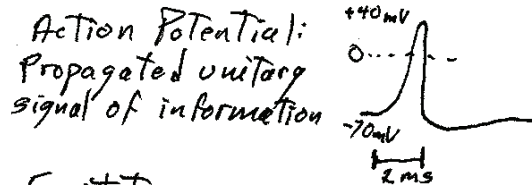
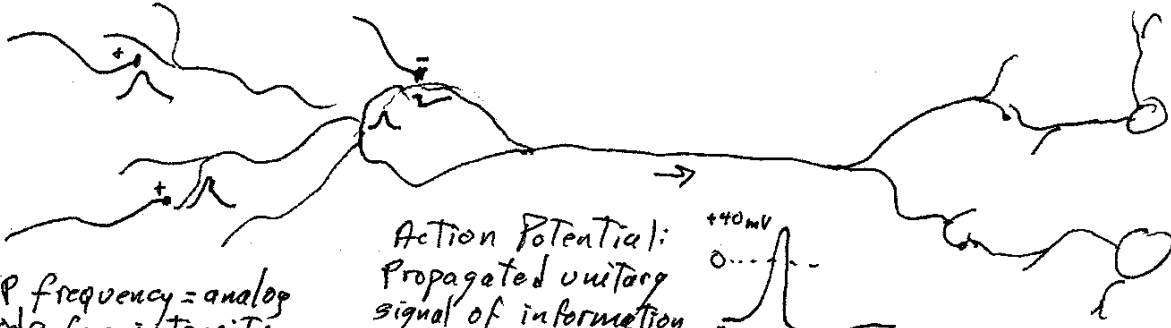


I. Neuronal signal electrically

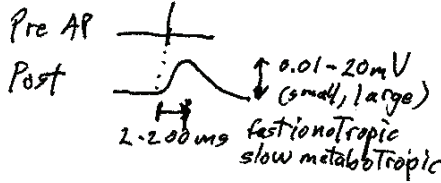


AP frequency = analog code for intensity

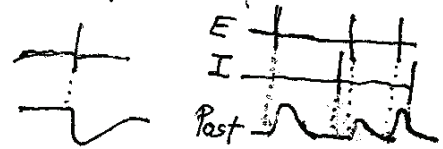
II. Inputs

A. Synapses onto dendrites and soma, from other neurons

Excitation  $\rightarrow +\Delta V_m = \text{depolarization} = \text{EPSP}$

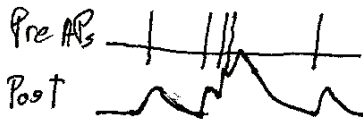


Inhibition  $\rightarrow -\Delta V_m = \text{hyperpolarization} = \text{IPSP}$

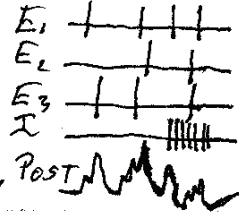


B. Synaptic Integration

Decremental conduction of PSPs to soma, where they summate

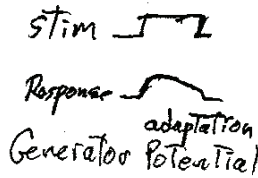
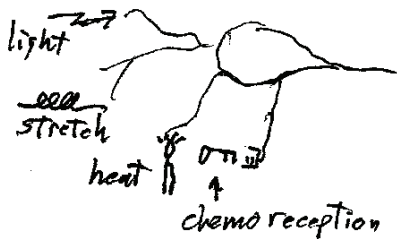


Temporal Summation: Response  $\propto$  Frequency

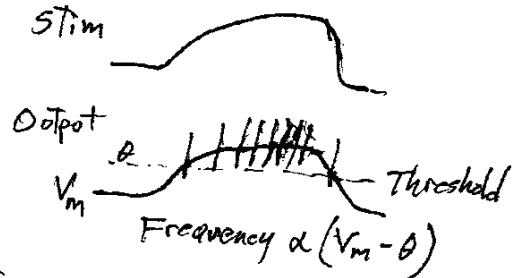


Spatial Summation: Response  $\propto$  # (nearly) simultaneous inputs

C. Sensory Transduction



III Conversion of inputs to APs (excitation)



IV Output

receptor  $\rightarrow$  ePSP or iPSP or metabotropic/biochemical response  
 release of transmitter (excitation-secretion coupling)

Most signals are alterations in membrane potential

V Plasticity: synapses change strength, thresholds change, cells grow + retract } neural circuits change; behavior adapts

VI Course Outline - Origins of:

