McPherson Eye Research Institute
UNIVERSITY OF WISCONSIN–MADISON

InSights
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Growing Healthier Vision

IN JULIE MARES' LAB

Why do we have plant pigments in our eyes?

Professor Julie Mares' (PhD) research team has asked this question for the past twenty years. In fact, the question goes back over two hundred years, since a yellow spot was first noticed in post mortem specimens of human eyes.

In recent decades, researchers have confirmed that these yellow pigments might protect the retina from blue light damage, an idea first proposed by Nobel laureate George Wald in 1945, which is especially important as we age and the harmful effects of excess blue light accumulate.

The biochemical structure of these pigments – lutein, zeaxanthin and mesozeaxanthin – was identified about 30 years ago. They are structural isomers, having the same molecular formula but different shapes. Humans can absorb these carotenoid plant pigments and others, like beta-carotene, from their diet. However, of the eight most abundant carotenoids in human blood, *only lutein and its isomers* are taken up into the neural retina. They are the predominant carotenoids in vision processing areas in the brain, acting to lower the exposure of eye tissues to blue light. They are also strong antioxidants, helpful in reducing cell damage and inflammation.

Why is this important?

There is a potential link between these carotenoids and the development of age-related macular degeneration (AMD) – the leading cause of severe and often progressive vision loss in people over 60 years of age. Professor Mares' team and that of co-principal investigator Dr. Barbara Blodi are conducting the first long-term population study to determine whether women with high densities of these plant pigments in the eye (commonly referred to as macular pigment or MP) are less likely to develop age-related macular degeneration over fifteen years; or, if they already have AMD, are less likely to undergo progression of the disease. This Carotenoids in Age-Related Eye Disease Study (CAREDS) has tracked women who completed baseline study visits in 2001-2004 (CAREDS1), and are currently – 15 years later – being invited back for follow-up study visits (CAREDS2). CAREDS2 will also, in Dr. Yao Liu's lab, be the first to study the relationship of macular pigment to the development of glaucoma over time.

In CAREDS1, researchers observed that levels of macular pigment vary widely (>10-fold) across individuals. CAREDS2 will help determine the levels of macular pigment needed to preserve vision with age and to protect against more generalized aging of the neural retina. It will also quantify the amount of lutein intake from foods and supplements – data required to set guidelines for adequate intakes, which are currently lacking. Lutein and zeaxanthin supplements now on the market vary widely, from 5 mg – the amount we get from eating a diet rich in fruits and vegetables – to more than 10 times that amount, approximately 60 mg. Levels that are effective and safe over the long term are unclear.

Results from CAREDS1 also suggested that even among women with a genetic predisposition for developing AMD, the odds of developing the disease might be decreased three-fold by following a healthy lifestyle (not smoking, eating enough fruits and vegetables, and getting enough physical activity.) CAREDS2 will determine whether these and other factors found to contribute to higher (thus beneficial) levels of macular pigments in the first study, continue to maintain higher pigment levels as the women age. The bottom line goal: to test a variety of preventive measures, including those which would increase macular pigment, in order to lower the risk of AMD.

RIGHT: Dr. Mares' ideal breakfast -- Two soft-boiled eggs over mashed avocado with lemon juice, and rainbow chard.

BOTTOM: Mares lab members, L-R, Top: Tom Lawler, Julie Ewing; **Middle:** Diane Pauk, Jim Onofrey, Kristen Hall, Julie Mares; **Bottom:** Kim McIntyre, Krista Christensen, Zhe (Jason) Liu.

Dear Friends of the McPherson ERI,

It gives me great pleasure to announce the establishment of a new endowed professorship within the Institute – the David and Nancy Walsh Family Professorship in Vision Research. The Walsh family has supported vision research and the McPherson Eye Research Institute for many years; indeed, David Walsh was the first chair of the Institute's Advisory Board. The Walsh family's continued commitment to the McPherson ERI through this professorship is extraordinary, as are the matching contributions from Dr. Alice McPherson and John and Tashia Morgridge. The David and Nancy Walsh Family Professorship in Vision Research will be held by "a member of the McPherson Eye Research Institute in any school or department who is performing cutting-edge vision research" – a guideline that reflects our mission to advance vision research by fostering multi-disciplinary collaborations.

