Journal of Computational Electronics 2: 245–249, 2003


# Ion Channels as Devices

BOB EISENBERG
*Department of Molecular Biophysics, Rush Medical College, 1653 West Congress Parkway, Chicago IL 60612, USA*
beisenbe@rush.edu

**Abstract.** Ion channels are proteins with a hole down their middle that control an enormous range of biological function. Channels are devices in the engineering sense of the word and engineering analysis helps understand their function. In particular, the current through channels is driven by the power supply of concentration gradient and electrical potential maintained by across membranes by cell metabolism. The current is controlled by the physics of ion permeation in a narrow charged tube. The wall of the tube contains a few fixed charges; the tube is less than 1 nm in diameter. The density of charge (mobile or fixed) in the tube is enormous, ∼10 molar. (Liquid water is ∼55 molar.) Movement of ions through this tube can be well described as the movement of charged spheres according to the Poisson-Drift-Diffusion equations of computational electronics. Selfconsistent computation of the electric field is a necessity. The chemical specificity of channels seems to arise from the crowding of charge in their narrow tunnel. A purely physical description of the energetics of crowded spheres is enough to explain the complex patterns of selectivity found in several types of channels.

**Keywords:** ionic channels, engineering analysis, selfconsistent, Poisson-Drift-Diffusion, crowded charge

## 1. Introduction: Ion Channels

Ion channels are proteins with holes down their middle of enormous biological importance [1–3] that control the flow of current and molecules in and out of cells. They are appealing objects for investigation because thousands of scientists study their properties every day, often one protein molecule at a time, using the powerful methods of molecular biology and electrical engineering. They are appealing objects for *physical* investigation because channels use simple physics and structures to perform their wide range of important biological tasks.

It is natural to think of ion channels as electrical objects, as it was to think of biological membranes as electrical objects [4,5], because current is the usual property measured from channels, or membranes, for that matter, but there is more to it than that. Tissues, cells, and membranes have electrical properties of great importance, but it is not clear how precisely (and usefully) they can be described as purely electrical objects: metabolic and chemical properties of tissues and cells are important.

Ion channels, on the other hand, are devices. They fulfill the definition of device used in engineering. Ion channels have well defined terminals, inputs and outputs. They use (fairly) complex internal structure and physics (on an atomic scale) to create a simple (and useful) input/output relation (on a microsecond scale). Ion channels use external energy from a power supply to maintain the I/O relation despite the variable demands of a changing environment. I will argue that viewing an ion channel as a device is more than an amusing analogy. Rather, *viewing channels as devices is the key to understanding how they work.*

The idea of a device helps distinguish engineers from physicists, chemists, and mathematicians. Physicists and chemists often consider general properties of systems with simple boundary conditions imposed on a domain of simple shape. Mathematicians often study 'operators' (e.g., differential equations) in an infinite domain or with simple boundary

conditions, emphasizing the generality of their resulting work.

## 2. Engineering Analysis of Ion Channels

Physiological systems have always been analyzed in the engineering spirit, even before engineering was a separate discipline ('physiology' has been a central discipline of biology for centuries, even millennia). The goals of physiology seem to be identical to the goals of engineering: learn what a system does, learn how the system uses anatomical structure and physical laws to do it, and make the system do it better. The distinction between engineering and physics is not always apparent to non-engineers, so we take a little detour—which many readers may wish to overlook—to explore that topic.

## 3. Engineering is not Physics

Engineers interested in devices study quite different things from physical scientists because engineering systems are built to be controlled by their boundary conditions. The properties (and mathematics) of such systems is quite different from those of isolated systems using the same physics or chemistry.

Engineers usually focus their attention on the inputs and outputs of their device and on the approximate relations between input and output. They pay less attention to the details of the internal properties of the device, whether those are the structural properties (e.g., circuit design or anatomy) or the details of the underlying physics. An amplifier amplifies in much the same way whether it is made of vacuum tubes, germanium, or fluidics, for that matter.

Engineering is about making devices for useful purposes. Engineers analyze and construct their systems using as little detail as necessary. Of course, in some parts of their devices enormous detail must be known; but in other parts very little detail is needed, macroscopic conservation laws and constitutive equations are enough, even though these laws are so general (and thus vague) that one can hardly imagine systems that do not follow them.

Usually, engineers ignore the overall energy balance of their device (i.e., including power supply) although there are important exceptions (e.g., designing devices for low fuel consumption). The thermodynamic balancing which lies at the historical heart of traditional thermodynamics and statistical mechanics is not of central concern.

