Watt Webb
Applied and Engineering Physics

# Watt W. Webb

## THE HIGH TECH PATH

### To Experiment Is the True Way

I've changed fields six times since I've been at Cornell, and I've changed career directions six times before that. After 12 years in industry with various responsibilities, Cornell was a great choice because of Applied and Engineering Physics' flexibility in accommodating a variety of interdisciplinary research.

What I've found most productive and most enjoyable is trying to invent new technologies to solve what we call the "impossible problems." I've always been sensitized to unsolved problems. My maternal family crest bears the Latin motto "tentanda via est," meaning to experiment is the true way. So I guess I was born this way. It may be amusing that my undergraduate major at MIT was business and engineering administration, which I am often reminded is my most valuable study in preparation for professorial responsibilities at Cornell.

### The Impossible Problems

Each challenge raises its own questions. Why is it important? Is it valuable to the knowledge and welfare of society? First, I have to recognize what is important to learn, then, how to discover the measurement pathways and make them work. If an experimental problem looks like it's a mess—hard to understand—it may still offer a challenge of great significance. If the alleged concepts seem to be nonsense, then the first step is to reformulate the question; this step often defines the experimental approach. Thinking about experiences in other fields often suggests new approaches. And sometimes that leads to invention of new solutions to the impossible problems. If the new solution is really reliable, it may become useful worldwide. That is a very satisfying reward for our efforts.

We actually solve many of our problems through interdisciplinary collaborations. It is particularly important to me to be able to think and communicate in ways that scientists in other disciplines can understand and appreciate. Most relevant now is biology versus physics, which are usually vastly different disciplines. Usually physicists know little biology, and biologists know little physics. We try to work across the interface. Our students and collaborators learn across the disciplinary boundaries so that they can understand each other, and our research group combines many disciplines. Since we nucleated the biophysics community here in about 1970, we have developed

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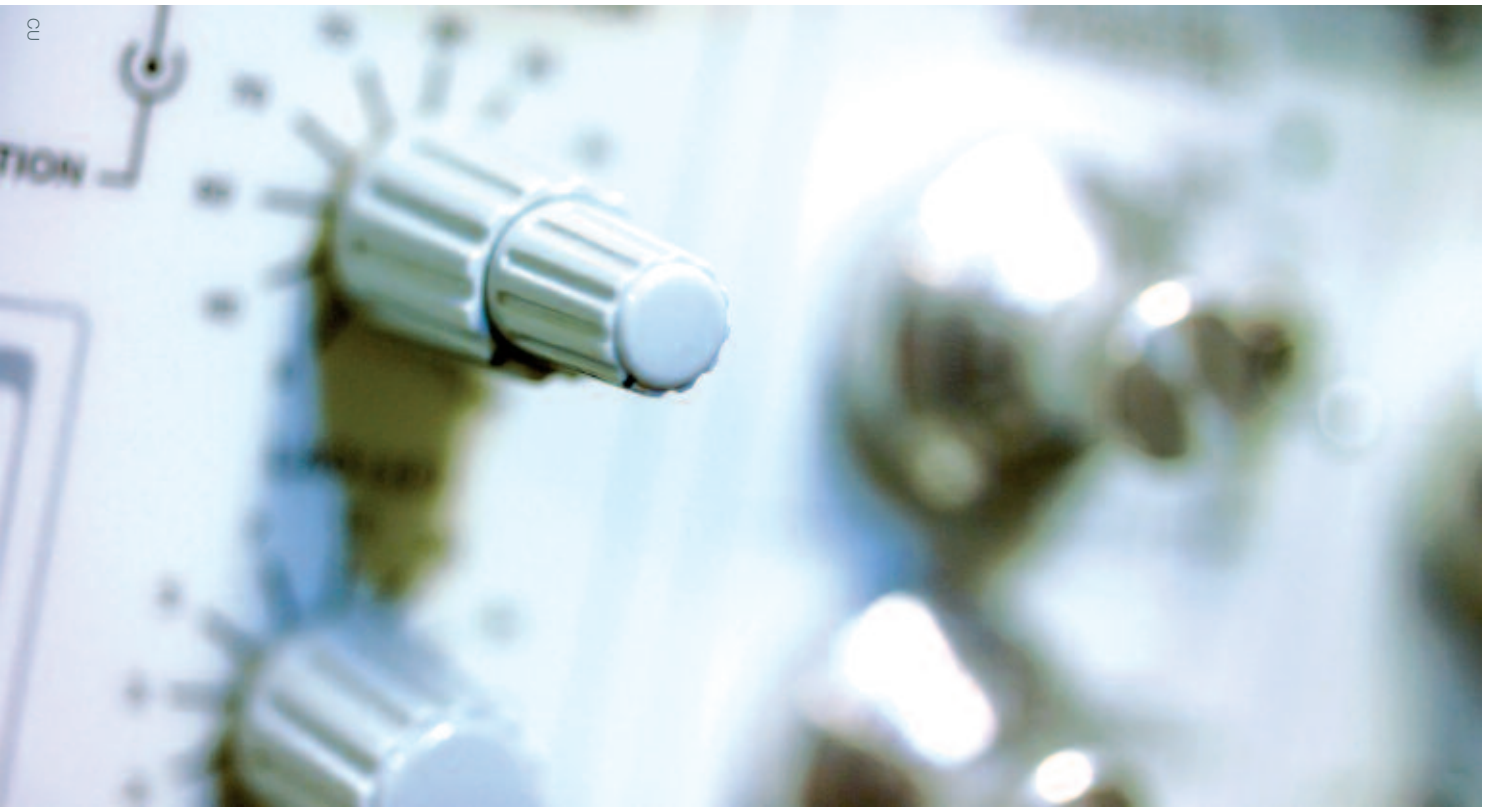
collaborations across campus amongst biologists and physical scientists, and our involvement in these collaborations has succeeded in solving interesting "impossible problems."

