HST 723. Neural Coding and Perception of Sound
Neurons, Channels, Synapses, Neurotransmitters. by John Guinan

From a neurophysiological-signaling point of view, a cell is a bag of ions surrounded by an insulating membrane that has a variety of trans-membrane ion-selective channels in it. Inside a typical mammalian nerve cell there is a high potassium concentration (K^+), a high chloride concentration (Cl^-) and a low Sodium concentration (Na^+), while outside the cell there is high Na^+, a high Cl^- and a low K^+ (i.e. ~ KCl inside and NaCl outside). These concentration differences lead to a voltage difference between the inside and the outside of the cell that can be understood by considering a pure "concentration cell" (Fig. 1).

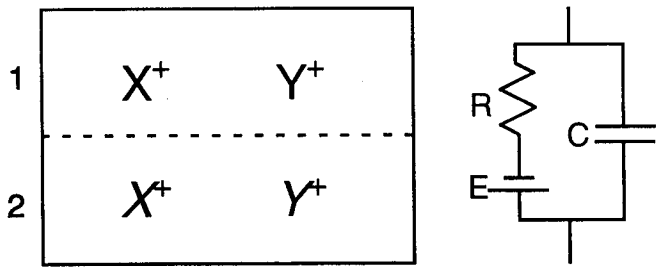

Fig. 1. A Concentration Cell and its circuit.

In a "concentration cell" with two compartments containing different concentrations of ions, separated by a membrane with channels permeable to one ion, a voltage develops across the membrane. At equilibrium, the "voltage force" is equal and opposite to the "concentration force" so that the net flow of ions across the membrane is zero. This voltage is the "Nernst equilibrium potential", E.

$$E = \frac{RT}{zF} \ln \frac{C_2}{C_1}$$

Where E is the potential difference.
R is the gas constant (8.314 joules degree^{-1} mole^{-1}).
T is the absolute temperature.
z is the charge on the ion,
F is Faraday's constant (96,500 coulombs / mole)
C1, C2 are the concentrations of the ion.

$$E = 58 \log_{10} \frac{C_2}{C_1}$$

for a single-valent ion at room temperature (E in mV).

A model for the ion channels is a battery at the Nernst potential (E) in series with a conductance which expresses the mobility of the ion through the membrane. In parallel with this is a capacitor produced by the membrane separating two conducting media (Fig. 1, right). If there are several ions that ago through the membrane, a first order model is a parallel combination of the circuits for each ion, i.e. for each ion there will be a battery (at the Nernst potential for that ion) plus a conductance expressing the ion permeability of that ion. In biological membranes, ions typically go through membrane channels. An appropriate model is a set of parallel circuits for each ion going through a channel, with the circuits for each channel in parallel.

To maintain their internal ion concentrations, cells have ion pumps. These pumps use metabolic energy to move ions against their concentration-potential gradient. If an ion has no pump (e.g. sometimes Chloride has no pump) then it will be distributed passively across the membrane, i.e. its intracellular concentration is set by the membrane potential (which is controlled by other ions).

A membrane with ion Channels in it.

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A typical Neuron.

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Aidley, 1971

A WELL-STUDIED CHANNEL: THE ACETYLCHOLINE RECEPTOR

The ACh receptor is probably the best understood synaptic receptor both in terms of structure and function. The amino-acid sequence of the ACh receptor is known and a great deal about its physical structure is known (See diagram at top right). Individual ACh receptor channels have been extensively studied by the patch clamp technique. When two ACh molecules are attached, a channel opens to a fixed conductance (Fig. 2 B) for a random duration (Fig. 3).

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Model for the Postsynaptic membrane of the Nerve-Muscle Junction

Even though individual Acetylcholine (ACh) receptors act in an all-or-none fashion, a cholinergic synaptic region (one that contains ACh receptors) typically has thousands of receptors each acting independently and probabilistically. The same is true for other types of ion channels. The result is that the gross properties of the postsynaptic membrane can be adequately modeled by a lumped circuit.

A lumped model for a cell with an cholinergic synapse is shown in Figure 8. Each ACh channel allows both Na^+ and K^+ to pass through (Na^+ a little better than K^+). This is represented at the top-right in Figure 8 by two ion-channel pathways in parallel being switched on by the ACh switch. In the top-left of Figure 8, the non-synaptic part of the membrane is represented by parallel pathways for each main ion. In the top part of the figure, the conductance for each ion is represented separately. In the bottom part of the figure each part of the membrane is represented by an equivalent single-branch circuit (a Thevenin-Equivalent). Cholinergic synapses form on both neurons and muscle cells. In both kinds of cells the intracellular fluid is high in potassium and low in sodium, so that E_K has a large negative value (-60 to -90 mV) and E_{Na} has a large positive value (+40 mV).

