

Mass Action in Ionic Solutions

Bob Eisenberg
Mathematics and Computer Sciences Division
Argonne National Laboratory
9700 South Cass Avenue
Argonne, IL 60439

Department of Molecular Biophysics and Physiology
Rush University
1653 West Congress Parkway
Chicago IL 60612

May 17, 2011

Bullets

- The law of mass action describes reactants as ideal simple fluids made of concentrations of uncharged noninteracting particles.
- Ionic solutions consist of interacting charged particles and are not ideal. The law of mass action is misleading if used with rate constants independent of concentration. Interactions of reactants can then be mistaken for complex properties of the chemical reaction or its enzymatic catalysts.
- The theory of complex fluids deals with interactions in a mathematically self-consistent way. It is a field theory that deals naturally with boundary conditions and flows. It seems a good starting place for a nonequilibrium theory of ionic solutions and mixtures in bulk and in proteins.
- The variational theory of complex fluids is well suited to describe mixtures like biological solutions. When a component or force is added, the theory derives—by mathematics alone—a new set of partial differential equations that automatically captures the interactions of the new with the old.
- A variational theory of ionic solutions has been implemented and shown to be computable. Numerical inefficiencies have delayed a thorough comparison with experiments.

Summary

The law of mass action describes reactants as simple ideal fluids of concentrations of uncharged noninteracting particles. Ionic solutions contain interacting charged particles and are not ideal. Interactions of reactants can then be mistaken for complexities in chemical reactions or enzymatic catalysts. The variational theory of complex fluids describes flowing mixtures like biological solutions. When a component is added, the theory derives — by mathematics alone — a new set of differential equations that automatically captures all interactions. A variational theory of ionic solutions (as complex fluids) provides computable description of ions in solutions and proteins. Numerical inefficiencies have delayed experimental verification.

Biography

Bob has been Chairman of Molecular Biophysics at Rush University since 1976. He was tutored at Harvard College by John Edsall in the early years of molecular biology and worked with John Pappenheimer and Steve Kuffler. He graduated *summa cum laude* after three years. His Ph.D. was with Paul Fatt in Bernard Katz' Biophysics Department, University College London. Alan Hodgkin was external examiner, and Andrew Huxley, a continuing mentor. Bob studies biology, from molecules to muscles, using anything that helps: experiment, instrument design, simulation, and theory. He is the senior designer of the AxoPatch Clamp amplifier, used in thousands of laboratories to record picoamp currents through single channel molecules.

A great deal of chemistry concerns ions in water. Chemistry and chemists were born in aqueous media. Almost all biochemistry is done in water solutions because ions in water are life's solutions. Pure water denatures most proteins and is lethal to biological cells. The liquid of life is made of water and ions.

A great deal of chemistry concerns reactions between ions. Reactants are often ions said to move along a path in phase space over a high barrier that separates and defines reactants and products. In fact, if one imagines that reactants follow Langevin equations of motion in one dimension moving from one concentration to another, it is possible to provide a (nearly) exact mathematical description of a chemical reaction as stochastic transport of individual ions from one set of concentrations to another. Transport is then a stochastic biased random walk, a drift-diffusion process over a barrier. Of course, one must not forget the well known problems of describing any chemical reaction as motion along a single path (see 'Rate Models have Their Place' p. 23-27⁹ for references). The Langevin drift-diffusion treatment¹⁴ gives rate constants an exact mathematical meaning as conditional probabilities of an (originally) doubly conditioned stochastic process (see eq. 5.12¹⁵).

Chemical reaction between ions can be written in the usual mass action form involving concentrations (number densities) of ionic reactants without further approximation. The theory of stochastic processes is used to precisely define concentrations as measures of the Brownian (back and forth) trajectories of the ions in the Langevin equations.^{9 14}



$$\text{where } J_k = \overbrace{l \cdot k_f \cdot C_k(\text{Left})}^{\text{Unidirectional Efflux } J_{out}} - \overbrace{l \cdot k_b \cdot C_k(\text{Right})}^{\text{Unidirectional Influx } J_{in}}. \quad (2)$$

The rate constants are conditional probabilities.¹⁴

$$J_k = \underbrace{C_k(L)}_{\text{Source Concentration}} \underbrace{\left(\frac{D_k}{l}\right)}_{\text{Diffusion Velocity}} \underbrace{\text{Prob}\{R|L\}}_{\text{Conditional Probability}} - \underbrace{C_k(R)}_{\text{Channel Length}} \underbrace{\left(\frac{D_k}{l}\right)}_{\text{Channel Length}} \underbrace{\text{Prob}\{L|R\}}_{\text{Conditional Probability}} \quad (3)$$

$$\text{or } J_k = \overbrace{l \cdot k_f C_k(\text{Left})}^{\text{Unidirectional Efflux } J_{out}} - \overbrace{l \cdot k_b C_k(\text{Right})}^{\text{Unidirectional Influx } J_{in}}, \quad \text{where} \quad (4)$$

