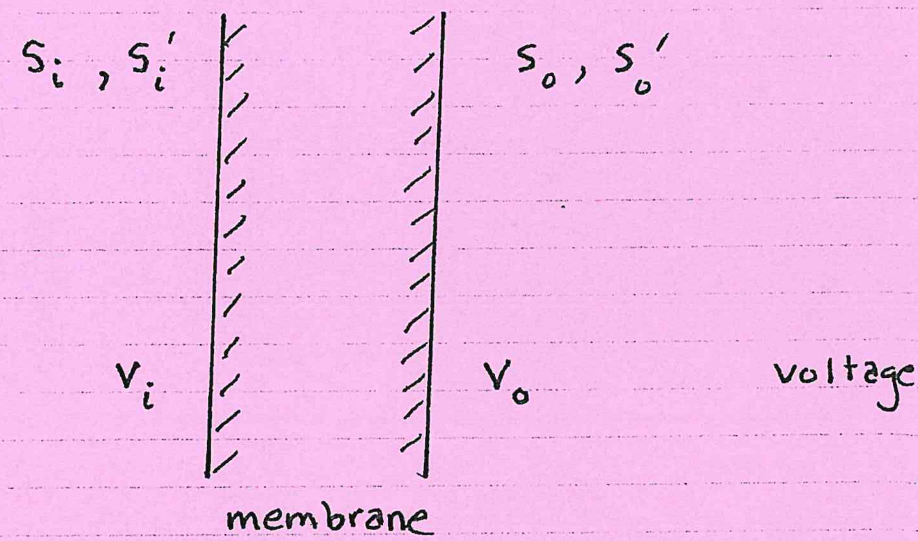
Transmembrane ionic transport

Ionic concentrations inside and outside cells are typically different and as a consequence the electric potential across the membrane is not zero.

Cations (positive) are designated by S.
Anions (negative) are designated by S'.



Remarks

(1) $S = Na^+, K^+, Ca^{2+}$ whereas $S' = Cl^-$

(2) Typically membrane only permeable to S (not S')

(3) If $[S_i] \neq [S_o]$ concentration then this gradient induces a flux of S until the induced potential

$$V = V_i - V_o$$

balances electrodiffusion.

Typical Values (mM)

		intra	extra	
Skeletal Muscle	K^+	150	4.5	→
	Na^+	12	145	←
	Cl^-	4.2	116	←
Squid Axon	K^+	400	20	
	Na^+	50	440	
	Cl^-	40	560	
	Ca^{2+}	0.0003	10	
Generic Mammal	K^+	139	4.5	
	Na^+	15	145	
	Cl^-	20	116	
	Ca^{2+}	< 0.0002	1.8	

Some cells that have electrical behavior:

- muscle
- heart
- neurons
- sensory cells
- endocrine (pancreas, hypothalamus, ..)

Electrodiffusion Summary

1) Planck's Equation for flux of charged particles

$$\vec{J}_\phi = -u \frac{z}{|z|} c \vec{\nabla}\phi$$

where

u = ion mobility
z = ion valence
c = ionic concentration
ϕ = electric potential
$\vec{E}$ = $-\vec{\nabla}\phi$ electric field

2) Einstein Diffusivity

$$D = \frac{uRT}{|z|F} \qquad \frac{RT}{F} = 25.8\,\text{mV} @ 27^\circ C$$

$F = 96485$ Coul/mole , $R = 8.31$ J/mole/°K (Gas Const)

3) Nernst-Planck Electrodiffusion

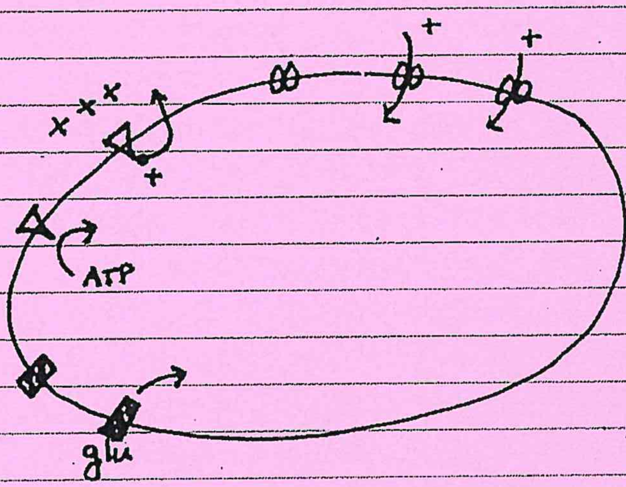
$$\vec{J} = -D\left(\underbrace{\vec{\nabla}c}_{\text{diffusive flux}} + \underbrace{\frac{zF}{RT} c \vec{\nabla}\phi}_{\text{electro flux}}\right)$$

Remark: A low velocity $\vec{v}$ the drag force $\vec{f} = \frac{1}{u}\vec{v}$ where u is the mobility. For a sphere from Nav-Stokes $u = (6\pi\mu a)^{-1}$, μ = viscosity, a = radius. Then

$$D = \frac{kT}{6\pi\mu a} = ukT = \frac{uRT}{|z|F}$$

since $R = N_A k$, $N_A = 6.02 \times 10^{23}$ particles/mole.

