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Meeting Doug Henderson

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ABSTRACT

Doug Henderson brought his profound knowledge of ionic solutions to biology in his study of ion channels. Ion channels are proteins that conduct ions and electric current across otherwise insulating membranes. The ions are so crowded in these protein channels that the competition between charge and space dominates their properties. Here is how that work started from an unjustified claim (by me), a rather rude question by Doug Henderson, a fortunate reply and a memorable drive, all resolved by a calculation by Dezsö Boda.

1. Introduction

It all began with a prayer, so Doug and Dave would say, as I chatted in the lab at Brigham Young University (BYU) with David Busath and his students. Here is the story:

It all began, I would say, with the work of Doug Henderson that I had known for a very long time.

All of life occurs in ionic solutions, so Doug's work is known to all biologists interested in how ions change biological function. Most biological cells respond to ions, but nerve cells and muscle cells are the most notable examples.

(Physical scientists: think of the oceans where life started. All of life originated in oceans and we all carry a little bit of an ancient ocean inside our cells, and more of the present oceans outside the cells, in our blood [1], and in the plasmas of life.[2]).

Doug's view of "What is liquid?" [3] has been a bedrock of our understanding since that paper was written, and a broken metaphor is appropriate: as slippery and hard to grasp as a liquid is, Doug's understanding of what is a liquid was as solid as rock.

You can imagine then how I as a biologist who had worked on ions, nerve, and muscle since 1960, and who had worried about them even as a teenager, felt when I shook hands with this handsome, tall, distinguished gentleman in (or rather just outside) the lecture room of Brigham Young University, with its magnificent overwhelming view of the mountains in my favorite state Utah. (I must admit that I favor the beauty of Boulder and Torrey UT, even Hanksville, over Provo but undoubtedly that is the result of too many western movies in my youth as well as the overwhelming appeal to me of the red and sometimes white cliffs of those extraordinary places).

I was about to give a lecture to BYU faculty organized by my friend since the 1970's David Busath. David was and is a distinguished biophysicist who has been generous to me in many ways for which I will always be grateful. I had started working on the detailed properties of ionic solutions late in my career (around 1985) having been focused on muscle (and applied mathematics) until then. I was focused then (and now) on the electrical not chemical properties of those solutions but was so ignorant that I identified ionic solutions with their salt ions with the holes and electrons that carry current in silicon semiconductors.

You may wonder how a liquid can be like silicon and that is a very very good question. The subject is of such importance for future work that I detour into a discussion of material that I in fact never discussed in detail with Doug Henderson.

A psychiatrist who was told that "I can make a vacuum tube in a piece of sand if I can control the electric charges and field in the sand" might well doubt the sanity of the speaker. But that is exactly what William ('Bill') Shockley [4] of Bell Labs thought in the 1940 s. The implementation of those ideas has led directly to all of our digital technology [5–15], from transistors to computers, to cell phones, to digital displays. If Shockley and his associates had not pursued this idea, we would not have all that technology in my opinion. And his business associates who funded all this work [16] deserve as much credit as the scientists [17–19] who worked for Shockley. They had to have confidence and invest in that confidence despite the wildly intelligent, but wildly abrasive personality Shockley showed the world.

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As unlikely as it seems Shockley was right. Electrical properties are very much the same in liquids, solids and near vacuums if the charges and electric fields are the same. My understanding [20,21] that electricity in Doug Henderson's salt solutions was very much like that in vacuum tubes and silicon was not the problem, hard as that is to believe [22,23]. If the charges and the electric field are the same, the properties are the same, ... ***almost.***

But it was the "almost" [24,25] that Doug was to teach me [26,27] and that made all the difference.