$$k_f \equiv \frac{J_{out}}{C_k(L_{eft})} = k \{R_{ight} | L_{eft}\} = \frac{D_k}{l^2} \text{Prob}\{R_{ight} | L_{eft}\} = \frac{D_k}{l^2} \frac{\exp(z_k F V_{trans} / RT)}{\frac{1}{l} \int_0^l \exp(z_k F \phi(\zeta) / RT) d\zeta};$$

$$k_b \equiv \frac{J_{in}}{C_k(R_{ight})} = k \{L_{eft} | R_{ight}\} = \frac{D_k}{l^2} \text{Prob}\{L_{eft} | R_{ight}\} = \frac{D_k}{l^2} \frac{1}{\frac{1}{l} \int_0^l \exp(z_k F \phi(\zeta) / RT) d\zeta}.$$
(5)

R is the gas constant, F is Faraday's constant, T is the absolute temperature, V_{trans} is the electrical potential across the channel.

This pleasingly intuitive (as well as mathematically rigorous) description is misleading, however, because of assumptions hidden in plain sight. Assumptions are particularly easy to overlook in 'laws' (like mass action) we learn early in our careers, before our critical skills are fully developed.

Reactants are assumed ideal in the law of mass action that was derived originally for uncharged gases so dilute that particles do not interact. Mass action was later embedded in the beautiful theory of simple fluids.^{1,20,41} The law can be applied to charged dilute solutions if interactions are described by mean (time averaged) electric fields independent of the concentration of any species, including reactants.

In this idealized view, different concentrations of ions screen the same way so that idealized rate constants do not vary with concentration. The actual—not idealized—rate constants of chemical reactions depend on the concentration of all mobile ions, of all species, including the reactants. More mobile charges mean more screening, different energy, and different rate constants. The actual rate constant for one ionic species would then depend on the concentration of all other species (as well as on the concentration of its own species) because the average field itself depends on the concentration of all species. Screening is produced by all charges of all types that move in response to an electric field.

Variable rate constants are needed to make the law of mass action describe reality. Most chemists do not like to vary constants and avoid doing so. As a result, the law of mass action (as usually used with constant rate constants) is not very useful. Indeed, it is misleading. To ensure its validity, special experimental conditions must be chosen in which interactions do not occur, or do not vary with concentration. These special conditions rarely occur in biological or engineering applications. There, interactions are often substantial, and vary with concentration.

Rate constants in the real world vary with concentration. If rate constants in models are not allowed to vary, but rate constants in the real world vary with concentration, the models must be modified somehow or other to fit data. One way is to introduce additional states into the model of the chemical reaction. Another way is to invoke conformational changes or allosteric interactions in enzymes that catalyze reactions. Of course, intermediate states and conformational changes do occur in the real world and can be important. They are not all figments of forced fitting of idealized ideas to real data.

When reactants interact, the free energy of one type of reactant depends on all species present.^{9,29,35,37,40,49} The free energy then has a component in excess of that in an ideal gas. The

excess component is important whenever reactants are concentrated or screened by an ionic atmosphere.

Reactants near catalysts, or enzymes, or in ion channels are often very concentrated

because evolution (like an engineer) often maximizes the rate of reactions by maximizing the number density of reactants. Indeed, one imagines that most chemical reactions that proceed at high rates have large local concentrations of reactants. The local concentrations differ substantially from the ‘well stirred’ spatially uniform concentrations of classical theories and so theories of chemical reactions that allow spatial gradients of reactants are likely to differ substantially from classical theories of the same reaction, that assume (impossibly) well stirred reactants. States and rates, allosteric and conformational changes needed to fit data are likely to be quite different if (some of) the concentration dependence found experimentally arises from the excess (nonideal) free energy of the interacting reactants themselves.

Ionic Solutions are not ideal. This paper argues that ionic solutions are very often—indeed, almost always—non-ideal and so the law of mass action (with constant rate constants) is not valid. The paper argues that in ionic solutions ‘everything [usually] interacts with everything else’ through the electric field. In concentrated solutions, additional strong interactions occur because two ions cannot occupy the same space. Steric repulsion produces excess free energy that depends on the crowding of charges. These terms can dominate behavior in active sites of enzymes, in ion channels, and in catalysts, or near electrodes.

An ion interacts with ions nearby in its ionic atmosphere even in solutions as dilute as 1 mM Na^+Cl^- . The ionic atmosphere around an ion usually has the opposite charge from the ion and so the electric field extending into the bulk solution is reduced (screened) by the ionic atmosphere. Solutions with a higher concentration of any mobile ion produce more shielding of a central charge because more ions can move to balance the central charge. The free energy (of even dilute Na^+Cl^- solutions) contains a large ‘excess’ component that scales with the square root of concentration. Ideal solutions do not contain this term. The square root dependence arises because ‘everything’ interacts with everything else through the mean electric field. Simple fluids do not behave this way. In simple fluids, ‘nothing interacts with nothing’ is the starting rule.

