Life's Solutions are Complex Fluids

A Mathematical Challenge

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Abstract

Ionic solutions are so important that they are often ignored. Chemical reactions have been studied for more than a century in ionic solutions. 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 precise composition of biological solutions is important. Gradients of Na^+, K^+, Ca^{2+}, and Cl^- ions provide energy to drive signals through the nervous system, and energize transport in most cells. The signals of biology ('biosignals') themselves are usually ions, often just Ca^{2+}. Ionic concentrations range from 10^{-11} M to 10^{-1} M to 10^{2} M in different biological systems, from hormones, to Ringer solutions, to solutions in and near enzyme active sites, binding proteins and ion channels. The electric field of ions is always important. Ions interact with each other, and everything else that is charged, to maintain global electroneutrality. Otherwise, electrons are stripped off atoms and bio-compounds are destroyed. Bio-solutions contain a myriad of other charged compounds from simple organics like carbonate, to organics like ATP, and macromolecules like DNA, RNA, and proteins; even the organelles of cytoplasm are themselves charged, rather like colloids. Nearly all components of living solutions are charged. All interact through the electric field. Everything interacts with everything else.

Classical thermodynamics and statistical mechanics describe systems in which nothing interacts with nothing. Even the highly refined theory of simple fluids does not deal very well with electrical interactions, boundary conditions, or flows, if at all. Electrical interactions, boundary conditions, and flows are essential features of living systems. Life without flow is death and so a different approach is needed to study biology alive.

The theory of complex fluids deals with interactions, boundary conditions, and flows quite well as can be seen in its successful treatment of liquid crystals.

I advocate treating ionic solutions in general as complex fluids, with microelements that are the solutes and components of the solution. Enzyme active sites are a special case where some solutes are reactants. Solutes are crowded into active sites of enzyme by the high density of protein charges. The electric field links chemical reactions to charges in the protein and surrounding solutions. Interactions potentiate catalysis and control biological function.

I suspect that most chemical reactions that occur in liquids also need to be treated by the theory of complex fluids. The electron movements of these reactions occur in a temporary highly concentrated fluctuation, a transient spatial inhomogeneity in the bulk solution. The electron movements of these reactions (described by quantum mechanics) are coupled to the electric (and sometimes steric) fields of the bulk solution. I suspect the electron movements, inhomogeneities, and chemical reaction (in the condensed phase) need to be treated by the theory of complex fluids because everything interacts with everything else, in this system, as in so many others.

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 problem, with the greatest potential, is too close to see.

All of biology occurs in salt solutions evolved from the primitive oceans of the earth [241, 240, 139, 473, 474]. Water without the ions of the ocean is lethal. Almost all cells burst when exposed to pure water. Most enzymes denature in distilled water. The need for ions in water is thus general and general in biological systems. The need for ions is specific(as well as general). Not just any ion will do. Most biological systems require quite specific salt solutions to function and those salt solutions are almost always mixtures involving definite concentrations of Na^+, K^+, Ca^{2+}, and Cl^- ions.

Ions in water are life's plasma [148]. 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. The selective flows of ions coordinate contraction of muscle. They allow the heart to function as a pump. The concentration of ions is important. Concentration often regulates function the way the gas pedal in a car controls its speed. The location of ions is important. The same ion (often divalent calcium Ca^{2+}) in different locations is a different signal, even if both locations are in the same cell. The biological role of ions is a central subject in physiology and medicine [61].

Selectivity. Different ions have different specific biological functions just as signals in different wires in a computer have different specific functions. Life cannot be understood without knowledge of the diversity of chemical signals, just as a computer cannot be understood without knowledge of the voltages in its wires. These signals are a central subject in biochemistry, cell and molecular biology, and medicine [7, 470, 492]. The diversity of chemical signals depends on the selectivity of biological systems to ions. Different ions are recognized selectively by the proteins of life, whether those proteins are ion channels or enzymes.

The origin of selectivity has been considered mysterious. Indeed, the origin of specificity has been called the central question of life, by Nobel prize winner Aaron Klug [402]. The origin of selectivity in many systems is not known, or is in dispute, but in some cases selectivity can be calculated and results of experiments predicted before they are performed, treating ions with physical theories developed to deal with mixtures of ions in non-biological systems. There are three ion channel proteins (of great importance throughout biology) where this approach has been successful, over a wide range of conditions [372, 201, 497, 373, 496, 517, 58, 57, 191, 193, 194, 196, 59, 154, 197, 314, 432, 55, 141, 221, 313, 121, 195]. The inverse problem has been solved showing how to determine the internal charge structure of a channel protein from measurements of current voltage relations, in the presence of random and systematic error [18, 19, 66] .

Ionic mixtures have been studied experimentally in some detail since around 1900. Kraus [312] provides a fine summary of the classical literature written for mathematicians. Laidler [321] et al provides a good introduction to physical chemistry for mathematicians. Fawcett [165] is a

useful clear textbook of electrochemistry. The first pages of Fraenkel [173] summarize the present state of knowledge, as I see it too.

After all this time, one would imagine that the specific properties of ionic mixtures of such significance to biology would be understood. But they are not. This fact is hard to believe, particularly for workers in adjacent sciences, where complex phenomena of heterogeneous fluids are computed with striking success by computational fluid dynamics [11, 522, 528], able to compute very complex phenomena indeed, from ocean waves [339] to liquid crystals [190, 132, 133]. One of the motivations for this paper is simply to document the lack of understanding of life's solutions, of ionic mixtures, as stated so clearly in the literature of physical chemistry.

The lack of success in computing the most elementary properties of ionic solutions is in striking contrast to the range of accurate experimental data available for many years, reaching back to the 1930's, and even earlier [312, 235, 420, 176, 31, 416, 29, 410, 175, 477, 174, 259, 399, 468, 520, 324, 406, 316, 69, 398, 93, 407, 137, 348, 33, 136, 317, 321, 165, 424, 233, 285, 298, 299, 297, 403, 224, 307, 309, 56, 74, 286, 323, 3, 124, 239, 270, 277, 308, 318, 319, 335, 336, 356, 495, 151, 173, 172, 262, 295, 296, 436, 519, 150, 141, 189, 264, 378, 413, 412, 523, 191, 198, 199, 200, 491, 232, 391, 417, 421, 437, 122, 135, 462, 41]. The gap between data and theory provides an important opportunity for the present generation of scientists, particularly given the biological and technological significance of ionic solutions. I believe that advances in mathematics and computational science warrant a fresh look at ionic questions.

The question is where to start? when dealing with all this experimental data.

The place to start is calculations of current voltage curves in standard electrochemical cells described in textbooks of electrochemistry [28, 52, 53, 165, 321, 391, 430, 441, 442, 516] and polarography [63, 414]. Current voltage relations are the fundamental data from which most of the classical properties of ions (used to describe biological systems) are derived. The most important derived quantity is the activity of ions, the generalization of number density or concentration appropriate for nonideal solutions. The activity of ions plays the role of height and weight in the gravitational field. It is the fundamental determinant of energy. Gradients of activity drive flow. The activity equals the concentration in infinitely dilute solutions of noninteracting particles called ideal solutions or perfect gases.

