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**Mathematics of Life’s Solutions**

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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 nowadays but sometimes the biggest problems, with the greatest potential, are too close to see. The study of ionic solutions as they occur in life is one of the big problems and opportunities.

**Biology occurs in saltwater solutions** that evolved from primitive oceans of the earth. Biological plasmas contain many types of organic ions, DNA, RNA, amino acids, and proteins, as well. Ions in water are life’s plasma [[2](#_ENREF_2), [3](#_ENREF_3)]. They are the electrolytes outside and inside cells. Without proper electrolytes, water is lethal to cells and proteins. Biological plasmas are certainly not simple fluids. The mathematics of ionic solutions needs to be the mathematics of complex fluids, in my view.

Different ions control different biological processes. 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 a wide variety of life’s essential processes.

Calcium ions (Ca2+) and complex organic ions (e.g., hormones) control many processes. Calcium signals organize heart muscle to pump blood. Calcium tells cells to release chemical signals. Calcium in one place means one thing. Calcium in another means something else, rather the way voltages in different places in a computer mean quite different things..

Physical chemists and physiologists have studied ‘bio-salts’—sodium (Na+), potassium (K+ ), calcium, and chloride (Cl−) ions that are nearly hard spheres—for more than a century. Early workers had to cope with ionic solutions without mathematical tools that deal with interactions self-consistently. Theoretical chemistry exploited the idea of ideal solutions at chemical equilibrium in a most imaginative and powerful way. These idealizations allowed study of atoms when their existence was still 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 and untidy interactions. Chemists have treated each type of ion one at a time, at equilibrium. Interactions, flows and boundary conditions have not been treated self-consistently. The chemical tradition deals with idealized simple fluids—and chemical reactions—as if they occur without spatial gradients. Even without modern mathematical and computational methods, the chemical tradition achieved remarkable success by restricting its gaze.

**The mathematical tradition used** the Poisson-Boltzmann PNP (Poisson-Nernst-Planck) equations to deal with interactions of point charges. PNP is widely used even today to describe transistors and semiconductor devices. It was only natural to hope PNP would do as well with ionic solutions. Mathematicians understandably were more interested in the (mathematical) solutions of the equations than in ionic solutions themselves, particularly the messy nonideal solutions of finite size particles.

PB-PNP deals successfully with a few isolated biological phenomena that occur in vanishing concentrations of monovalents of one type. These situations are sometimes significant, but ***natural biological function almost always occurs in physiological solutions beyond the reach of Poisson-Boltzmann*** ***equations.***[[10](#_ENREF_10)]: “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”.

***Poisson-Boltzmann PNP theories fail because they include particles as points. In reality, the size, shape, and microdynamics of particles are important in almost all solutions.*** In 1M solutions, ions of diameter 2Å are roughly 8Å apart. The electric field and entropy of such a system are not those of point particles.

The difficulties with Poisson-Boltzmann PNP theories acquire startling importance near electrodes in batteries, or near DNA, ion channels or enzymes, where ions are crowded together in mixtures with divalents at number densities >10M. (For comparison, solid NaCl is 37M.) Indeed, ***Poisson-Boltzmann theories fail most dramatically where ions are most important, near structures that use ions to perform macroscopic functions.***

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

Work on Poisson-Boltzmann PNP sets the stage on which the moving dance of biology can now be studied, as it is actually lived. A review of the numerical analysis of PB in SIAM Review [[11](#_ENREF_11)] motivated this article, catalyzed by discussions with Chun Liu and Wei Cai. Analysis of the PB equations provides the initial iterates for numerical procedures needed to solve the big problem (with all interactions). Eventually the big problem must itself be addressed.

The big problem requires mathematics that describes interacting electrolytes in devices. Mathematics can start with bio-ions described as hard spheres diffusing in a uniform dielectric. Such analysis is already feasible. Ionic solutions can be studied with the existing theory of complex fluids.

**It will take an army of mathematicians** to study the ionic solutions of physical chemistry and biology as complex fluids. Mathematicians must learn the experimental traditions of physical chemistry and physiology before they can address long standing unsolved problems. They must rework their tools to deal with the realities of electrolytes in solutions and near channels, proteins, and electrodes. No one can know how these tools will succeed (and fail) without trying. But challenges can only be met by trying. I believe daunting interactions of ions, microelements, and the macroscopic world can be handled automatically and self-consistently by the theory of complex fluids.

Other molecules—beyond the bio-ions—will need models with more microdynamics. Reduced models of these molecules are often already known, and can be improved by appropriate extensions of the theory of inverse problems, I suspect. Chemical reactions can be treated by the theory of complex fluids, I imagine, as interactions of microelements (reactants) 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 face formidable challenges. They must deal **simultaneously** with mixtures and flows over ~10 orders of magnitude of size, time, and concentrations [[3](#_ENREF_3)]. They must couple atomic motions of proteins to macroscopic electric fields if they are to compute action potentials of nerves. Simulations so far have not dealt with divalents, mixtures, large concentrations, flow, or macroscopic boundary conditions. Calibration remains in the future. Simulations may eventually reach these goals with the help of further iterations of Moore’s law. Meanwhile, simulations may serve as models of microelements in multiscale theories of complex fluids.