It is difficult to deal with the interactions of real solutions in the classical theory of simple fluids, because every species interacts with every other species.^{2,7,9,16,18,21,29,30,33,39,40,49} All ions produce the ionic atmosphere, not just ions of one type. And so every ion interacts with every species. Theories of simple fluids are not designed to deal with such interactions. Usually the interactions are treated only in pairs, and put in ‘by hand’. Interactions are usually scaled by at least one adjustable parameter for each pair-wise interaction. Multibody interactions are treated by truncating closure expansions, even though the expansions have not been proven to be convergent or asymptotic.

The theory of complex fluids is designed to deal with all interactions, not just pair-wise interactions. It offers an alternative view of ionic solutions. This paper describes a variational version of the theory of complex fluids designed to deal with interactions of ions, crowded or dilute, automatically and self-consistently. Scientific success cannot be claimed: the theory is too new and untested. Mathematical success, however, can be claimed (somewhat immodestly), because the theory deals with interactions by mathematics alone, established with theorems, proofs of existence and uniqueness. The theory deals with mixtures and interactions systematically, in a unique way, with minimal parameters, by algebra alone, even when new components are added to the solution. It should be emphasized that the theory concerns measures

of the trajectories of ions. The theory is more than a continuum model or mean field theory. Continuum equations are used throughout the theory of stochastic processes to describe properties of discrete random events, like the throwing of coins.

Classical Theories of Dilute Solutions. Classical theories of ions in dilute (< 150 mM) solutions of Na^+Cl^- usually involve the Poisson Boltzmann equation with its mean electric field. The PB equation idealizes ions as point charges. It appears in various versions, as the Gouy-Chapman equation of planar solution interfaces and, linearized in spherical coordinates, as the Debye-Hückel theory of dilute solutions of spherical ions. PB is an equilibrium theory in which everything is at equilibrium at all times in all conditions. Flow is zero in PB equations. The distribution of velocities follows a Maxwellian distribution that is an even function of velocity and so has zero mean. Flux of a Maxwellian distribution is identically zero.

Extensions of PB to include flux (arising from a displaced Maxwellian¹⁴) have many names. Drift-diffusion equations for the quasi-particles of semiconductors—holes and (quasi)‘electrons’⁸—are used to design our digital technology.³⁶ Poisson-Nernst-Planck PNP equations are drift-diffusion equations for ions used to design channels and nanodevices in biophysics and physical chemistry.^{3,5,15} I introduced the nickname PNP¹² to emphasize the relation⁸ between transport of quasi-particles in semiconductors and ions in solutions. The permanent (‘fixed’) charge (e.g., acidic and basic side chains of proteins) might play as important a role in ion channels as doping does in transistors, and so I included these charges explicitly, and emphasized their role, more or less for the first time, in a series of papers, reviewed in^{8,9,15}. I was (and am, so far unsuccessfully) looking for the biological analog of triodes in which large ‘diode’ currents—flowing with rectification in a channel between two terminals—are modulated by tiny currents, charges, or potentials at a third terminal, corresponding to a grid, base, or gate in tubes (valves), bipolar, or field effect transistors.

The PNP treatment of ions is seriously inadequate because ions are not points. Ions cannot overlap. The finite diameter of ions has a surprisingly large effect on electrostatic energies because the energy of the electric field of a sphere is not well approximated by the electric field of a point. The electric field of a sphere and a point deviate just where the field is strongest, near the origin. An arbitrary ‘distance of closest approach’ has to be invoked to make PB or PNP satisfactory even at ~ 1 millimolar concentration (p. 55⁴⁹). It is not clear how to consistently choose a *single* distance of closest approach (independent of the type and concentration of ions) in mixed solutions with many types of ions. There are logical difficulties as well. It is not clear how an ion in the center of its own atmosphere has a substantial and significant diameter while the same ion is just a point when part of the ionic atmosphere of its neighbors.

A generation of physical chemists just now retiring studied the effects of finite size of ions. The scientists may retire, but finite size ions remain. As one of that generation—George Stell—said “... it is almost never valid to use Debye-Hückel under physiological conditions” (gentle paraphrase of⁴⁶). This is a view repeated many times by many workers of that generation, see^{2,7,16,18,21,30,33,39} and other references too numerous to cite. Three large books^{29,40,49} compile the relevant experimental results and document some six classical (phenomenological) equations p. 47⁴⁹, latter increased in number.^{35,49}

Idealizations fail to fit the data because the finite size of one ion type changes the free energy of other types. **No ion type can be treated independently of the others.** It is not correct to write equations in which a property of one ion depends on the concentration of just that ion. **The**

electrochemical potential of one ion depends on all other ions. Hundreds of papers reviewed in ^{2,7,9,16,18,21,29,30,33,39,40,49} show that the concentration of one ion changes properties of other types of ions. Everything interacts with everything else. All the ions interact with each other through the electric field, and through crowding. Mixtures of ions are nothing like ideal.

