



Bob Eisenberg <bob.eisenberg@gmail.com>

Re: A perspective on Feynman and Biophysics

Bob Eisenberg <bob.eisenberg@gmail.com>

Mon, Jan 6, 2014 at 8:36 AM

Reply-To: bob.eisenberg@gmail.com

To: Rob Phillips <phillips@pboc.caltech.edu>

Cc: Bob Eisenberg <beisenbe@rush.edu>, Bob Eisenberg <bob.eisenberg@gmail.com>

Dear Rob,

Please call me 'Bob': I barely remember to respond if someone calls me Professor or Robert (although I caused massive trouble at Taipei University Math Dept when they could not find a passport for Bob Eisenberg!)

I was most pleased to hear " I look forward to learning more about your thoughts on how notions of Brownian motion need to be amended in the context of the crowded and charged cellular interior."

The issue is multifaceted and so we need to keep different facets distinct to avoid confusing multiple reflections. (Sorry for the extended metaphor but the horrible weather in Chicago has strange psychological effects.)

1) The amendment of Brownian motion that is needed is to include NONideal properties of ions.

These are discussed at (embarrassing) length in two papers I attach. The "Mass Action" paper was **solicited** by a member of the National Academy in Physical Chemistry (Rich Saykally) and refereed by other members of the National Academy and the facts cited are not in dispute. The Faraday Discussion paper was invited (by Pavel Jungwirth and Dor Ben-Amotz) and presented to a significant meeting of physical chemists at Queens Oxford 18 months ago, and is meant to address the issue of nonideality to physical chemists.

2) There are two well documented and reasonably well understood causes of nonideality for the spherical "bio-ions" Na^+ , K^+ , Ca^{++} , and Cl^- :

2a) they are charged and so their free energy has a large component that varies with the SQUARE ROOT of 'ionic strength' and not linearly (as required for an ideal solution).

2b) the finite diameter of the ions makes a substantial (30% for monovalents, much more for divalents) on activity

3) In any nonideal solution like this, the FREE ENERGY OF ONE ION DEPENDS (separately) ON THE CONCENTRATION OF EACH OTHER ION. It is NOT true that the free energy of (say) sodium only depends on sodium.

4) Treatments in classical biochemistry (check the textbooks if you doubt this) and enzymology do not discuss the issue of nonideal solutions at all. They ASSUME CONTRARY TO EXPERIMENTAL FACTS (known to physical chemists for a very long time) that the activity of a reactant is independent of the concentration of salt, and of the nature of the salt. It is very important to understand the consequences of this assumption. It is an experimental fact that the concentration of ions changes the free energy (per mole) of ALL charged species (e.g., reactants) because of screening/shielding. It is an experimental fact the nature of the ion (chiefly its diameter) changes the free energy as well (with large differences between sodium and potassium and calcium). When classical theories see an effect of concentration of one or all ions on a rate constant, they attribute this effect to a change in the enzyme/protein/ion channel. In fact, much of this effect must come from interactions of the ions themselves near (as well as in) the protein. Interactions are what make ionic solutions nonideal. I imagine (this is supposition not established fact) that the protein modifies the ionic interactions to control and perform biological function.

I attach a paper "Ionizable Side Chains" that evaluates the number density of side chains in some 543 enzymes of known structure. Combined with the necessity of electroneutrality (within a few Debye/Hjerrum lengths of the side chains), this implies that the number density of ions near active sites is many molar. For comparison, the number density of solid NaCl is 37 M. Ion channels have been known for a very long time to have such number densities of ions. I attach a long invited review "Crowded Charges" from Advances in Chemical Physics (refereed by a winner of the National Medal of Science and Wolf Prize and member of the National Academy in Physical Chemistry) which argues that the crowding of bio-ions is a major theme in biophysics, if not biology.

5) The relevance to Brownian motion is that precisely the same issues are involved in classical Brownian motion theory. Classical Brownian motion theory assumes POINT ions (no diameter) that interact with a zero electric field (Einstein) or a nonfluctuating (in time) electric field (Langevin).

It is obvious that the fluctuating concentrations of ions that are the central property of Brownian motion must also produce fluctuating number density of electric charge and thus fluctuating electric fields and forces.

These electrical forces are very strong indeed (I do not have to tell you about the first paragraphs of Feynman's Vol 2 on Electricity where he eloquently argues the case for macroscopic systems. Electric forces are very strong in any atomic scale theory of ions in solution or channels).

6) How to fix the problem?

6a) Numerically, the problem can be fixed by using the procedure that is universal in computational electronics, namely to compute the electric field "on the fly" by solving Poisson every time charges move. This approach is documented in detail (with code!) in the recent text

Vasileska, D., S. M. Goodnick and G. Klimeck (2010). Computational Electronics: Semiclassical and Quantum Device Modeling and Simulation. New York, CRC Press.

