Living Transistors:
a Physicist's View of Ion Channels

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Abstract

Ion channels are proteins with a hole down the middle embedded in cell membranes. Membranes form insulating structures and the channels through them allow and control the movement of charged particles, spherical ions, mostly Na^+, K^+, Ca^{++}, and Cl^-. Membranes contain hundreds or thousands of types of channels, most of which are closed at any time. Channels control an enormous range of biological channel by opening and closing in response to specific stimuli by mechanisms that are not yet understood in physical language. Open channels conduct current of charged particles following laws of electrodiffusion rather like the laws of electrodiffusion of quasiparticles in semiconductors. Open channels select between similar ions using a combination of electrostatic and 'crowded charge' (Lennard-Jones) forces. Orbital delocalization does not seem to be involved in determining selectivity in the channels studied so far. Channels play a role in biology as important as transistors in computers, and they use rather similar physics to perform part of that role.

Transistors are everywhere in our life, so widespread that our children hardly know they exist. The singular importance of transistors is hidden nowadays in the millions of FETs that remember our snapshots. The importance of transistors was obvious to everyone when radios contained just four.

Transistors are the vital elements of our electronic technology because they amplify and switch so well according to the simple laws of electrodiffusion. In a semiconductor switch, only a few hundred holes or electrons are needed to switch or control signals of billions of charges every billionth of a second in devices so small that they can easily be held on our wrist or even in our ear, if we need to. Transistors switch quickly because the mass of the holes and electrons in semiconductors is tiny, even though the holes and electrons are quasi-particles[1] weighing hundreds of times more than real electrons.

Transistors are not the only tiny elements that control current flow in our wrist or ear. While physicists and engineers were creating transistors in germanium and silicon, biophysicists—that I call channologists—were discovering life's transistors in biological cells. These analogs of transistors are specialized proteins that control electricity (and much else) in the biological tissues and cells of our wrist or ear. Life's transistors are ion channels.

Ion channels are proteins with a hole down their middle (Fig. 1) that provide a controllable path for electrodiffusion of ions through biological membranes (Fig. 2). The electrodiffusion of ions in channels follows simple laws closely related to those of semiconductors [4; 5; 14] even though current through channels is carried by real, not quasi-particles. Current flow in water solutions, and ion channels, is carried by spherical ions dissolved in water chiefly Na^+, K^+, Ca^{++}, and Cl^-. (The charge on these ions is permanent in the sense that it does not change under biological conditions.)

Biological membranes are insulators that surround biological cells. Membranes without channels are nearly perfect insulators preventing DC current flow; membranes provide the insulating and isolating substrate through which channels can control the flux of ions, current, and electricity, much as SiO_2 provides an insulating and isolating substrate for transistors. Membranes delimit and define biological cells.

Biological cells are the fundamental unit of life.[1] Nearly all biology occurs in cells (Fig. 2). Ion channels control flows in and out of cells and so an enormous range of cellular life is controlled by these proteins in health [18] and

[1] I wish the negative quasi-particles of silicon/germanium were called (something like) 'semi-electrons'—short for semiconductor electrons—so they are not confused with isolated electrons. Surprisingly few scientists are aware that the negatively charged quasi-particles of silicon/germanium are not the isolated electrons of physics textbooks.

disease [2]: in that sense, ion channels are the transistors of life, controlling life nearly as completely as transistors control technology.[12; 13; 21; 29]

Ion channels are used to control most functions of cells because they act as gatekeepers for cells, providing paths for the movement of ions and messages in and out of cells, in particular, controlling (nearly) all the electrical properties of cells and tissues. Information processing and signaling in the nervous system use electrical signals controlled by channels; sensory organs make electrical signals using channels; contraction of voluntary (skeletal) muscle and cardiac muscle is controlled by electrical signals and channels. The heart functions as a pump because its contraction is coordinated by channels. Kidneys, lungs, stomach, intestine, endocrine glands, sweat glands use channels to transport substances—you name your tissue of interest, except red blood cells, evidently. Diseases strike channels and the study of 'channelopathies' is one of the fastest growing areas of medicine. (Search for 'channelopathy' on the internet to see what I mean.) Thousands of molecular biologists study channels every day, manipulating the channel protein (or its DNA blueprint) with the magnificent tools of molecular biology, recording current through single channel molecules using the reconstitution and patch clamp methods of Nobel laureates Sakmann and Neher [27]. Hundreds of structural biologists map the location of individual atoms of channel proteins, thanks to Nobel Laureate Rod MacKinnon, more than anyone else. Channologists form a significant fraction of all biologists because channels are the controllers of so much biological function in health and disease.

Why do ion channels have such an important role in biology? This question cannot be answered by experimentation and theory alone, the way most questions are answered in physics today, even though we can understand how channels work, by physics as usual. Channels have come to be important as part of the evolutionary process that created them; and evolution is a chaotic process (in the mathematical sense of the word), reset by random catastrophes at stochastic intervals. It is not clear that enough can ever be known in hindsight to reconstruct the trajectory of evolution of a specific channel, as much fun as it is to try. Without understanding the evolution of channels, we cannot understand why they have such important roles. Without understanding the evolution of channels, we may never know why particular channels have particular functions. A complete description of a process *at a single time* is often not enough to regenerate (i.e., 'determine' in the language of mathematics) the previous history (i.e., trajectory in time) of that process, particularly if the process, like evolution, involves many interacting variables and has a complex stochastic history. For that reason, even exhaustive experimentation may well be insufficient to understand how channels came to do what they do today.

