Happy Holidays!!!

from

Ardyth and Bob Eisenberg

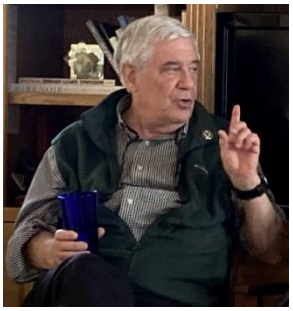
December 2022

Ardyth Eisenberg

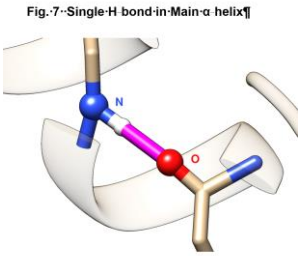
Holiday greeting, friends and loved ones!

'Tis the season for an Eisenberg update. These were the highlights of our year:

- THE 80TH BIRTHDAY TOUR – We celebrated Bob (and showed off what 80 looks like) in many venues: Sawyer, Michigan with Bob's children and a collection of grandchildren (thank you, Emily, for hosting); River Forest with friends (thank you, Catherine, for all your help); Philadelphia with friends and some colleagues; Boise with my family and friends (thank you, Barb for hosting and thank you, Maila for flying in from Portland). The Tour ends in April 2023, in New York City, where we'll celebrate with Bob's brother and sister-in-law.
- UTAH, THE NEXT GENERATION – We introduced grandsons Alastair and Henry to our favorite places in Southern Utah. They literally scampered up rocks the first time they were out of the car, and hiked several demanding trails in the heat. We walked with them on easy trails and did drop-offs and pick-ups the rest of the time. A great trip was had by all.
- THE SCATTERING OF THE CLAN – For the past two years we've had the sheer pleasure of being within walking distance of five of our now-six grandchildren. This was bound to change with young adults. Alastair and Holly and her new partner Abby have moved to the north side of Chicago. Henry has entered The Ohio State University as a freshman and is taking school life by storm. James and Catherine have stayed in place, much to our delight. Chris still lives near Washington, DC, programming computers for the government.
- THE REST OF THE CLAN – Ben still lives in our building and helps whenever I ask, no matter how silly the request. Emily and her husband Ben are still in Sawyer, Michigan. Jill has moved to California. Sally and her partner Reid still live in Charleston, SC. We're delighted we could see all of them this year, despite their geographic range. My family in Boise are all well and happy. Seeing them last July made me want to visit more often and I hope to do this in 2023. (Watch out, you guys!)
- THE WALLPAPER PROJECT – This is worth noting because we survived it. Our 20-year-old wallpaper was literally falling off the walls. It was time. We had no choice. After looking at about 10,000 patterns and ordering about 100 swatches, we did it. The wallpaper crew was here most weekdays in October. The dust and disruption were beyond belief, but worth the ordeal. Most of the house is back together. "Most." I still have to hang a couple of walls of old and new pictures. It will be my New Year's resolution.
- GIRLFRIENDS – Lots of breakfasts and lunches here in Chicago keep me energized (you know who you are). Visits with Maila (who I've known since the fifth grade) and Adele (who I've known since the first day of college) were too special for words.
- WORK – And, yes, we still work. I put in five or six hours a day on legal matters. Bob has one or two regular Zooms a week with mathematicians in China and Canada. He's still doing new science at the speed of a 40-year-old. He'll tell you more.
- A TRIBUTE TO KAY ANDREOLI – "Kay-Who-Introduced-Me-to-Bob" is the reason you're reading this letter. She set up our blind date in June 1989 (then bragged about it every chance she had!). She died in August and I had the honor of joining her family for a memorial in October. There are no words for our love for her or her elan (not an overstatement) or her intellect. We miss her and dedicate this holiday letter to her and her accomplishments.



December 2022 Bob Eisenberg



My 60th year doing science found me **eager to try something quite new.**

As a few of you know, I was trained in molecular biology as an undergraduate by John Edsall, who did so much to bring molecular biology to Harvard, and America. Neither molecular biology nor its many Jewish scientists were welcomed with enthusiasm at the other university in a town called Cambridge. Hence the LMB–Laboratory of Molecular Biology— was created and 12 Cambridge Nobel Prize-winners not part of Cambridge University. Harvard Deptt of Chemistry has 7 Nobel Prizes.

