Focussed Research Group on Ion Channels: Mathematical Modeling and Analysis (16frg212)

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1 Introduction

Life occurs in electrolyte solutions made of mixtures of 'bio-ions' (sodium Na^+, potassium K^+, calcium Ca^{2+}, and chloride Cl^-), along with many other charged components. The ions in biological mixtures (called 'Ringer solutions' in general) carry information that controls biological systems. The selective flow of some of these ions are the signals of the nervous system, coordinate contraction of muscle and allow the heart to function as a pump. One of the key components of many complex biological systems is the ion channels, proteins that embedded in cell membranes. Developing new mathematical and computational tools for ion channels is the main focus of this Focused Research Group.

Molecular Biology has shown that most of biology is controlled by proteins [1], and a handful of atoms in those proteins have crucial importance [2, 3]. Proteins called ion channels are the controllers of most biological function because they are nanovalves that control the flow of signalling ions and electric current through the otherwise impermeable membranes of cells [4]. Ion channels are proteins with a hole down their middle that open and close in response to stimuli and allow some ions but not others through the membrane. Thousands of scientists study ion channels every day because of their crucial role in health and disease. Almost every biological system is controlled by ion channels in the same sense that a gas pedal controls the speed of a car. About one third of all the proteins in a human are ion channels or their close relatives called transporters. Many diseases ('channelopathies') occur when ion channels malfunction [5]-[14]. Epilepsy is a sadly common example along with many others easily documented in a google search on 'ion channel disease' or channelopathy.

Ion channels are more easily analyzed than many other proteins because their function does not involve changes in electron orbitals (i.e., it does not involve covalent bond changes or quantum chemistry like enzymes). Channels are also unusual because they perform many of their functions with just one structure that does not change on the biological time scale from 10^{-6} to 10 seconds. Channels pass a definite current when open that is independent of time and of the duration of opening to an accuracy better than we can measure. (Accuracy of measurement is $\pm 1\%$ or better.) Biology occurs in a narrow temperature range (at one temperature in warm blooded animals) and flow through channels is driven only by electrical migration and diffusion, with convective effect only outside the channel in the cases that have been studied. The physics involved is much simpler than that in many problems routinely analyzed in applied mathematics and in fact resembles closely the physics of semiconductor devices in which current is carried by the diffusion and migration of quasi-particles (holes and 'electrons') represented in mathematical models as points.

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In this FRG, we brought together a group of applied mathematicians involved in biological modelling, mathematical analysis, and scientific computing of fundamental problems in neuroscience (Huang, Liu, Wylie) and biologists (Eisenberg, Liang), and young researchers in both areas (Perez-Rathke, Song, Wu) to address fundamental issues related to Ion channels and related problems. The main objectives of the FRG were to discuss fundamental issues arising in the context of ion channel modeling: 1) K-selective ion channels, 2) the stability and switch behaviour of ion channels, and 3) a special calcium selective channels.

In addition, we also selected several relevant problems in biology and physiology where mathematical models could be applied to test the theory by comparing the results with experimental observations. The objective is to develop a unified theory for coupled ionic and water transport in biological tissues that is self-consistent and applicable to a wide variety of problems in neurophysiology of the brain. Below, we describe some of the problems that we studied during the FRG.

2 Modelling the Ion Channels

2.1 Ion selectivity in potassium channels

Ion channels are selective. One class of ion channels selects calcium Ca^{2+} ions over sodium Na+ ions by a very large (nearly immeasurable and in that sense infinite) factor. This selectivity is resonably understood, as shown by some 50 papers reviewed in [15]-[21]. Another class of ion channels selects potassium K^+ over Na^+ and over Ca^{2+} ions by around a 100 fold, even though potassium is larger in diameter than Na^+ or Ca^{2+}. While there are extensive attempts to understand this large ion selectivity, and compute it from atomic detail structures and their atomic scale movements, there are no papers as far as we know that predict the concentration dependence of the selectivity (as different types and concentrations of the ions are added to the K^+ ion solution), or the current-voltage relations of the channel. The concentration dependence and current-voltage curves are the natural function of the channel, or in other words (for the same thing), the concentration dependence and current-voltage curves define the K+ channel as a device.

In order to understand the mechanism of selectivity, we propose to study a specific example [22]. We will use the inverse problem approach: fit the experimentally observed current-voltage relationships by searching for an unknown function that combines the effects of fixed charges and geometric variation of the channel. This will be carried out jointly by the research groups at Penn State (C. Liu) and York (Huang), with collaborations with the biologists (Eisenberg and Liang's group at UIC).

This type of problem is traditionally approached (in the experimental, theoretical, and simulation literature) by doing a catalog of responses to various possibilities (e.g., of different dielectric coefficients in different regions of the protein and of the pore within the protein). We will also consider attacking the problem directly by using the methods of inverse problems (e.g., Tikhonov regularization) which has been used with surprising success already in closely related ion channel problems [16, 23, 24].We are reasonably confident that it can be done in the near future.

2.2 Stability of channel conductance

Single channel molecules open and close allowing (nearly) zero current though, or a definite current, determining the open channel conductance (current divided by electrical potential difference). The open channel conductance is entirely independent of time once the channel is open, and has the same value whether the channel is open a few microseconds or a few seconds, even tens of seconds. The channel is a highly charged object with number densities of permanent charge (e.g., the acidic carboxylate groups of glutamate side chains) that are more than 5 molar [25, 26], sometimes much more. For reference the number density of solid NaCl is 37 molar. The permanent charge of the protein is very close (often less than 10^{-10} m) to the permeating ions and so the electrical forces are huge. Small changes in position of the permanent charges would produce large changes in the electric force and even larger (relative) changes in conductance, because some terms in the equations determining conductance depend on the exponential of the electric force and potential.

