

IONS, CHANNELS, CURRENTS, AND ELECTRICAL POTENTIALS

Ion Currents

Courses in physics and electrical engineering courses usually deal with electrical current as a flow of electrons or sometime of “holes.” In biology, currents are carried by charged atomic or molecular species, ions.

With ions, you can still use a generalization of Ohm’s law as a first-order approach to analyzing biological currents:

$$\text{Flow} = \text{Force} * \text{Conductance.}$$

The “Force” for ion currents, however, is not simply due to electrical potential.

Chemical species, even uncharged, will undergo net directional flow if there are differences in concentration of a species within a system or across a barrier. This net directional flow is just due to random processes. Molecules bounce around; if there are more in one place than in another, then there are more to bounce away from the one place than from the other.

There is thus a net macroscopic flow of any chemical species from a region of high concentration to a region of low concentration. Once its concentration is equalized throughout the system, there is still dynamic random motion, but there is no net direction to the flow.

Electrochemical potential

Similarly to the electrical potentials used to quantify forces acting on current flow, a “chemical potential” can be used to quantify the forces acting on chemical flows. The “chemical potential” of substance i in ideal solution is:

$$\mu_i = \mu_i^0(P, T) + RT \ln c_i$$

where $\mu_i^0(P, T)$ depends only on pressure P and absolute temperature T , R is the gas constant, and c_i is the concentration of substance i . The term $\mu_i^0(P, T)$ differs among chemical substances and quantifies the energetics of chemical reactions. The term $RT \ln c_i$ quantifies the energetics of concentration differences. For this course, you don’t have to worry about where this logarithmic relation between concentration and chemical potential comes from, but you must recognize its importance.

If a chemical species is charged, then its flow may be driven by gradients of both electrical and chemical potentials. The “electrochemical potential” of a charged chemical substance i with charge z_i per molecule is:

$$\mu_i = \mu_i^0(P, T) + RT \ln c_i + z_i F V$$

where F is the Faraday constant (number of coulombs per mole: 96,500), and V is electrical potential.

If substance i doesn’t undergo chemical transformation, and it is at the same temperature and pressure on two sides of a membrane, then its term μ_i^0 is the same on both sides. The difference in its electrochemical potential across the membrane (“inside” of membrane, versus “outside” as reference) is thus:

$$(z_i F V_{in} + RT \ln c_i^{in}) - (z_i F V_{out} + RT \ln c_i^{out})$$

or

$$z_i F (V_{in} - V_{out}) + RT \ln (c_i^{in} / c_i^{out})$$

This difference in electrochemical potential is a measure of the driving force for flow of substance i across the membrane.

If we call $V_m = V_{in} - V_{out}$ (the “membrane potential”) we can write:

driving force = $z_i F(V_m) + RT \ln(c_i^{in} / c_i^{out})$.

No Net Flow—No Net Force

Say that some system maintains a fixed concentration ratio of ion i across the membrane. There will be no net driving force acting on that ion, and thus no net flow of that ion, at one particular electrical potential difference for any given concentration ratio. The electrical potential difference that balances off the concentration ratio for the ion (often called the “equilibrium potential” or “Nernst potential” for the ion) is:

$$E_i = \frac{RT}{z_i F} \ln(c_i^{out} / c_i^{in}).$$

For “typical” values of intracellular and extracellular ion concentrations in mammalian tissues at body temperature ($T=310^{\circ}\text{K}$) we can calculate:

Typical Nernst equilibrium potentials

Ion	c_i^{in} (mM)	c_i^{out} (mM)	E_{ion} (mV)
K^+	150	5	-91
Na^+	10	140	+71
Cl^-	30	120	-48
Ca^{2+}	0.0001	1.2	+125
Mg^{2+}	0.5	1	+9
HCO_3^-	20	25	-6

Note that no two of these ions have the same Nernst equilibrium potential. Thus at most one of these ions can be in equilibrium at the same time across this cell’s membrane.

As a rule of thumb, for systems between room temperature and mammalian body temperature, about a 60 mV electrical potential difference can counteract a 10-fold concentration ratio for a singly charged ion.