But I believe we can know enough to understand how channels work, and to manipulate and control them, even if we cannot understand how they came to

work that way. I believe we can understand channels much as we understand complex inanimate devices, much as we now understand transistor devices.

Transistors work because engineers and physicists built a structure providing a useful current voltage relation, that follows a simple input output relation, when power is supplied to drive holes and semi-electrons through them. Ion channels work because evolution built a structure and used particular physics to drive ions through them, providing a useful current voltage relation, that follows 'laws' (input output relations) just being discovered in the last few years.

Channels work (mostly) by opening and closing. The holes down the middle of channels switch stochastically from closed to open to closed forming a random telegraph signal. The open probability (i.e., duty cycle) of the channel controls the total charge movement (i.e., integrated current of ions) across the membrane. Each of the thousands of types of channels have different controllers of their duty cycles; they have different types of gates that respond to different types of signals. Some channels respond to chemical signals of a molecule or two, others respond to mechanical stretch, still others, respond to electrical potential itself. Engineers are trying to make channel devices that exploit their special sensitivity, hoping channels are no harder to handle in a technological environment than the soap films of our liquid crystals, LCD monitors and TV sets.

The gating process of channels has an analogous role to the gating process of transistors, but it does not have analogous physics. Channels use gating motions that involve mass and friction and transistors do not. The gating of transistors does not involve substantial movement of mass but rather depends on changes in the shape of the electric field. An analogy between gating in transistors and channels [21; 29] confuses the essentially different physics of opening and closing in the two devices. The physics is different not because one system is physical and one is biological, but because changing the electric field and changing the location of mass are different, in whatever context the change occurs. The physics is different also because of the state of our knowledge. We have essentially complete understanding of gating in transistors over the entire range of scales from macroscopic function to atomic structure. We have no agreed upon knowledge of the gating mechanism of channels. Many biologists are working on gating, but agreement on even the structural basis of gating is not yet at hand.

Despite these differences, the analogy between current flow in a transistor and an open channel is good physics—*once the channel is open*, after the channel protein has finished its conformation changes.[12; 13] Indeed, current flow in transistors and the *open* channel follow nearly the same mathematical laws because the current flow of ions and quasi-particles is governed by nearly the same physics.

Ions and quasi-particles move under the control of gradients of concentration and electric potential. The paths of holes and semi-electrons are

ballistic (more or less). The paths of ions are (more or less) the trajectories of mathematical Brownian motion. The collective properties of both can be measured by the partial differential equations of probability theory which we often call by the name of the physicists who first wrote them, e.g., Fokker Planck or Nernst Planck equations, even Fick's law, although Fick was a physiologist and not a physicist.

Electric potential plays a particularly important role when these laws are applied to channels because the channels are so small. The pores of ion channels are from 4 to (say) 9 Å in diameter, and the control regions of channels are thought to be only a few Angstroms long. The pores are so small that only a few elementary charges carried by a few ions are enough to produce substantial potentials; pores have tiny capacitance. These potentials are important because the potential scale of biology is small; cell membranes are lipid films, formed of two layers of lipid molecules only some 30 Å thick—think of soap bubbles or films of olive oil thin enough to form black films on still water—and so breakdown occurs at potentials of hundreds of millivolts. (The reader should work out the field strength to see why.) Most of life's processes and most of channel function occurs at potentials smaller than 200 mV; indeed control occurs at potentials of 1–2 mV, much smaller than the thermal potential of 25 mV $= k_b T/e$ under biological conditions. Thus, the location and nature of electric charge have a large role in gating channels and biological function.

In fact, biological pores typically contain a handful of permanent charges in their walls. These charges reside in the atoms of the amino acids that make up proteins, and play a role quite analogous to the role of doping in transistors. In the ordinary case, these permanent charges do not change value as ions move through open channels. The charges also do not change position, if position is measured in averages on the biological time scale of μsec and longer, although the positions certainly fluctuate a great deal on the atomic scale of the speed of sound (see p. 845 of [5]). How these charges move and change, as the channel gates, as proteins change conformation, or as proteins do chemistry, making and breaking covalent bonds, is an important area of future physical investigation. Indeed, I have long suspected that generation and recombination of 'permanent' charges of amino acids—in protein biochemistry called protonation and deprotonation of acidic and basic residues)—play a crucial role in the function of transport molecules closely related to channels.[12]

The physics of ion motion in channels is the physics of electrodiffusion much as it is in transistors. Electricity and diffusion interact. Diffusion moves charge, charge changes the electric field. The equations of electricity and diffusion must be solved together, just as they are in computational electronics. The diffusion field of ions is created by the difference in the concentration of ions inside and outside cells. These concentrations are described by inhomogeneous

Dirichlet boundary conditions (different concentrations at different places) that inject mass, and energy into the channel. The electric field is created by different types of charge: the charge of other ions, the permanent charges of the protein, the induced (polarization) charge on molecules and at interfaces, and the charge on electrodes and in surrounding baths. The charged surface of proteins is an inhomogeneous Neumann boundary condition: the jump in normal derivative of the potential (weighted by the different dielectric coefficients) is set by the permanent charge on the boundary.

