A new terahertz medical imaging tool could provide early detection of corneal disease

Recent research in medical imaging found that tools based on terahertz (THz) frequency illumination could help map the distribution and movement of water near the surface of body tissues. ***Dr Warren Grundfest*** *and* ***Dr Zachary Taylor****, at The UCLA Henry Samueli School of Engineering and Applied Sciences, are developing a new imaging tool for non-contact high-resolution measurements of corneal hydration. This could be a promising method to accurately detect and study cornea-related diseases and pathologies, such as Fuchs' endothelial dystrophy, intraocular lens implantation complications and corneal graft rejection.*

Terahertz (THz) imaging is an emerging non-destructive scanning and imaging technique used within several settings, ranging from pharmaceutical and biomedical applications, to integrations in tools for security and aerospace industries. Ongoing research in THz for medical imaging has revealed that THz frequency illumination may be ideal for mapping the distribution and movement of water in physiological tissues. This might be particularly useful for quantifying the water content within the corneal tissue which is generally much less heterogenous than other tissue systems in the human body. A group of scientists, engineers and clinicians in California are investigating this possibility, trying to develop an imaging tool that can provide accurate measurements of corneal hydration, to help detect and study corneal disorders.

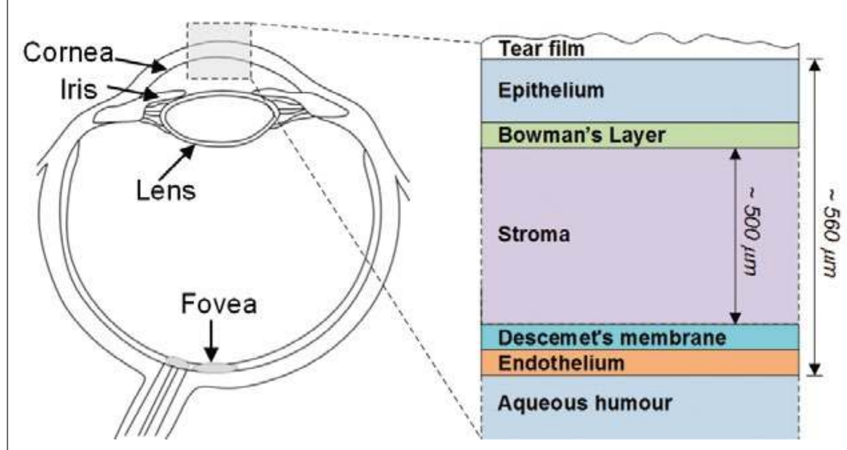
Right: The cornea forms the outer most layer of your eye. It is approximately 79% water by volume. Many diseases can perturb the endothelium which leads to changes in stromal water content. These changes are hard to detect in the early stages.

IMAGING CORNEAL DISORDERS

Corneal disorders, such as Fuchs' endothelial dystrophy, affect a considerable number of people worldwide – particularly within the elderly population. They often result in chronic vision impairment and commonly those affected require surgical intervention. One of the key physiological problems behind these disorders is believed to be an increase in hydration of the corneal tissue, referred to as Corneal Tissue Water Content (CTWC). In fact, many corneal disorders are characterised by an abnormally high CTWC, which causes a swelling of the cornea and subsequent blurring of vision. This makes CTWC an important diagnostic target for doctors and physicians looking to diagnose corneal disorders: not only does it allow the disease to be observed, but it also indicates potential tissue damage. Until now there have been no efficient non-invasive ways of accurately and directly measuring CTWC in situ. New research conducted by the Californian researchers aims to change this.

