NATIONAL SCIENCE FOUNDATION

Summer Institute on Nanomechanics and Nanomaterials and Micro/Nanomanufacturing

in collaboration with
The Argonne-Northwestern Institute

A Short Course on:

Novel Super-Resolution Methods for Bioimaging

April 27 – 28, 2013
Town and Country Hotel, San Diego, California
in Collaboration with
The International Conference on Metallurgical Coatings and Thin Films

Instructors
Harald Hess (Janelia Farms)
Hu Cang (Salk Institute)
Zhaowei Liu (University of California San Deigo)
Cheng Sun (Northwestern University)
Hao Zhang (Northwestern University)

Course Organization
This short course will begin with an overview of novel imaging techniques for biological system. The diffraction limit poses the physical limit of the highest spatial resolution can can be obtained from the optical far-field. Many novel imaging techniques were therefore developed to provide optical resolving power way beyond the diffraction limit. This course will review the imaging methods including optical superlens, optical Hyperlens, Strcuture Illumination (SI), Photoactivated Localization Microscopy (PALM), STochastic Optical Reconstruction Microscopy (STORM), Stimulated Emission Depletion (STED), Photoacoustic (PA), and Optical Coherent Tomography (OCT) will be presented. The short course will end with the discussion of how future development of the new imaging technique with superior imaging resolution and specific materials contrast suitable for investigating various biological samples and systems.

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April 27, 2013

2:00–2:15	Introduction – Cheng Sun, Northwestern University
2:15–3:30	3D Imaging at the limits with Photo-Activated Labels and Electrons– Harald Hess, Janelia Farms
3:30–3:45	Break
3:45–5:00	Single Molecule Super Resolution Imaging – Hu Cang, Salk Institute

April 28, 2013

8:30–10:00	Super Resolution Optical Imaging: Structured Illumination Microscopy (SIM) - Zhaowei Liu, University of California San Deigo
10:00–10:15	Break
10:15–11:45	Super Resolution Optical Imaging: Stimulated Depletion Microscopy (STED) - Zhaowei Liu, University of California San Deigo
1:00–3:00	Photoacoustic microscopy and optical coherence tomography – Hao Zhang, Northwestern University
3:00–3:15	Break
3:15–4:45	Imaging Beyond the Diffraction Limit Using Optical Metamaterials – Cheng Sun, Northwestern University
4:45–5:00	Conlusion – Cheng Sun, Northwestern University

Registration Fee

Status	Registration Fee	Deadline
Fellowship Application	Covered by NSF	March 15, 2013
Early Registration	$800	April 1, 2013
Registration	$1000	

Location

The course will be held at the Town and Country Hotel in San Diego, in collaboration with the International Conference on Metallurgical Coatings and Thin Films (ICMCTF).

Accommodation

In collaboration with our ICMCTF co-host, a block of rooms has been reserved at the Town and Country Hotel. When making reservations, please mention the ICMCTF meeting to receive discounted rates. The reservation number is: 1-800-77-ATLAS. For participants who are receiving fellowship support (see below), we will make reservations on your behalf at double occupancy. If the fellowship recipient wishes to occupy a single room, he/she will be responsible for the difference.

Registration

Please register through the NSF Summer Institute website:

http://summerinstitute.mech.northwestern.edu/

Fellowships

U.S. professors, post-doctoral researchers and graduate students can apply for fellowship support through the website noted above. Fellowship applications are due March 15, 2013. Each fellowship award covers the following:

Full registration

Up to three-night stay at Town and Country based upon double occupancy

Contact

Website: http://summerinstitute.mech.northwestern.edu/
Email: summerinstitute@mail.mech.northwestern.edu
For details about the ICMCTF meeting of our co-host, please consult the following website:
http://www2.avs.org/conferences/icmctf/