Ions are a compressible plasma within the incompressible liquid formed by water and ions [155]. The concentration and type of ions varies enormously in biology. Evidently, evolution has used this variation to produce and control most biological functions. Electrodiffusion is to life what current flow is to computers. It is the fundamental process in nearly everything the system does.

The free energy per mole, the activity of the ions, can serve many biological functions. In trace concentrations (smaller than say 10^{-7} M), concentration of a particular ion (in a particular place in a particular biological cell, or subcellular organelle) is a specific signal. In large concentrations (e.g., the 0.2 M solutions of sodium ions Na^+ outside cells) the ions serve as sources of (free) energy for many processes of great importance, like signaling in the nervous

system. In enormous concentration (say 20 M) ions create a bizarrely specialized environment (in ion channels [141] and active sites of enzymes [159, 280]), more like an ionic liquid [13, 37, 309, 404, 438, 514] than an ideal solution. In channels, this environment allows specificity and control in a protein nanovalve. In enzymes, this environment creates an electrostatic glove wrapping the chemical reactants and must have a decisive importance in the mechanism of catalysis [511, 512, 459, 509, 502], in my opinion. I hasten to add that how this electrostatic glove is important in catalysis remains a mystery, at least to me. Channels and enzymes are intimately related [159, 147], variations on a theme, intertwined as obviously and as mysteriously and successfully as themes in Bach's F major Toccata (BWV 540).

The free energy per mole of ionic solutions is difficult to calculate. It is difficult calculate the properties of pure solutions of monovalents (e.g., Na^+Cl^-) over a wide range of concentrations, particularly at high concentrations. Calculations of pure divalents (like $Ca^{2+}Cl_2^-$) are even more problematic. The activity of ions in mixtures particularly as they flow cannot be described at all well by existing theories. References supporting this strong statement include [520, 495, 477, 468, 410, 408, 407, 398, 399, 335, 321, 319, 318, 316, 312, 296, 286, 284, 270, 262, 259, 235, 175, 176, 172, 165, 137, 136, 124, 42, 41, 40, 38, 37, 33, 4, 3].

Ionic solutions are not ideal. The behavior of ions is nothing like the behavior of infinitely dilute ideal solutions (of uncharged noninteracting particles) assumed in textbooks of biochemistry and physiology, even in elementary textbooks of chemistry and electrochemistry. The behavior of ions is better captured by chemical engineers [308, 520], who need to compute the properties of electrolytes and mixture if they are to deal with salt solutions in their flow reactors, chemical plants and factories. The empirical formulations used by chemical engineers, however, are not derived from physical models. They include many parameters that cannot be transferred from one condition to another. The parameters need to be modified when the models are applied to new conditions [276, 343, 384, 452]. How to modify the parameters is not known. So I conclude the theories of chemical engineers do not work very well.

Only a few of the empirical formulations of chemical engineering apply to flow [287, 421]. The properties of ionic solutions most important for life occur in flowing solutions. These properties are not addressed by classical thermodynamics or statistical mechanics, or even by the theory of simple fluids, for the most part. Not addressed, the problems posed by flow cannot be solved. In biology, flow ceases only with death. Classical methods treat ionic solutions as very complicated simple fluids. Classical methods are not powerful enough to deal with flow.

I am aware of the difficulties and challenges involved in attacking this long lasting problem. After decades (approaching a century) of efforts by many of the most able physicists, including Lorentz, Debye, Onsager, Kirkwood, and so on, there is no satisfactory theory for salt water or the closely related ionic mixtures inside animals and plants even when flows are identically zero, at thermodynamic equilibrium. There are essentially no theories—satisfactory or not—that deal simultaneously and self-consistently with the convection, diffusion, and migration, along with volume regulation of cells, vital to the function of kidney, heart, lungs,

etc. Such models must include single atom ions (like sodium Na^+, potassium K^+, calcium Ca^{2+}, and chloride Cl^- that I call '*bio-ions'* because of their biological importance), complex organic molecules that are ions like ATP, sugar acids, carboxylic acids, and bioamines, all of which have essential roles, along with nearly all of the organic chemicals and polymers described in biochemistry texts. They are all ions, of some complexity, most with complex structure and internal dynamics obviously involved in their biological function. The tools of classical physical chemistry based on ideal solutions at thermodynamic equilibrium are unequal to the task of describing let alone understanding and predicting the properties of these solutions, in my opinion.

Understanding the physical properties of these ions form a central problem in all of biology, unsolved, in my view, because of the lack of tools.

Modern analytical methods (of the self-consistent theory of complex fluids, for example) and modern numerical and computational methods (made possible fundamentally by 50 years of diligent exploitation of Moore's law [351, 380, 381]) can attack and probably solve these problems. But first the mathematicians who know these methods must learn of the problems.

If mathematicians analyze the wrong equations, their results will be less helpful than they wish, not worthy of the efforts involved.

Mathematicians are understandably more interested in the solution of equations than in their justification. The issues of ionic solutions are less interesting to them than the issues of mathematical solutions. Thus, it is entirely understandable that mathematicians have concentrated almost all their efforts on the Poisson Boltzmann PNP (Poisson Nernst Planck) system. After all the PNP system has been remarkably successful in dealing with semiconductor systems [486, 357, 228, 358, 451, 363, 279, 242, 352, 263, 488] and it is natural to hope that success would extend to ions in solutions and biological systems [127, 129, 128, 331, 330, 328, 329, 358, 327, 65, 107, 334, 332, 109, 108, 430, 326, 325, 25, 27, 81, 82, 157, 39, 75, 160, 158, 26, 78, 79, 83, 96, 146, 145, 338, 395, 76, 95, 117, 131, 161, 192, 252, 320, 333, 394, 8, 70, 112, 118, 152, 223, 253, 275, 383, 94, 97, 111, 272, 396, 448, 481, 98, 99, 115, 140, 198, 251, 254, 273, 274, 449, 482, 483, 116, 153, 144, 360, 385, 484, 5, 38, 6, 101, 113, 119, 149, 349, 494, 114, 361, 364, 439, 493, 19, 66, 100, 156, 2, 142, 143, 463, 18, 36, 350, 464, 347, 141, 337, 523, 524, 121, 475]. Much other literature is cited in [38, 160, 158].

The sad fact is, however, that PNP treats ions as points, and that treatment is inadequate for ion solutions. The finite diameter of ions makes the electric field very different from that of points. The crowding of ions makes the entropy very different. And the fact that different ions have very different diameters means that complex layering phenomena characterize mixtures of ionic solutions. No single 'distance of closest approach' can do. Different ions approach different distances. Layers of different charge density and sign can and do result.

Equations that deal with ions as points miss these phenomena. Biology and evolution have not missed these phenomena. Biology and evolution use the finite diameter of ions to

build systems that allow animals to survive. And equations must deal with the finite diameter of ions if they are to allow biologists to understand life.

Biological systems cannot be understood if ions are treated as points. PNP equations will miss the problems that matter most to living systems because the PNP equations leave out most of the nonideal properties of ionic mixtures, particularly those containing divalents, like seawater and the solutions inside animals.

