Rush University

Department of Molecular Biophysics and Physiology
1750 West Harrison Street, 12th Floor, Chicago IL 60612 USA
voice: + 312 942 6454 FAX 312 942 8711
email: beisenbe@rush.edu

C. T. (Tim) Kelley
Editor SIAM Review
tim kelley@ncsu.edu

Gail Corbett
Editor SIAM News
corbett@siam.org

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Dear Editors,

We hope you will help us choose the appropriate forum for the attached comments. We believe SIAM NEWS would be a good choice, because it is widely visible. An article in SIAM NEWS would help so many members of SIAM reach towards biology. We describe what we (immodestly enough) think is a productive application of mathematics to a central problem in biology and chemistry.

The central problem is the mathematical description of the ionic mixtures (solutions) in which life occurs. The function of most of the proteins in a living system depends on the properties and composition of ionic solutions in a sensitive and specific way. Most of chemistry is done in aqueous solutions that contain ions and often mixtures of different types of ions. The ionic solutions of life are mixtures that involve calcium and do not resemble the ideal solutions of textbooks or the Poisson Boltzmann equation. Analysis of the Poisson Boltzmann equation is certainly an essential first step in applying mathematics to the role of ions in biology. But it is only a first step that is useful for developing methods and dealing with a few isolated biological situations. It does not deal with the main issues of biological importance.

The mathematical treatment of ionic mixtures we think appropriate is that of the self-consistent theory of complex fluids and its close cousin transport theory in semiconductors (and probably other theories of transport we do not know much about). 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, ranging from atomic scale steric interactions of excluded volume to the macroscale interactions with charge 'at infinity' that

couples to ion channels (on the atomic scale) to produce the (macroscale) action potential of nerve and muscle [67, 65, 64, 62, 73, 74].

The 'plasmas of life' and the solutions of chemistry can be viewed productively as complex fluids that need to be analyzed self-consistently with several fields across many scales. The (single atom) ions of these plasmas (like sodium and chloride ions) themselves are (relatively simple) microelements that perturb the electric field by their finite size, and introduce other steric constraints. Molecules in chemical solutions in general are multi-atom microelements that have complex shape, internal dynamics, and interactions with all elements and fields on several scales. And polymers, including DNA, proteins, and nylon, are macroscale molecules made of multi-atom monomers. Polymers have their special properties because they are both a micro and a macro-element that interacts dramatically with other ions, forces, and boundary conditions.

We have included in this document many more references than would be appropriate for SIAM News so editors and referees can evaluate our statements of fact. The large existing literature of physical chemistry shows that a widely used simple mathematical model (Poisson Boltzmann theory) is not very useful. We can remove many of the references from a printed version of the paper, or make the full reference list available on the internet ourselves or through SIAM or through the arXiv, if the editors wish to accept the paper for publication.

We are aware of the difficulties and challenges involved in attacking this long lasting problem, as well as its importance. 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, potassium, calcium, and chloride), complex organic molecules like ATP, sugars, carboxylic acids, and bioamines, all of which have essential roles. The tools of classical physical chemistry based on ideal solutions at thermodynamic equilibrium are unequal to the task.

These are central problems in all of biology, unsolved, in our view, because of the lack of tools. Modern analytical methods (of the selfconsistent 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) can attack and probably solve these problems. But first the mathematicians who know these methods must learn of the problem. If they analyze the Poisson Boltzmann equations, they will miss the problems that matter most to living systems.

Thank you for your help in this unusual request. We think you might want to consult experienced investigators in math and chemistry to evaluate our assertions. In math, we think of David Kinderlehrer and Robert Pego from Carnegie Mellon University, Weishi Liu from Kansas University, Martin Burger from University of Muenster, Joe Jerome from Northwestern University, or Charlie Peskin of the Courant. Wei Cai (UNC Charlotte) provoked this letter and document with his admirable paper in SIAM Review and should be consulted, in our opinion. Among the physical chemists, Stuart Rice and Douglas Henderson can provide a good choice of names, as well as review our work. Rich Saykally of UC Berkeley and Tony Watts of Oxford Biochemistry are experimental physical chemists quite familiar with these issues. Wolfgang

Nonner of the University of Miami Medical School can provide names of biophysicists and review the material himself as well, if you wish.

