BME 5742 Biosystems Modeling and Control

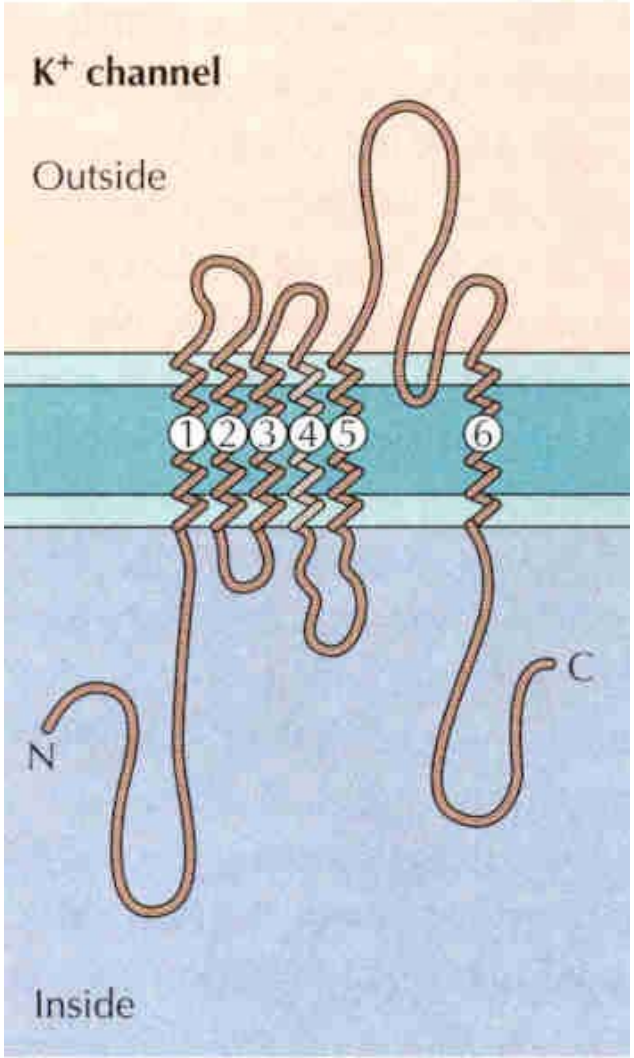
Lecture 34

Hodgkin-Huxley Model for Nerve Cell Action Potential

Part 2

Voltage-Gated K^+ Channels -1

- All voltage-gated channels belong to a large family of related proteins.
- K^+ channels consist of 4 identical sub-units, each containing 6 trans-membrane α helices.
- Voltage gating is mediated by helix #4, which contains multiple positively charged amino acids.



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Voltage-Gated K^+ Channels -2

- Voltage gating is mediated by helix #4, which contains multiple positively charged amino acids.
- Membrane depolarization induces the movement of these positive charges towards the outside of the cell, shifting the position of the segment, and thus opening the gate.