The surfaces of the proteins are not maintained at fixed potentials. They are not connected to sources of charge. On the other hand, the electrodes on either side of the membrane are typically maintained at different fixed potentials and so form Dirichlet boundary conditions that inject mass, energy, and current into the system.[2] Channel systems are necessarily far from equilibrium when they function as devices because their function is (usually) to conduct current.

Equilibrium thermodynamic analysis of a device (or channel) is usually not helpful, if the goal is to understand and control it. The function of devices has little to do with their thermodynamics and so thermodynamics tells little about how devices work or can be controlled: devices do not work at thermodynamic equilibrium, i.e., when their power inputs are all connected to the same zero potential.

Indeed, the analysis of devices is in many ways the core of engineering and is really quite different from the analysis of general physical systems. Devices have a purpose, usually summarized in an input output law, valid only under a limited set of conditions. The goal of studying devices is to understand and manipulate that input output law and so it is rarely worth studying devices under general conditions. It is particularly useless to study conditions in which devices do not work (unless one is interested in failure).

Devices in biology can be defined by similar sentences, although it is important to define ‘purpose’ more precisely and objectively. As any physiologist or physician can tell you, the purpose of a an organ, tissue, cell, or cell component is its input output relation. The purpose of the heart is to pump blood according to an input output relation; the purpose of cardiac muscle is to shorten so the heart can pump; the purpose of channels in cardiac muscle is to initiate and coordinate the contraction of the cardiac muscle, and so on. The purpose of each structure in cardiac muscle is clear: the purpose is to provide a definite output for a given input that can be used by other structures to sustain the life of the animal (so it can survive and reproduce, if one wishes to reach all the way to evolutionary biology

[2] In biological cells, active processes using chemical energy maintain average potential and concentration across membranes. Signaling in nerve and muscle fibers involves transient changes in electrical potential but the potential between signals is maintained constant in healthy cells. In experiments, specialized apparatus, made of transistors, maintains and controls these variables.

in our discussion). In favorable cases, these input output relations in biology can be written quantitatively and objectively as equations or computer programs. The purpose of biological devices is no more vague and subjective than the purpose of an amplifier.

The input output relations in biological systems often form a hierarchy of scales, with smaller devices providing outputs needed by larger devices for the overall function of the cell, tissue, or organ. In the case of nerve fibers, and cardiac muscle to a lesser extent, one can write and solve equations across almost the entire length scale from molecules to macroscopic function. These are the device equations of the biological system and I believe the purpose of the biological system is to execute these design equations in nearly the same sense that the purpose of a typical amplifier is to multiply a voltage by a constant.

Device equations tell how to use an amplifier; thermodynamics does not. Device equations describe current-voltage relations of transistors. Device equations must have spatially inhomogeneous boundary conditions if the input and output of the device are to be distinguished. The goal of much of biology, as of engineering is to design and control devices, not to study every possible property of the device. Thus, the boundary conditions that control the device and keep it working properly must be included in the analysis. Analysis of differential equations with spatially uniform boundary conditions, or with boundary conditions defined vaguely at infinity, cannot easily describe the inputs and outputs of devices and so is of limited use when dealing with biological or engineering systems.

Scientists have only begun to discover the ‘device equations’ that describe the input output relations of channels. We seek equations that tell us how the potential and concentrations far from channels control their function. The electric potential outside the channels, in baths and on electrodes, can be measured but the potential inside channels is not known. The electric potential in proteins can only be calculated from the equations defining the electric field. These equations depend on all charge and so must include all the charges present. The electric field is produced by charges, but it also exerts force on charges and changes their location in an important way, called shielding or screening. Thus, the value of the electric field changes significantly with experimental conditions.

Shielding plays a very important role in determining the electrical properties of systems with mobile charge, in many cases dominating those properties.[7; 16; 23] Proteins are like that. All the charge in proteins—permanent and mobile and induced (i.e., polarization charge created by the electric field)—creates potential, but potential fields move only some charge. The moved charge screens permanent charges and has a dramatic effect on the net effect of those permanent charges. Indeed, bulk ionic solutions are in some sense ‘perfectly screened’ [16; 23]. In a system like a channel protein containing both permanent

and mobile charge, the electric potential can be maintained constant, as conditions and shielding vary, only if the inside of the channel protein is connected to a source of charge. Channels (and most proteins) do not have such sources.

Proteins are usually described in the tradition of chemical kinetics., The binding and transport properties of proteins—as well as the chemical reactions in which proteins participate—are traditionally described by rate constants independent of concentration, ionic strength, and other conditions.[1; 10; 17; 18] The dependence of these rate constants on the structure of the protein is not specified: the rate constants describe binding as a chemical reaction along a reaction coordinate over a potential (energy) barrier, but the structural meaning and physical basis of the potential energy barrier is rarely specified in traditional models. Rate models describe current through open channels as the movement of ions over a potential barrier.[17; 18] Barriers are assumed constant and are not calculated from the structure of proteins and their distribution of charge: the size and shape of the barrier and the distribution of charge are not mutually consistent with Maxwell's equations, e.g., Poisson's equation. Thus, the barriers (and rate constants) in traditional rate models of proteins are immune from the effects of screening/shielding that determine many of the physical properties of systems of mobile charge.[7; 16; 23]

