

## The Intersection of Chemistry and Biology: An Interview with Professor W. E. Moerner

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Professor W.E Moerner earned two B.S. degrees, in Physics and Electrical Engineering, and an A.B in Mathematics from Washington University in 1975. He earned an M.S and Ph.D. in Physics from Cornell University in 1978 and 1982, respectively. Moerner worked for nearly a decade in the IBM Almaden Research Center, and joined Stanford University as a Professor of Chemistry in 1998. He has received many accolades throughout his career, including membership to the National Academy of Sciences in 2008, the Irving Langmuir Prize in Chemical Physics in 2009, and the Nobel

Prize in Chemistry in 2014. His work primarily focuses on single molecule spectroscopy, and he is widely credited for the first successful imaging of a single molecule. (Photo credit: Linda Cicero, of Stanford News Service.)

JN: Your work concerning the imaging of single molecules obviously has a profound impact on the physical sciences, but what do you anticipate the long-term societal effect of your work will be?

WM: The ability to see single molecules is an important scientific advance, and that's the way we viewed it at the beginning, more than 25 years ago, when we first observed single molecules. It was at low temperatures and liquid helium where we first detected single molecules, something far away from what you might consider a more broad application. The original work, when I was at IBM, had to do with storing bits. At first, the work wasn't storing a bit with one molecule but with many molecules per bit, but a limit that arose out of that was to try and see if you could observe a single molecule. We proved that we could do that.

I want to make it clear that a very fundamental scientific start can ultimately turn into a broad range of applications that you can't

necessarily envision at the very beginning. When you explore new areas of science, people can then think of ways to use these new discoveries in different ways.

For example, after that original breakthrough, we were then able to view single molecules at room temperature in the mid-90s. This science is very exciting because you see the effects of one molecule that you don't necessarily see in a group of molecules. You can see how molecules with the same structure that exist in different environments or states behave differently. You can figure out if the molecules march to different drummers or not. And, in fact, they do, especially if the molecules are in a complex system like a cell or a solid or a polymer or so forth.

So, why is that important? It turns out that the molecules changing, moving from one state to another in reaction to something we control results in us having an access to a kind of switch into what the state of the molecule is. Something that essentially started as a physics project became more of a chemistry project to understand what kind of photochemistry could make the molecules change. We put that together with engineering ideas to image single molecules in biological systems.

I want to explain very briefly how that works. You can imagine that an individual molecule is like a very tiny light source. If you place these all along a structure that you want to observe, and you shine a light on it that causes all of these molecules to emit at the same time, you get a very blurry image. Even though each one is a light source, there's this physical effect called diffraction that says that an object that may be an infinitely small point source appears to be as big as half of the wavelength of the light we are shining on it. Practically, given the visible light we use, that gives us a limit of about 250 nm. This means that everything will be blurry on that 250 nm scale. For that reason, light microscopy was thought to be too low resolution, because if two molecules are close together, you can't distinguish them unless they were farther than 250 nm apart. It is possible to get more fine imaging with x-rays, but the powerful thing about light is that it's non-invasive: it can look at cells and allow them to keep living while we are doing the experiment. Other high-resolution imaging methods will destroy them.

This diffraction problem previously made all optical microscopy images fundamentally blurry on this 250 nm scale. That's a problem because the dimensions of a cell's proteins are closer to 10 nm or 5 nm. Now that we can use these single molecules as labels, and you use a way to make most of them be off, and then come back on at different times, it's like blinking fireflies that light up different parts of the structure at different times. By doing that over a period of time, you sample all the positions of the structures and get resolution far beyond this previous fundamental limit.

You asked how does this affect society, and that's a very broad question, but it ultimately has to do with how we can use this. We can now use this to see structures inside cells that you couldn't observe before with

visible light, and see them changing with time. Since you can see better inside a living cell, you can apply this to either the science of cell biology or the study of diseases that result from cells that are misbehaving, or any other situation where you want to explore and learn how things work.

JN: You've mentioned a fairly diverse background. This started as work from IBM, turning from a Computer Science problem to a Chemistry problem. Clearly, interdisciplinarity has a huge impact on your work and how you approach things. Do you anticipate working with other disciplines to explore the potential of this technique?

WM: At the moment, we work closely with biologists and people interested in biomedical problems to apply this method to looking at all types of biological systems, whether it's DNA, RNA, protein structures inside cells, cell membranes, or even amyloid fibers that are important for brain diseases.

