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Ionic channels: natural nanotubes described by the drift diffusion equations

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Ionic channels are a large class of proteins with holes down their middle that control a wide range of cellular functions important in health and disease. Ionic channels can be analysed using a combination of the Poisson and drift diffusion equations familiar from computational electronics because their behavior is dominated by the electrical properties of their simple structure.

Key words: tonic channels, natural nanotubes, drift diffusion equations.

1. Generalities

Mesoscopic devices are relatively new to engineering but—in the form of proteins—they have performed a surprising fraction of the work of life for a very long time. Proteins are the preferred device of evolution, because evolution acts directly on genes, which can only make proteins. Genes are the one-dimensional blueprints for proteins. Genes specify the amino acids (peptides) which are linked like beads into a string to make a protein. Each bead has different fixed charge and (somewhat) different chemical properties. The polypeptide string becomes the functioning protein when it is folded into a three-dimensional structure that can act as a device.

Many proteins should be studied as devices. Most proteins function far from equilibrium and have well-defined inputs and outputs. Neither the structure nor the chemistry of most proteins make much sense if studied at equilibrium and thus isolated from function. Proteins at equilibrium are dead, about as interesting as a transistor with its terminals soldered together. Ionic channels are a class of proteins that have been studied as devices with some success.

2. Specifics: ion channels

Ionic channels control the flow of substances in and out of cells and, by controlling the flow of ions, they are produce nearly all the electrical activity of living systems. A substantial fraction of the drugs used by physicians act directly or indirectly on channels.

Channels come in many different types. Hundreds of types are now known [1], and thousands probably remain to be discovered. Each channel type has a specific role in a biological system and is (usually) well

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tuned for its task. Some types of channels are devices that respond to mechanical force ('touch'). Others respond to electrical potential (and thereby create the action potentials that are the digital signals of our nervous system). Many respond to specific chemicals. Channels are devices with specialized inputs that control specific outputs, the flow of particular types of ions across cell membranes. Channels are highly selective in how they respond and what they respond to.

Ionic channels function in two ways. They open and close in response to stimuli in a process called gating. Once open, they select between different species of ions. (Remember that in biology current is nearly always carried by ions: Na^+, K^+, Ca^{++}, and Cl^- are the chief carriers of current and each is controlled by different types of channel proteins. Indeed, there are tens to hundreds of types of K^+ channels, Ca^{++} channels and so forth.)

Unfortunately, not enough is yet known to analyse gating as a property of the device, because we do not know the structure or basic operating mechanism of a channel with typical gating. (The structure of only a few types of channels are known and as of today they do not include one with typical gating properties.) This situation is likely to change dramatically in the near future, but as of now, device analysis works best on the other main property of channels, its conduction of current. The structure of a channel does not change (in the mean) while it conducts current. An ionic channel is a hole in the wall that functions by electrodiffusion. If there is any protein that we should be able to analyse as a device, it is an ionic channel.

3. Traditional kinetic models

Open channels have until recently mostly been studied in the tradition of gas phase chemical kinetics [2] but the chemical tradition has not been successful in predicting their function [3], namely in predicting the current that flows through them under a range of conditions, because gases are so different from the condensed phases of liquids and proteins.

Simulations of the molecular dynamics of proteins and channels are appealing and popular [4, 5] but their high-resolution produces serious limitations in size and scope. Molecular dynamics done in the biological tradition has not included a definite concentration of ions, nor a potential across a channel, nor has it been able to compute current through the channel. Thus, it has little to say about the channel as a device despite the power with which it describes a channel as a structure. These limitations may be removed if the Monte Carlo methods of computational electronics are used to simulate channels.

Channel proteins can be described at lower resolution as a distribution of fixed charge using a mean field theory nearly identical to the drift diffusion theory of computation electronics. Extensive experimental evidence supports the theory [6]: it fits data from some seven types of channels measured over a wide range of voltages and concentrations. Its parameters are reasonable and can be checked against independent experimental evidence in favorable cases.

The one-dimensional theory we use to describe an open channel represents the structure of the channel's pore as a cylinder of variable cross-sectional area $A(x)(\mathrm{cm}^2)$ along the reaction path x (cm) with dielectric coefficient $\varepsilon(x)$ and a density of charge $\rho(x)(\mathrm{coul} \cong \mathrm{cm}^{-1})$. eN_A is the charge in 1 mole of elementary charges e, i.e. the charge in a Faraday. The charge $\rho(x)$ is as follows.

(1) The charge $eN_A \sum_k z_k C_k(x)$ of the ions (that can diffuse) in the channel, of species k of charge z_k, and mean concentration ; $C_k(x)$; typically $k = Na^+, K^+, Ca^{++}$, or Cl^Γ.

(2) The permanent charge of the protein $P(x)(\mathrm{mol} \cong \mathrm{cm}^{-1})$, which is a permanent part of the atoms of the channel protein (i.e. independent of the strength of the electric field at x) and does not depend on the concentration of ions, etc, and so is often called the fixed charge. $P(x)$ is really quite large because the channel is so small. One charge in a cylinder 6 Å diameter and 10 Å long is a concentration of $6 \times 10^{21}\ \mathrm{cm}^{-3} \approx 10$ M. Interestingly, mean field theories in electrochemistry are known to 'become exact for large electric fields, independent of the density of hard spheres' [7, p. 315], 'independent of

interactions of molecules in the fluid phase' [8, p. 972]. Also, some channels are thought to have as many as six charges in half that length or volume, giving ~100 M charge: NaCl in the selectivity filter of such channel may be more like table salt than sea water.

