Neuronal Models - part II

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Single neuron models

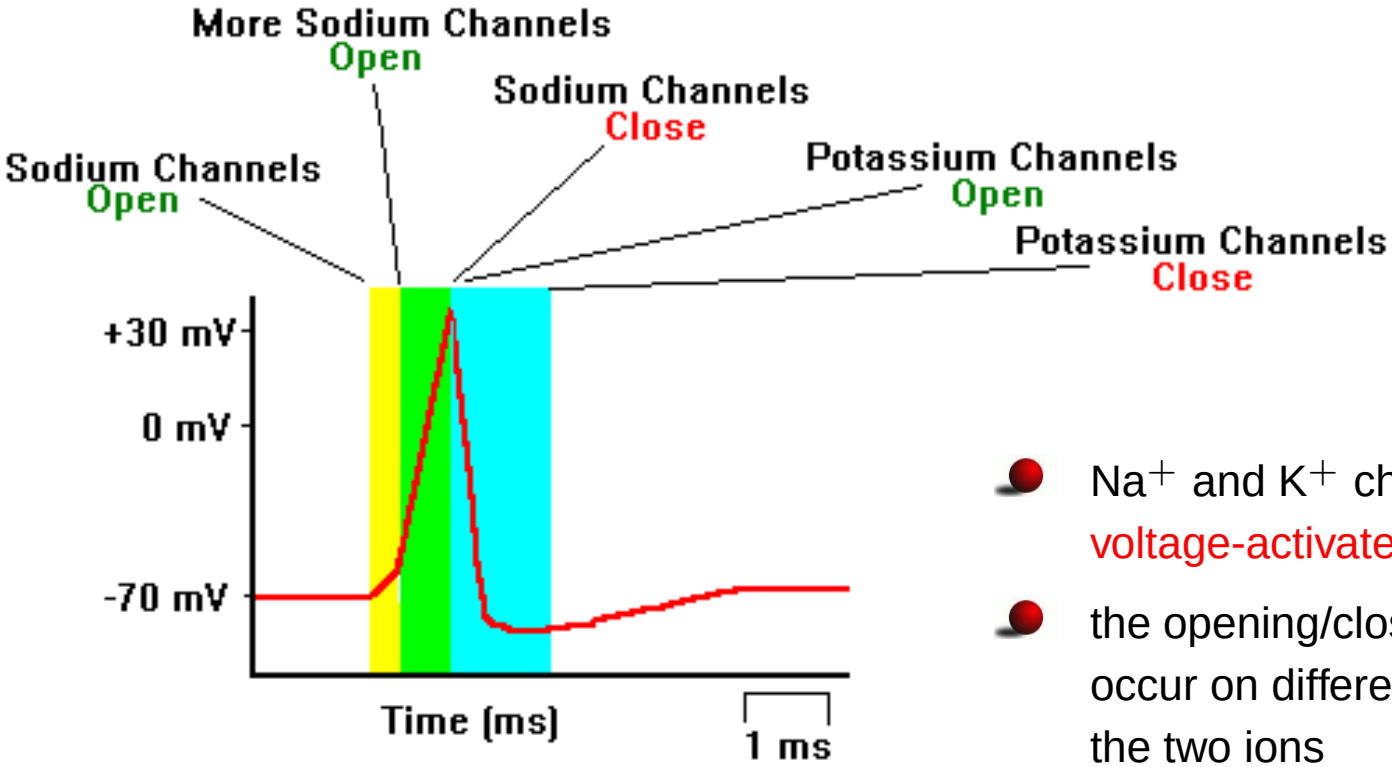
Single neuron models describe the dynamics of the membrane potential:

- realistic models:
  - Hodgkin-Huxley model - 4 variables $\longrightarrow$ squid giant axon
  - models for other types of neuron
- reduced models (*FitzHugh-Nagumo model* - 2 variables)
- formal models (*leaky integrate and fire model* - 1 variable) $\longrightarrow$ only dynamics below the firing threshold

Origin of action potential

Inactivation and activation of ion channels

When stimulated with PPSE the membrane potential increases from the rest potential $V_{rest} \simeq -70$mV towards the firing threshold ($\Theta \simeq -55$ mV) , $\rightarrow$ emission of ACTION POTENTIAL