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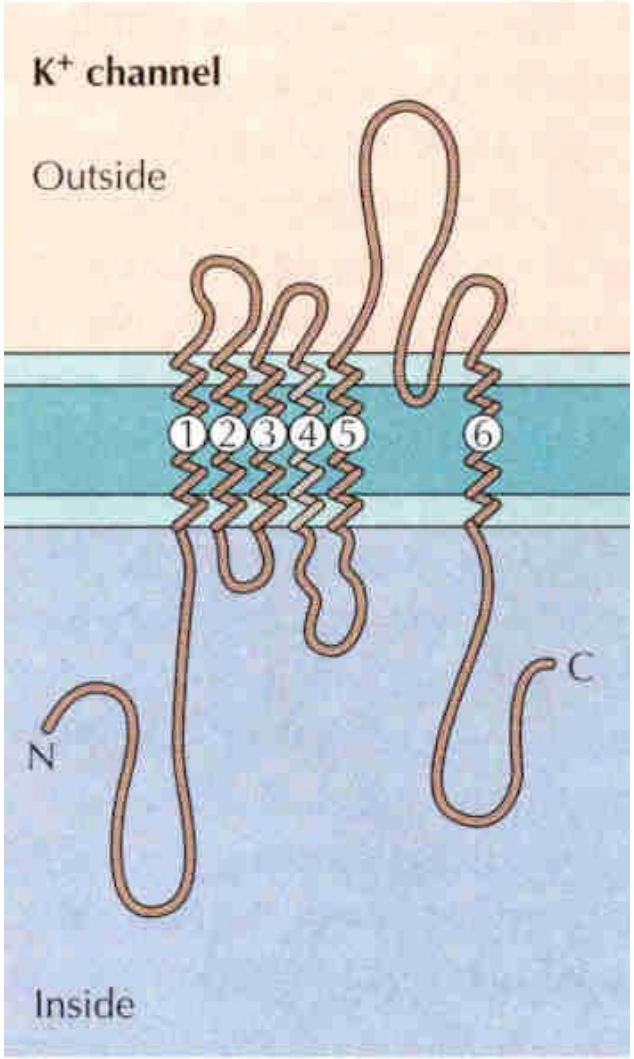
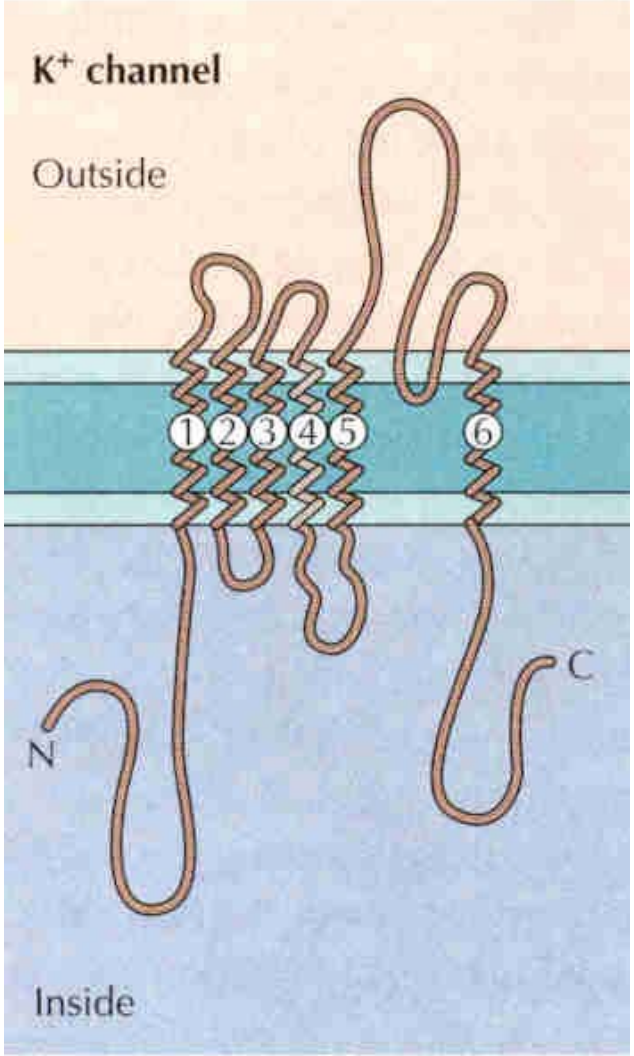


Voltage-Gated K^+ Channels -3

- Subsequent inactivation of the K^+ channel is then mediated by ICF-side portions of the polypeptide chain, which bind to the ICF-side “mouth” of the channel pore and prevent further ion flow.



