Life’s Solutions are Not Ideal

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Abstract

Life occurs in ionic solutions, not pure water. The ionic mixtures of these solutions are very different from water and have dramatic effects on the cells and molecules of biological systems, yet theories and simulations cannot calculate their properties. I suggest the reason is that existing theories stem from the classical theory of ideal or simple gases in which (to a first approximation) atoms do not interact. Even the law of mass action describes reactants as if they were ideal. I propose that theories of ionic solutions should start with the theory of complex fluids because that theory is designed to deal with interactions from the beginning.

The variational theory of complex fluids is particularly well suited to describe mixtures like the solutions in and outside biological cells. When a component or force is added to a solution, the theory derives — by mathematics alone — a set of partial differential equations that captures the resulting interactions self-consistently. Such a theory has been implemented and shown to be computable in biologically relevant systems but it has not yet been thoroughly tested in equilibrium or flow.
Life in water are life’s solutions. Pure water is lethal to most cells. Most proteins denature in distilled water. Electrolyte mixtures in water — not water itself — are the liquid of life.

The concentration and type of ions are important in biology. Most cells live in a small range of ions and concentrations. Changing the type or concentration of ions changes the function of most enzymes, binding proteins, or channels, as well as cells and tissues. Details of the mixture of ions in our plasma and around our cells have profound effects. Just ask a clinician about blood pH.

Surprisingly little is known about the physical properties of salt mixtures like those inside and outside cells. A prominent chemist recently reported (in an overview of specific ion effects) “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.” Experimental measurements have been available for some 100 years. A generation of physical chemists sought explanations but only produced empirical equations for a subset of phenomena. Realistic simulations are just beginning to address the issues in the simplest (unrealistic) cases, rarely dealing with divalents, mixtures, or flow.

Many physical chemists have told me of their frustration at this lack of understanding. I am alarmed as a biologist that life’s solutions are so little understood.

Theories of the Ideal. Classical theories of ionic solutions are of limited use because they stem from the theory of ideal gases. In one of the triumphs of 19th century physics, physicists showed how gases could be approximated as swarms of point particles without electrical properties, extending that triumph to the liquid state. Chemists and biologists naturally tried to extend the triumph of ideal gas theory to ions in water despite the evident difference in density, charge, and thus interactions. That extension is used to this day.

But life’s solutions are nothing like these ideal gases of noninteracting particles. All electrolyte solutions — even those as dilute and nearly ideal as 1 mM Na⁺Cl⁻ — are dominated by the electrical interactions called shielding or screening. Their free energy does not scale linearly with the number density of particles as in ideal gases. The free energy contains a large ‘excess’ component that (for Na⁺Cl⁻) scales with the square root of concentration. Even in dilute solutions ‘everything’ interacts with everything else through the mean electric field.

Theories of the Dilute. Dilute (< 150 mM) solutions of Na⁺Cl⁻ and their mean electric fields are usually described by the Poisson-Boltzmann equation. The PB equation idealizes ions as point charges. It appears in various disguises 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 equations only describe equilibrium conditions in which nothing flows.

Extensions of PB to include flow have many names. Drift diffusion equations are used to design our semiconductor technology. The Poisson-Nernst-Planck equations of physical chemistry and biophysics are drift diffusion equations often called PNP to emphasize the relation between semiconductors and ionic solutions.

The PNP treatment 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.

A generation of physical chemists just now retiring studied these effects, reported in the classics of the statistical mechanics literature. The scientists may retire, but finite size effects have not disappeared. As one of that generation—George Stell—put it “…it is almost never valid to use Debye-Hückel under physiological conditions” (paraphrase of 110). This is a view repeated many time by many workers of that generation, see and other references too numerous to cite here. Two large books compile the relevant experimental data for equilibrium systems and document the many attempts to fit it along with references already cited.

The idealizations fail 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. The independence principle of Hodgkin and Huxley is incorrect in bulk solutions and inside channels that are occupied by more than one type of ion. Hundreds of papers reviewed in (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 molecular biology and biophysics, or their texts, probably because mathematical descriptions of interactions were so arbitrary and awkward in traditional theories.

