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Bob Eisenberg <bob.eisenberg@gmail.com>

Spontaneous Gating may be the cause of your numerical problems

Bob Eisenberg <beisenbe@rush.edu> **Sun, May 1, 2011 at 7:02 AM**
Reply-To: beisenbe@rush.edu
To: bzlu@lsec.cc.ac.cn
Cc: Chun Liu <liu@math.psu.edu>, Bob Eisenberg <beisenbe@rush.edu>

Dear Ben

We have SO much to talk about.
Thanks for the extra paper. I agree
entirely that the interaction of charges with
the wall of the channel could be very important.

Indeed, I should warn you that numerical disasters
are a sign of something that may be very very important.

For a long time---I first thought of this in the 1980's and published
it in the 1990's if I remember correctly--I have wondered why single
channels suddenly open and close to a current level independent of
time (in an an ensemble mean sense). The opening occurs in about
1 microsecond. The duration ranges from less than can be measured
(i.e., less than 1 microsecond) to many seconds, even minutes, perhaps.

These sudden openings occur in almost all channels and are the
"operatonal
defintiion" in the lab of a single channel. If a channel record does not look
like
this, it is rarely recorded or published. The reason is that it is obvious in the
lab
that mishandling of a preparation or mistakes in an experiment etc change
a good channel (with the expected properties) into a messy one.

Of course, we simply do not know how to tell if some channels 'naturally' open
in a more complex way to a variable level but none have been studied and the
great majority behave cleanly.

The question is why.

I have long thought and published that the likely explanation is that the open AND CONDUCTING channel is a special sort of (nonlnear) eigenstate that only occurs in a small fraction of channels that are actually open when their contents plus physical properties match some condition (which is unknown).

Stochastic simulations (see attached) show what theory implies (see attached)
that the great majority of trajectories of ions enter and leave a channel ON THE
SAME SIDE (we call these cis trajectories for the Latin word used by chemists
to mean on the same side). These trajectories carry no IONIC current or flux across the channel (although they do contribute to the displacement current see attached and Zeev Schuss new book

1. Schuss, Z., Theory And Applications Of Stochastic Processes: An Analytical Approach 2009, New York: Springer. 470.
which I highly recommend.

They contribute a great deal to the properties of the channel nonetheless.

My guess (no better than that) is that they channel opens when the random contents
of the channel (produced almost entirely by cis trajectories) matches some criteria
that allows conduction, e.g., the contents change the potential profile so the profile
WITH THE CIS IONS IN THE CHANNEL no longer has a barrier. Then more ions
rush in, and the channel conducts in an autocatalytic process.

This spontaneous gating is the fundamanetal process. The "gating" of classical biology
is the MODULATION of this spontaneous gating produced by OTHER STRUCTURES
that interact and thus bias and control the spontaneous gating, is my guess.

How can one discover this?
One of Chun's goals has been to reduce the size of the system we simulate with EnVarA
so it deals with individual ions. EnVarA is NOT a continuum model. It is a model of the
measures of energy and dissipatin. THOSE MODELS CAN BE DISCRETE and Chun
has actually done such calculations and published them.

We have all sorts of numerical problems that oru colalborators (and we) have not been
experienced enough to solve. THIS IS A PROBLEM WORTHY OF YOUR TALENTS.
namely to discover the physical basis os spontaneous openings and closings of channels
(and the flat top of the current record).

If you are doing TIME INDEPENDENT calculations, one sign that you are getting close
to this phemomenon would be NUMERICAL TROUBLES.

The true time dependent problem (that EnVarA seeks to measure....remember EnVarA
is time dependent) would show gating. THE TIME INDPENDENT PROBLEM WOULD
SHOW INSTABILITY.

You may have sniffed that when you found

> "*Even though, I still met numerical trouble/disater, and only one or two*
> *sphere case were treated in the paper, and finally I did not continue and*

extend the work (because hydrophobic interaction was also naturally therein)"

I suggest the following

a) implement the TIME DEPENDENT PNP equations with finite size AND WITH THE INTERACTIONS
WITH THE WALL. [Be sure to allow a variety of interactions with the wall. The key may be to put some
of the wall's charge on a strong spring that allows a little motion. This is a better representation of a dielectric
thatn a dielectric cosntant and should be computable. The spring can have a nonlinear response that you
can play with to look for gating]. I am sure you can find these equations in the JCP paper on EnVarA or
more clearly in the math paper on the same subject but if you have trouble finding the right tree in the
big forest let me know and I will identify their location exactly for you.

2) look at the conditions that gave you instability in your treatment of wall--ion van der Waals and look
for a a bistable spontaneous gating response. BE CAREFUL TO USE DIMENSIONAL UNITS AND REALISTIC
VALUES OF PARAMETERS since you will need to be in the right domain. Spontaneous gating is very
robust so you do NOT have to get the math just right, but SPONTANEOUS gating only occurs in VERY narrow
pores (there are a few reports in 2 nm diameter pores and one verbal report in 10 nm pores, but it does
nto occur in synthetic nanopores usually).

3) pray...in Chinese, in your home dialect, ...and in American/English!!!!!!!!

I hope you have the time (and inclination) to do this. Few people have the skills or intelligence (or diligence
and work habits) to actually finish a project like this. Your accomplishments show you have all of that.