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Nicholls, Martin, Wallace, 1992

A simple circuit model for a neuron with an excitatory synapse

If we neglect the dendrites and consider a neuron to be just a spherical cell body, it can be modeled as a composite ion channel (the Thevenin equivalent of all of the ion channels) in parallel with the membrane capacity (Fig 1, left). Such a neuron can be characterized by its rest potential, its conductance and its time constant.

Activation of an excitatory synapse on this neuron creates an Excitatory Postsynaptic Potential (EPSP) that can be modeled as briefly closing the switch on a composite ion channel (Fig. 1, right). If we know the neuron's rest potential, conductance and time constant, we can use the circuit to calculate the current that must have flowed through the synapse to create the EPSP. Such calculations show that activation of a synapse is typically very short (e.g. mostly over 1 ms) even though the EPSP may be much longer (Fig. 7.6).

More recently it has become possible to measure intracellularly from neurons with a high-conductance patch pipette that allows the neuron to be voltage clamped and synaptic currents to be measured directly. Such measurements show that the simple model neglects the effects of many ion channels that are often present in neurons. Nonetheless, the simple model provides a starting place for understanding of neurons and EPSPs.

Inhibitory synapses

An inhibitory synapse can be modeled in the same way as an excitatory synapse, as a neurotransmitter-activated conductance in series with a battery, with the main difference being that the battery of an inhibitory synapse is at, or more negative, than the membrane rest potential. The series of measurements shown below were directed at determining an appropriate model for inhibitory synapses on spinal motoneurons. The membrane voltage of the neuron, V_N, was changed by passing a current through an intracellular electrode. The amplitude of the inhibitory postsynaptic potential (IPSP) was measured as a function of V_N. The amplitude of the shocks that evoked the inhibition was held constant, which presumably held constant the amplitude of the underlying change that produced the IPSP.

The amplitude of the IPSP as a function of V_N is shown in Fig. 7.16. The IPSP varied approximately linearly with V_N and crossed zero at -80 mV. A linear change with no current at -80 mV would be produced by a linear conductance in series with a battery at -80 mV, as shown in the circuit. The value of a synaptic equilibrium potential is determined by the ions that go through the synapse (i.e. the conductance of the synapse for each ion), and the Nernst equilibrium potentials for these ions. Other measurements show that the equilibrium potential for spinal-motoneuron IPSPs is due to both K^+ and Cl^- ions. These are the two main ions that produce inhibition throughout the central nervous system.

The interaction of EPSPs and IPSPs.

Shown below are intracellular recordings from spinal motoneurons showing EPSPs and IPSPs evoked at a variety of times relative to each other. From these records, we can see that the effect of simultaneous EPSPs and IPSPs cannot be accounted for by linear addition of the voltage changes. A better prediction of the result is produced by the circuit model which takes into account the underlying conductance changes that produce the EPSPs and IPSPs. Note that the conductance change occurs only at the beginning of EPSPs and IPSPs, not in their tails.

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(Aidley 1971)

A neural model that includes both excitatory and inhibitory synapses:

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Consider what the IPSP would look like from a synapse which opened channels that only passed ions for which there were no "pumps". If there is no pump for an ion, the ion distributes itself to be in equilibrium at the normal rest potential, i.e. Vion = Vrest. When the synapse is activated, the conductance is increased but since Vion = Vrest, there is no change of Vm from Vrest. However, activation of this synapse still "inhibits" in the sense that it reduces the effect of excitatory synapses. One way of looking at the effect of this kind of inhibitory synapse is that it tends to "clamp" the voltage at the rest potential.

Synaptic Transmission mediated by G-Proteins

So far we have discussed only fast synapses that act by directly opening a membrane channel (ionotropic synapses) but there is a kind of synapse that acts indirectly through a "G-Protein" (metabatropic synapses). "G-proteins" are trimer proteins that bind guanine nucleotides (guanosine diphosphate, GDP, and guanosine triphosphate, GTP). In the rest state, the α subunit of the G protein is bound to GDP and to the other two subunits at the receptor on the membrane (Fig. 6c). In the activated state, the αsubunit binds to GTP, dissociates from the receptor, diffuses in the cell, and acts on other target proteins to modify their properties. There are lots of different kinds of G proteins which can act on many different target proteins. One of the main characteristics of G-Protein mediated synaptic transmission is that it lasts a long time. This contrasts greatly with typical ionotropic synaptic transmission which is fast. Channels that are opened by activated G proteins are modeled like any other channel, as a conductance in series with a battery.