I believe that an ionic solution should be viewed as a specific type of complex fluid that couples hydrodynamics to electrostatics and to the microstructure of charged particles, their excluded volume and even their shape. Ionic solutions are complex fluids in which atoms interact with nearby confining structures through several types of forces. Ionic solutions are complex fluids in which the behavior of individual atoms and proteins (e.g., ion channels) is changed by charge on far distant boundaries. I believe that existing methods of the self-consistent theory of complex fluids will allow rapid progress on previously intractable problems.

The mathematical treatment of ionic mixtures I think appropriate is that of complex fluids and its close cousin the theory of transport in semiconductors. As many mathematicians know very well, the theory of complex fluids is designed to deal with fluids with interacting microelements that involve many types of physical forces and fields, that interact across all scales [258, 265, 341], ranging from atomic scale issues of excluded volume to the macroscale fields of electrostatics, even involving boundary conditions 'at infinity' that can couple to the atomic scale, as they do to create the propagating electrical signals of the nervous system.

'Plasmas of life' and the solutions of chemistry can be viewed productively as complex fluids, in my view. The bio-ions of biological plasmas themselves are (relatively simple) microelements that perturb the electric field by their finite size, and introduce other steric constraints. The long range of the electric field guarantees that 'everything interacts with everything else'. The significant size of the ions distorts the electric field substantially. The impenetrability of the ions (see p. 630 of [44]) implies steric constraints that dramatically change the entropy and free energy of concentrations of monovalents greater than ~ 100 mM, or mixtures, particularly those involving divalent ions. The theory of simple fluids is not able to deal well with these complexities as they are found in experiments. A fully self-consistent treat of complex fluids can only do better, I think.

Molecules in solution in general are not as simple as bio-ions. Molecules are microelements that have complex shape and internal dynamics. Molecules interact with all other elements and fields on several scales. Polymers, including proteins, are macromolecules that involve atomic scales and also macroscales. Side chains of the polymer can be microelements themselves. Think of side chains of proteins. One polymer molecule itself can also be a macroelement cm in size (think of our finger nails).

Side chains of proteins are often acids (i.e., have permanent negative charge) or bases (i.e., have permanent positive charge) that mix in an electric stew [365] with water and bio-ions. Polymers are both micro and macro-elements that interact dramatically with other ions through the electric field and steric constraints, as well as their internal properties. Indeed, the

organelles of cells (mitochondria, ribosomes, nucleoli, etc.) are macroelements that form crucial components of the complex fluid inside cells that biologists call cytoplasm.

Outside cells, bio-ions are not alone. In blood, bio-ions are part of what biologists call plasma (when mixed with glucose). Biological plasmas form the highly complex fluid of blood when they mix with a zoo of organic molecules and cells like red and white blood cells and many others. If anything needs analysis as a complex fluid, it is surely blood!

Chemistry occurs in complex fluids. One can argue that classical chemistry (that occurs in the liquid phase) occurs in a complex fluid and needs to be studied as liquid crystals are, by the theory of complex fluids.

Chemistry is about chemical reactions, in which electrons change their relation to nuclei, and so change the properties of molecules dramatically. Chemists have focused their attention on the molecule, atom, and electron for some one hundred and fifty years, so they could develop chemical knowledge and technology. Chemistry textbooks usually ignore the fluid in which chemical reactions occur. This was just as well since mathematical methods to deal with interactions of chemicals and surrounding fluids were not known until very recently.

Chemical reactants in general can be viewed as microelements in a complex fluid. The theory of complex fluids guarantees that models involving chemical reactions and the fluid will be self-consistent. Models of each microelement (reactant) will be needed but models involving all microdynamics of reactants are likely to be intractable. But reduced models of these reacting molecules are often already known. Those have been the output of research in the chemical sciences for a very long time. These models of reactants can be formalized and perhaps improved by appropriate extensions of the theory of inverse problems, I suspect. The theory of inverse problems can help identify the variables that determine macroscopic flows and separate them from the variables that do not have large effects. Reduced models are models that account for the important variables that determine macroscopic flows and phenomena.

Chemical reactions can be treated by the theory of complex fluids applied to reduced models. I imagine the theory will include interactions of microelements (reactants) involving rearrangements of internal (electronic) structures of reactants, according to Schrödinger's wave equation of the electron, coupled to the local transient highly concentrated environment of ions and water in which the reaction occurs, and to the ions and water (and boundary conditions) of the bulk solution in general.

Dilute ionic solutions. Fortunately, the study of bio-ions does not depend on the study of the Schrödinger equation. Bio-ions can be studied by classical methods of physical chemistry, starting with the theory of dilute ionic solutions.

Historically, the mathematics of ***dilute*** ionic solutions is often idealized by the family of Poisson Boltzmann equations, starting (as far as I know) with the Gouy Chapman and Debye Hückel theories of a century ago, more or less. (Dilute ionic solutions have concentration below 1 mM, if one adopts the stringent view of experimental physical chemists, p. 55 of [520]. A less stringent concentration limit is good enough from my point of view, say 50 or even 100 mM.)

Reincarnated as the Poisson Boltzmann or (in different form) as the Born model of ionic solutions, such equations have also received a great deal attention as beginning models of proteins in biological systems [505, 502, 498, 500, 509, 510, 210, 217, 411, 431, 213, 303, 212, 236, 64, 208, 214, 218, 513, 209, 257, 506, 126, 397, 455, 454, 211, 504, 508, 453, 256, 16, 219, 14, 17, 204, 237, 255, 15, 515, 206, 207, 171, 222, 501, 507, 134, 188, 355, 479, 489, 88, 90, 125, 203, 354, 362, 428, 450, 490, 89, 202, 289, 353, 460, 503, 24, 67, 73, 130, 205, 271, 392, 499, 72, 84, 87, 167, 292, 374, 379, 459, 281, 471, 476, 527, 85, 138, 288, 290, 512, 71, 86, 220, 302, 346, 415, 511, 10, 245, 282, 291, 301, 335, 336, 375, 467, 525, 91, 173, 172, 215, 296, 344, 390, 92, 216, 376, 466].

Poisson Boltzmann equation. The mathematical properties of the Poisson Boltzmann equation have been reviewed recently in SIAM Review [518], which can serve as an entry to this immense literature, as can [38, 160, 150]. It is gratifying to see that the power of modern computational mathematics is being focused on ionic solutions [518, 335, 336, 523, 92, 524, 68] and much more work no doubt that I do not know about. This is certainly an essential first step in applying mathematics to the role of ions in biology.

But the Poisson Boltzmann models analyzed with powerful computational mathematics are only a beginning. These models have a severe limitation. They treat ions as points. The Poisson Boltzmann family of equations is too crude to deal with the concentrations of monovalent ions like sodium, potassium and chloride that occur in biology. These equations fail altogether for the divalent ions like calcium ions that play such an important role throughout biology. These equations do very poorly for the mixtures that are the plasma of life (and the sea water of our oceans). In fact, it is well known, as we have already said, that Poisson Boltzmann is only valid for solutions of one type of monovalent (e.g., sodium chloride), in concentrations below say 10^{-1} M [312, 235, 420, 176, 31, 416, 29, 410, 175, 477, 174, 259, 399, 468, 520, 324, 406, 316, 69, 398, 93, 407, 137, 348, 33, 136, 317, 321, 165, 424, 233, 285, 298, 299, 297, 403, 224, 307, 309, 56, 74, 286, 323, 3, 124, 239, 270, 277, 308, 318, 319, 335, 336, 356, 495, 151, 173, 172, 262, 295, 296, 436, 519, 150, 141, 189, 264, 378, 413, 412, 523, 191, 198, 199, 200, 491, 232, 391, 417, 421, 437, 122, 135, 462]. And of course the Poisson Boltzmann treatments do not deal with flow at all, not even with the stationary (tracer) unidirectional fluxes that define active and passive transport in biological systems [247, 249, 250, 22, 23, 48, 61] as reviewed in the useful historical collection [478] and analyzed by mathematician Ludwig Bass [34, 35, 368, 369].