The standard work in the field is
Jacoboni, C. and P. Lugli (1989). The Monte Carlo Method for Semiconductor Device Simulation. New York, Springer Verlag.

Implementing this approach for finite size spherical bio-ions remains a challenge, we (and more importantly others, e.g., Vasileska) are working on, but this is a technical not conceptual issue.

6b) Analytically (working on MEASURES of the random motion such as probability of number of ions: the concentration is the marginal probability of locating an ion in a small region) one can now write variational principles THAT INCLUDE DISSIPATION (as a matter of pure mathematics. The theorems have been established and published some 5 years ago although they are not yet well known in the physics community. Work led by Chun Liu at Penn State.) And from these principles one can DERIVE the fully consistent partial differential equations (or sometimes integrodifferential equations) that describe the number density of each ion, including all interactions. The variables in such an analysis automatically satisfy EVERY boundary condition and field equation included in the model (if the algebra is done right). Please ask for references if you want to explore this further.

There are several versions of the pde's of this variational theory. Applications are just emerging as numerical issues are resolved. There are about 5 papers doing that so far, with more coming: I just attended a two day meeting in Taipei on this subject.

7) Finally, I must mention the issue of crowded cytoplasm and other ionic species beyond the spherical bio-ions.

7a) No one knows how to deal with dissolved organic acids and bases (i.e., charged species) of complex structure in a way consistent with Poisson, properties of spherical bioions, and nonideality. No one knows how to simulate these either. For example, no CALIBRATED simulations of spherical bioions let alone organics in multicomponent Ringer's solutions (or intracellular solutions with just bioions) have been published at all. The reason is (I can tell you as one of many who have tried) is that simulations simply cannot deal with any accuracy with mixtures or with divalents.

7b) In the case of ion channels (but not necessarily enzymes), it is a well know experimental fact (since the days in which Hodgkin replaced the axoplasm of nerve fibers with ionic solutions) that channel function is determined by ions and what I call co-factors (e.g., cyclic AMP, sperimine, ATP itself sometimes, ...). When these are all present, the channel behaves as it does in the cell (in most cases), and so we do not worry about other effects of crowding. Of course, there are nearly 1000 channel types known now, and some of these interact with cytoskeleton and others will have other SPECIFIC interactions with crowded cytoplasm elements. I do not know how to deal with these either.

I will be pleased and thankful if you manage to read this far.

But the question you raised is really many questions and a scientist of your standing thus needs many answers.

Please be encouraged to question and criticize anything I wrote.

The reality of nonideality of ionic solutions looms large.
The reality that biochemists and biologists know almost nothing
of the nonideality of ionic solutions also looms large.
Controversy is expected and necessary as biochemists and biologists
learn to confront this reality, and I suspect such is needed
as the classical theory of Brownian motion is revised to
deal with the reality of charged nonideal particles in thermal motion.

Thus it would be natural for you to seek documentation, particularly
from a physiologist/biophysicist at an obscure medical school.

That documentation is easy to provide if you wish.

In summary, a leading experimentalist just wrote in a book on this subject

**“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.”**

Kunz, W. "Specific Ion Effects"
World Scientific Singapore, 2009; p 11.

As ever
Bob

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On Sun, Jan 5, 2014 at 4:06 PM, Rob Phillips <phillips@pboc.caltech.edu> wrote:

Dear Prof. Eisenberg,

Thanks very much for your kind and interesting note. I look forward to learning more about your thoughts on how notions of Brownian motion need to be amended in the context of the crowded and charged cellular interior.

All the best,
Rob

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On Jan 3, 2014, at 9:40 AM, Bob Eisenberg wrote:

Dear Prof. Phillips,

It was delightful to read your account of the Feynman Lectures which meant so much to me and my life as a biophysicist.

Thank you!

I am writing also to point out something that physicists often do not realize, and Feynman did not. Much of chemistry, and biology, uses descriptions of diffusion (in the form of Brownian motion and even macroscopically) and chemical reactions that do not incorporate the electric field at all, and so are in fact inconsistent with the electric field.

The attached point out the most obvious case, Brownian motion of charged particles (like those studied by Brown himself) fluctuating in number density while the electric field is assumed to be independent of time and in fact zero.

In my view, consistent treatment of fields is as important in biology (and chemistry) as in physics, and has only just begun now that we finally have a variational principle (derived by pure math alone, no approximations no guesses, only theorems) that can handle dissipative systems. (Of course, the variational principle while always yielding consistent pde's can also be consistently wrong if the physics it includes is incomplete).

All discussion, comments, suggestions, questions, and criticisms are most welcome.

As ever
Bob

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