Misrepresenting potential profiles as constants, independent of conditions, is particularly serious, because it implies the injection of charge and energy into the system just at its most sensitive place, at the peak of potential barriers, where function is controlled. Models with this defect are unlikely to provide much insight into function. This failure of the chemical tradition to deal with the fundamental properties of the electric field is a significant source of the difficulties scientists have in calculating drug binding and protein function and folding, in my opinion, although not necessarily in the opinion of others. If my view is correct, no amount of computer resources will resolve these problems until the electric field is dealt with in a calibrated way, i.e., in a way shown to give the macroscopic results measured in simple systems. [9; 20; 28]

In a physical analysis, current flow through open channels must be computed by a combination of Poisson and transport equations so that the electric field that moves charge—and is in itself changed when charge moves—can be computed self-consistently. The equations must be solved together to predict fields, much as current flow is analyzed in transistors in computational electronics, because transport changes charge, charge changes potential, and potential changes transport.[28] The central lesson of computational electronics is simple: ***whenever the configuration of charge changes, the electric field must be recomputed*** including boundaries, even if that requires re-computation on the time scale of femto to picoseconds, even if that precludes the use of periodic boundary conditions.[9; 20] The potential landscape of a protein or channel indeed determines the forces on ions and substrates—and determines protein function, drug binding, and so on—

but the potential landscape must be calculated from all the charges present, including at the boundaries, and must be recalculated every time charge moves, as is done in computational electronics, with atomic resolution in space (Å) and time (femtoseconds).

The implications of this statement for statistical physics are profound, as they are for biophysics, both at equilibrium and in general. Langevin equations of Brownian motion always require Poisson's equation in this view if particles have significant charge anywhere on their surface.[3] Transport changes charge densities, charge changes potential, and potential changes transport, whether we work at the macroscopic or atomic scale of resolution, and so the equations of transport and electric field must be solved together, and they must be solved including boundary conditions, and are hard to treat with periodic boundary conditions, if they are different at different locations. Einstein's and Langevin's equation (in which ink particles move randomly in an electric field, even if the field is zero and therefore not shown explicitly) must always be coupled to a Poisson equation so the fluctuating field can be computed from the charges and their fluctuating position.

If the Brownian motion is calculated in a mean electric field, as Einstein and Langevin did, the calculation does not describe the actual random motion of charged particles, which occurs in fluctuating fields. Estimates of variance are obviously wrong in such calculations. Estimates of means may also be wrong because Langevin equations coupled to Poisson are very nonlinear processes. The mean value of such processes can depend on the fluctuations of the underlying noise. Indeed, qualitative properties of coupled Langevin-Poisson processes are likely to be quite different from the qualitative properties of the mean field Langevin systems studied by Einstein and Langevin. Ions of one type—in mixed solutions containing other types of ions—may move against their own gradient of electrochemical potential if the electric field driving their migration is dominated by other ions, for example, those present at much larger number densities.

The Einstein/Langevin treatment of diffusion also does not allow flow, if it is used in the high friction Smoluchowski limit, with a Maxwellian distribution of velocities. The Maxwellian is symmetrical and thus has identically zero mean velocity and flow. Spatially nonuniform boundary conditions (that produce nonzero mean velocity and flow) can be combined with the high friction limit only if velocity is preserved as a variable: asymptotic analysis and singular perturbation theory are needed for this purpose. Derivation of device equations with distinct inputs and outputs requires careful mathematics in the high friction limit.

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[3] The ink particles that Brown and Perrin studied and Einstein and Langevin described are charged colloids. Note that a water molecule is highly charged locally even though its global charge is zero and the field created by this charge extends many diameters, well beyond the repeat distance used in most simulations of water or proteins that employ periodic boundary conditions.

Transistors and semiconductors are analyzed by computational electronics, one of the most successful of the computational sciences. Computational electronics calculates the properties of transistors with considerable accuracy (say 1%) with essentially no adjustable parameters, a striking accomplishment in multi-scale analysis. Computational electronics starts with the atomic properties of matter and successfully calculates the macroscopic currents by which transistors function on long time scales. This computational success over an enormous range of scales is one of the main reasons electronic and semiconductor technology has been so successful. This multiscale success is what is sought in computations of ionic solutions and proteins but—I think it fair to say—is not yet in hand.

The treatment of the electric field and electrodiffusion in computational electronics is strikingly different from their treatment in ionic solutions and proteins and one must suspect that the difference has something to do with the relative success of the fields in computing useful macroscopic properties. The focus in computational electronics is on the electric field and the flow of current. It is taken for granted that the field and flow must be computed 'to infinity'. The field computation must include the boundaries where power is supplied by different voltages at different places. The calculations must include spatially inhomogeneous boundary conditions. Periodic boundary conditions do not easily accommodate such conditions, particularly 'at infinity' and so are (essentially) never used in computational electronics. [9; 20; 28] In computational electronics, care is taken to describe the electric field over all space and time, even if some atomic detail must be sacrificed. In computational chemistry and biology care is taken to describe atomic detail, even if the long range properties of concentration and electric field must be sacrificed.