The biological viewpoint is straightforward. We trust you understand that most mathematicians are applying their talents to relatively small problems in the world of biology, at least small in the perspective of experimental biologists. We here present an opportunity (we think) to help focus the skills of mathematicians on a **central** set of unsolved problems in both biology and chemistry. We think that variational methods long used for conservative systems, and sometimes for purely dissipative systems, can now be used to deal with ionic solutions. In essence, we propose that ionic solutions be treated with the self-consistent theory of complex fluids, and not with traditional chemical approximations based on the theory of (infinitely dilute, uncharged) ideal gases. The simplest version of this question grows out of the Poisson Boltzmann equations we directly address in the paper: How do charged spheres behave in a frictional dielectric in which everything interacts with everything else? Fortunately, a huge literature of physical chemistry shows that a simple model of hard spheres in a frictional dielectric is a suitable first (and often second!) approximation to the properties of the mixed single atom ionic solutions of living systems. Fortunately, the theory of complex fluids already has dealt with similar problems.

We hope you agree that this question is a good one to bring to the attention of your readership.

We are

Ever yours

Bob Eisenberg

RS Eisenberg
Bard Endowed Professor and Chairman
Department of Molecular Biophysics and Physiology
Rush University

Chun Liu (with permission)

Chun Liu
Professor
Department of Mathematics
Pennsylvania State University

Mathematics for Life's Solutions

Bob Eisenberg
Department of Molecular Biophysics and Physiology
Rush University and Medical Center
Chicago IL
beisenbe@rush.edu

Chun Liu
Department of Mathematics
Pennsylvania State University
State College, PA
liu@math.psu.edu

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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 problem, with the greatest potential, is too close to see. We are trying to see the big picture of ionic solutions, and thank Stuart Rice, Douglas Henderson, and Dirk Gillespie, and our collaborators Tai-Chia Lin, YunKyong Hyon, and Allen Hrong for the perspectives they have taught us and the many workers on Poisson Boltzmann equations who have set the stage on which we can now play out the moving dance of biology as it is actually lived.

All of biology occurs in salt solutions evolved from the primitive oceans of the earth. Water without the ions of the ocean is lethal. Almost all cells burst when exposed to pure water. Most enzymes denature in distilled water. Ions in water are life's plasma [36].

Ionic solutions in biology are mixtures involving divalents like calcium ions. The selective flow 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. Different ions have different specific biological functions just as signals in different wires in a computer have different specific functions. Indeed, the physical and chemical origin of specific properties can be viewed as the central question of life, as seen by Nobel prize winner Aaron Klug [127].

Ionic mixtures have been studied experimentally in some detail since around 1900. Onsager [60] spent much of his life studying mixtures [122, 121, 123]. Kraus [97] provides a nice summary of the classical literature for mathematicians. Fawcett [41] is a useful clear textbook of electrochemistry and Laidler [103] et al provides a good introduction to physical chemistry for mathematicians. The first pages of Fraenkel [44] summarize the present state of knowledge, as we 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.

The activity of ions, like the height of a mass in a gravitational field, is the place to start. Amazingly enough, the activity of ions in mixtures remains a mystery. The behavior of ions is nothing like the behavior of infinitely dilute ideal solutions (of uncharged noninteracting particles) assumed in textbooks. The empirical formulations used by chemical engineers [95, 164] are not derived from physical models. They include many parameters that need to be modified when the models are applied to new conditions.

The empirical formulations of chemical engineers do not apply to very concentrated salt solutions. Biological solutions are very concentrated where they are most important, close to DNA, in and near active sites of enzymes and proteins, and in and near ion channels. There, number densities (i.e., concentrations) are often many molar, not so different from solid sodium chloride (37 molar).

Only a few of the empirical formulations of chemical engineering apply to flow [85, 139]. Flow ceases in biology only with death. The properties of ionic solutions most important for life are not addressed by traditional approaches. Unaddressed, they cannot be solved.

