

Failures of Poisson Boltzmann to deal with the Nonideal Properties of Ionic Solutions

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I have had months of friendly discussion with many mathematicians concerning the limitations of Poisson Boltzmann theories of ionic solutions. I have discussed the facts and given extensive reference lists in several publications. I have sent many mathematicians copies of the physical chemistry papers documenting these inadequacies. However, many mathematicians insist on saying something to the effect that Poisson Boltzmann theory is a good approximation to properties of ionic solutions in biological systems, e.g., including proteins, ion channels and nucleic acids. This is simply untrue. Almost all biology occurs in solutions that are more than 200 mM in concentration, that are mixtures of different monovalent species, and that contain divalents. The concentrations of divalents are physiological regulators of an enormous range of function. Under these conditions, excess free energy is important and physical chemists agree there is no satisfactory model of that excess free energy. Poisson Boltzmann is a particular embarrassment because it leaves out the effects of finite size of ions and those effects are known to be dominant determinants of excess free energy.

The situation is actually much worse than just stated. It is very well known that the concentrations of ions near electrodes, ion channels, binding proteins, nucleic acids, enzyme active sites, most membranes and most proteins are in the molar range, often reaching values beyond 10 molar. Under these conditions, excess free energy dominates the properties of ionic solutions. Excess free energy of this type is not even present in Poisson Boltzmann or PNP theories.

The fact that mathematicians have willfully been ignoring the experimental properties of ionic solutions known for more than fifty years made me realize that if someone did not speak out correctly, we stood risk of having happen in biophysics what has happened in other fields with disastrous consequences: the rejection of an important reality by a large fraction of an academic community because that reality was not mathematically inconvenient.

The general view of ionic solutions is stated in the classical literature by

- 1) George Stell and C.G. Joslin, The Donnan Equilibrium: A Theoretical Study of the Effects of Interionic Forces. *Biophys J*, 1986. 50(5): p. 855-859.

“Under physiologically appropriate conditions, we find that it is almost never valid to use Debye-Huckel theory to calculate ionic activities: it is important to take proper account of ion size.”

2) Torrie and Valleau Journal of Physical Chemistry, 1982: 86: 3251-3257

“It is immediately apparent that Classical Theory has Broken Down completely. It ... fails to show [the] qualitative behavior [and] is seriously in Error for quite low concentrations and charges”

“When the counterions are doubly charged ... the classical theory Fails Altogether even for quite low concentrations and charges”

3) Fraenkel Molecular Physics, 2010. 108(11): p. 1435 – 1466 has a fine historical introduction giving the modern view of Poisson Boltzmann and many references supporting this view.

4) The two books Zemaitis, et al, and Pytkowicz (see reference list below) are classical compilations of experimental data and theoretical models that attempt to deal with the issues just quoted. Zematis et al, has a discussion of nine different empirical models that attempt to describe non ideal effects.

5) Kontogeorgis and Folasis is the most recent compilation of data and theories that I know of.

Here is my view, written as a letter to mathematicians

Dear Mathematical Friends,

I have recently had the sad task of reviewing a fine mathematical paper on linearized Poisson Boltzmann which seems entirely unaware of the view of that equation by the entire community of physical chemists.

It is very sad to have fine mathematicians working in such ignorance of the work of generations of physical chemists.

Here is what I wrote about that work and I attach a a partial set of references (I hasten to immediately apologize if I left out work you prefer or work of your own that contributes importantly to this field. I simply took the references immediately at hand in my reference lists and I know that leaves out many many that I should know about and refer to.)

As ever
Bob

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The paper is a substantial contribution and the authors have done a fine job of responding to the criticisms except one.

That one in my view is crucial.

The Poisson Boltzmann equation is NOT a good approximation to the properties of ions near DNA at all, and not near the active sites of enzymes, which is where many proteins perform their function.

It is VERY well known that the number density of ions close to DNA is many molar.

It is VERY well known that the number density of ions close to active sites of enzymes, close to ion channels, and close to binding proteins is many molar. In electrochemical cells, used universally in our technology of batteries, as well as the huge electrochemistry industry, concentrations near electrodes is very high.

It is VERY well known that most protein function, and DNA function is sensitive to the concentration of divalents and occurs in solutions containing mixtures of monovalents, calcium, and magnesium.

It is VERY well known that an enormous range of biological function is controlled physiologically by concentrations of calcium ions, in the same sense that an accelerator (gas pedal) controls the speed of a car.

There is no reference I know of in the physical chemistry literature that says that Poisson Boltzmann is a good approximation for (1) mixtures of monovalents of biological concentrations, (2) mixtures including divalents (3) any ionic solution when concentrations are above 500 millimolar.

The authors must not be permitted to continue the myth that linearized PB is successful in describing the properties of proteins or DNA in the natural cellular environment, no matter how long biochemists or mathematicians have believed that myth.

NEAR ion channels (not just in them), NEAR binding proteins (not just in them), NEAR enzymes (not just in them), ion concentrations are far above the few millimolar in which the Poisson Boltzmann equation is adequate in the view of physical chemists. In those regions DIVALENT concentrations are very important. I am unaware of ANY physical chemistry reference that says that Poisson Boltzmann is an adequate approximation when either divalents are present, OR concentrations are in the molar region.

I suggest that the authors say something like "Linearized Poisson Boltzmann has widely been used as an initial approximation to biological salt solutions. Nonetheless, physical chemists do NOT accept it as a reasonable approximation to the properties of solutions with divalents, or with concentrations like those near enzymes, nucleic acids, ion channels, or binding proteins. We believe, however, that it is reasonable to attack the mathematical issues in the linearized domain before the nasty realities of concentrated solutions are dealt with."

The authors have evidently not examined the references I cited previously.

I therefore attach a much larger set of references documenting the treatment of ionic solutions of concentration larger than (say) 100 mM NaCl, and divalents and mixtures. These references represent complete compilations of the experimental data and the theoretical models of such solutions as of the dates of their publication. NONE OF THESE REFERENCES SUPPORT THE USE OF POISSON BOLTZMANN FOR SOLUTIONS OF PURE MONOVALENTS OF CONCENTRATION LARGER THAN (SAY) 100 mM, or of divalents (of any concentration), or of mixtures of monovalents, let alone for the multimolar concentrations of ions (in mixtures of monovalents and divalents) found near nucleic acids, ion channels, binding proteins, enzyme active sites, most proteins, membranes and electrodes in electrochemical devices as they are actually used.

The authors should be reminded that **ALL physiological solutions are more concentrated than 100 mM, they all contain divalents, and they are all mixtures.**

The following reference list is numerous but are still a small subset of what has been done on this subject. Some of the references extend to closely related subjects. I chose only references I happen to have at hand. There are large numbers of papers I have inadvertently ignored, no doubt and some may be very important.

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