Little trace of these facts appears in the conventional wisdom of biochemistry, molecular biology or biophysics, or their texts, probably because mathematical descriptions of interactions are so arbitrary and ugly^{35,49} compared to the seductive beauty of idealized theories.^{1,20,41}

Interactions in Crowded Charged Solutions. Interactions need to be described naturally and self-consistently when mathematical models describe real solutions. Traditional models deal with interactions in an *ad hoc* and often subjective way. They add pair-wise interactions one at a time into a theory of simple (noninteracting) fluids. It is not clear that any finite sum of pair-wise interactions can approximate the interactions of all types of particles with each other. Traditional models indeed are phenomenological and use a large number of ill-determined coefficients that change as any component of the system is changed.^{26,29,35,37,39,49} This paper proposes a mathematical approach—from the theory of **complex** fluids^{6,32,34,48}—that objectively and automatically captures all interactions. This approach is designed mathematically so its differential equations describe all the forces, interactions, fields, and flows of complex mixtures with a minimal number of parameters.

Ionic solutions seem not to have been treated previously as complex fluids. The mathematics of this approach has been proven (in theorems and existence proofs) and has been shown to be practical and useful in physical applications. But the application to ionic solutions appears to be new. I now argue that a variational approach is more or less essential when flows are involved or concentrations are high, in the molar region.

Ion concentrations are large in most devices—physical or biological—that use them. Ions are packed closely next to electrodes in batteries, power cells, and other electrochemical devices. Ions are at enormous densities in ion channels because the fixed charge of acidic and basic side chains of proteins demands equal amounts of charge nearby. (Small violations of even local electroneutrality would produce electric fields comparable to forces between valence electrons and the rest of the atom. Such strong electric fields are known to ionize atoms and destroy proteins, channels, and membranes.) Calcium and sodium channels have ~30 molar concentrations of ions—comparable to the 37 M concentration of solid Na^+Cl^- . The charge density of side chains in active sites is ~20 M in ~600 enzymes, found in an automated search of a library of enzymes of known structure and function.²⁴

The crowded conditions of active sites of enzymes (like channels¹³) form a special environment likely to have important effects on chemical reactions and biological function. The mathematics used to describe this crowded environment must deal naturally with interactions because everything is coupled. Everything interacts with everything else. Nothing is ideal. The free energy of one ion depends on the concentration of others.

Electrolyte Solutions as Complex Fluids. I suggest starting a theory of electrolytes^{11,23} with the theory of complex fluids of mixtures of hard spherical ions in implicit (primitive) solvents.^{2,16,33} More complex representations of ions and solvent can be added later as needed to fit data.²²

The variational theory of complex fluids^{6,32,34,48} has been developed by mathematicians interested in abstract as well as practical issues: how to derive Navier-Stokes equations from variational principles. The theory has been used by physicists interested in liquid crystals and

other systems containing complex components that change shape and size, even fission and fuse, as they mix and flow far from equilibrium. The flows successfully computed can be much more complicated than those we see every morning in our showers and bathroom sinks. The liquid crystal displays (LCD's) of our everyday technology are successfully computed.^{6,32}

The theory of complex fluids deals naturally with nonequilibrium properties. It deals with flows driven by pressure, concentration, and voltage gradients all together. Describing such flows of ionic solutions has been the despair of physical chemists. The ionic interactions that cannot be described at rest are even harder to describe in flow.^{26,43} Each flowing species has its own mobility, and each mobility depends on the concentrations, flows, and nonideal properties of all the other ions. Every nonequilibrium property interacts with every other nonequilibrium property, as well as with every equilibrium property, which in turn interacts with all the others. It is obvious that pair-wise descriptions cannot possibly describe the flows of ions, solvent, and solution in electrolytes.

Life is not at equilibrium. Dealing with nonequilibrium mixtures is particularly important in life. Biological systems live only when they maintain large flows to keep them far from the equilibrium of death. Nearly every system in biology requires nonequilibrium conditions and flows of mixed ionic solutions, as does manmade technology. Electron flows are the electrical signals in coaxial cables of our technology. Ionic flows are the electrical signals in the cables (nerve axons) of our nervous system and Purkinje fibers and transverse tubules of our cardiac and skeletal muscles.

Our technology is like our life. Flows are needed to create the conditions that allow devices or axons to have simple properties. Amplifiers follow simple laws only when energized by power supplies. Axons inactivate when they have no resting potential. An amplifier without power follows no simple law. Only when it is powered is the output proportional to the input. Many highly nonlinear devices (usually transistors) are needed connected into a complex circuit structure (working far from equilibrium) to produce an output proportional to the input. In engineering, thermodynamic equilibrium occurs when power fails. In biology, thermodynamic equilibrium occurs when organisms die.