Membrane Potentials	Transmission	Synaptic Potentials	Generator Potentials	Action Potentials	Synaptic Integration	Neural Plasticity
p. chem of Membranes + aqueous pores	Transmitter Release	Transmitter Receptors	Sensory Transduction	Voltage-dependent ion channels	Dendritic electrotonus	of synapses and ion channels

Disciplines: physiology, biophysics, biochemistry, cell biology, molecular biology, structural biology

$V_m$  due to separation of ions by plasma membrane, and ion permeation through channels  
 Begin with consideration of ions in solution and at membranes

Reading for first week: B. Hille Ion Channels of Excitable Membranes 3rd ed ch 1, 10, 14, 20

I. How easily can an ion penetrate a lipid membrane?

The Born free energy to "form" an ion charge  $zq$  radius  $r$  is  $G = \frac{z^2 q^2}{8\pi \epsilon_0 K r}$

$z$ : valence  $q = e$  (elect. chg)  
 $\epsilon_0$ : permittivity free space  
 $= 8.85 \times 10^{-14} \text{ F/cm}$   
 $r \approx 1 \text{ \AA} = 10^{-8} \text{ cm}$  (0.9600 Å)  
 $N$ : Avogadro's No  
 $K_w = 84$   $\epsilon_r = 5$   
 dielectric constants

to move a mole of ions from water to lipid,  $\Delta G = \frac{z^2 q^2 N}{8\pi \epsilon_0 r} \left( \frac{1}{K_w} - \frac{1}{K_l} \right) = 33 \text{ kcal/mole}$

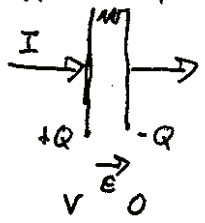
$\frac{P_l}{P_w} = e^{-\Delta G/RT} = 2 \times 10^{-25}$  = penetration probability or partition coefficient (Boltzmann Law)  
 $RT = .592 \text{ kcal}$

rms velocity @ r.t. =  $10^4 \text{ cm/s}$ , for 100nm, collision rate =  $6 \times 10^{23} \times 0.1 \times 10^{-3} \times 10^4 \text{ cm/s} = 6 \times 10^{23} / \text{cm}^2 \text{ s}$

penetration rate = 12 ion/cm<sup>2</sup> per 10 sec  
 ∴ collision rate × penetration probability ∴ ions enter only through aqueous channels!  
 (For a 50-μm dia cell, 1 ion crosses every 3 hours!)

For a 50-μm dia cell, 1 ion / 300 hours

The membrane lipid interior is an insulator separating 2 conductive layers = capacitor  
 If a current is "forced through", charges build up, producing an electric field and a voltage difference, while no real current actually crosses the membrane. The proportionality between current and the rate of voltage build up, or of charge and voltage difference, is defined as capacitance.



$I = C \frac{dV}{dt}$      $Q = \int I dt = \int C \frac{dV}{dt} dt = CV$

Apply Gauss' Law to one side of membrane of surface area  $S$ :  $\oint \epsilon E ds = \epsilon ES = Q$

Charge Density  $\frac{Q}{\text{cm}^2} = \frac{Q}{S} = \epsilon E = -\epsilon \frac{dV}{dx} = \frac{\epsilon V}{w} = \frac{\epsilon_0 K}{w} V = \frac{C}{S} V$

Capacitance Density  $(\text{F/cm}^2) = \frac{C}{S} = \frac{\epsilon_0 K}{w}$      $\epsilon_0 = 8.85 \times 10^{-14} \text{ F/cm}$   
 $K = 5$      $w = 5 \times 10^{-7} \text{ cm}$  (5nm)  $\Rightarrow \frac{C}{S} \approx 0.9 \mu\text{F/cm}^2$

II Ion Flow in Aqueous Solution

A. Diffusion Bulk Flow Simply due to diff. collision rates across "boundary" betw diff concentrations

Flux Density  $\vec{J} = -D \nabla C$  in 1-D  $J_{\text{diff}} = -D \frac{dc}{dx}$      $D_{Na} = 1.3 \times 10^{-5} \text{ cm}^2/\text{s}$  diff betw Na, Cl  
 $D_{Cl} = 2 \times 10^{-5} \text{ cm}^2/\text{s}$  → chg sep in solution → electric field

B. Drift of charges in electric field  $\vec{F} = zq \vec{E} = \text{velocity} \cdot \text{frictional coefficient} \text{ vel} = zq \vec{E} / \text{fric} = F / \text{fric}$