Computational electronics computes the electric field in this way because understanding devices requires such computation. It was apparent from the beginning that any model of a transistor must include the value of the voltage applied to its leads. It is obvious to an engineer that devices cannot execute their device equations without power supplies and so devices can only be understood if their analysis includes different boundary potentials at different locations. After all, anyone who has built a device containing FETs knows the importance of the potential applied to transistor terminals. A FET can be many different devices depending on the voltages applied to it, and the engineer chooses the device he wishes by adjusting the values of the power supply voltages. It is obvious that these voltages must be included in theory, if the different devices are to be defined, let alone understood. What is not obvious, but is in fact true, is that even low resolution equations of computational electronics describe transistors quite well, with a single set of parameters, if those equations include spatially inhomogeneous boundary conditions, power supplies, and flow. The key is to understand the electric field including, of course, the sources that produce it.

The nonequilibrium properties of the device do not have to be described in much detail in most device equations because flux usually arises from the spatial nonuniformity of boundary conditions—not from complex properties of the differential operators. The differential operators are the same whether the device is turned off, at equilibrium, with spatially uniform boundary conditions, or in operation, with spatially nonuniform boundary conditions. The differential operators describing the physical model of devices are the same whether the power supply is present or not. The essential properties of devices are seen even in low resolution models, in which the velocities fall into a simple Maxwellian distribution displaced by a constant, which is the mean velocity, the flux in different units, in fact.

Computational electronics had the insight from its very beginning that current flow in semiconductor solids—whatever its physical mechanism—should be described in the tradition of device analysis. Computational electronics described current flow in semiconductor solids as the consequence of the mean electric field applied to terminals, just as current flow was described in vacuum tubes.[26, particularly p. 65, 11, and 144)] I suspect this approach seemed so natural to the founders of semi-electronics that it was nearly unconscious, but whatever the historical reason, this insight is remarkable and is not used in computational chemistry or biology. In computational chemistry and biology, current flow and electric fields are sometimes not computed at all, and certainly do not have a central place.

The novelty and significance of the treatment of semiconductor devices should not be forgotten, just because it is now usual, taught to millions of students each year. Everything in our semiconductor technology depends on this insight that the electric field dominates and must be computed and understood in general, from transistor terminal to terminal, including the spatially nonuniform potentials and current flow that make transistors work.

This approach to the analysis of electrodiffusion grew naturally from the analysis of vacuum tubes (or valves at they were more aptly called in the mother tongue of English engineers). Viewed naively, electrons in a vacuum and (quasi-particle) electrons in a solid semiconductor do not seem similar. It is certainly not clear that they should follow similar transport laws. Nonetheless, electrons and semi-electrons are similar, and follow similar laws, and so transistors could be built using the experience of vacuum tube design, starting first with the description of the mean electric field created by the steady potentials applied by power supplies.

Computational electronics says it is the field that matters, more than anything else. Devices with similar electric fields behave in (qualitatively) similar ways, *no matter how the fields were created*, no matter what carries the current (within reason). Mimic the electric fields of a triode, and you will have an amplifier and

switch, no matter where the fields are created, if anything flows in those fields in a reasonable way.

Mimic the fields of a vacuum or semiconductor diode in a protein and you will have a rectifying channel. That is an unmistakable prediction to a computational engineer.[4] But the analyses of electrodiffusion must include flow and spatially nonuniform boundary potentials, as well as Langevin/Poisson equations, if they are to describe devices, as well as electrodiffusion. Only in the last decade or so have channologists realized [3; 8; 19; 22] that the principles and tools of computational electronics can be used to understand the rectification of current flow through open channels studied in detail since the time of Hodgkin and Huxley, the 1950s, and glimpsed much earlier, nearly one hundred years ago.

This then is the proper and useful analogy between transistors and channels. *Transistors alive are the open channels of cell membranes*; once open, channels and transistors both follow the same laws of electrodiffusion.[12; 13]

Of course, the analogy between semi-electron and hole flow and ionic current is not complete. The electrical property of rectification is not the only or the most important property of ions in solution or in open channels. Proteins and ions have chemical properties that quasi-particles lack; and computational chemistry must join computational electronics if the resulting chemical properties of channels are to be understood.

The chemical properties of ion channels and proteins are of great interest both for historical and scientific reasons. Historically, the great majority of workers in molecular biology have been trained in chemistry, not in physics or electronics; only a few of us were lucky enough to be trained both by molecular biologists and channologists. Thus, the chemical properties of proteins are described on nearly every page of any textbook of biochemistry or molecular biology, but even the most elementary discussion of electricity is not found there. (Search for a dielectric constant, or any equation at all, in textbooks of biochemistry, if you wish to check this sweeping statement.)

Biologists study the chemical properties of channels and proteins because they are so striking. Channels and proteins, for example, select between different chemicals (e.g., drugs) with great specificity; channels respond selectively to ions that differ only a little in diameter or charge, with otherwise identical chemical properties.[1; 2; 18] The chemical selectivity arising from channels has long been considered one of the special characteristics of life.