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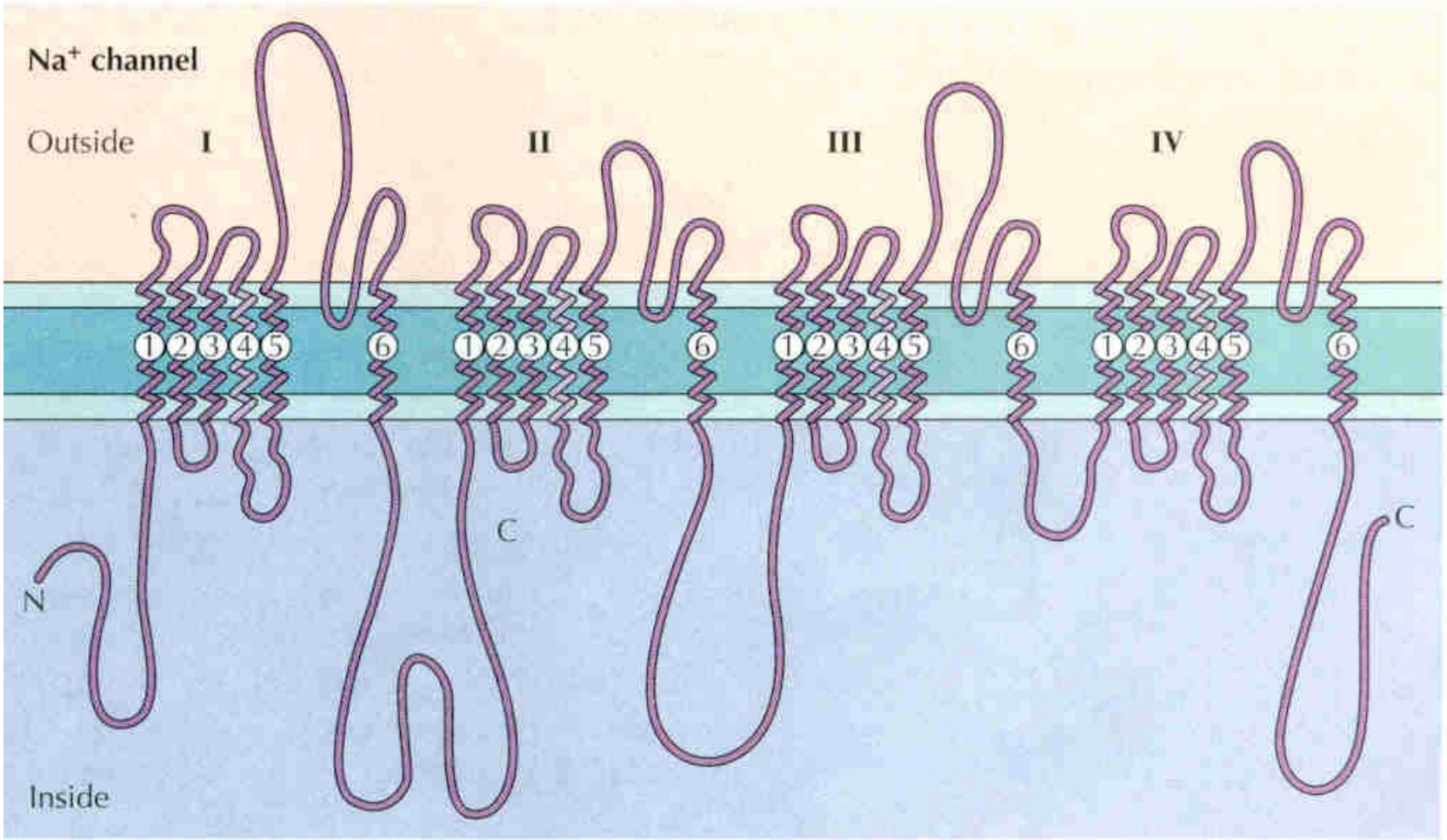
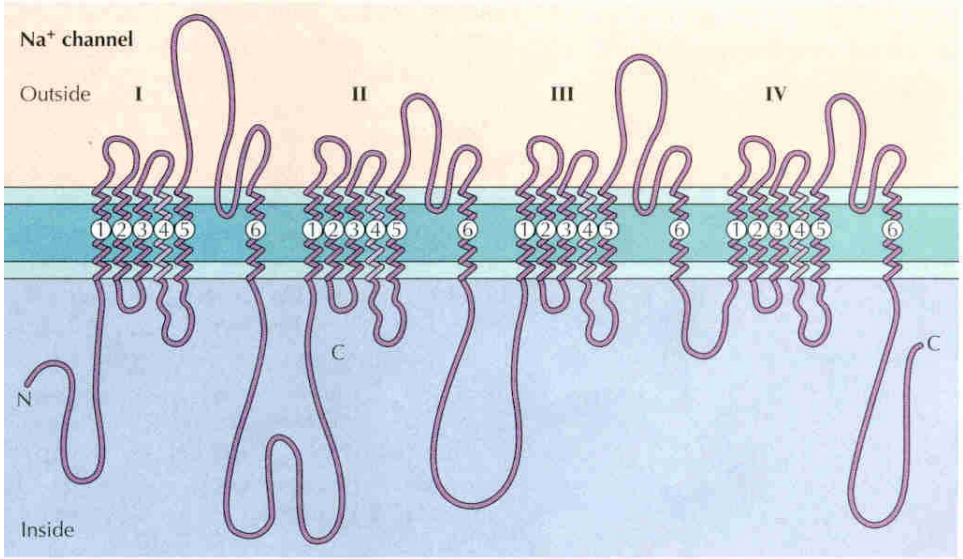
Structure of a Voltage-Gated Sodium Channel - 1



