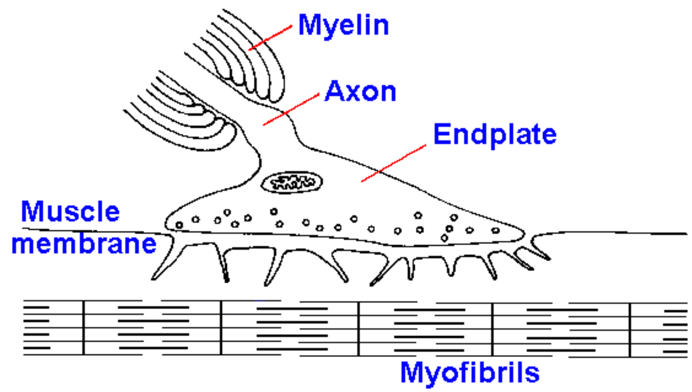
Diseases related to defects in sodium channel inactivation

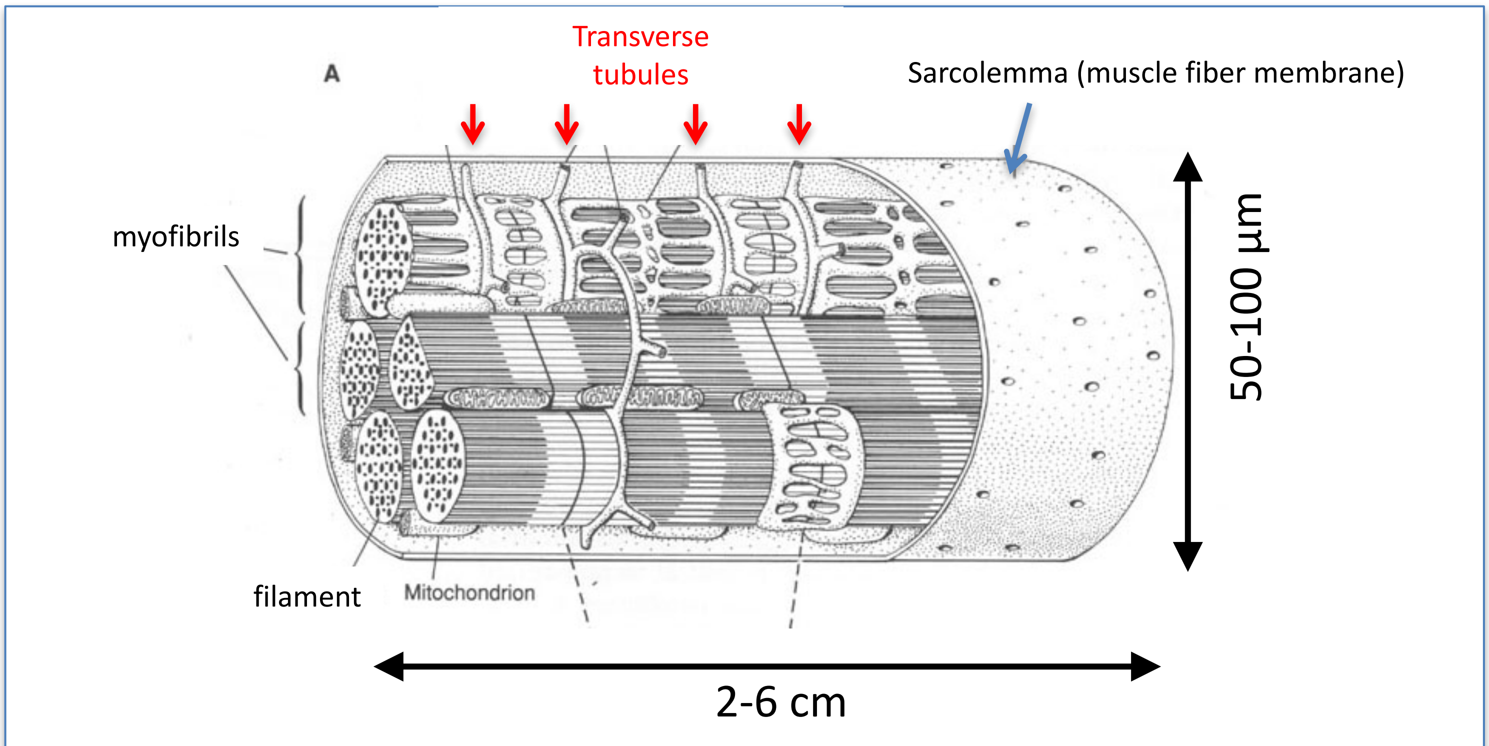
Diseases related to defects in sodium channel inactivation