Course Description

3D Imaging at the limits with Photo-Activated Labels and Electrons

Fluorescence microscopy, is limited in its ability to resolve densely labeled features smaller than the optical diffraction limit. However special photoactivated fluorescent proteins or dyes can be harnessed in a technique called Photo-Activated Localization Microscopy, PALM, to give enhanced resolution. PALM images of protein location and organization are illustrated with mitochondria, lysosomes, actin networks, endoplasmic reticulum, bacteria, and focal adhesions. An extension to 3D, using an interferometry, can measure the vertical position of fluorescent molecules to nanometer precision with the highest photon efficiency. This can be combined with PALM to give full 3 dimensional molecular coordinates of genetically tagged proteins with ~ 10-20 nm resolution and has revealed the protein nanostructure architecture of focal adhesions. In another 3D project, electron microscopes, EM, can be customized for in high throughput imaging for neural tissue or cells. Correlating PALM and electron microscopy gives EM images which can be colorized with protein locations.

Speaker:

After a PhD in Physics at Princeton, Harald Hess pursued hydrogen atom trapping and Bose-Einstein condensation at MIT, various low temperature scanning probe microscopy at Bell Labs, and then left for an industrial position developing advanced equipment for hard disk drive and semiconductor inspection and production. During a liberating period of unemployment, he and a colleague, Eric Betzig, learned about photoactivatable fluorescent proteins and developed PALM (photo-activated localization microscopy) to reveal details of structure beyond the diffraction limit. He is now gainfully employed at Janelia Farms extending PALM to 3D and 3D electron microscopy techniques for cells and neural tissue.

Single Molecule Super Resolution Imaging

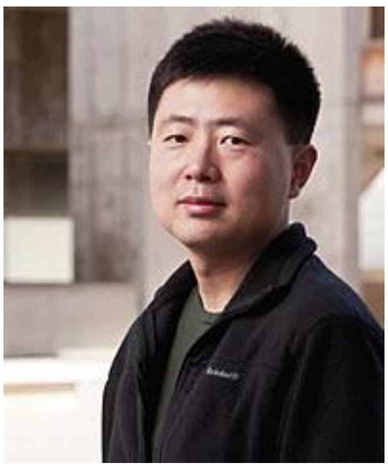
The invention of single-molecule super-resolution imaging, including PALM and STORM, has increased the resolution of light-microscopy to the level of electron microscopy, (10-20 nm 3D resolution), and allows biological processes to be recorded at the molecular level, in real time, and in living cells. This super-resolution capability has fundamentally transformed the field of Biophotonics. This lecture will provide a comprehensive view on current status of the single-molecule super-resolution imaging. The topics that this lecture will cover are:

- History of the single-molecule super-resolution imaging.
- *The principles of the single-molecule super-resolution imaging.*
- *Current applications of single-molecule imaging*.
  We will discuss several high-impact applications of the single-molecule imaging, including studies of nucleus, membrane proteins and cytoskeletons.

- *Limitations and future directions*.
  We will discuss several areas of active research, including faster, more accurate and more sensitive super-resolution image reconstruction algorithms (Bayesian, compressive sensing and cloud computation), light-sheet illumination for deep tissue imaging; adaptive optics and helix point spread function approaches for 3D super-resolution imaging, and development of novel fluorescence proteins and fluorophore for single-molecule super-resolution imaging.

Through this lecture, attendees will get a through understanding of the history, principles, applications, limitations and future perspective of the single-molecule super-resolution imaging.

Speaker:



Dr. Hu Cang is an Assistant Professor at the Waitt Advanced Biophotonics Center at the Salk Institute. He received a M.S. in Electrical Engineering and a Ph.D. in Chemical Physics from Stanford University. He joined the faculty of Salk in 2012. His current research focuses on developing novel single molecule super-resolution imaging techniques for the study of chromatin architecture in nucleus. He has published 24 papers in top journals including *Nature*, *Nature Methods,* and *Physical Review Letters*. These works have had a broad impact; been highlighted by *Analytical Chemistry*, *Nature Photonics*, *Nature Materials,* and *Nature;* and received more than 1,600 citations to this point. He is a recipient of the Annual Review of Physical Chemistry Award in 2005, and Ray Thomas Edward Career Development Award in 2012.