It was natural to believe, as I did for decades, that the special chemical selectivity of channels arose from special chemistry. I thought that selectivity

[4] But it remains the task of the channologists to check that prediction and find its limitations. Hence, this paper and my work for many years. [12, 13]

came from ‘chemical interactions’ between ions and special binding sites on proteins, designed by evolution to bind ions specifically.[10] It seemed natural to describe chemical interactions in the tradition of chemical kinetics, as chemical reactions, involving delocalization of electrons in the outer orbits of the atoms of the protein, requiring the solution of Schrödinger’s equation one way or another.[17] But these ideas did not work very well. No one was able to design and build selective channels using this chemical tradition.

Chemical specificity can arise another way. Chemical specificity can arise from physical factors, not involving delocalization of outer electrons, not involving binding sites with specific atomic geometry. In highly concentrated solutions, for example, the free energy per mole of Na^+ and K^+ are quite different, even though the ions differ only in diameter. Modern physical chemistry shows that the energy necessary to crowd spheres together in large concentrations depends a great deal on the diameter and charge of the spheres.[4; 14] The main chemical property of such solutions (the free energy per mole usually called ‘the activity’) is determined by the diameter and charge of these spheres, much more than by anything else. The special chemical properties of water, the hydration shells around ions, and other chemical phenomena, are not involved, to a first order, or even second order, except as they determine the dielectric properties of the concentrated salt solution. If the number density, diameter, and dielectric properties of the salt solution are known, the free energy per mole can be calculated accurately without regard to other chemical properties of the solution.

In this view, concentrated salt solutions are viewed as compressible plasmas; the (volume of the) solution itself is incompressible, but (the number densities of) its components are not. The number densities of components of the solution vary a great deal and that variation determines many of the properties of the solution, even though the gravimetric density of the solution is nearly invariant.

Computational chemistry has given us a computational theory of selectivity in concentrated salt solutions. The question is whether this theory is relevant to ions in channels. The answer is that the theory is relevant if ions in channel proteins behave much as concentrated salt solutions do in computational chemistry.

Ions in a channel protein are highly concentrated because proteins in general—and active sites and channel pores in particular—‘bristle with charge’.[30] The large density of permanent charge on the walls of ion channels, and on the active sites of proteins, guarantees a large concentration of ions nearby: deviations from electric neutrality must be small, even in the tiny structures of proteins and channels because proteins can only tolerate small voltages.

The ions in and near channels are mobile even though they must stay close to the permanent charge of the protein; these ions conduct substantial current,

much as holes and semi-electrons conduct current in transistors even though they are bound to the underlying matrix of crystalline charge (and doping). But the free energy of ions is determined by their size, as well as their charge—an effect absent in semiconductors—because holes and semi-electrons have no size and thus no chemical properties.

The number densities of ions in channels are enormous. The L-type calcium channel, which controls the contraction of the heart, and is the target of the 'calcium channel blockers' used by many of our physicians, has four permanent negative charges in its active site. The four mobile positive charges nearby have a number density of some 30 molar, $\sim 2 \times 10^{22}$ cm^{-3}. The charges are very crowded indeed (water is ~ 55 molar). When occupied by Na^+ (which has one charge), the pore contains 4 ions, a number equal to the number of permanent charges on the protein. When occupied by Ca^{++} (which has two charges), the pore contains 2 ions, half that number. Ca^{++} is much less crowded at some 15 molar than Na^+ at 30 molar; less free energy is needed to crowd Ca^{++} ions into an L-type calcium channel than Na^+. Ca^{++} ions also shield permanent charge more effectively than Na^+: they bring two charges to a location where Na^+ brings one. (Na^+ and Ca^{++} happen to have nearly the same diameter). The channel binds calcium selectively over Na^+ for both these reasons.

I conclude that physical effects, calculated with physical theories and simulations, are enough to understand the biological property of selectivity of L type calcium channels.[6; 11; 15; 24; 25]

The question then is to find the role of the protein among these physical effects: what is the role of the channel protein in this combination of computational chemistry and electronics? After all, without the protein there is little selectivity. Surely the properties of the protein determine the selectivity of the channel. Evolution acts only to make proteins, evolution needs a selective channel to allow the heart to contract (for example), so the protein must control selectivity. But how does the protein control selectivity, if the forces of selectivity come from the physics of crowded charge?

In our view, [6; 11; 15; 24; 25] the answer is that the structure (and charge distribution) of the protein guarantees the existence of crowded charge; physics controls the energy of those charges. The channel protein determines selectivity in much the same way that an engine block determines the properties of an automobile motor. In one sense, the engine block does little. Its job is to hold things in place and not to move. In another sense, the engine block does everything. If the engine block warps even a tiny amount ($\sim 10^{-5}$), pistons seize up, and the motor dies.

In this view of selectivity, due to Wolfgang Nonner, more than anyone else, the channel protein provides the structure for selectivity, just as the engine block

provides the structure for the automobile motor. The channel protein provides the permanent charge and dielectric charge, in the right place; it provides mechanical strength. The channel protein controls selectivity much as an engine block controls combustion. Both provide the arena in which physics and chemistry provide the energy that drives the machine. In this view, the protein should be viewed as a solid machine built at considerable cost, which stores free energy, and is *not* in a configuration of minimum free energy, any more than an engine block or amplifier is itself in a configuration of minimum free energy. A channel protein in this view is a device, a simple kind of machine, not a complex chemical system at or near equilibrium.

