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# State of Ion Channel Research

**Bob Eisenberg <beisenbe@rush.edu>** **Sun, Oct 3, 2010 at 7:20 AM**
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Cc: Gary Leaf <leaf@mcs.anl.gov>, Dmitry Karpeev <karpeev@mcs.anl.gov>
Bcc: Ardyth at Gmail <ardyth.eisenberg@gmail.com>, Bob Eisenberg <beisenbe@rush.edu>, "Stuart A. Rice" <s-rice@uchicago.edu>

Dear Rick and Jorge and Paul,

I understand that the Ion Channels project with MCS is being reviewed, as is only appropriate.

You should be aware of several particularly significant breakthroughs relevant to the review.

In brief, we have discovered a unique way to deal with the multiscale issues of ions, channels, and enzymes, by using a variational approach that AUTOMATICALLY AND RIGOROUSLY constructs a variational field theory of the elements of the model (at whatever scale).

Biological problems are inherently wildly complex because they have interacting components and multiple scales. The mathematics and computer science used to deal with them must deal consistently and correctly with interactions and must be valid across scales.

Direct simulations in atomic detail have not addressed these issues yet and may not be able to (see atached article on multiple scales) in most important biological cases.

Classical models are unable to deal with multiple components consistently and so they miss the complexiy that is the hallmark of biology.

Variational methods create NEW partial differential equations when a new component is added. The PDEs are always

consistent (although they can be wrong if the underlying energetic model is wrong or inconsistent).

Variational methods are used very widely in high energy and condensed matter physics for these reasons.

We are using them for a wide range of biological problems, from atoms (ions), to molecules, to membranes, cells and tissues.

I would be a sad mistake if ANL and MCS walked away from this work just as it reaches fruition. I was proud to put my ANL affiliation on the central review (Crowded Charge) solicited by Stuart Rice, which could not have been written without your support.

I would like to continue to be able to do so, working with whatever people you feel appropriate at Argonne.

1) Working with Chun Liu, we have developed a variational approach to ions in channels, proteins, and solutions which allows systematic computation of intermediate scale models of these systems.

This is very very important as the attached publications demonstrate.

The multiscale paper demonstrates the challenges facing atomic resolution models. These are formidable.

The Variational Paper demonstrates the power of the variational approach to physical chemists.

The PNP repulsion paper demonstrates the power of the variational approach concisely for mathematicians.

The Crowded Charge review is a large review solicited by Stuart Rice demonstrating the power of the method and significance of it for physical chemists.

2) Working with Jie Liang of UIC, we have combined the power of bioinformatics, structural biology, and the physical approach to evaluate the special adaptations found at the active site of enzymes. It turns out these are very very charged, with a charge density of more than 20 M being found in the some 490 enzymes that we have selected with our screens (out of thousands we will screen) with known three dimensional structures of

active sites. For comparison SOLID NaCl is 37 molar.

This is a major discovery since it shows a physical property that must be dealt with in any model of enzymes or channels. For example, molecular dynammics force fields are calibrated in zero concentration solutions. It is obvious that such calibrations are unlikely to be appropriate for the extraordinarily concentrated conditions at active sites.

3) Working with Yoichiro Mori and Chun Liu, we have developed a field theory of water flow and electrodiffusion in cells and tissues. There is hardly any biological system that does not use water flow and electrodiffusion in its function, whether the heart, the kidney, the brain (in stirring its extracellular space), and so on. Believe it or not, no one has been able to write consistent field equations until now. This is now possible because of the variational approach. This work will lead to direct applications in everything from botany, to cell biology, to water desalination, and waste extraction, all of which depend on water flow and electrodiffusion.

4) Working with Fred Cohen and Chun Liu, we have developed a phase field method, exploiting the variational approach to allow the actual calculation of movies of membrane motion and viral fusion. No one has even tried this up to now. It seems likely this work can in fact be extended to describe cell motility in general.

These projects should be pursued with energy at Argonne in my view, and both should be exploited as a bridge between MCS,. biology, and the APS where structures are being discovered daily that need analysis with both methods.

That of course is, and should be, up to you.

I also attach a CV and a copy of the abstracts we are submitting to the Biophysical Society meeting next year.

These include the first PHYSICAL calculations of membrane pore formation using variational methods. These will soon be extended to show the fusion of viruses (e.g., HIV) to membranes. Preliminary work has already done this.

They also include the first statement of the field equations for electrodiffusion and water flow in systems of membranes like tissues and cells.

Both of these developments are extensions of the variational method.