We are aware of the difficulties and challenges involved in attacking this long lasting problem, as well as its importance. 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 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, potassium, calcium, and chloride) complex organic molecules like ATP, sugars, carboxylic acids, and bioamines, all of which have essential roles. The tools of classical physical chemistry based on ideal solutions at thermodynamic equilibrium are unequal to the task.

These are central problems in all of biology, unsolved, in our view, because of the lack of tools. Modern analytical methods (of the selfconsistent 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, reviewed in [162]) can attack and probably solve these problems.

But first the mathematicians who know these methods must learn of the problem. If they limit themselves to the Poisson Boltzmann equations, they will miss the problems that matter most to living systems. Analysis of the Poisson Boltzmann equation is an essential first step in applying mathematics to the role of ions in biology. But it is only a first step that is useful for developing methods and dealing with a few isolated biological situations. It does not deal with the main issues of biological importance because the Poisson Boltzmann equation leaves out most of the nonideal properties of ionic mixtures, particularly those containing divalents, like sea water and the solutions inside animals.

We view an ionic solution as a specific type of complex fluid that couples hydrodynamics to electrostatics and to the microstructure of charged particles, for example, 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 directly changed by charge on far distant boundaries. We believe that existing methods of the selfconsistent theory of complex fluids will allow rapid progress on previously intractable problems.

The mathematical treatment of ionic mixtures we think appropriate is the self-consistent approach that has had much success in several areas, for example, in the theory of complex fluids and the transport theory 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. Classical treatments focus on liquid crystals [30, 104, 49, 50]. Doi's wonderful review [29] uses variational methods that we have tried to generalize [29, 111, 110, 112, 152, 147, 148, 149] and extend to other systems [75, 39, 76, 77, 119, 145, 35, 36, 37, 31, 146, 147] that involve atomic scale repulsion (produced by excluded volume) and the macroscale fields of electrostatics, even involving boundary conditions 'at infinity' that couple to the atomic scale to produce the action potentials of nerves and muscle [67, 65, 64, 62, 73, 74].

The 'plasmas of life' and the solutions of chemistry can be viewed productively as complex fluids. The single atom ions of biological plasmas (like sodium, potassium, calcium or chloride ions) themselves are (relatively simple) microelements that perturb the electric field by their finite size, and introduce other steric constraints. Molecules in solution in general are microelements that have complex shape, internal dynamics, and interactions with all elements and fields on several scales. And polymers, including proteins, are macromolecules that involve

atomic scales and macroscales. Polymers are both a micro and a macro-element that interacts dramatically with other ions through the electric field and steric constraints, as well as through their internal properties.

Historically, the mathematics of *dilute* ionic solutions (concentration below 1 mM, if one adopts the stringent view of experimental physical chemists, p. 55 of [164], p. 125 of [7]) is often idealized by the family of Poisson Boltzmann equations, starting (as far as we know) with the Guoy Chapman and Debye Hückel theories of a century ago, more or less. 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 solutions.

The mathematical properties of the family Poisson Boltzmann equation have been reviewed recently in SIAM Review [162], which can serve as an entry to this immense literature, as can [11, 40, 37]. It is gratifying to see that the power of modern computational mathematics is being focused on ionic solutions [162, 107, 108, 167, 24, 168, 20] and much more work no doubt that we do not know about. This is certainly an essential first step in applying mathematics to the role of ions in biology.

We note that the Poisson Boltzmann models analyzed with powerful computational mathematics are only a beginning. These models have a severe limitation. 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 that Poisson Boltzmann is only valid for solutions of one type of monovalent (e.g., sodium chloride), in concentrations below say 10^{-3}M (p. 125 of [7]; p. 55 of [164]).

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 [63, 66, 68, 3, 4, 13, 18] as reviewed in the useful historical collection [156] and analyzed by mathematician Ludwig Bass [8, 9, 115, 116].

The powerful mathematics reviewed in [162] 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, sometimes very useful, but natural biological function almost always occurs in physiological solutions and conditions beyond the reach of the Poisson Boltzmann family of equations, because those conditions involve transport, flow, and divalent ions.

