

LECTURE 1, 25 JAN 2005

(1) course content and format, review syllabus (five units)

- (A) NEUROMODULATION
- (B) REFLEXES and CPGs
- (C) NEURAL CONTROL OF BREATHING
- (D) NEURAL CONTROL OF APPETITE AND BODYWEIGHT
- (E) NICOTINE AND ADDICTION

(2) teaching philosophy -

- (A) primary literature
- (B) prepare you for graduate/medical education
- (C) knowledge starts in the lab with primary data (analysis --> interpretation)
- (D) come prepared, I do.

(3) scoring and grading - think like graduate students - knowledge > score - open book, open notes.

(4) texts:

- (A) Hille, B. Ion Channels of Excitable Membranes, Third Edition, 722 (Sinauer Associates, Sunderland, MA, 2001). **required**
- (B) Kaczmarek, L.K. & Levitan, I.B. Neuromodulation: the biochemical control of neuronal excitability, ix, 286 p. (Oxford University Press, New York, 1987). **required**
- (C) Fain, G.L. Molecular and cellular physiology of neurons, x, 693 p. (Harvard University Press, Cambridge, Mass., 1999). **recommended** (on reserve at library).

(5) what is systems neuroscience?

- (A) integrative - multiple levels of organization
 - (i) molecular/biochemical
 - (ii) cellular neurophysiology
 - (iii) networks/circuits
 - (iv) behavior
- (B) i assume you know cellular neurophysiology...
 - (i) we must use this as a basis for integration

(6) ion channels and carriers

- (A) diverse and ubiquitous - fundamental elements of cell excitability - establish resting potentials - mediate action potentials (and other forms of excitability) - mediate ionotropic synaptic potentials.
- (B) ion channels are water-filled pores - rate of ion passage $\sim 1E+6/\text{sec}$ - must be a pore
- (C) cells 3 billion years ago evolved transporters/carriers for access to metabolites carriers/transporters - proteins make small motions in lipid bilayer, which exposes transport binding sites to intracellular and extracellular spaces.
- (D) carriers setup ionic gradients - different concentrations intracellularly and extracellularly
- (E) excitation/signaling utilize ion channels that open and cause large/rapid ion fluxes
- (F) **gating** - opening and closing of the pore based on specific physiological stimuli -
 - (i) voltage
 - (ii) neurotransmitter
 - (iii) chemical stimulus (oxygen, protons/pH, carbon dioxide, calcium, ATP)
 - (iv) mechanical deformation (sensory transduction, hair cells)
- (G) **selective permeability** - ion channels restrict/permit certain ions to flow passively down their specific electrochemical gradients at high flux rates (e.g., $1E+6/s$)

above)

- (i) high throughput is a feature of ion channels, not carriers.
- (H) ion fluxes = electric currents
- (I) electric currents influence voltage trajectory of neurons
- (J) electrical activity ultimately generates chemical signals via calcium-mediated exocytosis -
 - (i) muscle contraction
 - (ii) neurotransmitter secretion
 - (iii) neurohormone release
 - (iv) digestive enzymes

(7) Ohm's law (ion channels are current-conducting pores)

(A) **current (I, i)** - defined as the flow of *positive* charges from *outside* to *inside* of neurons, measured in **amperes (A)**, which is the flow of one **coulomb (C)** of **charge (Q)** per second ($I = dQ/dt$, or in units, $A=C/s$).

(B) **potential difference (E)**, a.k.a. **voltage (V)** - measure of force to cause current flow. by definition, a **joule** of work (W) is needed to move a coulomb of charge across 1 volt (V) of potential difference ($W=EQ$, or in units, $J=VC$).

(i) NOTE: V and E are interchangeable, both denote potential difference/voltage.

(ii) NOTE: sometimes voltage will be called **electromotive force (emf)**

(C) **conductance (g)** - measure of the ease of current flow (in siemens, S).

(i) Ohm's law: $I=gV$.

(D) **resistance (R)** - measure of impedance to current flow (in Ohms, Ω). reciprocal of conductance ($g=1/R$)

(i) Ohm's law: $V=IR$.

(E) membrane is bilayer of lipids, not ion permeable

(E) total conductance of a membrane is therefore the sum of all elementary conductances in parallel (consult physics text for parallel/series circuits)

(8) membrane is a capacitor (neurons live in the world of voltage)

(A) stores and separates charges (across two conducting solutions)

(B) **capacitance (C)** - measures charge needed to setup a potential difference.

(i) capacitor law: $Q=CV$.

(C) **farad (F)** - unit of capacitance, a 1 F capacitor stores 1 C of charge with an applied voltage of 1 V.

(D) with a current I , the rate of change of voltage is the time derivative of the capacitor law: $I = dQ/dt = C(dV/dt)$

(E) VERY IMPORTANT: the property of capacitance gives membrane the ability to maintain a voltage, and change its voltage in the presence of currents.

(i) NOTE: conductances/resistors cannot hold voltages, as soon as current ceases, or the channels are no longer gated in the open state, they have no voltage: only the cell membrane (with capacitance) and hold a voltage).

(9) parallel conductance model (voltage responses are time dependent)

(A) charging: $V=IR(1 - \exp(-t/\tau))$

(B) discharging: $V=IR(\exp(-t/\tau))$

(C) $\tau = RC$, more capacitance generally slows down voltage responses.

(D) consult a physics or cellular neurophysiology text for RC circuit review.

(10) equilibrium potentials (Nernst equation)

(A) Given concentration gradients (Hille: Table 1.3, p.17)

(B) ... and selective permeability

(C) a permeant ion **diffuses** down its concentration gradient until counteracted by an electrical force (called **electrophoresis**) that arises due to charge separation.

(D) when diffusion and electrophoresis are equal and opposite, there is no net

charge flux and the voltage is at the **equilibrium potential** for that permeant ion.

(i) equilibrium potential, a.k.a.

(a) Nernst potential

(b) reversal potential

(c) zero-current potential

the **Nernst equation**: $E = (RT/zF) \cdot \ln([C]_{out}/[C]_{in})$

(a) Equations 1.11a-d in Hille give specific ion expressions (p.15-16)

(b) Hille: Table 1.2 (p.16) gives values of RT/F for different temperatures

(E) NOTE: ion flux ceases at the equilibrium potential

(11) current-voltage relations (I-V curves) see Hille Fig. 1.6 (p.19)

(A) IV curve of g , $2g$, $3g$ - total conductance => slope of the I-V curve ($g=I/V$)

(B) Add an Nernst potential - now E_{rev} causes an offset, shifting the I-V curve

(i) but not changing its slope (i.e., the underlying conductance)

(a) **chord conductance equation**: $I = g(V - E_{rev})$

(b) example of parallel conductance membrane with K^+ conductance, write chord conductance equation, $I = gK(V - E_K)$

(C) Add voltage-dependent gating - **rectification** occurs when conductance changes as a function of voltage, i.e., $g=f(V)$

(i) conductance segments of the I-V curve extrapolate to equilibrium potential

(D) hard vs. soft voltage-dependence compare Fig. 1.6 C and D (p.19)

(i) use chord conductance equation to calculate $g = f(V) = I/(V - E_{rev})$.

(ii) this gives the conductance-voltage relation (g-V curve)

(12) ASSIGNMENT FOR NEXT:

(A) obtain Hille book.

(B) obtain Kaczmarek & Levitan book.

(C) read Hille Chapter 2 on classical biophysics.

(D) read Kaczmarek & Levitan Chapters 1-2 on Neuromodulation and techniques.