Re: now that the Phys Rev E paper is in press.... let's get back to research =)

Bob Eisenberg <beisenbe@rush.edu>   Thu, Jul 5, 2012 at 4:51 AM
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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 $+\infty$
vs. $-\infty$)"

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)

Burger Inverse Problems As published April 2007 SIAP.pdf
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