Endowed chairs and professorships are critically important to the McPherson ERI and to the UW, since they provide consistent funding to advance the most progressive and transformative ideas. The McPherson ERI is fortunate to now have ten such endowed positions. Seven of these chairs and professorships have been endowed by the Retina Research Foundation (RRF) in Houston, Texas, which was founded by Dr. Alice McPherson. Closer to home, Dr. Monroe and Sandra Trout from Appleton, Wisconsin have established two endowed McPherson ERI positions: the Sandra Lemke Trout Chair and the Timothy William Trout Professorship in Eye Research. Needless to say, we are grateful to be stewards of these deeply impactful positions and we are committed to using them to strengthen and expand our research mission.

One very important component of our vision research efforts is in the area of prevention. I have said it often – it is better to keep what you have than replace what you've lost. As such, I am especially pleased that Dr. Julie Mares is on the cover of this newsletter. Her work has conclusively shown that taking care of yourself in specific ways – including minding your nutrition – can help preserve vision or can slow vision loss. As we continue to look for cures and therapies for those who have lost vision, we will remain tireless in our efforts to help people keep the vision they have in good working order.

Thanks for your help, and enjoy the spring!

David M. Gamm, MD, PhD

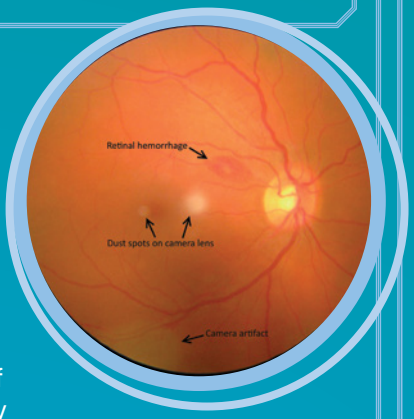
RRF Emmett A. Humble Distinguished Director, McPherson ERI
Sandra Lemke Trout Chair in Eye Research

Artificial intelligence + vision = progress

at the McPherson ERI

Computer vision—an interdisciplinary field encapsulating Artificial Intelligence (AI), machine learning, and deep learning—studies how useful information can be automatically extracted from a digital image. A revolution has swept computer vision over the last ten years with the advent of robust, real-world realization of the long-standing concepts of AI, whereby computer systems are able to perform tasks such as learning and decision-making that normally require human intelligence. Machine learning holds the potential to extract valuable diagnostic and research information from images of nearly all types, including those pertaining to the eye. However, there is great need to better automate and assess these AI strategies in order to improve research results and clinical decision-making.

AI is an important and growing branch of the collaborative network that makes up the McPherson Eye Research Institute. Here we highlight the works of interdisciplinary McPherson ERI research teams developing machine learning methods within four main subject areas: Vision Applications, Biomedical Imaging, Computational Imaging and Image Analysis.



FPRC training image used to tune computer algorithms in distinguishing pathology from image artifacts

Vision Applications

The recent partnership between deep learning technologies and retinal imaging has emerged successfully at the Fundus Photograph Reading Center (FPRC), where **Drs. Barbara Blodi** and **Amitha Domalpally** have confirmed that Artificial Intelligence can accurately identify stages of diabetic retinopathy using retinal photographs. Computer algorithms are also being developed to identify macular degeneration and to screen for glaucoma suspects.

Because AI is currently considered a medical device by the Food and Drug Administration (FDA), rigorous clinical trials are required prior to use in patient care. The quality of the data used for training the algorithm is key to its success. Drawing on the FPRC's almost 50 years of evaluating retinal images for clinical trials, grounded in meticulous training and quality control of human image readers, experienced FPRC readers can leverage deep learning technologies to improve the accuracy of clinical trial data. The high quality data generated by these human readers are then used for training and testing deep learning algorithms. Algorithms are also being developed to improve workflow and increase efficiency in high-volume clinical trials—which includes weeding out images without any pathology, which thus do not require reader interpretation.