I **would like to help you make a discovery of importance worthy of**

those skills and accomplishments!!!
Here is one possibility.

(there are others to be sure, including your goal of having an integrated package
with finite size and, I believe, time dependence built in, using Chun's EnVarA as its base, building on
what you have already done and coded.

As ever
Bob
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2011/4/30 <bzlu@lsec.cc.ac.cn>

> Dear Bob,

Yeah, agree with you.

It is always good to know that there are better things are waiting to do :)

Hope that van der Waals interaction among ion atmosphere and hard sphere approximation and similar terms added to PNP can help us capture the RIGHT THING !!

Here I may add one more comment: In ion-channel study, in addition to ion-ion vdw interactions (as in your papers and preprints), there may need to include the vdw interactions between ions and protein. I have a small paper (see attached) that introduces the ion-solute vdw iin PNP model. But the work was for a specific technical task (avoding molecular surface meshing :)), other than for correlations and so on. Even though, I still met numerical trouble/disater, and only one or two sphere case were treated in the paper, and finally I did not continue and extend the work (because hydrophobic interaction was also naturally therein). But it is an unfinished taks for me.

Now, with you and Chun, and within your more general picture, hopefully we can come closer to the REAL THING as you said, or at least it is quite possible for us to make the model solved. It would be great for me to have chance to work with you and Chun together. Look forward to seeing you all this summer.

Best,

Ben

-----原始邮件-----
发件人: "Bob Eisenberg" <beisenbe@rush.edu>
发送时间: 2011年4月30日 星期六
收件人: bzlu@lsec.cc.ac.cn
抄送: "Chun Liu" <liu@math.psu.edu>, "Bob Eisenberg" <beisenbe@rush.edu>
主题: Re: Re: I was very impressed .....

Dear Ben

What impressive work!
I agree entirely with your program.
Without these practical packages
biologists will flounder around, and not
attack the key problems.

As much as I like what you have done,
I think the underlying equation is not up
to the task.

I think you should implement the attached.
[We have a many word version in JCP but
I suspect you would prefer the attached.
I also attach a CV with a live link to the JCP
paper. Just search the document for Hyon
and you will find it soon enough]

I also include a popular article I am working on
(this is draft form) which makes the point as
eloquently as I can.

I think you can apply your fabulous programs and
packages to 'our' (really Chun's) PNP modified
CONSISTENTLY to have finite diameter in it
and then we would have THE REAL THING!!!

Hope you agree, and hope we Chun, you, and I
can do it together, starting this summer.

As ever
Bob

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2011/4/30 <bzlu@lsec.cc.ac.cn>

> Dear Bob,
>
> Thanks for help trimming the references :) I would love to read them and learn.
>
> I also attached some of our recent works I present in my talk. The first three are PNP related (the first one is a preprint that may come out within a couple of weeks on Biophysical J), the fourth paper is a description about our package AFMPB (Adaptive fast multipole boundary element Poisson-Boltzmann solver) release, the fifth is the molecular mesh generation paper.
>
> Very recently, we have made progresses on: parallel finite element solver for PB/PNP models (already tested on 3D protein with 1-2000 CPUs); more stable algorithm for PNP (might be stable for SMPBP as well); molecular volume mesh generation. I think the related publications should come out no later than next year. So, I hope and expect these work can be useful and form a complete tool chain for our future simulation studies.

Best wishes,

Ben

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抄送: "Chun Liu" <liu@math.psu.edu>, "Bob Eisenberg" <bob.eisenberg@gmail.com>, "Bob Eisenberg" <beisenbe@rush.edu>
主题: Re: I was very impressed .....

Dear Ben

Good to hear from you.
Thanks for the kind wordsI\
Sorry I missed the last days
of the meeting.

Do you have any papers I should
read to get better acquainted with
your work?

The attached may interest you .....
There is less here than there seems.
A lot of the articles are short and the
big one is mostly words you heard
during the meeting.

ALL questions, comments, criticisms,
suggestions are most welcome.

as ever
Bob

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On Fri, Apr 29, 2011 at 1:47 AM, <bzlu@lsec.cc.ac.cn> wrote:

> Dear Bob,
>
> Yeah, "Ben" is surely OK, this is what people usually call me in US.
>
> Thanks for all of these encouraging messages, and also thank for your impressive talks and comments I heard in last three days.
>
> I think it is the right time for me to meet you and Chun on this meeting as I'm just trying to learn to come to this attractive area.
>
> As you said, there should be a lot of issues to for us to do together, and I''m also looking forward to seeing you and Chun in China before long.
>
> All the best wishes,
> Ben

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主题: I was very impressed .....

Dear Dr. Lu, or Ben, if first names are OK, and I chose the right one,

I was very impressed with the tremendous range of results in your
talk yesterday and look forward to our get together in Shanghai in
a few weeks. There are a remarkable range of problems we can
solve using your numerics and Chun's formulation of the problem(s).

I hope you and Chun share my view and we can make this happen
together.

Ever yours
Bob Eisenberg

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3 attachments

BCER JCP Barrier Crossing.pdf
1916K

EKS annotated with corrections and comments April 2010.pdf
588K

Ramo Shockley Biophysical Journal Volume 87 December 2004 37163722 3716 - Copy.pdf
174K