Hyperkalemic Periodic Paralysis – Hyper PP

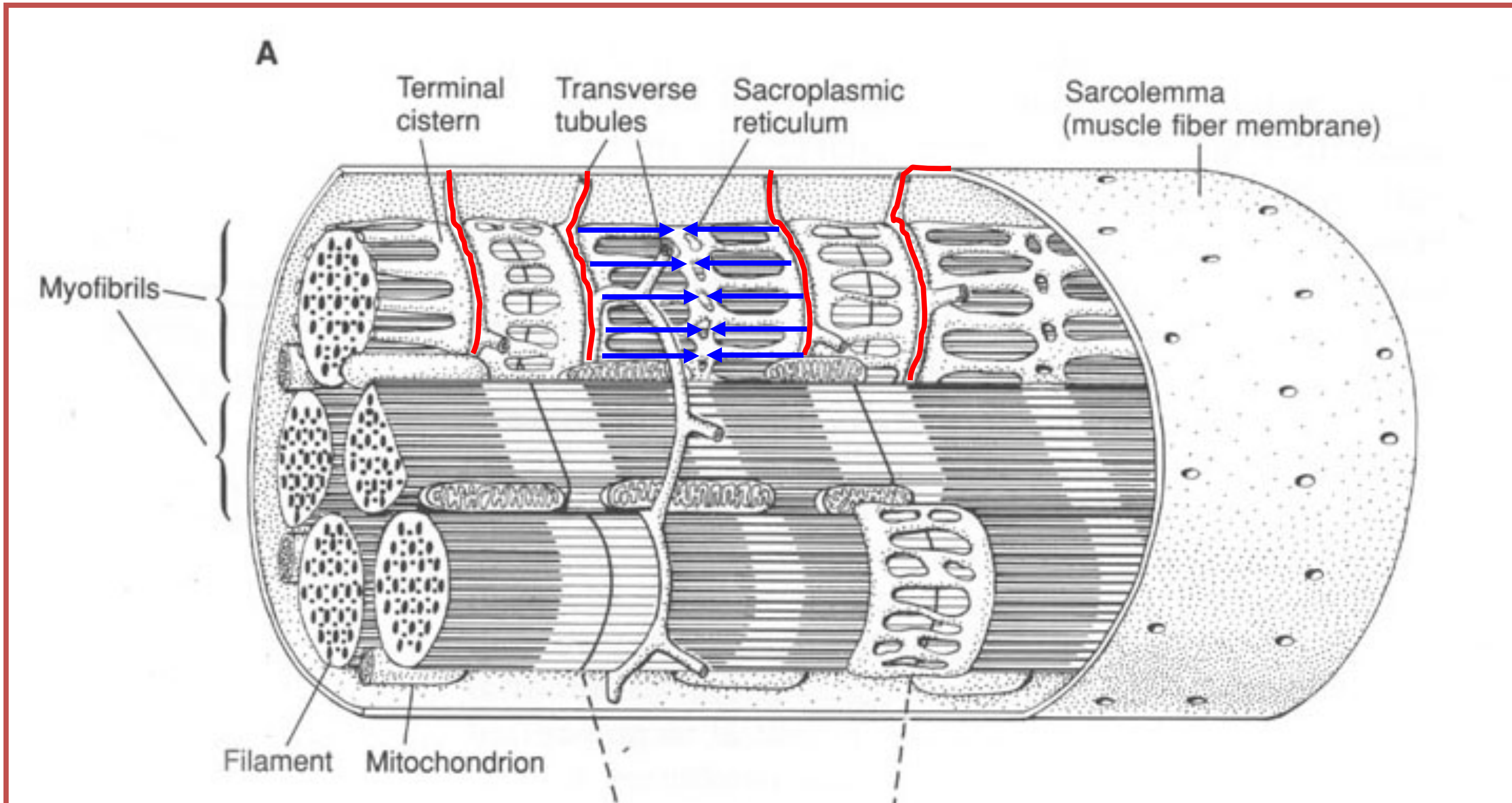


Structure of Muscle Fiber

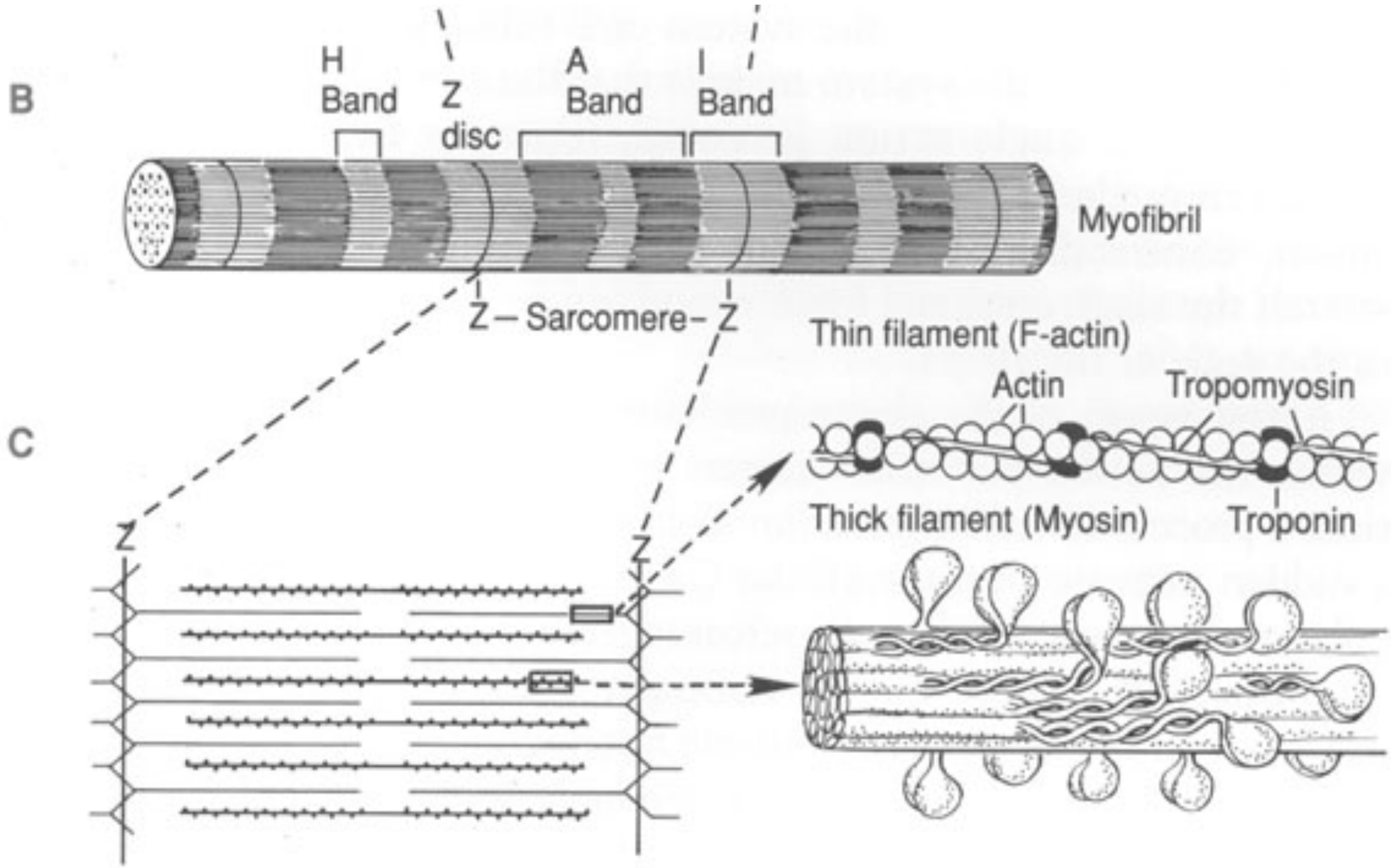




Muscle Fiber AP Leads to Ca Release in Myofibrils



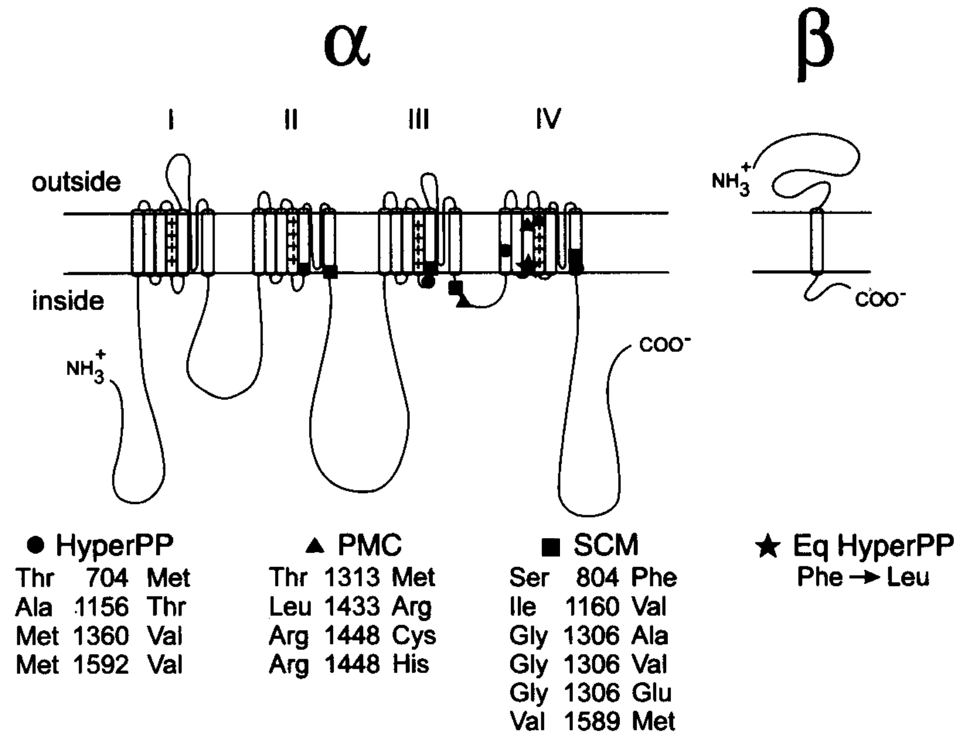