In his Visual Impairment and Accessibility Technology Research Lab at the Waisman Center, **Dr. Ender Tekin** develops technological solutions to improve access to educational resources and environments for individuals with vision loss. His group combines signal processing, computer vision, and machine learning to develop apps and other software to facilitate timely availability of textbooks and class materials. Currently he is using deep learning techniques to classify images from textbooks, which are usually inaccessible to students with visual and other print disabilities.

Computational Imaging

With their respective lab groups, Drs. Kevin Eliceiri (LOCI), **Mohit Gupta** (Computer Sciences), and **Andreas Velten** (Biostatistics & Medical Informatics) each design computational imaging systems. This requires leveraging modern computational and machine learning tools for extracting meaningful information from visual data in real time. For example, the Eliceiri lab recently partnered with Google on the implementation of a machine learning system within an image analysis package. This can be run during or after data acquisition to extract key features of a cell targeted by disease.

Biomedical Imaging

Biomedical Engineering professors Dr. Paul Campagnola, **Dr. Jeremy Rogers**, and **Dr. Melissa Skala** each use machine learning as an analysis tool.

The Campagnola group relies extensively on machine learning for classification of normal and diseased tissues based on collagen morphology observed in Second Harmonic Generation (SHG) images. In collaboration with Vikas Singh, the group has used various computational techniques to classify a spectrum of ovarian tumors and pulmonary fibrosis. These approaches are applicable to any disease characterized by changes in collagen architecture, such as understanding the collagen structure of the sclera or cornea as it changes with age or in diseased states.

The Rogers group is developing ocular imaging modalities that make use of scattered light that is normally discarded. Using this scattered light enables measurement of very small changes in cell structure and can give insight into cellular function. Machine learning is used to analyze the complex scattered light signal, informing next-generation tools to discern targeted retinal cell structures and specific retinal layers.

The Skala group is interested in identifying sub-populations of cells with distinct metabolism, as markers of early disease. Cellular metabolism is imaged with autofluorescence microscopy, and machine learning is then used to segment single cells, to discriminate sub-populations of cells, and to identify relationships between the location of cells and their disease potential. Machine learning is also used to relate changes in metabolism to changes in tissue and cellular structure, and can monitor treatment response for diseases such as age-related macular degeneration.

Image Analysis

Dr. Richard Bruce (Radiology) is focused on building efficient data repositories and pipelines. Associating relevant and high quality clinical metadata, including things like genetic markers and other relevant clinical data, is foundational to establishing ground truth data ensuring a trained and validated machine learning tool. In addition to advancing automated diagnosis, machine learning is also being used to solve fundamental challenges including improving image quality, reducing image artifacts, reducing radiation dose, increasing imaging speed, reducing the need for intravenous dye agents, defining anatomy, and classifying images.

Dr. Vikas Singh (Biostatistics & Medical Informatics) and his group work on designing new algorithms for image and data analysis motivated by problems in computer vision, machine learning and medical image analysis. These algorithms can be extremely useful in evaluating images from diverse research contexts and clinical datasets. (See Figure 1)

Dr. Xiaojin (Jerry) Zhu (Computer Sciences) and his group are pushing the frontier of machine learning research with their interest in machine teaching—an emerging area where the goal is to precisely control how and what a learning system learns. Such a system will assist the computer in designing optimal education curricula for students. Zhu's group works with collaborators in Psychology and Education Psychology to test machine teaching on human students in diverse subjects such as chemistry, geology, and arithmetic.

Zhu is also interested in analyzing the trustworthiness of AI, given the considerable societal anxiety about its potential hazards. His group conducts analyses on certain safety guarantees of AI systems, including debugging the machine learning pipeline, interpretability of machine learning models, fairness in machine learning, and defending adversarial attacks on machine learning.