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. This paper proposes a mathematical approach—from the theory of complex fluids—that objectively and automatically captures all interactions. This approach derives differential equations that describe all the forces, fields and flows (and interactions) with a minimal number of parameters.

Life’s (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 life’s solutions appears to be new. I now argue that a variational approach is more or less essential when flows are involved or number densities of ions—that we call ‘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 known to destroy ion channels and proteins.) Calcium and sodium channels have 20 to 40 molar concentrations of ions. For comparison, solid NaCl has a number density (in chemical units) of 37 molar. Active sites of
enzymes have densities of acidic or basic side chains as large as ion channels. The charge density of side chains in active sites is ~20 molar in ~600 enzymes, found in an automated search of a library of enzymes of known structure and function.65

The crowded conditions of active sites and channels form a special environment likely to be important for 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.

**Law of Mass Action.** Even the law of mass action — taught so early in our educations that many take its validity for granted — depends on the ideal properties of reactants.95 The derivation of the law uses expressions for energy and entropy of ideal gases of uncharged point particles. Indeed, the rate constants of the law of mass action can be constants, independent of concentration, only if the reactants are ideal, dilute, and their free energy is described by simple formulas that depend only on the number density (and charge) of one species at a time. Special conditions can be chosen to approximate these ideal conditions, and these conditions are widely used in idealized measurements of enzyme kinetics, but channels and enzymes rarely actually function in these special conditions. Channels and enzymes work in mixtures of ions, with tightly specified concentrations of ‘control’ molecules often including calcium ions.

When reactants interact, the free energy of one type of reactant depends on the concentrations (and types) of all species present.28,76,85,90,114 The free energy then has a component in excess of that in an ideal gas. **The excess component is important whenever reactants are charged.** It dominates when reactants are at high number density as they are in the immediate vicinity of catalysts, or enzymes, or if they have a ‘high cross section for reaction’ for any reason. Indeed, as chemical reactions are studied in three dimensions, without assuming well stirred “zero dimensional” solutions, it will be interesting to see how many reactions occur at low concentration. One imagines that most chemical reactions that proceed at a reasonable and interesting rate have local concentrations of reactants near enzymes or catalysts (or near other reactants) that are large. The concentrations of reactants in these interesting regions are unlikely to be those assumed in approximations that assuming perfect stirring, in my view. Engineers and evolution are likely to choose systems that maximize the rate of reactions.

The law of mass action will have variable reaction rate ‘constants’ whenever reactants are charged. It will have variable reaction rate ‘constants’ whenever a reaction proceeds rapidly because of a large local concentration of reactants.

We conclude that life’s reactions, likes its solutions, often need to be analyzed by a mathematics that deals naturally with interactions. Fortunately, the (mathematical variational) theory of complex fluids84,113 does this. The theory 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.21,81

**Electrolyte Solutions as Complex Fluids.** I suggest that work on electrolyte solutions should start with the theory of complex fluids21,81,84,113, beginning with the relatively simple case of
mixtures of hard spherical ions, because that mathematics deals consistently and automatically with interactions. More complex representations of ions and solvent can be added later on.

The theory of complex fluids brings along another advantage. It can deal with nonequilibrium properties of ionic solutions. It deals with flows driven by pressure, concentration, and voltage gradients. 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.\textsuperscript{15,70,100} 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 every equilibrium property interacting with every other equilibrium property.