Sliding Filament Model



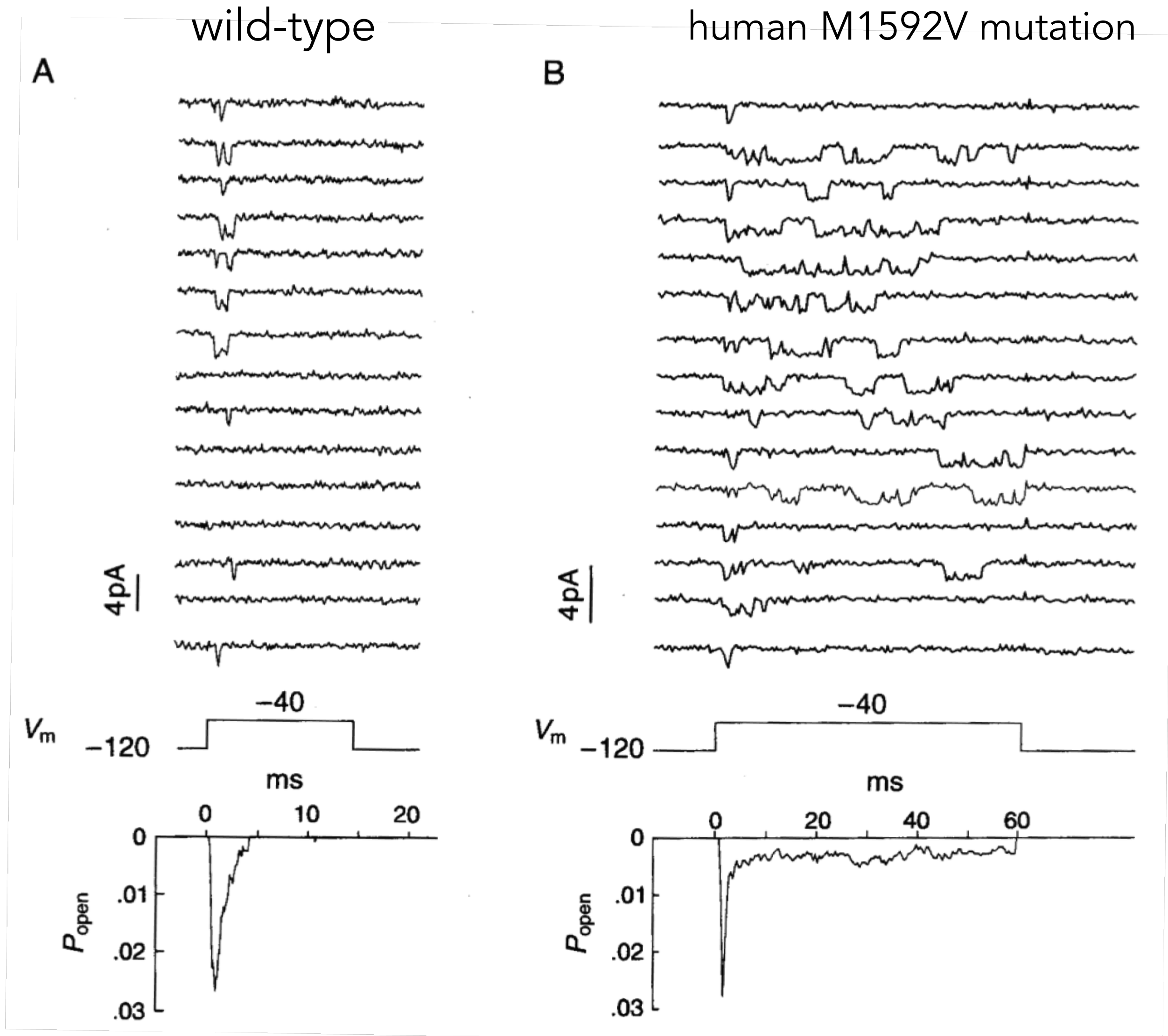
Andrew Huxley, Hugh Huxley, 1954

Diseases related to defects in sodium channel inactivation

Myotonia and Periodic Paralysis are associated with mutations of the Na channel (skeletal isoform only)