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Presynaptic Inhibition

Although most inhibition is through inhibitory synapses that end on a neuron, one kind of inhibition, "presynaptic inhibition" is produced by a synapse that ends on the presynaptic terminal of an excitatory synapse (Fig. 7.21 right). This kind of inhibition was first found in studies of monosynaptic EPSPs in spinal motoneurons when a certain set of nerves was found that reduced the amplitude of the EPSP (i.e. inhibited the EPSP) but without producing an IPSP (Fig. 7.21, left). This inhibition was also unusual in that it had a very long time course; it lasted hundreds of ms (Fig. 7.21).

Presynaptic Inhibition is produced by the synapse *depolarizing* the presynaptic terminal. Although a naive view might be that a slow depolarization would cause more transmitter to be released, detailed studies on more accessible presynaptic terminals (squid giant synapses, these can be depolarized by passing currents with an intracellular electrode) show that a slow, long-lasting depolarization reduces the size of the presynaptic action potential and causes it to release less transmitter.

Modulation of Synaptic Transmission

Synaptic transmission can be modified by a variety of substances called "Neuromodulators". Even at the nerve-muscle junction where conduction is normally one-to-one, there is modulation of synaptic transmission. As shown below, release of Norepinephrine by nearby sympathetic axons produces a slow increase in the PSP evoked by a single pre-synaptic spike so that in the "modulated" state, one pre-synaptic spike can evoke several post-synaptic spikes. In this case, the modulator has both a presynaptic effect (it increases the number of quanta released) and a postsynaptic effect (it decreases the resting conductance of the muscle fiber near the synapse).

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Neurotransmitters

The action of a transmitter is determined by its receptors. There are two classes of receptors:

Ionotropic - a receptor that acts by opening a membrane channel.

Metabotropic - a receptor that acts by making metabolic changes.

Certain receptors almost always have the same kind of receptor, so by knowing the transmitter you can know what the synapse does.

Each receptor has a pharamacogical profile that provides a means to identify it, e.g. the receptor is activated by chemicals A,B,C each with binding affinities K_A, K_B,K_C, and it is blocked by chemicals D,E,F each with binding affinities K_D, K_E,K_F,

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Neuronal Junctions and Electrical Synapses

Neurons situated next to each other may have no membrane specializations (i.e. have normal cell membranes with normal 20 nm gaps, Fig. 6.3a), or have a variety of membrane specializations (Fig. 6.3 b-f). One specialization, called a desmosome (Fig. 6.3b) is thought to mechanically hold cells together. Chemical synapses have been divided into two morphologic types, 1 and 2. Type 1 synapses have spherical vesicles and membrane thickenings that are asymmetric (thicker on the post-synaptic side); these are usually excitatory. Type 2 synapses have oval vesicles (often called pleomorphic or flat) and membrane thickenings that are symmetric; these are usually inhibitory. Another kind of junction is a "gap" junction, called that because there is a small 3.5 nm gap between the pre and post synaptic membranes. Gap junctions form electrical synapses, i.e. they produce a high conductance connection between two cells. They have the curious property that they allow passage of ions from cell to cell and along the extracellular space but without mixing these two sets of ions. How this is done is illustrated in Fig. 9-7. Another kind of junction (not shown) is a "tight junction" (e.g. between the cells lining the endocochlear space). In tight junctions, the outer leaflets of the plasma membrane are so close that they obliterate the space between the cells so that no ions can pass.

Gap junction are commonly found between neural glial cells in the CNS, and in the cochlea joining "supporting cells". Gap junctions are also found between the dendrites in some central neurons. Thus, there are electrical synapses in the CNS. In most cases, however, CNS synapses are chemical.

DENDRITES

The starting point for understanding dendrites is the passive cable model. With this view, dendrites act like a passive (lossy) cable (Fig. 1). In such a system, synapses that are close to the soma will have a large, fast effect, while those that are far from the soma will have a much smaller and slower effect (Fig. 7).