Dealing with nonequilibrium systems is particularly important in life. Nearly every system in biology requires nonequilibrium conditions and flows of 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 (axon) 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 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 to produce that simple relation between input and output. In engineering, thermodynamic equilibrium only occurs when power supplies are turned off and devices no longer function. In biology, thermodynamic equilibrium only occurs at death. Theories developed to exploit the special properties of thermodynamic equilibrium had an enormously important role in the historical development of science,\textsuperscript{12,41} but they must be abandoned in their original form, if the interacting nonequilibrium reality of life’s solutions are to be explained as they are actually measured. One can argue that semiconductor technology was possible exactly because semiconductor physicists never assumed equilibrium.\textsuperscript{64,98,108} (Compare the constant field theory in semiconductors\textsuperscript{89} and with the physiological version\textsuperscript{11,19,52,102-104} by Hodgkin and Katz, and Cole’s student Goldman.\textsuperscript{17,43,51})

Flow. The variational theory of complex fluids is likely to help in the analysis of flow. 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 boundaries with known properties, like the 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 constituents 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. 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 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 the components 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 described, the field equations will be incorrect, albeit self-consistent
mathematically. For example, if a chaotropic additive changes the free energy of water, a
primitive model\textsuperscript{3,4,6,8} 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 in the solutions of life.

This variational approach is in contrast to attempts to simulate macroscopic properties by
direct calculation of motions of all atoms in molecular dynamics. The problems of scale are
much larger and more serious than often discussed, see reference\textsuperscript{27}. The problems of dealing with
life’s structures (with 0.1\% accuracy in three dimensions) that change significantly in 10\textsuperscript{14} sec
are serious, particularly because the structures perform their natural functions by moving on the
10\textsuperscript{-4} sec time scale. In quantitative applications, molecular dynamics is limited (for the time
being) by its inability to calculate the properties of mixtures of electrolytes. 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\textsuperscript{84,113}, building on the work of many others,

\[
\frac{\delta E}{\delta \vec{x}} - \frac{1}{2} \frac{\delta \Delta}{\delta \vec{u}} = 0
\]

This principle has been applied to a model of ionic solutions in which the ions are represented as
spheres in a uniform frictional dielectric.\textsuperscript{29,62} 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.\textsuperscript{61}

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.

\[
\frac{\partial c_n}{\partial t} = \nabla \cdot \left[ D_n \left\{ \nabla c_n + \frac{c_n}{k_n T} \left( z_n e \nabla \phi - \int \frac{12 \varepsilon_{n,n} (a_n + a_n)^{12} (\vec{x} - \vec{y})}{|\vec{x} - \vec{y}|^4} c_n (\vec{y}) d\vec{y} \right. \right. \right. \right.
\]

\[
\left. \left. \left. \left. \int \frac{6 \varepsilon_{n,p} (a_n + a_p)^{12} (\vec{x} - \vec{y})}{|\vec{x} - \vec{y}|^4} c_p (\vec{y}) d\vec{y} \right) \right) \right) \right) \right) \right) \right) \right)
\]
combined with the Poisson Equation

$$\nabla \cdot (\varepsilon \nabla \phi) = - \left( \rho_0 + \sum_{i=1}^{N} z_i e c_i \right) \quad i = n \text{ or } p$$  \hspace{1cm} (3)

We write the equation only for negative monovalent ions with valence \( z_i = -1 \) 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. \( k_i T \) 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. \( \varepsilon \) (without subscript) is the dielectric coefficient. The electrical potential is \( \phi \). \( \rho_0 \) represents the charge density of the protein, as it represents the charge density of doping in semiconductors. \( \rho_0 \) depends on location and is zero in bulk solutions.

We note that the field satisfies the dissipation principle.

$$\frac{d}{dt} \left\{ k_B T \sum_{i=n,p} c_i \log c_i + \frac{1}{2} \left( \rho_0 + \sum_{i=n,p} z_i e c_i \right) \phi + \sum_{i,j=n,p} \int_{\vec{y}}^{\vec{y}} \left( \Psi_{i,j} c_i d\vec{y} \right)^2 \right\} = - \left\{ \sum_{i=n,p} \frac{D_{i,n,p}}{k_B T} \left( \frac{\nabla c_i}{c_i} + z_i e \nabla \phi - \sum_{j=n,p} \nabla \left( \Psi_{i,j} c_i d\vec{y} \right) \right)^2 \right\} d\vec{x}$$  \hspace{1cm} (4)

\( \Psi_{i,j} \) represent the Lennard Jones crowded charges terms defined in 29,62.

