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Bob Eisenberg <bob.eisenberg@gmail.com>

Assertion to be considered: Computing IV relations of nanovalves like channels is a sensitive ill posed problem

Bob Eisenberg <beisenbe@rush.edu> Thu, Jul 5, 2012 at 4:53 AM
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To: jbardhan@alum.mit.edu, Claudio Berti <cberti@arces.unibo.it>, Dirk Gillespie <dirk_gillespie@rush.edu>, Bob Eisenberg <Bob_Eisenberg@rush.edu>, Wolfgang Nonner <wnonner@med.miami.edu>, Martin Burger <martin.burger@uni-muenster.de>, "Heinz W. Engl" <heinz.engl@univie.ac.at>, Chun Liu <liu@math.psu.edu>, Tai-Chia Lin 林太家 <tclin@math.ntu.edu.tw>, Allen Tzyy-Leng Horng 2 <tlhorng123@gmail.com>, Douglas Henderson BYU <doug@chem.byu.edu>
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with a more appropriate subject line
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On Thu, Jul 5, 2012 at 4:51 AM, Bob Eisenberg <beisenbe@rush.edu> wrote:

> Dear Jay, and friends and collaborators,
>
> In thinking of these problems, I suggest reading the attached
> paper carefully on "Inverse Problems related to Ion Channel Selectivity"

Here we (Martin Burger, an accomplished and talented young mathematician, now Prof. at the University of Muenster; Heinz Engl, gifted mathematician, a world leader in Inverse Problems, author of textbooks on the subject, now Rector, i.e., head, of the University of Vienna)

show **BY ACTUAL CALCULATION** using methods and software well tested and used on many previous problems (by Heinz Engl and a large group of collaborators) that the inverse problem of a channel is NOT NOT NOT ill posed.

> The phrase "inverse problem" is shorthand for a small set of problems, think specifically of the problem of determining the spatial distribution of permanent charge from measurements of current voltage relations in a variety of solutions and concentrations.

I repeat the INVERSE PROBLEM IS NOT NOT NOT ILL POSED.

Obviously, we expected that the inverse problem would be ill posed. The result that we actually found by calculation (using regularization methods designed to handle ill posed problems) was the opposite. The result was clearly well posed. The spatial distribution of permanent charge was NOT NOT a sensitive function of the data. (For those of you unfamiliar with inverse problem methods the sensitivity is a COMPUTED OUTPUT of the analysis. Sensitivity here is not a vague phrase. It is a specific mathematical functional used throughout the analysis.

Indeed, it never occurred to me that the inverse problem would be well posed. I was sure it would be ill posed. That is why I spent years working on this problem (and many trips to IPAM, Linz, etc etc) with people who were world leaders dealing with ill posed problems (Heinz Engl and his collaborators who actually have a successful company that does these problems for a living)

But what we found was that the data was so good (IV relations from single channels often have signal to noise ratios of at least 40 to one) and probed the phase space so well (by measuring a many concentrations and in several types of solutions) that the results were very well posed.

(In fact the numerical problem was we had too much data, not too little).

Why do I write this? For personal comfort? For the sake of history? NO NO NO

I write because have finally realized, many years after the fact, confirmed by discussions with Chun Liu,

this result implies that the forward problem is the sensitive one that is (nearly) ill posed.

Say it again

The forward problem of computing IV curves from permanent charge is the ill posed problem.

And when I thought about it. This was obvious and should have been from the beginning.

After all what is a nanovalve?

It is a device designed so that atomic scale changes in structure (etc) produce macroscopic effects on flow.

So

Channels are nanovalves designed to produce IV curves exquisitely sensitive to structure.

Which is another way of saying that the forward problem of predicting IV curves is exquisitely sensitive to structure.

Which is another way of saying that the forward problem is ill posed.

This suggests that regularization methods (e.g., Tikhonov) should be used on the forward problem.

Of course, channels are nearly enzymes, so this suggests that structure function relations of channels, enzymes, and binding proteins are all ill posed problems that should be treated with regularization methods.

See

Eisenberg, R. S. (1990). "Channels as enzymes: Oxymoron and Tautology." Journal of Membrane Biology 115: 1–12. Available on arXiv at the link http://arxiv.org/abs/1112.2363.

Jimenez-Morales, D., J. Liang and B. Eisenberg (2012). "Ionizable side chains at catalytic active sites of enzymes." European Biophysics Journal 41(5): 449-460. Available on web at the link Reprints/2012/Jimenez-Morales_EBJ_2012.pdf

What do you (all) think of that proposal?

