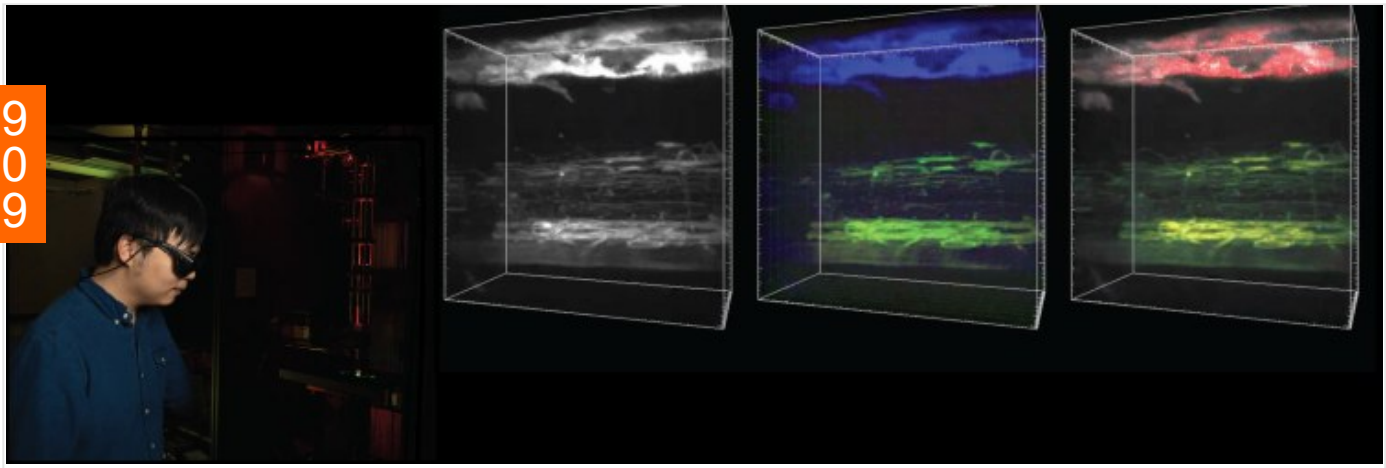

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Your Motivation Matters: Engineering to Heal

Written by: Leslie Lestinsky

Yide Zhang found himself interested in electronics at an early age.

“I enjoyed video games as a child, my favorite was a Nintendo game called *Shadow of the Ninja*,” remembered Yide. He let a friend borrow this game only to have it returned, broken. His father suggested to a discouraged young Yide, “why don't we put a needle in it?” As it turned out, that needle fixed the game (Yide knows now, it was a resistor that was broken within the video game cartridge).

This event and more borrowed games returned broken captivated Yide and made him want to discover more about electronics and their engineering.

Fast forward a few decades. As an undergraduate at Huazhong University of Science and Technology, he worked on a project that used memristors to simulate artificial neural networks and emulate functions of the brain. Yide was inspired by how intricate and complex the brain is. Scientists and researchers have so much yet to learn about this amazing organ. He wanted to press on in academia and explore the brain further–how he could use engineering expertise to heal it.

Yide began looking into the cross-sections between electrical engineering (EE) and brain imaging, optics, and biomedical disciplines. While exploring top researchers in these fields,

he discovered Department of Electrical Engineering (NDEE) Professor Scott Howard.

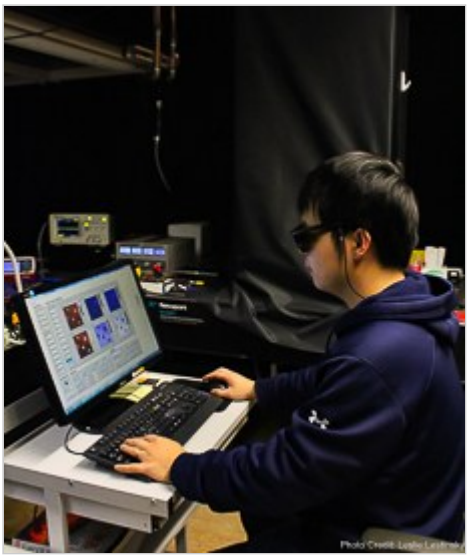
NDEE alumnus Yide Zhang during one of his last meetings with advisor, NDEE professor Scott Howard.

He contacted Prof. Howard and sent his CV. Howard's quick reply and professionalism settled the decision for Yide–this was who he wanted to spend a significant season of his life studying under.

"The brain is extremely complicated but fascinating to explore. I wanted to research the brain using optical and electrical engineering methods, and possibly find a way to heal brain damage or treat neurodegenerative diseases."

To understand how the brain works, Yide focused on developing novel fluorescence microscopy techniques that were capable of imaging the brain. These techniques could possibly also advance the work of researchers and medical personnel in a wide variety of fields. More specifically, Yide aimed to improve imaging speed, resolution, penetration depth, and functionality of fluorescence microscopes using multiphoton microscopy (MPM), fluorescence lifetime imaging microscopy (FLIM), super-resolution microscopy, adaptive optics, and deep learning methods.

His first breakthrough came when he discovered a simple, yet highly effective imaging method based on the principle of stepwise optical saturation (SOS). By linearly combining two conventional microscopy images obtained at low excitation powers, the resolution became extended beyond the diffraction limit. SOS microscopy provided super-resolution imaging deep in scattering samples.