These equations have been integrated numerically in the papers cited to predict binding of ions in crowded conditions, or the flow of ions through channels. The calculations are successful and the methods are feasible. But numerical problems limit the routine application to realistic structures and so optimization of parameters are not yet possible. Until parameters are optimized one unfortunately cannot tell how well the theory actually deals with data.

**Conclusion.** The variational treatment of ionic solutions has substantial advantages. It describes systems in which everything interacts with everything else, as they do in life and its solutions. The variational theory can be a complete description of all the properties of ionic solutions 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.

The variational treatment of electrolyte solutions has just started. It begins in the right place, in my view, with the successful theory of complex fluids. But the variational approach is not yet sufficiently developed or checked. Other approaches are being used2,36,37,42,47,61,62,67,71,72,76,79,80,93,100,107,112,115 (and many overlooked or forgotten by me, no doubt).
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 like plasma or blood, or with flow at all. These properties are essential to life. Analysis must not assume properties incompatible with life: life’s solutions are flowing mixtures of unequal diameter and variational methods deals naturally with these complexities and interactions.

The ionic mixtures of life’s solutions need to be understood. Life depends on the bulk flow and electrodiffusion of multicomponent systems. It is often controlled by trace concentrations of messengers, often divalent calcium ions. We need to calculate the properties of sea water, or the plasmas in our body, with a physical theory that lets us understand and change what these solutions do to our proteins, cells and tissues. Variational methods give hope, at least to me, that this can be done.
References