Structure of a Voltage-Gated Sodium Channel - 2



- Na^+ channels, unlike K^+ channels, consist of a single polypeptide chain, which contains 4 repeated domains that look each like a K^+ channel sub-unit.
- Again, helices #4 are related to the voltage gating activation.

Hodgkin-Huxley's Postulates for K^+ Channels

- Each K^+ channel has 4 gates. Each gate can be OPEN or CLOSED. The channel is OPEN if <u>all</u> gates are OPEN.
- All 4 gates are identical.
- The gates operate independently of one another.
- The gate closing and opening probabilities depend on the cell membrane voltage.

K^+ Gate OPEN State Probability

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

The fraction of K^+ gates that are in OPEN state at time t is denoted as n(t).

This is also the probability that a given K^+ gate is OPEN at time t.

K^+ Gate OPEN Rate Explained

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

- 1-n(t) is the fraction of CLOSED gates. The rate of opening gates is larger if there are more closed gates. (For instance, if n=1, then all gates are OPEN, and then the rate of opening more gates is 0)
- Likewise, the rate of closing gates depend on the number of OPEN gates.

K^+ Gate Opening and Closing Rate Functions

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

- The opening rate constant $\alpha_n(v)$ [time^{-1}] is an increasing function of v. Increasing cell membrane v encourages K^+ gates to open.
- The closing rate constant $\beta_n(v)$ is a decreasing function of v. Increasing cell membrane v discourages K^+ gates from closing.

Depolarization

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

- The increasing of v increases the K^+ channel conductance.
- The increase of K^+ channel conductance causes E to go from a positive value to negative value. We call it “depolarization”.

K^+ Channel Conductance

$$g_K = \bar{g}_K n^4$$

- Here we use the assumption that all gates are independent.
- Since n is the probability that one gate is OPEN, for the channel to be OPEN, we need all 4 gates to be OPEN.
- Constant of proportionality (gKbar) is the conductance when all K^+ gates in all channels are OPEN.

Difference between Na^+ and K^+ Channels

- When an upwards voltage is applied, the K^+ conductance rises monotonically, settles at an elevated level, and stays there as long as elevated voltage is maintained.
- Na^+ channel conductance (if a voltage rises) rises only briefly, and then falls back to a low level, even when elevated voltage is maintained←→ Na^+ inactivation.