A few figures are enough to tell the story of the limitations of the Poisson Boltzmann family of equations: a graph of activity vs. ionic strength shows how badly Poisson Boltzmann does (Fig. 7.22, p. 303 of Laidler's textbook [103] or Facwcett's, Fig 3.6 p. 128; or figures in the definitive reference [164] starting on p. 57). Or one can consult innumerable references, including [97, 59, 138, 47, 6, 135, 5, 132, 46, 155, 45, 69, 125, 154, 164, 106, 129, 99, 21, 124, 25, 130, 34, 113, 7, 33, 100, 103, 41, 142, 58, 83, 91, 92, 90, 128, 55, 94, 96, 14, 22, 84, 105, 1,

28, 61, 79, 80, 95, 101, 102, 107, 108, 114, 159, 38, 44, 43, 71, 88, 89, 150, 163, 37, 35, 48, 72, 118, 134, 133, 167, 51, 52, 53, 54, 158, 57, 120, 136, 139, 151, 27, 32, 153, 12].

The definitive electrochemistry monograph should be quoted at length. Barthel [7] says on p. 125, "The limiting laws of all solutions properties based on the expressions for point-shaped ions … yield correct statistical thermodynamic equations for the properties of electrolyte solutions, but these are restricted to such low concentrations that their experimental verification often proves to be an unsolvable task."

A paraphrase in plainer American would be

> **"Poisson Boltzmann expressions are only valid when ions are present in trace concentrations—often unmeasurable—typically, some $10^5\times$ less than their concentrations in sea water or biological solutions.**

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 0.1M or so."** This quotation states the common knowledge of the physical chemistry community for many decades, earlier stated, for example, by Torrie and Valleau [155], 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". Many review papers and textbooks have quotations of similar pungency (e.g., [7, 41, 44, 103, 106, 105, 154]) and many physical chemists have used stronger language than we use here.

It is unfortunate that the ***experimentally measured*** nonideal properties of ionic solutions are uncited in modern studies, perhaps unknown to modern workers, although accurate measurements were available nearly a century ago. The 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 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. Sometimes the internal dynamics of the molecules are important, as they are in the microelements of many complex fluids. In ionic solutions including organic molecules (that make up the biochemistry of life), microelements would describe each species of amino acid, hormone, metabolite and so on. Each chemical species has its own internal microdynamics that couple with the rest of the system. Mathematics is needed that will selfconsistently describe such complex systems. Different resolution models of the microdynamics will be needed for each chemical species (and type of molecule) because different features are important in some types of molecules (that bend but do not vibrate for example) and different chemical species couple to macroscopic fields in different ways, depending, for example, on how much electric charge they carry.

In the simplest ionic solutions, ions are single atoms of sodium, potassium, calcium and chlorine (called chloride) resembling hard charged spheres. But most of the molecules in biological solutions are made of many atoms joined by covalent bonds and so have complex shapes and exceedingly complex movements and internal 'vibrations' as well. 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).

Even the simplest ionic atomic solutions need a theory of complex fluids to deal with the microstructure of the ions, their spherical shape and (excluded) volume. 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.

Physical chemists have known of the importance of finite diameter of ions 'forever'. It was always apparent that one could not define a **SINGLE** effective diameter for an ion in a Debye Hückel theory of ionic mixtures like those in sea water or extra or intracellular solutions in living systems. The distance of closest approach would clearly be different for different ions (of different diameter) in a mixture. A single 'distance of closest approach' will not do justice to the complexity of the system. Multiple distances of closest approach can produce layering. Layers of opposite charge might be possible under some conditions; even layering that could act like PN or PNP junctions of semiconductors. (Think of electrolytic and modern electrochemical capacitors.) The electric field—even its shape—must depend on the number density of each type of ion. Crudely speaking, 'everything depends on everything else' in the inner shell of the ionic atmosphere.