Dr Taylor and Dr Grundfest are two of these researchers working to develop a non-invasive imaging tool based on THz frequency illumination, which could help measure the hydration levels of the cornea's tissue. Current methods of measuring CTWC are based on ultrasonic or optical thickness measurements, which can be measured very accurately. However, mapping the cornea's hydration using these thickness measurements can be extremely inaccurate. Dr Taylor and Dr Grundfest's newly-developed imaging system would allow scientists and clinicians to acquire spatio-temporal variation maps of CTWC from patients. The method is a direct measurement of water content and therefore avoids the inaccurate and non-specific thickness to water content mappings used by current techniques.

THz medical imaging might be particularly suitable to measure water content in the cornea because its tissue



Corneal Morphology
- 400 µm – 700 µm thick
- ~ 79% water by volume/weight
- Provides the majority of the focusing power of the eye
- Refractive power and optical scattering strongly linked to water content

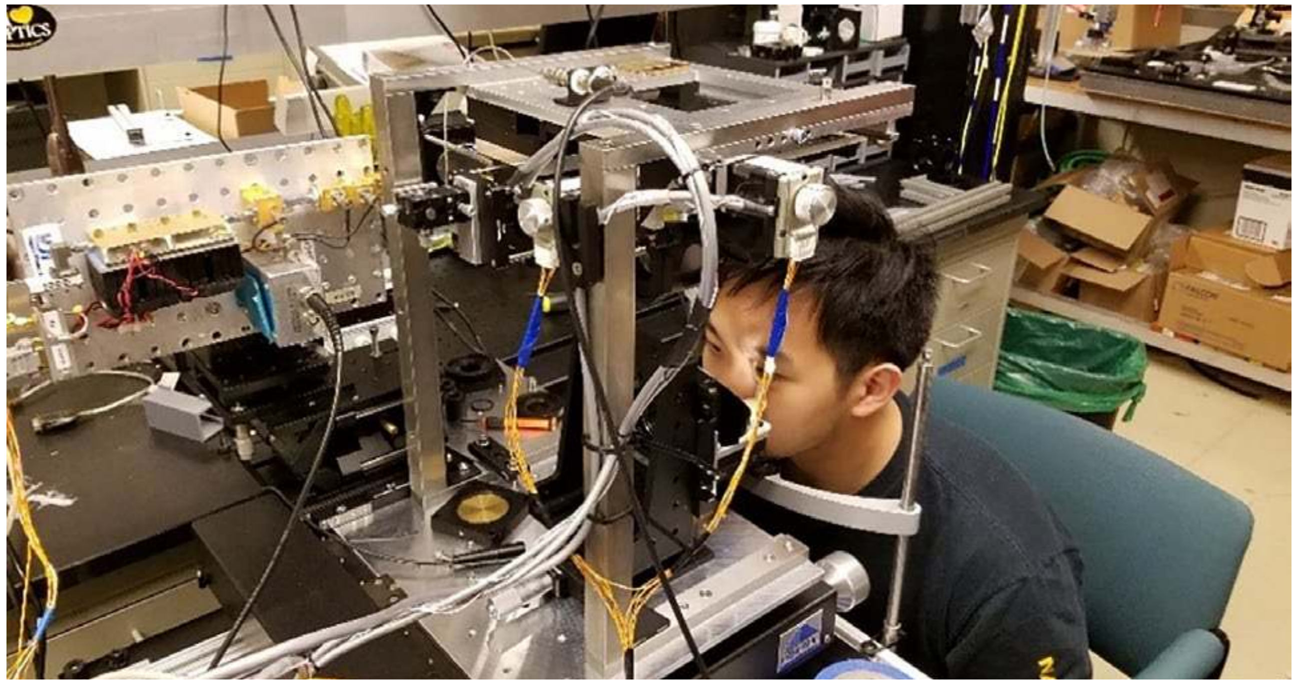
structure and geometry is generally much less varied than any other tissue in the body (e.g., in the lungs, liver, etc). Furthermore, this variation is typically less than the wavelength of the target THz illumination enabling researchers to treat the cornea as a perfectly spherical, hydrated film sitting on top of a body of water (aqueous humour).