The powerful mathematics reviewed in [518] needs to be applied to more realistic models of ionic solutions to be useful in dealing with biological function in general. Specific experimental situations certainly exist in which the Poisson Boltzmann approach is useful, but natural biological function almost always occurs in solutions beyond the reach of the Poisson Boltzmann family of equations.

Limitations of the Poisson Boltzmann family of equations are well known to physical chemists and are identified and discussed in innumerable references, including [312, 235, 420, 176, 31, 416, 29, 410, 175, 477, 174, 259, 399, 468, 520, 324, 406, 316, 69, 398, 93, 407, 137, 348, 33, 136, 317, 321, 165, 424, 233, 285, 298, 299, 297, 403, 224, 307, 309, 56, 74, 286, 323, 3, 124,

239, 270, 277, 308, 318, 319, 335, 336, 356, 495, 151, 173, 172, 262, 295, 296, 436, 519, 150, 141, 189, 264, 378, 413, 412, 523, 191, 198, 199, 200, 491, 232, 391, 417, 421, 437, 122, 135, 462, 41]. As recently stated by leading experimentalists,

> **"It is still a fact that over the last decades, it was easier to fly to the moon than to describe the free energy of even the simplest salt solutions beyond a concentration of 0.1 M or so."**

This quotation states the common knowledge of the physical chemistry community for many decades, earlier stated, for example, by Torrie and Valleau [477], referring to the Poisson Boltzmann family of models:

> **"It is immediately apparent that classical theory has broken down completely. It …. fails to show [the] qualitative behavior [and] is seriously in error for quite low concentrations and charges".**

In verbal discussions, physical chemists customarily describe theories of point particles with language that reflects their feelings more than their rational analysis. Theories of ionic solutions that describe ions as points elicit an emotional response from physical chemists, because such theories have been known to be inadequate for nearly a century. The fundamental difficulty is that classical theories are obviously unable to fit data at any useful concentration, see the text of Barthel. *et al.,* [33] who say on p. 325, with slight paraphrase,

> **"Theories with point ions are restricted to such low concentrations that their experimental verification often proves to be an unsolvable task."**

The classical text of Robinson and Stokes ([420] not otherwise noted for its emotional content) gives a glimpse of these feelings (usually confined to verbal discussions) when it says on p. 302

> **"In regard to concentrated solutions, many workers adopt a counsel of despair, confining their interest to concentrations below about 0.02 M, ... "**

Theories fail altogether in the view of these experimentalists [33], [420] unless they deal with screening and also include a distance of closest approach.

The despair comes (I imagine) from the immediate realization that a distance of closest cannot be defined uniquely when different types of ions of different diameter are present, and so theories that describe ions as points are either unable to deal with data (if they do not include a distance of closest approach) or illogical (if they try to describe mixtures of bio-ions, like biological solutions, with a single distance of closest approach).

Feelings are made worse when one realizes that all biology occurs in mixtures of ions of quite different diameter. Ions of quite different diameter are likely to produce layering of charge in their ionic atmosphere. Charge is likely to layer in concentric shells around a central ion, if the ions have different signs of charge, or even just different charges (like K^+ and Ca^{2+}). In these cases, the layering will produce complex electric fields, allowing rectification, and other phenomena of great complexity , as layering does near charged walls [267, 31, 37, 260, 262] and in semiconductors. Layering of charge is responsible for most of the remarkably useful

nonlinear properties of semiconductor devices, including transistors and the full range of nonlinear devices that make our digital technology possible [457, 472, 363, 488, 147]. The frustration of dealing with an illogical inappropriate theory that obscures such important phenomena tends to produce an emotional response among physical chemists, as it would in most of us.

Many review papers and textbooks have quotations of similar pungency (e.g., [33, 165, 173, 321, 324, 323, 468]). Many physical chemists have used far stronger language in private than I think appropriate to reproduce here. They particularly are concerned by the motivation of workers in other fields who ignore nearly one hundred years of experimental physical chemistry, all of which comes to the same conclusions, just discussed, and is easily accessible in papers, reviews, monographs, and textbooks.

It is understandable that mathematicians are unfamiliar with the reality of ionic solutions, despite the physical chemists knowledge and feelings. The problems with point theories arise when fitting real data, which is complex and not at all ideal. The experimental setups that measure nonideal properties of ions are intricate. The variables used to describe the ionic solutions are not familiar and the literature is hard to deal with in practical library terms. It is very large (see compendia [235, 420, 106, 410, 259, 520, 398, 308, 318, 264]) but it is hard to find in computer archives because so many of the measurements were made before 2000.

Mixtures like biological solutions are never ideal or simple. The experimental work shows very clearly, however, that nonideal properties are particularly important in mixtures like sea water and the various 'Ringer' solutions outside and inside cells, where calcium ions always play an important role, and in the highly concentrated solutions in and near DNA, enzyme active sites, ion channels, and the electrodes of electrochemical systems. The first pages of Fraenkel [173] states the situation well in a few paragraphs.

The most important reason for the failure of the Poisson Boltzmann theories is simple. Those theories treat ions as points, but in almost all solutions the size and shape of particles are important. The chemical tradition is based on the theory of simple fluids built on the understanding of ideal gases [60, 429] which are infinitely dilute without interactions. The modern theory forms a beautiful highly refined body of work [29, 32, 234, 233, 417], but it still does not easily accommodate long range fields, and their boundary conditions, finite size (because the closure problem remains unsolved), or multiple body interactions. Nonuniform (spatial) boundary conditions, and flow are not present in most of these theories despite their importance in technology and biology. Even extracellular solutions in the biological context are too complex to be viewed as simple fluids, in my opinion, because they are (nearly) always away from equilibrium, with flows of some component or other, and are mixtures involving long range forces, boundary conditions, and multiple body interactions of impenetrable bio-ions.

Not all biological solutions are as simple as extracellular solutions of bio-ions. Not all extracellular solutions are so simple. Most biological solutions contain organic molecules made

of many atoms joined by covalent bonds and so have complex shapes and exceedingly complex movements and internal 'vibrations' as well. These molecules are so complex and interesting from a chemical point of view that the entire profession of organic chemistry has been devoted to their study for nearly 150 years. (A glance at the literature of organic chemistry, through a search of the internet, shows a depth and complexity approaching that of the entire discipline of mathematics!) In the simplest context, think of ATP, or amino acids, or even the natural bicarbonate buffer found throughout life (unavoidable because the CO_2 of the atmosphere dissolves into any solution exposed to air). All of these molecules consist of many atoms joined by covalent bonds with various properties that allow a wide variety of internal motions, both vibrations and rotations. All of these molecules have many atoms with a definite permanent charge, so the atoms interact by the electric field directly, by the properties of their covalent bonds, and by their resulting impenetrability. Any solution of an organic molecule is a highly complex fluid.