Our first such problem was brought to us by a new chemistry professor, Elliot Elson, around 1969, leading to our collaborative invention of a new concept in chemical physics called fluorescence correlation spectroscopy, which still provides new information about the dynamics of the molecular processes that control living cells and their interactions with their environment. One of the issues we encountered was how molecules move, aggregate, and react on the surface of the cell. So we developed several new techniques to find out, and we continue to study these problems. Although we learned a lot, many challenges remain in the physics of molecular cell biology—so many on cell membranes that I decided to return to this problem a few years ago, and since then we have discovered some unexpected physical phenomena in cell membranes.

We discovered early on that fluorescence is an ideal marker for observing the mobility of molecules in cells and measuring molecular signaling in cells and tissues. Just one or two molecules can stimulate some biological behaviors of a cell, and we needed to see how. Studying these sparse molecules using the sensitivity of fluorescence has been a theme in much of our subsequent research.

About 20 years after discovering the exciting challenges of biophysics—we had continued to search for ways to "see" what takes place inside living cells—Winfried Denk, then a graduate student and postdoc, and I invented multiphoton microscopy, a powerful technology which is now widely used worldwide. This technology has allowed us to image fluorescent markers deep in tissue. This was the result of research for methods to solve a problem—what's going on deep in living tissue, not just at the surface. Now we are finding that the intrinsic fluorescence of the tissue itself, which can be locally excited and imaged by multiphoton microscopy, is a powerful tool for research and for medical diagnostics.

We use multiphoton microscopy to image the cancer cells deep in tissue. No extra fluorescent stain is needed in the specimen—you and I fluoresce, and animals and plants fluoresce



characteristically. Thus, this intrinsic biological fluorescence provides a sensitive indicator of biological processes and structures. My colleagues Rebecca Williams and Warren Zipfel, Applied and Engineering Physics, are using multiphoton microscopy in collaboration with Alexander Nikitin, Biomedical Sciences, for cancer research. They look at the onset of cancer in living tissues and diseased transgenic animals in order to recognize the beginning of cancer. We've been using it in many important studies directed toward medical applications in collaborations with physicians at Weill Cornell Medical College.