Driving force and conductance

Now let’s see the quantitative implications of considering both electrical and chemical forces. Use the definition of the “equilibrium potential” for ion i to write the driving force for flow of the ion in a more compact form:

$$\text{driving force} = z_i F(V_m - E_i).$$

The “conductance” of the membrane to the ion is simply the ratio of the ion’s net flow to this driving force. The current for each ion i can be written in terms of the conductance, g_i :

$$I_i = g_i(V_m - E_i).$$

This form is consistent with the conventions of cellular electrophysiology, in which an outward current (outward movement of a positive ion or inward movement of a negative ion) is positive. A (positive) conductance g_{ion} leads to a positive (outward) current if there is a positive driving force ($V_m - E_{ion}$).

A few related issues are potentially confusing. First, this type of conductance is a “chord” conductance, not a “slope” conductance. That is, this conductance is *not* the local slope of a relation between current and electrical potential.

Second, recall that the driving force is defined per mole of the ion. If two systems have the same concentration ratio for i across their membranes but one system has a larger absolute concentration, then that system may have a larger net flow than the other and thus show a higher conductance in these terms. The “conductance” is thus not simply a function of the barrier to current flow; it will also depend, at least, on the concentration of the ion carrying the current.

Third, the symbol “ g_i ” might leave the impression that conductance is constant. This is simply not the case for most interesting ion conductances in biology. The concentrations of other ions, the presence of

chemicals that interact with the conductance pathway, even the electrical-potential difference itself, may have great effects on the conductance of a membrane to an ion. These types of influences on conductances underlie much of biological signaling. For example, determining experimentally how ion conductances change with membrane potential, ion concentrations, and time formed the basis for Hodgkin and Huxley's explanation of action potentials in nerves.

Biological ion channels

The pioneering work of Hodgkin, Huxley and Katz in the late 1940s and early 1950s indicated that ion flow across cell membranes was mediated by individual molecular-scale aqueous "channels" across the membrane. Different channels were thought to have different selectivity among ions—e.g., some selective for potassium, others for sodium ion. Whether a channel was "open" or "closed" depended on the membrane potential, with the kinetics of response to a change in membrane potential differing among channel types. The experimentally-determined characteristics of ion flow across squid giant axon membranes could be modeled by cooperative processes, in which a number of subunits of a channel needed all to be in particular voltage-dependent states for the channel to be open.

This conceptual approach provided the first quantitative description of the mechanism of the "action potential" that transmits electrical signals along nerve axons. Work by Katz and his colleagues then demonstrated that the signal from a nerve that makes a skeletal muscle contract also works via a channel. In this case, a channel on the surface membrane of the muscle cell is opened by a chemical signal, acetylcholine, which is released by the nerve terminals in response to an action potential in the nerve. The acetylcholine-sensitive channel on the muscle membrane was found to be permeant to many cations, but not to

anions. Studies of the detailed time-course of responses to acetylcholine indicated that this channel had not only "open" and "closed" states, but also a special "desensitized" state that had to revert slowly to the "closed" state before the channel could open again.

This concept of molecular-scale channels, based on work at the cellular level, has now been amply verified at the molecular scale. Recordings have been made of currents through individual channels; the gene and protein sequences of many types of ion channels have been determined, including channels directly responding to acetylcholine or to other neurotransmitter molecules; physical subunit structures have been found that correspond to the type of cooperatively-acting subunits hypothesized by Hodgkin, Huxley and Katz; natural and induced mutations of channel sequences have begun to demonstrate the particular portions of the channel proteins that provide selectivity among ions, sensitivity to chemical ligands, and dependence on electrical potential difference across the membrane in which the channels are embedded.

Some types of channels are affected more indirectly by external chemical signals. In these cases, an external chemical signal binds to a non-channel membrane protein that initiates a series of intracellular chemical reactions. The "second messengers" thus produced by the cell then affect the states of ion channels. For example, although acetylcholine binds directly to proteins that form an ion channel in skeletal muscle, it does not bind directly to ion channels on "smooth muscle" cells of internal organs. In smooth muscle, acetylcholine exerts its effects through "second messengers" instead.