Internal dynamics of organic molecules are important, as they are in the microelements of many complex fluids, if the molecule is more complex than a sphere. Many of the important molecules dissolved in a biological plasma are much more complex than a sphere. All the metabolites of classical biochemistry are organic molecules of some complexity. Nucleic acids and proteins are polymers with internal motions of great complexity. Clearly, the internal dynamics of metabolites and polymers need to be included in a complete description of a biological plasma. No one has known how to do that (historically: [139, 473, 474]). Treating these systems as microelements in a complex fluid represents a new departure of great potential.

Even the simplest solutions need a theory of complex fluids. The electric field of the ionic spheres depends on their diameter; the steric exclusion of the spheres involves large excess (free) energies because the number density of these spheres is very large where it matters. Even in solutions like sea water, the number density in the ionic atmosphere *near each ion* is large enough to make the finite size of ions important. The electric field near a dense mixture of spheres is quite different from the electric field of an infinitely dilute set of points. The steric repulsion of the crowded sphere is also important. The inner shell of the ionic atmosphere would be very different if ions were points.

Free energy of one type of ion depends on the number density of *ALL* other types of ions in real ionic solutions. This is the fundamental fact that makes simple treatments of ionic mixtures so difficult. The idea that ions move independently in bulk solution is simply false. Only under the most extreme conditions (e.g., monovalents below 1 micromolar concentration) is independence a decent approximation. Even at 1 millimolar concentration the ions of a monovalent salt like Na^+Cl^- are strongly coupled by the electric field and do not behave independently at all. That is exactly why PNP and Poisson Boltzmann were introduced.

In biological conditions, ionic solutions are nothing like ideal. Everything interacts with everything else. The 'driving force' for the movement of any type of ion depends on the concentration (and perhaps flow) of all other types of ions.

This is an experimental fact apparent in the tables of measurements from innumerable laboratories [41, 106, 235, 259, 264, 308, 318, 410, 420, 520] and the many attempts to simulate or model such systems [235, 420, 408, 410, 418, 259, 399, 520, 324, 406, 316, 69, 398, 315, 137, 33, 136, 232, 165, 62, 403, 224, 307, 74, 166, 227, 284, 286, 300, 323, 3, 124, 239, 270, 293, 308, 318, 319, 356, 495, 151, 173, 172, 262, 295, 294, 296, 400, 491, 519, 521, 141, 189, 264, 41]. Many important attempts and measurements undoubtedly exist that regrettably I do not know about.

In the idealized solutions of textbooks, solutes are totally isolated and solutions exist without containers or boundaries. Nothing interacts with anything in these idealized solutions but ***'everything interacts with everything'*** in the reality of ionic mixtures of living solutions. Nothing interacts by repulsion in the family of Poisson Boltzmann theories, although of course everything interacts electrostatically as points would. Geometric shapes and interactions between ionic particles do not exist in Poisson Boltzmann, so spherical (and of course other) shapes cannot 'distort' the electric field or have excluded volume. Molecules cannot have internal motions in Poisson Boltzmann, if they can be said to exist at all.

Ions are usually crowded where they are important. These difficulties all acquire startling importance near electrodes in electrochemical cells or near DNA, ion channels or enzymes, where ions are crowded together sometimes to the exclusion of water. Indeed, Poisson Boltzmann theories fail most dramatically to describe ions in just those places where ions are most important, near and in the structures that use ions to control or perform macroscopic functions.

Recently, these problems have been noticed by mathematicians and a number of approaches have been tried in papers I know of [335, 91, 92, 523, 524, 37, 268, 266, 155, 423, 422, 198, 426, 200, 191, 425]. (No doubt many papers have, to my regret, escaped my attention.) These approaches differ in many ways and it is far too early to choose among them. In my opinion, the correct model and the correct mathematics to implement that model are both unknown. All the models and methods must be tested against actual experimental data before scientists and mathematicians can choose intelligently among them. Fortunately, a great deal of experimental data has been available for a very long time, and new techniques are providing new data all the time. The data best known to me concern the flow of ions through proteins called ion channels [102, 103, 105, 104, 226] that control a large fraction of life.

Ion channels are among most important devices in biology. Channel proteins are natural nanovalves that control the flow of ions and thus a wide range of biological phenomena [244, 159, 158, 141, 147]. The following description of ion channels is adapted from an article I have written for the Springer *Encyclopedia of Applied Electrochemistry* (editors: Savinell, Ota, Kreysa) that will appear in the next year or two.

Ion channels are proteins with holes down their middle that control the flow of ions and electric current across otherwise impermeable biological membranes [21, 359, 246, 435]. The flow of Na^+, K^+, Ca^{2+}, and Cl^- ions have been central issues in biology for more than a century. The flow of current is responsible for the signals of the nervous system that propagate over

long distances (meters). The concentration of Ca^{2+} is a 'universal' signal that controls many different systems inside cells. The concentration of Ca^{2+} and other messenger ions has a role in life rather like the role of the voltage in different wires of a computer. Ion channels also help much larger solutes (e.g., organic acid and bases; perhaps polypeptides) to cross membranes but much less is known about these systems.

Ion channels can select and control the movement of different types of ions because the holes in channel proteins are a few times larger than the (crystal radii of the) ions themselves. Biology uses ion channels as selective valves to control flow and thus concentration of crucial chemical signals. For example, the concentration of Ca^{2+} ions determines whether muscles contract or not. Ion channels have a role in biology similar to the role of transistors in computers and technology[147]. Ion channels control concentrations important to life the way transistors control voltages important to computers.

Specifically, the selectivity of the ryanodine receptor of cardiac and skeletal muscle can be understood with a model with less than a dozen parameters that never change value [191]. Detailed properties of the current through the channel were successfully predicted (in quantitative detail, with errors of a few per cent) with this model, often before the experiments were performed. Predictions were successful after drastic mutations, and in many (>100) solutions, of widely varying composition.

The calcium channel of cardiac muscle has a complex pattern of binding of ions that can be understood (over four orders of magnitude of concentration in many types of solutions, containing Na^+, K^+, Rb^+, Cs^+ , Ca^{2+}, Ba^{2+}, Mg^{2+}, and so on) with a model containing two or three parameters [59]. Specific mutations change this model of a calcium channel into a sodium channel [58] just as the mutations change the selectivity in experiments. A reduced model can explain these data. The model has just three parameters that never change value, namely the diameter of the channel, the dielectric coefficient of the solution, and the dielectric coefficient of the protein. Ion diameters in the model never change value. Reduced models of this type have not yet accounted for the selectivity of potassium channels and it is not clear if they can. Reduced models are not alone in this failure. High resolution models of potassium channels are also unable to compute selectivity under a range of concentrations resembling those found in experiments and biological systems. References to this immense literature can be found in [1]

Simulations of reduced models [491] and analysis [377, 421] give a feel for how far one can go with simple models of hard spheres in a dielectric in physical systems. Gillespie's work on ion channels [191] shows how far one can go in biological channels that use flow (see his Supplementary material), along with [58, 57, 59] reviewed in [141].

