Advances in Optical Imaging and Biomedical Science Symposium
June 1-2, 2009
NEI 40th Anniversary Event

This symposium was held on June 1-2, 2009 at NIH. The meeting was organized by NEI and jointly supported by NEI and NIBIB as a part of the NEI 40th Anniversary Symposia Series. The meeting brought together many of the world's leading experts in ocular imaging technology to discuss the current state of the art in optical coherence tomography (OCT), adaptive optics (AO), fluorescence imaging, and other technologies particularly important for imaging ocular tissues.

The purpose of this report is to provide suggestions for future directions and needs in optical imaging and represents the consensus of invited speakers (see list below). Although the following recommendations are focused primarily on vision science and ophthalmology, many are relevant to a broad range of issues and biomedical applications.

Summary Outline

Section 1: Challenges for the next generation of ocular imaging devices

The main technical challenges in creating the next generation of supercameras for ophthalmic imaging include, but are not limited to:

- Improving the speed of image acquisition
- Removing the artifacts of eye motion from retinal images
- Developing better and faster software for processing ocular images
- Encouraging software sharing
- Understanding the safety limits of light intensity
- Integrating multiple imaging modalities
- Developing new methods to image function as well as structure

Section 2: Accelerating the translation of advanced technologies from the physical sciences and engineering into biomedical research

- Increase emphasis on multidisciplinary approaches to enhance imaging technology by:
    - Supporting multidisciplinary workshops to provide venues for exchange of ideas of physical and biological scientists, engineers, and clinical researchers.
    - Support formation of multidisciplinary teams to develop and apply imaging technology to biomedical research. Specific incentives and creative solutions are needed to attract physical and computer scientists and engineers to work on biomedical applications that demand imaging solutions.

Section 1. Challenges for the next generation of ocular imaging devices.

Since the invention of the ophthalmoscope in the middle of the nineteenth century, there has never been a period of more rapid technical development in retinal imaging than the last two decades. We now have entirely new ways of imaging the living human eye in which an entire 3-D volume of a region of retina can be acquired at a microscopic spatial scale. We can see retinal structure with unprecedented contrast and resolution and this is transforming the diagnosis and treatment of retinal disease. Nonetheless, the future of ophthalmic imaging faces a number of hurdles to overcome if we are to create a new generation of imaging devices that surpass the remarkable advances of the last 20 years. Below we list the most important hurdles we identified, emphasizing that this list is by no means exhaustive and that there are many other technical needs for which resources should be allocated.

- **The need for speed**. Several talks at the meeting highlighted the remarkable gains in speed achieved in OCT since the first axial scans were made at a single location in the retina to the present situation in which an entire high resolution 3-D volume can be obtained in seconds. The development of spectral domain OCT (SDOCT) alone has increased speed by roughly 2 orders of magnitude and frequency-swept OCT provides additional gains. These increases notwithstanding, image acquisition speed remains a fundamental limitation to the scientific and clinical value of the new imaging technologies. There is no evidence that we are approaching any fundamental, insurmountable limits of speed, which also encourages continued emphasis on this direction.

- **The need for eye motion correction**. One of the reasons that speed is so important in ocular imaging is because the eye is always in motion due to naturally occurring eye movements. This problem can be exacerbated in patient populations that have inferior fixation ability. The shorter the image acquisition time, the less image blur and distortion due to eye motion. A complementary approach to increasing speed is to correct for eye motion. Eye motion correction can be achieved either through active tracking and image stabilization during image acquisition or through clever post-processing to remove eye movement artifacts. Many approaches are promising such as recent success in locking on a single cone photoreceptor in the living monkey eye. However, current commercial devices are inadequate in this regard, and much work remains to identify the most effective methods to correct for eye motion and to engineer robust systems to tackle this formidable problem in clinical settings. We recommend an increased focus on this important problem keeping in mind that there are a number of possible solutions that should be explored.