My whole life has largely been learning about different fields. I started out studying electrical engineering in my undergraduate years. An EE fellowship was what actually got me to the college I went to. I loved the physics and math courses that I was taking so I got three degrees in all three of those fields. Then I went to graduate school in physics, but it became chemical physics because we were looking at molecules in solids. Then I went to IBM research because the skills that I had learned allowed me to contribute to the optical storage scheme I mentioned earlier: storing bits or data in molecules. To actually explore that properly, I had to learn a lot about molecules. It was more like chemistry in that there were chemists making new molecules for our experiments, but it was like physics in that we were studying them using optical methods, which required things I had learned in my earlier electrical engineering study. When I moved to academic research, the possibility of exploring biological systems opened up. These methods are also applicable to polymers and material systems, but there's bigger interest right now in the biological applications.

JN: What do you think are the big problems that chemistry's tackling right now, and how do you anticipate that other disciplines might help chemists approach those problems?

WM: To talk a little broadly about chemistry in general, there are different parts of chemistry that are pressing hard on a number of interesting areas. For example, there's a whole piece of chemistry that's thinking about energy problems and catalysis: how do you do what you need to do to split water properly or to catalytically get energy out of a reaction. You want to do these things in the cleanest possible way without creating a lot of side products. There's a strong interaction between chemistry and energy-related problems. Other parts of chemistry involve making molecules that can become related to drugs. There's an obvious connection there between

chemistry and medicine. There's a whole part of our department that's related with chemistry, engineering and medicine for human health: it's the ChEM-H program that we have here at Stanford now, started by some chemistry and biochemistry professors in connection with many departments across campus. There are other connections to biology where we're trying to understand from a physical point of view how biological systems work. Other parts of chemistry involve polymers and understanding how to properly connect them to material science problems. So a lot of people will say that chemistry is a very central science because of all of these connections to many different departments through these core skills in making molecules, studying molecules, and understanding molecules through theoretical analysis. There's a strong interaction with a lot of different fields at the present time.

Personally, I find that many of the interesting problems are found at the boundaries between conventional disciplines. So we're in this interesting time in our world where people have to become experts in a given field, so that they can be skilled, but you can perhaps use these skills in intersections with other fields.

JN: You've mentioned that chemistry is a very central discipline to a lot of other sciences. Can you think of any disciplines that aren't traditionally associated with chemistry that you think could benefit from a more chemical perspective?

WM: In the case of computer science, given that there's a continuous push to drive Moore's law as far as possible, some people think that we'll come to a limit at some point. There's a need for a new scheme to imagine really dense storage or calculation, and it's not outside the realm of possibility that chemical effects could affect those parts of the computer industry. You can theoretically imagine a bit inside a single molecule, perhaps, and certain other absorbing species such as, for example, a particular kind of defect in diamond wherein some vacancies in the diamond bind with nitrogen. That's like a little molecule: that's an object that has its own structure and its own behavior, and that's a system that's being actively pursued for advanced quantum computing applications. It came partly from the physics community, but it has some chemistry and materials aspects to it if you really want to make it practical. Lots of things that we do on molecules are directly related to those interesting systems.

JN: Before we end this, do you have any closing comments?

WM: I can comment a little bit upon some aspects of this whole area of science that has become exciting now, in terms of super-resolution in molecule imaging. It arose out of a time when there these great industrial research labs, like IBM or Bell Laboratories, where science could be pursued. The fundamental work performed there turned into the

applications work. I want to remind people that basic science research, even though it may not seem to have an application in the short term, can easily have an application ten or twenty years down the road. We shouldn't focus only on applications; we should always be exploring the boundaries of science. In our current time, these industrial research labs are not so large, and I'm hoping that our society will continue to have support for basic research. We have to explain that sometimes to our legislators and our community.

I also want to say that a lot of students here at Stanford are interested in science, and come here intending to study science, which is wonderful. It's also important to remember that what really matters is someone's passion, to have something that drives you, to have something wake you up in the morning because you want to do more of it. This doesn't happen automatically: I urge people to pursue their passion, even if it doesn't involve the sciences. You need passion to make it through the times when experiments don't work, to have the drive, motivation, and energy to keep opening new doors and, whenever something causes a problem, to have a way to go around it and turn failures into learning experiences. All of that is driven by passion.