INITIAL TESTING

Before they began developing their imaging tool, Dr Taylor and Dr Grundfest studied the cornea and its electromagnetic properties extensively. From this, they proposed the first ever CTWC gradient models, as well as devised ways to identify CTWC from variations in THz reflectivity. The team initially tested their new imaging tool on the corneas of live rabbits. They attempted to measure their CTWC using a custom-built THz imaging system and millimetre-wave reflectometer and explored correlations between the imaging data and central corneal thickness (CCT) measurements.

Corneal disorders affect a considerable number of people worldwide, and can often result in chronic vision impairment – commonly requiring surgical intervention

Initial results were very promising but revealed unanticipated electromagnetic properties. Data from the millimetre wave measurements correlated well with CCT, while the THz and CCT measurements demonstrated no correlation. From their findings, the procedure appeared to alter the thickness of the cornea but not the CTWC. This perturbation in thickness, combined with the constant corneal water content, created a standing wave resolvable with the millimetre wave system and unresolvable with the THz system. This is the first experimental validation of a long-held belief that trends in CCT are not necessarily associated with changes in CTWC. Two key concepts were extracted from this initial work. Firstly, the cornea is an optical thin film at THz frequencies. Secondly, successful clinical translation of the technology will require non-contact measurements; a mode of operation generally not possible at THz frequencies.



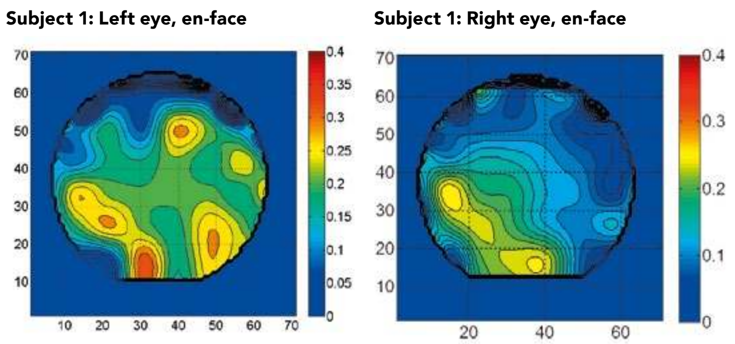
Above: Postdoctoral researcher Shijun Sung scanning his cornea with a prototype THz imaging system. The system scans the imaging beam while the patient's head stays fixed using standard ophthalmic chin and forehead rests.

TRIAL AND ERROR: FURTHER TESTING

To address the challenges identified in the first stage of work, Dr Taylor teamed up with researchers from TU Delft in the Netherlands, Chalmers University in Gothenburg, Sweden and VTT in Helsinki, Finland. A new optical system was designed, constructed and tested in partnership with colleagues specialising in physical optics. Pilot testing of the system was completed on a group of volunteers, which informed modification in preparation for upcoming pilot clinical trials. This work has produced what is believed to be the first non-contact THz image of a live human's cornea ever to be published.

A PROMISING TECHNOLOGY

Through their initial studies, Dr Taylor and Dr Grundfest collected a number of observations that will be useful for the research community and their development of THz frequency, ophthalmologic imaging tools. Their research has been met with a huge degree of excitement by the scientific community, with two of their research studies receiving the 2015 Terahertz Best Paper Award, in May last year.



Reflectivity at 650GHz
- Image acquisition time: ~20 seconds
- Imaging subject stays completely stationary
- Optics modification was crucial to imaging feasibility success

Above: En face, non-contact, THz reflectivity maps of cornea from a volunteer subject. More reflectivity equates to higher water content.

Dr Taylor and Dr Grundfest's imaging tool could make a real difference to the way corneal disorders are diagnosed and studied

If perfected in a way that allows for accurate imaging and measurements of CTWC, Dr Taylor and Dr Grundfest's imaging tool could make a real difference to the way corneal disorders are diagnosed and studied. The aim is to provide a non-invasive and accurate way of measuring hydration of the corneal tissue – something that is not yet possible. Not only does this research offer a more efficient way of diagnosing corneal disorders, but also of exploring the relation between specific disorders and the tissue's CTWC.

