Dear friends and family,

Ardyth's Part:

To paraphrase poet James Russell Lowell: "and what was so rare as a day in 2020?"

Our year began normally. Bob visited Taiwan and was so pleased to see Tai Chia Lin recovering from a nasty disease. I visited Boise for a reunion with a beloved uncle not as young as he once was and my brother and sister. Then, on March 4, we set off for Philadelphia, driving, to spend a month so Bob could work at the University of Pennsylvania. We packed disinfecting wipes and liquids, but at that point masks weren't *de rigueur* – or even seen in public. People were wary of Covid, but not actively protecting themselves..

On Tuesday, March 11, Bob and I set off separately for a quick visit to New York City. Looking back, it's astonishing that we spent time in NYC (and on public transit) in March and escaped the virus We returned March 12 to learn that Penn had just shut down for the semester, thus ending Bob's work. We packed the car in an hour and headed back to Chicago. I call it "Escape from Philadelphia." We talked about virus loads and overloads. We put the disinfecting wipes in the front seat and used them religiously on all surfaces when we stopped for gas and food. We went to a Starbucks and asked a barista to fill our coffee thermos. But Starbucks had stopped handling personal containers, and he gave us a paper cupful.

Bob will write more of the trip. How quickly things change, and in ways we'd never imagined. And here we are. We've been scrupulous about staying in and avoiding contact with people. Bob grocery shops only once a week, in the early morning. We take walks, although those are fewer as the weather turns. We've visited the Morton Arboretum, which has timed entrances for safety. And our one "road trip" (fifty miles each way) was to the Midewin National Tallgrass Prairie. The rest of the time we've been working (a lot), learning our way around YouTube, Netflix and Hulu; and ranting at the politics on cable news.

We miss the Chicago Symphony Orchestra and having weekly EisenDinners with grandchildren. On the other hand, we've had more interesting conversations with them on Zoom than we did at the dinner table. Although we didn't go out to eat that often, we miss being able to decide to go out to eat. On the other hand, I'm having more fun than ever trying and making up new recipes. We miss not getting together with friends, but we probably see them more often on Zoom than we did in person. I miss the Joffrey Ballet and the Goodman Theater. In some ways, music on YouTube is better than in person, but nothing replaces the immediacy of live dance and theater.

At the risk of sounding a little Pollyanna-ish, there are some silver linings in our confinement: Bob and I knew from our first date that we were well-suited for each other and we've lived with that joyous reality for over 30 years. Being alone, almost uninterrupted (except by work), has brought us even closer together. (We've even learned to maneuver around each other, wordlessly, in our

galley kitchen.) This is a gift we might not have found any other way. We know our grandchildren better as people than we did before. We've seen how much one can take for granted in ordinary living and how precious it is. Here's to a 2021 where we can put all this knowledge to work in a more normal setting.

Bob's Part:

My trip in January to see Jinn-Liang Liu and Allen Horng in Taiwan was as productive as pleasant. A molecular theory of ion solutions came from that, perhaps the first to deal with water as a finite size molecule and actually predict experimental data from bulk solutions (almost no channels in this paper) in solutions with a wide range of compositions and concentrations. Of course, much more needs to be done, but we hope we have set a standard for physical necessities (finite size of molecules), mathematical precision (everything is precisely defined and computable), and chemical and biological relevance (we calculate curves that can be superimposed on experimental data as experimentalists plot them). Our goal is to make it easy for other scientists to climb on our shoulders, see further than we do, much more productively than if we start from the same ground level, rubbing shoulders not always in the most constructive way possible.

Yoichiro Mori was kind enough to invite me for a prolonged stay at the University of Pennsylvania, where I have been giving seminars on and off since autumn 1965. Ardyth and I are particularly happy to share Philadelphia and have taken children and grandchildren there to show them around. We are fanatics about the Barnes Foundation (about 60 Cezannes) and the Philadelphia Art Museum (with ***two*** fantastic Cezanne Mt. St. Victoire from Le Lauves, only one listed in their catalog, however), and enjoy the Philadelphia Orchestra when they remember to practice. And we saw Brian Salzberg and Ana Lia Obaid who are very special friends since the 1970s and 1980s when they helped look after our children at Woods Hole, MA.