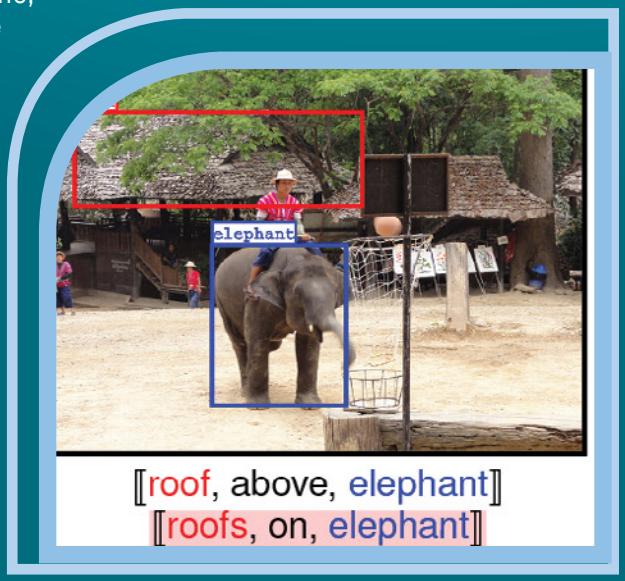


FIGURE 1: The AI/computer vision algorithm developed by Singh's group uses information about objects and their environmental relationships in large image sets on the web to accurately identify the same objects in new, previously unseen images. His group is now applying these ideas to brain images and clinical datasets—where instead of objects and their relationships in natural images, he seeks to identify pathologies in brain images and identify previously unobserved features with possible clinical repercussions.

6th annual
McPherson Eye Research Institute
endowed lecture

McPherson Eye Research Institute
UNIVERSITY OF WISCONSIN–MADISON

Microengineered physiological biomimicry:
HUMAN ORGANS-ON-CHIPS

D. Dan Huh, PhD
Wilf Family Term Assistant Professor,
Department of Bioengineering
University of Pennsylvania

Human organs are complex living systems in which specialized cells and tissues are assembled in various patterns to carry out integrated functions essential to the survival of the entire organism. A paucity of predictive models that recapitulate the complexity of human organs and physiological systems poses major technical challenges in virtually all areas of life science and technology. This talk will present interdisciplinary research efforts to develop microengineered biomimetic models that reconstitute complex structure, dynamic microenvironment, and physiological function of living human organs, including the eye.

SAVE THE DATE
21 ST
MAY 2018

Microbial Sciences Building
1550 Linden Dr UW-Madison 608/265-4023 info@vision.wisc.edu

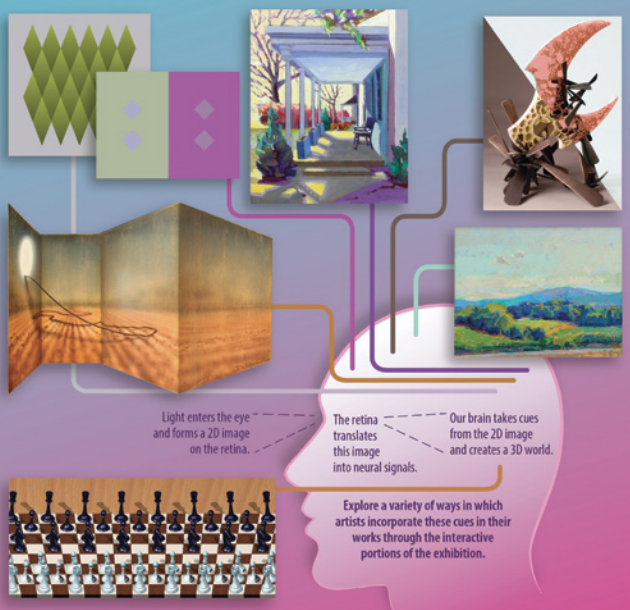
Reception - 3:30 PM Ebling Foyer
Lecture - 4:30 PM RM 1220

Monday, May 21, 2018

ART WORKS
Visual perception as a tool

McPherson Eye Research Institute

Artists use aspects of human perception as tools in creating their works



MANDELBAUM & ALBERT FAMILY VISION GALLERY
JANUARY 25 – MAY 25, 2018
9th floor, Wisconsin Institutes for Medical Research

Please support the McPherson ERI anytime at vision.wisc.edu/giving.
We greatly appreciate your help in advancing vision research!

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