In real ionic solutions, the free energy of one type of ion depends on the number density of **ALL** other types of ions. This is an experimental fact apparent in the tables of measurements from innumerable laboratories [12, 26, 59, 69, 72, 95, 101, 132, 138, 164] and nowadays best from databanks on the web. For example, the Department of Chemical and Biochemical Engineering, CERE Technical University of Denmark, has 139,175 experimental data [sic] at *http://www.cere.dtu.dk/Expertise/Data_Bank.aspx* on February 10, 2012.. Many attempts to model and simulate such systems come to the same conclusion [59, 138, 131, 132, 137, 69, 125, 164, 106, 129, 99, 21, 124, 98, 34, 7, 33, 57, 41, 19, 128, 55, 94, 22, 42, 56, 81, 84, 93, 105, 1, 28, 61, 79, 86, 95, 101, 102, 114, 159, 38, 44, 43, 71, 88, 87, 89, 126, 158, 163, 165, 35, 48, 72, 12]. Many important attempts and measurements undoubtedly exist that regrettably we 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 dilute solutions and in the family of Poisson Boltzmann theories that describes dilute solutions (of a single monovalent salt like sodium chloride, without divalents or other types of salts), 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.

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 we know of [107, 23, 24, 167, 168, 10, 77, 76, 39, 141, 140, 52, 144, 54, 51, 143]. (No doubt many papers have, to our regret, escaped our attention.) Simulations [158] and analysis [117, 139] 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 [51] shows how far one can progress in dealing with biological channels that use flow (see his Supplementary Material), along with [16, 15, 17] reviewed in [35].

These approaches differ in many ways and it is far too early to choose among them. In our 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.

We write to emphasize the importance of this problem and to try to motivate mathematical work in this field. One can hardly hope to understand living systems if one cannot deal with the simplest properties of the solutions in which they exist. One can hardly hope to understand DNA, proteins, and ion channels if one cannot deal with the simplest properties of the ions they use to perform their functions.

Simulations of molecular dynamics have made amazing progress in the last decades thanks to the efforts of numerical analysts and computational scientists exploiting many iterations of Moore's law. But simulations by themselves so far have not been able to describe *even qualitatively* most of the properties of ionic solutions probably because the electric field couples all scales so strongly even in simple solutions like sodium chloride at solutions more concentrated than a few millimolar. Indeed, interactions are so strong, variable, and subtle that the definition of the properties of single ions (hypothetically non-interacting) is a daunting task taking 664 pages and 2406 references [72].

Simulations have not been attempted of most biological plasmas, like sea water, which are mixtures of monovalent salts (sodium chloride, potassium chloride, and bicarbonates) in which divalents (like calcium and magnesium chloride) are always important, let alone simulations of extracellular solutions in which trace concentrations (10^{-10} M) of (ionic) hormones and (ionic) messengers (10^{-7}M) are vitally important as bearers of specific biological signals. Simulations do not account for the activity—let alone flows—of mixtures of ions in biological solutions where calcium is always important. It is hard to know how one could even

write force fields—of the type used in classical or polarizable molecular dynamics depending on only the distance between two locations, independent of boundary conditions and the locations of other particles—that would work in the concentrated environments near and in DNA, enzyme active sites, or ionic channels.[157, 109, 70]

Simulations may someday be able to deal with such issues, one by one, if verification and validation become professionally required career goals as important as speed and size of calculations. But it seems that simulations can **by themselves** never solve these problems **all at once** as they must. Simulations must deal at once with all the scales that life uses at once. All these scales occur at once as life moves along. Interactions of so many types across so many scales are just too much [38, 35] to deal with numerically. Rather, one will need an approach that combines the resolution of atomic scale molecular dynamics with the range of macroscopic theories (that sometimes have to reach to infinity, when they deal with action potentials for example [67, 65, 64, 62, 73, 74]).

We remind our colleagues that such force fields and simulations must actually calculate the activities of ionic solutions and mixtures correctly in the solutions that actually exist in animals and plants. These are the solutions used by our experimental colleagues and they must be calculated correctly if the simulations of molecular dynamics are to deal with experiments as they are actually done.

Biological experiments are designed the way they are for a reason. Indeed, the history of physiology, which extends recognizably to Aristotle and Harvey, well before biochemistry or engineering existed as sciences, was devoted to the design of such solutions. Biology has first concerned itself with the structures (the discipline of anatomy) and function (physiology) and drug sensitivity (pharmacology) of its systems, so the enormous complexity and diversity of biological systems could be handled first reproducibly, and then intelligently (with the advent of biochemistry in the 19th century and then molecular biology in the 1940's).