The solid background of silicon, or the vacuum background of a vacuum tube, or the liquid background of an ionic solution are not a problem. What is a problem is the different correlations of charges in the systems. The correlations imposed by the periodic nature of semiconductor crystals (of germanium or silicon) create quasi particles called holes and 'electrons' that behave as ions with zero diameter. Correlations create these particles but the particles have zero size. Electrons in vacuum tubes have very very small size and so their correlations are also almost all electrical. Ions in water are different they have strong correlations produced by (among other interactions) the size of the ion. They are huge compared to the size of electrons in a vacuum tube and even larger—grammar does not let me say "huge-er"—compared to the holes and electrons of semiconductors that are indistinguishable from points. It is important to remember, however, that the electrodynamic interactions of charges in ionic solutions are very large and extend long distances. The other correlations are all short range (e.g., less than 20 ion diameters) and so at longer distances than that electrodynamic correlations dominate. The boundaries that confine a system in a setup are almost always far away. Even the boundaries that define a natural system inside the setup are often more than 20 diameters away. Thus boundary conditions are mostly electrodynamic, with the notable exception of ionic channels, where correlations other than electrodynamics balance the electrodynamics forces in their crowded environment creating the charge space competition so dear to Doug Henderson's heart. It is not often realized that the dynamic part of electrodynamics is directly relevant to the macroscopic behavior of ion solutions. Ions move in femtoseconds as every molecular dynamics simulation illustrates in astronomical abundance (over the milliseconds needed to recreate biological time scales for example). Femtosecond movements produce large velocities and thus large displacement currents proportional to the time derivation of the electric field. The resulting currents are significant and cannot be neglected without justification [23,28–33]REF As Feynman [34] so emphatically puts it in Section 15–6 "... Coulomb's law ... is to be used only for statics." along with Table 15–1 that labels Coulomb's law as "False In General. (true only in statics)". These issues are particularly important because they change the nature of shielding (screening) in ionic solutions and systems [35]. The sum rules [36–38] so important to the Hendersons of physical chemistry apply at longer times (greater than say nanoseconds. Sum rules do not apply at short times because ions do not have time to move to screen charge. Electrodynamics then dominates and screening and shielding, such as they are, are produced only by dielectric charges. In such systems, radiation occurs (because of the rapid time scales, enormous rates of change of electric fields, and the displacement current term that allows electric fields to propagate in a vacuum devoid of charge). Radiation flows to arbitrary distances, often without attenuation, i.e., to infinity, in the unbounded unconfined systems typically considered in statistical mechanics. In confined systems, radiation flows until it is intercepted by structures with their boundary conditions [39]. The tension between these inescapable properties of electrodynamics and the usual treatment of statistical mechanics (in the tradition of ideal uncharged noninteracting gases) is significant [40].

After this detour into electrodynamics, that includes lots of material unknown to me in Doug Henderson's lifetime, I return to the historical narrative. Wolfgang Nonner and I had realized that fact [41–43] while avoiding lectures in a physics institute at the University of California Santa Barbara and found a paper [44] saying how we should deal with the nonzero size of ions in solution. We did not know that Doug was a leader in this field. Nor did we fully realize that what we read was true only in solutions without structure that were part of biological molecules or systems.

But Wolfgang and I were biophysicists who had for decades learned the first chapters of many textbooks, without reading the rest of the book. We had built important electronic circuits that way (It is immodest but true to point out that one of the amplifiers I designed the AxoPatch, with Rick Levis and Alan Finkel, using only first chapter knowledge has been the world leader in sales since roughly 1987 and is still in some ways the best available: few electronic devices are usable, let alone nearly the best, after 35 years or so!). We had used the first chapters of anatomy, histology, physiology, and biophysics texts that way, as well as electronics, so why not do so with physical chemistry. (I speak for myself here and do not associate Wolfgang with this cursory and lazy way of learning things.).

So we calculated the properties that made biological cells so special directly from the theory paper we read [44] and were amazed that the properties came out right, over something like 8 orders of magnitude of concentration of calcium ion. Specifically, we worried about biological proteins that sit in cell membranes and have holes (channels) down their middle to let ions move through the protein and across the membrane. How could some of those channel proteins let only calcium ions through and keep the sodium and potassium (and chloride) ions out of the hole and stop them from crossing the membranes into cells? (This is called the 'selectivity' problem.).

