Bob Eisenberg <bob.eisenberg@gmail.com>

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

**Engl Heinz** <heinz.engl@univie.ac.at>                    Sat, Jul 7, 2012 at 8:50 AM
Reply-To: "beisenbe@rush.edu" <beisenbe@rush.edu>
To: "beisenbe@rush.edu" <beisenbe@rush.edu>

Dear bob
martin is of course right.
Regularization was used just to change the original ill-posed inverse problem into a neighboring well-posed one.
Regularization stabilizes, which was precisely necessary because of the ill-posedness of the inverse problems.
And it has its limitations as martin describes. Depending on the degree of ill-posedness (smoothing properties of the forward problem), there is some kind of "resolution limit" which describes the maximal accuracy/stability which you can get by regularizing an ill-posed problem.
So, via regularization we MADE the problem less sensitive t data noise.
Best regards
heinz

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--- Ursprüngl. Mitteilung ---
Von: Bob Eisenberg
Gesend.:  07.07.2012, 14:46
An: Martin Burger
Cc: jbardhan@alum.mit.edu; Claudio Berti; Dirk Gillespie; Bob Eisenberg; Wolfgang Nonner; Martin Burger; Engl Heinz; Chun Liu; Tai-Chia Lin 林太家; Allen Tzyy-Leng Horng 2; Douglas Henderson BYU; Xiaofan Li
Betreff: Re: now that the Phys Rev E paper is in press…. let's get back to research =)

Dear Martin

I am sorry if I misunderstood our results and confused people.

I of course do not really understand the definition of ill posed
and well posed in terms of continuous dependence on data.
I do not know what that means or how to test a particular case.

What I did think I understood was "sensitivity of conclusion to data"

Here I thought we had shown that our estimate of permanent charge
distribution was not very sensitive to our data (after we used regularization
methods).

It is also quite clearly true that many estimates of IV curves are in fact

very sensitive to locations of permanent charge (in almost any model)
and that sensitivity is an essential part of channels being nanovalves.

So the academic issue here is the relation of ill posedness to sensitivity.

The practical issue is whether the sensitivity of estimates of IV curves
to location of charges might be made easier to compute if regularization
methods were used on the forward problem.

As ever
Bob

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On Sat, Jul 7, 2012 at 7:08 AM, Martin Burger <martin.burger@wwu.de<mailto:martin.burger@wwu.de>> wrote:
Dear Bob,

I am sorry that have to clearly disagree on that.
In classical terms the inverse problem is ill-posed, i.e. it does not depend continuously on the data. We employ
regularization methods to overcome these issues, but note that regularization methods introduce some prior
knowledge about the permanent charge we want to reconstruct. Also our reconstructions indicate that we cannot
get very precise information about the charge distributions but rather a rough idea about the charges that can be
further interpreted with prior knowledge. A well-posed problem should mean we can compute a quantity with high
precision without using prior knowledge.

The issue about too much data for the numerics is also intriguing: due to the ill-posedness the data do not carry
much information. So if we use a lot of data we slow down the numerical solution since we have to solve many
forward problems, but it does not improve the results a lot. The question in the tradeoff between numerical
efficiency and quality of reconstructions is which set of voltage and bath concentration to use in order to get
maximal amount of information in as few data as possible.

The forward problem of computing IV from permanent charge is definitely well-posed, this is related to the forward operator, which even in our joint paper we prove to be well-posed unter suitable conditions.
There may be one issue in the forward problem in the sense of nonuniqueness, which you would hope for somehow in the case of gating (?)

Regards
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Bob Eisenberg <beisenbe@rush.edu<mailto:beisenbe@rush.edu>> schrieb:

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<https://ftp.rush.
edu/users/molebio/Bob_Eisenberg/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<mailto: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)