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By Bob Eisenberg

It is hard to see big things from up close, in math and science, as in the world. Many mathematicians approach biology for interesting problems, but sometimes the biggest problems, which offer the greatest opportunities, are too close to see. The study of ionic solutions as they occur in life is one such problem.

Biology occurs in saltwater solutions—biological plasmas—that evolved from primitive oceans of the earth [2,3]. Biological plasmas contain large concentrations of the bio-ions sodium (Na^+), potassium (K^+), and chloride (Cl^-), variable concentrations of Ca^{2+} and much lower concentrations of organic acids and bases of many types. Without proper ions, water is lethal to cells and proteins.

Bio-ions control a wide variety of biological processes. The Hodgkin–Huxley equations couple atomic changes in proteins (ion channels) and macroscopic flows of ions in nerves. Propagating signals called action potentials are the result. Ions, proteins, macroscopic flows, and gradients are coupled in many of life's essential processes.

Calcium ions and complex organic molecules (e.g., hormones) control many processes. Calcium signals organize heart muscle to pump blood and prompt cells to release other chemical signals. Calcium means one thing in one place, something else in another place, rather as voltages in different places in a computer mean quite different things.

We view these bio-ions as nearly hard spheres, with different diameters and permanent charge, independent of the local electric field, surrounded by water. Because ions are strongly coupled by electrical and steric forces, I believe that the mathematics of ionic solutions needs to be the mathematics of complex fluids. Ionic solutions are not simple fluids.

Chemical/Mathematical Traditions

Physical chemists and physiologists have studied mixtures of bio-ions for more than a century. Early scientists had to cope with ionic solutions without mathematical tools that deal with interactions consistently. Theoretical chemistry exploited the idea of ideal solutions at chemical equilibrium in a most imaginative and powerful way. These idealizations allowed the study of atoms even when their

existence was still being debated. Experimental measurements included current–voltage relations that allow detailed tests of theories of ionic solutions.

The chemical tradition succeeded because it focused on idealized systems without interactions. Its paradigm was the infinitely dilute, uncharged, perfect gas, without boundary conditions or untidy interactions. Chemists have treated ions separately, one type at a time, in solutions at equilibrium. Interactions, flows, and boundary conditions have not been treated consistently. Without modern mathematical and computational methods, the chemical tradition achieved remarkable success by restricting its gaze, but the chemical tradition deals with idealized simple fluids—and chemical reactions—as if they occurred without spatial gradients.

The mathematical tradition used the Poisson–Boltzmann (PB) and Poisson–Nernst–Planck (PNP) equations to describe interactions of point charges. PB–PNP is widely used even today to model transistors and semiconductor devices. It was only natural to hope that PB–PNP would do as well with ionic solutions. Mathematicians understandably were more interested in solutions of equations than in properties of solutions of ions, particularly the messy nonideal properties produced by finite-sized? interacting particles.

PB–PNP succeeds in certain isolated cases—for example, those with vanishing concentrations of monovalent ions of one type. Although these cases can be significant, natural biological function almost always occurs in physiological solutions beyond the reach of PB–PNP equations.

As Torrie and Valleau [10] put it: “It is immediately apparent that classical theory [Poisson–Boltzmann] has broken down completely. It . . . fails to show [the] qualitative behavior [and] is seriously in error for quite low concentrations.”

PB–PNP theories fail because they treat ions as points. In reality, the size, shape, and microdynamics of ions are important in almost all solutions. In 1M solutions, ions of diameter 2\AA are roughly 8\AA apart. The electric field and entropy of such a system are not those of point particles. (For the classical chemical units of number density: $1\text{M} = 1\text{Molar} = 6.02 \times 10^{23}$ particles per liter = 6.02×10^{26} particles per cubic meter.)

The difficulties with PB–PNP theories acquire startling importance near DNA, ion channels, or enzymes, and in electrodes of batteries, where ions are crowded together in mixtures with divalents at number densities higher than 10M. (For comparison, solid NaCl is

37M.) Indeed, PB–PNP theories fail most dramatically where ions are most important, near structures that use ions to perform macroscopic functions.

Devices—whether ion channels or enzymes, or batteries—concentrate ions in some regions (to maximize flow) and deplete them in others (to maximize control). A theory must deal seamlessly with large ranges of concentration if it is to deal with the devices of engineering or biology.

An Army of Mathematicians Is Needed

A review of the numerical analysis of PB in SIAM Review [11] motivated this article, catalyzed by discussions with Chun Liu and Wei Cai. Thank you both! Analysis of the PB equations provides the initial iterates for the development of numerical procedures needed to solve the big problem (with all interactions). Work on PB–PNP sets the stage on which the moving dance of biology can be studied, as it is actually lived.

Work on the living problem, however, requires mathematics that describes interacting ions in devices. The mathematics can start with bio-ions described as hard spheres diffusing in a uniform dielectric. Such analysis is beginning. These solutions of bio-ions can be studied with the existing theory of complex fluids. More realistic descriptions of ions and water can be used later if needed.

It will take an army of mathematicians to study the ionic solutions of physical chemistry and biology as complex fluids. Mathematicians will need to learn the experimental traditions of physical chemistry and physiology before they can address longstanding unsolved problems. They will have to rework their tools to deal with the realities of ions in solutions and near channels, proteins, and electrodes. I believe that daunting interactions of ions, microelements, and the macroscopic world can be handled automatically and consistently by the theory of complex fluids.