1. Abbas, Z., Gunnarsson, M., Ahlberg, E. & Nordholm, S. Corrected Debye-Huckel Theory of Salt Solutions: Size Asymmetry and Effective Diameters. The Journal of Physical Chemistry B 106, 1403-1420, doi:10.1021/jp012054g (2002).
2. Abbas, Z., Ahlberg, E. & Nordholm, S. Monte Carlo Simulations of Salt Solutions: Exploring the Validity of Primitive Models. The Journal of Physical Chemistry B 113, 5905-5916, doi:10.1021/jp808427f (2009).
3. Alberts, B., Bray, D., Johnson, A., Lewis, J., Raff, M. & Roberts, K. Essential Cell Biology. Third edn, (Garland, 1998).
4. Barbosa, M. C. & et al. A Stable Local Density Functional Approach to Ion-Ion Correlations. EPL (Europhysics Letters) 52, 80 (2000).
5. Barker, J. & Henderson, D. What Is "Liquid"? Understanding the States of Matter. Reviews of Modern Physics 48, 587-671 (1976).
6. Barlow, C. A., Jr. & Macdonald, J. R. in Advances in Electrochemistry and Electrochemical Engineering, Volume 6 Vol. VI (ed P. Delahay) 1-199 (Interscience Publishers, 1967).
7. Barthel, J., Krienke, H. & Kunz, W. Physical Chemistry of Electrolyte Solutions: Modern Aspects. (Springer, 1998).
8. Bazant, M. Z., Thornton, K. & Ajdari, A. Diffuse-Charge Dynamics in Electrochemical Systems. Physical Review E 70, 021506 (2004).
9. Berry, S. R., Rice, S. A. & Ross, J. Physical Chemistry. Second Edition edn, (Oxford, 2000).
10. Boltzmann, L. Lectures on Gas Theory. (University of California, 1964).
11. Boron, W. & Boulpaep, E. Medical Physiology. (Saunders, 2008).
12. Brush, S. G. The Kind of Motion We Call Heat. (North Holland, 1986).
13. Cercignani, C., Illner, R. & Pulvirenti, M. The Mathematical Theory of Dilute Gases. Vol. 106 (Springer-Verlag, 1994).
14. Che, J., Dzubiella, J., Li, B. & McCammon, J. A. Electrostatic Free Energy and Its Variations in Implicit Solvent Models. The journal of physical chemistry 112, 3058-3069, doi:10.1021/jp7101012 (2008).
15. Chhih, A., Bernard, O., Barthel, J. M. G. & Blum, L. Transport Coefficients and Apparent Charges of Concentrated Electrolyte Solutions: Equations for Practical Use. Ber. Bunsenges. Phys. Chem. 98, 1516-1525 (1994).
16. 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).
17. Cole, K. S. Four Lectures on Biophysics. (Institute of Biophysics, University of Brazil, 1947).
18. Darnell, J., Lodish, H. & Baltimore, D. Molecular Cell Biology. 2nd Edition edn, (Scientific American Books, 1990).
19. Davson, H. A Textbook of General Physiology, 4th Edition. 4th edn, (Churchill, 1970).
20. de Levie, R. & Moreira, H. Transport of Ions of One Kind through Thin Membranes. *Journal of Membrane Biology* 9, 241-260, doi:10.1007/bf01868055 (1972).
21. Doi, M. & Edwards, S. F. *The Theory of Polymer Dynamics*. 408 (Oxford University Press, 1988).
22. Dufreche, J. F., Bernard, O., Turq, P., Mukherjee, A. & Bagchi, B. Ionic Self-Diffusion in Concentrated Aqueous Electrolyte Solutions. *Phys Rev Lett* 88, 095902 (2002).
23. Dufreche, J. F., Jardat, M., Turq, P. & Bagchi, B. Electrostatic Relaxation and Hydrodynamic Interactions for Self-Diffusion of Ions in Electrolyte Solutions. *The journal of physical chemistry* 112, 10264-10271, doi:10.1021/jp801796g (2008).
24. Durand-Vidal, S., Turq, P., Bernard, O., Treiner, C. & Blum, L. New Perspectives in Transport Phenomena in Electrolytes. *Physica A* 231, 123-143 (1996).
25. Durand-Vidal, S., Simonin, J.-P. & Turq, P. *Electrolytes at Interfaces*. (Kluwer, 2000).
26. Eisenberg, B. Living Transistors: A Physicist’s View of Ion Channels. Version 2. [http://arxiv.org/q-bio.BM](http://arxiv.org/q-bio.BM), arXiv:q-bio/0506016v0506012 0506024 pages (2005).
27. 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).
28. Eisenberg, B. Crowded Charges in Ion Channels. *Advances in Chemical Physics (in the press) also available at http:\arxiv.org as Paper arXiv 1009.1786v1* (2010).
29. Eisenberg, B., Hyon, Y. & Liu, C. Energy Variational Analysis Envra of Ions in Water and Channels: Field Theory for Primitive Models of Complex Ionic Fluids. *Journal of Chemical Physics* 133, 104104 (2010).