Amazingly, the paper we read showed how that could happen using a ridiculously oversimplified picture of one of these channel proteins as lots of charges fixed in place (as charges are in silicon semiconductors that make up our transistors and computers). The size of the calcium ion and its electric charge interacted with the size and charges of the protein (in our oversimplified model) and it produced an approximation to calcium selectivity [45,46] that no one had been able to compute before, and indeed no one can compute in a fundamentally different way to this day [47–56]. (My colleagues will argue about what 'fundamentally different' means of course, but for us the computation must include the biologically relevant five orders of magnitude of concentration of calcium used in biological systems.).

As you can imagine, Wolfgang Nonner and I were very excited about this and I planned just to mention it in the middle of my talk, which was about the analogy between transistors and ion channels and their electrical properties and reported our work on that which David Busath was interested in and had helped with.

I had hoped to meet Doug and chat with him about these ideas before my talk but my intense interactions with Dave Busath and his lab made that impractical. I shook hands with Doug, said I worked on ions in biological channels and systems, moved into the magnificent lecture room, shut out some of the view, so we could see slides, and started my talk.

The talk was rather more formal in style than I was used to in the USA, although having spent much time at Harvard and Cambridge UK that did not bother me. As a good Brooklyn boy, I pretended to ignore it and just did my thing.

My thing led me to say after talking about current flow in channels that Wolfgang Nonner and I had found something very surprising and problematic but that was so important that I wanted to report on it here, for the first time anywhere (if my memory is right: someone should check that before it is believed). We had

found that the "Mean Spherical Approximation" could account for one of the most important properties of biological membranes and channels, if we simply assumed that the channel provided a lot of fixed charges with a definite diameter and these charges mixed with ions going through the hole in the protein. The key ideas were that the ions had definite size and charge, and the ions attached to the protein could mix with those ions but the protein charges were confined to that space. This idea seemed a useful albeit very crude approximation to Wolfgang and me because we were familiar with work [57,58] (mostly in Germany) on ion exchange membranes, which made similar over approximations but did NOT allow the ions and protein charges to have finite diameter.

No sooner did I say this result, than a certain dignified handsome tall scientist stood up and said "You can't do that. The MSA (his name for the Mean Spherical Approximation that he had established as much as anyone [59,60], although Wolfgang and I did not know that at the time) only applies for homogeneous systems (nonscientists: systems without proteins, i.e., systems as far from a channel protein as you can imagine). Your system is inhomogeneous".

The dignified Doug Henderson sat down, not really expecting an answer I suspect (since there was none possible logically), and the audience had a moment of shocked silence. Doug was well known for being more than polite, and soft spoken. Rarely did he ask critical questions, never before, I am told, had he interrupted a talk (without being called upon, I should add, by the chair of the session or the speaker) at all, let alone to say the speaker spoke nonsense!

Fortunately, my combative nature had been calmed by the supportive and kind environment at BYU and in Dave Busath's lab, and so I said "Professor Henderson, you are quite right. We hope you will show us how to do this right.".

Then I quickly moved along to other material not so obviously ill founded.

Fortunately, Doug agreed (albeit reluctantly) to show us how to do it right. He was sure that a better calculation would give a very different result. Wolfgang did not think so. I had no idea, but only wanted to know how the calculation would come out. So Doug agreed to take a detour from his ongoing work with Dezsö Boda (which was the best that I knew of on these subjects) and show us we were wrong. He found a way to do the MSA in a confined space with protein charges and persuaded Dezsö to do the calculations. Specifically, Doug "designed a simple model of ions confined in cylinders and persuaded Dezsö to perform Monte Carlo (MC) simulations for that model."[1] Remember Wolfgang and I had done the calculation in an unconfined space and applied it to a system which was as confined as one could be [24,25,27].

I met Doug and Wolfgang in Salt Lake City so I could show them Moab (then my favorite red rock: I had not discovered Torey and Boulder UT yet). We met at the airport and I drove to Moab in an unforgettable drive (through Price). Doug and Wolfgang argued the entire four hours, plus lunch. But that was not a problem: we all enjoyed the arguing, being used to the verbal conflict that is an essential part of producing fine science.

The problem was that both Doug and Wolfgang had good and bad sides.

No, not good and bad sides of themselves or their personalities (they are both wonderful agreeable people all the time in my many years of experience with them, often under stressful circumstances, some produced by my not so good sides). They had bad sides for their hearing! In fact, I think they were quite deaf on (at least) one side and the deaf sides were facing each other.