Behind the Bench

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Research Objectives
Dr Taylor and Dr Grundfest's research focuses on developing a new imaging tool for non-contact, high resolution measurements of corneal hydration. Their collaboration since 2011 at The UCLA Henry Samueli School of Engineering and Applied Sciences has led to many publications and the Terahertz Best Paper Award in 2015.

Funding
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Collaborators
Sophie Deng, MD, PhD, Professor of Ophthalmology, Jules Stein Eye Institute, University of California at Los Angeles.

Bio
Dr Grundfest received his BA from Swarthmore College in 1974, before completing his MD at Columbia University in 1980. He completed his Surgery Residency at the Cedars-Sinai Medical Center, and is currently a Professor at UCLA in the Departments of Bioengineering, Electrical Engineering and Surgery.

Dr Taylor received his BS in electrical engineering from UCLA in 2004. He later went on to study the same discipline at the MS and PhD level at UCSB. He currently works as an Adjunct Assistant Professor at UCLA in the Departments of Bioengineering, Electrical Engineering, and Surgery.

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Q&A

When and how did you first start developing the THz-based imaging tool to measure corneal hydration?
This imaging programme grew out of initial work on burn wound severity assessments using THz imaging. Burn wounds are characterised by rapid accumulation and resorption of oedema (excess tissue water). One of the key challenges with burn wound imaging is accounting for/overcoming physiological variation, and we are always on the lookout for more predictable tissue systems. By chance, an ophthalmology colleague mentioned difficulties in obtaining accurate measurements of corneal hydration. A cursory review of corneal properties revealed extremely limited physiological variation and limited tissue heterogeneity on the relevant length scales. Our excitement was further increased by the inadequacy of optics based systems. We started with imaging excised bovine cornea which led eventually to NIH funding.

What do you feel have been your most promising findings so far?
Our most promising finding is that the cornea is a lossy thin film at THz frequencies. This means that corneal tissue may exhibit specific, narrow band properties as a function of morphology and reflectivity measurements; combined with thickness maps this will enable accurate maps of absolute water content. Optical thin film metrology is a mature field and we are currently adapting these techniques to the measurement of tissue water content.

Who do you believe could benefit the most from future applications of the tool developed through your research, and why?
We believe that ophthalmologists will benefit the most, initially. Numerous corneal diseases associated with abnormally raised CTWC are detected through visual assessment where the water content is sufficiently high to make the cornea appear cloudy. THz imaging may enable detection of these pathologies long before they become visually detectable thus enabling earlier intervention and improved patient outcomes.

How long do you think it might take for your tool to enter healthcare settings and what remains to be done until then?
We are confident that our THz imaging technology can assess corneal water content in vivo. The major challenge for us will be uncontrollable patient movement. Most of the planned use cases will be in the clinic with patients sitting in a chair, in a fashion similar to what you may have seen at the optometrist. People can't sit perfectly still and the eye exhibits rapid movements, called saccades, that contribute to uncertainty in eye positioning. The timeline for clinical translation rests largely on our ability to overcome uncontrollable corneal movement.

What are your plans for future research and investigation?
We are focused on three major thrusts. The first is extensive optical redesigns to enable rapid scanning. The second is incorporating phase sensitive source detector technology to enable rapid, coherent detection of magnitude and phase. The third is a large pilot human trial to understand the unique constraints associated with operating THz components in the ophthalmology clinic setting. Following successful completion of these engineering and evaluation tasks we plan to conduct a large scale clinical trial on patients undergoing corneal graft surgery. In the long term, we would like to investigate applications in traumatic brain injury and are currently evaluating the physiological mechanisms that link elevated intracranial pressure to raised CTWC.