Super Resolution Optical Imaging: Structured Illumination Microscopy (SIM) and Stimulated Depletion Microscopy (STED)

The imaging resolution of a conventional optical microscope is limited by the diffraction to a few hundreds of nanometers. Emerging technologies developed within last one to two decades offer new possibilities to image at 10-100 nanometer deep sub-wavelength scales. In this lecture, I will focus on the structured illumination microscopy (SIM) and the stimulated depletion microscopy (STED), two widely used optical super resolution technologies for biomedical imaging. Detailed working principles, recent development, application examples, and theoretical limitations will be discussed.

Speaker:

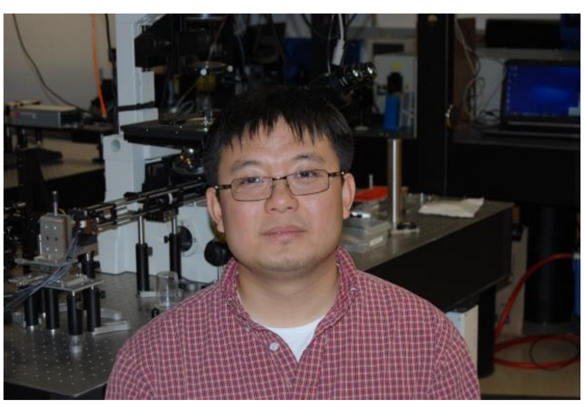
Zhaowei Liu is an Assistant Professor in the Electrical and Computer Engineering Department at UCSD. He received his Ph.D. in Mechanical and Aerospace Engineering (MEMS/Nanotechnology) from UCLA in 2006, and was subsequently a postdoctoral researcher in NSF Nanoscale Science & Engineering Center (NSEC) and Mechanical Engineering at UC

Berkeley. In 2008 he joined the faculty at UCSD. His research is primarily in the fields of nanophotonics, super-resolution imaging and sensing, metamaterials, plasmonics, and micro/nanofabrication. His work on optical hyperlens was selected to the Discovery Magazine's top 100 science stories in 2007. The first experimental demonstration on negative refraction at visible light frequency was selected to the Time Magazine's top 10 scientific discoveries in 2008. He is a recipient of the 2010 Richard E. Morley SME Outstanding Young Manufacturing Engineer Award, UCSD 2010 Hellman Faculty Fellowship Award, and 2010 Kavli Fellow from National Academy of Sciences.

Photoacoustic microscopy and optical coherence tomography

Optical microscopy has been a critical component in modern biomedical research and clinical diagnosis. In this short course, we will focus on fundamentals and applications of photoacoustic microscopy (PAM) and optical coherence tomography (OCT). PAM is a hybrid imaging technology that combines pulsed laser excitations with ultrasonic detection to form a volumetric image of optical absorption properties distribution in an object. The unique capability of PAM is to measure hemodynamic parameters such as total hemoglobin concentration and hemoglobin oxygen saturation, which can be correlated with early pathological signs of various diseases. Currently, PAM has been used in animal models for skin, brain, musculoskeletal, cardiovascular, and ophthalmic diseases. OCT is an interferometric technology that can image microanatomy and blood flow with a very high axial resolution. To form an image, a wide-band low-coherence light is used to shine a sample; the reflected light from the sample then interfere with the light reflected from a reference mirror and is detected by a spectrometers. After a spectral-domain resampling and inverse Fourier transform, a cross-sectional image is reconstructed. OCT is widely used in almost all major blinding diseases is being explored for cardiovascular and brain diseases. Because PAM and OCT each provide distinctive contrast mechanism, combining PAM with OCT can potentially be even more powerful in disease diagnosis and treatment evaluations.

