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Ionic Channels as Natural Nanodevices

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Abstract. Ion channels are proteins with a hole down their middle important in a wide range of biological functions yet simple enough to be analyzed as devices in the engineering tradition.

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Ion Channels

Ionic channels are proteins with a hole down their middle that control a wide range of biological function because they control the movement of ions and electricity across the otherwise insulating membranes that define biological cells. Ion channels control electrical signaling in the nervous system; they coordinate the contraction of muscle, including coordinating heart muscle so it can function as a pump; they regulate uptake of foodstuffs in the intestine, secretion of hormones, and secretion of many components of urine. It is hard to find a class of proteins of more general medical and biological significance than ion channels: indeed, transport proteins, either ion channels or their close relatives, take up about one third of the human genome.

Electrical current in biology is nearly always carried by ions, typically charged spheres with diameter somewhat smaller than the diameter of the hole in the channel protein. The channel protein is made of amino acids containing many charged atoms. These charged atoms are arranged to make the charged surface of the hole through the protein. Some of these atoms may dangle into the hole, acting as 'mobile' charge spheres that compete with ions for space in the narrow hole. But these mobile charges are 'immobile' in the sense that they cannot leave the hole. The dangling charges and charged surface of the protein are quite analogous to the doping of a semiconductor. They provide permanent charge that creates bias potentials (here both chemical and electrical) that allow the channel to have complex properties and function as a device.

Molecular Biology

Molecular biology is concerned with the arrangement of the atoms of proteins, more than anything else. The triumph of molecular biology is the technology that allows nearly complete control of the sequence of amino acids that make the protein and decent control of the resulting protein itself. In favorable cases, the location of every charge in the protein is know from x-ray crystallography of proteins in a state close to natural; in many cases, these charges can be changed by mutating the DNA that codes them. Thus, in a very practical sense molecular biologists have nearly complete control of proteins, including channels, at an atomic resolution difficult to match in solid state physics.

Channels as Devices

Ion channels are devices in the engineering sense of that word: they have signal inputs and power supplies; they have outputs; they use their own complex structure to convert input to output. Ion channels have a definite function that can be described by simple 'laws', when they function within their design limits. It is not necessary to describe all the motions of all the atoms of an engineering device to understand and control how it works. It should not be necessary for proteins or channels either, in my opinion.

Ion channels can be described by a device (design) equation in the same sense that transistors can be, not as complete descriptions of all the channel or semiconductor can do under any condition, but as adequate

descriptions of what they do when they function as they should. Of course, channels are not transistors: the current carrier in channels is ions, and the power supply is the concentration gradient of ions, maintained by other systems in the biological cell.

The currents that flow through individual ion channels are measured in hundreds if not thousands of laboratories every day because of their enormous medical and biological importance: a substantial fraction of all drugs used by physicians act directly or indirectly on channels. The currents measured from a single channel range from 0.5 pA to (say) 100 pA. Smaller currents cannot be directly measured because of signal to noise problems; improvements in performance would most likely have great practical importance since the current of calcium channels (for example) can hardly be resolved although calcium channels are of the greatest importance in regulating biological function, e.g., the contraction of the heart and mood states of the brain.

Channels as Sensors

The electrical current through a cell membrane is determined by the number and type of channels that are open during the time the current is measured. There are many types of channels, probably tens of thousands although only a few hundred are presently known. Each channel type has a special function: many respond to specific stimuli. For example, many 'agonist' activated channels are magnificent chemosensors. One channel molecule opens for milliseconds, and passes currents of picoamps in response to one or two agonist molecules of a specific chemical type. Other ionic channels respond to voltage; others to pressure, light, etc.

Channels respond to signal inputs mostly by changing the fraction of time they are open. The current measured from a single ionic channel forms a random telegraph signal and the 'duty cycle' (i.e., open probability) is a sensitive function of the signal input.

Little has been known about the structural or physical basis of these gating phenomena, although much more will be known in the near future, no doubt.

More is known about the currents that flow once the channel is open. If only one type of ion carries significant current, open channel current can be described by device equations in the tradition of computational electronics: although the precise level of atomic detail needed is not known; indeed, it may well vary from channel type to channel type. Crudely speaking, the charge on the channel wall acts as the doping does in a diode; the current flow is that predicted by the Poisson-Drift-Diffusion equations (called Poisson Nernst Planck equations in the biophysics literature).

Selectivity

Ions of different type move differently through open channels and this selectivity has been considered a hallmark of biological systems for more than a century. Recently, it has become clear that one of the most selective channels—the calcium channel of the heart—can be understood quantitatively if the spherical nature of ions is included in the Poisson Drift Diffusion equations. The breakthrough in understanding occurred when it was realized that the presence of a few charges (four negative charges in this calcium channel) on the wall of the channel guarantees the presence of (nearly) four mobile positive charges in the channel's hole. The hole is so small, however, that those mobile charges occupy a large fraction (e.g., 20%) of the space in the channel. It takes substantial (free) energy to crowd these ions into such a small space. The competition between charge and volume produced by this crowding—enforced by electroneutrality—is enough to explain selectivity using well established theories and simulations of the energetics of highly concentrated ionic solutions, at least in this channel.

Computational Electronics and Biology

Open channels form an obvious link between computational electronics and computational biology and chemistry. The electric field in channels, and the function of channels as devices, are best studied in the engineering tradition, in my view. The structure of channels is known and manipulated in the atomic detail of computational biology. The ions that move through channels in such concentrated solutions are studied in computational chemistry. Understanding channel function will require an engineering approach using the insights and conclusions of all these disciplines.

Ionic movements are measured quite directly in ionic channels and so theories and simulations are easy to falsify and experiments can be done over an enormous range of conditions (ion concentrations can be varied by factors of thousands and electrical potentials are varied by many kT/e). The principles of ionic movement in proteins can be studied in ion channels.

Channels and Computational Biology

It seems likely that the principles of ionic movement and control in ionic channels are shared by many protein functions. After all, most enzymes have active sites with highly charged walls, and the properties of charged spheres are insensible to the nature of the surrounding protein.

Thus, it may be that some of the central problems of computational biology—e.g., protein folding and drug binding—can be approached using the principles that emerge from the study of ion channels. If the role of the competition between charge and space (demanded by electroneutrality) is given due consideration, and the processes of folding or drug binding are viewed with design equations, some of the difficulties of all-atom simulations may disappear.

In any case, the study of ion channels as physical objects—that use molecular structure to perform biological function—should form a significant part of the engineering science of the next generation.