## 4. Ion Channels

How do we implement these lofty abstractions when working on ion channels? We seek to study what channels do. We use the anatomical complexity and thermodynamic properties only to understand the function, i.e., the device equation of channels: we try to use as little detail as needed to understand how channels work.

At first, this task seems hopeless. Channel functions are too numerous and diverse to summarize in a single equation, of course. Channel proteins are a substantial fraction of all the proteins in the body, particularly if you include their close cousins transporter proteins. Channel proteins sense mechanical forces; they sense voltage; they respond specifically to an enormous range of chemicals. Channels are used to control a substantial fraction of the functions of life. Any attempt to summarize all this behavior in a single equation seems hopeless and bewildering, if it concentrates on the diversity of channel function.

The signals that provide the control are remarkably diverse, but the output signal is always the same, namely the current through the channel, or a simple function of the current, e.g., its integral. Thus a single device equation describing the current through a channel is a reasonable goal, albeit one which is a reach well outside our present day grasp.

In the engineering spirit we concentrate our attention on the simplicity and not the diversity and see how well we can understand the output of channels, the current flow.

Current through the channel is determined by the properties of the channel, once it is open, and the properties of the opening process. The channel currents studied by biologists are samples of a random telegraph process, switching from closed to open, creating a rectangular waveform of current. Once open, the channel has a fixed structure, on the microsecond time scale of biological function. The current through the open channel is remarkably constant (in time, under one set of conditions) and is reproducible like a physical variable from day to day and lab to lab, protein to protein (as long as they are of the same type). The slightest change in channel structure (i.e., even 10 picometers) would produce a substantial change in current, because the structure of the protein is so highly charged and so

near the tiny pathway in which current flows. The open channel current does not show internal correlations. It does not vary with time. The channel structure does not change once the channel is open (on the biological time scale).

The opening process is quite different. The fraction of time the channel is open is different from condition to condition and the variable that controls that time is different from channel type to channel type. The thousands of biologists who study the hundreds of channel types every day try to describe, control, and manipulate this opening process (for the most part) [2,3]. Here we avoid the diversity and complexities of the opening process and concentrate on the properties of the channel, once open, which allow engineering analysis in the usual tradition.

The current through the open channel is determined by the driving forces (i.e., power supply) acting on the channel and by the structure of the channel itself. The driving forces are the power supply and the structure has the role of the doping profile and geometry of the channel of a Field Effect Transistor (FET). Traditional biophysical experiments report the current carried through the channel by a particular type of ion—remember electrons do not carry current through protein channels. The current is studied with different gradients of concentration and potential and different types of ions much as an engineer would study the current voltage (IV) relations of an unknown device.

Much more can be done, however, than simply measure IV relations. Molecular biologists have taught us how to access the blueprint of the channel protein—its genetic code, e.g., DNA, that determines its sequence of amino acids—and how to manipulate it. With these methods, we can vary the fixed charge profile of the channel protein more or less as we wish, albeit with hard work. It is harder to know the three dimensional structure of the channel protein, i.e., the precise arrangement of atoms and charges, but in favorable cases that is known, and wonderful effort is being spent to increase the number of favorable cases, particularly in Rod MacKinnon's lab [6–11].

The goal then is to understand, manipulate and predict how much current flows through a channel, given the concentration and potential gradient across the channel and the distribution of fixed charge in the channel. The goal is to discover the device equation that governs the movement of ions through the channel.

## 5. PNP: Poisson Nernst Planck Theory

The drift diffusion equations of computational electronics, called *PNP* in biophysics, do surprisingly well in predicting the current through ion channels, as many authors have shown by now [12–21], even while showing the limitations of such low resolution analysis evident to its first users in biology [22–26]. The channel protein is represented as a doping profile specific to the particular type of channel. The concentration and electrical potential gradient between the baths supplies the power to drive the current. The IV relations can be computed in some detail in a variety of channel types as long as only one type of ion—with one diameter, charge, and diffusion coefficient—carries the current. When the type of ions is varied, more chemical detail needs to be introduced to describe the effects of the diameter and charge density of the ion, as well (perhaps) as the properties of its outer shells of electrons (i.e., its 'chemical' properties).

## 6. Crowded Charge

The question is how to introduce chemical detail? Here, the engineering approach is most helpful. Rather than trying to deal with atomic detail of ions and protein on the femtosecond 10 pm length scale of ionic motion, we try analysis using as little atomic detail as needed to describe the properties of concentrated ionic solutions. In particular, we assume that *all* the chemical properties of ions arise from their different diameter and charge (and diffusion coefficient). We ignore (in this initial working hypothesis) specific chemical properties produced by more complex interactions of electron orbitals.

