Mass Action in Ionic Solutions

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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. Ions in water are the liquid of life.

A great deal of chemistry deals with 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 transport from one set of concentrations to another. Transport is then a stochastic drift-diffusion process over a barrier. Of course, one must not forget the usual caveats about describing any chemical reaction as motion along a single path (see 'Rate Models have Their Place' p. 23–27 of reference[9]). The Langevin drift-diffusion treatment[13] gives rate constants an exact mathematical meaning as conditional probabilities of an (originally) doubly conditioned process (see eq. 5.12 of reference[15]).

The reaction can be written in the usual mass action form, without further approximation, as we have shown previously.[9][13]

$$Left \underset{k_b}{\overset{k_f}{\rightleftarrows}} Right \tag{1}$$

where

$$J_k = \overbrace{l \cdot k_f \cdot C_k(Left)}^{\substack{\textbf{Unidirectional } \textbf{\textit{Efflux}} \\ J_{out}}} - \overbrace{l \cdot k_b \cdot C_k(Right)}^{\substack{\textbf{Unidirectional } \textbf{\textit{Influx}} \\ J_{in}}} . \tag{2}$$

The rate constants are conditional probabilities.[13]

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

or

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

where

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

$$k_b \equiv \frac{J_{in}}{C_k(Right)} = k\{Left|Right\} = \frac{D_k}{l^2}\text{Prob}\{Left|Right\}\frac{D_k}{l^2}\frac{1}{\frac{1}{l}\int_0^l \exp(z_k F \varphi(\zeta)/RT)d\zeta}.$$

$$(5)$$

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

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

A key assumption in the law of mass action is that reactants are ideal, described by equations derived originally for uncharged gases so dilute that their particle do not interact and later generalized to simple fluids.[48,1,20,41] Some further generalization is possible in the idealized framework. If the particles of the gas are charged, and dilute, the law can be generalized to include interactions through the mean (time averaged) electric field if those interactions are independent of concentration of reactants and all other species.

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 of chemical reactions depends on the concentration of all mobile ions, of all species, including the reactants. More mobile charges means more screening, different energy, and different rates and rate constants. The rate for one ionic species would then depend on the concentration of all other (mobile) species (as well as on the concentration of its own species) because the average field itself depends on the concentration of all mobile species.

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. In the real world, rate constants vary with concentration.

When reactants interact, the free energy of one type of reactant depends on the concentrations (and types) of 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. 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 so they can have large 'reaction cross sections'. The local concentrations differ substantially from the 'well stirred' spatially uniform concentrations of classical theories.

This paper argues that ionic solutions are very often — indeed, almost always — nonideal 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'. In concentrated solutions, strong interactions occur because two ions cannot occupy the same space. Steric repulsion produces free energy terms that depend on the crowding of charges. These terms can dominate behavior in active sites of enzymes, ion channels, in catalysts or near electrodes.

Even ions in bulk solutions as dilute as 1 mM Na^+Cl^- have significant interaction. Ions interact through the ionic atmosphere. 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 by the ionic atmosphere. More concentrated solutions 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. 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 put in 'by hand' scaled by at least one adjustable parameter for each pair wise interaction.

The theory of complex fluids is designed to deal with interactions like this. 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 selfconsistently. 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.

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 all the time in all conditions. Flow is zero in PB equations. The distribution of

velocities follows a Maxwellian distribution that is an even function with zero mean. Thus, flux is identically zero.

Extensions of PB to include flux have many names. Drift diffusion equations for the quasiparticles of semiconductors — holes and electrons — are used to design our digital technology.[36] Poisson-Nernst-Planck equations are drift-diffusion equations for ions used to design channels and nanodevices in biophysics and physical chemistry.[3,5,14,15] I introduced the nickname PNP[12] to emphasize the relation[8] between transport of quasiparticles in semiconductors and ions in solutions. I was (and am) looking for the equivalent of triodes in channels, proteins, or transporters, to go along with the well known rectifying (diode like) properties of ionic channels.

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 swarm of spheres is not well approximated by the electric field of points. The electric field of a sphere deviates from that of a point just where the field is strongest, near the origin. An arbitrary distance of closest approach has to be added to make PB or PNP at all reasonable. It is not clear how to consistently choose a *single* distance of closest approach in solutions with many types of ions. Attaching a distance of approach to an ion also produces logical inconsistencies. The ion in the center of its own atmosphere has finite diameter. The same ion, however, is given zero diameter in its role as a member 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 leave the scene, but the effects of finite size remain. As one of that generation — George Stell — put it "… it is almost never valid to use Debye-Hückel under physiological conditions" (gentle paraphrase of reference[46]). This is a view repeated many time 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 the several phenomenological models used to describe the data.

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] (to choose only a few citations) 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 were so arbitrary and awkward in traditional theories.[49]

Interactions in Crowded Charged Solutions

Interactions should be described naturally and self-consistently in mathematical models of real solutions. Traditional models deal with interactions in an *ad hoc* and often subjective way. They add interactions one at a time 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 derives differential equations that describe all the forces, interactions, fields and flows 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.