Transmembrane transport



membrane is a phospholipid bilayer and is impermeable

ion channels (down gradient)

ion pumps (up gradient) - need energy

receptors (nonionic transport)

Cell capacitance

Neutral membrane separates different ionic concentrations (intra, extracellular). As such, the membrane has a capacitance C typically given in Farads/m^2 of cell surface.

$$C = \frac{k\varepsilon_0}{d}$$

is the capacitance of a plate

k = dielectric constant of media

ε_0 = permitivity of free space

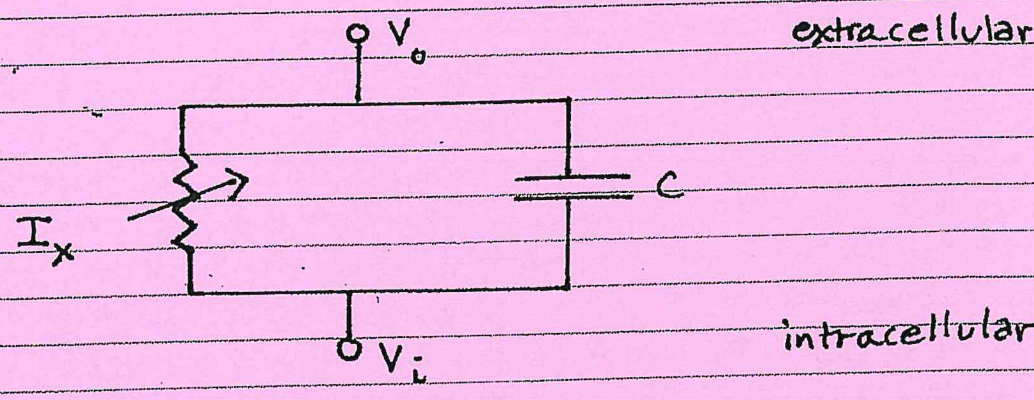
d = plate thickness

Membrane circuit model

For a (plate) capacitor $Q = CV$ where Q is total charge. Thus, capacitive current is

$$I = \frac{dQ}{dt} = C\frac{dV}{dt}$$

Regard whole cell as a circuit



Here I_x is an (sum of) ionic current(s).

Conservation of charge then implies

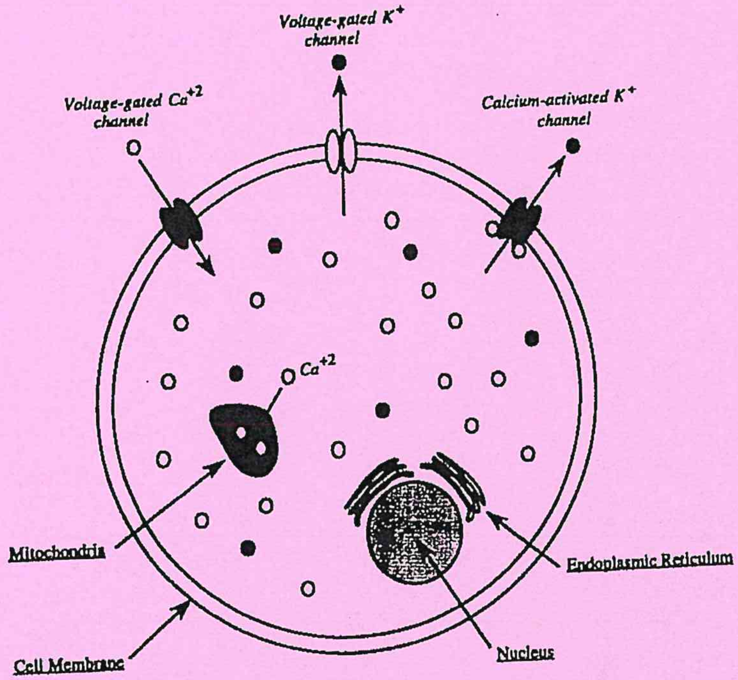
$$\boxed{C\frac{dV}{dt} + I_x = 0}$$

For a given ionic channel (or pump)

$$I_x = g_x (V - V_x)$$

where conductance g_x

Single Cell Models-generic



$$\frac{dv}{dt} = -\sum_X I_X(v, w, \vec{c}) \ , \tag{4}$$

$$\frac{dw}{dt} = \frac{w_\infty(v, \vec{c}) - w}{\tau(v, \vec{c})} \ , \tag{5}$$

$$\frac{d\vec{c}}{dt} = \varepsilon \vec{h}(v, w, \vec{c}) \quad , \vec{c} \in \mathbb{R}^K \quad , \tag{6}$$

v = potential across cellular membrane
I_X = membrane ionic current through channels of type X
w = channel activation parameter
$\vec{c}$ = concentrations of agents which regulate the electrical activity

General Single cell model

$$C_m \frac{dV}{dt} = \sum_x I_x(V, \phi, c) + I_a(t)$$

$$\frac{d\phi_i}{dt} = \frac{\phi_{\infty,i}(V) - \phi_i}{\tau_{\phi,i}(V)} \qquad i = 1, 2 \ldots N_i$$

$$\frac{dc_j}{dt} = f_j(V, c)$$

where

V = membrane potential

ϕ_i = subunit gating variables

c_j = ionic or chemical concentrations

Broadly

I_x = current thru channel or pump of type X. Ion specific

I_a = experimentally applied current or currents from elsewhere, i.e. coupling, synaptic.