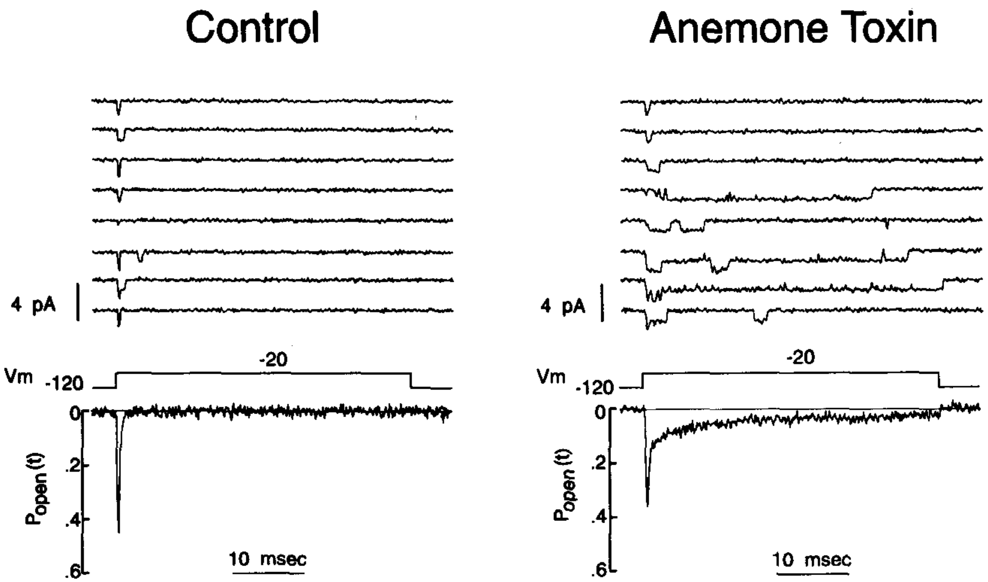


Sodium channel mutations



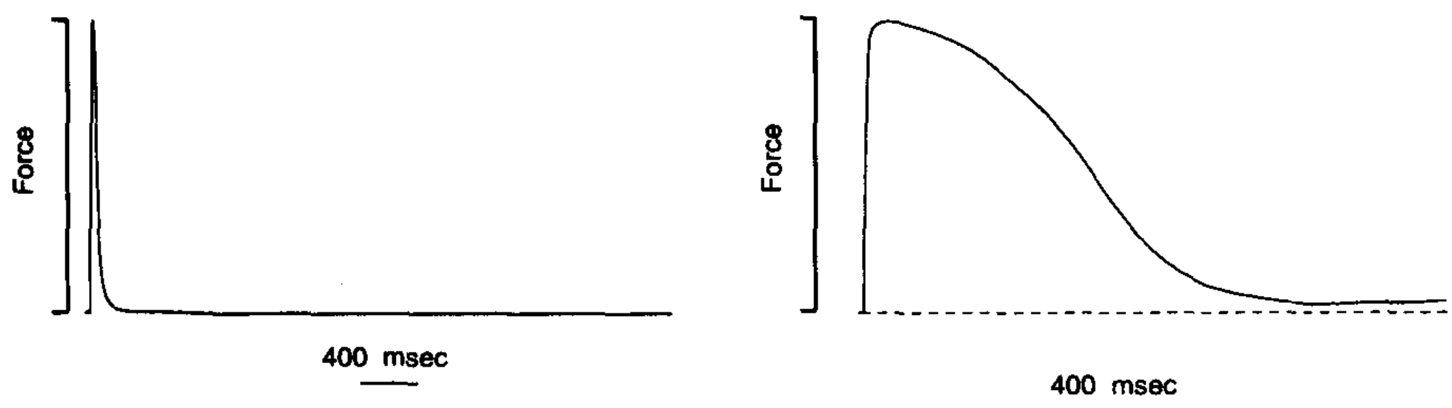
Diseases related to defects in sodium channel inactivation

Sea anemone toxin (ATXII, 10uM) partially blocks sodium channel inactivation.



Diseases related to defects in sodium channel inactivation

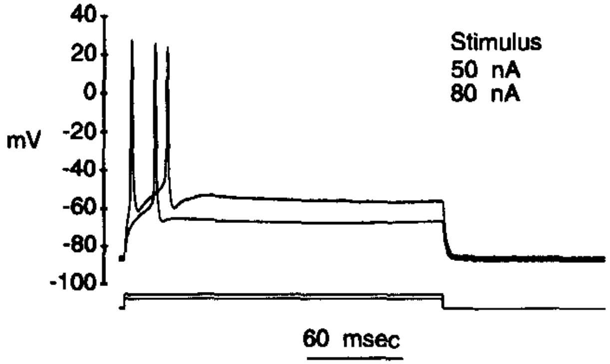
Sea anemone toxin (ATXII) also prolongs muscle fiber twitch duration.



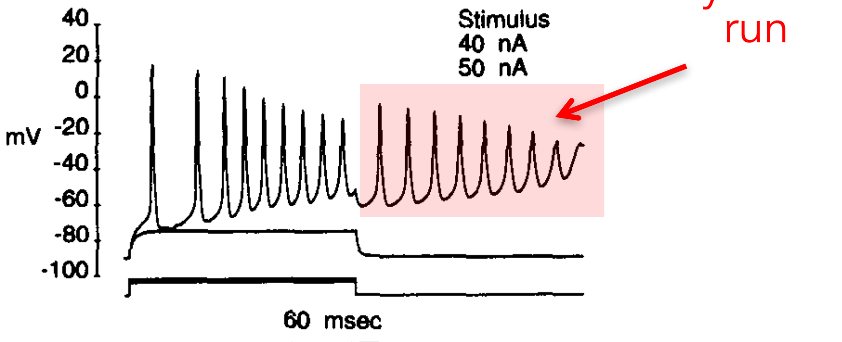
Diseases related to defects in sodium channel inactivation

Sea anemone toxin (ATXII) prolongs spiking in muscle fiber.

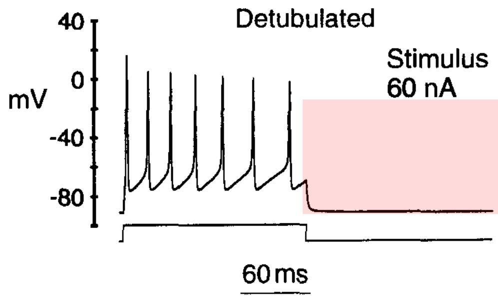
Control



ATXII

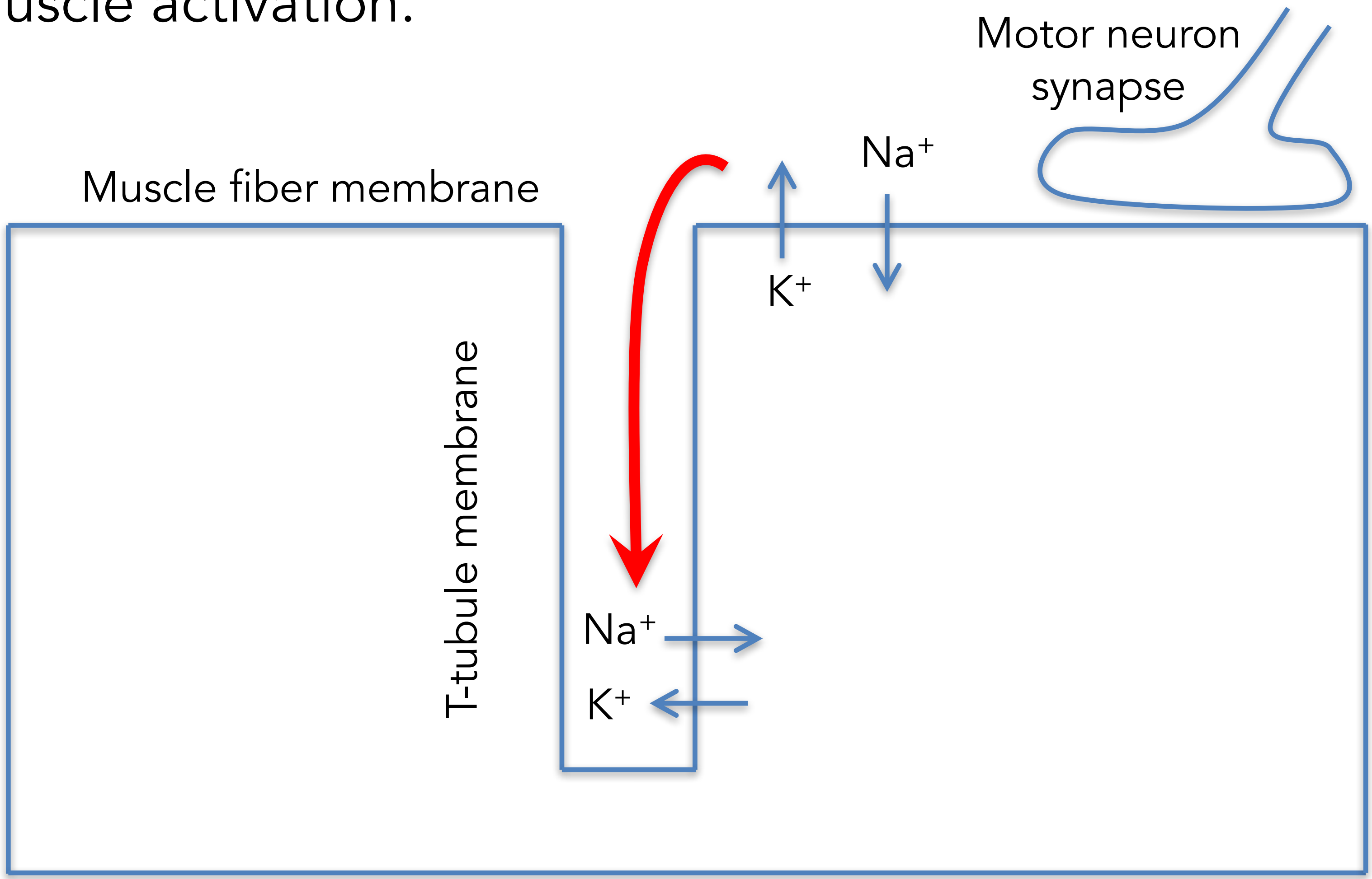


Osmotic shock breaks T-tubules and eliminates myotonic run



Diseases related to defects in sodium channel inactivation

Hypothesis for how persistent sodium leads to persistent muscle activation.