Ions are present at very high concentrations in most devices — physical or biological — that use them. Ions are packed closely next to electrodes in practical 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 (and usually ions) nearby. (Small violations of even local electroneutrality would produce electric fields comparable to forces between valence electrons and nuclei of atoms shielded by inner electrons. Such strong electric fields are known to destroy ion channels and proteins.) Calcium and sodium channels have 20 to 40 molar concentrations of ion comparable to the 37M concentration of solid NaCl. Active sites of enzymes have densities of acidic or basic side chains nearly as large as ion channels. 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 and channels 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 with the theory of complex fluids of mixtures of hard spherical ions in implicit (primitive) solvents. More complex representations of ions and solvent can be added later as needed to fit data.

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 flow in wildly nonequilibrium systems. The flows successfully computed by the theory of complex fluids can be much more complicated than those we see every day when water flows from a faucet. The liquid crystal displays (LCD's) of our technology are computed by these theories.[6,32]

The theory of complex fluids deals naturally with nonequilibrium properties of ionic solutions. It deals with flows driven by pressure, concentration, and voltage gradients all together. Describing such flows 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.

Dealing with nonequilibrium mixtures is particularly important in life. Nearly every system in biology requires nonequilibrium conditions and flows of mixed ionic solutions, as does manmade technology. Living systems live only when they maintain large flows to keep them far from equilibrium. 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.

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. An amplifier with power supplies disconnected or set to ground potential follows no simple law. Only when is it is energized is the output proportional to the input. It takes many highly nonlinear devices (usually transistors) working far from equilibrium connected into a complex circuit structure to produce that simple relation between input and output. In engineering, thermodynamic equilibrium only occurs when power fails. In biology, thermodynamic equilibrium only occurs when the organism fails and dies.

Theories developed to exploit the special properties of thermodynamic equilibrium had an enormously important role in the historical development of science,[4] 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. One can argue that semiconductor technology was possible exactly because semiconductor physicists never assumed equilibrium.[42,45] They always dealt with separate input, outputs and power terminals. These ports are in different places and the resulting spatially nonuniform boundary conditions nearly always produce flow.

Flow

The variational theory of complex fluids is likely to help in the analysis of flow of ionic mixtures. Variational principles can describe the energy and friction ('dissipation') of the components of complex fluids. The field equations derived from these principles describe spatial variation and flow within a set of spatially nonuniform boundaries and boundary equations like those imposed by electrodes or the insulating walls of an electrochemical cell. 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 as expressed in the underlying variational principle and the boundary conditions. The partial differential equations that form a field theory are derived from variational principles by mathematics alone. Only algebra is used. No approximations or additional arguments are needed to describe interactions.

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. 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.

The interactions arise automatically from a variational principle if the component is added into the energy and dissipation after the Euler-Lagrange process is used to derive partial differential equations of field theory. The interaction terms are objective outputs of a mathematical analysis. They are not assumed. If a new component is added into the variational principle, the interactions of all the components with all others arise automatically in the resulting partial differential equations.

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 to see if it actually works. The field equations of a variational theory will always be consistent mathematically, but they will be consistent physically only if they contain enough detail. We do not yet know what detail is needed to deal with the range of conditions found in chemistry and biochemistry.

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 are much larger and more serious than often discussed, see reference[10] 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 the structures perform their natural functions by moving on the 10^{-4} sec time scale. 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 scale in biological mixed solutions. In qualitative applications, molecular dynamics provides an indispensable dynamic extension of the statics of structural biology.

Variational Analysis

The variational analysis of ionic solutions, and ions in channels, can begin with the energetic variational principle of Chun Liu[34,48], building on the work of many others,

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

This principle has been applied to a model of ionic solutions in which the ions are represented as spheres in a uniform frictional dielectric.[11,23] 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, but it will certainly need to be extended to include much more 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.

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

combined with the Poisson Equation

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

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.

$$\frac{d}{dt} \int \left\{ k_B T \sum_{i=n,p} c_i \log c_i + \frac{1}{2} \left(\rho_0 + \sum_{i=n,p} z_i e c_i \right) \varphi + \sum_{i,j=n,p} \frac{c_i}{2} \int \tilde{\Psi}_{i,j} c_j d\vec{y} \right\} d\vec{x} = -\int \left\{ \sum_{i=n,p} \frac{D_i c_i}{k_B T} \left| k_B T \frac{\nabla c_i}{c_i} + z_i e \nabla \varphi - \sum_{j=n,p} \nabla \int \tilde{\Psi}_{i,j} c_j d\vec{y} \right|^2 \right\} d\vec{x} \qquad (9)$$

(with $\overbrace{}^{\text{Dissipative}}$ over the left side and $\underbrace{}_{\text{Conservative}}$ under the right side)

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

These equations have been integrated numerically[11,23] 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 that can be studied so optimization of parameters has not been done. Until parameters are optimized, one unfortunately cannot tell how well the theory actually deals with the wide range of data in diverse conditions and applications.

Each application seems to require separate analysis. It does not seem possible to give general energetic expressions for the rate constants that provide useful insight, but one can hope for the seemingly impossible. The insights concerning rate constants, unidirectional fluxes, and conditional probabilities in eq.(1) - (5) took more than a decade to develop.

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] (and many other papers inadvertently overlooked, I fear) to deal with solutions of a single monovalent species at equilibrium 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.

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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.

Bullets

- The law of mass action describes reactants as ideal simple fluids made of uncharged noninteracting particles.

- Ionic solutions consist of interacting charged particles and are not ideal.

- 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.

- 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 so far prevented thorough comparison with experiments.