Theories developed to exploit the special properties of thermodynamic equilibrium had an enormously important role in the historical development of science,^{1,4,20,41} but they must be abandoned in their original form, if the interacting nonequilibrium reality of ionic solutions is to be explained as it is actually measured and used in life and technology. One can argue that semiconductor technology was possible exactly because semiconductor engineers never assumed equilibrium^{42,45} or spatial uniformity of fields. They did not even assume spatially uniform boundary conditions. They always dealt with separate input, outputs and power terminals and so with different boundary conditions at different places. The resulting spatially nonuniform boundary conditions produce gradients of electrochemical potential and (almost always) flow with its inevitable friction and dissipation. The engineers abandoned the beauty of equilibrium theories so they could build devices. Their devices only work when they dissipate heat.

The variational theory of complex fluids is designed to deal with flows of mixtures. Variational principles describe the energy and friction (dissipation) of the components of flowing complex fluids. The field equations derived from these principles describe flow within spatially nonuniform boundaries like those imposed by electrodes or concentrations of ions inside and outside biological cells. The field equations are not restricted to chemical equilibrium. They deal with flow as they deal with no flow. Both are consequences of the components and forces

expressed in the underlying variational principle and the spatially nonuniform boundary conditions. The partial differential equations of the field theory are derived from variational principles by mathematics alone. Only algebra is used. No approximations or additional arguments are needed to describe interactions.

Additional components. If a new component is added to a complex fluid, the component interacts with everything else in the system, and the resulting analysis must reflect that interaction. Interactions are not pair-wise, not even approximately. These interactions have rarely been guessed in full when analysis begins with the differential equations instead of a variational principle. There are too many possible descriptions and too many interactions that are easily overlooked.

If a new component is added into the variational principle, the interactions of all the components with all others appear automatically in the resulting partial differential equations. These are the interactions of the energy and dissipation terms in the variational functional and in the functions of the resulting differential equations. The interaction terms of the differential equations are objective outputs of a mathematical analysis, the Euler Lagrange process. They are not assumed.

Of course, the variational principle is not magic. If the components of the energy or dissipation are incorrectly or incompletely described, the field equations will be incorrect physically, albeit self-consistent mathematically. For example, if a chaotropic additive changes the free energy of water, a primitive model^{2,16,18,33} of an ionic solution (with constant free energy of water) will fail. We cannot know how important such effects are from mathematics. A physical theory must be constructed and compared to specific experimental data^{29,40,49} to see if it actually works. The field equations of a variational theory will always be consistent mathematically, but they will be consistent physics only if they contain enough detail to deal with the conditions of experiments. We do not yet know what detail is enough to deal with the range of conditions found in chemistry and biology.

Simulations. This variational approach contrasts with attempts to simulate macroscopic properties by direct calculation of motions of all atoms in molecular dynamics. The problems of going from atomic to macroscopic scales—in simulations that are calibrated and actually fit experimental data over a range of nonequilibrium conditions—are much larger and more serious than most scientists have wished to consider.¹⁰ Calibrated and accurate simulations are usually needed when dealing with devices, whether in technology or biology, because devices often balance two different forces. Small differences then determine the qualitative properties of the device.

The problems of dealing with life's structures (with 0.1% accuracy in three dimensions) that change significantly in 10^{-14} sec are particularly serious, because biological structures perform their natural functions by moving 10^{10} times slower than atoms. In quantitative applications, molecular dynamics is limited (for the time being) by its inability to calculate the properties of flowing mixtures of electrolytes on the biological time scale (10^{-4} to 10^9 sec) and length scale (10^{-11} to 10^1 meter) in biological mixed solutions (with significant components ranging in concentration from 10^{-11} to 10^1 M).

On the other hand, in qualitative applications, molecular dynamics provides an indispensable dynamic extension of the statics of structural biology. Molecular dynamics—along with structural and molecular biology—are absolutely needed to construct appropriate reduced models for variational analysis.

Variational Analysis. The variational analysis of ionic solutions, and ions in channels, can begin with the energetic variational principle of Chun Liu^{34,48}, built on the work of many others,

$$\overbrace{\frac{\delta E}{\delta \vec{x}}}^{\text{Conservative 'Force'}} - \overbrace{\frac{1}{2} \frac{\delta \Delta}{\delta \vec{u}}}^{\text{Dissipative 'Force'}} = 0 \quad (6)$$

This principle has been applied to a model of electrolytes in which ions are represented as spheres in a frictional dielectric.¹¹ This primitive model of an ionic solution—that uses a dielectric to describe implicitly the properties of water—is well-precedented and more successful than most in dealing with experimental data,^{2,16,33} but it will certainly need to be extended to include more chemical and atomic detail.²²

If ions are modeled as Lennard Jones spheres, the variational principle produces ‘Euler Lagrange’ equations of a drift-diffusion theory with finite sized solutes, a generalization and correction of PNP.