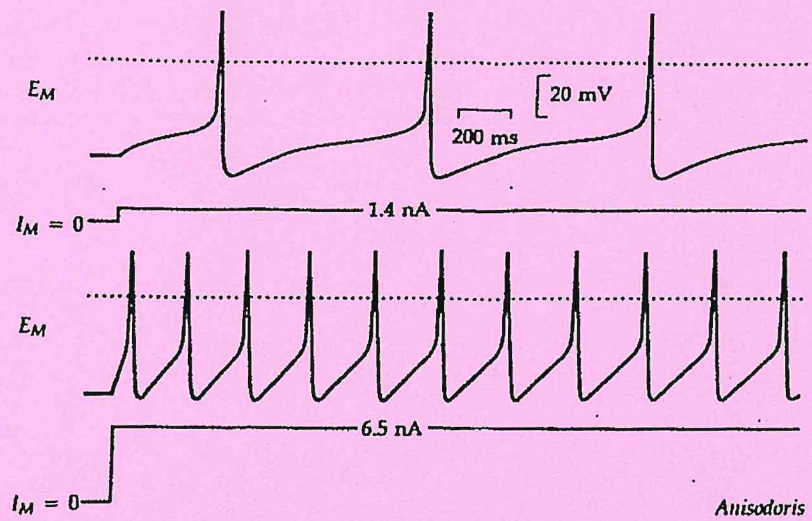
C_m = membrane capacitance

Examples of excitable cells

Cell	Type	Stimulus
Mechanoreceptor Photoreceptor Chemoreceptors Thermoreceptors	neuron neuron neuron neuron neuron	mechanical light smell heat electrical
Muscle		electrical mechanical
Pancreas Hippocampal	endocrine endocrine	hormone electrical hormone electrical

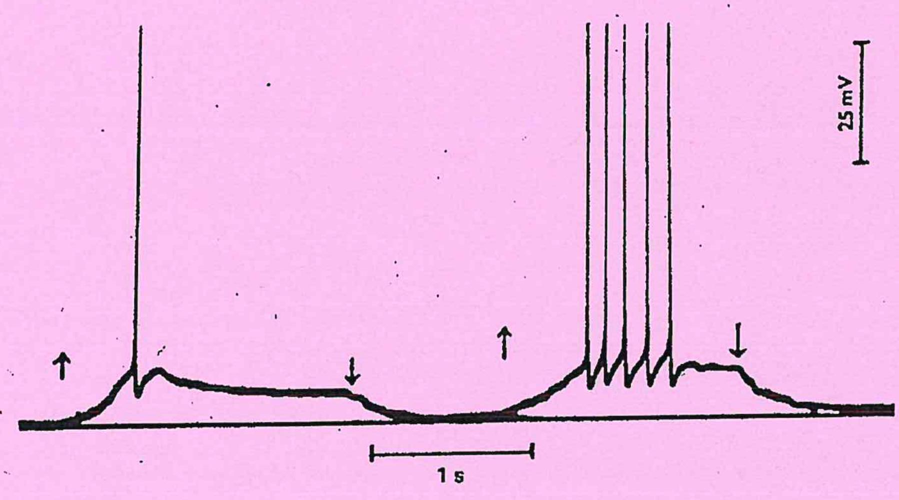
REPETITIVE FIRING OF AN ISOLATED NEURON

(*Anisodoris* neuron, soma electical stimulus) (Seaslug)



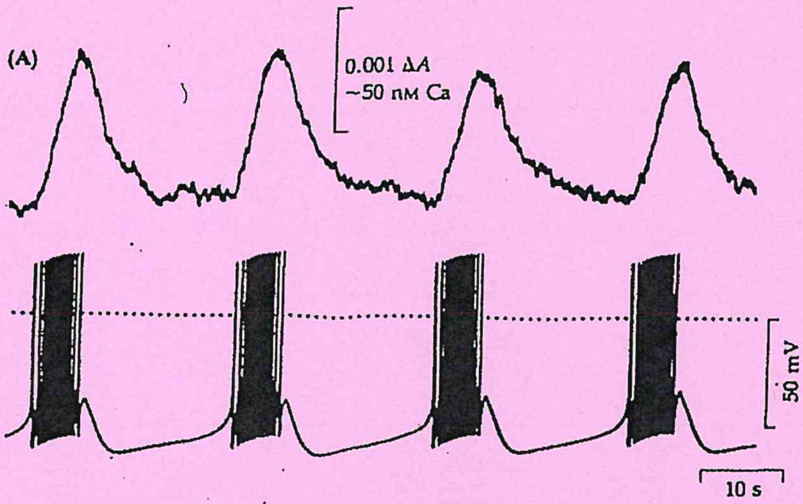
REPETITIVE FIRING OF AN MECHANORECEPTOR NEURON

(*Crayfish* neuron, mechanical (stretching) stimulus)