- **The need for software development.** Given high acquisition speeds, digitization of images, and image processing, a tremendous amount of data is generated. In many laboratories, the time required to process data from each patient is the single largest bottleneck en route to scientific discovery. In translating imaging technologies into clinical diagnostic images, the need for immediate feedback is essential. Given the need for speed mentioned above and the interest in capturing ever widening amounts of retinal real estate in 3D images, this problem will only get worse without the parallel development of automated software analysis. This includes software for eye motion correction, visualization, and feature analysis such as the development of improved segmentation algorithms for identifying specific retinal layers that are disrupted in retinal disease. Software that allows the automated return to the same retinal location repeatedly and reproducibly in the same patient would facilitate longitudinal studies of disease progression and/or the efficacy of therapy. *We recommend that NIH explicitly solicit funding for software development. In addition, we recommend that mechanisms of software sharing be explored: Currently, image processing tools are developed separately by each group, often duplicating work done by other groups and often being sub-optimal given that most imaging groups are not expert at image processing. Sharing image-processing code would be more efficient, more cost effective and would lead to significantly more rapid development of new capabilities. This is a challenging goal in the competitive research environment, but could broadly accelerate the goal of translation.*

- **The need for improved estimates of light safety.** The more light one can put onto the retina, the faster an image can be acquired and the better the quality of the image, but there are very important safety limits for light intensity. Recent evidence suggests that the light safety standards do not adequately protect the eye under some conditions. There may well be other situations, especially in the infrared, where the light safety standards can be relaxed, and this information could be valuable in increasing the quality of the images we can acquire with new technologies. We now have better tools for evaluating retinal phototoxicity than previously when the original standards were established, and with the subsequent development of new imaging technologies, it is important to refine our estimates of safe light levels.

- **The value of integrating imaging technologies in the next generation of supercameras.** Despite the remarkable advances made through the introduction of new imaging technologies such as SDOCT, some of the most successful imaging platforms will combine multiple modalities in a single instrument, such as OCT and AO, OCT and multiphoton microscopy, or AO and fluorescence. For example, OCT can now provide exquisite axial resolution of a few microns while AO can provide comparable transverse resolution**.** The two technologies together provide resolution smaller than most retinal cells in all three spatial dimensions. A host of other exciting approaches were presented at the meeting to increase contrast and

resolution including Doppler imaging, polarization imaging, and fluorescence imaging. These can be combined with other methods to form many different sets of capabilities depending on the scientific need. We anticipate a major integration of camera modalities (e.g., flood illumination, OCT, scanning laser ophthalmoscopy, etc.) and performance enhancing peripherals (adaptive optics; fluorescence; super-resolution techniques; polarization sensitive detection; retina tracker; biomarkers; sophisticated image processing and visualization software).

- **The promise of functional imaging.** There is increasing excitement about combining new functional imaging with structural imaging. For example, we can currently monitor blood flow with Doppler OCT and monitor the response of single photoreceptors to light with interferometric methods that can detect subtle changes in the refractive index inside single cells. For clinical applications, we need to develop non-invasive ways to assess function. These methods include measuring intrinsic scattering changes of retinal cells in response to stimulation, localized sensitivity thresholds (microperimetry), and the combination of electroretinography with high resolution imaging. In the future, it will be routine in the laboratory to use light to monitor the electrical activity of single neurons and the circuits they make in the living eye and brain. In addition, recent studies with channel rhodopsin show that it is possible, not only to monitor neurons optically, but also to control their activity with light. This opens up an exciting new field where specific neurons in a circuit can be targeted and their functional roles revealed through optical manipulation with light concordant with optical monitoring of their neural response. Moreover, great strides are being made in the ability to track the transport of single molecules in living cells with fluorescence microscopy. Molecular biology is generating a broad array of wonderful new tools, often using extrinsic fluorophores that can be married to new high resolution imaging technologies such as adaptive optics for application in the living eye. The meeting highlighted an example of the powerful convergence of molecular biology and advanced imaging technology with a talk that marshaled both to reveal the mechanism for motility in single cells.

