Bob Eisenberg <bob.eisenberg@gmail.com>

Suggestions to make project easier PNP-steric project

Bob Eisenberg <beisenbe@rush.edu> Thu, Aug 30, 2012 at 1:17 PM
Reply-To: beisenbe@rush.edu
To: jinnliu@mail.nhcue.edu.tw, Bob Eisenberg <beisenbe@rush.edu>
Cc: Chun Liu <liu@math.psu.edu>, Tzyy-Leng Horng <tlhorng123@gmail.com>, 林太家 <tclin@math.ntu.edu.tw>

Dear Jinn

I have read the paper and am impressed with the diligence, energy, and care you (et al) have applied to this problem.

I have a set of comments and suggestions designed to make the problem easier, convergence and numerical problems easier, by taking advantage of experimental and biological realities.

The basic philosophy is NOT to include properties that make computing hard UNLESS the biological evidence requires their presence.

1) Protein surface. I think NO singularities of any kind should be included in the protein surface. These are NOT NOT known to exist or matter. They are artifacts of the ball rolling scheme. The facts are these

a) the protein surface can not be well defined by any known physics. The surface location will depend on what physical variable is being used. The distance of closest approach of each ion type will depend on the diameter of the ion. The effective dielectric constant (e.g, amount of polarization charge in some place for a given change in potential across the channel) will have a different location from the distances of closest approach or the space of a given diffusion coefficient etc etc

b) the protein surface is determined by crystallography of proteins in a strange mechanical state (just because they are crystallized) and strange chemical environment (because the 'mother liquor' used for crystallization is wildly different from physiological solutions. It is also the same on both sides of the channel whereas in the real world solutions NEED to be very different on the two sides of most channels)

c) the surface has fantastic dynamics we know nothing about. The motions of the surface atoms are extremely strongly coupled to nearby ions. We know nothing about this and its frequency and concentraiton dependence etc.

All this means that it is not wise to work very very hard dealing with structural details that make math hard.

I suggest de focussing the image of structure (i.e., passing it through a low pass filter, i.e. smoothing the structure)
and getting rid of these problems

2) In many of our calculations it is very very important that messy behavior near the boundaries not reach into the channel.
The bath must be macroscopic . I do not know if your bath is big enough.

3) In real experiments THREE or more ions are always present with one being a shunt path that does NOT go

through
the channel but rather around it. If you have just two ions, there is see saw like coupling between the fluxes of those ions
because of electrical neutrality. That is likely to make numerics much harder. An extra ion that goes AROUND the channel
(not through it) is likely to make things much easier.

4) In real experiments capacitance to ground is VERY important in low pass filtering (in time) potentials so stable readings can be made. The capacitance to ground is at the electrode itself and also from each tiny volume of solution to ground. These act as low pass filters. They can be included in your equations if you write a flow equation for CURRENT (not flux of ions) and let go of one of the flux equations (e.g., for the shunt path ion).

As ever
Bob

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On Wed, Aug 29, 2012 at 8:00 PM, jinnliu <jinnliu@mail.nhcue.edu.tw> wrote:

> Dear All,

Attached is a manuscript that I keep writing along the way of my 3D PNP code development in order to help my students to read the code and to do PNP research with me. Please take a look.

If you have students who would like to use my code, this manuscript might help. The code is written in C++.

One of the most difficult problems on running a 3D PNP code is that it is very hard to get convergence under realistic biological conditions. It usually blows up.

I am now working on Project F, the first realistic GA channel model in my code development. Once this is done, I then can move onto your steric PNP model.

My students here are slow but helpful to keep me working on the code. I have been toying around with the code for more than one year with a very enjoyable pace. It will be much more fun if we have a team of students playing with it together.

Best,

Jinn

-----Original message-----
From: Bob Eisenberg<beisenbe@rush.edu>
To:林太家<tclin@math.ntu.edu.tw>
Cc:jinnliu<jinnliu@mail.nhcue.edu.tw>,Chun Liu<liu@math.psu.edu>,Tzyy-Leng Horng<tlhorng123@gmail.com>
Date: Mon, 27 Aug 2012 07:01:32 -0500
Subject: Re: PNP-steric project
Dear All

Please let me know how I can help!
There is an enormous amount of work to do once we have a 3D code! Several hundred channels and transporters are known of great biological interest, and they all work in somewhat different variations on the same theme, in the same way that a BMW engine, and lawn motor, and maybe even a gas turbine are variations on the theme of internal combustion.

Of course, once we understand the key elements controlling function of one channel much of the complexity of the 3D code will prove inessential for THAT ONE application, but it is very hard to guess what is essential and what is not ahead of time.

Please let me know if I can help in ANY way.

Below are a few books which may interest you.
Fran Ashcroft's is a popular introduction.
The FACTS books document the number of channels and transporters know more than ten years ago. The number has grown substantially since then.

As ever
Bob

Conley, E. C. (1996). The Ion Channel Facts Book. I. Extracellular Ligand-gated Channels. New York, Academic Press.

Conley, E. C. (1996). The Ion Channel Facts Book. II. Intracellular Ligand-gated Channels. New York, Academic Press.

Conley, E. C. and W. J. Brammar (1999). The Ion Channel Facts Book IV: Voltage Gated Channels. New York, Academic Press.