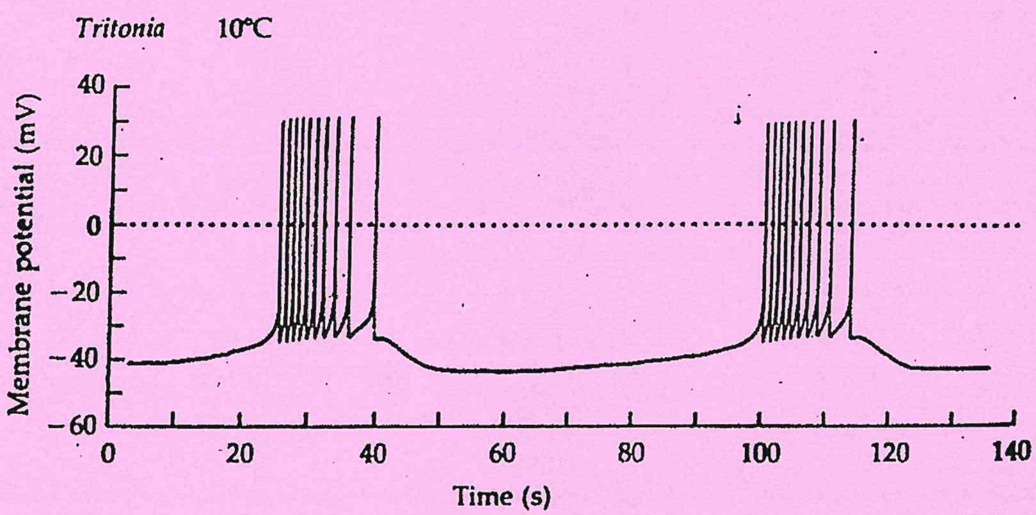
PARABOLIC BURSTING IN A PACEMAKER NEURON

(*Aplysia* neuron, slow calcium oscillations) (snail)



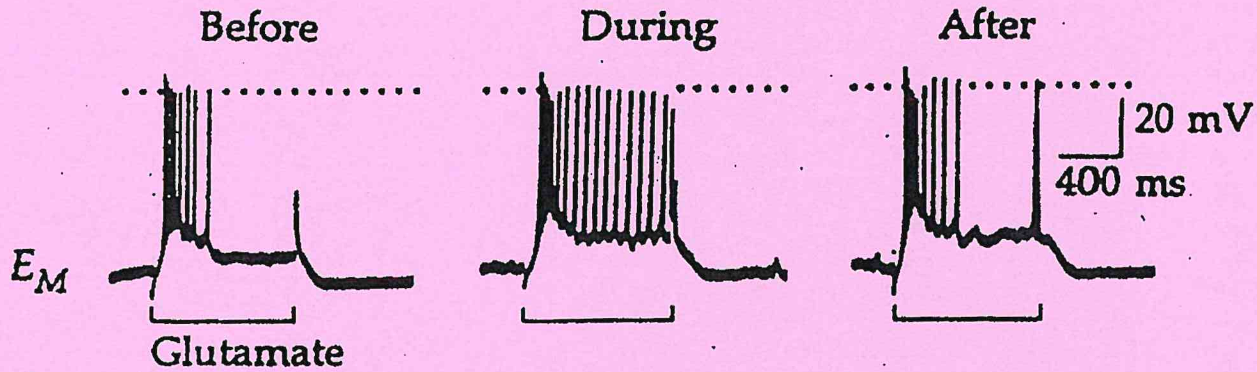
BURSTING IN A PACEMAKER NEURON

(*Tritonia* neuron)



