



Bob Eisenberg <bob.eisenberg@gmail.com>

Fwd: Our view of electrochemical systems in biology

Bob Eisenberg <beisenbe@rush.edu>

Sun, Sep 18, 2011 at 3:52 PM

Reply-To: beisenbe@rush.edu

To: Julie Mitchell <jcmitchell@wisc.edu>

Thought this might interst you....

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Return Address for email: beisenbe@rush.edu

Bob aka RS Eisenberg

Bard Endowed Professor and Chairman
Dept of Molecular Biophysics & Physiology
Rush University
1653 West Congress Parkway
Chicago IL 60612 USA
Office Location: Room 1291 of
Jelke Building at 1750 West Harrison

Email: beisenbe@rush.edu

Voice: +312-942-6467

FAX: +312-942-8711

FAX to Email: +[708-455-8542](tel:708-455-8542)

Department WebSite: <http://www.phys.rush.edu/Personal>

WebSite: <http://www.phys.rush.edu/RSEisenberg/>

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----- Forwarded message -----

From: **Bob Eisenberg** <beisenbe@rush.edu>

Date: Sun, Sep 18, 2011 at 3:50 PM

Subject: Re: Report on Visit to Oxford

To: Werner Kunz <Werner.Kunz@chemie.uni-regensburg.de>
Cc: "Stuart A. Rice" <s-rice@uchicago.edu>, Chun Liu <liu@math.psu.edu>, Pavel Jungwirth <pavel.jungwirth@marge.uochb.cas.cz>, Jean-Pierre Hansen <jph32@cam.ac.uk>, Pierre Turq <pierre.turq@upmc.fr>, Douglas Henderson BYU <doug@chem.byu.edu>, Wolfgang Nonner <wnonner@med.miami.edu>, Dirk Rush <Dirk_Gillespie@rush.edu>, Dezső Boda ++ Gmail <dezsoboda@gmail.com>, Gary Leaf <leaf@mcs.anl.gov>, Jim Fonseca <jefonseca@gmail.com>, Tai-Chia Lin 林太家 <tcclin@math.ntu.edu.tw>, Allen Tzyy-Leng Horng 1 <tlhorng@math.fcu.edu.tw>, Yoichiro Mori <ymori@umn.edu>, Ron Elber <ron@ices.utexas.edu>, Ross Macdonald <macd@email.unc.edu>, Monte Pettitt <pettitt@uh.edu>, josef_barthel <josef.barthel@chemie.uni-regensburg.de>, Rich Saykally <saykally@calmail.berkeley.edu>, "Berg, Jeremy (NIH/NIGMS) [E]" <bergj@nigms.nih.gov>, Mike Holst <mjhsan@ccom.ucsd.edu>, Andy McCammon <jmccammon@ucsd.edu>, Tony Watts <anthony.watts@bioch.ox.ac.uk>

Dear Werner

Thanks for your email.

I did not receive a reply from Ninham. Perhaps it was trapped by a spam filter somewhere. Could you forward it to me?

About "our approach" I should perhaps say a few more words.

We believe we have shown that a primitive model of three biological systems captures the energies involved in THEIR selectivity well enough to deal (and sometimes predict before experiments were done) all the biologically relevant behavior of these channels once they are open.

We do NOT believe such a model will be adequate in bulk solution, or for other channels etc etc.

In our view, biological systems should be viewed as devices that have been built by natural selection to provide a specific function needed for the survival of the species. They provide that function in many cases by using only a tiny subset of the available interactions. We believe we have guessed those correctly for the three channel types we have studied.

In our view, the GENERAL approach we would like to be identified with is that of a variational calculus approach to ionic solutions because ionic solutions are mixtures in which everything interacts with everything else (literally) through the electric field and (in most cases) through excluded volume forces, as well perhaps as many other things (e.g., hydration shells, local polarization).

We believe a theory MUST deal with interactions selfconsistently as a matter of mathematics. (Specifically, this means the results of the analysis must actually satisfy Gauss law for example, not by argument but by

demonstration that the results really do satisfy Gauss' law). We believe that the theory must include boundary conditions on a FINITE size system because that is the only way experiments are done and in fact it is (in almost all cases) the only way the boundary conditions can be written unambiguously. The thermodynamic limit IN ITSELF does not specify boundary conditions for the electric field, for example, and the well known divergence of Coulomb double body potentials (when integrated in an infinite domain) is an example. As a matter of mathematics this divergence cannot be "argued away" because the arguments are not unique. Different arguments give different results.

We believe a biologically complete (or even applicable) theory must allow spatially nonuniform boundary conditions and thus macroscopic flow because that is how biology occurs. Devices do not function without flow in almost any case.

Turning to specific approaches in the literature: it is obvious from your book and innumerable experimental papers (including the 11 volumes of Josef Barthel, if I count correctly) that DH does not fit data involving monovalents in the biological concentration range, and does not fit divalents and mixtures at all. Thus it is of limited use.

The other approaches (e.g., force fields) I cannot evaluate because the theories using them are almost never selfconsistent. This does NOT mean I think the physics of these other theories does not apply. It does mean that I think the only way to tell if the physics applies is to fit A WIDE RANGE OF DATA WITH ONE SELFCONSISTENT MODEL including the physics in question.