Yide working with SOS microscopy

He collaborated on this project with Research Assistant Professor Prakash Nallathamby and Professor Ryan Roeder from the Department of Aerospace and Mechanical Engineering as well as Professor Joel Boerckel. He then shared this approach with Department of Biological Sciences Professors Cody Smith and Siyuan Zhang. Using Yide's innovative SOS imaging technique, the team was able to better see how brain microglia in mice and zebrafish repairs neurons. This EE advancement brought them a step closer to understanding methods that might successfully heal brain damage.

"Physics places limits on how small of a thing we can see. Yide used a physics trick to break those limits," explained Howard.

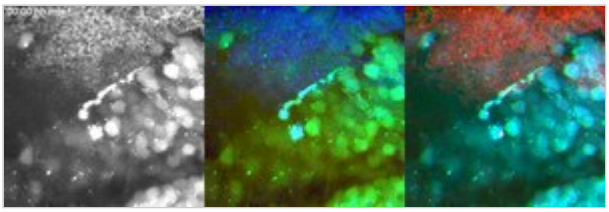
The work Yide has done throughout his PhD that he is most proud of is related to FLIM. This is a significant tool for biomedical research. FLIM provides additional information, such as ion and dissolved oxygen concentrations, pH, and refractive index, other than

fluorescence intensity. This is achieved by measuring the fluorescence decay lifetime of excited fluorophores.

“If you take a picture of something in the distance, you will get a good picture of that object, but you won't be able to tell the accurate distance between you and that object,” explained Yide. “FLIM allows you to get a picture of that object but also know exactly how far away it is. In other words, much more data and information becomes available.”

Despite these benefits, the application of FLIM systems so far is only limited to a few labs. Existing FLIM techniques are usually slow, noisy, and hard to implement due to expensive instrumentation and time-consuming post-processing algorithms.

Yide found a solution to that problem.



A sample of some of Yide's FLIM images

He engineered phase multiplexing (PM) FLIM, an innovative FLIM method that acquires high-quality fluorescence lifetime images as fast as conventional two-photon intensity imaging.

Not only does PM-FLIM achieve sustainable, long-term *in vivo* 4D FLIM of intact zebrafish and mice brains for the first time, it can also be implemented easily. This is done by upgrading existing two-photon microscopes using cost-effective components and Yide’s open-source software.

“He is a truly exceptional individual that has excelled in every way as a PhD student,” said Howard. “It's exceedingly rare to find a student that made significant contributions in developing new theoretical approaches. He experimentally validated his new approach, designed and built from scratch every aspect of one of the most advanced fluorescent microscopes in the world and collaborated with biomedical researchers to study challenging problems in biology. All while surpassing the theoretical limits to imaging speed, resolution, and measurement accuracy.”

Yide and Prof. Howard in the lab.

Yide received the NDEE Graduate Student Research Award in 2016, a Berry Family Foundation Graduate Fellowship from the Advanced Diagnostics and Therapeutics Initiative in 2017, and the Notre Dame Integrated Imaging Facility Best Biological Imaging Publication in 2018. In 2019, he won the Notre Dame Center for Research Computing Award for Computational Sciences and Visualization. And as the cherry on top of this sundae, this past spring he was awarded the JenLab Young Investigator Award at the SPIE Photonics West conference this year.

Professor Lihong V. Wang from the California Institute of Technology set up a job interview with Yide, right there at the conference. The next day, Yide was offered a post-doc position, working alongside Professor Wang, a top scientist and researcher in photoacoustic imaging.

Yide receiving the JenLab Young Investigator Award at SPIE Photonics West 2019 Conference.

“I decided to work on photoacoustic imaging during my post-doc because the penetration depth of even the most advanced fluorescence microscope is around 2 millimeters, which is almost negligible compared to the size of a human brain (~10 centimeters),” said Yide. “Photoacoustic techniques, on the other hand, can image the brain at a depth orders of magnitudes deeper than fluorescence microscopy.”

Looking past the post-doc position, Yide knows he wants to continue down the professional path of academia.

“I chose academia because it allows the freedom to work on what inspires me, not what the market dictates,” said Yide. “I look forward to working on new research questions important to society and solving those problems.”

As Yide reflects on his experience at Notre Dame, the people he’s worked with will leave the largest imprint on him.

“The faculty and staff on this campus are very friendly, everyone is genuinely nice,” said Yide. “I appreciate that the most about Notre Dame.”

He praised NDEE professors Thomas O'Sullivan, Alan Seabaugh, and of course, Scott Howard for their willingness to support his research throughout his PhD.

Yide with NDEE professors Seabaugh, Howard and O'Sullivan at his PhD defense.

“Professor Howard has always been there to lend helpful advice. I would not have achieved what I did without his guidance and support.”

Professor Howard also reflected on the commencement of Yide’s studies at NDEE, “Yide's departure will be bittersweet. We will miss him, but I’m excited to see what he'll do next. His post-doctoral position at Caltech with Professor Wang is very competitive. This is just the start of the many good things to come.”

As Yide moves forward, he leaves behind some words of wisdom for current graduate students.

“Your motivation matters. You will truly be devoted to your research only if your motivation and interest matches your research direction,” Yide said. “A PhD is about generating new knowledge. Every time you talk with your advisor, set a goal to show them something new (reports, research of your own or others’, etc.) Never be satisfied with your current achievements, because learning and researching is like rowing upstream, not to advance is to drop back.”

A very motivated Yide, meeting with then advisor, NDEE professor Scott Howard