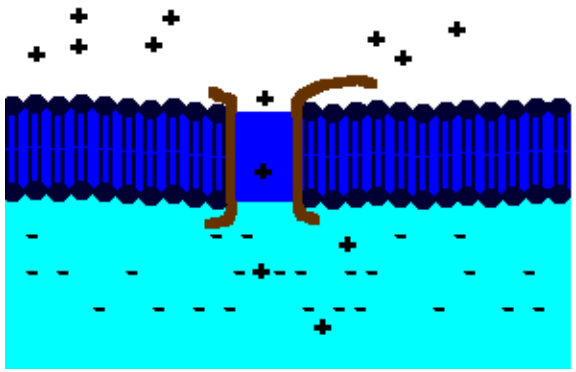
$[Na^+]_e >> [Na^+]_i$ $[K^+]_e << [K^+]_i$

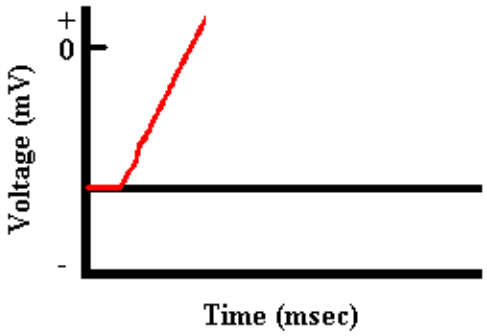
- Na^+ and K^+ channels are voltage-activated by depolarization
- the opening/closure of the channels occur on different time scales for the two ions
- depolarization, hyperpolarization, ripolarization

Origin of action potential

Depolarization and ripolarization of the membrane

Depolarization of the membrane

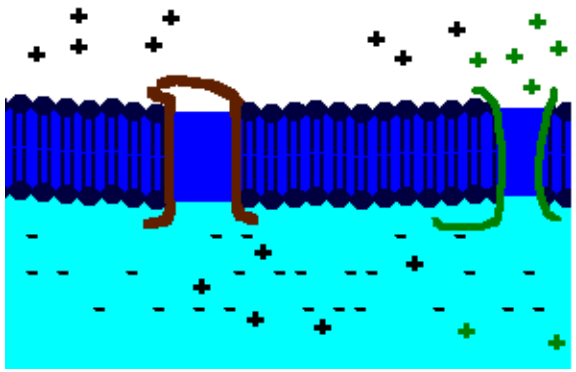


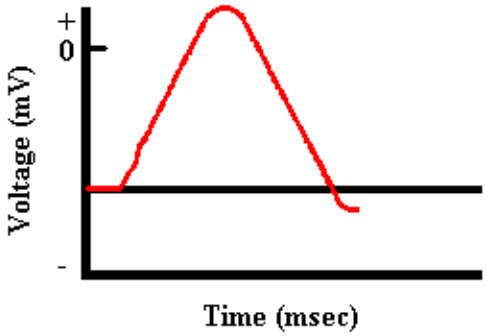


Na^+ flows inside the cell

$V_m \rightarrow E_{Na+} = +55$ **mV**

Ripolarization of the membrane





K^+ flows outside the cell

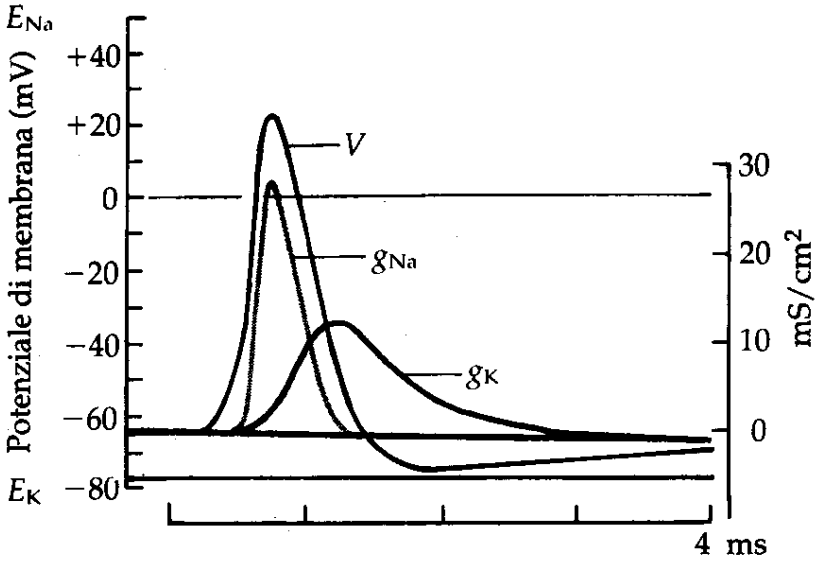
$V_m \rightarrow E_{K+} = -75$ **mV**

Origin of action potential

Currents involved in generation of action potential

For the squid giant axon three currents are involved:

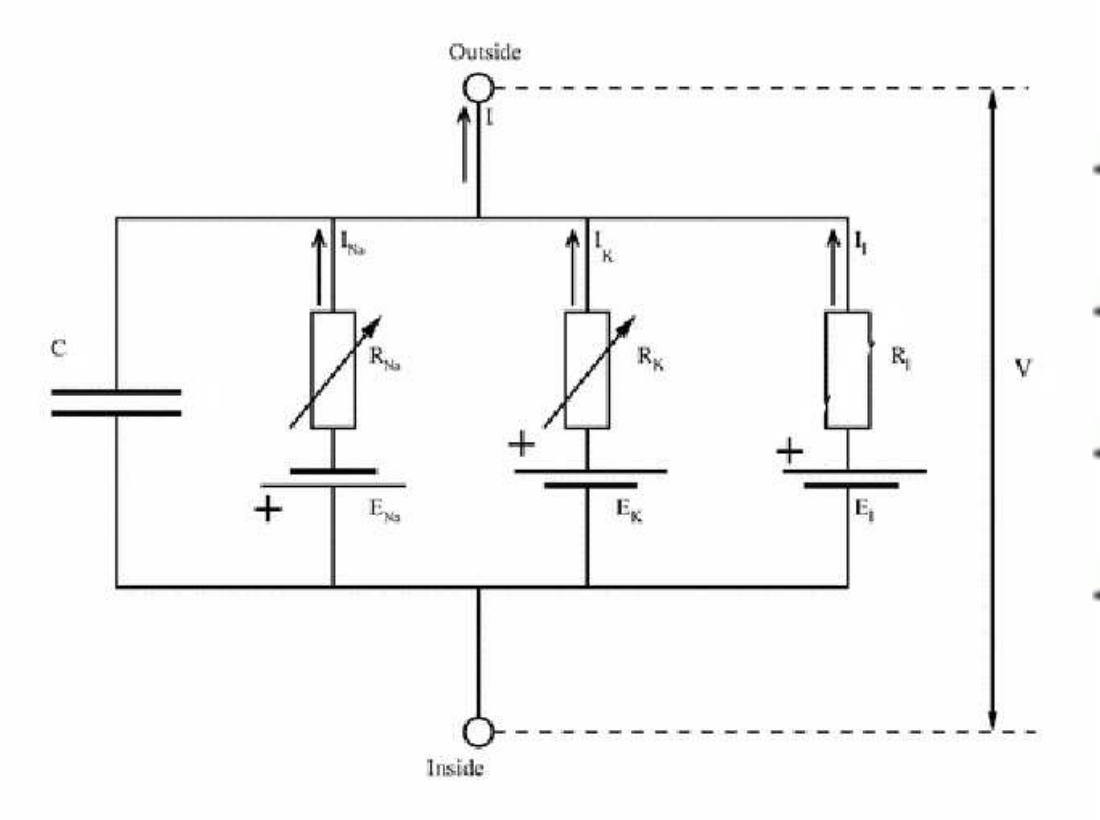
- Sodium current: $I_{Na} = g_{Na}(V - E_{Na})$ —- $g_{Na} = \frac{1}{R_{Na}} = g_{Na}(V)$
- Potassium current: $I_K = g_K(V - E_K)$ —- $g_K = \frac{1}{R_K} = g_K(V)$
- Leakage current (essentially due to chlorine Cl^- but it takes into account also the effect of other minor ionic currents): $I_L = g_L(V - E_L)$ —- $g_L = \frac{1}{R_L}$ is linear



- Na^+ and K^+ channels are voltage-activated
- conductances of Sodium and Potassium are non linear
- the sodium and potassium currents are non linear in the membrane potential V

Origin of action potential

Electric scheme of the membrane



- Circuit equivalent to a portion of membrane
- Nodes Law
  $I(t) = I_C + I_{Na} + I_K + I_L$
- Capacitive current
  $I_C = dQ/dt = CdV/dt$
- Ionic currents through Na^+ and K^+ voltage-activated channels $\longrightarrow I_{Na}$ e I_K (non linear)
- Leakage current $\longrightarrow$ (linear)

$$C\frac{dV}{dt} = -I_{Na} - I_K - I_L + I(t)$$

What are the functions $g_{Na}(V)$ e $g_K(V)$?