30. Eisenberg, D., Eisenberg, D. S. & Kauzmann, W. *The Structure and Properties of Water*. (Oxford University Press, 2005).
31. Eisenberg, R. & Chen, D. *Poisson-Nernst-Planck (Pnp) Theory of an Open Ionic Channel*. *Biophysical Journal* 64, A22 (1993).
32. Eisenberg, R. S. in *New Developments and Theoretical Studies of Proteins* Vol. 7 (ed Ron Elber) 269-357. Published in the Physics ArXiv as arXiv:0807.0715 (World Scientific, 1996).
33. Eisenberg, R. S. Computing the Field in Proteins and Channels. *J. Membrane Biol.* 150, 1–25. Also available on http:\arxiv.org as Paper arXiv 1009.2857v1001 (1996).
34. Fawcett, W. R. *Liquids, Solutions, and Interfaces: From Classical Macroscopic Descriptions to Modern Microscopic Details*. (Oxford University Press, 2004).
35. Fedorov, M. V. & Kornyshev, A. A. Ionic Liquid near a Charged Wall: Structure and Capacitance of Electrical Double Layer. *The Journal of Physical Chemistry B* 112, 11868-11872, doi:10.1021/jp803440q (2008).
36. 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).
37. 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).
38. Franks, F. & Chemistry, R. o. *Water: A Matrix of Life*. (Royal Society of Chemistry, 2000).
39. Friedman, H. L. *Ionic Solution Theory*. (Interscience Publishers, 1962).
40. Friedman, H. L. Electrolyte Solutions at Equilibrium. *Annual Review of Physical Chemistry* **32**, 179-204, doi:10.1146/annurev.pc.32.100181.001143 (1981).
41. Garber, E., Brush, S. G. & Everitt, C. W. F. (MIT Press, Cambridge MA, 1986).
42. Gee, M. B., Cox, N. R., Jiao, Y., Bentenitis, 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).
43. Goldman, D. E. Potential, Impedance and Rectification in Membranes. *J. Gen. Physiol.* **27**, 37–60 (1943).
44. Grochowski, P. & Trylska, J. Continuum Molecular Electrostatics, Salt Effects, and Counterion Binding—a Review of the Poisson–Boltzmann Theory and Its Modifications. *Biopolymers* **89**, 93-113 (2008).
45. Hansen, J.-P. & McDonald, I. R. *Theory of Simple Liquids*. Third Edition edn, (Academic Press, 2006).
46. Harned, H. S. & Owen, B. B. *The Physical Chemistry of Electrolytic Solutions*. Third edn, (Reinhold Publishing Corporation, 1958).
47. 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).
48. Henderson, L. J. *The Fitness of the Environment: An Inquiry into the Biological Significance of the Properties of Matter*. 317 (Macmillan, 1913).
49. Henderson, L. J. *Blood. A Study in General Physiology* (Yale University Press, 1928).
50. Hille, B. *Ionic Channels of Excitable Membranes*. 3rd edn, (Sinauer Associates Inc., 2001).
51. Hodgkin, A. L. & Katz, B. The Effect of Sodium Ions on the Electrical Activity of the Giant Axon of the Squid. *J. Physiol.* **108**, 37–77 (1949).
52. Hodgkin, A. L. The Ionic Basis of Electrical Activity in Nerve and Muscle. *Biological Reviews* **26**, 339-409 (1951).
53. Hodgkin, A. L. & Huxley, A. F. Currents Carried by Sodium and Potassium Ions through the Membrane of the Giant Axon of Loligo. *J. Physiol.* **116**, 449-472 (1952).
54. Hodgkin, A. L. & Huxley, A. F. A Quantitative Description of Membrane Current and Its Application to Conduction and Excitation in Nerve. *J. Physiol.* **117**, 500-544. (1952).
55. Hodgkin, A. L. & Huxley, A. F. The Components of Membrane Conductance in the Giant Axon of Loligo. *J Physiol* **116**, 473-496 (1952).
56. Hodgkin, A. L. & Huxley, A. F. The Dual Effect of Membrane Potential on Sodium Conductance in the Giant Axon of Loligo. *J Physiol* **116**, 497-506 (1952).
57. Hodgkin, A. L. Ionic Movements and Electrical Activity in Giant Nerve Fibres. *Proceedings of the Royal Society of London. Series B* **148**, 1-37 (1958).
58. Hodgkin, A. L. The Ionic Basis of Nervous Conduction. *Science* **145**, 1148-1154 (1964).
59. Hodgkin, A. L. Chance and Design in Electrophysiology: An Informal Account of Certain Experiments on Nerve Carried out between 1934 and 1952. *J Physiol* **263**, 1-21 (1976).
60. Hodgkin, A. L. *Chance and Design*. (Cambridge University Press, 1992).
61. Howard, J. J., Perkyns, 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).