## The Great Challenges

Several areas of biophysics are offering great challenges in our collaborative research using multiphoton microscopy and other nonlinear microscopies. The most common structure in our bodies or in any animal's is collagen. It comprises the tendons and lubricating layers in our knees and elbows, which hurt when the collagen is not working right. We can image collagen. There are a variety of different structures in collagen, some good and some unsatisfactory. Williams has developed nonlinear microscopy methods that enable us to distinguish them. Now we aim to design tools that orthopedic surgeons can use to identify the collagen problems present in their patients.

Another challenge is applying our cancer, collagen, and cellular recognition imaging with multiphoton microscopy and nonlinear microscopies deep into tissue for application to disease sites that are under medical treatment, or should be. Taking tissue biopsies has been the main alternative, where samples of the diseased tissues are cut out and sent to a pathologist who fixes them in formaldehyde, stains them, and looks at them in a process that takes several days to a week. Alternatively, we can immediately image a piece of the same samples with multiphoton microscopy. This approach has allowed us to test applications of multiphoton microscopy in various kinds of cancer in collaborations at Weill Cornell Medical College.

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We have three collaborations at Weill Cornell Medical College to do just that. There are two areas. One is cancer surgery: assisting surgery in removing cancers without doing too much other damage. The other area is to try to understand and diagnose some of the molecular processes in neurodegenerative diseases, like Parkinson's disease, Alzheimer's disease, and frontotemporal dementia, using techniques we have developed over several years in other collaborations.

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The technique of multiphoton fluorescent microscopy has proven to be very successful, with at least 200 scientific publications now using it. One of its big advantages is that it can image with three-dimensional resolution deep into tissue. Now we're exploring ways of going much deeper, into endoscopic applications. This challenge involves solving numerous "impossible problems" of engineering physics. This is a crucial step to adapting the instrumentation technology for effective medical use. We have been strongly motivated to approach this "impossible problem" by three surgeons at Weill Cornell Medical College—Douglas S. Scherr, Ash Tewari, and Marcus Loo—and by local orthopedic surgeon Russell R. Zelko, who learned of our ability to image collagen types while repairing collagen damage in my wife and me.

## Teaching +

Our interdisciplinary discussions and collaborations have been and are absolutely essential to the discoveries that have made it possible to solve our important "impossible problems" in biophysics and physiology. My interactions with our great students, postdocs, and collaborators have been and are the most satisfying activities of my career. The ubiquitous successes of our alumni are rewarding to me, too.

The essence of my teaching is helping graduate students, now research students and postdoctoral students, find their ways into appropriate interdisciplinary pathways, so that they can focus their activity toward productive and satisfying careers that suit their special talents. How do we start students in research? I offer a selection of a few problems to think about, from which they choose a problem area in which to begin. I urge them to explore our entire lab and learn what others are doing. This exploration broadens their knowledge of our capabilities and challenges and often leads them to select or invent interesting approaches to problems that they choose or create. Many will study several different problems leading to broad research experiences. It's been my honor and my privilege to work with a highly creative, intelligent, and interactive group of graduate students, postdocs, and collaborators throughout my career.

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## Early Highlights of a Multifaceted Career

Back in my industrial engineering days, I was engineering manager of an automated welding development lab, where I learned to solve a variety of engineering problems. However, I realized I needed to know more physical science. As an undergraduate at MIT, I didn't study very hard. I sailed all over the country on MIT's championship racing team and led target shooting competition, winning more national championships. I had devoted my time to competitive sports and many other extracurricular activities, which did provide experience in team leadership, and I had majored in business and engineering administration. Now here I was, faced with a physical problem about which I knew nothing. The problem was to measure the plasma temperature of high-current electric arcs consisting of an ionized gas, very much like a star. Knowing nothing about measuring plasma temperatures, I searched an astrophysics book to learn the methods of measuring stellar temperatures, and this worked for me: our plasma temperatures were about 5,500° C, about like the sun. This experience led me back to MIT for graduate school.

