NANO-BIOMEDICAL RESEARCH

I. Nano-to-Macro-Scale Optical Cavities based Tools for Ultrasensitive Cytomics and Proteomics Applications

This project involves a thorough investigation of the control of light radiation in biological matter with novel *optical cavities* to provide unprecedented detection sensitivity and spatial precision. This task is particularly important in cellular nanomechanics and single molecule experiments, where the detected optical signals are extremely low in power. The initial technological aspects of this project include exploration of different geometries of cavities enclosing the specimen of interest, and examination of a variety of detection schemes to significantly increase the contrast, and hence the resolving power of conventional lens-based microscopes. In addition, we are addressing fundamental theoretical questions on the radiation nature of a single emitter / scatterer embedded within an optical cavity, as well as the limits it imposes on the achievable temporal and spatial resolution in disordered media. This optical-cavity based technology will be employed in cytomics and proteomics applications that up to now have suffered from low sensitivity and imaging contrast. Examples of such applications include label-free, 3D biomechanical imaging with nanoscale precision, and high-throughput, ultra-sensitive lab-on-a-chip-based molecular recognition.

II. Far-Field Optical Imaging and Sensing at the Nanometer-Scale

The inability of a conventional lens to discern details below a quarter of a micrometer poses a fundamental limit to the measuring power of optical systems. In our lab, we are developing new far-field optical microcopy methods with nanometer-level resolution and precision. These technologies are necessary for live imaging and sensing of biological systems at the molecular level and will complement the resolution of electron and scanning probe microscopes. Two specific projects in this research direction are described below:

A. Three-Dimensional Far-Field Fluorescence Nano-Imaging

To date, probing biology *in vivo* with 3D optical resolution at the molecular level is limited. To provide this capability, novel far-field fluorescence microcopy methods with nanometer resolution will be developed in our lab. These techniques will be based on the phase of low-level light [A. Bilenca *et al.*, *Opt. Express* **14**, 7134-7143 (2006); A. Bilenca *et al.*, *Optics Express* **15**, 2810-2821 (2007); A. Bilenca *et al.*, *Annals of the New York Academy of Sciences* **1130**, 68-77 (2008)]. Our preliminary results showed ~5-13 nm optical resolution in 3D using simple control samples; ~25-50 fold improvement over conventional optical microscopes. Unlike available systems for far-field fluorescence nano-imaging, our novel imaging strategy does not require the use of high-intensity light sources, which can damage biological samples. In addition, we will employ sophisticated analytical and Monte-Carlo tools [A. Bilenca *et al.*, *IEEE Photonics Journal* **1**, 119-127 (2009); A. Bilenca *et al.*, *Opt. Express* **13**, 9822-9833 (2005)] to address central theoretical questions, such as how does the accuracy of the phase measurement depend on the number of photons detected through biological matter. Moreover, our lab is developing advanced bio-nanoimaging processing techniques for providing nanoimaging of living systems at high-speed [A. Bilenca *et al.*, Paper 7571-37, *PhotonicsWest'10*, 2010; A. Bilenca *et al.*, Paper 7571-37, Paper JWA64, *CLEO'10*, 2010]. Our initial results have demonstrated a 6-to-15-fold increase in the imaging speed of super-resolution photo-activated localization microscopy using novel image processing algorithms. Our optical nanoscopy technologies will ultimately be applied to study living biological systems.

B. Optical Nano-Probing of Local Interactions in Biomolecular Complexes

The drawback of classical fluorescence bio-sensing strategies, such as fluorescence fluctuation spectroscopy (FFS), lies in their inability to trace the motion of the interacting molecules. In our lab, we are investigating a new form of fluorescence bio-sensing strategy to track molecular dynamics with *nanoscale* precision. We expect that our technology will outperform current bio-sensing techniques in numerous aspects including superior count-rate per molecule and background signal and higher localization accuracy of the interacting molecules (up to sub-nanometers). This technology will ultimately be applied for probing dynamics in model membranes and cells in 3D.