On the other hand, no changes in conductance (on the biological time scale slower that 2×10^{-6} second) are observed. This is incompatible with our knowledge of the structure of proteins (that can be directly measured by the temperature dependence of x-ray diffraction patterns or by direct measurement with NMR)

that we investigate the possibility that the conductance is determined by some special "eigen" state of the channel protein and the ions it contains, as supported by recent work [27]-[29]. Another possibility is that multiple steady stable solutions exist due to the non-convex nature of the energy functional that describes the interaction of the mobile ions and fixed charges.

It was concluded that one possible approach is to various models of ion channels and permeation and looking for the stability of their solutions and the time and voltage dependent signatures of any instabilities or stable multiple solutions. This will be carried out jointly by the research groups at Penn State (C. Liu) and York (Huang), with collaborations with the biologists (Eisenberg and Liang's group at UIC).

2.3 Y-shaped calcium channels

Recently, the structure has been determined of a Y shaped calcium selective channel of great biological importance [30]. The Na/Ca transporter of this structure is found in cardiac muscle (and many other cell types) where it is crucial for the maintenance of contractile activity. Some believe this transporter is a key player in the origin of hypertension a disease that plagues a large fraction of humans, over the age of say 50.

Discussions during the FRG lead us to believe that a reasonable approach is to construct a one-dimensional model that connects three half-channels using the PNP framework, and look for behaviour resembles the transporter. This will be carried out jointly by the research groups at Penn State (C. Liu) and York (Huang), with collaborations with the biologists (Eisenberg and Liang's group at UIC).

2.4 Dimension reduction

A problem related to the ion channels is the reduction from the three-dimensional setting to one dimension. This issue was discussed previously [31, 32] with homogeneous Neumann conditions for both concentrations and electric potential and the fixed charge appears in the source term in the three-dimensional Poisson equation. At the FRG, an alternative approach was discussed. Since the fixed charge comes from an interpretation of the molecular structure of the ion channel, it can be modelled by the surface charge and included in the Robin type of boundary condition for the electric potential. Therefore, we have two competing length scale, one determined by the strength of the surface charge, and the other by the Debye length (consisting of the ion concentration and the channel width). At the proper distinguish limit, we can then reduce the three-dimensional model to a one-dimensional model. This will be carried out jointly by the research groups at Penn State (C. Liu) and York (Huang), with collaborations with the biologists (Eisenberg and Liang's group at UIC).

The research problems on the modelling of ion channels identified by the FRG are of fundamental importance. Progresses made on these problems would make significant contribution to our understanding of electrophysiology in cells. Below we will describe a different kind of problem related to electrophysiology at the tissue level. It will serve as a canonical problem for developing a consistent mathematical model applicable to many other problems including the transport of ions, water and other molecules in the brain.

3 An Variational Model for Water Circulation in Eye Lens

The problem faced by all cells is that they contain negatively charged impermeant proteins and electrical neutrality requires the intracellular chloride concentration must be less than that outside of the cells. Therefore chloride would be driven into the cells by chemical gradient, if not countered by the negative membrane potential difference maintained by the sodium-potassium pump and Na and K selective ion channels.

In a tissue such as the eye lens, cells form a syncytia via gap-junctions that allows ions and water to flow on the scale much larger than that of the individual cells, created by special structure of lens. As a result, other molecules can be transported from one part of the tissue to the other due to steady circulation of water inside the lens. For example, oxygen, glucose and other nutrients are carried by water along the extrcellular clefts to the innermost cells while the intracellular water flow carries the waste products from the inner cells to the surface cells of the lens [33].

At the FRG, previous models [33]-[35] were discussed and it was concluded that a consistent mathematical model can be derived based on the variational approach. In addition, modifications can be made to the existing models by taking into the effect of cell membranes on membrane fluxes. These will be carried out jointly by the research groups at Penn State (C. Liu) and York (Huang), with collaborations with the biologists (Eisenberg and Liang's group at UIC).

4 Summary

The approach to biology of the FRG is both novel and classical. It is novel because we seek reduced engineering style models that are no more complex than needed to describe the actual function of the biological system, and how it depends on structural controllers of function (typically a handfull of amino acid side chains). It is classical because this engineering approach is precisely the approach of classical British physiology that has yielded nearly a score of Nobel Prizes, including some at the atomic scale of molecular biology (Max Perutz, the father of x-ray crystallography famously said "I am a physiologist" because his concern was how hemoglobin transported oxygen.)

What is novel is the use of mathematics to express the engineering approach. The philosophy of doing only what is important, of finding the controlling function, of always working away from equilibrium (because life at equilibrium is dead), is common to both engineering and physiology. The use of the mathematics of inverse problems to implement this approach is novel, paritcularly the explicit involvement of sensitivity functions to determine what is important and what is invariant.

A mathematical approach to biological systems that deals explicitly with ions, water, and their convection, diffusion, and migration has not been possible until recently, even though the experimental evidence for all effects and their interactions was overwhelming (and known since the 1930's if not earlier). Mathematics is now possible because the energy variational methods pioneered by Chun Liu and many others allows treatment of systems that are globally interactive, which were not accessible by consistent mathematical methods without variational methods. However, a lot remains to be done.

The goal of the FRG is to develop neat engineering descriptions of biological systems, from molecules to cells and tissues, that allow the trial and error methods of molecular biology to be replaced by the physical approach so productive in our technology.

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