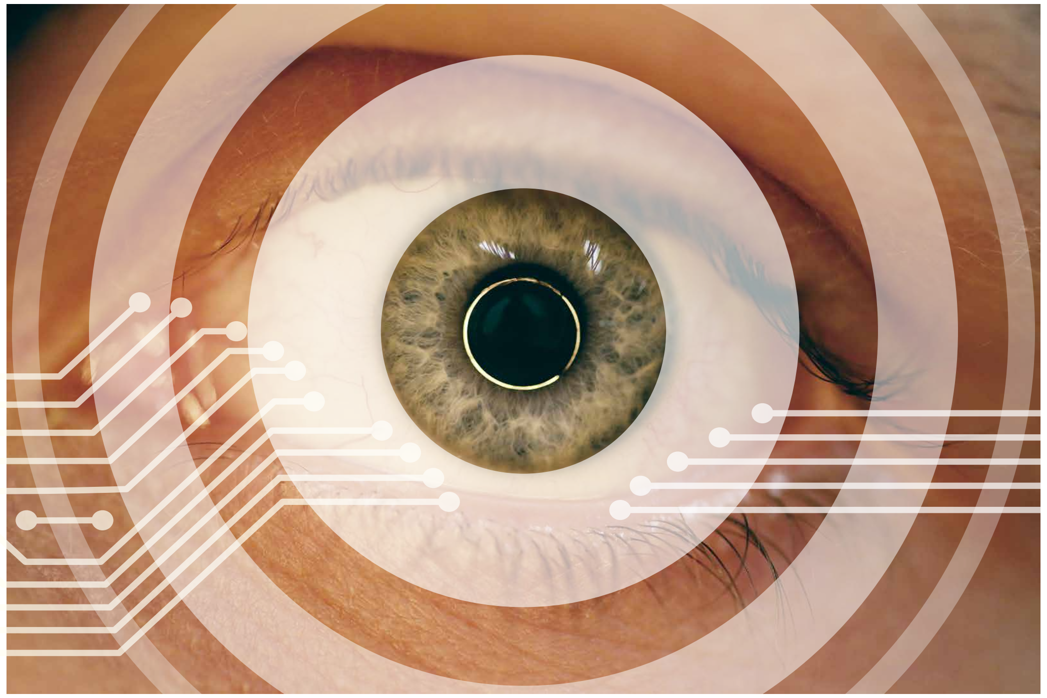


New Sight for Sore Eyes

A formidable team of Caltech and University of Southern California (USC) investigators has geared up to understand, protect, and repair a critical living system outside the usual gamut of engineering research. Their investigatory target is a complex, delicate structure consisting of a membrane enclosing a ball of liquid in which precisely shaped gelatinous bodies are arranged to control and respond actively to light, a system designed to turn the incoming light into data for neural information processing—a system known as the human eye.

Eyes, fragile but crucial for human and almost all other animal life, pose difficult challenges, both for basic research and for effective solutions to the medical problems that such research investigates. Caltech professors Yu-Chong Tai and Hyuck Choo work with students and postdocs along with distinguished USC faculty and medical professionals on a range of these challenges, using multidisciplinary approaches spanning nanotechnology, electrical engineering, biomedical engineering, physics, optics, photonics, and optomechanical engineering.

Meeting these challenges offers the potential for significant human rewards. While the most widely feared disease is cancer, as Tai notes, next on the list is blindness. And there, he says, the medical bar is high: "People usually don't make enough effort to maintain their eyes until it's too late. On the other hand, for the blind, having their vision even partially restored would represent a major advance."

New tools are changing the game—tools that have the potential to diagnose eye conditions, to restore vision to the blind, and to make state-of-the-art medical eye-examination technology available much more widely around the world, even in places with limited health systems. The Caltech and USC teams hope to deliver revolutionary new systems that may soon enable patients in remote areas around the world to be examined rapidly, without having to have their eyes chemically dilated and then be immobilized for many hours in clinics. If these new systems succeed, many more patients will receive full eye exams instead of brief looks.

For example, the measurement of pressure within and around the eye's liquid center illustrates one of the unique Caltech and USC medical engineering approaches. Intraocular pressure has long been recognized as a critical diagnostic parameter for ophthalmology. Higher pressure is a symptom and warning of glaucoma, a common cause of blindness and other pathologies.