Flux Density  $\vec{J}_{\text{drift}} = F / \text{fric} = zq \vec{E} c / \text{fric} = zq \mu' c \vec{E}$      $\mu' = 1 / \text{fric} = \text{mobility in cm}^2/\text{V} \cdot \text{sec}$

Def Potential  $V$      $\vec{E} = -\nabla V = -\frac{dV}{dx}$  (1-D)     $J_{\text{drift}} = -zq \mu' c \frac{dV}{dx}$

conventionally,  $\mu$  means as cm/s |V/cm for an ion of chg  $q$ , i.e.  $\mu = (\mu' q)$  Then  $J_{\text{drift}} = -z \mu c \frac{dV}{dx}$

Current Density  $I = zq J = -z^2 q \mu c \frac{dV}{dx}$  current in amps/cm<sup>2</sup>     $[ \vec{I} = -\sigma \nabla V ]$  Ohm's Law  $\sigma = \text{conductivity } \frac{\text{siemens}}{\text{cm}}$   
 $\sigma = z^2 q \mu c$  = 1/resistivity ohm-cm

III Nernst-Planck Eqn : Net Flux in an electrochemical gradient  
 both  $D$  +  $\mu$  are inverse frict coefs. Both  $\propto \frac{1}{r}$  Also depends on Temp (av velocity)

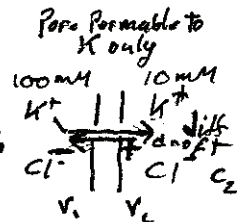
Einstein Reln (1905)  $D = \frac{kT}{\gamma} \mu$  Net flow = sum of diff + drift flows

$J = -D \frac{dc}{dx} - z\mu c \frac{dV}{dx} = -\frac{kT}{\gamma} \mu \frac{dc}{dx} - z\mu c \frac{dV}{dx}$  as flux The Nernst-Planck Eqn

$I = -z\mu kT \frac{dc}{dx} - qz^2 \mu c \frac{dV}{dx}$  as current

IV Single Ion Equilibrium

As ions flow through a pore, charges separate,  $\bar{E}$  develops, +  $\Delta V = V_{in} - V_{out}$  develops  
 flow stops when counter drift = diffusion



$J = 0 \Rightarrow \frac{kT}{\gamma} \mu \frac{dc}{dx} = -z\mu c \frac{dV}{dx}$   $\int_1^2 dV = -\int_1^2 \frac{kT}{z\gamma} \frac{1}{c} dc$   $V_2 - V_1 = \frac{kT}{z\gamma} \ln \frac{c_1}{c_2} = 59 \log_{10} \frac{c_1}{c_2}$  in mV if  $z=1$

V Single Salt Equilibrium

Consider membrane permeable to  $K^+$ ,  $Cl^-$ ;  $Na^+$  +  $A^-$  also present  $K^+$  +  $Cl^-$  equilibrate

	in	+	V	-	out
K	23				10
Na	37				100
Cl	15				110
A	95				0
	mM				

$V = \frac{kT}{\gamma} \ln \frac{K_o}{K_i} = \frac{kT}{\gamma} \ln \frac{Cl_i}{Cl_o} \Rightarrow \frac{K_o}{K_i} = \frac{Cl_i}{Cl_o}$   $K, Cl = K_o Cl_o$  Donnan Rule (for monovalent ions)

The Donnan Rule holds if system is at Equilibrium

VI Permeability

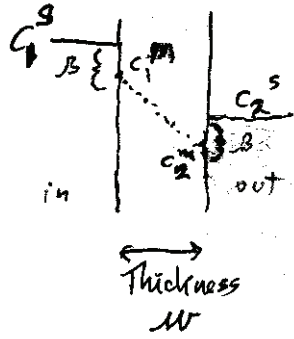
Membrane permeability is defined as the ratio of flux to concentration difference for a diffusible (uncharged) substance, using concentrations in both solutions

$J \stackrel{\circ}{=} -P \Delta C^s = -\frac{\mu kT}{\gamma} \frac{dc^m}{dx} = -\frac{\mu kT}{\gamma w} \Delta C^m = -\frac{\mu kT \beta}{\gamma w} \Delta C^s$

We already have  $P_{is}$   
 Fick's Law, Einstein Reln  
 $C^m$  is membrane (or at ends of channel/pores)

Assuming  $\frac{dc^m(x)}{dx}$  is constant  
 and  $\frac{dc^m}{dx} = \frac{\Delta C^m}{w}$

where  $\beta = \frac{C^m}{C^s}$   $C^m = \beta C^s$   
 The partition coefficient into the membrane (into the pore, really, see sec. I)