Section 2. Accelerating the translation of advanced technologies from the physical sciences and engineering into biology and medical research.

History is replete with examples of advances in imaging in vision science and ophthalmology arising from the physical sciences. For example, Johannes Kepler, an astronomer, proposed the first clear theory of retinal image formation in 1604. Helmholtz, a physicist, invented the ophthalmoscope. Of course, this translation path is not peculiar to optical imaging of the eye; MRI, which has revolutionized medical imaging, evolved from the discovery by physicists of nuclear magnetic resonance in the 1930s. Ophthalmic OCT, introduced in 1991, arose from a revolution in photonics that created, for example, short coherence sources and optical fibers. Adaptive optics for high-resolution retinal imaging

was borrowed from astronomy where it has revolutionized the resolution of ground-based telescopes. There can be little doubt that many future advances will have similar roots in engineering and the physical sciences. As just one example that was discussed at the meeting, new methods to exceed the diffraction limit (e.g. stimulated emission depletion microscopy (STED), photo-activated location microscopy (PALM), structured illumination) are under development, and there is considerable excitement about whether these techniques can be adapted to image structure and function at a subcellular level in ocular tissues.

Multidisciplinary Research Teams

The application of imaging technology in biology and medicine may be among the most cogent examples of the necessity of multidisciplinary approaches. The translation of imaging technology requires effective communication among at least five disciplines: physical scientists, engineers, biologists, clinical researchers, and clinicians. Provincialism and the internal reward structure within each of these groups inevitably lead to inefficient technology transfer. Sometimes the engineer or physical scientist is simply unaware of the biological and medical applications of their work. Similarly, the biological and medical researchers are often unaware of potential technical solutions. Unfortunately, compartmentalizing science means that the vast majority of meetings are organized to bring together people working in the same field. Expanded emphasis on small meetings and workshops that bring together the aforementioned expertise is essential.

Cultural differences between these five groups also slow translation. The different criteria that engineers and scientists use to evaluate the merits of an idea are well appreciated, and the gulf between scientists or engineers, on one hand, and clinicians, on the other, may well be even larger. These differences sometimes appear in the evaluation of grant proposals that involve imaging technology. For example, NIH study sections populated by scientists sometimes place a priority on hypothesis-driven research that impedes the engineering of new technologies that could profoundly accelerate their own research. The complementary problem also exists: study sections populated by engineers sometimes emphasize engineering milestones and performance specifications with less attention to the scientific importance or medical relevance. Since the 1990's, the NIH has addressed this gulf in numerous ways such as creation of the Bioengineering Consortium (BECON) that yielded various solicitations including Bioengineering Research Grants and Bioengineering Research Partnerships, and, of course, the creation of NIBIB. These were important milestones in recognizing that biomedical research needs multiple approaches by collaborative activities of investigators from multiple disciplines and include hypothesis-driven as well as design or development driven work. Continued attention to multidisciplinary solicitations to address the needs outlined above are critical to continued advancement in ocular imaging.

Finally, one of the advantages of optical imaging of the eye is that the cost of these instruments is typically small in comparison with, say MRI or an astronomical telescope. Nonetheless, the formation of teams engaged in creating and deploying imaging technology is expensive. This necessitates larger scale projects that, in times of limited resources, may be more challenging, but, in the long run, will provide more bang-for-the buck.

Invited Speakers

Moderator, David Williams, University of Rochester

Johannes De Boer, VU University, Amsterdam, The Netherlands
Scott Fraser, California Institute of Technology
Jim Fujimoto, Massachusetts Institute of Technology
Giovanni Gregori, University of Miami School of Medicine
Christoph Hitzenberger, Medical University of Vienna, Austria
David Huang, University of Southern California
Joe Izatt, Duke University
Don Miller, Indiana University
Austin Roorda, University of California Berkeley
Ben Vakoc, Harvard Medical School
Clare Waterman, National Hear Lung and Blood Institute