As ever
Bob

PS I am sending copies of this email to collaborators who I think may be interested. All comments, DISSENTS, criticisms, discussions, are MOST WELCOME since what I write has profound implications for all we have done and should do on the channel problem.

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On Thu, Jul 5, 2012 at 3:45 AM, Jay Bardhan <jbardhan@gmail.com> wrote:

> Hi everybody,
>
> Now that all the craziness of the spring is over, I hope we can get to business on testing whether provable-quality approximations of ICC can give meaningful speedups for ion-channel simulations.
>
> I've calculated the singular values for the relevant parts of the ICC matrices and included them as plots attached to this email. What you can see in the file "singular-values-zoom.png" is that only about 140 "modes" (think dipole, quadrupole... etc) are captured accurately by the 682-element simulation. Therefore, if this surface representation is good enough for the BD/MC simulations, we ought to be able to take 140 modes from a finer surface mesh ICC matrix and get _even better_ results, while still being ~10X faster than the 682-panel simulation! (The reason is that the same modes are captured better in the finer surface mesh.)
>
> The "tolerance" below is the checking of how many singular values are greater than the given threshold. This is just one approach, commonly taken in some approximation tasks.
>
> Claudio, if I send you these different approximations in the full matrix form, you should be able to just use those approximate "A" matrices in your code directly in place of the actual ICC matrix (i.e. what you sent me). Does that make sense? This way we can check how accurate the approximations are, for quantities like what Bob suggested in a previous email, before changing the code to the faster algorithm; plus, when we get to changing the code, we will already have in place the results that will verify the faster algorithm's implementation. Specifically, Bob suggested
>
> "a) estimates of reversal potential
> b) estimate of slope conductance at small potentials
> c) estimate of current at zero potential ('reversal current')
> d) some estimate (what??) of selectivity
> e) some estimate of rectification (ratio of slopes of IV at +\infinity vs. -\infinity)"
>
> Thanks very much,
> jay

For numpanels = 682
For tolerance 0.05, 94 vectors needed (0.049217)
For tolerance 0.01, 266 vectors needed (0.009934)
For tolerance 0.005, 322 vectors needed (0.004672)
For tolerance 0.001, 430 vectors needed (0.000840)

For numpanels = 1014
For tolerance 0.05, 90 vectors needed (0.048593)
For tolerance 0.01, 388 vectors needed (0.009946)
For tolerance 0.005, 484 vectors needed (0.004835)
For tolerance 0.001, 622 vectors needed (0.000973)

For numpanels = 1248
For tolerance 0.05, 84 vectors needed (0.049891)
For tolerance 0.01, 452 vectors needed (0.009940)
For tolerance 0.005, 558 vectors needed (0.004919)
For tolerance 0.001, 725 vectors needed (0.000996)

For numpanels = 1274
For tolerance 0.05, 86 vectors needed (0.049647)
For tolerance 0.01, 519 vectors needed (0.009981)
For tolerance 0.005, 626 vectors needed (0.004984)
For tolerance 0.001, 786 vectors needed (0.000901)

For numpanels = 1560
For tolerance 0.05, 83 vectors needed (0.049549)
For tolerance 0.01, 556 vectors needed (0.009559)
For tolerance 0.005, 648 vectors needed (0.004962)
For tolerance 0.001, 864 vectors needed (0.000983)

For numpanels = 1568
For tolerance 0.05, 86 vectors needed (0.049117)
For tolerance 0.01, 567 vectors needed (0.009972)
For tolerance 0.005, 723 vectors needed (0.004877)
For tolerance 0.001, 915 vectors needed (0.000993)

For numpanels = 1950
For tolerance 0.05, 87 vectors needed (0.049238)
For tolerance 0.01, 676 vectors needed (0.009607)
For tolerance 0.005, 770 vectors needed (0.004946)
For tolerance 0.001, 1032 vectors needed (0.000999)

For numpanels = 1960
For tolerance 0.05, 86 vectors needed (0.049070)
For tolerance 0.01, 644 vectors needed (0.009952)
For tolerance 0.005, 850 vectors needed (0.004976)
For tolerance 0.001, 1100 vectors needed (0.000994)

For numpanels = 2450
For tolerance 0.05, 86 vectors needed (0.049951)
For tolerance 0.01, 785 vectors needed (0.009956)
For tolerance 0.005, 991 vectors needed (0.004993)
For tolerance 0.001, 1317 vectors needed (0.000987)