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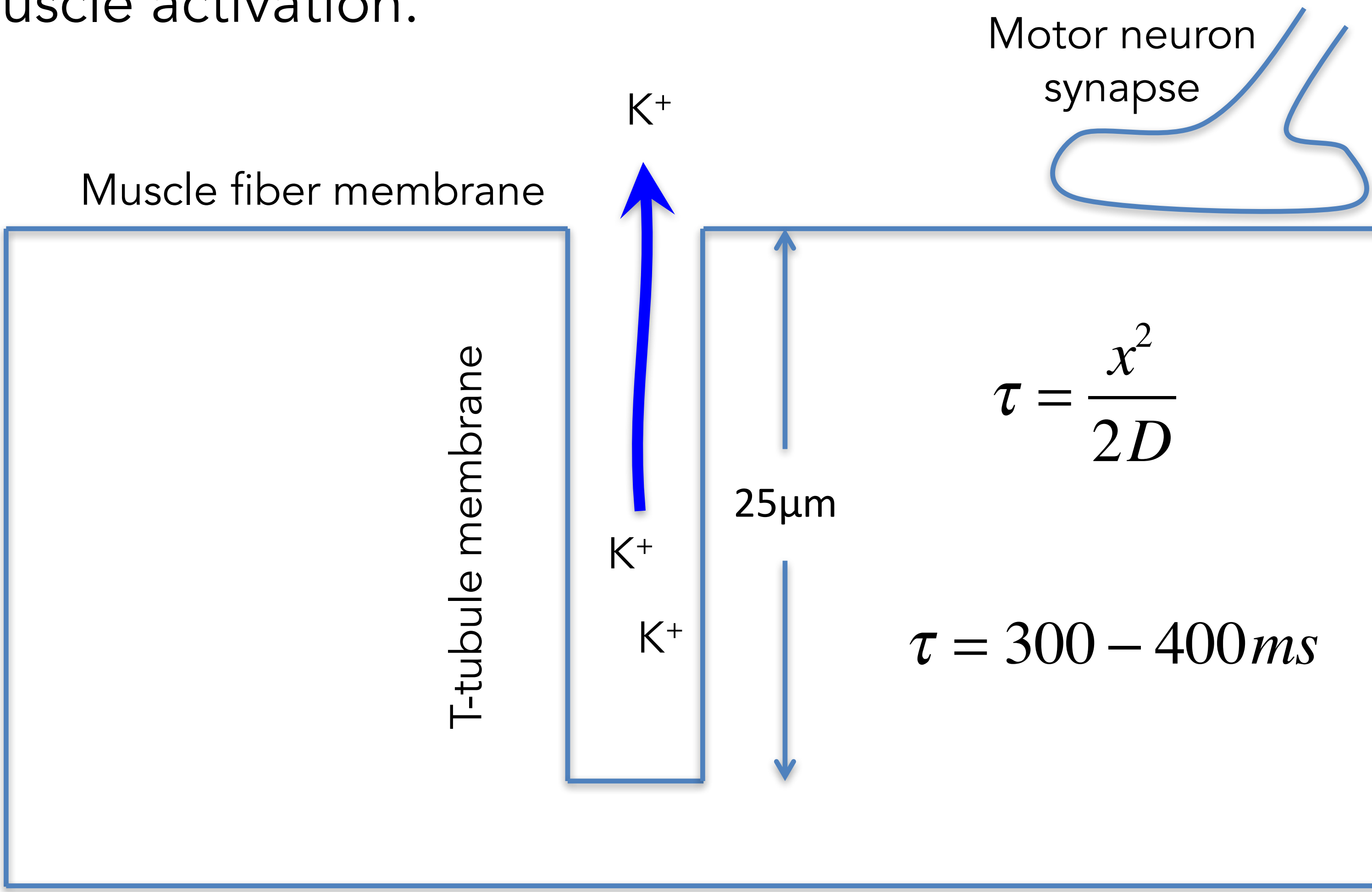

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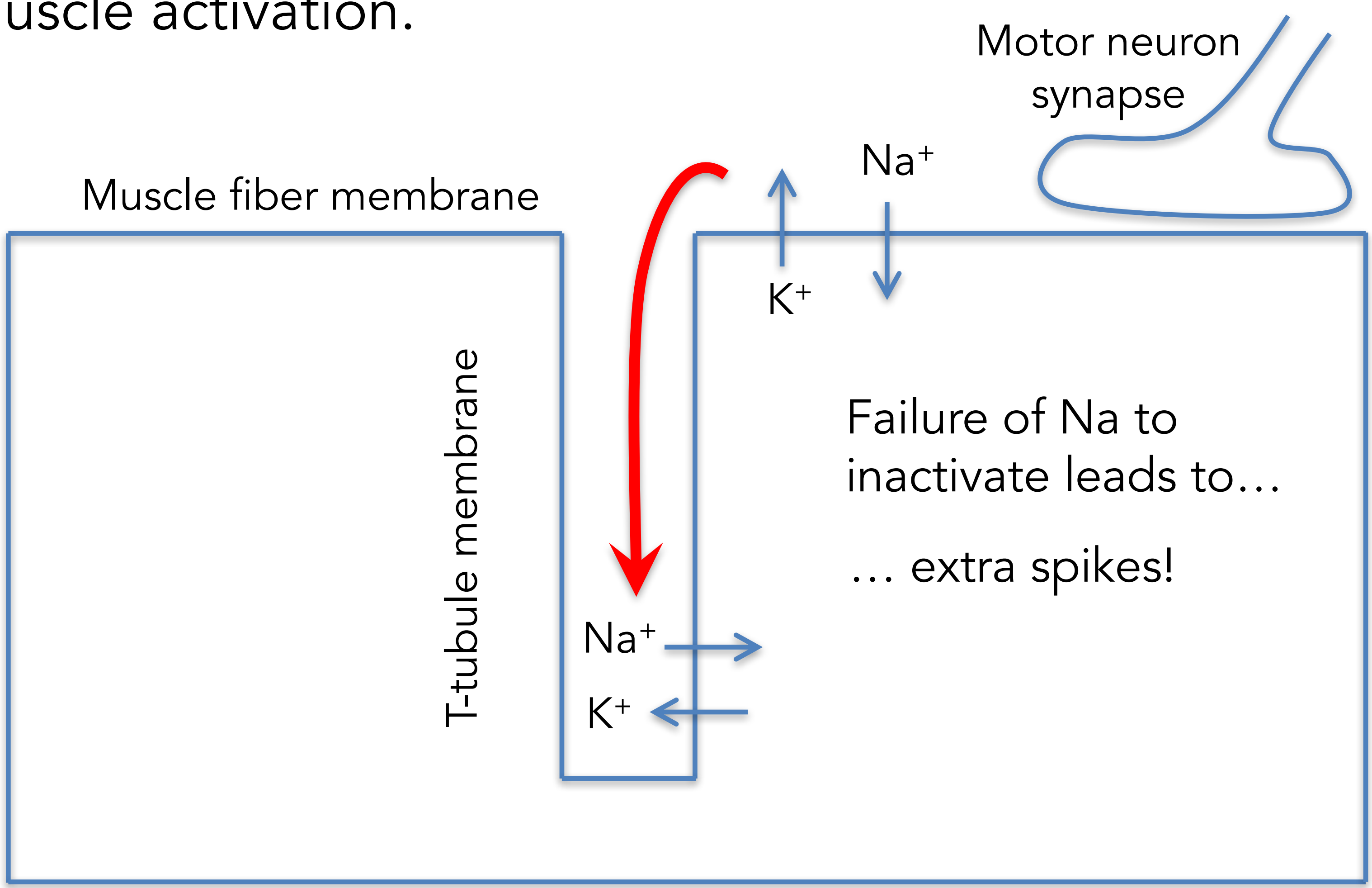

