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Bob Eisenberg <bob.eisenberg@gmail.com>

Re: Paper is on the way

Bob Eisenberg <beisenbe@rush.edu> **Mon, May 9, 2011 at 7:15 PM**
Reply-To: beisenbe@rush.edu
To: Jie Liang <jliang@uic.edu>
Cc: David Jimenez-Morales <djimen5@uic.edu>, Bob Eisenberg <beisenbe@rush.edu>

Dear Jie

The precise definition is actually mathematical

Consider a simulation at say 0.1 femtosecond resolution.

Consider the volume of interest.

Count the number of particles found in that volume during the time interval that is appropriate for the physics and then divide by the time interval and volulme to get number density.
The units we choose to describe the number density are irrelevant except to emotion.

For ion channel permeation the time interval clearly has to approximate the time it takes for an ion to cross the channel.
That is a first passage time and is around 0.1 microseconds.

Thus, the time interval for accumulating the number of ions has to be something between (say) 0.01 microseconds and the biological time scale itself, i.e., the time of single channel measurements which starts at 10 microseconds.

Now there is a different question that lurks in people's minds, half spoken.

Imagine that ions do not move significantly in (say) 1 femtosecond.

Then one could count contents for that interval.
Many times then the channel would be empty.

This kind of snapshot is what people often have in mind when they make static calcualtions of atoms (using Coulomb's law say to compute the electrical force).

There is nothing wrong with this IF THE FUNCTION AND MEASUREMENTS
ARE ON THE FEMTOSECOND TIME SCALE.

But if the function and measurements are on a much longer time scale, the snapshot measurements have to be combined ('averaged') in some way to be relevant.

It should be obvious that a calculation on a time scale of femtoseconds cannot be overlaid or extrapolated to microseconds without a theory or model.

That averaging procedure is the essence of the multiscale problem.

Macroscopic treatments guess the averaging procedure.

MD ignores the averaging procedure.

Neither is right, in both cases for obvious reasons.

That is why we do science not math. We can tell what is 'right' (enougjh) by comparing with experiments. If the experiments are on the 0.1 millisecond
time scale or slower, MD cannot be compared with the experiments in any direct way. For example the trajectories in MD go back and forth a fantastic number of times (they approximate Brownian motion). They don't look anything
like the average trajectory on the biological time scale.

Finally, there is an extra important fact. We KNOW from both math and science
that there are macroscopic laws that are absolutely accurate (conservation

of
the number of particles in a simulation should be exact) or fantastically accurate
(Maxwell's equations; gravitation; conservation of mass; even Ohm's law over a wide range).

These accuracies are true INDEPENDENT OF AN ATOMIC SCALE THEORY
OR CALCULATION. No one can understand how these laws emerge from atomic motion. But it is a scientific fact that they do.

An essential part of ALL science is not to fuss with experimental facts for which
there is no theoretical explanation. No one has any idea why the charge on an
electron is what it is, but that does not mean we reject using that number (etc).

So we all have to deal with the realities of multiscale. Some things are best described on one scale and some on the other.

at the moment it is fashionable to think everything needs to be understood on the atomic scale. But frankly that is a fantastic mistake. We could not fly our airplanes or build our computers etc etc if they had to be calculated that way.

For us, number density is an exactly defined variable. How that relates to the function of channels or enzymes etc is a totally different question that has to be resolved by actually computing the prroperties of enzymes and channels as they actually function. Some will be successfully computed on one scale and some at another in my view.

What is for sure is that the prejudice against macroscopic measurements will
slow things down and may stop progress altogether if it leads to dishonesty, i.e., to ignoring the actual scale on which these things work.

As ever
Bob

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On Mon, May 9, 2011 at 6:44 PM, Jie Liang <jliang@uic.edu> wrote:

> Thanks!
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> I can see the confusion about molar concentration at small volume, but the idea of number density would fix this emotional issue!
>
> Jie
>
> On 5/9/2011 10:35 AM, Bob Eisenberg wrote:

Dear David

thanks for the feedback.
I will add some more words about the other pockets.
The key point is that the active sites are defined by
ADDITIONAL independent information beyond the
charge density.

The student was confused. We DEFINE our numbers
as number density. We divide the number about
Avogradro's number.

period.

Molar has no significance logically beyond that.

Now emotionally, ... that is a different story

As ever
Bob
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On Mon, May 9, 2011 at 10:13 AM, David Jimenez-Morales <djimen5@uic.edu <mailto:djimen5@uic.edu>> wrote:

Dear All,

I want to share with you the feedback we got from the Protein Folding Conference. This is a very different audience compared to the BPS: everybody knows very well the structure of proteins.

Surprisingly, and although our poster was out of topic, again a lot of people came to see the poster, which, I think, points out that, whatever we are doing, is somehow attractive.

- The most frequent asked question was about "what about the charge
density of other pockets?". Absolutely everybody asked about other pockets, and if the charge density could be use to predict the right functional pocket.

- One student told me that those molar numbers don't make sense: it's impossible to have 20M. I explained how we calculated it and he agreed is right, but he said that those number might make sense microscopically, but not macroscopically.

Best,
David

On Sun, May 8, 2011 at 9:59 AM, Bob Eisenberg <beisenbe@rush.edu <mailto:beisenbe@rush.edu>> wrote:

Dear David and Jie

Thanks for your patience with me.

The restrictions of Nature have forced
a nearly complete rewriting of the paper,
which is much to the good I think.

I will have something for you to evaluate
later today or tomorrow.

Thanks again

As ever
Bob

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