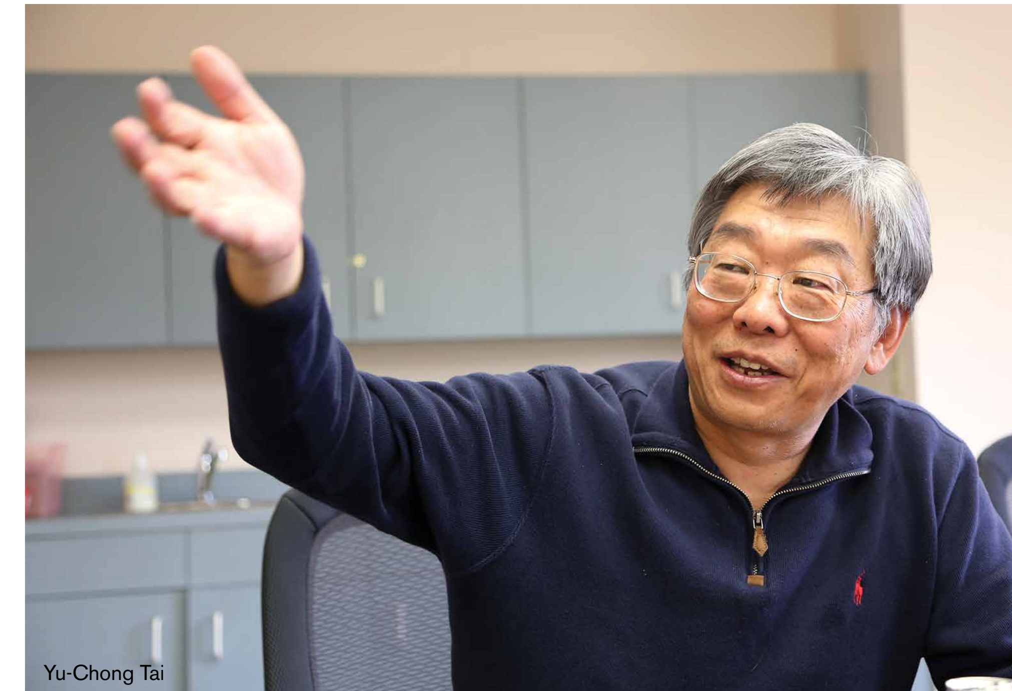
But pressure measurements and diagnoses have been almost exclusively done in medical offices several times a year and sometimes late in the game, long after pressure buildup has started. Thus either the pressure may not be at dangerous levels the day of the exam or treatment, or abnormally high pressure will have gone undiagnosed before extensive, irreparable damage has been done.

Doctors have discovered—by exhaustive (and exhausting) marathon tests—that ocular pressure varies a great deal over time, going from normal to high and back again. These changes may be associated with the progression of disease. This has led, as ophthalmologists have long noted, to late or incomplete diagnoses—less than half of the patients who have glaucoma are diagnosed early enough for optimal treatment.

Modern medical technology now allows blood pressure, blood sugar, and many other medical variables to be monitored virtually continuously by portable devices, including modern smartphone apps. Work using very different approaches and on separate paths by Professors Tai and Choo at Caltech is leading to similar modernizations in the realm of eye measurements.

Tai has been working on the problem the longest, consulting for more than a decade with a neighbor who happens to be a prominent ophthalmologist and biomedical engineer—Mark Humayun, an MD and PhD who is director of the USC Institute for Biomedical Therapeutics and co-director of the USC Roski Eye Institute.

"We have elected," says Humayun, "to collaborate with engineers at Caltech because they have some specific knowledge that we need and we think it very important for the medical application—and, well, because they're just nice people."



Yu-Chong Tai

Hyuck Choo

Eye-implantable microelectromechanical systems (MEMS) are potential ophthalmological game changers in many ways, says Humayun. "The eye is a great spot for MEMS because it's small, and so it's constrained by size, and the tissue is very delicate and also often transparent. So all those things make it a specific challenge that MEMS is able to address."

Tai and Humayun have been developing a new pressure sensor to make the monitoring process easier. Nine years ago, they reported the first prototype of an "implantable micromechanical parylene-based pressure sensor for unpowered intraocular pressure sensing"—that is, a fitted and flexible plastic device that can be implanted within the eye and activated externally to report pressure.

PROGRESS REPORT

Armand R. Tanguay (left) and Mark Humayun

This device has been continually improved for use in high-risk patients.

Pressure monitoring remains critical. Choo is collaborating with University of San Francisco (UCSF) colleague David W. Sretavan on perfecting an optomechanical system designed to report intraocular pressure continuously for hours at a time. "Other than the time that the patient is asleep, we can monitor the pressure pretty much around the clock, during all activities," whenever the eye is open, he says.

The research involves studies that, Choo explains, "followed a [glaucoma] patient's pressure for a week or two, 24 hours a day, to see how the pressure changes. The study found that the patient's pressure actually changed over the course of a day. Furthermore, there's a particular time of the day that the pressure spiked. Clinicians believe that this pressure spike is what causes the damage to the optic nerve."

Glaucoma research is also aimed at discovering exactly what causes the spikes and investigating possible cures for the disease. Intensive work is already being done on rabbit eyes, says Choo. "It involves a sensor that has a wireless electronic or optical automatic readout capability to understand the relationship between the pressure and optic nerve damage as well as other immune responses that occur in the eye. To put all of this into a single package is a very efficient approach. It really speeds up the progress."

On the horizon is an implantable device that not only measures intraocular pressure but also responds to it. "If we can develop a device that controls the pressure by draining a little bit of fluid, it would be really revolutionary!" Humayun says.