Diseases related to defects in sodium channel inactivation

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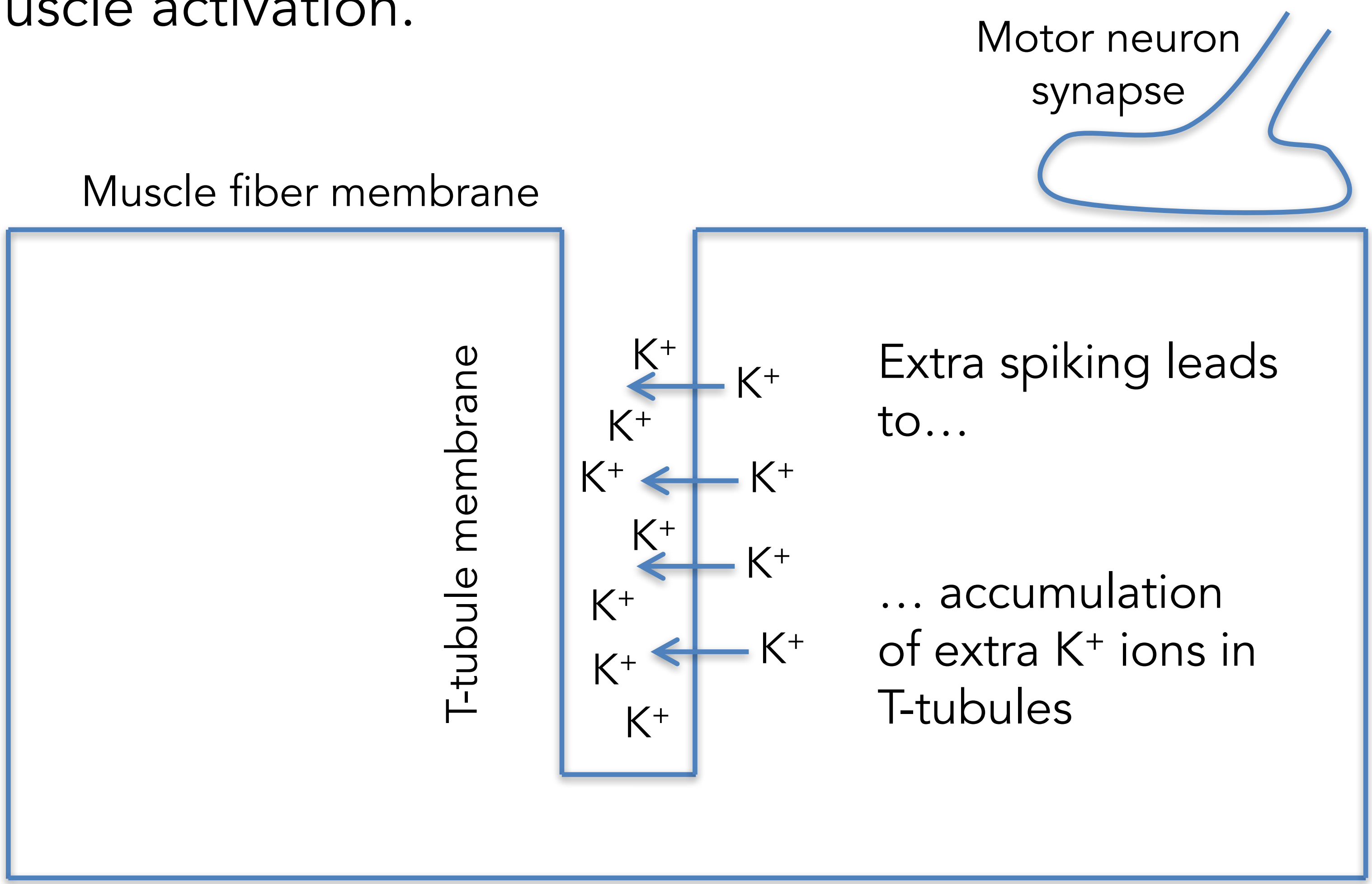
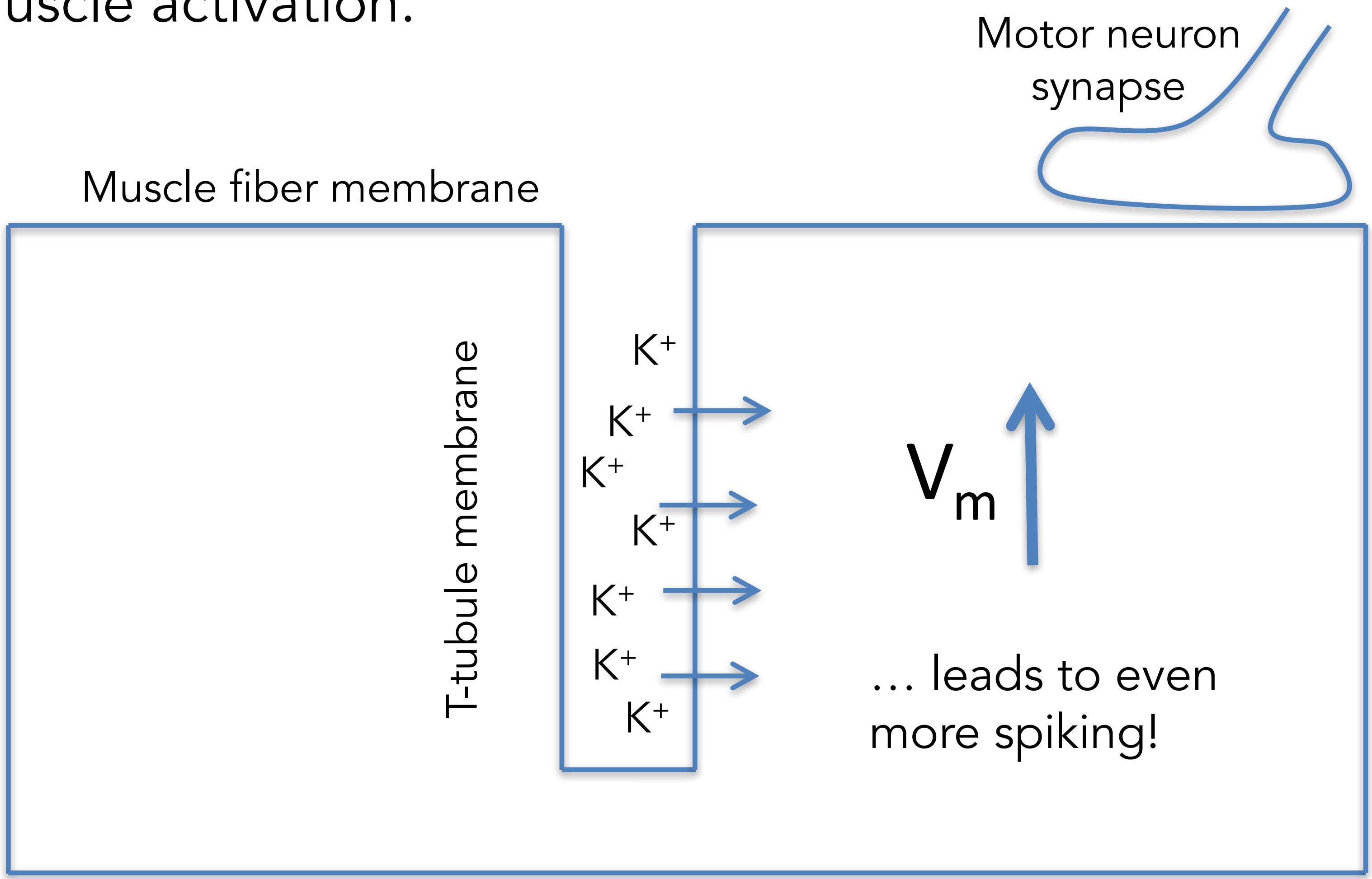