In the last decades physical chemists have shown that the free energy per mole (i.e., the 'activity' and its non-dimensional measure the activity coefficient) can be calculated if the ionic solution is treated as a compressible plasma of spherical charges moving in a background dielectric [27–32]. This treatment is at first confusing, for those with a background in traditional chemistry, because the density of the overall solution is (nearly) constant although the density of ions is very variable. What is particularly surprising is that the water molecules that make up the dielectric do not have to be treated in atomic detail; it is enough to describe them as a uniform dielectric with the dielectric constant of the ionic solution (not that of pure water). More chemical detail (e.g., details of hydration shells or hydrogen bonding) is not needed.

This treatment successfully describes the main properties of selectivity in the three types of channels studied to date in some detail [33–36] and it seems to work as well for the K channel of considerable interest [37].

Each channel type uses the physics of crowded charge with a different twist to produce the device properties needed for biological function.

The calcium channel seems the simplest. For our purposes, the $Ca^{++}$ channel is simply 4 glutamate sidechains that put 8 half charged spheres into the pore of the channel. These spheres are imagined to interact with the ions moving through the channel as they would in a bulk solution, but they are confined to one phase. The glutamates are tethered, unable to move into the bulk solution. They contribute (negative) charge, a great deal of charge in fact; they exclude volume, but (at least in this model) they do not interact in any chemically specific way with the ions in the channel. Selectivity arises between ions because the ions have different diameters and charges. In particular, the L-type $Ca^{++}$ channel distinguishes $Ca^{++}$ and $Na^{+}$ because the channel contains different densities of these ions. When only $Ca^{++}$ is present, two $Ca^{++}$ are in the channel (to balance the 4 negative charges of the glutamate); when only $Na^{+}$ is present, *four* $Na^{+}$ are in the channel. The (free) energy needed to crowd the extra two spheres into the channel is enough to account for some 60% of the selectivity of the channel; the better shielding provided by $Ca^{++}$ (which brings two charges to the edge of the glutamic oxygens where $Na^{+}$ brings one charge) accounts for about 35% of the selectivity [33].

Remarkably, the specific arrangement of atoms (which shows up as an entropy term in this model) contributes a very small amount to the selectivity, which came as a considerable surprise to those of us raised in the chemical tradition of protein crystallography, although perhaps it should not have been a surprise, if we remember that entropic terms in ionic solutions are often about 1 $k_B T$ in size [33].

The role of the channel protein in this model is specific but simple. It does *not* contribute specific chemical energy to the system; that is to say, no orbital delocalization or other classical chemical effects are involved. Rather, the channel protein supplies the charge, mechanical strength, and dielectric environment necessary to allow a crowded charge model to work. The protein forces the ions so close together that their crowding provides the energy difference of selectivity.

The $Na^{+}$ channel works in a different way. It has only one fixed charge and so when $Ca^{++}$ is present, it is unable to balance the fixed charge within the channel itself. Rather, ions just outside the channel must be involved. Thus, the electric field outside the channel must be included in the analysis and the properties of the channel depend on the details of structure. Without knowledge of those details, one cannot go too far. Suffice it to say that present day work shows that crowded charge describes the main features of selectivity in the $Na^{+}$ channel [35] even without knowledge of the details of the channel structure.

The $Cl^{-}$ channel seems to work with a different twist [34]. It embeds amino acids in the wall of the channel that have unfavorable ('hydrophobic') interactions with ionic solutions. If a small energetic penalty is included in the crowded charge model, the contents of the channel change in a striking way: the density is less than that in the bath (i.e., the bath is crowded, or the channel diluted, depending on how you wish to think of things). Furthermore, larger ions are favored over smaller ions by the channel, mostly because they have larger surfaces and thus larger hydrostatic force acting on them.

In this way, it seems possible to account for the main biological properties of several types of ion channels.

## 7. General Implications

What is perhaps most striking about this work is how little it says about the specific structure of the channel protein, how little it resembles the analysis growing from the magnificent structural details presented to us by structural biology. What is used in these models are certain specific measures of the protein, namely the location of charges, the volume of spaces, and the dielectric environment. What is not used in these models is the exact location of each atom.

The specific properties of the channel in these models come from well known physical forces described in the engineering tradition, with as little detail as needed to explain their biological consequences. The resulting properties of the channel fit well with experiments, particularly considering how little is in the model, but the properties are very different from those assumed in most biochemistry textbooks. The electrical potential contributes a dominating term to selectivity, although that term is absent in most biochemical analyses of selectivity or binding. The binding 'constant' defined in traditional analyses to be independent of concentration is an output of our model and is found to vary

enormously with concentration [33]. Thus, our engineering analysis heads in quite a different direction from traditional biochemical treatments of selectivity.