For substance of species  $i$   $P_i = \frac{\mu_i kT \beta_i}{\gamma w}$

VII A Salt in solution e.g. NaCl

apply Nernst-Planck

assume little charge separation (local space charge neutrality)

$c_{Na}(x) \approx c_{Cl}(x) = c(x)$ , and  $J_{Na} = J_{Cl}$  in steady state

$$J_{Na} = -M_{Na}c \frac{dV}{dx} - \frac{kT}{\delta} M_{Na} \frac{dc}{dx} = M_{Cl}c \frac{dV}{dx} - \frac{kT}{\delta} M_{Cl} \frac{dc}{dx} = J_{Cl}$$

$$\int dV = \int \frac{M_{Cl} - M_{Na}}{M_{Cl} + M_{Na}} \frac{kT}{\delta} \frac{dc}{c} \quad \Delta V = V_2 - V_1 = \frac{M_{Cl} - M_{Na}}{M_{Cl} + M_{Na}} \frac{kT}{\delta} \ln \frac{c_2}{c_1}$$

= 12 mV per 10 fold dilution of NaCl  
1.1 mV KCl

	M Na	K	Cl
cm/s	5.2	7.6	7.9
v/cm	x 10 <sup>-4</sup>		

for 2 different salts diffusing in opposite directions, from  $c_1$  to 0, a similar derivation yields

$$\Delta V = \frac{kT}{\delta} \frac{c_1(M_K - M_{Cl}) - c_2(M_{Na} - M_{Cl})}{c_1(M_K + M_{Cl}) - c_2(M_{Na} + M_{Cl})} \ln \frac{c_1(M_K + M_{Cl})}{c_2(M_{Na} + M_{Cl})}$$

0 to  $c_2$  for  $c_1$  KCl vs  $c_2$  NaCl

The Henderson Equation for a 'Liquid Junction'

Since  $M_K \approx M_{Cl}$ ,  $V$  is minimized if  $c_1 \gg c_2$  which is why we use 3M KCl electrodes

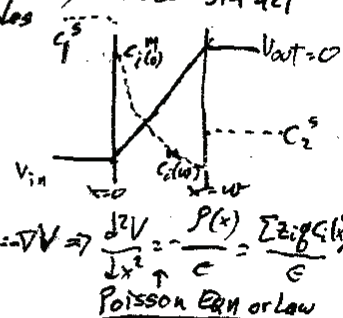
VIII Multi-Ion Permeability Through a Membrane (channel)

To preserve space charge neutrality,  $\sum I_i = 0$  otherwise charge builds up infinitely

If ions flow independently, each follows Nernst-Planck. To get an  $I_i - V$  curve for

A. each ion, N-P must be integrated, requiring an additional assumption.

Assume negligible internal (intrachannel) charge density,  $\rho$ . Gauss's Law:  $\frac{\partial E}{\partial x} = \frac{\rho}{\epsilon}$   $E = -\nabla V \Rightarrow \frac{d^2V}{dx^2} = -\frac{\rho(x)}{\epsilon} = \frac{\sum z_i q c_i(x)}{\epsilon}$   
if  $\rho(x) = 0 \Rightarrow \frac{d^2V}{dx^2} = 0 \Rightarrow \frac{dV}{dx} = \text{const} = \frac{V}{w}$   $V = V_{in} - V_{out}$  Take  $V_{out} = 0$   $V = V_{in} x/w$  in  $0 \leq x \leq w$   
This is the Goldman or Constant Field Assumption



So, for each ion  $i$ , N-P gives

$$I_i = \frac{q z_i \mu_i V}{w} c_i^m - z_i \mu_i k T \frac{d c_i(x)}{dx} = -z_i \mu_i k T \left[ \frac{d c_i(x)}{dx} - \frac{q z_i V}{k T w} c_i(x) \right]$$

Note: This is a 1st order DE in  $c_i(x)$  - which is therefore an exponential function of  $x$

To solve this for  $I_i - V$  function, multiply by  $e^{g z_i V(x)/kT}$  = integrating factor