But first the community of scientists who know these methods must study the reality of 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 not deal with the action on the stage.

**Biological reality must determine mathematical treatment: interactions on all scales.**Poisson-Boltzmann theories and simulations have not dealt with the biological realities of divalents, mixtures, or molar concentrations because everything interacts with everything else in ionic solutions. The free energy of one type of ion depends on the number density of ***ALL*** other types of ions.

The ‘thermodynamic driving force’ for a single ion does not depend on just the concentration of that ion, as assumed tacitly in much chemistry and biophysics. The thermodynamic driving force ***itself*** depends importantly on ***ALL*** types of ions. Flow of any one ion depends importantly on all other ions, even in bulk solutions. ***Classical treatments ignore interactions among ions and are likely to attribute complexities entirely to enzymes, channels, or chemistry that involve the ions themselves.***

**Non-equilibrium can be easier.** Simplifying biological (or engineering) devices can inadvertently make them much more difficult to study. **Biological d**evices (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. Amplifiers are much easier to study when energized by power supplies.

**Biological reality must determine mathematical treatment: flows.** Biological systems without flows are dead. One cannot expect living systems to be the same devices when dead as they are when alive, whether those systems are corpses or crystals.

Gradients and flows create the devices and machines of engineering. One cannot expect engineering systems to be the same devices when the power supplies are turned off. Engineering devices are hardly worth studying when their power supplies are turned off and simple device laws no longer hold true.

**Mathematics must describe biological reality** and experiments as they are actually done. Scientists cope with complex systems by ***simplifying systems and then adding back components or fields, one by one.*** It is difficult to describe this hierarchy of systems if one deals with each system individually, without interactions, in the ideal tradition of chemistry. Laboratories use inconsistent models of the system and make different choices of parameters. It is hard to compare inconsistent models.

A hierarchy of inconsistent models is a challenge to the scientific process. The scientific (social) process may not converge. It is understandable, nearly inevitable in such circumstances that theories of mixtures of electrolytes (e.g., equations of state) should include large numbers of vaguely defined parameters, not useful beyond the conditions in which they were measured.

Scientists have been crippled by their lack of self-consistent mathematics, not by their lack of skill or energy, in my opinion. They did their best with the mathematical tools they had. Self-consistency can make an enormous difference. Self-consistency is an enormous help in focusing attention, and decreasing distracting discord, as it has been in computational electronics. Inconsistent models are particularly damaging in systems of ions and microelements that interact on many scales, as they flow, between boundary conditions. A recent treatise ([[5](#_ENREF_5)]: 664 pages and 2406 references) shows what happens when a system in which everything interacts with everything else is diligently analyzed to exhaustion without self-consistent treatment of interactions.

**Variational Methods.** Scientists need to replace their idealized noninteracting models with a self-consistent treatment in which everything can interact with everything else. Mathematicians working on ionic solutions [[7](#_ENREF_7), [12](#_ENREF_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 them to solve the big problems.

**Energy Variational methods embody physics.** The variational methods I prefer—with admitted bias on my part—are not arbitrary mathematical structures. Energy variational methods aspire [[1](#_ENREF_1), [6](#_ENREF_6)] to be a natural extension of thermodynamics, joining free energy and dissipation functionals, as envisioned by Onsager and followers. These methods combine [[1](#_ENREF_1), [4](#_ENREF_4), [8](#_ENREF_8), [9](#_ENREF_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 equation for incompressible flow [[6](#_ENREF_6)] illustrates the approach.

**Challenge**. I challenge mathematicians to apply their tools and skills to biological reality. Mathematicians can use self-consistent theories of complex fluids to allow systematic analysis and improvement of models of the plasmas of life. Computations are needed of current voltage relations in complex mixtures of ions of many types and concentrations. Computations are underway for bio-ions that are nearly hard spheres. Theories of complex fluids need to be applied to classical unsolved problems of chemistry and biology, involving plasmas of bio-ions, organic compounds, proteins and nucleic acids. Theories of simple fluids are not adequate.

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I am restricted here to a dozen references. A longer version of this note is available on the arXiv (XXXX) where discussion and citations are more complete. Continual joyous interactions with Chun Liu have shaped my thoughts and this paper. Gail Corbett and Ardyth Eisenberg provided remarkably useful editorial advice, but I alone am responsible for remaining confusions, errors, and indiscretions. Support and encouragement from Rush Medical College made this work possible. I am grateful to all.

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