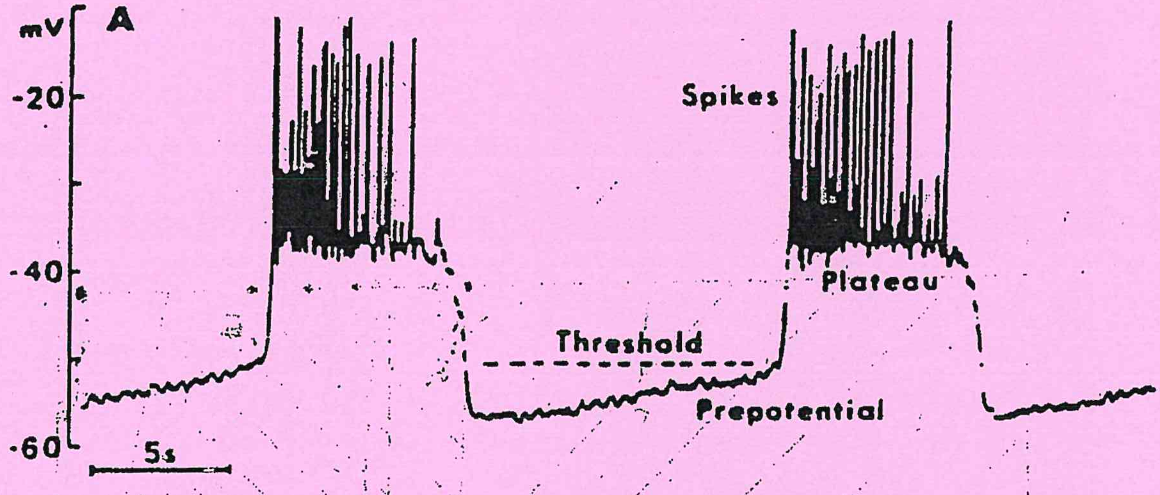
BURSTING INITIATED BY HORMONES

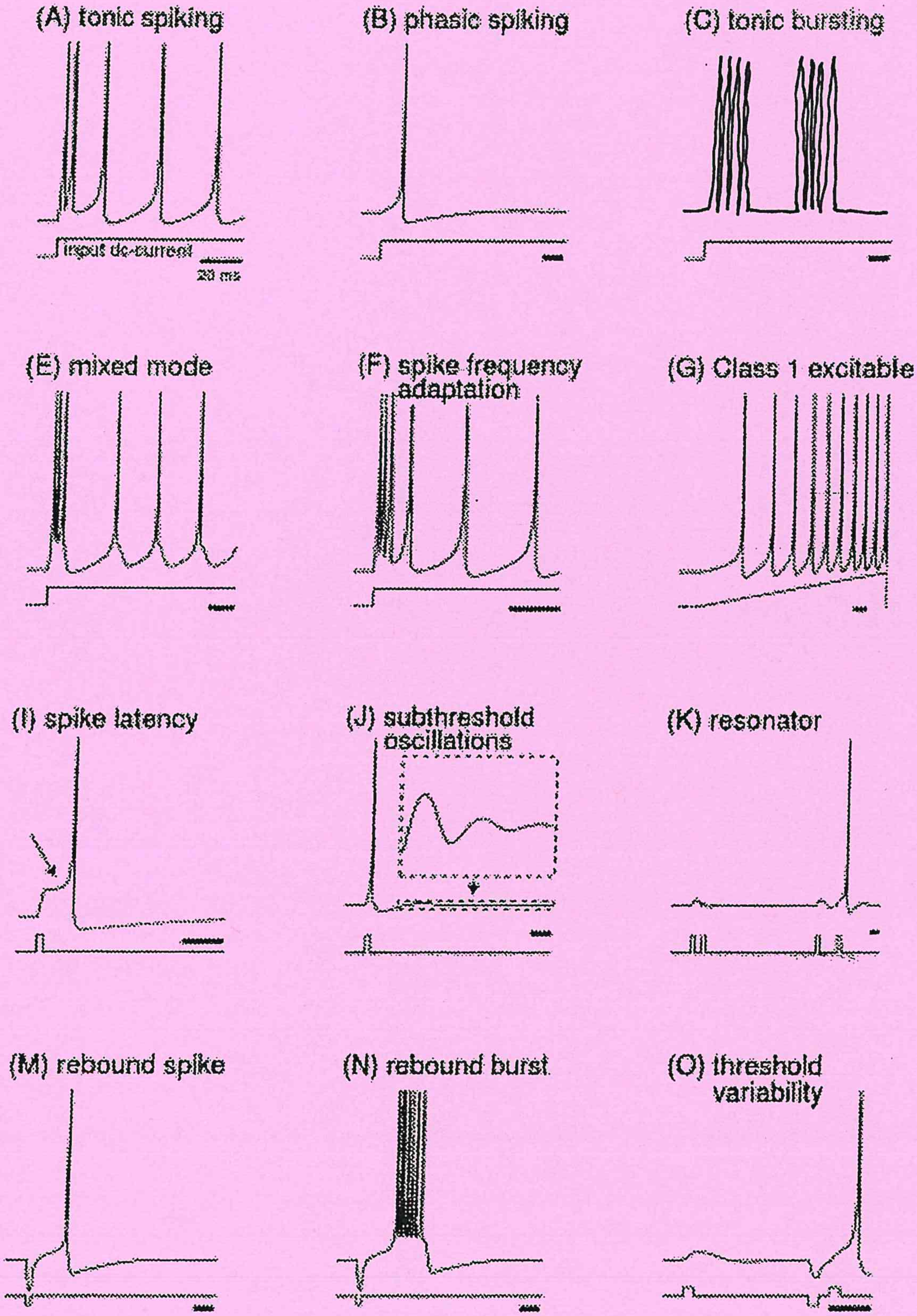
(pyramidal cells in hippocampus, Norepinephrine stimulus)



BURSTING IN PANCREATIC β-CELL

(*mouse* β-cell, glucose stimulus)




(A) tonic spiking
input dc-current
20 ms
(B) phasic spiking
(C) tonic bursting
(E) mixed mode
(F) spike frequency adaptation
(G) Class 1 excitable
(I) spike latency
(J) subthreshold oscillations
(K) resonator
(M) rebound spike
(N) rebound burst
(O) threshold variability