Two experimental abstracts demonstrate the development of a new preparation

of ion channels that will allow, FOR THE FIRST TIME, measurements of current routinely in single channels, of known structure, mutated to have selectivity designed by the variational method. Every piece of this has been done before but not in a high throughput system. This system should become the testbed of nanoengineered biomimetric valves and channels.

Below is a letter I wrote to Gary and Dmitry about all this.

If you feel uncomfortable reviewing the scientific content of this work, which is of course the only way the work can be rationally justified, please feel free to seek advice from outside reviewers. I suspect that Stuart Rice of the UofC can help organize such a review if you wish. He is familiar with most of the fields involved, except Bioinformatics. There you have plenty of in house expertise, as of course, you do in some types of variational analysis as well.

I feel it would be a shame if ANL abandoned this work of one of its Senior Scientists, just as it reaches full flower, combing applied mathematics, computational science, bioinformatics, and molecular biology to learn how the molecules, cells, and tissues of life actually work.

Ever yours
Bob Eisenberg

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Dear Gary and Dmitry,

Thanks for asking about future plans for our channel work. Things are really hopping so it has become clear that we have many projects in computational biology of channels that we should do together.

1) Selectivity of sodium channels. As you know, sodium channels are responsible for all signaling in the nervous system. They can only function because they are selective for sodium over calcium (a divalent positive ion), chloride (a monovalent negative ion), and potassium (a monovalent positive ion). We have a model with just two parameters that explains the main selectivity date for this channel but the origin of the selectivity has not been investigated. That means we should do calculations of the binding of lithium, sodium, potassium, rubidium, and cesium as well as the divalents calcium, barium, and strontium, and perhaps nickel and cadmium. Most of these have been studied in great experimental detail. These ions have to be studied at say different concentrations and several mixtures, so you can see there is much computing to do. There are about 4 papers worth doing here.

2) Brownian dynamics of ions in channels. Claudio Berti has found a way to greatly speed the selfconsistent calculations of ions in channels, the original project that we could not make work. His code is working and can now be applied to (for example) computing time dependent currents in the sodium channel we are talking about studying in (1) above. There are several papers waiting to be done here.

3) Jie Liang is a leading worker in BioInformatics (at the University of Illinois Chicago) and he, his student David Jiminez-Morales, and I have recently surveyed data bases of protein structure to determine the charge of active sites. Thus, we combine bioinformatics and physis. We find that in some 420 proteins of known crystal structure there is an enormous charge density in active sites, specifically more than 20 molar. For reference, solid NaCl is 37 molar. There is a great deal to be done here searching data bases of specific types of enzymes, and looking for specific charge characteristics of their active sites.

4) Fred Cohen, Rolf Ryham, and I have been working with Chun Liu to apply his phase field variational approach to compute fluid properties of membranes and make movies of pore formation, and vesicle fusion of viruses (like HIV) to cells. This variational principle and approach needs to be applied to a wide range of membrane fusion problems in cell biology. Once this is working routinely it will generate substantial grant funding. The first calculations are being done right now but are not yet routine.

5) The DFT approach you and Matt worked on has produced one publication already and needs development and maturation into a fully working code.

6) Yoichiro Mori, Chun Liu, and I have written the first variational field theory of ion and water flow in cells and tissues. This is a selfconsistent theory of how ions and solutions are involved in function. It needs to be applied systematically to a range of tissues from heart, to kidney, to brain, to adrenal cortex, etc.

7) Charge layering is an important phenomena in the absorption of ions to clays and ion exchangers used to detoxify waste. YunKyong Hyon, Chun Liu, and I have developed a new variational principle to account for layering. Much work needs to be done to see how well this principle works in real DoE applications of ion exchangers.

8) I am one of the investigators on Ian Foster's Computational Institute

Beagle Grant. It would be natural to share that with you all on projects 2) and 4) above.

9) I wrote most of a grant to Dexuan Xie and Ridg Scott U of C on the applicaiton of field theory of dielectrics to ion channels. It has been funded and the work is going on right now.

Please let me know if this list needs amplification in any way.

As ever

Bob

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**6 attachments**

**PNP Repulsion Communications in Mathematical Sciences as accepted.pdf**
696K

**Crowded Charges arXiv1009.1786v1 Sept 10 2010.pdf**
2508K

**As Published EnVara J. Chem. Phys. 133, 104104 (2010).pdf**
451K

**Multiple Scales in the Simulation of Ion Channels and Proteins July 20-3.pdf**
415K

**Abstracts for Biophysics 2011 as of October 1 2010 HighLights.pdf**
157K

**__CV_September_09_2010_(JT).pdf**
552K