 

Dear Friends and Family December 2010

We have whizzed through another year, enhanced by many of you, and, as always, by work, music and travel. Here are the highlights, in that order:

YOU: We savored every minute we spent with friends and family this year. It was never enough and we want more in 2011. On the family front, most of our loved ones are well and the few who have life challenges are meeting them head-on. We take special, continuing delight in our entire extended family, and do what we can to help (at least, we think we're helping).

Those of you who visited brought pleasure and other places to us. Among our visitors were a fifth-grade friend of mine who I lost track of in the early 70s. Two more Boise friends spent time in Chicago and made up for 20 years of being out of touch. And, of course, we welcomed many of Bob's friends and colleagues to our table. Cooking for scientists is a particular privilege.

WORK: Bob is up to his hairline in formulas and theories about how zillions of ions behave when they squeeze through channels into cells. I helped by editing a few of his papers. Although I don't understand the theories (obviously, from this paragraph!), I've debated with him long enough to know when his reasoning is solid and when it's specious, and can point that out unceremoniously. (Which is what wives are for.)

My on-again, off-again legal practice got busy when I became second chair on a big, complicated case. This should keep me occupied for a long time. Twice a week, I still work out at the gym with a trainer who puts real work into my life, albeit with adult supervision. I also got my volunteer feet wet by working for a Cook County candidate for office. He lost, but the work (and observing the nit and grit of local politics) was worthwhile.

MUSIC: Lots of it. The Chicago Symphony performed all of the Beethoven symphonies in June, along with some of his chamber music and overtures. Some weeks, we were at Symphony Center three evenings. I took a class on the symphonies at the same time, and enjoyed every second of being awash in the music.

TRAVEL: Our 2010 started in Taipei, where the Taiwanese ring in the calendar New Year with a night of fireworks, then get ready for the Chinese New Year. I kept an e-journal, with pictures, and will happily send it to anyone who's interested. It was a grand adventure, full of new friends, sights, sounds and tastes.

Cump Sherman at Home

Guess Where?

Le Bois of Boise

We've had the pleasure and privilege of poking into many new parts of our country this year, all the way from Asheville, NC to Zanesville, OH, with stops in between. We have a new appreciation for Americans' goofiness and elegance, from the four-story picnic basket in Ohio that is headquarters for a large (ahem) basket-maker to the sumptuousness of the Biltmore Estate in Asheville. Near Knoxville, TN, the highway leading to the famed Smoky Mountains is a ten-mile boulevard of commercial family entertainment of all stripes and colors, competing for the attention of car-trapped five-year-olds. Houston drips with moss and personifies Texas. Nauvoo, IL, an historic home of Mormonism, shows the power and danger of mixing religion and politics. Woodstock, IL, home of an annual Mozart festival, is still 19th-Century Midwest. It's easy to see how big this country is from an airplane, but the nooks and crannies of America give a real sense of the depth and breadth. Our highlights this year were three family celebrations in New York (including walks along the new High Line elevated park) and a spur-of-the-moment, just-us vacation in Yosemite National Park. Bob also traveled to several other destinations, which he may want to talk about. And, finally, when we were home, we "stay-cationed," visiting Chicago-area tourist attractions that locals often take for granted.

It has been a very good year. We know we are blessed with love and health, and we cherish our good fortune. And we cherish you: You are the comfort and joy of our lives – and sometimes the delightful goofiness. Happy holidays, one and all!

Dear Anyone silly enough to want an update on science, even during the holidays,

I have been trying to extend Chun Liu's brilliant energy variational breakthrough this year, along with developing other work that will be seen in seven posters at the Biophysics Meeting in February. You can find an introduction to what I am talking about for those of you who want the background (pun intended) in the hyperlink to our 2009 Christmas Letter. I occasionally have to tend the Department as well: mostly its wonderful people take care of themselves, except when the outside world of the NIH or Rush Administration perturbs things (for what they think are necessary reasons, no doubt).

Thanks to Chun's breakthrough, we can now calculate things we could not dream of even approximating before, and the calculations are correct in the math sense, which they never were before (to scientists: 'correct' in math means selfconsistent solutions of all the field equations and boundary conditions) but the calculations remain as right or wrong as the underlying picture and model, of course. (Note to the knowing: developing the numerical methods and writing the computer programs to do the calculations is a very difficult task, involving as much hard work, fancy mathematics and unusual skills as the theory itself, because calculations describe every complicated behavior the system can do. The whole point of Chun's breakthrough is that it (must!) describe(s) everything—everything from fast sonic booms to the slow diffusion of salts. So the numerics have to handle both explosions and slow drifts. And then there are programming errors to remove, the bugs that have invaded computers since the first moth was found in a rack of memory circuit boards at Harvard [1].