Hodgkin-Huxley model

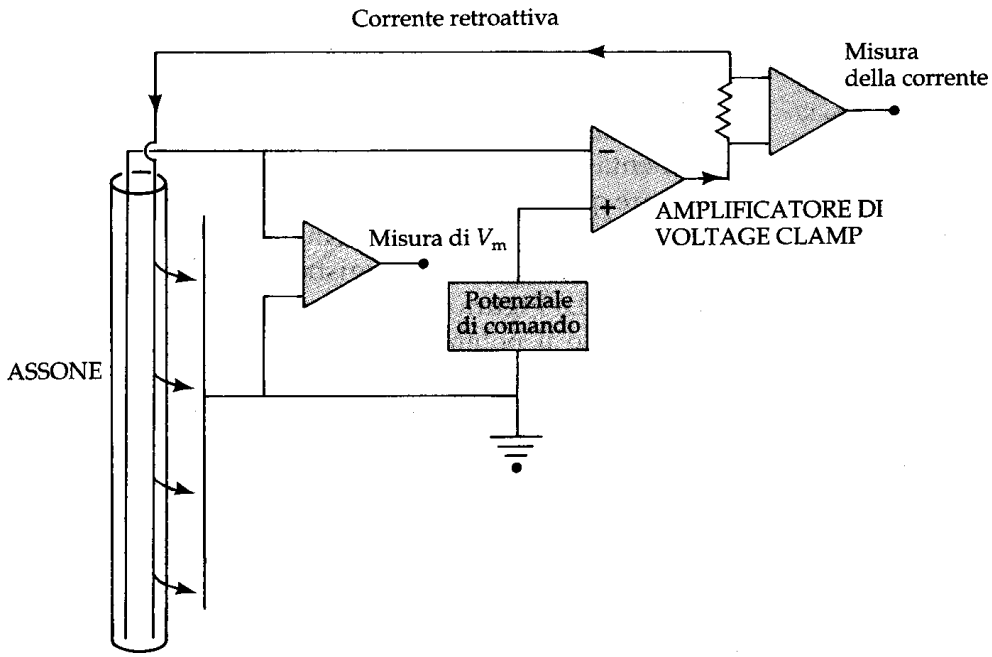
Hodgkin

Hodgkin-Huxley model reproduces the dynamics of the membrane potential and of the ionic currents experimentally measured for the squid giant axon.

Huxley

Voltage-Clamp experiment

Voltage clamp experiment consists in inserting two electrodes in the squid giant axon, and it allows to measure currents/conductances keeping constant the membrane potential.



Positive effects of voltage clamp:

- to get rid of the capacitive current $I_C \equiv 0$;
- time trend of the currents following a depolarizing voltage step
- space-clamp $\longrightarrow$ same potential all along the axon

Hodgkin-Huxley model

Ionic currents and conductances - 1

Hodgkin-Huxley measured the singol ionic current by using drugs for selective block of the channels and they elaborated this model:

- for the ionic currents I_{Na} and I_K: $I_i = g_i(V)(V - E_i)$
- equilibrium potential E_i given by Nernst equation
- the conductances $g_i(V)$ depend on gating variables measuring the instantaneous activation /inactivation of the channels
- $g_K = G_K n^4(V,t)$ where $n(V,t)$ is the gating variable for activation of K^+
- $g_{Na} = G_{Na} m^3(V,t) h(V,t)$ where $m(V,t)$ and $h(V,t)$ are the gating variables for activation and inactivation of Na^+

Hodgkin-Huxley model

Ionic currents and conductances - 2

$$I_{Na} = G_{Na} m^3(V,t) h(V,t)(V - E_{Na}) \qquad I_K = G_K n^4(V,t)(V - E_K)$$

Interpretation of the model:

- voltage-dependent channels control the outflow of K^+ and the inflow of Na^+;
- the gating variables $0 \leq X = m, n, h \leq 1$
- the gating variables control the opening of "gates " ("gate m", "gate n", "gate h")
- every gate can have two state: open with probability X or close with probability $1 - X$
- gating variables interpreted as fraction of open gates or probablility of opening
- the transition opening/closing is regolated by a rate equation with different rates in the two directions $X \overset{\beta_X}{\rightarrow} (1 - X)$ and $(1 - X) \overset{\alpha_X}{\rightarrow} X$