$$\frac{\partial c_n}{\partial t} = \nabla \cdot \left[D_n \left\{ \nabla c_n + \frac{c_n}{k_B T} \left(z_n e \nabla \phi - \int \frac{12 \varepsilon_{n,n} (a_n + a_n)^{12} (\vec{x} - \vec{y})}{|\vec{x} - \vec{y}|^{14}} c_n(\vec{y}) d\vec{y} - \int \frac{6 \varepsilon_{n,p} (a_n + a_p)^{12} (\vec{x} - \vec{y})}{|\vec{x} - \vec{y}|^{14}} c_p(\vec{y}) d\vec{y} \right) \right\} \right] \quad (7)$$

combined with the Poisson Equation

$$\nabla \cdot (\varepsilon \nabla \phi) = - \left(\rho_0 + \sum_{i=1}^N z_i e c_i \right) \quad i = n \text{ or } p \quad (8)$$

We write the equation only for negative monovalent ions with valence $z_n = -1$ to keep the formulas reasonably compact. Programs have been written for all valences. $c_{p,n}(\vec{y})$ is the number density of positive p or negative n ions at location \vec{y} . $D_{p,n}$ is the corresponding diffusion coefficient. $k_B T$ is the thermal energy, k_B the Boltzmann constant, and T the absolute temperature. $\varepsilon_{n,n}$ and $\varepsilon_{n,p}$ are coupling coefficients. $a_{p,n}$ are the radii of ions. ε (without subscript) is the dielectric coefficient. The electrical potential is ϕ . ρ_0 represents the charge density of the protein, as it represents the charge density of doping in semiconductors. ρ_0 depends on location and is zero in bulk solutions.

We note that the field satisfies the dissipation principle.

$$\begin{aligned}
 & \overbrace{\frac{d}{dt} \int \left\{ k_B T \sum_{i=n,p} c_i \log c_i + \frac{1}{2} \left(\rho_0 + \sum_{i=n,p} z_i e c_i \right) \phi + \sum_{i,j=n,p} \frac{c_i}{2} \int \tilde{\Psi}_{i,j} c_j d\bar{y} \right\} d\bar{x}}^{\text{Dissipative}} \\
 & = - \underbrace{\int \left\{ \sum_{i=n,p} \frac{D_i c_i}{k_B T} \left| k_B T \frac{\nabla c_i}{c_i} + z_i e \nabla \phi - \sum_{j=n,p} \nabla \int \tilde{\Psi}_{i,j} c_j d\bar{y} \right|^2 \right\} d\bar{x}}^{\text{Conservative}}
 \end{aligned} \tag{9}$$

$\tilde{\Psi}_{i,j}$ represent the Lennard Jones crowded charges terms defined in references^{11,23}.

These equations have been integrated numerically¹¹ to predict binding of ions in crowded conditions, or the time dependent, voltage and concentration dependent flow of ions through channels. These physical variables determine the conditional probabilities, and rate constants of eq.(1)-(5). The calculations are successful and the methods are feasible. But numerical inefficiencies limit the number of cases and complexities of structures that can be studied so optimization of parameters has not been done. Until parameters are optimized, and realistic structures computed, one unfortunately cannot tell how well the theory actually deals with the wide range of data^{2,7,9,16,18,21,29,30,33,39,40,49} in diverse conditions and applications.

Conclusion. The variational treatment of electrolyte mixtures has just started. It begins in the right place, in my view, with the successful variational theory of complex fluids. The variational treatment has substantial advantages. It describes solutions in a systematic way, even those in which everything interacts with everything else, as they do in life and its solutions. A variational theory can be a complete description of all the properties of ionic mixtures in flow and in equilibrium. It can be a good approximation to the properties of ions in and around proteins when the protein has a well defined average structure. But the variational approach is not yet sufficiently developed or checked. Other approaches are being used^{17-19,21,22,25,27-29,31,38,43,44,47,50} to deal with solutions of a single monovalent salt like Na^+Cl^- at equilibrium (and many other papers inadvertently overlooked, I fear) and one hopes for their early success.

It is not clear, however, that other approaches can deal with divalents like Ca^{2+} , or with multicomponent systems with ions of unequal diameter and charge, as they flow. Life's solutions are flowing mixtures of ions of unequal diameter—think of blood or biological plasmas. Theories and simulations must deal naturally with these complexities, interactions and flows. Variational methods give hope, at least to me, that this can be done.

Acknowledgement

It has been a privilege and great fun to help Chun Liu extend his fluid reach to grasp ionic solutions. Even he could only grasp the part solidly established by generations of physical chemists. I am most grateful for those generations of work and in particular for how much I have been taught by John Edsall, Jean-Pierre Hansen, Doug(las) Henderson, and Stuart Rice, along with many others.

Support was provided by the NIH, GM076013. Time for thoughts is provided by Rush Medical College and Argonne National Laboratory. I am grateful for all the administrative work they did not ask me to do.