Na^+ Channel Inactivation

- Inactivation plays a crucial role in the pulse propagation mechanism.
- Need to assure that pulses that are created propagate in a unique direction (i.e. no backflow).
- The temporarily inactivated Na^+ channels prevent such backflow.
- Pulse's decaying voltage reaches the next group of channels and it still large enough to cause activation there, and essentially a pulse re-generation.

Hodgkin-Huxley's Postulates for Na^+ Channels

- Each Na^+ channel has 4 gates. Each gate can be OPEN or CLOSED. The channel is OPEN if <u>all</u> gates are OPEN.
- The four gates are not identical. There are "m-gates" and "h-gates".
- The gates operate independently of one another.
- The gate closing and opening probabilities depend on the cell membrane voltage.

Qualitative contrasting of m- and h-gates

- Both types of Na^+ gates have different closing and opening rate functions.
- The m-gates are encouraged to open by increasing voltage.
- The h-gates are encouraged to close by increasing voltage.
- Differential equations for m(t) and h(t) has the same structure as that of n(t).

OPEN Probabilities equations for m and h Na^+ gates

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

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

- Here, $\alpha_m(v)$ and $\beta_h(v)$ are increasing functions of v.
- Whereas, $\alpha_h(v)$ and $\beta_m(v)$ are decreasing functions of v.
- Increasing v encourages opening of m gates, and closure of h gates.

Comparison of m and h Gates

- The response of m gates to voltage changes is about ten times faster than the response of h gates to the same voltage.
- The K^+ gates ("n gates") have the same speed as that of the Na^+ h gates.

Conductance of Na^+ Channels

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

- Each Na^+ channel has 3 m-gates and 1 h-gate.
- Constant of proportionality (gNabar) is the hypothetical conductance when all Na^+ channels and all their gates are OPEN.

Leakage Channels

- Leakage channel has a constant (voltage independent) conductance g_L=gLbar.
- Leakage channels correspond roughly to Cl^- channels, but they are not necessarily specific to Cl^- ions.
- Leakage channel potential E_L is close to what we denoted earlier as E_{Cl}. It is somewhat less negative than the rest potential.

Hodgkin-Huxley Equations (1952)

$$C\frac{dv}{dt} + g(v - E) = i_o(t)$$

$$g = g_{Na} + g_K + g_L$$

$$E = \frac{g_{Na}E_{Na} + g_K E_K + g_L E_L}{g_{Na} + g_K + g_L}$$

Hodgkin and Huxley also developed curve fitting to the α and β functions (see a later slide)

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

$$g_K = \bar{g}_K n^4$$

$$g_L = \bar{g}_L$$

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

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

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

What is $i_o(t)$?

- This is the input current (per unit area of the membrane) applied as an external input.
- For instance, one may consider it as a pulse of current (representing a sensation picked up by a dendrite)
- Or – it could be related to an action potential created further up stream by another group of gated channels.

Hodgkin-Huxley Fitted Closing and Opening Rate Functions for Squid Axon ([v]=mV, [α]=[β]=(ms)$^{-1}$)

$$\alpha_m(v) = 1.0\frac{\frac{v+45}{10}}{1-e^{-\frac{v+45}{10}}} \qquad \beta_m(v) = 4.0e^{-\frac{v+70}{18}}$$

$$\alpha_h(v) = 0.07e^{-\frac{v+70}{20}} \qquad \beta_h(v) = 1.0\frac{1}{1+e^{-\frac{v+40}{10}}}$$

$$\alpha_n(v) = 0.1\frac{\frac{v+60}{10}}{1-e^{-\frac{v+60}{10}}} \qquad \beta_n(v) = 0.125e^{-\frac{v+70}{80}}$$