Little did Edsall or I think that the structure of hemoglobin that he showed me one afternoon in 1959 in Nature Magazine would be the first of 199,277 other structures known today(https://www.rcsb.org/.

None of us, no one at all, thought that thousands of scientists would be computing the motions of individual atoms in those structures with less effort than we needed in 1959 to compute $\log x$.

Today, computations of this sort are so easy that scientists are drowning in data. And these computations are vitally important to everyday medical practice, in treating cancers and designing vaccines, for example. The mRNA vaccine was designed with the insights from these computations.

These insights are qualitative. Quantitative progress has been frustrating because it is difficult to tell what came from the approximations made by enthusiastic scientists, and what actually comes from the protein. This is hardly a new problem in science, but it remains irritating. Quantitative Analysis of the structures of proteins is the only way out of this dilemma (in my opinion) which is exactly why there is no engineering without numbers. Engineers know they need numbers or their machines will not work.

This year, I've tried another approach, based on something Rick Mathias and I used around 1980 to analyze muscle, heart, epithelia, and the lens of the eye. Rick and I used wildly varying voltages—with the fancy name 'stochastic signals' to perturb muscle fibers. We used mathematics (called Fourier Analysis of Stochastic Signals) to see what is going on. The resulting structural analysis of biological systems was quite successful. We had used an engineering and mathematical approach to understand biology..

Now, 40 years later, ***I got the crazy idea that the wildly varying positions of the atoms in a chemical bond might be analyzed the same way Rick and I had analyzed voltages***. I guessed that the math would not care where the wildly varying signals came from.

So the question was, Is a bond between atoms so rigid that it could be analyzed like an electrical circuit? We chose the hydrogen bonds (H-bonds) that help hold proteins in their functional shape because they are so important in every protein, as Edsall had taught me in 1960.

It's easier to ask questions than answer them in science, as in life, but at least in science sometimes you can tell if you have an answer. Wildly varying signals can be analyzed by math to see if they are coherent. The coherence function can tell us if the signals share properties—cohere—by Fourier analysis of their power.

I proposed coherence analysis to the brilliant undergraduate Stanley Nicholson (IIT=Illinois Institute of Technology) working with David Minh's protein group, to try to tell if the H bond was rigid or not. If two signals are coherent, they have the same power (at all frequencies and times). Electrical circuits are not natural. They are in fact designed so they are coherent. It did not seem likely that natural systems like the atoms of proteins would be coherent but Stanley and I were willing to give it a try. Stanley would learn a lot even if the project failed. Stanley mastered the modern stochastic software in days, not the years it had taken Rick Mathias and me to write our original version. And with David's enormous help Stanley learned to deal with the movements of the atoms of our model protein.

Amazingly, the result was unambiguous. The wild idea worked and worked unequivocally. This H-bond is rigid. We have also found that groups of atoms also form rigid structures as they interact with neighboring groups. The coherence analysis requires no assumptions about the locations of the atoms (unlike all other approaches I know of), so our colleagues have found the results convincing.

Our dreams. We believe this coherence analysis will turn into a generally useful tool for studying the motions of many proteins. We hope it will lead to the study of the crucial properties by which proteins change shape. Time will tell how well we do: umpteen other scientists have the same goal. And artificial intelligence methods are very popular nowadays. They have been successful even when poorly defined, and subject to disagreements that are hard to resolve. Coherence analysis of man-made machines is perfectly defined in engineering. and not open to disagreement. Coherence analysis of evolution- made machines may not be quite so convincing, but is likely to be more convincing than other methods because it is defined precisely.

Our method is defined precisely by mathematics. That will be ***both a blessing and a curse.*** As a blessing it will give unique results. As a curse, the unique results will be hard to twist into the preconceptions that structural and molecular biologists (like all of us) use to understand their worlds. Scientists, particularly molecular biologists, often prefer vague descriptions over the crystalline beauty of successful mathematics, so I am not counting on easy acceptance. But the struggle to exploit a new approach will be fun, as well as the science itself, as are the wonderful interactions with Stanley and David.