Scientifically, the prolonged stay was most welcome because Yoichiro and I had shared interests since I met him a few weeks after he arrived in New York's Courant Institute. (He asked me to call him 'Joe' ostensibly to make greetings easier but also to avoid my horrible mispronunciation, I suspect. And we have spent weeks working together in Minneapolis with Chun Liu on many problems of interest.

It was not to be. No sooner were Ardyth and I settled in a nice apartment and done some food shopping than Yoichiro suggested I visit New York to give a seminar at the Flatiron Institute, kindly organized by Mike Shelley.

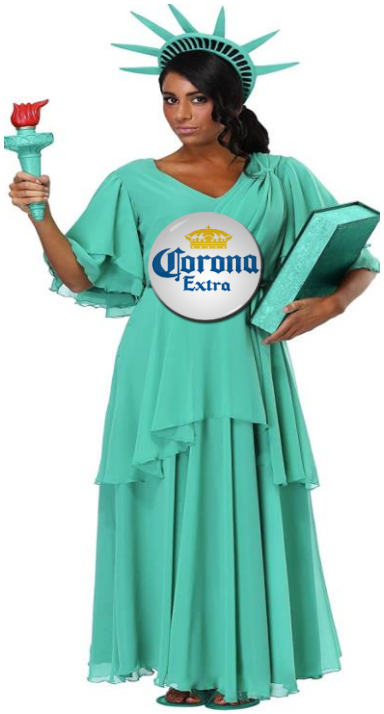
By then there was a rumbling thunder of viral concern: I had been warning friends for years that an international epidemic was highly likely, and in fact stockpiled medications at home for the whole family if that should be of the flu variety. I had known of Covid from early January. Indeed, daughter Jill and I stockpiled all sorts of wipes and disinfectants a few hours after China announced that Covid could be passed one person to another. (We still have unopened boxes.) But we did not stockpile masks, particularly N95 masks, being ignorant of Covid's mode of transmission as a chit chat disease, the ultimate socially transmitted disease.

Despite some worldly wisdom, we behaved as humans do, governed more by denial than wisdom, and happily took the road trip to Philadelphia, sampling American country cooking along the way. We have discovered that close to a McDonalds there is almost always a local restaurant with gluten free goodies for Ardyth, where the BLTs are excellent, the hamburgers are to be avoided, and quite often there are superb specialties, and always entertaining clientele and waiter/waitresses that Ardyth insists I call 'servers'.

Anyway, back to Mike Shelley and the Flatiron. Ardyth and I went to New York City by separate trains and were sensible enough to avoid people, but I do not remember wearing a mask. I gave my seminar after a remarkable lunch featuring sandwiches from every nationality of delicatessen that can be found in that part of Manhattan. Fortunately, this did not include the Eisenberg Jewish Deli, where the less is sampled, the better, until the next generation of owners emerge.

But during my talk, many of the more senior faculty had their phones ring, and left the room to return with a grim look. Many had been told their University would be closing the next day.

Fortunately, we safely returned from New York City to Philadelphia (although we now know that Covid was raging in New York at that time) and Yoichiro and the administration at Penn were more than helpful. We packed up and were on our way home by lunch time Thursday, without my being able to give a seminar at Penn before it closed, and hardly being able to say goodbye to Ana Lia or Brian. We reached Chicago on Friday evening after a marvelous meal in a small town restaurant (John's Diner near Cumberland) in Pennsylvania which had specialties in Greek, Italian, English (the real thing), and of course American food. No, we did not taste more than one or two.



Since our return, Ardyth and I have taken advantage of our status as ancients, and stayed in lock down nearly the whole time. One memorable exception was a very quick early visit to IIT (which wants to be called Illinois Tech, nowadays) to get some books. As I drove home, I stopped for a Italian Beef at Fabulous Freddies Italian Eatery, Chicago style, juicy with sweets, and as I walked out I saw an apparition: a walking Statue of Liberty with an unforgettable corona (hat) carrying a placard advertising "Corona Beer". I did not dare photograph her, so I do not think most of you will believe this story, particularly because the brand name Corona Beer was suspended and perhaps terminated a few days later. Here is a web version which gives an improved version of the real thing.

My family life since Covid came to town has been almost entirely by Messenger Portals (taught to us by Chris and Ben) and Zoom but it has brought us great joy.