Diseases related to defects in sodium channel inactivation

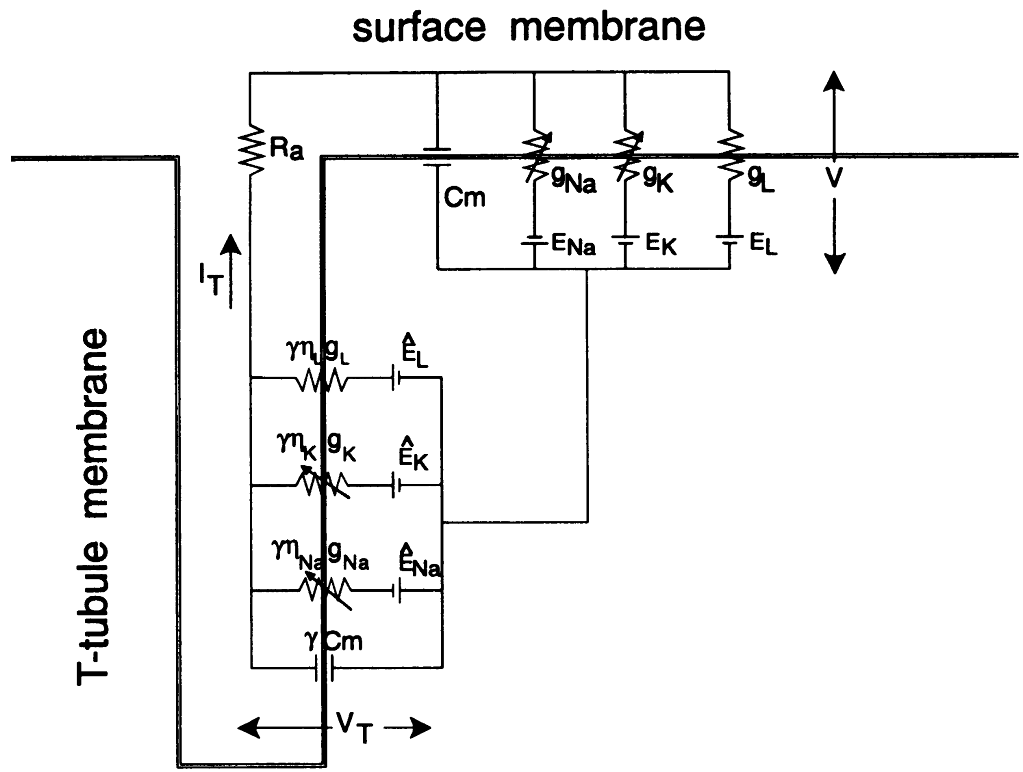
Hypothesis for how persistent sodium leads to persistent muscle activation.



Diseases related to defects in sodium channel inactivation

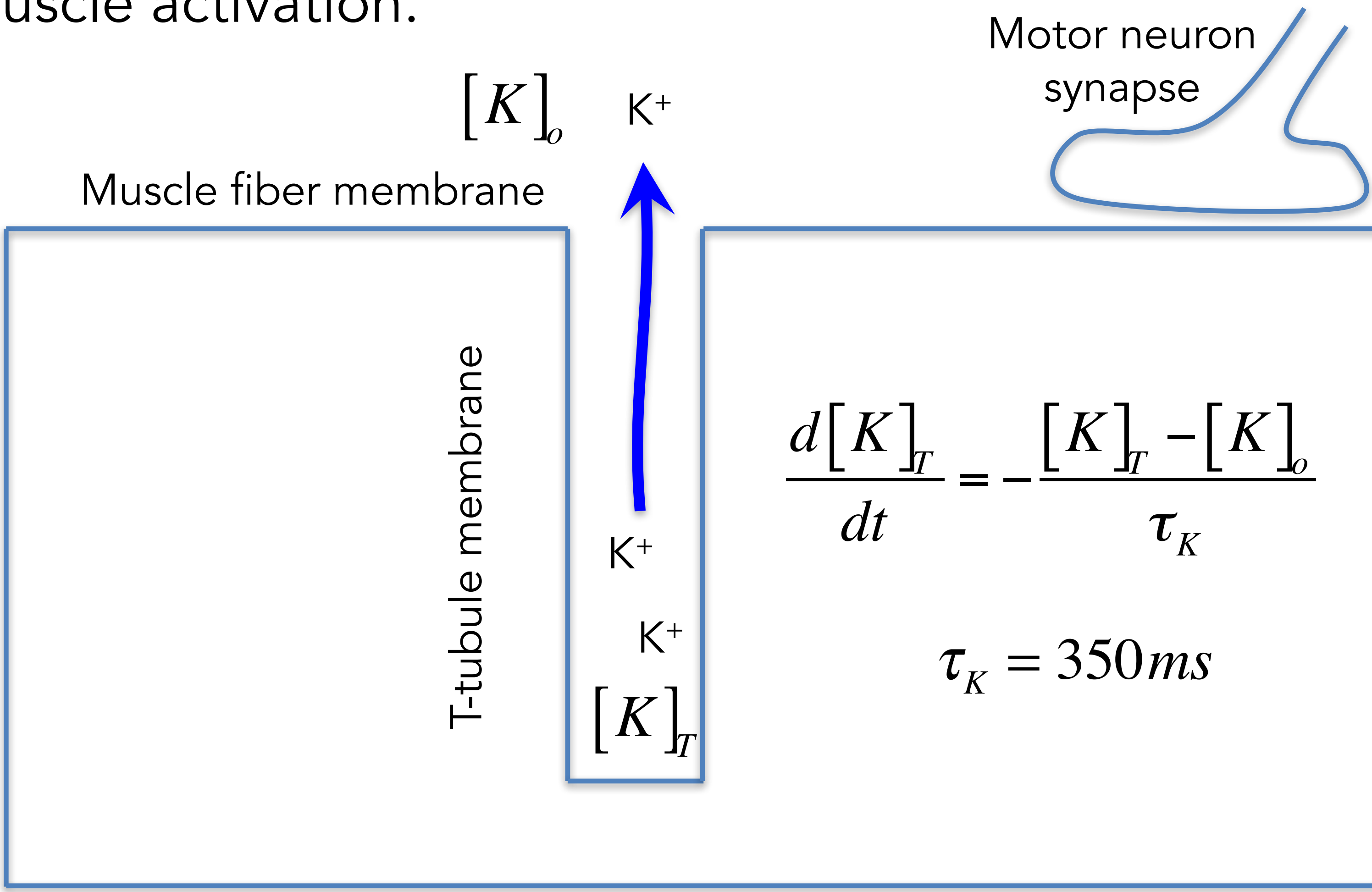
Equivalent circuit model of muscle fiber membrane and T-tubule.