Although it still appears that the passive cable model is appropriate for many neurons, it is increasingly clear that dendrites are often far more complex. It has always been realized that the passive cable model is a problem for neurons that have very complex arborizations on the end of a long dendrite because it seemed almost impossible for the synapses on these arborizations to have much influence on the soma; they are too far away for passive conduction to do much. Recently it has been shown that some neurons conduct action potentials (similar to, but not the same as action potentials in axons). Such action potentials provide a way for distant synapses to influence the soma. In addition, dendritic action potentials may start in the soma and travel out into the dendrites. Such dendritic action potentials may provide a signal that triggers changes in the dendritic synapses that take place with memory. Very recently it has been shown that there can be selective transport of material from the nucleus to specific places in a dendrite and that this may also be part of forming a memory.

ACTION POTENTIALS

Signals are carried over long distances in the nervous system by action potentials. Action potentials are produced by two kinds of ion channels: sodium selective channels and potassium selective channels. These channels have the special property that their conductance depends on the past history of the voltage across the membrane, such channels are called "voltage-gated" ion channels. When the membrane potential is at rest, both sodium and potassium channels are mostly "off". When the membrane is depolarized past a "threshold", the sodium conductance increases which lets sodium ions into the cell and depolarizes the cell further. This is "positive feedback". The time constant for turning on the sodium channels is fast (< 1 ms). "Threshold" is reached when the depolarization is large enough that further depolarization is self sustaining. This increase in sodium conductance forces the membrane potential toward the sodium equilibrium potential, which is typically 30-40 mV positive. If the conductance increase of the sodium channel were all that was present, the membrane would depolarize to the sodium potential and stay there. Two things act to cause the membrane potential to go back to the rest potential: (1) When the membrane is depolarized, the sodium channels are slowly ($\tau > 1$ ms) turned off or "inactivated", and (2) When the membrane is depolarized, the potassium channels are slowly ($\tau >$ 1 ms) turned on. Turning on the potassium channels pulls the membrane potential toward the potassium equilibrium potential (about - 80 mV). Typical time courses of the sodium and potassium conductances and a resulting action potential are shown in the figure.

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Nicholls, Martin, Wallace, 1992

Sodium and Potassium Channels

Since Sodium and Potassium channels are controlled by the membrane voltage but themselves change the membrane voltage, studying them requires controlling the membrane voltage with a "voltage clamp". The original separation of the sodium and potassium currents by Hodgkin and Huxley was done mainly by the difference in their time courses (Figs. 3 & 4). Now it is possible to selectively block sodium and/or potassium channels chemically and to study the channels that remain unblocked.

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PROPAGATION OF ACTION POTENTIALS

Action potentials are propagated by the action potential in one place causing nearby places to be depolarized thereby triggering action potentials in these nearby places. In a myelinated axon, action potentials take place mainly at the "Node of Ranvier" and conduction "jumps" from one node to the next. This creates faster conduction of action potentials than in unmyelinated axons. In myelinated axons, the speed of propagation of action potentials is approximately proportional to the axon size. When axons are excited by extracellular shocks, larger axons are depolarized more easily and thus have lower thresholds than smaller axons.

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Aidley, 1971

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Aidley, 1971

The Site of Initiation of Action Potentials in Spinal Motoneurons

In many neurons, action potentials are initiated at the initial segment (IS) of the axon hillock. From there they propagate both out along the axon and, in some neurons, back into the soma and perhaps into the dendrites. The reason spikes start at the initial segment (and not the soma) is that there is a higher concentration of sodium channels at the initial segment than in the soma.

In the figures below, IS = initial segment, SD = soma and dendrites, M = the Myelinated axon's first node of Ranvier. Orthodromic = going in the normal direction, i.e. a spike going out the axon away from the soma. Antidromic = going opposite to the normal direction, i.e. a spike going toward the soma in the axon, or its continuation into the soma (which may actually be the normal direction there).

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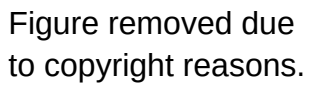
(Catterall 1984)

Synaptic Plasticity and Learning.



NMDA = N-Methyl D-Asparate (a kind of glutamate receptor)

(Jessell & Kandel 1993)

LTP = long term potentiation.

Hebbian Synapses = simultaneous firing of two synapses results in long-term potentiation of both synapses. In practice, this usually is taken to mean if neuron A consistently activates neuron B, then the synaptic efficacy of A on B is increased.

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