62. Hyon, Y., Eisenberg, B. & Liu, C. A Mathematical Model for the Hard Sphere Repulsion in Ionic Solutions. *Communications in Mathematical Sciences (in the press)* also available as preprint# 2318 *(IMA, University of Minnesota, Minneapolis)* http://www.ima.umn.edu/preprints/jun2010/jun2010.html (2010).

63. Jacobsen, R. T., Penoncello, S. G., Lemmon, E. W. & Span, R. in *Equations of State for Fluids and Fluid Mixtures* (eds J.V. Sengers, R.F. Kayser, C.J. Peters, & H.J. White, Jr.) 849-882 (Elsevier, 2000).

64. Jerome, J. W. *Analysis of Charge Transport. Mathematical Theory and Approximation of Semiconductor Models.* (Springer-Verlag, 1995).

65. Jimenez-Morales, D., Liang, J. & Eisenberg, B. Active Sites of Enzymes Are Crowded with Charge. *Biophysical Journal* **100**, 218a (2011).

66. Joung, I. S. & Cheatham, T. E. Determination of Alkali and Halide Monovalent Ion Parameters for Use in Explicitly Solvated Biomolecular Simulations. *The Journal of Physical Chemistry B* **112**, 9020-9041, doi:10.1021/jp8001614 (2008).

67. 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).

68. Jungwirth, P., Finlayson-Pitts, B. J. & Tobias, D. J. *Introduction: Structure and Chemistry at Aqueous Interfaces.* *Chemical Reviews* **106**, 1137-1139, doi:10.1021/cr040382h (2006).

69. Jungwirth, P. & Winter, B. Ions at Aqueous Interfaces: From Water Surface to Hydrated Proteins. *Annual Review of Physical Chemistry* **59**, 343-366, doi:10.1146/annurev.physchem.59.032607.093749 (2008).

70. 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 Yaeger) Ch. 3, 223-338 (Plenum, 1983).

71. Kalcher, I. & Dzubiella, J. Structure-Thermodynamics Relation of Electrolyte Solutions. *The Journal of chemical physics* **130**, 134507 (2009).

72. Kalcher, I., Schulz, J. C. F. & Dzubiella, J. Ion-Specific Excluded-Volume Correlations and Solvation Forces. *Physical Review Letters* **104**, 097802 (2010).

73. Kalyuzhnyi, Y. K., Blum, L., Reiscic, J. & Stell, G. Solution of the Associative Mean Spherical Approximation for a Multicomponent Dimerizing Hard-Sphere Multi-Yukawa Fluid. *J. Chem. Phys.* **113**, 1135-1142 (2000).