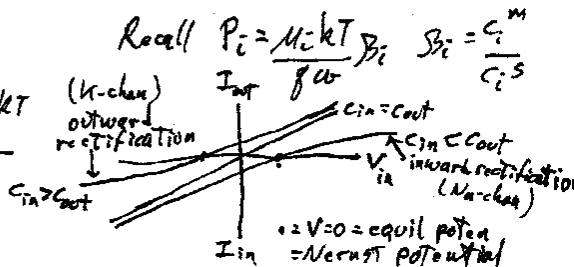
$$I_i \int_0^w e^{g z_i V(x)/kT} dx = z_i \mu_i k T \int_0^w d [c_i(x) e^{g z_i V(x)/kT}]$$

$$I_i \frac{w}{(-g z_i V/kT)} (1 - e^{g z_i V/kT}) = -z_i \mu_i k T (c_{out}^m - c_{in}^m e^{g z_i V/kT})$$

$$I_i = \frac{g z_i^2 \mu_i V}{w} \frac{c_{in}^m - c_{out}^m e^{-g z_i V/kT}}{1 - e^{g z_i V/kT}} = \frac{g^2 z_i^2 \mu_i V}{k T} \frac{c_{in}^m - c_{out}^m e^{-g z_i V/kT}}{1 - e^{g z_i V/kT}}$$

Goldman-Hodgkin-Katz Single Ion Eqn H.K 1949

not linear or ohmic unless  $c_{in} = c_{out}$



# Derivation of GHK

Assume  $f(x) = \frac{\partial^2 V}{\partial x^2} = 0 \Rightarrow \frac{\partial V}{\partial x} = \text{constant} = \frac{V_{in} - V_{out}}{x_{in} - x_{out}} = -\frac{V}{w}$

from N-P Eqn for each ion  $i$

$$I_i = \frac{q z_i^2 \mu_i V c_{i,m}(x)}{w} - z_i \mu_i kT \frac{d c_{i,m}(x)}{dx} = -z_i \mu_i kT \left[ \frac{d c_{i,m}(x)}{dx} - \frac{q z_i V}{w kT} c_{i,m}(x) \right]$$

multiply by  $e^{q z_i V(x)/kT}$

$$I_i e^{q z_i V(x)/kT} = -z_i \mu_i kT e^{q z_i V(x)/kT} \left[ \frac{d c_{i,m}(x)}{dx} - \frac{q z_i V(x)}{w kT} c_{i,m}(x) \right]$$

$$= -z_i \mu_i kT \frac{d}{dx} \left[ c_{i,m}(x) e^{q z_i V(x)/kT} \right]$$

$$I_i \int_0^w e^{q z_i V(x)/kT} dx = -z_i \mu_i kT \int_0^w d \left[ c_{i,m}(x) e^{q z_i V(x)/kT} \right]$$

because  $V(x=w) = 0$   
 $V(x=0) = V$

$$I_i \frac{-w}{q z_i V kT} (1 - e^{q z_i V/kT}) = -z_i \mu_i kT (c_{i,m,out} - c_{i,m,in} e^{q z_i V/kT})$$

multiply by  $-\frac{q}{q} \cdot \frac{q z_i V}{w kT} \cdot \frac{1}{1 - e^{q z_i V/kT}}$ , substitute  $c_{i,m,out} = P_i c_{i,s,out}$

$$I_i = \frac{q^2 z_i^2 \mu_i kT P_i V}{q \mu kT} \frac{(c_{i,s,out} - c_{i,s,in} e^{q z_i V/kT})}{1 - e^{q z_i V/kT}}$$

Note  $P_i = \frac{\mu_i kT P_i}{q \mu}$

multiply by  $\frac{-e^{-q z_i V/kT}}{-e^{-q z_i V/kT}}$

$$I_i = \frac{q^2 z_i^2 P_i V (c_{i,s,in} - c_{i,s,out} e^{-q z_i V/kT})}{kT (1 - e^{-q z_i V/kT})}$$

GHK  
 I-V rel'n for each ion  $i$  in a channel

B. Multi-Ion Flow. steady-state requires  $\sum I_i = 0$  To preserve space charge neutrality  
 let  $z_i = \pm 1$  monovalents only  $c_i = \text{cation}$   $a_i = \text{anion}$   $z = -1$

$$\sum I_i = 0 = \sum (P_i c_i^{in} + P_i a_i^{out}) - \sum (P_i c_i^{out} + P_i a_i^{in}) e^{-M} \quad M = gV/kT$$

$$V = \frac{kT}{g} \ln \frac{\sum (P_i c_i^{out} + P_i a_i^{in})}{\sum (P_i c_i^{in} + P_i a_i^{out})} \quad \text{Goldman Eqn (1943)}$$

$V =$  steady state potential for mixed ion channel (e.g. AChR, GluR...)