Hodgkin-Huxley model

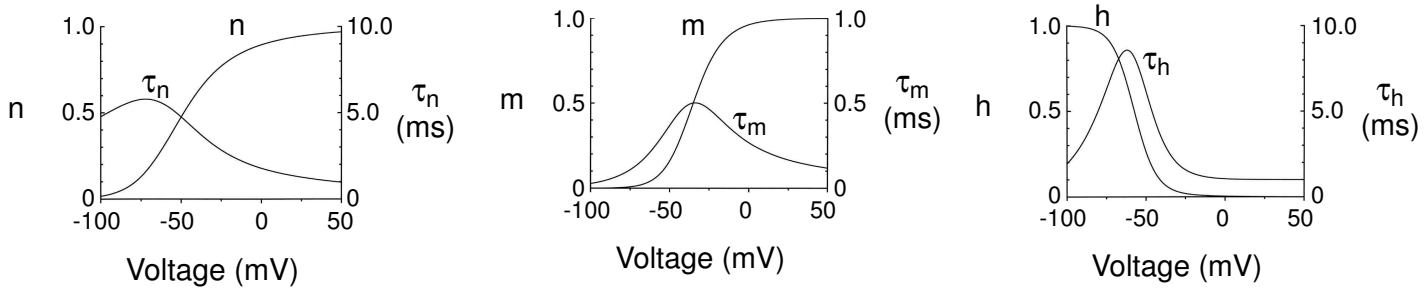
Gating variables dynamics

The dynamics of gating variables $X(t)$ is written as

$$\frac{dX}{dt} = \alpha_X(V)(1-X) - \beta_X(V)X = \frac{X_\infty(V) - X}{\tau_X(V)}$$

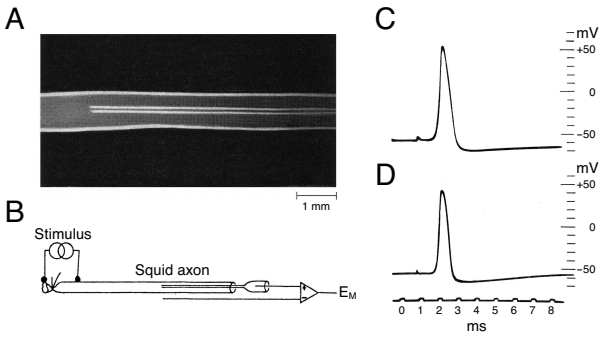
- $\tau_X(V) = 1/(\alpha_X + \beta_X)$ is the relaxing constant of X(t)
- $X_\infty(V) = \alpha_X/(\alpha_X + \beta_X)$ is the equilibrium value di X(t)

experimentally obtained by Hodgkin-Huxley for n , h , m .



- gates n, m open with depolarization of the membrane; gate h closes with depolarization
- for $V \sim V_{rest} \rightarrow \tau_m \sim 0.4ms << \tau_n, \tau_h \sim 5ms \rightarrow$ the activation of Na^+ is much faster than the activation of K^+

Hodgkin-Huxley model



$C = 1\mu F/cm^2$ - Membrane capacitance

V - Membrane potential (mV)

I_j - Ionic currents ($\mu A/cm^2$)

G_x - max conductances (mS/cm^2) $G_{Na} > G_K \gg G_L$

$$C\dot{V} = \sum_j I_j + I_{syn} = -G_{Na}m^3h(V - V_{Na}) - G_K n^4(V - V_K) - G_L(V - V_L) + I_{syn}$$

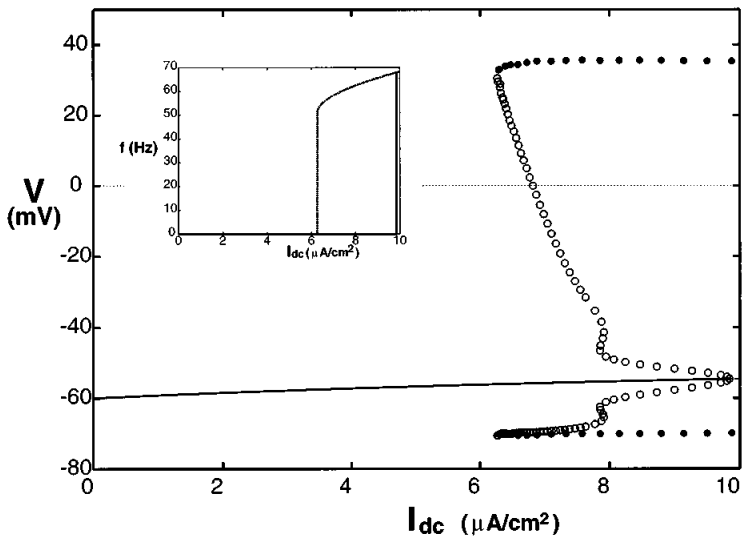
$$\dot{X} = \alpha_X - X(\alpha_X + \beta_X) \qquad X = n, m, h \qquad \text{gating variables}$$