FIGURE 1 Equivalent circuit diagram for the model of the electrical behavior of a muscle fiber. The voltage and time dependence of the variable conductances are given by Eqs. 6, 7, 9, and 10. γ is the ratio of the T-tubular membrane area to surface membrane area. The ηs represent the density of ion channels in the T-tubular membrane relative to that of the surface membrane.



Diseases related to defects in sodium channel inactivation

Hypothesis for how persistent sodium leads to persistent muscle activation.

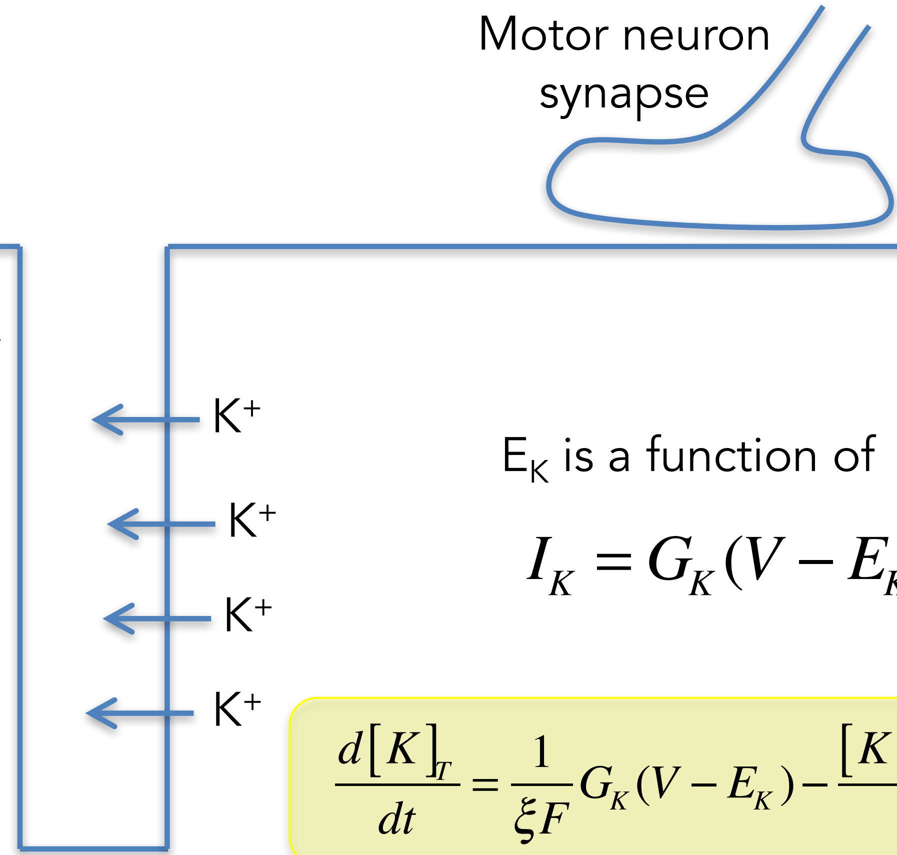


$$\frac{d[K]_T}{dt} = -\frac{[K]_T - [K]_o}{\tau_K}$$

$$\tau_K = 350ms$$

Diseases related to defects in sodium channel inactivation

Hypothesis for how persistent sodium leads to persistent muscle activation.



I_K = K-current into T-tubule

$$\frac{d[K]_T}{dt} \propto I_K$$

$$\frac{d[K]_T}{dt} = \frac{1}{\xi}\frac{1}{F} I_K$$

ξ = volume of T-tubule

F = Faraday constant (C/mol)
$= 9.6\text{x}10^4$ (C/mol)

E_K is a function of $[K]_T$!!

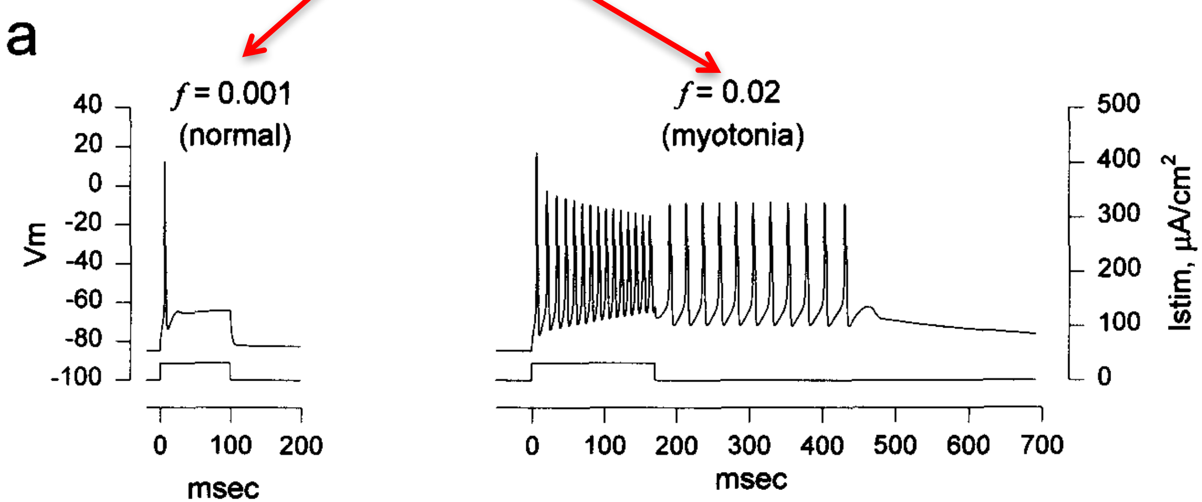
$$I_K = G_K (V - E_K)$$

$$\frac{d[K]_T}{dt} = \frac{1}{\xi F} G_K (V - E_K) - \frac{[K]_T - [K]_o}{\tau_K}$$

Diseases related to defects in sodium channel inactivation

Computer model of effects of defective Na-channel inactivation

Fraction of Na channels that fail to inactivate



Failure to inactivate was modeled by settting h=1 for a fraction of the channels

Diseases related to defects in sodium channel inactivation

Computer model of effects of defective Na-channel inactivation showing transition from myotonia to paralysis