$\neq$  equilibrium There is no equilibrium currents are flowing concs would run down without pumps.

e.g. squid  $P_K : P_{Na} : P_{Cl} = 1 : 0.03 : 0.1 \Rightarrow V = -70 \text{ mV}$  also what the resting membrane  $V$ -independent  
 $K_i = 400$   $Na_i = 10$   $Cl_i = 70$   $Na_o = 460$   $Cl_o = 540$  leak channel is like, for  $P_K + P_{Na}$ . Conversely,  $Cl^-$  flows through separate resting channels.  
 often used to determine permeability ratios for ion channels.

Other models - e.g. single barrier models (sharp  $dV/dx$  and  $dc/dx$  at one point) give other  $V-i$  curves  
 (even multiple non-equal barriers) (multiple equal barriers) but similar "reversal potential" (when  $I$  reverses) as functions of  $P_i$   
 For details, see B.Hille

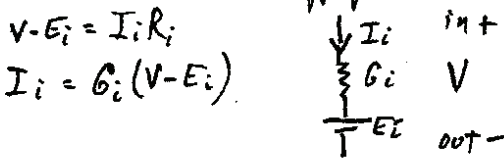
**X** Equivalent circuits: Single Ion Channel  
 Start with N-P  $I-V$  reln, no constant field assumption

$$\int_{out}^{in} dV = - \int_{out}^{in} \frac{I_i dx}{\int z_i^2 n_i c_i(x)} = \int_{out}^{in} \frac{kT}{z_i g} \frac{dc_i(x)}{c_i(x)}$$

$$V = I_i \int \frac{dx}{\int z_i^2 n_i c_i(x)} + \frac{kT}{z_i g} \ln \frac{c_i^{out}}{c_i^{in}}$$

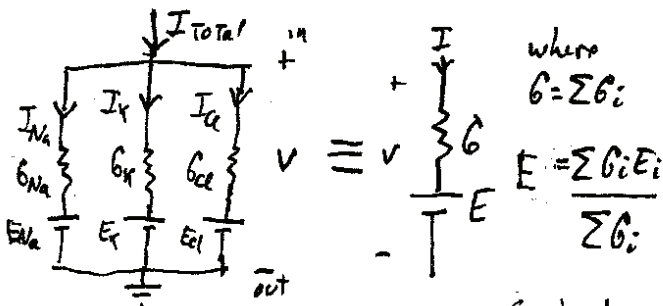
$V = I_i R_i + E_i$  is an approximation appropriate for small  $\Delta V$

a concentration-dependent resistance. Since  $C(x)$  varies with  $V$ , the resistance is also voltage-dependent (as shown for case of Goldman assumption)



**X** Multi-Ion (Lumped) Equivalent Circuits - 2 approaches:

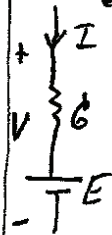
#1 Treat each ion separately best if each flows through its own channel



$E$  is not the Goldman potential each  $G_i$  is both voltage + concentration-dependent

Can be shown by basic electric circuit theory Ohm's + Kirchhoff's Laws

#2 a Goldman channel best for mixed permeability channels e.g. AChR, GluR...



here  $E$  is again the Goldman potential

$$G = \frac{dI_{tot}}{dV} \quad \text{from sum of Goldman + H-K current eqns}$$

$G$ : fact  $V$  approximately constant esp over limited  $\Delta V$  esp for AChR, GluR...

$G$  always depends on concentrations

a 10x dilution (symmetrical)  $\rightarrow$  10x  $\downarrow$  in  $G$  (confirmed experimentally)

$$\text{near } E_{Goldman} \quad G = \frac{dI}{dV} \Big|_{I=0} = \frac{g^3 V}{k^2 T^2} \frac{B \cdot C}{C - B} \quad B = \sum (P_i c_i^{in} + P_i a_i^{out}) \quad c_i: z = +1$$

$$C = \sum (P_i c_i^{out} + \sum P_i a_i^{in}) \quad a_i: z = -1$$

The G-H-K  $I-V$  relation accurately describes vertebrate  $I-V$  curves for  $Na, K$  channels but in squid, instantaneous  $I-V$  ( $G_{Na}, G_K$ ) are linear - still a matter of debate just why

$$\frac{I}{V} = \frac{I}{V} = \text{constant} = \dots = -\frac{V}{\dots}$$

MCB261 II

# The Goldman Eqn for monovalent salt mixture

4A

cations  $Z_i = +1$  concs:  $c_i^{out}, c_i^{in}$   $I_i = \frac{\delta^2}{kT} P_i V \frac{c_i^{in} - c_i^{out} e^{-M}}{1 - e^{-M}}$  where  $M = \delta V / kT$

