Bob Eisenberg <bob.eisenberg@gmail.com>

Re: Ion Channels GRC

Bob Eisenberg <beisenbe@rush.edu> **Mon, Feb 20, 2012 at 1:54 PM**
Reply-To: beisenbe@rush.edu
To: "Kobertz, William" <William.Kobertz@umassmed.edu>, "Nichols, Colin" <cnichols@wustl.edu>
Cc: Wolfgang Nonner <wnonner@med.miami.edu>, Douglas Henderson Gmail <douglashend@gmail.com>, Dirk Rush <Dirk_Gillespie@rush.edu>, Dezső Boda ++ Gmail <dezsoboda@gmail.com>
Bcc: Pancho <FBezanilla@uchicago.edu>, "Stuart A. Rice" <sarice@uchicago.edu>, Rich Saykally <saykally@calmail.berkeley.edu>, Mark Ratner <ratner@northwestern.edu>, "George C. Schatz" <schatz@chem.northwestern.edu>, "Magleby, Karl L" <KMagleby@med.miami.edu>, Ardyth at Gmail <ardyth.eisenberg@gmail.com>, Bob Eisenberg <beisenbe@rush.edu>, Nani Ana Correa <nanicorrea@uchicago.edu>, Gary Leaf <leaf@mcs.anl.gov>, Jim Fonseca <jefonseca@gmail.com>, Paolo Carloni <p.carloni@grs-sim.de>, Justin Finnerty <j.finnerty@grs-sim.de>, Chun Liu <liu@math.psu.edu>, Yoichiro Mori <ymori@umn.edu>, Tai-Chia Lin 林太家 <tclin@math.ntu.edu.tw>, Dave David Stepp <david.m.stepp@us.army.mil>

Dear Bill and Colin,

Thanks for your fast and clear reply.
I greatly appreciate your interest and
kindness in replying so professionally.

But I think there is a serious problem
here NOT personal but scientific.

A group of some of the most accomplished
physical chemists in the world--NOT me-- think that ion
selectivity problems in biology should not be
done independently of the massive EXPERIMENTAL
and theoretical work on ions in physical systems.
There are literally thousands of papers on the subject
in physical chemistry and chemical engineering and
huge data bases devoted to the subject. Abundant
references are found in the slides attached and
papers I sent this morning.

That approach over the last years has been
extendign to ion channels. It has dealt with EXPERIMENTAL data
as studied by biophysicists 'forever' (binding curves
in many different solutions, effects of mutants, IV
curves in many different solutions), we think
successfully in the case of voltage activated
sodium channels, L type calcium channels
and most notably the RyR receptor. It has
not been applied successfully to the K channel.

Many of the workers who I suspect are speaking
on permeation and selectivity at the Gordon Conference
have not published binding or IV curves or results of
mutations **in a range of solutions and conditions** and
have not dealt with experimental data of this type at all

(which is the classical data directly related to function as I was taught it by Hodgkin for example).

The issue is **how to have the experimental community of ion channel workers who come to the Gordon Conference deal with these facts**, or if you disagree with the facts, with these opinions in a professional manner. It cannot be done by ignoring the work of hundreds of physical chemists for nearly a century.

It simply cannot be done in the context of 10 minute talks.

I include a recent talk of mine (and there are many of my colleagues who I am sure have done at least as well in the large numbers of meetings that have been devoted to this approach to selectivity) to see what is involved in a presentation for experimentalists.
This was given at Oxford Biochemistry, hardly a hot bed of mathematics, a few months ago, and frankly it was well attended (no empty seats) and well received by many channel workers who are not theoreticians at all. I do not know if people agreed with the approach or not, they were all old colleagues, and they would have muted criticism out of their kindness.

BUT THEY BEHAVED PROFESSIONALLY AND LISTENED and dealt with the science as science.

Do you agree there is a real issue of science involved here?
Namely, how can this material be presented so it is dealt with fairly by the experimental ion channel community?
If you think there is an issue, how do **you** think it should be dealt with?
I am eager to find some way to nurture the interactions of the physical chemistry and channel community. We need all of us to figure out how channels work, in my view.

As ever
Bob

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2012/2/20 Kobertz, William <William.Kobertz@umassmed.edu>

Hi Bob,

Yes, Colin is correct that speaker list is essentially set. However, we are continuing the tradition of picking 8 - 10 15-min talks from the posters. So I also concur with Colin, please come if you can.

Best,
Bill

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From: Nichols, Colin [cnichols@wustl.edu]
Sent: Monday, February 20, 2012 10:05 AM
To: beisenbe@rush.edu; Kobertz, William
Cc: Wolfgang Nonner; Douglas Henderson Gmail; Dirk Rush; Dezső Boda ++ Gmail
Subject: RE: Gordon Conference and Selectivity of Calcium, Sodium, and RyR channels: an approach based on physical chemistry

Dear Bob

Good to hear from you. I will defer to Bill to give you the detailed answer, but I am pretty sure that the speaker lists for the meeting are now fully filled.

However, the meeting itself is probably not yet fully subscribed and for my part it would be great to have you - and your colleagues - in attendance!

Best wishes, Colin

From: bob.eisenberg@gmail.com [bob.eisenberg@gmail.com] On Behalf Of Bob Eisenberg [beisenbe@rush.edu]
Sent: Monday, February 20, 2012 5:27 AM
To: WILLIAM.KOBERTZ@umassmed.edu; Nichols, Colin

Cc: Wolfgang Nonner; Douglas Henderson Gmail; Dirk Rush; Dezső Boda ++ Gmail
Subject: Gordon Conference and Selectivity of Calcium, Sodium, and RyR channels: an approach based on physical chemistry

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Dear Dr. Kotertz and Nichols, or Willian and Colin, if first names are OK, and I guess right,

The Gordon Conference on Ion Channels looks wonderful.
What progress in the some 50 years since I first went to one of the meetings!