Current-voltage curves

The most widely used ways for studying processes involving movement of ions across membranes involve one of the variants of the “voltage-clamp” protocol as developed by Hodgkin, Huxley and coworkers. Measure the electrical potential difference across the membrane, and apply (and record) the current across the membrane needed to reach some desired membrane potential. This can be done for a sheet of epithelial tissue, for a single cell, or for a piece of cell membrane. A useful way to present this information is to plot the current required to achieve any membrane potential as a function of that potential. This is a “current-voltage” or “I-V” curve.

(For many ion-transport processes, such as those involved in the action-potential mechanism, the time-course of the current required to obtain a new membrane potential contains important information. In that case you need to choose the current at some uniform time or times after the change in membrane potential.)

I-V curves can be obtained for many different conditions, designed to obtain information about particular ion-transport processes. Pharmacological agents and altered ion concentrations can be used to obtain information more-or-less specific to individual types of channels.

A channel conductance is constant if and only if its I-V curve is a straight line. The slope of the line then equals the conductance.

The I-V curve for a channel specific for one ion passes through the voltage axis at the ion’s Nernst equilibrium potential: no net force, no net flow. Manipulating ion concentrations and determining how the zero-current potential changes can thus help to determine which ion or ions permeate a particular channel type.

If more than one ion can permeate a channel, the zero-current point for the

channel’s I-V curve is the potential where the currents of the two ions balance to zero. This potential will be a weighted average of the Nernst potentials for the permeant ions. The weights are related to the conductances of the channel for each of the ions. If one ion predominates in terms of conductance, then the zero-current point will be close to that ion’s Nernst potential.

Sensory transduction

Formally, transduction is changing one form of energy into another. For vertebrate sensory systems, transduction of environmental signals eventually leads to coding in terms of action potentials in “afferent” nerves that bring the information to the brain.

Even at the very first steps in vertebrate sensory transduction, ion channels are involved. In primary receptor cells for vision and smell, stimuli from the environment lead to changes in production of “second messengers” that then affect ion channels in the receptor cells’ membranes. In the primary sensory cells of the auditory and vestibular systems, the hair cells, ion channels are directly gated by mechanical stimuli.

Resting cell membrane potential

So what determines the electrical potential difference across a cell membrane? The “Resting Potential” of a cell is simply the membrane-potential difference at which there is no net current and no net solute flow. Since different ions are found to have different “Nernst equilibrium potentials” across cell membranes, this zero net ion flow does not mean zero net force acting on the ions.

Equilibrium vs. Steady state

The “steady state” that occurs in a living organism is substantially different from equilibrium. In a steady state, compositions and volumes of body fluid compartments are constant because of zero net *flow* for each of the internal components of the system. Zero net flow is obtained by a balance of individual transport processes and chemical reactions, each of which has a non-zero driving force and proceeds at an appreciable rate. Unlike equilibrium with zero net *force* to drive transport or reactions, a steady-state

balance of flows requires an “open system” that can exchange matter or energy with the environment, because energy must be continually expended to keep the system in a steady state away from equilibrium.

Ion pumps

At the cellular level, this continuing energy expenditure involves a set of ion pumps and transporters that are coupled directly or indirectly to the consumption of ATP. These energy-consuming processes balance the passive leaks of ions down their electrochemical potential gradients.

First approximation—weighted average of Nernst potentials

In principle, to figure out a cell’s resting potential, all we have to do is figure out what value of membrane potential leads to zero net current. In one hypothetical situation, that’s easy. Say that the ion pumps work perfectly well at keeping intracellular concentrations constant, while extracellular concentrations are maintained constant by the investigator (in an experiment) or by the homeostatic mechanisms of the body (*in vivo*). Then each ion has a well-defined Nernst equilibrium potential. Also assume that the ion conductances are independent of membrane potential, and that the rates of the ion pumps are not affected by membrane potential. Then the resting potential of the cell is simply the conductance-weighted average of the Nernst potentials of the permeant ions. Thus if the conductance to one ion is quantitatively dominant, the membrane potential will be close to that ion’s equilibrium potential.