Beyond the bio-ions, more components of extra and intra-cellular solutions—organic ions, amino acids, even nucleic acids and proteins—can be added as microelements as needed. Reduced models of some of these components are already known. Organic and biochemists have been making reduced models of these components and their chemical reactions for 150 years. I suspect that their reduced models could be improved by appropriate extensions of the theory of inverse problems. Chemical reactions could be treated by the theory of complex fluids, as interactions of microelements (reactants), bio-

ions, and water, involving rearrangements of internal (electronic) structures of reactants, according to Schrödinger's wave equation of the electron.

Simulations are an alternative approach, favored by computer scientists. But simulations of biological plasmas present formidable challenges: They must deal simultaneously with mixtures and flows over some 10 orders of magnitude in size, time, and concentration [3]. They must couple atomic-level motions of proteins to macroscopic electric fields if they are to compute action potentials of nerves. Simulations so far have not included divalents, mixtures, large concentrations, flow, or macroscopic boundary conditions. Calibration remains in the future. Simulations may eventually reach these goals with the help of more powerful computers. Meanwhile, simulations can serve as models of microelements in multiscale theories of complex fluids.

But first the community of scientists who know the theory of complex fluids will need to study real-world electrolytes. If they limit themselves to uncalibrated simulations of tiny systems, to Poisson–Boltzmann equations and point particles, their work will have limited value. It will not apply to most living systems. It will set the stage of life, but it will not account for the action on the stage.

Math and Biological Reality

Biological reality determines mathematical treatment in several ways:

First, real biological solutions are characterized by interactions on all scales: Everything interacts with everything else in ionic solutions. PB–PNP theories and simulations have not plumbed the biological realities of divalents, mixtures, or molar concentrations. The free energy of one type of ion depends on the concentration of all other types of ions. The thermodynamic driving force for a single ion depends not only on the concentration of that ion—as assumed tacitly in much of chemistry and biophysics—but rather on all ions present. Even in bulk solutions, flow of any one ion depends importantly on all other ions. Classical treatments often attribute complexities of the ions themselves entirely to enzymes, channels, or chemistry.

Second, biological reality means that non-equilibrium can be easier. Simplifying biological (or engineering) devices can inadvertently make them difficult to study. Biological devices (like nerve membranes) have evolved to follow simple robust laws in physiological conditions, where gradients of concentration and

potential are always present to drive flows. Devices at equilibrium, without gradients of electrical or electrochemical potential, no longer are devices at all. They follow no particular laws and are hard to study, analogous to amplifiers, which are hard to study when disconnected from power supplies.

Third, without flows, biological systems are dead. We cannot expect dead biological systems, whether corpses or crystals, to be the same as live systems. Gradients and flows create the devices and machines of engineering. Engineering devices are hardly worth studying when their power supplies are turned off and simple device laws no longer hold true.

Finally, mathematics must describe biological reality and experiments as they are actually done. Scientists cope with complex systems by simplifying the systems and then adding back components or fields, one by one. It is difficult to describe the resulting hierarchy of systems if each one is considered individually, without interactions, in the ideal tradition of chemistry. A hierarchy of inconsistent models is a challenge to the scientific process. It is understandable, nearly inevitable in such circumstances, that theories of mixtures of electrolytes (e.g., equations of state) should include many vaguely defined parameters, of little use beyond the conditions in which they were measured.

Scientists have been crippled by their lack of consistent mathematics. Different laboratories use different models of the system and make different choices of parameters. A recent magnificent treatise ([5]: 664 pages and 2406 references) shows how difficult it is even to define the properties of a single ion in a system in which everything interacts with everything else without a consistent mathematics of interactions. Consistency is an enormous help in focusing attention, and decreasing distracting discord, as the case has been in computational electronics.

A Promising Approach

Scientists need to replace their idealized noninteracting models of ionic solutions with a consistent framework in which everything can interact with everything else. Mathematicians working on ionic solutions [7,12] are well aware that variational methods allow components and fields to be added or subtracted in functionals, from which differential equations are derived by the Euler–Lagrange process. Mathematicians need to spread their knowledge of variational methods to the physical chemists, physiologists, and molecular biologists of the world. Mathematicians need to help

scientists deal with the solutions of life. I prefer energy variational methods because they embody physics. Energy variational methods aspire [1,6] to be a natural extension of thermodynamics, joining free energy and dissipation functionals, as envisioned by the Nobel prize-winning physical chemist Lars Onsager (1903–1976) and followers. These methods combine [1,4,8,9] the least action principle of mechanics with the maximum dissipation principle of Rayleigh, later applied by Onsager, including eventual time-dependent relaxation to the steady state. The derivation of the Navier–Stokes equations for incompressible flow [6] illustrates the approach.

I hope that an army of mathematicians will take up the challenge of applying their tools and skills to biological reality. Mathematicians can use consistent theories of complex fluids to allow systematic analysis and improvement of models of the plasmas of life. Computations needed include current–voltage relations in complex mixtures of bio-ions. Theories of complex fluids need to be applied to classical unsolved problems of chemistry and biology, involving plasmas containing bio-ions, organic compounds, proteins, and nucleic acids. Theories of simple fluids are not adequate.

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