References

1. Barker, J. & Henderson, D. What Is "Liquid"? Understanding the States of Matter. *Reviews of Modern Physics* **48**, 587-671 (1976).
2. Barthel, J., Krienke, H. & Kunz, W. *Physical Chemistry of Electrolyte Solutions: Modern Aspects*. (Springer, 1998).
3. Bazant, M. Z., Thornton, K. & Ajdari, A. Diffuse-Charge Dynamics in Electrochemical Systems. *Physical Review E* **70**, 021506 (2004).
4. Brush, S. G. *The Kind of Motion We Call Heat*. (North Holland, 1986).
5. Coalson, R. D. & Kurnikova, M. G. Poisson-Nernst-Planck Theory Approach to the Calculation of Current through Biological Ion Channels. *IEEE transactions on nanobioscience* **4**, 81-93 (2005).
6. Doi, M. & Edwards, S. F. *The Theory of Polymer Dynamics*. 408 (Oxford University Press, 1988).
7. Durand-Vidal, S., Simonin, J.-P. & Turq, P. *Electrolytes at Interfaces*. (Kluwer, 2000).
8. Eisenberg, B. Living Transistors: A Physicist's View of Ion Channels. Version 2. <http://arxiv.org/q-bio.BM>, arXiv:q-bio/0506016v0506012 0506024 pages (2005).
9. Eisenberg, B. Crowded Charges in Ion Channels. *Advances in Chemical Physics (in the press)* also available at <http://arxiv.org> as arXiv 1009.1786v1 (2010).
10. Eisenberg, B. Multiple Scales in the Simulation of Ion Channels and Proteins. *The Journal of Physical Chemistry C* **114**, 20719-20733, doi:10.1021/jp106760t (2010).
11. Eisenberg, B., Hyon, Y. & Liu, C. Energy Variational Analysis Envara of Ions in Water and Channels: Field Theory for Primitive Models of Complex Ionic Fluids. *Journal of Chemical Physics* **133**, 104104 (2010).
12. Eisenberg, R. & Chen, D. Poisson-Nernst-Planck (*Pnp*) Theory of an Open Ionic Channel. *Biophysical Journal* **64**, A22 (1993).
13. Eisenberg, R. S. Channels as Enzymes: Oxymoron and Tautology. *Journal of Membrane Biology* **115**, 1-12. published in the Physics ArXiv as arXiv:0808.0130 (1990).
14. Eisenberg, R. S., Klosek, M. M. & Schuss, Z. Diffusion as a Chemical Reaction: Stochastic Trajectories between Fixed Concentrations. *J. Chem. Phys.* **102**, 1767-1780 (1995).
15. Eisenberg, R. S. Computing the Field in Proteins and Channels. *J. Membrane Biol.* **150**, 1-25. Also available on <http://arxiv.org> as arXiv 1009.2857 (1996).
16. Fawcett, W. R. *Liquids, Solutions, and Interfaces: From Classical Macroscopic Descriptions to Modern Microscopic Details*. (Oxford University Press, 2004).
17. Fraenkel, D. Monoprotic Mineral Acids Analyzed by the Smaller-Ion Shell Model of Strong Electrolyte Solutions. *The Journal of Physical Chemistry B* **115**, 557-568, doi:10.1021/jp108997f (2010).
18. Fraenkel, D. Simplified Electrostatic Model for the Thermodynamic Excess Potentials of Binary Strong Electrolyte Solutions with Size-Dissimilar Ions. *Molecular Physics* **108**, 1435 - 1466 (2010).