Conley, E. C. and W. J. Brammar (2000). The Ion Channel Facts Book III: Inward Rectifier and Intercellular Channels New York, Academic Press.

Griffiths, J. and C. Sansom (1997). The Transporter Facts Book New York, Academic Press.

Ashcroft, F. M. (1999). Ion Channels and Disease. New York, Academic Press.

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On Mon, Aug 27, 2012 at 6:24 AM, 林太家 <tclin@math.ntu.edu.tw> wrote:

> Dear Professor Liu, Jinn-Liang:
> Sorry to include your first name since your last name "Liu" is exactly same as Prof. Chun Liu in English but not same in Chinese. Here is our recent paper accepted by J. Phys. Chem. B. Please look at equation (2), (3), (6), (7) called the PNP-steric system. Now we need 3D code to do numerical simulations on the PNP-steric system so we may compare
> with results of MC and MD.
> Surely, there are several interesting problems for us to study.
> As I know, Allen (Tzyy-Leng)
> proposes to write his 3D code in the near future using spectral method. You are an expert of finite element

method and have much experience on the PNP system already. I think it would be great for us to cooperate each other without confliction. If you have interest to work together, I'll find chance to meet you and discuss about it. Hope to see you soon.

Best Regards

T.C.Lin

2012/8/26 jinnliu <jinnliu@mail.nhcue.edu.tw>

Dear TC,

Good. Let's see what can we do about your exciting PNP projects.

Best,

Jinn

-----Original message-----
From:林太家<tclin@math.ntu.edu.tw>
To:jinnliu<jinnliu@mail.nhcue.edu.tw>
Cc: Tzyy-Leng Horng<tlhorng123@gmail.com>,tclin None<tclin@math.ntu.edu.tw>
Date: Fri, 24 Aug 2012 18:13:43 +0800
Subject: Fwd: PNP-steric paper
Dear Professor Liu:
It would be our great pleasure to have you with us, especially you have your own 3D code. That's fantastic for us to work together. I'll go back to Taiwan at September 10th and hope to see you soon.

Best Regards

T.C.Lin

---------- Forwarded message ----------
From: **Tzyy-Leng Horng** <tlhorng123@gmail.com>
Date: 2012/8/24
Subject: Re: PNP-steric paper
To: jinnliu@mail.nhcue.edu.tw
Cc: 林太家 <tclin@math.ntu.edu.tw>

Dear Jinn-Liang,

That is what I and Tai-Chia have been discussing. We need more people from math. and many other disciplines to join in. It will never be too crowded, and there are always many problems waiting to be solved.
So far we only have
(1) Eisenberg: as biologist that gives important advices, helps writing good-quality paper (he is really good at that), and promotes the results.
(2) Chun Liu and Tai-Chia: construct math. model and provide analysis.
(3) I myself: do the numerical computing.

So far, we are lack of numerical computation experts most (you can clearly see why). We absolutely welcome senior and junior professors, post-doc, and Ph.D./master students to join us. We even welcome biologists and MD/MC experts to join in.

I and Tai-Chia are planning to organize a mini-workshop to keep warming this subject. Tai-Chia is currently in U.S. Let's wait till he is back.

Allen

2012/8/24 jinnliu <jinnliu@mail.nhcue.edu.tw>

Dear Allen,

I can see why you so excited about your new model and it's implication of tons of problems.
It is indeed very novel, realistic, and complicated.
I'll try to extend my 3D PNP solver to include new terms in steric-PNP.
It took me more than one year to complete my PNP solver which includes
linear and nonlinear PB equations.
Now it is almost ready to do full scale nonlinear 3D PNP and PB simulations on a GA or other
channel protein downloaded from the protein data bank.
As far as I can see, even with your simplified channel geometry, there are many mathematical
and numerical problems that deserve serious investigation.

However, 3D model simulations are very time-consuming, tricky in convergence, and having a lot
of uncertainty due to geometric and charge singularities of the channel protein from PDB.
I think we should recruit more people to do this.

Best,

Jinn
-----Original message-----
From: Tzyy-Leng Horng<tlhorng123@gmail.com>
To:jinnliu<jinnliu@mail.nhcue.edu.tw>
Date: Thu, 23 Aug 2012 23:15:19 +0800
Subject: Re: PNP-steric paper
Dear Jinn-Liang,

This is just the first step and we are developing more complicated models (and also doing higher-dimension computation) to solve for permeability (I-V curve) and gating. There are tons of problems to solve. Welcome to jump in and join us any time.

Allen

2012/8/23 jinnliu <jinnliu@mail.nhcue.edu.tw>

Dear Allen,

Congratulations.
Your effort on this subject for years is indeed fruitful.
Thank you for sending me your paper.

Best,

Jinn
-----Original message-----
From: Tzyy-Leng Horng<tlhorng123@gmail.com>
To:jinnliu<jinnliu@mail.nhcue.edu.tw>
Date: Mon, 20 Aug 2012 20:45:54 +0800
Subject: PNP-steric paper
Dear Jinn-Liang,

My first paper with Eisenberg, Tai-Chia and Chun Liu is accepted by Journal of Chemical physics.
Here I mail you a pre-print that may interest you.
Allen

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