Merry Christmas Everyone,

and

Best Wishes

for a

Happy and Prosperous New Year!

and

Happy Chanukah to those who like getting presents for eight days instead of one.
My mother Lucy tried it only once.

We're starting this letter as Thanksgiving breathes down our necks. We know this is the prelude to much conviviality and holiday spirit, but we're not quite ready, as usual. And, after all these years, we still don't know how it arrives so quickly. In any event, season's greetings, friends and loved ones!

In our last holiday letter, we noted that all of Bob's children had opted out of our pictures (and why should this be, when they're only aged 29 to 39 ???). Slowly, it dawned on us that they probably didn't care for top billing in our letters, either. With this major insight out of the way, here's a quick summary: All of them still live and work as they did last year (Ben and daughter Crystal, in River Forest; Emily and husband Ben Taylor, in Chicago; Jill and husband John Trowbridge and children James, Holly, Henry and Alastair, in Honolulu; and Sally, in New York City). They're doing well and continuing to generate vast amounts of totally justifiable pride in us.

Now we have extra room for this year's installment of "Bob's and Ardyth's Excellent Adventures." Bob has been busier than usual with science (see below), so we may not touch on all of his travels (no offense to you hosts out there). In March, we took a dream trip to St. Petersburg, Russia, and spent eight days at the Hermitage Museum with a small guided tour. A senior curator from the museum was with us most of the time. They don't make monarchies like they used to: Our minds are still awhirl with gilt, red carpets; two-story-high, room-sized mirrors; crowds of statues; exquisite paintings from all eras and genres; flocks of schoolchildren and soldiers visiting their heritage, and collections: ancient gold amulets and charms, porcelain, chairs by the dozens, urns of semi-precious stone that loomed over our heads. And, everywhere, the Russian spirit, prevailing over the Soviets and time.

Our other travel delight this year was Trieste, Italy, largely because of Bob's colleague and host, Paolo Carloni, who knows every good fish restaurant in the city. The other reason Trieste is special is because it's not a tourist destination, just a sweet Italian city. It's nestled on the cliffs next to the Adriatic Sea, near Venice, Slovenia and Croatia. While Bob worked, I lounged in the city squares, sipping Prosecco and watching Italians be Italians. And waiting for the next great dinner.

Before and after these journeys, Bob and/or I went to Long Beach, Boise; Park City, Utah; San Francisco, Dallas, Minneapolis, Boston, Long Island (for a glorious and joyous Jennifer Eisenberg-Ben Middleman family wedding); West Lafayette, IN

> (Mary Lundstrom introduced us to K-Dees with the best coffee beans – Killer Beans – we've ever tried: use the link or got to http://killerbeans.com/site/home.html; try the "Kalossi Knockout", i.e., Sumatra, to see if you like the style);

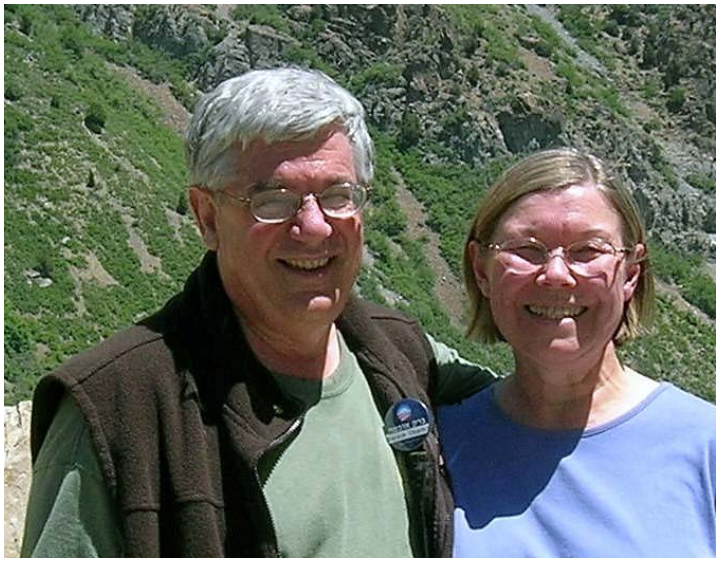
St. Louis; Springfield, IL (home of the Lincoln Museum), Detroit (which has a great, little-known art museum). A friend and I made our third visit to the Santa Fe Opera, always worth the flights and the drive.