Biology can be easier than chemistry. In many cases, biology can be described by reduced models that do not work in ionic solutions in general. The reason seems clear. Biological systems often evolve to have simple robust properties so the systems can interact with other biological systems in a reproducible way. Life consists of modules connected together into larger modules, and then into larger modules, again, eventually making organisms, and even populations of organisms. It is hard to see how life could exist if the modules themselves did

not have robust reasonably simple properties under natural conditions. Indeed, engineers take the same approach as evolution, although one uses logic (and the marketplace) and the other uses natural selection of random mutants (its own kind of marketplace). Engineering systems are designed to follow robust and simple rules. A collection of transistors connected randomly have no simple description. The same transistors connected with a definite structure can form an amplifier, with a robust and simple description. The amplifier multiplies its input by a constant. A specific and complex structure is needed to perform this simple function in engineering. A specific and complex structure is needed to perform simple functions in biology.

Both engineers and evolution use complex structures to make interacting physical laws execute simple robust behavior necessary for machines or life.

The most striking success of these reduced models has been the description of the main calcium channel that controls contraction in muscle (and appears in neurons and many other cell types as well, so far with unknown function), the Ryanodine Receptor RyR [164, 278, 371, 80, 76, 77, 78, 169, 370, 201, 497, 389].

Gillespie has shown that an extension of the reduced model called PNP-DFT [198, 199, 200] does remarkably well [191, 193, 196, 197, 314, 313] in predicting experiments of some complexity and subtlety (i.e., anomalous mole fraction effects and three cation mixtures) as well as drastic mutations changing charge densities from some 13 molar to zero. Specifically, the selectivity of the ryanodine receptor of cardiac and skeletal muscle can be understood with a model with less than a dozen parameters that never change value [191]. Detailed properties of the current through the channel were successfully predicted (in quantitative detail, with errors of a few per cent) with this model, often before the experiments were performed. Predictions were successful after drastic mutations, and in many—more than one hundred—solutions, of widely varying composition.

Many of these predictions were made before the experiments were done. Other experiments had been done previously, for work with a related but unsatisfactory reduced model that did not deal correctly with the impenetrability of bio-ions [80, 77, 78, 76]. That theory was developed [198, 199, 200] before variational methods were known to me, and is not self-consistent.

Reduced models have been applied to other channels. The calcium channel of cardiac muscle has a complex pattern of binding of ions that can be understood (over four orders of magnitude of concentration in many types of solutions, containing Na^+, K^+, Rb^+, Cs^+ , Ca^{2+}, Ba^{2+}, Mg^{2+}, and so on) with a model containing two or three parameters [59]. Specific mutations change this model of a calcium channel into a sodium channel [58] just as the mutations change the selectivity in experiments. A reduced model can explain these data. The model has just three parameters that never change value, namely the diameter of the channel, the dielectric coefficient of the solution, and the dielectric coefficient of the protein. Ion diameters in the model never change value. Reduced models of this type have not yet accounted for the selectivity of potassium channels and it is not clear if they can.

The original publications [155, 266] computed curves of binding selectivity in two classical channels of considerable biological interest the calcium channel of cardiac muscle [230, 310, 229, 9, 243, 366, 238, 367, 163, 365, 440, 59, 154, 55, 313] and the voltage activated sodium channel of nerve [247, 248, 22, 49, 45, 47, 110, 46, 401]. Both were represented by a reduced model of the protein in which side chains are represented as spheres free to move within the channel selectivity filter, but not able to move out of that region [58, 57, 59, 55, 221, 153, 141].

This model has proven remarkably successful in dealing with the important selectivity phenomena of these channels. A single model, with one set of parameters that are never changed, using crystal radii of ions, and one dielectric coefficient and one channel diameter, is able to account for selectivity data in a wide range of solutions (over 4 orders of magnitude of calcium concentration, and in solutions of varying K^+, Na^+, Rb^+ and Cs^+ concentration, for example). The calcium channel is represented by side chains Glu Glu Glu Glu and the sodium channel by Asp Glu Lys Ala. This work is reported in some 35 papers using various numerical methods including the variational model described here.

Inverse Problem has been solved. It has been possible to invert the analysis of reduced models of the calcium channel. The inverse problem of determining the distribution of side chains inside the channel from current voltage relations in a range of solutions has actually been explicitly solved, using established methods of inverse problems, including the effects of noise and systematic error [66]. In fact, the inverse problem was well-posed, with the problem being too much data, not enough, in contrast to the forward problem, where current voltage curves predicted by these models are exquisitely (and frighteningly) sensitive to tiny changes in the model, including tiny changes in diameter or structure[154, 141, 221]. In the forward problem, the structure is so important that it must be a computed consequence of the forces, an output of analysis, if results are to be reliable. Simulations must compute these structures (and the distribution of these structures) reliably if predictions of current voltage relations are to be robust.

Inconsistencies in DFT-PNP. The DFT-PNP method [198, 199, 200, 66, 193, 194, 197] model is built on an approximate treatment of ions in water [198, 199, 200] in which the excess free energy of a system without flow is simply added to the classical free energy of the PNP model. It does not deal explicitly, if at all, with effects of the electric field (e.g., relaxation and dielectrophoresis effects) identified and studied in classical work on ionic conductance [179, 177, 180, 186, 178, 181, 183, 184, 185, 182, 187, 287], even in textbooks [321]. DFT-PNP also assumes local equilibrium, as do other approaches using combinations of simulation and PNP equations [121, 54, 432]. Assumptions like these are reasonable in and near a channel protein, where the ionic atmosphere is dominated by the protein itself and flows are not too large. (It is interesting that those deviations that are found between theory and data for Gillespie's model of the ryanodine receptor ([191], see Supplementary Material) seem to occur mostly when flows are large and the assumption of local equilibrium is in danger.)

For bulk solutions in general, the lack of self-consistency in PNP-DFT prevents it from being automatically accepted as a good general model of ionic solutions in my view [287]. Use of DFT-

PNP for bulk solutions, will remain problematic in my view, until it is shown to agree with classical results and analysis of ionic conductance in bulk solutions [179, 177, 180, 186, 178, 181, 183, 184, 185, 182, 187, 287].

Local equilibrium assumed in DFT-PNP is inconsistent with global flow. I am concerned about the assumption of local equilibrium in DFT-PNP (applied to bulk solutions) because it is not consistent with the existence of flux. It must be clearly understood that any assumption of local equilibrium is also an assumption of local zero flux. It is not clear how a system can have zero local flux and long range substantial flux, particularly when the system is a nanovalve connected in series with a high impedance entry process, and macroscopic baths. It is not clear that the tension between incompatible assumptions can be resolved in a unique way giving well posed predictions to compare with experiments. Theories with ambiguous predictions can create significant confusion in science that takes decades to resolve.