Specific Constants used by Hodgkin and Huxley to Model Squid's Axon action Potential

$$C = 1.0 _[\mu A \cdot ms / cm^2]$$

$$E_{Na} = 45mV$$

$$E_K = -82mV$$

$$E_L = -59mV$$

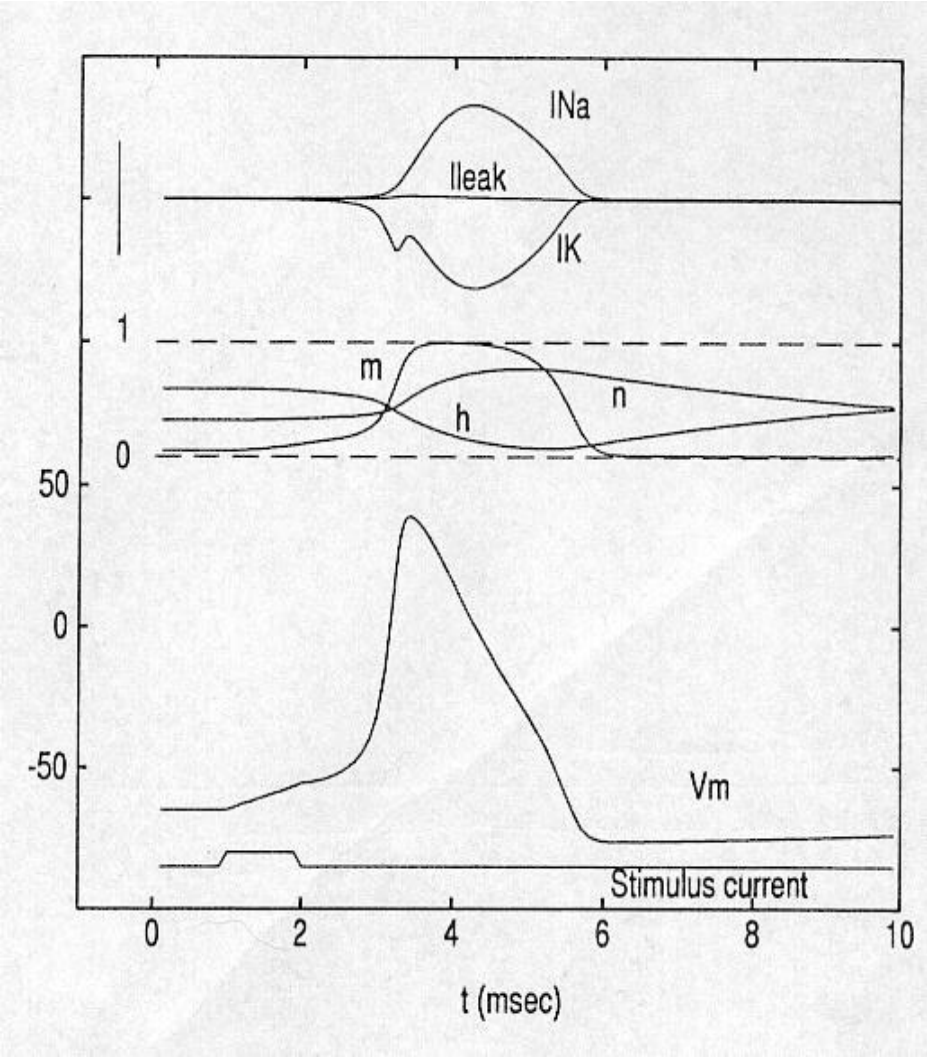
$$\bar{g}_{Na} = 120 _[\mu A \cdot mV / cm^2]$$

$$\bar{g}_K = 36 _[\mu A \cdot mV / cm^2]$$

$$\bar{g}_L = 0.3 _[\mu A \cdot mV / cm^2]$$

Human nerve cells may have different constants, and different α,β functions, but the general ideas hold true.

Simulation Results



- The applied current $i_o(t)$ slowly depolarises the membrane by charging up the capacitance.
- As V_m approaches the threshold ≈ -50mV, sodium channels begin to open, the resultant flow of N_a ions depolarises the membrane further.
- The state variables *m*, *h*, and *n* describe the closing and opening probabilities.