Speaker:



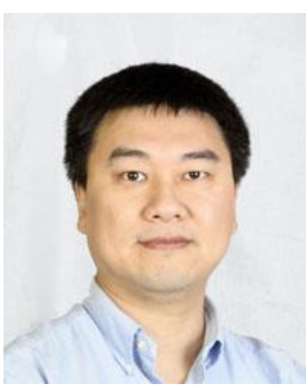
Dr. Hao F. Zhang is an Assistant Professor of Biomedical Engineering at Northwestern University, Evanston IL. He received his Bachelor and Master degrees from Shanghai Jiao Tong University in 1997 and 2000, respectively, and his Ph.D. degree from Texas A&M University in 2006. From 2006 to 2007, he was a post-doctoral fellow at Washington University in St. Louis. He is interested in novel optical imaging and sensing technologies with applications to both fundamental biomedical investigation and clinical diagnosis. For more information, please visit http://foil.northwestern.edu.

Imaging Beyond the Diffraction Limit Using Optical Metamaterials

Metamaterials are a new class of composite structures made of engineered meta "atoms" and "molecules" which enable the unprecedented electromagnetic properties that never exist in the nature. Especially, the predicted superlens made of metamterials breaks the fundamental diffraction limit, which may have profound impact in wide range of applications such as nano-scale imaging, nanolithography, and ultra-density data storage. I'll present a few recent experiments that demonstrated the unique superlens and hyperlens that breaks diffraction limit.

Furthermore, the recent developments of transformation optics and engineering metamateials have inspired a new generation of novel optical components in various areas. Compared to the optical and the microwave range, imaging at Tera-Hertz (THz) frequencies is still at an early stage of development due mostly to the great paucity of high performance modulator lens. I will discuss a systematics study in developing a three dimensional (3D) aberrations-less metamaterials lens through an integrated approach among theoretical design, numerical simulation, integrated 3D fabrication, and experimental characterization. Specifically, we applied transformation optics to "compress" the Luneburg Lens' spherical imaging surface into a planar one but meanwhile, maintaining its remarkable focusing properties, such as aberration-less imaging characteristics over a wide collecting angle. A series of simulations are performed to validate the design of the flattened Luneburg lens. Non-resonant metamaterials are chosen to realize the 3D Luneburg lens and the index variation can be achieved by fabricating "woodpile" structures with varying the dimension of the sub-wavelength dielectric structure. Fabricating Luneburg lenses that are optically large in all three dimensions is demonstrated using micro-stereo-lithography system. Finally, transmission terahertz time-domain spectroscopy (THz-TDS) is employed to characterize the performance of Luneburg lens.

Speaker:



Professor Cheng Sun is an Assistant Professor at Mechanical Engineering Department at Northwestern University since September 2007. He received his PhD in Industrial Engineering from Pennsylvania State University in 2002. He received his MS and BS in Physics from Nanjing University in 1993 and 1996, respectively. Prior to coming to Northwestern, he was Chief Operating Officer and Senior Scientist at the NSF Nanoscale Science and Engineering Center for Scalable and Integrated Nanomanufacturing at UC Berkeley. Dr. Sun received a CAREER Award from the National Science Foundation in 2009 and ASME Chao and Trigger Young Manufacturing Engineer Award, 2011.

Sun's primary research interests are in the fields of Emerging applications of nano-electronics, nano-photonics, nano-electromechanical systems and nano-biomedical systems necessitate developments of viable nano-manufacturing technologies. His research group is engaged in developing novel nano-scale fabrication techniques and integrated nano-system for bio-sensing and high-efficiency energy conversion.

The NSF Summer Institute is supported by the NSF CMMI Division. Additional financial support is provided by the following units at Northwestern University:
Department of Civil Engineering
Department of Materials Science and Engineering
Department of Mechanical Engineering
Materials Research Center
Nanoscale Science and Engineering Center
Center for Surface Engineering and Tribology
National Center for Learning and Teaching in Nanoscale Science and Engineering