When Bob and I weren't traveling or going to symphony or looking at museums, we were immersed in this year's one-of-a-kind political developments. By now, I know the talking heads by their voices alone. (Well, at least the ones on MSNBC and CNN.) We are still rejoicing that voters have chosen an intelligent, focused president and fulfilled the deepest promise of the Civil Rights Movement.

In my spare time, I've taken a few more music appreciation classes and resumed a theater subscription with a friend. Like everyone else, we've wrestled with our finances, trying to stay ahead of the economic chaos, which is like tilting at windmills. But, best of all, we've had a good year of togetherness and contentment and we've had some opportunities to do good deeds, so we are happy. We wish the same for you.

Ardyth had a happy year

And we two did too.



Ardyth asked me to add a few clumsy geeky comments about my professional life to her graceful words about family and travel: who am I to turn down a chance to talk? (By the way, where do you stand on a vexed question? is a colon : supposed to be followed by a capital letter? Mr. Niswender—Horace Mann School, 1950s—would have failed me in 10^{th} grade English if I had done that)

But first I have to say something about my jewelry, worn faithfully on my vest and coat (both) ever since the Iowa primary, an Obama pin. We are in a remarkable time, with the opportunity to do many things that have not been done for decades. Obama seemed to me a good bet ever since I read "Dreams from My Father" and compared it to the several biographies I had read of Senator Clinton. What has transpired has transfixed. We have a politician who has learned to raise unprecedented sums of money, who has lots of that available still, and the ability to raise more, and thus 'persuade' congressmen whose hearts and minds often follow their trousers, sorry their trouser pockets, where their wallets sit. We have the commitment of Congress already to spend $\$7\times10^{11}$, if I count the decimal points right in seven hundred billon). And that commitment was made to a Radical Republican Reactionary (Bush or Paulson, take your pick). So we have a President entering with much more power to spend money than ever in our history (except perhaps in 1861, 1918, and 1942). Now, let us hope Obama lives up to my (and more importantly his and his mother's) dreams, and spends it wisely. If he listens to Michelle Obama and Paul Krugman and he will do as well as can be done. [Check out http://krugman.blogs.nytimes.com/ and the fabulous live links in it if you feel compelled to learn some economics. Remember it is a science of a more or less conserved quantity – money and productive – as it flows in a chaotic path and stochastic resets governed by human (mob) psychology and greed.]

Now to professional matters: the Department at Rush has thrived in the last year because of the remarkable work of its labs, even in the most difficult funding environment since the 1980s. Three investigators had grants rated as (literally) the best in their NIH Study Sections, and these scientists work in different fields reviewed by different Study Sections. To those who fortunately don't need to know about these things, Study Sections in essence award NIH grants, typically $\$4 \times 10^6$ total over 4 or 5 years. Being #1 out of about 100 grants reviewed (in each batch) is rare enough. Having three independent labs doing that in one department is unheard of. This record is probably unmatched in the USA; it certainly shows the remarkable productivity and creativity of these scientists even as they age. It shows that the environment for research at Rush is excellent, and we all can be grateful to our Dean and President who have made that possible along with crucial help from a finance officer and a wonderful administrator in the Department. I take no credit at all for the science, but I sure can be a proud 'boss'! After 32.5 years as Chairman, I am still able to stay out of the way of first rate scientists and let them do their thing.

We have also been able to do significant recruiting for the first time in decades thanks to our Dean, President and finance officer. The Department is finally growing younger as well as older and finer.

My own science has been nowhere near as successful in raising money as the science of my colleagues, but we are thrilled to think we understand (finally) how Ca channels tell Ca^{2+} ions from Na^+ and how Na^+ channels tell Na^+ from K^+ (all with the same model involving only two parameters, set to the same values for both Ca and Na channels in many solutions,). Since I have been worrying about part of this (Na^+ *vs.* K^+) since October, 1959, I am indecently proud of this work, and grateful that we made a step to relieve my worries.