In this view, no particular arrangement of atoms is needed to produce selectivity, although certain specific structural properties are absolutely essential: for example, the calcium channel protein must keep its four carboxylate permanent charges in a narrow region to force the crowding of ions, i.e., to create a binding site. The channel protein does not delocalize electrons to provide a binding site. Rather, it produces a binding site by determining the permanent charge and volume of its pore, much as an automobile engine controls piston function by determining the diameter and strength of the cylinders in which pistons slide back and forth.

This physical view of selectivity is very different from that of structural biology, where biological function (and selectivity) is treated as the direct consequence of the location of atoms seen in x-ray crystallography of crystals of proteins. Early in my career, I was prejudiced against such a description, because it considers the structure as the cause of physical forces, ignoring the fact that the structure is not rigid, but is the result of (non-covalent) physical forces (constrained of course by the covalent bonds of the primary structure of the protein). I then believed I could not understand what a structure did until I understood the physics of its non-covalent forces and I felt I could not understand that physics until I could write and solve the relevant equations.

These early prejudices of mine may or may not have been right, but I certainly felt them long before I learned the relevant physics, the physics of crowded charge. The physics of crowded charge is now known and described by equations and simulations. We know now how to compute the properties of crowded charge by joining computational electronics and computational chemistry. Now, there is a better reason than my prejudice to question the role of delocalization of outer electron orbitals. The reason chemical effects (which certainly occur) are not important is that orbital delocalization involves little energy (in the case of the L-type calcium channel) compared to the energies of the electric field and crowded charge.

In the physical view, selectivity is mostly a physical consequence of the small size and large charge density of active sites of channels and proteins. Of

course, selectivity in the binding of asymmetrical molecules (like drugs) will involve the static shape of the drug molecules and their permanent electric fields, and selectivity will probably depend on the induced charge (i.e., field dependent polarization) of their electrons. Selectivity is likely in some cases to involve further delocalization of electrons, as well, as may occur in hydrogen bonds and other more covalent chemical bonds.

Nonetheless, one should start with the working hypothesis that selectivity comes from the electric field and crowded charge, before invoking chemical effects that are hard to measure or calculate in homogeneous condensed phases without protein. One should be sure to calculate the free energy of crowded charges accurately before one invokes other effects, particularly effects that are hard to measure or calculate precisely. Starting in this manner, I think one can do 'physics as usual' on important biological processes. One can make a specific model and refine and improve it by adding more effects, more physics, and quantum chemistry, step by step, as needed. Unfortunately, ***calibrated*** calculations of these other effects—on the biological time scale, in realistic ionic conditions, including trace μM concentrations of controlling modulators and ions—have not yet played a large role in simulations of drug binding or protein folding, for that matter.

The traditional biological approach, using verbal models, or reaction schemes from gas phase chemical kinetics, seems less likely to succeed, however poetic the words or complex the schemes. Physics as usual is more likely to produce a social and scientific process that converges towards understanding how channels work. The stakes are high, I think: understanding channels in the physical tradition will soon produce a biotechnology as important as the electrotechnology of semiconductors, if physicists are given a chance to do 'their thing'. After all, physicists only took decades to turn transistors into the foundation of 21st century (economic) life.

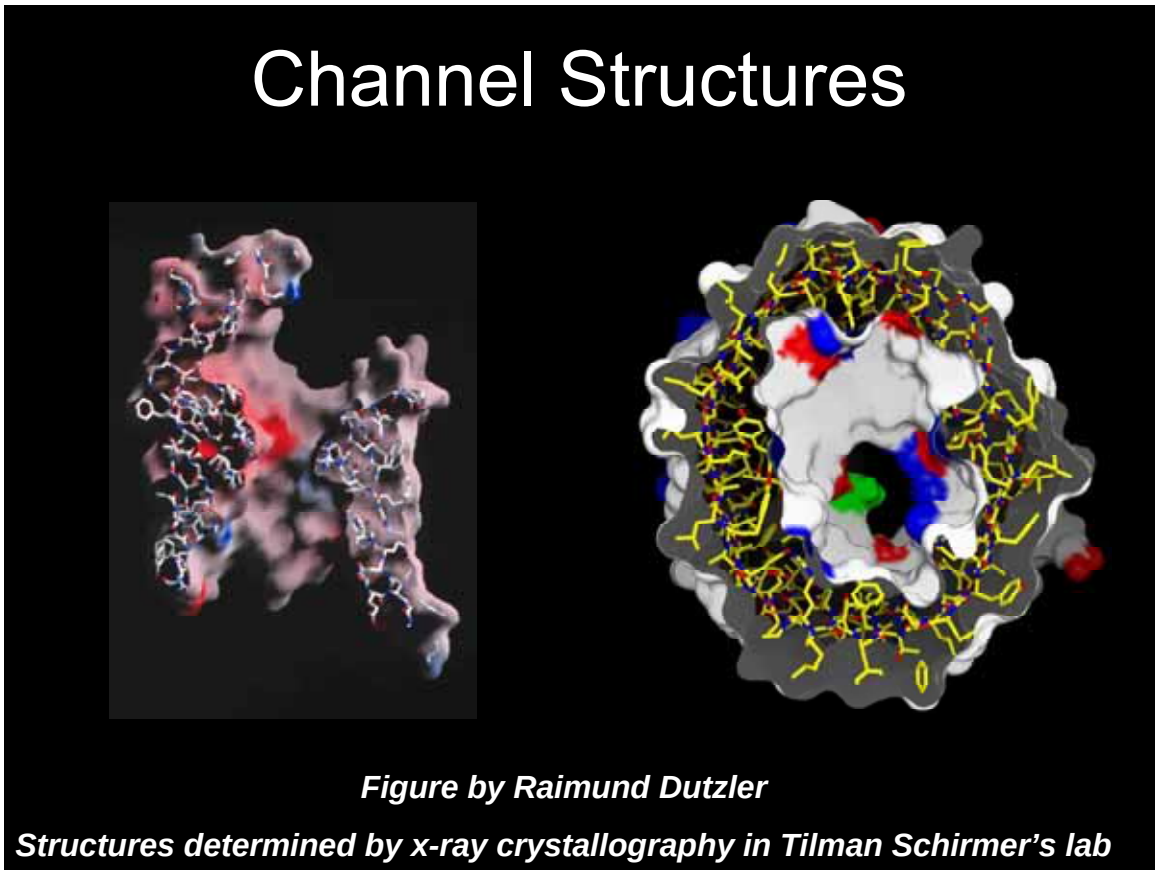
We have come a long path in considering transistors alive. Transistors have an important analog in life, ion channels. Ion channels control much of biological function, as transistors control technology. The physics of control of transistors and channels are quite different, while other properties of ion channels and transistors are quite similar. Electrodiffusion controls the motion of ions in channels, once they are open, much as it controls the motion of the quasi-particles, holes and semi-electrons, in semiconductors. But holes and electrons are not ions. Ions have size and chemical properties that holes and semi-electrons lack and so computational chemistry must be combined with computational electronics to understand the chemical selectivity of ions crowded into channels by the electric field. Simple models of crowded charge do surprisingly well as models of selectivity in highly selective biological channels. The combination of computational chemistry and computational physics should lead to a