An important advantage of the energy variational methods discussed later in this paper [342, 456, 522, 132, 345, 155, 269, 266, 524, 523, 382, 433] is their precise definition as part of the theory of complex fluids. The methods provide unique results because the mathematics is unique. The methods are, for example, indifferent to flow. The variational treatment of ionic conductance [267, 382, 266, 269, 155] makes no simplifying assumptions about local equilibrium: everything (that is in the model) interacts with everything else, to minimize the dissipation and (Helmholtz free energy) of the model. The methods work when flows are vigorous and when they are zero, at thermodynamic equilibrium. Thus, calculations can be done in the nonequilibrium situations and mixed ionic solutions used nearly always in experimental work.

Assumptions of local equilibrium have been made before, e.g., in the theory of Brownian motion over potential barriers, Kramers' problem [162, 170, 231, 306, 304, 311, 386, 387, 388, 393, 409, 445, 444, 443, 446, 448, 447, 449, 465, 485]. Subtleties and near paradoxes [170, 231, 485] were not resolved for years, until a self-consistent analysis was performed [162, 305]. That analysis took several years because we had to deal with a second order Langevin equation (with sets of doubly conditioned trajectories [162, 305] corresponding to the unidirectional fluxes of macroscopic biophysics) even though friction dominated the problems. Previous treatments (for example, those of Smoluchowski, Langevin, Einstein, and van Kampen) of a first order stochastic differential equation had to be replaced with a second order stochastic equation so a pair of boundary conditions could be satisfied. Those equations were solved using a singular perturbation analysis to introduce the high friction case into the resulting Fokker-Planck equations. A pair of boundary conditions was an absolute requirement in our view if we were to account for macroscopic diffusion, as described by Fick, in which ions move from one concentration to another and thus satisfy two boundary conditions. The classical treatments of Smoluchowski, Langevin, and Einstein use first order Langevin equations which can only satisfy one boundary condition and thus cannot account for the classical phenomena of macroscopic diffusion.

With this stochastic analysis, the paradoxes of flow at equilibrium resolved into the simplicity of the classical theory of mass action [150]. Much to the surprise of the authors, the

classical theory of the theory of mass action turned out to survive this detailed stochastic analysis of the underlying Kramers' problem. Diffusion between two concentrations as in Fick's original treatment of macroscopic diffusion could be written exactly as rate equations of the theory of mass action. The classical theory was preserved in form, but the rate constants of the diffusion reaction acquired more precise meaning. Explicit expressions for rate constants for diffusion. The rate constants were variables, not constants. Thus, classical work using rate formulations for diffusion were justified, under one set of conditions. But if conditions were changed, as is almost always the case in experiments and applications, rate constants had to be changed, if the theory was to describe diffusion over a barrier, i.e., Kramers problem. Solving this Kramers problem in a self-consistent way took a number of years. Replacing the inconsistent assumption of local equilibrium allowed derivation of a simple and powerful representation of diffusion as a chemical reaction.

Returning now to DFT-PNP, I make the obvious conclusion. The difficulties in DFT-PNP produced by the assumption of local equilibrium (inconsistent with the existence of global flow) are hard to foresee and are likely to be even harder to resolve. The complex phenomena of classical conduction theory (best described in Justice [287], in my view) may not all be present in DFT-PNP with its inconsistencies. DFT-PNP depends on physical approximations that were the best that could be done at the time [199, 198], but those approximations cannot substitute for mathematics, in my view, in the general case of bulk solutions.

I think it preferable to use methods that are inherently self-consistent and do not contain the possibility of internal paradox. An important advantage of the energy variational methods discussed below [342, 456, 522, 132, 345, 155, 269, 266, 524, 523, 382, 433] is their automatic extension of equilibrium operators to nonequilibrium situations (produced for example by spatially non-uniform boundary conditions) in a mathematically precise and defined way, always fully self-consistent.

Molecular Dynamics Simulations of Proteins. Proteins allow atomic scale structures to control macroscopic function so it is natural to seek understanding with models that include all atomic detail using the methods of molecular dynamics to compute atomic motion.

Simulations of molecular dynamics by themselves so far have not helped provide understanding of equilibrium let alone flow of living solutions, mixtures of mono- and divalents. Simulations of molecular dynamics do not describe the activity—let alone flows—of mixtures of ions in biological solutions that are always mixtures where calcium is usually important. Simulations have grave difficulties dealing with the range of concentrations that are controlled in biological experiments (roughly, 10^{-10} to 1 M). ***By themselves*** it seems that simulations can never solve these problems because of the multiscale issues that must be dealt with ***all at once.*** Interactions of so many types across so many scales are just too much [151, 141] to deal with numerically. Indeed, interactions are so strong, variable, and subtle that even the definition of the properties of single ions (hypothetically non-interacting) is a daunting task taking 664 pages and 2406 references [264] in a recent monograph from leading workers in the field.

It is hard to know how one could even write force fields (of the type used in classical or polarizable molecular dynamics) that would work in the concentrated environments near and in DNA, enzyme active sites, or ionic channels [480, 340, 261]. I remind colleagues that such force fields and simulations must actually calculate the activities of ionic solutions and mixtures correctly. It is not good enough to calculate them incorrectly or in some idealized infinitely dilute solutions. Biological molecules require bio-ions (that accompany the molecules in Ringer solutions, for example) to of the right type and in the right amount (i.e., concentrations). These are the solutions used by experimental colleagues and they must be calculated correctly if the simulations of molecular dynamics are to deal with experiments as they are actually done.

A major problem facing molecular dynamics is that atoms move a great deal, at the speed of sound, as a first approximation [43], and so computations must resolve 10^{-16} sec. Little biology happens faster than 10^{-4} seconds. Atomic scale computations must extend over 12 orders of magnitude in time if they are to compute biological function.

Current flow through channels depends on bulk concentrations of ions ranging from 10^{-7} M (or even much less) to 0.5 M. Concentrations of ions in and near ion channels (and in and near active sites of enzymes) are much higher, even larger than 10 M because the systems are so small and have large densities of permanent charge from acid and base side chains of proteins. Computations of these concentrations must include nonideal properties of highly concentrated interacting solutions and side chains because these are known to be of great importance in ionic mixtures or solutions greater than 50 mM concentration. Simulations in full atomic detail must also include staggering numbers of water molecules to deal with the trace concentrations of 10^{-11} to 10^{-7} M of signaling ions, e.g., Ca^{2+}.

Molecular dynamics of biological function must be done in nonequilibrium conditions where flows occur, because almost all biology occurs in these conditions. Simulations have difficulty dealing with the action potentials of nerve and muscle fibers. Molecular dynamics cannot compute the billions of trajectories of ions that cross membranes to make action potentials, lasting milliseconds to nearly a second, flowing centimeters to meters down nerve axons. Simulations at present cannot deal with flows that are controlled by channels on the atomic scale but couple to boundary conditions on the macroscopic scale, millimeters away from the channel. Many biological systems use atomic scale structures this way to control macroscopic function.

Simulations must deal with all issues of scale at once, because biology uses them all at once. For these reasons, molecular dynamics cannot deal directly with biological function, as of now. A multiscale approach with explicit models and calibrated links between scales seems unavoidable, as in the analysis of the propagating voltage signal of nerve fibers, and in engineering technology [141], in general.