Biology has learned how to safely simplify its systems, using the squid giant axon to understand mammalian nerve fibers, for example. Biology has learned which chemical components of biological solutions are essential to maintain function. Biology has learned to create 'preparations' on all scales, whether they are the macroscopic nerve-muscle preparations that taught us how synapses of the nervous system work, or the molecular scale paper/metal models of bacterial DNA [161, 160, 82] that discovered the chemical identity of mammalian genes, or the atomic scale ion currents that carry biological signals through single protein molecules called ion channels.

Some details matter in biological systems and some do not. Even the name of ionic channels depends on details of the calculation of the chemical potential of ions. The identification of a channel depends on the accurate estimate of the 'reversal' potential' of a channel current and its comparison 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 [71].

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. So theories and simulations must do the same.

Certainly, the mathematical treatment of ionic solutions must deal with flows [18]. 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. 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.

It is interesting that devices are also easier to study when they are energized, and follow a simple device law than when their power supplies are turned off and they follow no particular law at all. Physical scientists (especially chemists and biochemists) can make their tasks much more difficult when they try to simplify biological or engineering systems by studying them at (thermodynamic) equilibrium, without flows, when biological and engineering systems no longer are devices at all!

Mathematics must describe biological reality and experiments in the complexity in which actually occurs. Some complex systems can be described by variational methods [78, 20, 29]. 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.

Mathematicians are well aware that variational methods [2] allow components and fields to be added or subtracted in functionals, from which differential equations are derived by the Euler Lagrange process. They know that energy variational methods [111, 152, 166, 29, 112, 39, 78, 76, 168, 167] allow one to describe systems with energy and dissipation functionals from which partial differential equations are derived.

Variational methods produce partial differential equations that are always self-consistent, if the algebra is done correctly and this is an enormous advantage in focusing attention, and decreasing distracting discord, in areas of science that must deal with the complexities of ions of many types interacting on multiple scales while driven in movements by

many types of forces in structures of some complexity and fluids containing microelements such as organic molecules.

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. The rich variety of biological systems will require a range of methods. Self-consistent methods are necessary when ionic solutions are involved in the biological function of interest. Ionic solutions must be studied, in our opinion, with methods that allow atomic components (e.g., other ions like Mg^{2+}), microelements (e.g., ATP), forces (e.g., bulk transport of blood driven by pressure gradients), and structures (e.g., of constraining proteins like blood vessels) to be added with minimal free parameters. In this way, field equations for the flows and forces are always consistent with all forces in the systems.

The variational methods we have in mind for ionic solutions are not arbitrary mathematical structures. They arise from fundamental physical laws. For example, the variational methods we have in mind include a force balance equation [2] derived from the variation of the energy functional (i.e., the action) with respect to the trajectory (or flow map, as it is often called by mathematicians).

If the underlying models of ionic solutions are incorrect or incomplete, the results of a variational analysis will be incorrect or incomplete, of course, even if the mathematics arises from physical laws, and is correct, complete and self-consistent. Variational methods are helpful even when the underlying models of the ionic solution are incomplete. They allow incorrect or incomplete models to be improved efficiently. Unproductive disputes among theories that include different subsets of the interaction terms, or that have many adjustable parameters, are minimized when mathematical tools force field equations to include all interaction terms, with minimal parameters, because the mathematical tools are unavoidably selfconsistent.

We challenge mathematics to deal with biological reality. The mathematical analysis of ionic solutions is a topic of profound importance and opportunities. It looms almost too close to see. Work on idealized models like Poisson Boltzmann can provide useful tools and training to deal with the big problem. Such work provides the initial iterates for numerical procedures. But eventually the big problem must itself be addressed. We think eventually is now. It can be done.

Mathematicians can use methods like the energy variational approach to deal with the reality of charged spheres in a frictional dielectric model of water. They can then move to describe the water more and more realistically, as experiments dictate. Variational methods (and others) allow the systematic analysis and improvement of models of the mixed ionic solutions of life. These methods (and others) 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.

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