biotechnology of channels as important to industry—and more important to medicine and our daily life—as the electro-technology of semiconductors.

Captions

Fig. 1. A chemist's view of ionic channels. The vertices of the line segments represent atoms, whose locations have been determined by diffraction analysis of x-ray scattering from crystals of the protein. The surfaces are more or less surfaces of constant electrical potential, in a qualitative computation. Two different channels are shown, at right angles to each other. The hole down the middle is filled with a mixture of water molecules and ions (not shown), which conduct electrical current. The ions are at very high number density.

Fig. 2. A textbook author's view of channels in a biological cell. The membrane of the cell is an insulating structure in which channel proteins are embedded that allow and control the movement of charged particles, spherical ions, mostly Na^+, K^+, Ca^{++}, and Cl^-. Open channels conduct current of charged particles following laws of electrodiffusion rather like the laws of electrodiffusion of quasiparticles in semiconductors. Channels control an enormous range of biological channel by opening and closing: many types of channels are present in membranes, most of which are closed at any moment. For both these reasons, channels can be said to be life's transistors.



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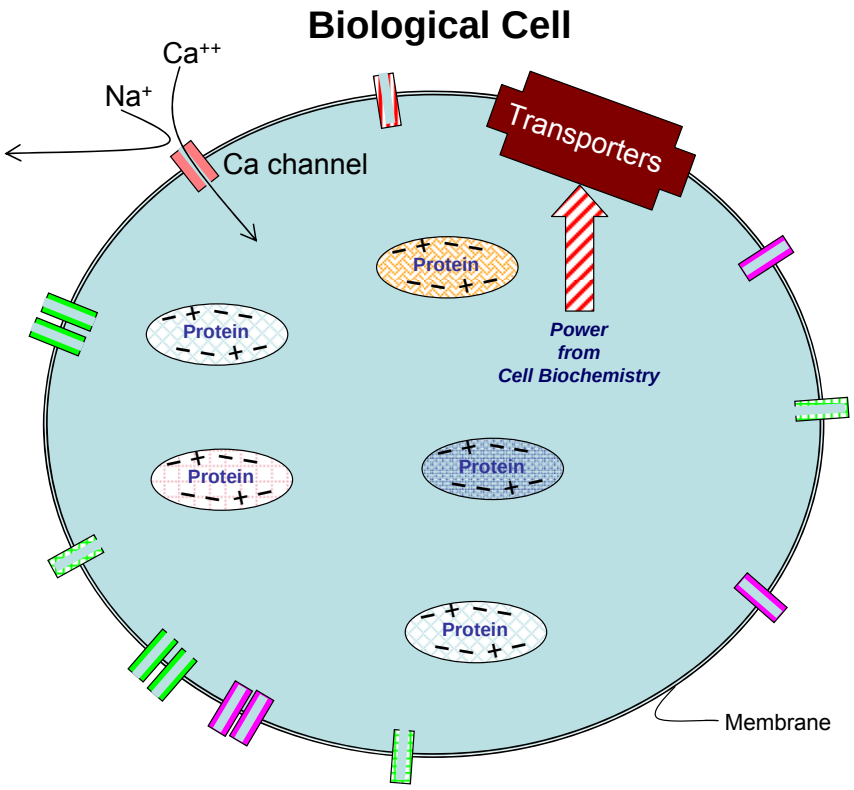

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