The discussions of force fields seems likely to waste everyone's time until

a) a specific set of data is agreed upon by which to evaluate the data. In my view, this obviously should be activity coefficients over a range of ionic conditions approximating those inside and outside cells AND INSIDE AND OUTSIDE ION CHANNELS AND ACTIVE SITES OF ENZYMES and binding proteins.

b) the theories are actually shown by direct examination of results to satisfy Gauss' law. Arguments about Particle Mesh Ewald etc are not sufficient. Anyone who constructs numerical solutions to systems of pde's for a living (e.g., anyone in computational fluid dynamics) knows that an agreed upon test suite to evaluate results is essential. This is taught in every computer science and numerical analysis course. I do not see why molecular dynamics and theories of ionic solutions etc should be exempt from this requirement.

c) the theories are selfconsistent in the sense that there is a mathematically unique way to add components, fields, and new boundary conditions.

I hope these ideas are helpful. Please note that the consistent themes are

a) when doing theory itself, one must follow the rules of mathematics and numerical analysis

and not have the
"anything goes" approach that characterizes so much of the older literature.

b) when doing science, one must stay very close to specific experimentation taken over a variety of conditions

c) biologically oriented work in physical chemistry is of limited use if it does not deal with divalents, mixtures of ions, flows of the type that occur in biology, and realistic NONperiodic conditions because those are all conditions used in almost all natural functions of living organisms.

d) engineers deal with these requirements all the time in the fantastically successful devices of semiconductor technology and many other places. If they can succeed so can we. But we must try.

e) one must face the reality that the law of mass action is used widely with constant rate constants while constant rate constants in fact fit very little experimental data. The need to use activities is hardly mentioned in most classical works on enzyme kinetics and the fact that nonideal activities depend on ALL COMPONENTS OF A SOLUTION is not mentioned at all as far as I can tell, although of course I am glad to be corrected.

As ever
Bob

PS I am sending a copy of this email to a number of friends in physical chemistry who may be interested. I encourage all and any questions, comment, suggestions and criticisms. That process itself will help substantially I believe.

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Bob aka RS Eisenberg

Bard Endowed Professor and Chairman
Dept of Molecular Biophysics & Physiology
Rush University
1653 West Congress Parkway
Chicago IL 60612 USA
Office Location: Room 1291 of
Jelke Building at 1750 West Harrison

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FAX: +312-942-8711

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On Sun, Sep 18, 2011 at 8:02 AM, Werner Kunz <Werner.Kunz@chemie.uni-regensburg.de> wrote:

Dear Bob,

thank you very much, especially for the copy of your talk that I really read with much pleasure.

In the meantime, Roland Netz sent you some comments on your question about Poisson-Boltzmann and DLVO. I attach another paper that might be of some interest. Another approach would be the one that is always proposed by Adrian Parsegian (and in part Barry Ninham). Personally, I do not think that "hydration forces" are a good idea to improve DLVO. This expression is simply a way of saying that solvent-averaged models are often inappropriate. Lifshitz-like theories also come to their limit when small distances are considered.

Your approach is really interesting, however, as all solvent-averaged models they have their limitations, when distances below say 1 nm matter. Then I believe, chemistry must be considered, i.e. the detailed structure of the hydration shell and all the other surrounding when the ions are in a confined medium. Whatever theory you use, sooner or later you must introduce models of ion-ion, ion-water and ion-macromolecule interactions. I believe that molecules exist, although physicists have always difficulties to accept that. They like to believe in forces and fields.

For a chemist, it is evident that ion specificities exist and that they can be even very specific.

On the other hand, I agree with Hakan Wennerstrom who recently summarized at the end of his career that DLVO is a very good theory. And I do not agree with my friend Kim Collins who recently gave a lecture saying that Debye-Hueckel is nonsense, because it cannot explain ion specificities especially in biological systems.

Let me put it in other words: if the approximations and consequently the limits of Debye-Hueckel, Poisson-Boltzmann and DLVO are rigorously taken into account, the theories are c o r r e c t and also valuable. However, they should not be used in cases, where they were not made for.

The only way to do better is, again in my opinion, to make discrete solvent models (like molecular dynamics) and to improve more and more the force fields. Once this is correctly done, then PB or DLVO can be used to fit these results. Concerning time-dependent quantities, this is of course more difficult and here your approach can be very helpful.

The importance of good force fields is more and more accepted. Dzubiella and Netz recently published new ones and in the group of Pierre Turq in Paris they also work on it. Just an example: recently Pavel Jungwirth wanted to simulate sulphate ions in biological solutions. To start with, he tried to calculate "simply" the osmotic coefficients of sodium sulphate solutions. The result was a disaster, until he got aware that one of the main contributions comes from the polarization of water molecules by the sulphate - a rather unexpected result. So I believe that the influence of ions on water polarization and water geometry is crucial for the understanding of specific ion effects.

This is in brief my point of view. I am keen having your answer.

Best wishes

Werner

>>> Bob Eisenberg <beisenbe@rush.edu> 15.9.2011 18:24 >>>