anions  $Z_i = -1$  concs:  $q_i^{out}, q_i^{in}$   $I_i = \frac{\delta^2}{kT} P_i V \frac{q_i^{in} - q_i^{out} e^M}{1 - e^M} \cdot \frac{-e^{-M}}{-e^{-M}} = \frac{q_i^{out} - q_i^{in} e^{-M}}{1 - e^{-M}}$

$$\sum I_i = 0 \Rightarrow \sum P_i c_i^{in} - \sum P_i c_i^{out} e^{-M} + \sum P_i q_i^{out} - \sum P_i q_i^{in} e^{-M} = 0$$

$$e^{-M} (\sum P_i q_i^{in} + \sum P_i c_i^{out}) = \sum P_i q_i^{out} + \sum P_i c_i^{in}$$

$$e^{-\delta V / kT} = \frac{\sum P_i q_i^{out} + \sum P_i c_i^{in}}{\sum P_i q_i^{in} + \sum P_i c_i^{out}}$$

$$-\delta V / kT = \ln \frac{\sum P_i c_i^{in} + \sum P_i q_i^{out}}{\sum P_i c_i^{out} + \sum P_i q_i^{in}}$$

$$V = \frac{kT}{\delta} \ln \frac{\sum P_i c_i^{out} + \sum P_i q_i^{in}}{\sum P_i c_i^{in} + \sum P_i q_i^{out}} \quad \text{or, for only Na, K,}$$

$$V = \frac{kT}{\delta} \ln \frac{P_{Na} Na^{out} + P_K K^{out}}{P_{Na} Na^{in} + P_K K^{in}} = \frac{(P_{Na}/P_K) Na^{out} + K^{out}}{(P_{Na}/P_K) Na^{in} + K^{in}}$$

XI What determines Internal Ionic Concentrations?

The concs set  $V$  (Goldman Potential). What controls  $c_i^{in}$

$c_i^{out}$  is plasma (a different non-neurobiological question is what determines  $c_i^{out}$ ...)

IN OUT

The Constraints:

$K^+$ 140	5
$Na^+$ 10	145
$Cl^-$ 4	110
$A^-$ 145	40

- 1) External Fixed  $K_o=5$   $Na_o=145$   $Cl_o=110$   $A_o=40$  (other impermeant anions)
- 2)  $A^-$  (amino acids) are set metabolically to 145 mM
- 3) space charge neutrality:  $K_o + Na_o = Cl_o + A_o$   
 $K_i + Na_i = Cl_i + A_i$
- 4) main permeability is to  $K, Cl$   
Donnan Equilibrium:  $K_o Cl_o = K_i Cl_i$
- 5) Osmotic Equilibrium:  $K_i + Na_i + Cl_i + A_i = K_o + Na_o + Cl_o + A_o$

Check it out!  
This specifies all  $c_i, q_i!$

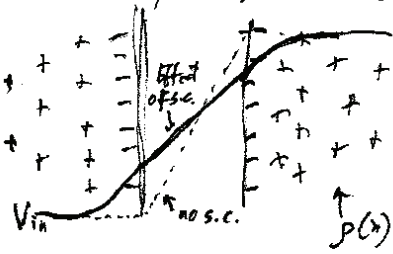
$V = -84 mV$

(cells are water permeable through aquaporins)

In reality, cells are also  $Na$ -permeable. This leads to a Goldman non-equilibrium steady state where  $\sum I_i = 0$  concentrations run down.  $Na_i$  is pumped back in (3  $Na^+$  for 2  $A^-$ ) using ATP, until  $Na_i$  reaches target level. This pump ultimately holds it all together. Poison it with  $Pb$  ouabain, + cells slowly depolarize of  $\sim 10 mV$  by balancing the  $Na$  leak + cancelling  $PNa$  from initial  $V_m$  of  $-84 mV$  to  $0 mV$ . With a  $Na$  leak, no solution of above constraints exists -  $K_i \rightarrow 5$ ;  $Na_i \rightarrow 145$ ;  $Cl_i \rightarrow 110$ ;  $OSM_i \rightarrow 355$ .  $OSM_o = 300$  water rushes in, cells swell & lyse

XII Consequences of Surface Charge (if time permits)

Phospholipids often have positive polar groups on membrane surfaces. Most membrane proteins have negatively charged amino acids on surfaces, which influence ion behavior near pore openings



The negative fixed surface charge of density  $\sigma$  (cgs/cm<sup>2</sup>) attracts a cloud of neutralizing + ions in a nearby layer to maintain electroneutrality. These local bulk charges  $\rho(x)$  (cgs/cm<sup>3</sup>) produce a local electric field in this layer (called diffuse double layer or Debye layer)