So Chun, Rolf Ryham, Fred Cohen, and I are calculating the formation of pores in membranes that allow viruses to fuse to cells. Rolf and Chun make movies of theoretical viruses fusing to cells and Fred knows how real viruses fuse. The only problem is finding a correct model, and enough time for Rolf to program the model, so it behaves correctly. Chun, Yunkyong Hyon, Pancho Bezanilla, and I are calculating the conformational change that senses voltage in nerve fibers in a project that is just beginning. Nani Correa, Pancho , and I are looking for bubbles in GLIC channels. If we find them, theory will follow. If not, what's the point of more theory?

Chun, Yoichiro Mori, and I are calculating how animal and plant cells change shape and size as they are challenged with new conditions. These processes of osmosis, as they are called, form most of classical physiology beautifully summarized by (John) Pappenheimer in his autobiographical paper [1]. Pappenheimer introduced me to classical physiology when I was sitting at his feet (in ~1956) as a high school questioner during the 'taping' of a television show for American Heart. (Old timers: the show was being filmed in the then exciting new technology of the kinescope in the studio that Toscanini—4H if I remember correctly, but I probably don't— used with the NBC Symphony. The kinescope broke down. I pestered Pappenheimer for several hours while repairs were repeatedly attempted. From then on I was hooked on physiology.) Yoichiro has written general equations that (for the first time as far as we know) can describe all of classical physiology, at least in the ideal case. Chun showed us how to write the equations neatly, nicely and as well as generally for the nonideal case (that we have not yet computed). Life's solutions are certainly not ideal—as all of you know full well. Neither are life's ionic solutions. Everything interacts with everything else (to a good first approximation) in the ionic solutions. I hope a paper I am writing says this forcibly enough so biologists and chemists will hear the message and stop denying the obvious.

Life's solutions are not ideal because the salts in them have size. (See next page. Look up electrolytes in Wikipedia if you really want to know more. I also wrote a few papers on this last year. If you want to read them, let me know.) The size of salts is generally important because technology and life usually crowd salts where they are used. Life and technology want to get the most 'bang for the buck' and so crowd ions to get as much (electric) current flow as possible. More than 30 papers by Wolfgang Nonner, joined by Dezső Boda, Dirk Gillespie, Doug Henderson, and then by Janhavi Giri and Jim Fonseca, and I have shown how much can be understood about the selectivity of sodium and calcium channels from the simplest ideas of crowded charge.

Following this lead, David Jiminez-Morales, Jie Liang, and I are now searching for crowded charges in proteins in general (Wikipedia again if you want to know more about proteins and the amino acids that make them.) The exact atomic structures of thousands of proteins are known. Your tax dollars at work at the NIH. David and Jie search the enormous database of proteins that have known structure as seen by x-rays in crystallography. I look at the results of their hard work and try to understand it physically, physiologically, and mathematically).

We find that the active sites of enzymes are enormously crowded with charge. In fact, the active sites have almost as much charge as the solid NaCl salt you sprinkle on your food, and some active sites have much more. (Solid NaCl is 37 Molar; enzyme active sites average 20 M, analyzed for sure from 150 x-ray structures, 600 structures on the way). This finding—which is as solid as it is new—is exciting a great deal of interest and I am running around even more than usual presenting and explaining it. When a biologist sees some unusual physics, she or he has good reason to think that it is used by biology, for something. If a tissue is transparent, the odds are that biology is using its optical properties to bend light rays and make a lens. Stephen Jay Gould wrote innumerable wonderful essays [3] about such things in case you want to know more about biological 'adaptations' as they are called.

The extreme density of charge in enzymes is probably used to help the protein speed up or control its chemical work. But so far this is just a guess (a 'working hypothesis') to be tested: we have not proven that the enormous charges actually do anything at all. And very often our initial guesses have turned out to be wrong. Charge densities as large as NaCl are expensive to produce in a protein, and hard to maintain. They surely are doing something, we think. Lots of people want to know what that something is, even before we have published anything, and we will try to help them find the answer, if we can.

Stay tuned!

References

[1] http://www.jamesshuggins.com/h/tek1/first_computer_bug.htm

[2] Pappenheimer, J.R., A Silver Spoon. Annual Review of Physiology, 2003. 49 p. 1-16. *I can send a copy*

[3] Gould, S.J., *Ever Since Darwin, Reflections in Natural History.* 1978.
The Flamingo's Smile: Reflections in Natural History. 1987.
The Panda's Thumb: More Reflections in Natural History. 1992.
Hen's Teeth and Horse's Toes. 1994. all are from Norton, New York.