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Night school success had convinced me that I could actually study; so graduate school went very well, and I received my Sc.D. in less than three years with virtually perfect grades. When I finished, I annoyed my professors by deciding to return to industry, to a fundamental research group in materials science, where I discovered how to make perfect filamentary crystals with theoretical strengths matching those now touted for nanotubes. However, 50 years before, we made not just carbon, but also iron, nickel, copper, palladium, chromium, and the hard crystals—silicon carbide and sapphire—of spectacular theoretical strength.

We also discovered, much to our surprise, that some of the microcrystalline phases inside ordinary structural alloys often had theoretical strength. Theoretical strength 50 years ago was a big event that was soon forgotten, in spite of the new understanding that we had created. Why? The material did not prove to be economically useful at the time. It was only useful knowledge that led eventually to other stronger materials. The oriented structures in the turbine blades of jet engines and the now ubiquitous carbon fiber reinforcements are evident consequences.

I abandoned the senior R&D administration responsibility to which I was promoted at my industrial lab and chose to come to Cornell, because it seemed way above other universities in accommodating flexibility and interdisciplinary interaction, both in research and teaching. I began working on critical phenomena: the fluctuations in continuous phase transitions. I can describe it this way. At a certain temperature and certain composition or pressure called the critical point, the transformation from one phase to the other is continuous; the interfaces between the two phases expand, and fluctuations dominate. We watched the interphase interface become very thick and diffuse and discovered that they display fluctuation dynamics as two-dimensional phonons. Since the two phases are almost identical, the system is indifferent about which phase it's in, and it fluctuates easily. The interface diffusiveness expected for nearly 100 years had never been observed, but we found it and measured it.

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(l. to r.) Front: graduate student Valerie Anderson, researcher Rebecca Williams, Watt Webb, postdoctoral researcher A. E. Liz Rhoades, postdoctoral researcher Huizhong Xu. Back: reseacher Karl Kasischke, professor Warren Zipfel, graduate student Dan Dombeck, visiting scientist Leonardo Sacconi, graduate student Jie Yao, graduate student Jesse McMullen, graduate student Keith McDonald.

In the 1960s, when I came to Cornell, Benjamin Widom, Chemistry and Chemical Biology, was developing the correct theory for this interface phenomenon, and we confirmed his theory in these first measurements ever. That was exciting! The only problem with this research area was that after Kenneth Wilson, formerly Cornell Physics, developed renormalization group theory, which provided a sound basis for the fluctuation theories, all of the theorists switched areas, so we did too.

Another exciting project arose in our concurrent research on superconductivity. The reason—here's an example of a carryover from another field—is interesting. At Union Carbide, I had initiated research on the so-called refractory metals, including titanium, niobium, tantalum, and tungsten, which melt at high temperatures. (I had already encountered them in my doctoral research.) These metals were then being used to make superconducting wire for very high magnetic field magnets. With undergraduate Mac Beasley, now a professor and formerly dean of Science and Humanities at Stanford, we designed and built a magnet that cooled down to liquid helium temperature and made enormous and stable magnetic fields, a factor of two better than before.

Our first experiment was to check the wire we had designed. We needed to know how strong it was. At that time, I had an empty lab with a few wooden tables on the top floor of shaky Rockefeller Hall. We tied one end of the wire to the steam pipe at the ceiling and the other end to a bucket above the floor and measured the stretching of the wire, as we poured water in the bucket. We had designed the right stuff! Sure enough, when we built that magnet [1960s], it was the first stable superconducting magnet. This stability was provided by an extra-thick copper coating on the wire that could shunt the supercurrent past defects, preventing the superconductor from suddenly heating up. This capability eventually enabled MRI, NMR, and modern high magnetic field techniques used today.