## 8. Conclusion

It may seem that a great deal is known from what is written above, but in fact only the main forces have been discovered, and perhaps not all of them. The analytical tools are barely adequate for the purposes we have used them and we need all the help we can get from physical scientists to refine our approach and include the detail clearly needed to describe more biological functions.

## Acknowledgments

This work has been supported by a series of grants from the NSF, NIH, and DARPA.

## References

1. B. Alberts *et al.*, *Essential Cell Biology*, 3rd edn. (New York: Garland, 1998), p. 630.
2. F.M. Ashcroft, *Ion Channels and Disease* (New York: Academic Press, 1999), p. 481.
3. B. Hille, *Ionic Channels of Excitable Membranes*, 3rd ed. (Sunderland: Sinauer Associates Inc., 2001), p. 1.
4. P. Lague, M.J. Zuckermann, and B. Roux, *Biophys J*, **81**(1), 276 (2001).
5. P. Lague, M.J. Zuckermann, and B. Roux, *Biophys J*, **79**(6), 2867 (2000).
6. R. MacKinnon, *Nature*, **416**(6878), 261 (2002).
7. Y. Jiang *et al.*, *Nature*, **423**(6935), 42 (2003).
8. Y. Jiang *et al.*, *Nature*, **423**(6935), 33 (2003).
9. V. Ruta *et al.*, *Nature*, **422**(6928), 180 (2003).
10. R. Dutzler *et al.*, *Nature*, **415**(6869), 287 (2002).
11. D.A. Doyle *et al.*, *Science*, **280**, 69 (1998).
12. S.-H. Chung *et al.*, *Biophysical Journal*, **75**, 793 (1998).
13. M.G. Kurnikova *et al.*, *Biophysical Journal*, **76**, 642 (1999).
14. B. Corry, S. Kuyucak, and S.-H. Chung, *Journal of General Physiology*, **114**(597–599) (1999).
15. S.H. Chung, T.W. Allen, and S. Kuyucak, *Biophys J*, **82**(2), 628 (2002).
16. S. Chung and S. Kuyucak, *Clin Exp Pharmacol Physiol.*, **28**, 89 (2001).
17. P. Graf *et al. Journal of Physical Chemistry B*, **104**, 12324 (2000).
18. W. Im and B. Roux, *J Mol Biol*, **322**(4), 851 (2002).
19. W. Im and B. Roux, *J Mol Biol*, **319**(5), 1177 (2002).
20. U. Hollerbach, *et al. Langmuir*, **16**, 5509 (2000).
21. U. Hollerbach, D.-P. Chen, and R.S. Eisenberg, *Journal of Computational Science*, **16**(4), 373 (2001).
22. D. Levitt, *Biophysical Journal*, **59**, 271 (1991).
23. D. Levitt, *Biophysical Journal*, **59**, 278 (1991).
24. D.P. Chen, V. Barcilon, and R.S. Eisenberg, *Biophys J*, **61**, 1372 (1992).
25. V. Barcilon, D.P. Chen, and R.S. Eisenberg, *SIAM J. Applied Math*, **52**, 1405 (1992).
26. R.S. Eisenberg, *J. Membrane Biol.*, **150**, 1 (1996).
27. J. Barthel, H. Krienke, and W. Kunz, *Physical Chemistry of Electrolyte Solutions: Modern Aspects* (New York: Springer, 1998).
28. S. Durand-Vidal, J.-P. Simonin, and P. Turq, *Electrolytes at Interfaces* (Boston: Kluwer, 2000).
29. J.-P. Simonin and L. Blum. *J Chem Soc, Faraday Transactions*, **92**, 1533 (1996).
30. J.-P. Simonin, O. Bernard, and L. Blum, *Journal of Physical Chemistry B*, **102**, 4411 (1998).
31. J.-P. Simonin, O. Bernard, and L. Blum, *Journal of Physical Chemistry B*, **103**, 699 (1999).
32. E. Waisman and J.L. Lebowitz, *Journal of Chemical Physics*, **56**, 3093 (1972).
33. W. Nonner, L. Catacuzzeno, and B. Eisenberg, *Biophysical Journal*, **79**, 1976 (2000).
34. D. Gillespie *et al.*, *Physical Chemistry Chemical Physics*, **4**, 4763 (2002).
35. D. Boda *et al.*, *Physical Chemistry Chemical Physics (PCCP)*, **4**, 5154 (2002).
36. T.A. van der Straaten, *et al.*, *J. Computational Electronics*, **1**, 335 (2002).
37. W. Nonner, L. Catacuzzeno, and B. Eisenberg, *Biophysical Journal*, **78**, A96 (2000).