For human medical care, facilitating internal ocular monitoring of other variables can change the game in a number of other ways. For example, a new surgical procedure can repair retinal tears and restore vision in a damaged eye by using a bubble within the eyeball to hold together the pieces of a retinal tear. However, it can only do so if the patient maintains a specific head position for more than 12 hours so that the bubbles will be properly positioned against the retinal tear and will push against the wall. At present, this can only be done with a patient immobilized face down in a hospital.

However, new electronic equipment developed by Choo and Professor Robert Grubbs is opening up a new possibility: an external device that actually tracks the position of the bubble inside the eye. The new system consists of a headband that is wirelessly connected to an iPhone. It actually tells the patient whether his or her head is properly positioned. If it's even slightly out of position, the system warns post-op care workers right away. Choo reports that a prototype is due for trial in summer 2016. It will be tested by UCSF collaborators Dan Schwartz and Frank Brodie.

These and other new and emerging technologies will not only change medicine in state-of-the art hospitals but may also change it in third-world settings. This is one of the attractions for the members of the Caltech and USC medical engineering team, which also includes Armand R. Tanguay of the USC Viterbi School of Engineering.

For example, Professors Humayun and Tanguay at USC, in collaboration with Professor Choo at Caltech, are harnessing ultra low light level imaging technologies to develop both improved surgical microscopes and ophthalmological imaging devices. "We're always trying to figure out different ways to measure and image the eye," says Humayun. "Our current cameras and imaging equipment are very sophisticated, but if you're in a rural area of China, India, or Africa, it is currently very difficult to bring these instruments into the field to perform screening and testing. Therefore, we've been thinking about an easy-to-use technology that one could take to the Serengeti, a device that anyone can use to upload images to the doctors in a clinic hundreds of miles away. We're really working at the edges of medicine, physics, and engineering to be able to do this."

Tanguay takes up the thread. He explains: "I don't know if you've ever had your eyes dilated, but it's a long process. Chemicals are used to expand the iris. There's a long waiting period before the ophthalmologist can actually do the examination. People are also very sensitive to light for a long time afterwards. But everyone's eyes naturally dilate rapidly at night, or in the dark," which provided an opening for the new technology.

Tanguay continues, "Because image sensor arrays are far more sensitive now than they were 20 years ago, we thought that we might be able to use ultra low light level imaging of the retina to allow a full ophthalmological examination in a darkened office without any chemistry at all. So then you could have very rapid examinations of many subjects with maybe even a handheld device or a small ophthalmoscope that would be inexpensive and hence far more accessible. This new idea got us at Caltech and USC really excited. We patented the concept at USC a few years ago, and we've been continually working on developing it further."

The eye pressure sensor is only one example of Humayun's work with Tai. In collaboration with Tanguay, the multi-university research team is also working toward developing an intraocular retinal prosthesis that is capable of restoring partial sight to the blind.

Humayun notes that, with Tai, "we've worked on a retinal implant technology that is very novel, very different than what currently exists. It potentially allows the manufacturing to be simpler, and therefore the cost of the eventual product to be lower. It also allows the implant to be smaller but with more resolution, and therefore to potentially provide better vision." Tanguay and Humayun have collaborated for a number of years on visual psychophysics experiments to better understand the natural coupling between head and eye movements, and they are developing an ultraminiature camera to implant directly into the eye in order to restore this natural coupling and replace an external camera that is typically mounted on a pair of glasses. Taken together, these advances could provide a retinal prosthesis that is so well integrated that the entire apparatus can be implanted directly into the eye.

Other members of the collaboration also have innovations approaching the market. Robert Grubbs, Caltech's Victor and Elizabeth Atkins Professor of Chemistry, is part of a team developing the targeted microbubbles that are used in retinal replacement for application in other body areas. Azita Emami, Professor of Electrical Engineering, is developing ocular microimplant technology for units that can remain in the eye for 10 years or even longer. Morteza Gharib, Hans W. Liepmann Professor of Aeronautics and Bioinspired Engineering, has patented a design for carbon nanotube microneedles for drug administration.

Graduate students are also picking up the threads and the unique perspective offered by the collaboration. "Our program relies on very deep engineering," says Tai. "Our students are recruited from engineering backgrounds, but for their graduate research, they need to solve medical problems. This is very different, because we believe that in order to solve a real-world medical problem, you need to have a really deep understanding of engineering."

But academic silos can interfere with the process—and both Caltech and USC are consciously avoiding the trap. "There's no lack of students who want to work on medically related projects, especially no lack of engineering students. But many engineering students don't have the opportunity to acquire the range of medical skills needed for research in this field," says Tai.

The students admitted to the Caltech medical engineering program have the opportunity to build on their engineering strengths and learn in a uniquely multidisciplinary environment that rewards original thinking and innovation. USC has implemented a novel Health, Technology, and Engineering (HTE) program that integrates engineering and medical students in a highly interactive curriculum and research environment that even includes hospital rounds.

The results may someday save the sight of you or someone you know.

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