## Greatest Aspiration Now

To make possible effective utilization of our nonlinear microscopic technologies in clinical medicine would give me great satisfaction. It would be a direct return to society for the support provided for our extended research. This effort is under way in collaborations at Weill Cornell Medical College and elsewhere.

## A Word on Research Funding

The most valuable discoveries are frequently not funded because the proposals appear too risky to the review committees. Consequently, discoveries like ours—multiphoton microscopy, fluorescence correlation spectroscopy, and many of our successful applications—were not funded directly. Instead, they were bootlegged on other science grants. Proposals for many such innovations are rejected

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because they are too far ahead of the acceptable research pathways whose likelihood of success is expected to be high. But scientific innovation is a non-risk, no return game!

## Banking or What?

My family was in the banking business as they had been for a couple of generations. My father wanted me to inherit the bank management from him, so I was required to work in the bank throughout high school—weekends and summers—therefore I knew a lot about business and passed most of my MIT business courses by advanced standing exam.

However, at MIT I thought I wanted to be a naval architect because I liked sailing. But after seeing the stacks of blueprints of ship designs, I quickly switched my interests to materials science and the philosophy of science, using time saved from the business courses. My undergraduate research thesis was a combination of metallurgy and business administration. The assignment was to redesign a foundry that made piston rings for steam locomotives—interesting but not exactly a view into the future. Later, while in industry in Niagara Falls, New York, I led Great Books Foundation courses. This was exciting, but also embarrassing, because three or four of my bosses came to my classes for the whole three-year sequence.

## Remembering My Very First Job

Because I had lung problems when I was a young child, I lived in the Southwest from about age four through eleven. My favorite was Tyrone, New Mexico, on the continental divide and absolutely beautiful because the shaft copper mines stained the creeks a beautiful blue-green. My first job was as a horse wrangler at ten years of age, before I had even been able to begin school. It was a delightful job. When the horses saw me coming, they would always follow me around, since they knew I was usually leading them to get fed. That was fun!

## On the Personal Side

My wife Page and I like to see the world, and we seem to travel almost anywhere to see an interesting art exhibition. We also love to sail. We sailed together the first time we met and have won many races together here, along the coast, and in the open sea. For years we raced our sailboats on Cayuga Lake, but local interest has faded away, and sailboats now rarely leave their piers. Most recently, we have cruised and raced on the Atlantic Ocean in our Swan 44, a great racing yacht that the two of us could previously handle anywhere by ourselves—even in two hurricanes. But now we aim to return to sailing a small boat on Cayuga Lake.

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We have three sons and one grandson. Our oldest son turned 50 last year, and he is an investment advisor. The other two—twins—are a couple of years younger. One is a professor of geophysics at Columbia, with research in physical oceanography. He watches the Earth and the ocean move. The other, a physicist with a degree from Cornell, is a research engineer solving impossible problems at IBM in Yorktown Heights, New York.

## What's Next?

I am 78, but my lab is as active as ever. How do I keep research going in order to achieve our stimulating current objectives? This is my concern now. I'd want to see progress continue in introducing multiphoton microscopy into clinical medicine and medical endoscopy. We are also making some surprising discoveries and developing new approaches to the molecular mechanisms underlying certain neurodegenerative diseases. I want to continue to explore basic ideas. One important challenge arises in our discovery that continuous phase transitions occur in the lipid membranes similar to our cell membranes and probably in real cell membranes. We hope to develop full understanding of that phenomenon and its association with many biologists' internally inconsistent concept called lipid rafts.

## Three Favorite Quotations

*Tentanda via est*: To experiment is the true way.
Virgil, *Georgica*

Science is built up of facts, as a house is with stones.
But a collection of facts is no more a science
than a heap of stones is a house.
Henri Poincaré

There is a hierarchy of facts. Some are without any positive bearing and teach us nothing but themselves … There are, on the other hand, facts that give a large return, each of which teaches us a new law.
Henri Poincaré

**On Being a Pioneer**
**It would have been sad not to be one in my career.**

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**For more information:**

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