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Necessity of multiscale analysis

Bob Eisenberg <bob.eisenberg@gmail.com> Wed, Oct 15, 2014 at 8:34 AM
Reply-To: bob.eisenberg@gmail.com
To: "Pettitt, Bernard M." <mpettitt@utmb.edu>, "Bob Eisenberg beisenbe@rush" <beisenbe@rush.edu>
Bcc: Chun Liu <liu@math.psu.edu>, Jinn Liang Liu 劉晉良 <jinnliu@mail.nhcue.edu.tw>, Yoichiro Mori <ymori@umn.edu>

Dear Monte

We are indeed converging!
I am writing back in two emails so I do not confuse two issues. This one is about where I am not sure we agree. The other one will be about atomic scale simulations where I am sure we do agree in thrust and appreciation of our ignorance, and where our different orientations (which I am happy to call prejudice on my part) lead to much better science than if we had the same thrust and approach (in my view).

Where I am not sure we agree is on the BIOLOGICAL NECESSITY of having explicit multiscale analysis, i.e., of coupling atomistic scale work (mostly simulations to be sure) with EXPLICIT MACROSCOPIC EQUATIONS.

Let me give two examples:

a) Many even most intracellular proteins and perhaps nucleic acids are highly sensitive to the activity of calcium ions. Many even most channels with an intracellular side (i.e. almost all channels) and many enzymes and binding proteins are CONTROLLED IN THEIR BIOLOGICAL FUNCTION by calcium activity. That is to say calcium activity has the same role in their function as a gas pedal does in controlling the speed of a car. The calcium activity that is the controller is almost always between 1e-8 and 1e-7 with 1e-6 being beyond the saturating value. There are of course handfuls (at least) of hormones that are of great biological importance that work between 1e-11 and 1e-10 molar.

In my view, atomistic simulations of such trace compounds/atoms are going to be very hard to ever do. Rather, **we need a multiscale approach in which the role of activity is describe by a macroscopic equation (in which activity is a well defined quantity) that is coupled to the atomistic description of the receptor for the trace compound/atom.**

I do not know how to do such coupling, but I think I know that it must be consistent on all scales, following the fundamental laws of electrostatics, Navier Stokes, and diffusion at all scales within the error limits applicable to that scale (the tricky part is that an error negligible on one scale can dominate when prolonged and integrated to another scale, or the lack of resolution unimportant on a macroscale can dominate on the atomic scale).

b) Some phenomena BY THEIR VERY NATURE do not exist without coupling between scales that involve macroscopic laws. The best example I know is the propagating action potential of nerve cells, which involves propagation lengths of meters, and interaction lengths of cm (or longer), within which the atomistic properties of a SINGLE SODIUM or POTASSIUM channel can be seen (in nowadays routine measurements) to depend on the voltage mm to cm distant.

The coupling here between atomic scale and meter scale is in fact completely understood, as are almost all the steps (with the exception of gating which can be described beautifully but is not fully understood: why do channels switch from one state with conductance entirely independent of time to another?) .

The key is that the intermediate scale equation is exact. It is called the telegrapher's equations in many pde books, or the transmission line equation in ee, or the cable equation (by biophysicists and Kelvin who derived it many years before Maxwell), and is the appropriate representation of Kirchoff's current law and Maxwell.

Here the intermediate scale equation exactly connects the function (i.e., flux of ions and flux of current, not quite the same thing) through channels and membranes with the current flowing down the nerve, that propagates the action potential. And the atomistic knowledge couples the voltage change produced by that current (that flows down the nerve) with the opening of the channel (i.e., with gating, that is widely thought to represent a conformation change. I believe it represents a conformation change of the PMF but I also believe that may be dominated by a conformation change in the electric potential field in many cases. That is after all how transistors gate, i.e., switch from non conducting to conducting).

I believe atomistic simulations BY THEMSELVES without an explicit telegrapher's equation of a propagating action potential are clearly impossible. The dielectric properties of the lipid membrane are crucial in this process (as shown by Cole and Curtis in 1939 in the famous picture of impedance during an action potential). Those properties are nearly perfectly represented as an ideal dielectric (an experimental fact established in hundreds of papers). That means that the polarization charge on the lipid membrane depends on ALL THE IONS AROUND. That polarization charge then changes the field on any one ion. So the energy of any one ion depends on

the locations of ALL the ions. That means that pair wise analysis fails. This argument of course is hardly original. Anyone who has thought about Poisson in the presence of dielectric materials (or polarization charge....the same dependence occurs atomistically of course) knows this.