19. Gee, M. B., Cox, N. R., Jiao, Y., Benteñitis, N., Weerasinghe, S. & Smith, P. E. A Kirkwood-Buff Derived Force Field for Aqueous Alkali Halides. *Journal of Chemical Theory and Computation*, null-null, doi:10.1021/ct100517z (2011).
20. Hansen, J.-P. & McDonald, I. R. *Theory of Simple Liquids*. Third Edition edn, (Academic Press, 2006).
21. Henderson, D. & Boda, D. Insights from Theory and Simulation on the Electrical Double Layer. *Phys Chem Chem Phys* **11**, 3822-3830, doi:10.1039/b815946g (2009).
22. Howard, J. J., Perkyñs, J. S. & Pettitt, B. M. The Behavior of Ions near a Charged Wall-Dependence on Ion Size, Concentration, and Surface Charge. *The journal of physical chemistry* **114**, 6074-6083, doi:10.1021/jp9108865 (2010).
23. Hyon, Y., Kwak, D. Y. & Liu, C. Energetic Variational Approach in Complex Fluids : Maximum Dissipation Principle. available at URL: <http://www.ima.umn.edu> as IMA Preprint Series # 2228 **26**, 1291 - 1304, available at URL: <http://www.ima.umn.edu> as IMA Preprint Series # 2228 (2010).
24. Jimenez-Morales, D., Liang, J. & Eisenberg, B. Active Sites of Enzymes Are Crowded with Charge. *Biophysical Journal* **100**, 218a (2011).
25. Joung, I. S. & Cheatham, T. E. Molecular Dynamics Simulations of the Dynamic and Energetic Properties of Alkali and Halide Ions Using Water-Model-Specific Ion Parameters. *The Journal of Physical Chemistry B* **113**, 13279-13290, doi:10.1021/jp902584c (2009).
26. Justice, J.-C. in *Comprehensive Treatise of Electrochemistry Volume 5 Thermodynamic and Transport Properties of Aqueous and Molten Electrolytes* (eds Brian E. Conway, J.O'M. Bockris, & Ernest Yeager) Ch. 3, 223-338 (Plenum, 1983).
27. Kalcher, I. & Dzubiella, J. Structure-Thermodynamics Relation of Electrolyte Solutions. *The Journal of chemical physics* **130**, 134507 (2009).
28. Kalcher, I., Schulz, J. C. F. & Dzubiella, J. Ion-Specific Excluded-Volume Correlations and Solvation Forces. *Physical Review Letters* **104**, 097802 (2010).
29. Kontogeorgis, G. M. & Folas, G. K. *Models for Electrolyte Systems*. (John Wiley & Sons, Ltd, 2009).
30. Kunz, W. *Specific Ion Effects*. (World Scientific 2009).
31. Kunz, W. & Neueder, R. in *Specific Ion Effects* (ed Werner Kunz) 11-54 (World Scientific 2009).
32. Larson, R. G. *The Structure and Rheology of Complex Fluids* (Oxford, 1995).
33. Lee, L. L. *Molecular Thermodynamics of Electrolyte Solutions*. 247 (World Scientific 2008).
34. Lin, F.-H., Liu, C. & Zhang, P. On Hydrodynamics of Viscoelastic Fluids. *Communications on Pure and Applied Mathematics* **58**, 1437-1471 (2005).
35. Lin, Y., Thomen, K. & Hemptinne, J.-C. d. Multicomponent Equations of State for Electrolytes. *American Institute of Chemical Engineers AICHE Journal* **53**, 989-1005 (2007).
36. Markowich, P. A., Ringhofer, C. A. & Schmeiser, C. *Semiconductor Equations*. (Springer-Verlag, 1990).

37. Myers, J. A., Sandler, S. I. & Wood, R. H. An Equation of State for Electrolyte Solutions Covering Wide Ranges of Temperature, Pressure, and Composition. *Industrial and Engineering Chemical Research* **41** (2002).
38. Paul, H. & Matthias, S. Binary Non-Additive Hard Sphere Mixtures: Fluid Demixing, Asymptotic Decay of Correlations and Free Fluid Interfaces. *Journal of Physics: Condensed Matter* **22**, 325108 (2010).
39. Pitzer, K. S. *Thermodynamics*. 3rd edn, 626 (McGraw Hill, 1995).
40. Pytkowicz, R. M. *Activity Coefficients in Electrolyte Solutions*. Vol. 1 (CRC, 1979).
41. Rice, S. A. & Gray, P. *Statistical Mechanics of Simple Fluids*. (Interscience (Wiley), 1965).
42. Riordan, M. & Hoddeson, L. *Crystal Fire*. (Norton, 1997).
43. Roger, G. I. M., Durand-Vidal, S., Bernard, O. & Turq, P. Electrical Conductivity of Mixed Electrolytes: Modeling within the Mean Spherical Approximation. *The Journal of Physical Chemistry B* **113**, 8670-8674, doi:10.1021/jp901916r (2009).
44. Shen, J.-W., Li, C., van der Vegt, N. F. A. & Peter, C. Transferability of Coarse Grained Potentials: Implicit Solvent Models for Hydrated Ions. *Journal of Chemical Theory and Computation*, null-null, doi:10.1021/ct2001396 (2011).
45. Shurkin, J. N. *Broken Genius: The Rise and Fall of William Shockley, Creator of the Electronic Age*. (Macmillan, 2006).
46. Stell, G. & Joslin, C. G. The Donnan Equilibrium: A Theoretical Study of the Effects of Interionic Forces. *Biophys J* **50**, 855-859 (1986).
47. Vrbka, L., Lund, M., Kalcher, I., Dzubiella, J., Netz, R. R. & Kunz, W. Ion-Specific Thermodynamics of Multicomponent Electrolytes: A Hybrid Hnc/Md Approach. *The Journal of chemical physics* **131**, 154109-154112, doi:10.1063/1.3248218 (2009).
48. Yue, P., Feng, J. J., Liu, C. & Shen, J. A Diffuse-Interface Method for Simulating Two-Phase Flows of Complex Fluids. *Journal of Fluid Mechanics* **515**, 293--317 (2004).
49. Zemaitis, J. F., Jr., Clark, D. M., Rafal, M. & Scrivner, N. C. *Handbook of Aqueous Electrolyte Thermodynamics*. (Design Institute for Physical Property Data, American Institute of Chemical Engineers, 1986).
50. Zhang, C., Raugei, S., Eisenberg, B. & Carloni, P. Molecular Dynamics in Physiological Solutions: Force Fields, Alkali Metal Ions, and Ionic Strength. *Journal of Chemical Theory and Computation* **6**, 2167-2175, doi:10.1021/ct9006579 (2010).