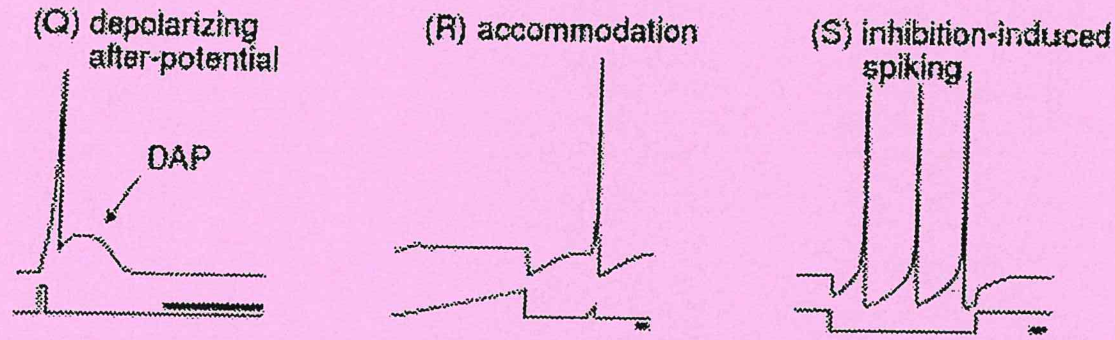


Figure 8.8: Summary of neurocomputational properties exhibited b;
see exercise 11. The figure is reproduced, with permission, from w
(An electronic version of the figure, the MATLAB code that ge
responses, and reproduction permissions are available at www.izhil

Ion pumps versus Ion Channels.

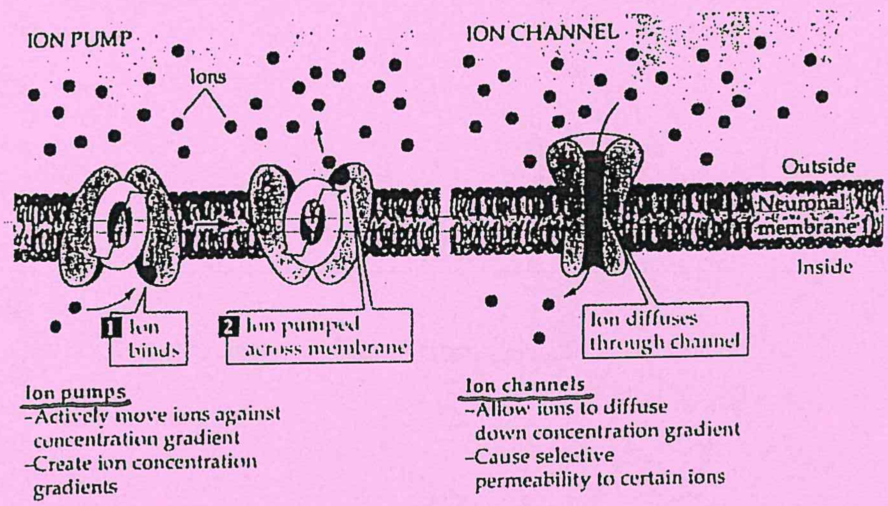
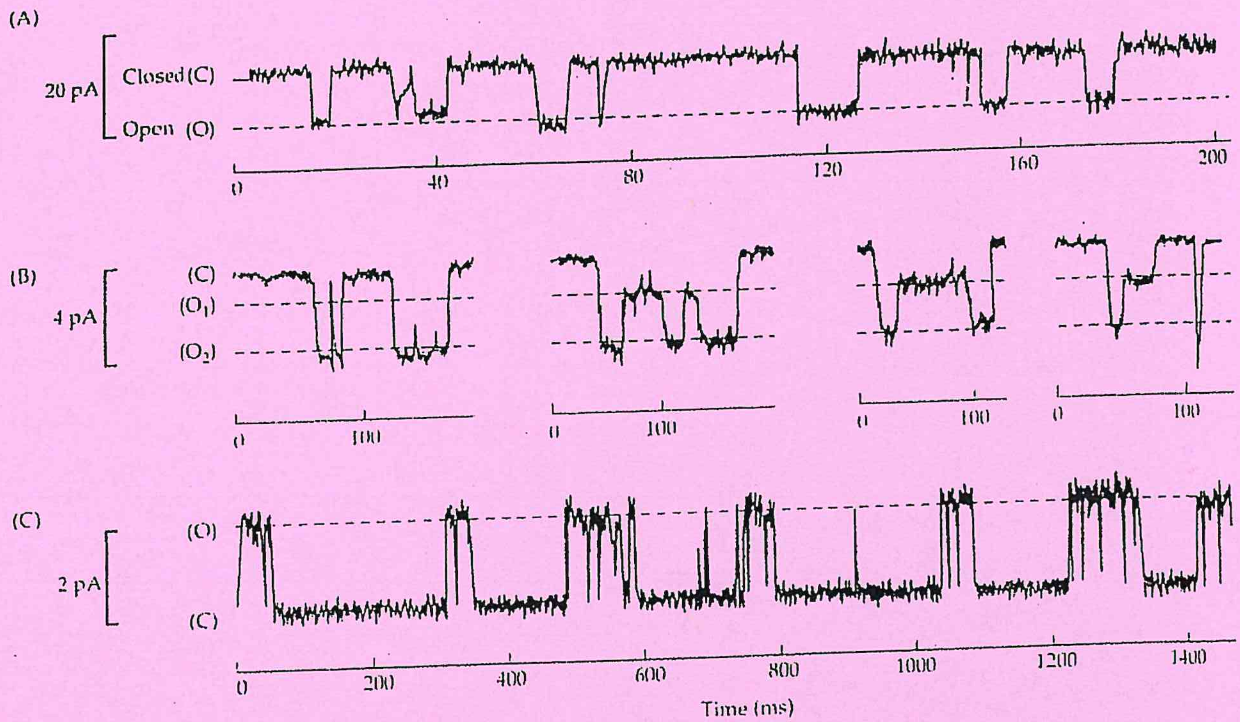
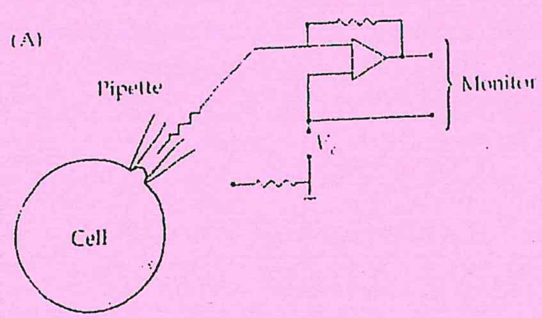
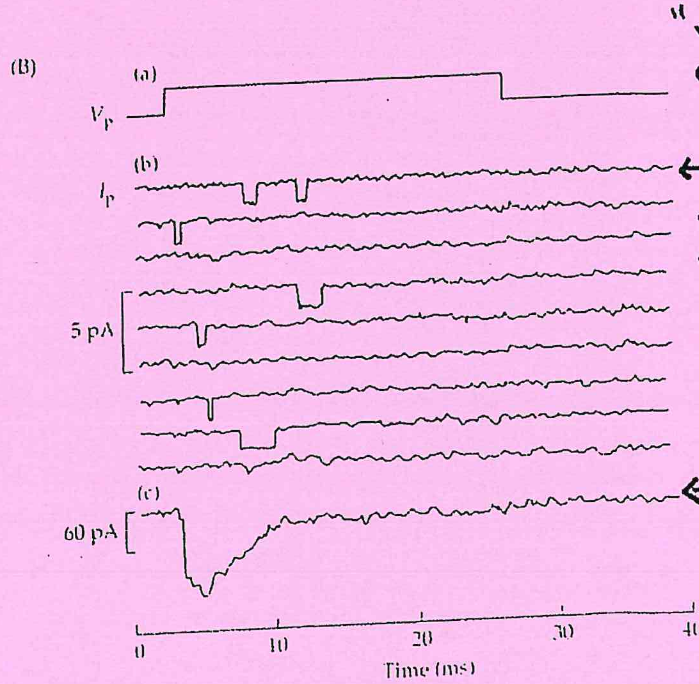