This approximation often works pretty well in practice, although there are some potential complications. We’ve already noted that conductances can depend on membrane potential. In addition, not all current-producing cell processes are channels. Some transporters in cell membranes that couple the motion of two or more ions can lead to net current flow.

Furthermore, not all processes that transport ions across the plasma membrane result in a current. Neither the $\text{Na}^+\text{-H}^+$ exchanger involved in acid-base balance nor the $\text{Na}^+\text{-K}^+\text{-2Cl}^-$ cotransporter important in renal and inner-ear function carries net current. Yet both can affect ion concentrations in cells, and thus the Nernst equilibrium potentials for those ions and the whole-cell zero-net-current resting potential. Despite these complications, a conductance-weighted average of Nernst potentials is a good place to start for an estimate of a cell's membrane potential.

What comes in must go out

Although ion channels may best be studied when the experimenter controls ion concentrations and potentials, that is not how they work *in vivo*. Channels in the plasma membrane are in a structure that surrounds the contents of the cell. If situations change in one membrane location, leading say to a local inward current, there must also be an outward current elsewhere through the cell membrane to continue the circuit. (The capacitance of cell membranes is important during transients, but steady-state current return will be via conductive paths.) For cells that are polarized, like hair cells, this means that we have to consider not only the specialized current entry channels but also the (potentially quite different) current exit channels.

Furthermore, in this type of situation, there will be extracellular currents to complete the electrical circuit. Many electrical measurements made in biological systems are effectively of these extracellular currents rather than of electrical potential differences across individual cell membranes.

Extracellular potentials

It's simplest conceptually to start thinking about electrical potential differences across a cell membrane. Nevertheless, bioelectric

potentials were studied long before it became technically possible to measure potential differences across cell membranes. Measurements of the electrocardiogram and early measurements of "receptor potentials," the electrical events associated with sense organs, were not accomplished by sticking an electrode into a cell. These rather were recordings taken by electrodes sitting on the surface of the body or perhaps within a tissue but not within a cell.

Even today, many of the most common electrical measurements associated with studies of auditory function are extracellular, not intracellular. The compound action potential, the cochlear microphonic, the auditory brainstem response, even the endocochlear potential are all extracellular recordings. How do these extracellular potentials correspond to events going on across cell membranes?

The best way to think about extracellular potentials is to apply Ohm's Law. A potential is the product of a current times a resistance. An extracellular electrode records a potential difference from some distant ground electrode located elsewhere on the body or in a tissue bath. That extracellular potential difference is determined by the resistance to current flow between the recording electrode and ground, and the current flowing past the recording electrode to ground.

So for a fixed recording location, the potential recorded from an extracellular electrode is primarily determined by extracellular current flow. If enough cells synchronously produce currents there may be enough net extracellular current to produce an appreciable extracellular potential.

How many cells is enough? One cell can be enough: about 70 years ago, Alan Hodgkin forced the extracellular currents generated by a nerve axon to flow through a high enough extracellular resistance to make

reliable measurements and perform some elegant experiments on the conduction of action potentials even before intracellular recordings were possible. Millions of cells are involved in the electrocardiogram, which represents the synchronized activity of muscle fibers in the heart. The classic receptor potential of the auditory system, the “cochlear microphonic,” arises from synchronous currents passing through some hundreds or thousands of hair cells when they are stimulated by sound.

References

For a somewhat different perspective on these topics, consult “The Molecular Biology of the Cell” by Alberts et al. (Garland, New York; 4th Edition, 2002), chapters 10 and 11. Chapter 10 deals with

the structure of cell membranes and proteins in cell membranes. Chapter 11 deals with ion transport, ion channels, action potentials, and synaptic function.

Introductory neuroscience texts also cover this material. “Principles of Neural Science” by Kandel, Schwartz and Jessell (McGraw-Hill, New York; 4th Edition, 2000) is generally well written, though voluminous. A particularly useful book specifically on ion channels is “Ionic Channels of Excitable Membranes” by B. Hille (Sinauer, Sunderland MA; 3rd Edition, 2001).

For further reading of research reviews or of classic experimental studies, consult the references at the end of Chapter 11 of Alberts et al., or talk with one of the faculty.