What may be new is the specific application to computing an action potential.

So I believe that the issue is HOW to do the multiscale analysis. NOT whether it is necessary.

It is necessary in these two important cases, and cannot be avoided if one wishes to deal with biological reality.

This argument can be extended as YOU showed me (in a converation at the IMA which I will never forget) to any atomistic calculation in which
c) force fields are calibrated in distilled water
d) activities and biological function are known to depend significantly on ionic concnetration and type
UNLESS the atomistic simulation is shown to produce the correct activities (those measured experimenally) by explicit calibration.

As ever
bob

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On Tue, Oct 14, 2014 at 9:23 AM, Pettitt, Bernard M. <mpettitt@utmb.edu> wrote:

Dear Bob,

I may have to disagree that we can not agree. There is nothing wrong with electrodynamics and statics like coulombs law. However, I'd say we are certain that marcoscopic rate equations are routinely violated at the atomic level when considering incomp letely averaged (let alone single molecule) results. As probabiliy averaged energetics give rise rise to thermo, averaged dynamics gives rise to kinetics. A single (even a few) structure may have energetics that are at odds with the thermo much as a single dynamical event (or a few) may be at odds with the overall kinetics. There is really no unexpected contradiction with small scale violations of macroscopic kinetics (or thermo for that matter). These are only apparent problems not real ones.

In channels you seek macroscopic comfort but are looking often at small number (compared to avagadro) single molecule events. I think my issues are that PNP is not completely internally consistent in terms of microscopic (atomic) details like dielectric theory versus taking the kinetic and dielectric continuum approach; that venerable framework may have been pushed about as far as y'all can take it.

My take,
Monte
On 10/12/2014 11:42 PM, Bob Eisenberg wrote:

> Dear Monte
>
> I think we are not going to agree.
>
> In my view, the laws of electrodynamics are
> universal true on all scales. The recent textbook
> by Andrew Zangwill presents this view very well.
>
> In my view, the rate equations are not the slightest
> bit atomic in resolution, they show no hint of the
> Brownian motion which can serve as a definition
> of an atomistic theory or simulation, and in
> fact the rate equations are derived from
> Brownian motion BY THE SAME MATH
> THAT DERIVES PNP for example.
>
> I attach a few papers where we do this derivation,
> first without atomic scale correlations, but with
> rigorous math (i.e., using only theory of stochastic
> processes) and then with correlations, showing
> that the nonequilibrium problem with correlations
> gives the same type of expansion as BBGKY (or
> whatever the initials) but of course now with pde's
> and boundary conditions. We sadly have done no
> better with the closure problems here than anyone
> else.
>
> The key papers are EKS, SNE, and the Mass Action
> paper has (what I immodestly think) is a beautiful
> rigorous interpretation of the rate constants for
> ion permeation.
>
> I think the issue is simple.
> The rate equations are at the same scale of approximation
> as PNP etc. The electric current in a sequence of rate

equations is not the same as Kirchoff/Maxwell requires it
to be.

How these issues play out in atomistic SIMULATIONS
(recognizable by the presence of overwhelming amounts
of Brownian etc motion) is another issue altogether and
of course of the greatest importance.

As ever
Bob

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On Sat, Oct 11, 2014 at 10:23 AM, Pettitt, Bernard M. <mpettitt@utmb.edu> wrote:

> Hi Bob,
> I think we have some definition problems. This and a good bit of the confusion may come from mixing microscopic and macroscopic. That is partially a results of the ion channel field history which started before we had the molecular structures in "molecular" biophysics. It seems a consistent view i.e. either molecular or macro solves this. As soon as you treat an ion in a continuum you have a mixed metaphor ready to thwart your intended clarity. Theoretical electrochem at electrodes for instance and biosensors in another case has already been through this. Abstract charge and real molecular charge should only mix with abstract fields and real molecular fields respectively. How we define "conduction" is why we disagree. You have outlined why we disagree in your very disagreement with me in my opinion.
> What do you think?!
> mp
> On 10/10/2014 5:27 AM, Bob Eisenberg wrote:
>
> > Dear Monte,
> >
> > Stay with you I will.....as long as you wish!!!

It is easier to write these things in a Word Document so I wrote one.

I am learning a lot from this discussion and hope we can continue.

In particular, while I am happy with what I have written about TRANSLOCATION of charge from one place to another and rate laws, I do not pretend to know how to extend my discussion to chemical reactions that occur or are said to occur in one location.

As ever
Bob

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