(3) The dielectric charge (i.e. the induced charge which is strictly proportional to the local electric field) is not included in $\rho(x)$ because it is described by $\varepsilon(x)$. It is generally small compared with the structural charge.

We make the usual mean field assumptions that the average charge $\rho(x)$ produces an average potential $\varphi(x)$ according to Poisson = s equation and that the mean electric field $-\nabla\varphi$ captures the properties of the fluctuating electric field which are important on the slow timescale of biology. These assumptions are hardly novel; indeed, it requires some extraordinary circumstances for them not to be true, in slow highly averaged systems

$$\varepsilon_0\left[\varepsilon(x)\frac{d^2\varphi}{dx^2}+\left(\frac{d\varepsilon(x)}{dx}+\varepsilon(x)\frac{d}{dx}[\ln A(x)]\right)\frac{d\varphi}{dx}\right]=-\rho(x)=-eN_A\left[P(x)+\sum_k z_k C_k(x)\right]. \quad (1)$$

The boundary conditions for the potential in the real world are set by the potentials in the baths surrounding the channel, i.e. the potential on the left is known and maintained at V_{appl} and that on the right is held at zero. The flow (i.e. flux J_k of ion k) through the channel is described in mean field theory by the diffusion equation, the Nernst–Planck equation (see [9, 10]; derived below) written in general form for channels of arbitrary variation in cross-sectional area $A(x)$ and diffusion coefficient $D(x)$

$$J_k=-D_k(x)A(x)\left(\frac{dC_k(x)}{dx}+\frac{C_k(x)}{RT}\frac{d}{dx}[z_kF\varphi(x)+\mu_k^0(x)]\right);$$
$$I=\sum_k I_k=\sum_k z_kFJ_k. \quad (2)$$

The flux J_k of ions is driven by the (gradient of) concentration and electrical potential, which together form the electrochemical potential $\mu_k = RT\log_e C_k(x) + z_kF\varphi(x)$. $D_k(x)$ is the diffusion coefficient of ion k in the channel's pore.

Specific chemical interactions are important when dealing with selectivity in mixtures of ions [11–13] and can be described by an excess chemical potential $\mu_k^0(x)$. In the one case considered in detail up to now, $\mu_k^0(x)$ can be computed from the volume of the ions and charged groups of the protein. Additional chemistry is not needed to explain the selectivity of the L-type Ca channels of cardiac muscle. This is surprising because the L-type Ca channels distinguish between ions with remarkable selectivity.

The L-type Ca channel is made of the selectivity oxygens of the glutamate locus of the protein. The selectivity oxygens are described as tethered ions with the same properties as carboxylate ions in bulk but confined to the subvolume of the selectivity filter. Ions such as Ca^{++}, Na^+, and Cl^- can move from phase to phase, but the selectivity oxygens cannot. Ions bind in, or are excluded from, the filter because the system has a more (or less) favorable free energy when ions are bound than when they are free. The free energy of binding/exclusion involves 'excess' terms that arise from the finite volume of ions.

The novel part of the analysis is the *ab initio* computation of the thermodynamic excess properties of ions in the selectivity filter using a statistical mechanical theory of bulk electrolyte solutions, the so-called 'primitive' version of the mean spherical approximation MSA [14, 15]. This theory represents ions as charged hard spheres and water as a continuous dielectric. The mutual exclusion of the finite ionic volumes and the electrostatic interactions (screening) among the ions produce the nonideal ('excess') components of the chemical potentials. The excess chemical potentials are generally different for different ionic species. No other effects (such as specific interactions between atomic orbitals of Ca^{++} and the molecular orbitals of the carboxylic groups) are considered in this model of the selectivity filter.

Predictions of current through the channel agree with experiment over the entire range of Ca^{++} concentration from submicromolar to 100 mM, in the presence of 100 mM NaCl, if the selectivity filter of the channel has a dielectric constant of 80 and a volume of $\sim 375\ (nm)^3$ the model, and the ions and carboxyl oxygens are given their crystal radii.

L-type Ca channels distinguish between Na^+ and Ca^{++} in two ways: (1) Divalent Ca^{++} screens the carboxylate groups of the EEEE locus more effectively than monovalent Na^+, and thus has more negative and attractive electrostatic energy there. (2) Four Na^+ displace about twice the volume of two Ca^{++}, with a significant change in the volume fraction occupied by ions and a resulting more attractive excess energy for Ca^{++}. With electroneutrality as the dominating constraint, the Ca^{++} channel can use volume exclusion to distinguish ions of nearly the same diameter, such as Na^+ and Ca^{++}, because equal charge excludes different volumes depending on the valency of the permeating ion. In this way, electrostatics facilitates selection by volume exclusion: substantial repulsion due to excluded volume selects against Na^+ (and other monovalent cations) compared with Ca^{++}.

4. Conclusion

Even the most biological property of the open channel—its selectivity between ions—can be understood from a primitive model of the physical interactions of ions of finite volume. It seems likely that Monte Carlo simulations in the tradition of computational electronics can be applied productively to a wide range of biological phenomena if they describe ions as objects (usually spheres) of finite volume.

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