I wonder if you think some of the work on the selectivity of sodium and calcium channels listed in the attached CV (yellow highlight, see p. 5 Publications) might be of interest and should be presented?

I believe the approach has been reasonably successful. For example, papers with Miedema describe one of the few channels that was built (i.e., mutated from ompF porin) to have calcium selectivity according to a theory, and that actually acquired (most of) that selectivity.

This material has been well received in the physical chemistry community, and three reviews of the work have been solicited (and refereed) by senior members of that community, who are members of the National Academy, winner of the National Medal of Science, and the Wolf Prize.

Here are those references

[1] B. EISENBERG, Crowded Charges in Ion Channels, Advances in Chemical Physics, John Wiley & Sons, Inc., 2011, pp. 77-223 also available at http:\\arix.org as arXiv 1009.1786v1
[2] B. EISENBERG, Mass Action in Ionic Solutions, Chemical Physics Letters, 511 (2011).
[3] B. EISENBERG, Multiple Scales in the Simulation of Ion Channels and Proteins, The Journal of Physical Chemistry C, 114 (2010), pp. 20719-20733.

The work has been recognized in the award of a Visiting Professorship to the Department of Chemistry in the Miller Institute of the UC Berkeley.

The work of Dirk Gillespie on the Ryanodine Receptor (see the other attached document, which may not be complete) might also be of interest. I believe he is the only one who has PREDICTED successfully current voltage curves of a mutant BEFORE the experiments were done. These curves were measured in a wide variety of solutions, symmetrcal, and asymmetrical. His work, along with earlier papers by Wolfgang Nonner and myself, have shown how the AMFE can arise without single filing.

The approach of these authors is based on well established models of ionic solutions that quantitatively deal with the specific properties of ions in bulk and inhomogeneous physical systems. Selectivity arose as an interdsiciplinary subject of interest to physical chemists and biologists but the fields have diverged in the last decades. Perhaps for that reason **some of the leaders in physical chemistry are coauthors and others have served as mentors and critics of the work since its beginning.**

This work includes some 40 refereed papers and analyzes binding vs concentration and current voltage curves in a wide variety of conditions with some success. More classical models based on rate theory and molecular dynamics have not dealt with such curves, typical of experimental measurements, to the best of my knowledge. The work has been extended to deal with the classical Eisenman approach and sieving models.

Here are those references

[1] D. KRAUSS, B. EISENBERG and D. GILLESPIE, Selectivity sequences in a model calcium channel: role of electrostatic field strength, European Biophysics Journal, 40 (2011), pp. 775-782.
[2] D. KRAUSS and D. GILLESPIE, Sieving experiments and pore diameter: It's not a simple relationship, European Biophysics Journal, 39 (2010), pp. 1513-1521.

The challenges facing molecular dynamics treatments of selectivity have been dealt with in an invited article refereed by members of the National Academy in Physical Chemistry

[1] B. EISENBERG, Multiple Scales in the Simulation of Ion Channels and Proteins, The Journal of Physical Chemistry C, 114 (2010), pp. 20719-20733.

We are presently computing current voltage relations of sodium, calcium channels with these models using five different versions of the approach, DFT-PNP (Dirk Gillespie, et al), EnVara PNP (Liu, Hyon, Eisenberg). Delta PNP (Horng, Lin, Liu, and Eisenberg), EnVarA^2-PNP (Flavell, Lin, Liu, and Eisenberg), particle based simulations (Berti, Gillsepie, Eisenberg). These unpublished results are likely to be of some interest since they are the only estimates of reversal potentials in a range of solutions from a selectivity model that I am aware of. They are of course a work in progress at the moment and each version has its strengths and weaknesses. That is why we are using so many approaches!

I thought it most efficient to contact you both about this, since there are four sessions that might accommodate this work.

(Alan Finkelstein / Ilya Bezprozvanny / Anna Greka)
(Clay Armstrong / Wompil Im / Benoit Roux / Steve Brohawn)
(Dick Horn / Cecilia Canessa / Todd Scheuer / Bonnie Wallace)
(Andrea Brueggemann / Gail Robertson / Nicole Schmidt)
Henry Colecraft / David Clapham / David Yue)

Alan, Clay, Wonpil, Benoit, Dick, Bonnie and David^2 have had discussions about this work at various times, but may not be familiar with more recent contributions. Please feel free to share this email with them, or of course any one else you wish.

Interdisciplinary efforts of this type, not the same as what most biologists do when they study selectivity, are hard to deal with no doubt in your administrative roles, given the little time on the schedule, but **when the physical chemistry community embraces an approach to selectivity, and that is applied to a range of classical ion channels, with some success, I believe that approach should be presented to the biophysical community for its review and criticism.** The Gordon Conference is obviously the right place for such presentation and discussion. Unpresented, it cannot be criticized, or checked in experiments, or corrected, or improved.

Thanks for your attention.

As ever
Bob Eisenberg

PS I am sending copies of this email to some of my coauthors in this work.

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2 attachments

Oxford BOCHEMISTRY Selectivity Talk Full September 6-1 2011.pdf
4755K

Oxford BOCHEMISTRY Selectivity Talk Full September 6-1 2011.pptx
7817K