Wolfgang Nonner and I only dreamed that such a simple model could go so far when we dreamed it up in the (temporarily) chilly (and drought stricken) paradise of the ITP (Institute for Theoretical Physics, now the Kavli Institute) at UC Santa Barbara many years ago (November 1998 Ardyth tells me).

For those interested, I print an Abstract I wrote a few weeks ago for the IMA (Institute of Mathematics and its Applications: University of Minnesota) explaining what I think is going on (I do not want to commit all my collaborators to this idea, which is only partially tested, and therefore surely partially wrong, as we will find out in the next few years by the usual scientific method of 'guess' (fun) and check (hard work, also fun for nerds and geeks).

Links to the relevant papers can be found easily—thanks to the programming of John Tang and hard work of Glenda Keaton and Luci Vaughn—by clicking on the link Bob Publications or by copying the following and pasting it into your browser
ftp://ftp.rush.edu/users/molebio/Bob_Eisenberg/Reprints/Webpages/Publications.htm

or by google-ing "Robert Eisenberg Publications Rush" [without the quotations]. At least the Googling (= google-ing) worked this morning. The key papers can be found by searching the list for "Steric Specificity" [without the quotes] or by clicking on PDF .

Self-organized Models of Selectivity in Ca and Na Channels

for IMA Workshop on Salvation

Bob Eisenberg November 19, 2008

Selectivity is one of the most important properties of living systems. One of the founders of molecular biology (Nobel Laureate Aaron Klug) recently said (with some hyperbole I suspect) "There is only one word that matters in biology and that is specificity."

My collaborators and I study selectivity in ion channels. Ion channels are proteins with a hole down their middle that are the (nano nearly pico)valves of life. Ion channels control an enormous range of biological function in health and disease. A large amount of data is available about selectivity in many channels. Selectivity in ion channels occurs without structural change of the channel protein (on the biological time scale of 10^{-5} sec or longer) and does not involve changes in covalent bonds (i.e., changes in shape of electron orbitals). Selectivity in channels involves only electrodiffusion—usually of charged hard spheres. Thus, physical analysis of selectivity in ion channels is easier than analysis of specificity in enzymes or many other proteins while being at least as important biologically.

A simple pillbox model with two adjustable parameters accounts for the selectivity of both DEEA Ca channels (Aspartate Glutamate Glutamate Alanine) and DEKA Na channels (Aspartate Glutamate Lysine Alanine) in many ionic solutions of different composition and concentration. The predicted properties of the Na and Ca channels are very different even though 'Pauling' crystal radii are used for ions and all parameters are the same for both channels in all solutions. Only the side chains are different in the model of the Ca and Na channels. No information from crystal structures is used in the model. Side chains of the channel protein are grossly approximated as spheres.

How can such a simple model give such powerful results when chemical intuition says that selectivity depends on the precise relation of ions and side chains? We use Monte Carlo simulations of this model that determine the most stable-lowest free energy-structure of the ions and side chains. **Structure is the computed consequence of the forces in this model and so is different in different conditions.** The relationship of ions and side chains vary with ionic solution and are very different in simulations of the Na and Ca channels. Selectivity is a consequence of the 'induced fit' of side chains to ions and depends on the flexibility (entropy) of the side chains as well as their location. The induced fit depends on the concentrations of ions in the surrounding solutions in a complex way. Thus, calculations in a single set of conditions are of limited use. In particular, calculations of 'free energy of binding' in infinitely dilute or ideal solutions are not likely to give useful estimates of binding in physiological solutions. Physiological solutions are typically ~ 200 mM, far from dilute.

The self-organized induced-fit model captures the relation of side chains and ions well enough to account for selectivity of both Na channels and Ca channels in the wide range of conditions measured in experiments, even though the components of the model are grossly oversimplified. Perhaps the simplified model works because the structures in both the model and the real channel are the most stable, self-organized, and at their free energy minimum, different in different conditions.

It seems that an important biological function can be understood by an oversimplified model if the model calculates the 'most stable' structure as it changes from solution to solution, and mutation to mutation.