Multiscale reduced models of ion channels are feasible. Reduced models of some open ionic channels have proven surprisingly successful [141] as previously discussed. In several cases, it has been possible to understand, and predict experimental results before they were done. Channels have been built that behave as expected [496].

Successful reduced models include surprisingly little atomic detail; for example, they treat water as a continuum dielectric and side chains as spheres. It is not clear why a sensitive biological function like selectivity can be explained with such little regard to the atomic details of hydration and solvation, but the evidence is clear. In several important cases, the explanation is successful.

Experiments depend sensitively on some variables but not on others. Experiments on ion channels are designed for a reason and typically depend sensitively on some variables but not on others. Even the name of ionic channels depends on the identification of their 'reversal' potential' with the gradient of chemical potential of a particular ion. Simulations must calculate the chemical potential of ions correctly in the bulk if ion channels are to be named correctly. Accuracy of ±5 mV is needed because the thermal energy of biological diffusion is $k_B T/e = 25\text{mV}$. Simulations must calculate the chemical potential of ions correctly in and near enzyme active sites, ion channels, and binding proteins if the function of these biological systems are to be understood. One step would be to show that molecular dynamics simulations correctly calculate the chemical potential of ionic mixtures near boundaries of physical systems [262].

Biological reality must determine the choice of mathematical treatment. Certainly, the mathematical treatment of ionic solutions in biology must deal with mixtures of different ions of widely different concentrations. Biologists typically deal with concentrations from molar to nanomolar, or even smaller, in their daily experiments.

Certainly, the mathematical treatment of ionic solutions must deal with flows [61]. Gradients and flows are used in biology to create the devices and machines of life, rather as they are in engineering. Engineering devices are hardly worth studying when their power supplies are turned off and their simple device laws no longer hold true. They also are far more complex and sensitive to irrelevant conditions, when they are at thermodynamic equilibrium, no longer a robust device. Living systems are much less interesting when they are dead, whether those systems are corpses or crystallized proteins. One cannot expect living systems to be the same devices when dead as they are when alive. Mathematics must describe biological reality and experiments as they actually occur.

Biology occurs in complex ionic system in which everything interacts with everything else. It seems obvious that such interacting systems need to be analyzed by mathematics designed to handle interactions, not be mathematics designed to handle ideal noninteracting systems (like the perfect gases of thermodynamics). The mathematics of interacting systems must always be self-consistent. Otherwise, descriptions of one set of conditions can only work under that set of conditions. When any condition changes, everything changes (if everything interacts with everything else), and so all interactions change. There seems no hope of catching such changes in interactions in a sequence or composite of non-interacting models. Rather, one needs a mathematical structure that deals with interactions automatically and self-consistently. In such a structure, interactions automatically change (as required and specified by mathematics) when any one physical condition or component is changed.

Mathematics must describe biological 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 ([264]: 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.

Importance of self-consistent analysis can be seen in the history of semiconductor physics and computational electronics [457, 486, 357, 228, 469, 30, 472, 451, 363, 427, 458, 279, 405, 263, 419, 120, 242, 352, 225, 168, 461, 123, 488, 487]. The analysis of semiconductor devices has always sought to be self-consistent. Interactions of point quasi-particles (holes and 'semi-electrons' [109, 149, 147]) have been treated self-consistently, along with both short and long range properties of the electric field. It is the correct treatment of interactions that has made possible the enormous progress of Moore's law [419, 457, 488, 380, 381, 351]. Without a correct mathematics of interactions, without self-consistent analysis, one must do trial and error experimentation. The methods of trial and error analysis have been wonderfully refined in the biological and pharmaceutical sciences. Nonetheless, refined as they may be, they are far from as efficient as self-consistent analysis. One cannot imagine an airplane [12], particularly a supersonic airplane, designed by trial and error analysis. Trial and error analysis cannot deal productively with highly interacting spatially varying systems with flows on all scales [11, 12, 20, 133, 283, 528, 50, 51, 190, 258, 322, 269, 434, 132, 345]. For that reason, I believe trial and error analysis of ionic and biological systems needs to be supplemented by self-consistent mathematics designed to deal with the interactions that characterize complex systems.

Complex systems are well described by variational methods [269, 68, 132] well known to mathematicians. Sadly, the power of these methods is not well known to biologists and chemists so I describe some of that power here, despite the danger that I am reiterating to mathematicians what they know better than I. Perhaps it is important for mathematicians to be reminded of the properties of self-consistent and variational methods that biologists and chemists do not know as well as they might.

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 [335, 526] 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.

Self-consistent energetic variational methods allow one to ***derive*** the differential equations that describe the system. It is difficult to write down such equations when many fields and components are involved without a derivation from a variational principle. It is all too easy to leave something out, including effects from different physics, described as a different field, often on different scales, or to invent many parameters that are hard to determine. It is difficult to know how to add components or fields without disturbing the other parts of a system of partial differential equations. A great deal of experimentation consists of simplifying systems and then adding back components or fields one by one. It is difficult to describe such situations self-consistently if one combines partial differential equations.

Variational methods allow components and fields to be added or subtracted in functionals, from which differential equations are derived by the Euler Lagrange process. Energy variational methods [342, 456, 522, 132, 345, 155, 269, 266, 524, 523] allow one to describe systems with energy and dissipation functionals from which partial differential equations are derived. The resulting partial differential equations are always self-consistent, if the algebra is done correctly.

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 [132, 269] to be a natural extension of thermodynamics, joining free energy and dissipation functionals, as envisioned by Onsager and followers. These methods combine [132, 155, 382, 433] 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 [269] illustrates the approach.

The mathematics of variational methods is consistent with itself, but it may not be consistent with the real world. Energy variational methods are not magic. If the underlying models are incorrect or incomplete, the results of a variational analysis will be incorrect or incomplete. But the variational results are never inconsistent mathematics and they can be derived to have minimal free parameters.

Conclusion. I write to tell the mathematical community of biological reality and mathematical challenge. The mathematical analysis of ionic solutions is a topic of profound importance and opportunities. It looms almost too close to see.

Mathematicians can use energy variational principles to deal with the reality of charged spheres in a frictional dielectric. They can then move to describe the water more and more

realistically, as experiments dictate. Energy variational methods allow the systematic analysis and improvement of models of the mixed ionic solutions of life. Energy variational methods allow molecules in solutions to be microelements in a self-consistent theory of complex fluids. Classical problems of chemistry and biology can be attacked with the computational power of modern mathematics when a self-consistent variational theory is used to describe the energy and dissipation of these systems.

The Big Picture. 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.

Work on the Poisson-Boltzmann equation [518] sets the stage on which the moving dance of biology can now be studied, as it is actually lived. 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**. I think eventually can be now. It can be done if the community of mathematicians wishes to make it so.

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 perhaps be treated by the theory of complex fluids, as already mentioned, as interactions of microelements (reactants) involving rearrangements of internal (electronic) structures of reactants, according to Schrödinger's wave equation of the electron.

Challenge. I challenge mathematicians to apply their tools and skills to the reality of ions in chemistry and biology. Mathematicians can use self-consistent theories of complex fluids to allow systematic analysis and improvement of models of the plasmas of ionic solutions, in life and in our chemical laboratories. 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. It can be done but not with theories of simple fluids.

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