It took me (the driver) awhile to figure this out, but soon after we had lunch at Provo, I realized that an argument without hearing would not work very well.

So for the remaining hours I simply repeated what each said (as politely as I could: neither Wolfgang nor Doug would admit to having a bad side, let alone to deafness) The reiteration aided their interaction substantially. It also helped me understand: Doug had an immeasurably high IQ and Wolfgang was in that league too, so the extra time I had to spend repeating things gave me a chance to understand a bit of what the arguments were about. Fortunately, the road from Price to Moab is unchallenging (until we crossed the old suspension bridge on the short cut I took so they could enter Moab unforgettably there and later by Arches National Park) and we were not in danger from my driving.

The next day we were sitting in an elegant motel/hotel lobby, arguing science to the wonder of staff and guests, when Doug said he had results from Dezsö. And they showed that the MSA and the Dezsö /Doug calculation agreed within 2.7% with the MSA Wolfgang and I had used even though one was properly confined, and the other was not.

I was thrilled. But Wolfgang spoiled it all. He was right and he rubbed it in. Wolfgang said in my memory of events "Dezsö defined the computation box wrong. He used the same size box in the MSA and his calculation and he should not have: the ionic spheres cannot get to the edge, so the MSA box is smaller by the diameter of the ions." He used the same size box in the MC simulation that was used in MSA before and he should not have: the ionic spheres cannot get to the edge, so the MC box is larger by the diameter of the ions." Doug thought for about 3 s and said "Your are right." He phoned Dezsö,who performed the calculation with revised parameters and sure enough with that correction the numbers agrees within 0.4%, if I remember correctly. Wolfgang mumbled that he (Dezsö) got the corners wrong, counting them twice but I said "Please be quiet. 0.4% is good enough for me!".

Wolfgang's memory is more detailed and more correct in other ways, although too modest in my view. I include it as an Appendix, with his generous permission.

And that began a collaboration that produced something many papers [26,27,45,46,61–73] among us and many many more by Doug, Dirk Gillespie, Dezsö Boda and others, including two memorable papers with Dave Busath [27,63].

Indeed, I am working on versions of this model to this day. You all may be amused to know that we still do not know why the MSA and the simulation were so similar. At least I don't know. I never asked Doug that question and until I wrote this paper I haven't had the nerve to ask Wolfgang or Dezsö or Dirk or their colleagues that question! I now know that at least some of them think the agreement is coincidental or a cancellation of errors. I leave it to the next generation to sort this out and hope they do because if there should happen to be a reason for the agreement, it might lead to important and useful simplifications and thus greater useful understanding of ionic solutions in confined spaces.

So that is how all this got started.

What a joy!!!

How lucky I am to have been able to ride along with such a wonderful men and scientists as Doug Henderson and Wolfgang Nonner.

Declaration of Competing Interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

[1] I am grateful to Dezsö Boda for the quotation which states in detail what Wolgang Nonner and I remembered more vaguely.

Acknowledgement

The paper has been substantially improved by the contributions of the not so anonymous (by their choice) reviewers, who of course participated in the events described, hopefully with accuracy of spirit and emotion as well as fact.

Appendix

The calculation, Wolfgang's memory, reproduced from an email of April 27, 2022, with his permission:

"The reason why I was so sure about the MSA already in Moab is more practical. Lesser has a pape* (that you handed me in a stack of others), in which he narrows down a pipe filled with hard spheres to see how narrow he can make it before the MSA fails against the gold standard, Monte-Carlo. It was excellent to almost down to 2 particle diameters. That's where the equations of state started diverging. Noticing that in the gray zone pipe diameter was effectively less than nominal, I subtracted the volume that particles on the wall would take away from others, no matter how packed. That volume is 1/2x(cube-sphere). When I corrected the pipe diameter (in the MSA density) by that amount per spot on the pipe wall, the MSA pressure curve was that of the gold standard. I thought there was not much magic in that pipe."

*We have not been able to identify the paper involved amidst the more than 300 papers contributed by Lesser Blum [74], most on the MSA, and many near charged walls and in confined spaces.

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