Figure 2.2 Ion pumps and ion channels are responsible for ionic movements across neuronal membranes. Pumps create ion concentration differences by actively transporting ions against their chemical gradients. Channels take advantage of these concentration gradients, allowing selected ions to move, via diffusion, down their chemical gradients.

↓ single channel events







"voltage clamp"

← single channel event

← probab. open (many chann)

FIGURE 6.10 Sodium Channel Currents recorded from cell-attached patch on a cultured rat muscle cell. (A) Recording arrangement. V_c = the command potential applied to the membrane patch. (B) Repeated depolarizing voltage pulses applied to the patch, with the waveform shown in (a), produce single-channel currents (downward deflections) in the nine successive records shown in (b). The sum of 300 such records (c) shows that channels open most often in the initial 1 to 2 ms after the onset of the pulse, after which the probability of channel opening declines with the time constant of inactivation. (After Sigworth and Neher, 1980.)

Two state K^+ channel

$$C \underset{\beta}{\overset{\alpha}{\rightleftharpoons}} O .$$

where C, O are closed and open states. Let

$$n = \text{fraction of } \underline{\text{open}} \text{ channels}$$

$$1 - n = \text{fraction of closed channels}$$

Tacitly assumed number of channels constant.

Law of mass action yields

$$(1) \qquad \frac{dn}{dt} = \alpha(V)\underbrace{(1-n)}_{C} - \beta(V)n$$

We assume the rates depend on Voltage.
∴ Can rewrite (1) as

$$(2) \qquad \frac{dn}{dt} = \frac{n_\infty(V) - n}{\tau_n(V)}$$

for

$$n_\infty(V) = \frac{\alpha}{\alpha+\beta} \qquad \tau_n(V) = \frac{1}{\alpha+\beta}$$

Thus a Nernst current with conductance g_K for ion K^+ might be

$$(3) \qquad I_K = \bar{g}_K n (V - V_K)$$

where $\bar{g}_K$ is the maximal conductance.