Professionally, there have been webinars at Illinois Tech and Rush, and then a webinar series at Duke Kunshan, a lecture at

Beijing University, and an ongoing webinar series at Krakow University, Poland.

There also have been innumerable work sessions leading to a number of papers now emerging, for example, on a tri-domain theory of water flow in the optic nerve of the central nervous system.[1] That paper emerged from years of work led by Huaxiong Huang, Shixin Xu and Yi Zhu starting with a mathematically well defined derivation of the fundamental flow field equations[2] (partial differential equations with boundary conditions inside the domain). We moved to a bidomain model of circulation by an osmotic pump[3] in the lens of the eye which derived and extended the engineering model of Rick my former student and colleague Rick Mathias. The many papers over some 40 years that described Rick's experiments on the lens helped us mold our model to the evolutionary miracle of a lens without blood vessels to allow circulation by the muscular pump of the heart. Rick had shown that the lens uses its own osmotic pump to move fluid instead of the heart! We then moved to the central nervous system. Here again we could mold our theory (now tridomain) to wonderful experiments on the optic nerve of the North Carolina mud puppy Necturus, led by Dick Orkand of the Harvard Neurobiology group, then department. Dick Orkand taught me microelectrode-ry in 1960 in Woods Hole and was good friend of Brenda and me at UCLA for some eight years. (It is a small world: he also was Brian Salzburg's boss at Penn a little later.)

The work on the optic nerve was particularly onerous because we had to deal with the complexity that evolution gave us: three different intertwined 'tissues'—glia, nerve, and extracellular space—and three kinds of flow (diffusion, electrical migration, and convection like water flow in a hose), of at least three kinds of salts (sodium, potassium, and chloride) and water, and the biological controllers of those flows, ion channels, transporters, and membranes. The trees were as dense as the trees in The Wilderness in Virginia (look up the Civil War battles of ***Chancellorsville*** and ***The Wilderness*****)**. What forest of meaning would emerge from our wilderness?

> (Civil War buffs: Confederates emerged from the wilderness of trees because of the maps of Jedediah Hotchkiss. Imagine the incompetence of the Union generals that **TWICE** moved nearly 100,000 troops into battle without maps! George Thomas would never have done that!)

The meaning turned out to be given to us—not from our work at all—but by clinicians and biologists interested in (1) aging, (2) Alzheimers, (3) anesthesia, (4) dementia, (5) diabetes, (6) epilepsy, (7) migraine, (8) sleep, (9) stroke and (10) traumatic brain injury. Many papers (many more than the eight cited in our paper) show that the movement of potassium and water we were calculating played a **central role** in those diseases and phenomena, some of which have plagued our family and perhaps yours as well.

Drop me a note if you want more detail or just stay tuned for the several years it will take for us to calculate specific models of many of these diseases and phenomena, with the hope that understanding will help lead to treatment.

It seems clear (at least to us) that understanding of the system of coupled flows in three ‘tissues’ under many conditions in many specialized structures requires explicit models and mathematics and not just the qualitative metaphors of classical biology and physiology.

Some think putting everything on the computer may work as well, but somehow we doubt it.

Engineers build systems (e.g., our computers) nearly as complex as animals. They have found it best not to compute everything, but rather to make a hierarchy of models, one on top of another (cognoscente: often with feedback around the layers of the hierarchy).

We believe that biology is (mostly) a hierarchy of devices as are our computers and that biological systems need to be analyzed the way engineers analyze their hierarchies of devices. The physics linking the devices is often that of electrodynamics because that physics is universal and precisely described by the Maxwell equations, from inside atoms to between the stars.

Now, if I can help mathematicians understand what a device is, and help them build some of that hierarchy I will have lots of fun and maybe do something useful in the next years.

1. Zhu, Y., et al., *A Tridomain Model for Potassium Clearance in Optic Nerve.* arXiv:2012.03303, 2020.
2. Xu, S., et al., *Osmosis through a Semi-permeable Membrane: a Consistent Approach to Interactions.* arXiv preprint arXiv:1806.00646, 2018.
3. Zhu, Y., et al., *A Bidomain Model for Lens Microcirculation* Biophysical Journal, 2019. **116**(6): p. 1171-1184 Preprint available at https://arxiv.org/abs/1810.04162.