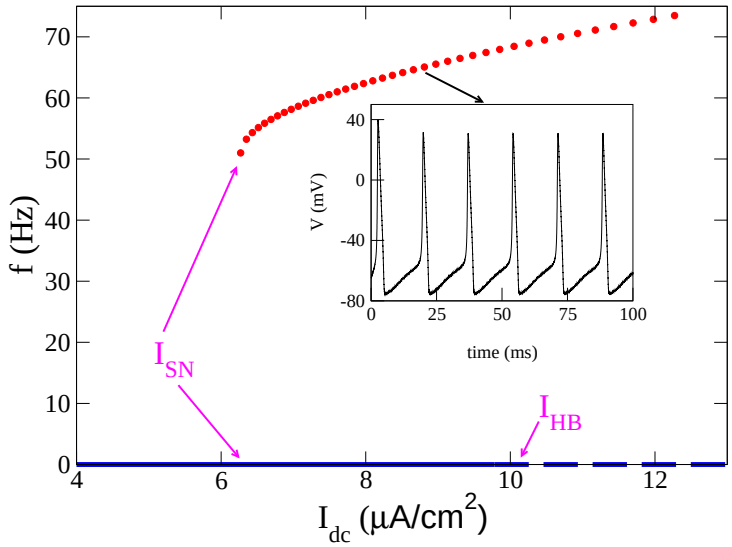
$\alpha_X = \alpha_X(V)$ and $\beta_X = \beta_x(V)$ are non linear functions of the membrane potential.

X	$\alpha_X(V)$ (s^{-1})	$\beta_X(V)$ (s^{-1})
m	0.1(V+40)/(1-exp(-(V+40)/10))	4exp(-(V+65)/18)
n	0.01(V+55)/(1-exp(-(V+55)/10))	0.125exp(-(V+65)/80)
h	0.07exp(-(V+65)/20)	1/(exp(-(V+35)/10)+1)