Gauss' Law  $\frac{dE}{dx} = \frac{\rho(x)}{\epsilon}$   $E = -\frac{dV}{dx} \rightarrow \frac{d^2V}{dx^2} = -\frac{\rho(x)}{\epsilon} = \frac{\sum z_i q c_i(x)}{\epsilon}$

By the Boltzmann rule

$\frac{c_i(x)}{c_i(0)}$  depends on relative potential energies

$\frac{c_i(x)}{c_i(0)} = e^{-z_i q V(x) / kT}$

Poisson's Law  
Gouy + Chapman combined Poisson to get

$\left(\frac{dV_{surf}}{dx}\right)^2 = \frac{2kT}{\epsilon} \sum c_i \left(e^{-z_i q V_{surf} / kT} - 1\right)$  electroneutrality requires  $\sigma = -\int \rho(x) dx = \epsilon \frac{dV}{dx}$

giving  $\sigma^2 = 2\epsilon kT \sum c_i \left(e^{-z_i q V_{surf} / kT} - 1\right)$  The Grahm Eqn.

Typical values are  $V_s \approx 20 mV$   $\sigma = \frac{1}{2} e \text{elec} \text{chg} / nm^2$

The Debye layer is about 5 Å thick (approx length const. since  $V(x)$  is not const. - it's not exactly exponential) and  $c(0) \approx 5 c(\infty)$  (big effect!)

s.c. depolarizes membrane interior - shift  $V$  dep of

Above eqns predict effect of  $c_i$  on  $V_s$  plotting shift in  $V$  dep of activation + inactivation

for many channels, one  $\sigma$  explains  $c_i$ -dep of  $V$  shift of  $q_{act} +$  inact for diff ions.

vs.  $c_i \rightarrow \sigma$ ; + then  $V_s$  under normal conds.

Sometimes a particular ion (often  $Ca$ ) binds to proteins of association constant  $K_a$ .

here  $c$  in ions/cm<sup>3</sup>

Then the Stern modification explains the data:

$\sigma = (K_a c e^{-z q V / kT} + 1) \sqrt{2\epsilon kT \sum c_i \left(e^{-z_i q V_s / kT} - 1\right)}$

for Mols/liter

ALL THIS IS IN B. HILLE "Ion Channels..."

more or less!

$k \rightarrow R = \text{univ. gas const.}$   
 $q \rightarrow F = \text{Faraday's const.}$   
 $= \text{charge on 1 mole}$

## Supplementary

How good is the assumption of space charge neutrality?

A. Example 1. If a drop of 100 mM NaCl is placed in a pool of water,  $\frac{\partial^2 V}{\partial r^2}$  can be measured to reach about 10 mV/cm<sup>2</sup> near the drop's margin, due to higher mobility of Cl<sup>-</sup>.  
 Gauss' law  $\frac{dE}{dr} = \frac{\rho}{\epsilon}$  or  $\frac{d^2V}{dr^2} = -\frac{\rho}{\epsilon}$  in water  $\epsilon = \kappa w \epsilon_0 = 7.4 \times 10^{-12}$  F/cm  
 so  $\rho = 7.4 \times 10^{-19}$  coul/cm<sup>2</sup>. since  $q = 1.6 \times 10^{-19}$  coul,  $\rho = 4.6 \times 10^5$  ions/cm<sup>2</sup>, which is  
 $\frac{4.6 \times 10^5}{6 \times 10^{23}} = 7.7 \times 10^{-19}$  moles/cm<sup>2</sup> =  $7.7 \times 10^{-16}$  Molar = 1 part in  $7.7 \times 10^{15}$  of 100 mM  
 = negligible!

B. Example 2. A membrane potential of 100 mV across  $\mu\text{F}/\text{cm}^2$  separates charges of  $Q = CV = 10^{-7}$  coul/cm<sup>2</sup> =  $6 \times 10^{11}$  ions/cm<sup>2</sup> = 1 picomole/cm<sup>2</sup>.  
 If these charges line up on either side of the membrane in the first row of ions (thickness = hydrated ion diameter  $\approx 5 \times 10^{-8}$  cm or 5 Å), then their concentration in this layer is  $10^{-12}$  M/cm<sup>2</sup>  $\cdot \frac{1}{5 \times 10^{-8}$  cm =  $2 \times 10^{-5}$  M/cm<sup>3</sup> = 0.02 M/liter. For salts present at conc. of 100 mM, only 20% of the ions in this first layer are un-neutralized, and the rest of the solution is electroneutral.