Multiple subunit models

- each unit is closed or open
- all units must be open for ions to flow

Two unit model

$$S_{ij} = \text{state of two units}$$

Here $i, j \in \{0, 1\}$, where 0 denotes closed

Assume S_{01} and S_{10} states identical.
Hence reaction equations are:

$$S_0 \underset{\beta}{\overset{2\alpha}{\rightleftarrows}} S_1 \underset{2\beta}{\overset{\alpha}{\rightleftarrows}} S_2 \qquad S_1 \equiv S_{10} + S_{01}$$

Let

$$x_i = \underline{\text{fraction}} \text{ of chonnels in state } S_i$$

Resulting differential equations

$$\dot{x}_0 = \beta x_1 - 2\alpha x_0$$

$$\dot{x}_1 = -\dot{x}_0 - \dot{x}_2$$

$$\dot{x}_2 = \alpha x_1 - 2\beta x_2$$

and chennels are conserved

(1) $$x_0 + x_1 + x_2 = 1$$

Using conservation of channels

(2) $\dot{x}_0 = f(x_0, x_2) = \beta(1 - x_0 - x_2) - 2\alpha x_0$

(3) $\dot{x}_2 = g(x_0, x_2) = \alpha(1 - x_0 - x_2) - 2\beta x_2$

Nonhomogeneous, linear, planar system.

If we define n to be solution of

$$\frac{dn}{dt} = \alpha(1-n) - \beta n$$

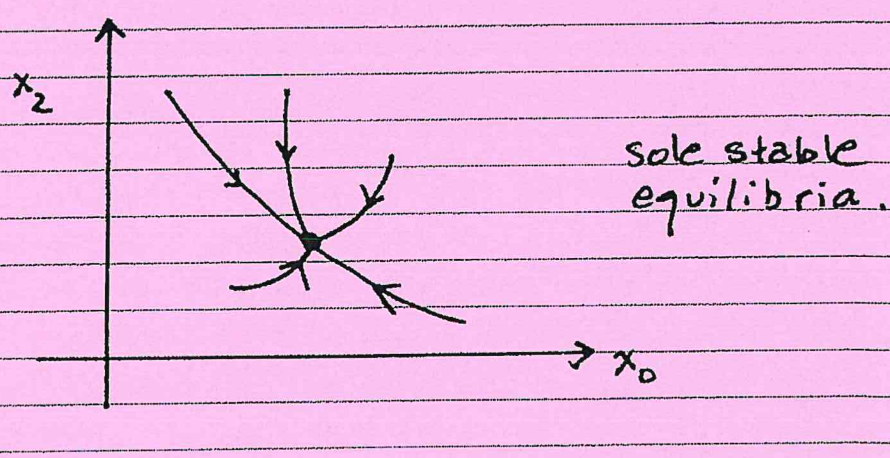
then

$$x_0 = (1-n)^2$$

$$x_1 = 2n(1-n)$$

$$x_2 = n^2$$

solves (1)-(3). Such a solution in (x_0, x_2)-plane



Linearization about this solution

$$\dot{x}_0 = (1-n)^2 + y_0$$
$$x_2 = n^2 + y_2$$

yields

$$\dot{y}_0 = -2\alpha y_0 - \beta(y_0 + y_2)$$
$$\dot{y}_2 = -\alpha(y_0 + y_2) - 2\beta y_2$$

which is homogeneous linear system with eigenvalues

$$\lambda_1 = -(\alpha+\beta) \qquad \lambda_2 = -2(\alpha+\beta)$$

Since $\lambda_k < 0$ we conclude

$$\boxed{\begin{aligned} x_0 &= (1-n)^2 \\ x_2 &= n^2 \end{aligned}}$$

Stable Invariant Manifold

Remarks

(1) n = "probability" that each unit open

(2) Current model for two subunits

$$I_K = \bar{g}_K n^2 (V - V_K)$$

where $\bar{g}_K$ = maximal conductance.

(3) For k subunits get n^k term

Na^+ multi unit channel model (sketch)

S_{ij} = i open m type subunits and
j open h type subunits

Assume 2-m type and 1-h type subunits.

$$\begin{tikzcd}
S_{00} \arrow[r, shift left, "2\alpha"] \arrow[d, shift right, "\gamma"'] & S_{10} \arrow[l, shift left, "\beta"] \arrow[r, shift left, "\alpha"] \arrow[d, shift right, "\gamma"'] & S_{20} \arrow[l, shift left, "2\beta"] \arrow[d, shift right, "\gamma"'] \\
S_{01} \arrow[r, shift left, "2\alpha"] \arrow[u, shift right, "\delta"'] & S_{11} \arrow[l, shift left, "\beta"] \arrow[r, shift left, "2\alpha"] \arrow[u, shift right, "\delta"'] & S_{21} \arrow[l, shift left, "\beta"] \arrow[u, shift right, "\delta"']
\end{tikzcd}$$

Only S_{21} state allows ions thru

$$\left.\begin{aligned}
&(1) \quad x_{21} = m^2 h \\
&(2) \quad \dot{m} = \alpha(1-m) - \beta m \\
&(3) \quad \dot{h} = \gamma(1-h) - \delta h
\end{aligned}\right\}$$ manifold defined here is stable

Other states

$$\begin{aligned}
x_{00} &= (1-m)^2(1-h) \\
x_{01} &= (1-m)^2 h \\
x_{10} &= 2m(1-m)(1-h) \\
x_{20} &= m^2(1-h) \\
x_{11} &= 2m(1-m)h
\end{aligned}$$

Resulting current I_{Na} given by

$$I_{Na} = \bar{g}_{Na} m^2 h (V - V_{Na})$$

where m, h satisfy (2)-(3).