Bifurcation diagram of HH model - 1

bifurcation parameter → constant synaptic current $I_{syn} = I_{dc}$



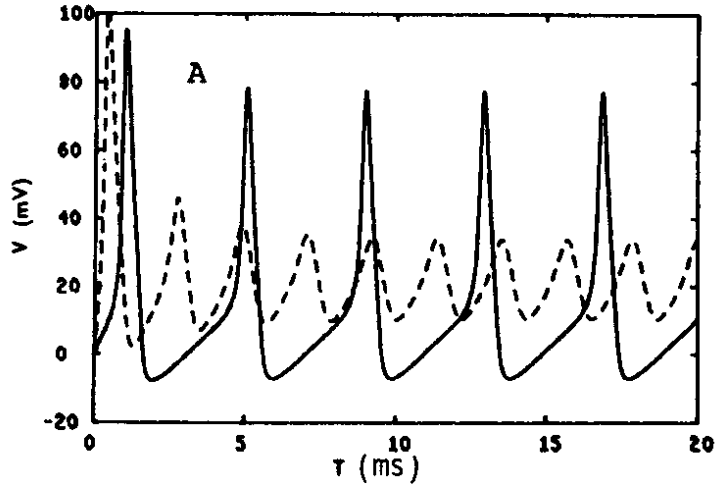


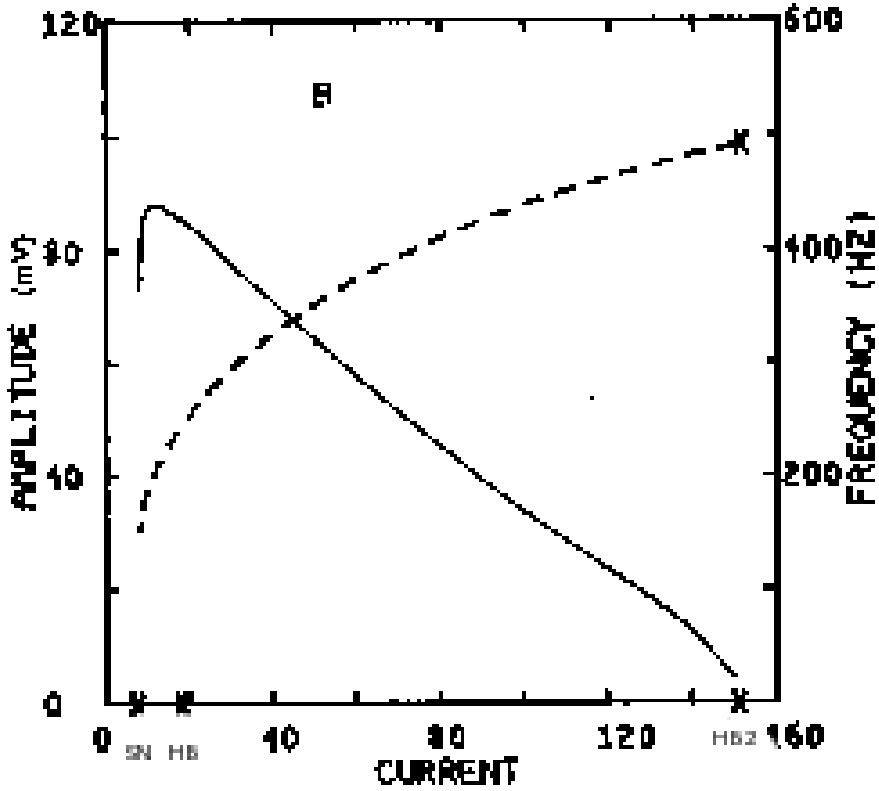
- $I_{dc} < I_{SN} \rightarrow$ stable fixed point (subthreshold oscillations) → silent neuron
- $I_{SN} < I_{dc} < I_{HB} \rightarrow$ bistability (stable fixed point and stable limit cycle)
- $I_{HB} < I_{dc} < I_{HB2} \rightarrow$ stable limit cycle with amplitude decreasing with the current
- $I_{dc} > I_{HB2} \rightarrow$ stable fixed point

- $I_{SN} \simeq 6.27 \mu A/cm^2$, $I_{HB} \simeq 9.78 \mu A/cm^2$, $I_{HB2} \simeq 150 \mu A/cm^2$
- SN → saddle-node bifurcation, HB → Hopf bifurcation, HB2 → Hopf bifurcation

Bifurcation diagram of HH model - 2

$I_{HB} < I_{dc} < I_{HB2} \rightarrow$ stable limit cycle





Higher and lower dimension models

- Hodgkin-Huxley model (1952) is the paradigm for all the realistic models based on the conductance
- Realistic models for neurons different from the squid giant axon take into account also other ionic currents (for example I_{Ca}) besides I_{Na} and I_K $\rightarrow$ higher dimension models
- bidimensional reduced models (*FitzHugh-Nagumo model*)

Bidimensional reduced models - 1

Approximations:

- steady state approximation: $m(t) \rightarrow m_0[V(t)]$
- $n_0(V) \simeq (1 - h_0(V))$, where n_0 and $h_0(V))$ are the stationary values $\rightarrow$ in general linear approximation $(b - h) \simeq an$ with a and b constants

If $m = m_0[V]$, $h = (b - w)$ and $n = w/a$:

- the HH equation for V becomes:

$$\frac{dV}{dt} = -\frac{1}{C}\left[G_{Na} m_0(V)^3 (b-V)(V-E_{Na}) + G_K (\frac{w}{a})^4 (V-E_K) + G_L((V-E_L) - I(t)\right]$$

- no equation for m, only one equation for $w \simeq n, h$

Bidimensional reduced models - 2

General form of a bidimensional reduced model [a]

$$\frac{dV}{dt} = \frac{1}{\tau}(F(V,w) + RI(t))$$

$$\frac{dw}{dt} = \frac{1}{\tau_w}G(V,w)$$

- $R = 1/g_L$, $\tau = RC$, τ_w is a constant
- $V \rightarrow$ membrane potential, $w \rightarrow$ recovery variable

[a] Gerstner and Kistler, **Spiking Neuron Models** - Kepler *et al* Biol. Cybern. 66, 381-387 (1992)