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Gordon Conference and Selectivity of Calcium, Sodium, and RyR channels: an approach based on physical chemistry

Bob Eisenberg <beisenbe@rush.edu> **Mon, Feb 20, 2012 at 5:27 AM**
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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

Gillespie Selectivity List.pdf
63K

Selectivity__CV_January_22_2012.pdf
865K