74. Khavrutskii, I. V., Dzubiella, J. & McCammon, J. A. Computing Accurate Potentials of Mean Force in Electrolyte Solutions with the Generalized Gradient-Augmented Harmonic Fourier Beads Method. *The Journal of chemical physics* **128**, 044106, doi:10.1063/1.2825620 (2008).
75. Kokubo, H., Rosgen, J., Bolen, D. W. & Pettitt, B. M. Molecular Basis of the Apparent near Ideality of Urea Solutions. *Biophys. J.* 93, 3392-3407, doi:10.1529/biophysj.107.114181 (2007).
76. Kontogeorgis, G. M. & Folas, G. K. *Models for Electrolyte Systems.* (John Wiley & Sons, Ltd, 2009).
77. Kron, I., Marshall, S., May, P., Hefter, G. & Königsberger, E. The Ionic Product of Water in Highly Concentrated Aqueous Electrolyte Solutions. *Monatshefte für Chemie / Chemical Monthly* 126, 819-837 (1995).
78. Kumar, A. & Patwardhan, V. S. Activity Coefficients in Mixed Aqueous Electrolyte Solutions with a Common Ion. *AIChE Journal* 38, 793-796 (1992).
79. Kunz, W. 348 (World Scientific Singapore, 2009).
80. Kunz, W. & Neueder, R. in *Specific Ion Effects* (ed Werner Kunz) 11-54 (World Scientific 2009).
81. Larson, R. G. *The Structure and Rheology of Complex Fluids* (Oxford, 1995).
82. Lee, L. L. *Molecular Thermodynamics of Nonideal Fluids* 512 (Butterworth-Heinemann, 1988).
83. Lee, L. L. *Molecular Thermodynamics of Electrolyte Solutions.* 247 (World Scientific 2008).
84. Lin, F.-H., Liu, C. & Zhang, P. On Hydrodynamics of Viscoelastic Fluids. *Communications on Pure and Applied Mathematics* 58, 1437-1471 (2005).
85. 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).
86. Loehe, J. R. & Donohue, M. D. Recent Advances in Modeling Thermodynamic Properties of Aqueous Strong Electrolyte Systems. *AIChE Journal* 43, 180-195, doi:10.1002/aic.690430121 (1997).
87. Macdonald, J. R. & Barlow, C. A., Jr. Theory of Double Layer Differential Capacitance in Electrolytes. *Journal of Chemical Physics* 36, 3062-3080 (1962).
88. Markowich, P. A., Ringhofer, C. A. & Schmeiser, C. *Semiconductor Equations.* (Springer-Verlag, 1990).
89. Mott, N. F. The Theory of Crystal Rectifiers. *Proc Roy Soc A* 171, 27-38 (1939).
90. 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).
91. Patwardhan, V. S. & Kumar, A. A Unified Approach for Prediction of Thermodynamic Properties of Aqueous Mixed-Electrolyte Solutions. Part Ii: Volume, Thermal, and Other Properties. *AIChE Journal* 32, 1429-1438 (1986).
92. Patwardhan, V. S. & Kumar, A. Thermodynamic Properties of Aqueous Solutions of Mixed Electrolytes: A New Mixing Rule. *AIChE Journal* 39, 711-714 (1993).
93. 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).
94. Pitzer, K. S. & Kim, J. J. Thermodynamics of Electrolytes. Iv. Activity and Osmotic Coefficients for Mixed Electrolytes. Journal of the American Chemical Society 96, 5701-5707, doi:10.1021/ja00825a004 (1974).
95. Pitzer, K. S. Thermodynamics. 3rd edn, 626 (McGraw Hill, 1995).
96. Resibois, P. M. V. Electrolyte Theory. (Harper & Row, 1968).
97. Rice, S. A. & Gray, P. Statistical Mechanics of Simple Fluids. (Interscience (Wiley), 1965).
98. Riordan, M. & Hoddeson, L. Crystal Fire. (Norton, 1997).
99. Robinson, R. A. & Stokes, R. H. Electrolyte Solutions. Second edn, (Butterworths Scientific Publications, 1959).
100. 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).
101. Rowlinson, J. S. The Perfect Gas. (Macmillan, 1963).
102. Ruch, T. C. & Patton, H. D. Vol. 1 500 ( W.B. Saunders Company, Philadelphia, 1973).
103. Ruch, T. C. & Patton, H. D. Vol. 2 558 ( W.B. Saunders Company, Philadelphia, 1973).
104. Ruch, T. C. & Patton, H. D. Vol. 3 391 ( W.B. Saunders Company, Philadelphia, 1973).
105. Selberherr, S. Analysis and Simulation of Semiconductor Devices. (Springer-Verlag, 1984).
106. Sengers, J. V., Kayser, R. F., Peters, C. J. & White, H. J., Jr. Equations of State for Fluids and Fluid Mixtures (Experimental Thermodynamics) (Elsevier, 2000).
107. 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).
108. Shurkin, J. N. Broken Genius: The Rise and Fall of William Shockley, Creator of the Electronic Age. (Macmillan, 2006).
109. Simonin, J.-P., Blum, L. & Turq, P. Real Ionic Solutions in the Mean Spherical Approximation. I. Simple Salts in the Primitive Model. Journal of Physical Chemistry 100, 7704-7709 (1996).
110. Stell, G. & Joslin, C. G. The Donnan Equilibrium: A Theoretical Study of the Effects of Interionic Forces. Biophys J 50, 855-859 (1986).
111. Vrbka, L., Vondrášek, J., Jagoda-Cwiklik, B., Vácha, R. & Jungwirth, P. Quantification and Rationalization of the Higher Affinity of Sodium over Potassium to Protein Surfaces. Proceedings of the National Academy of Sciences 103, 15440-15444, doi:10.1073/pnas.0606959103 (2006).
112. 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).
113. 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).
114. 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).

115. 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).