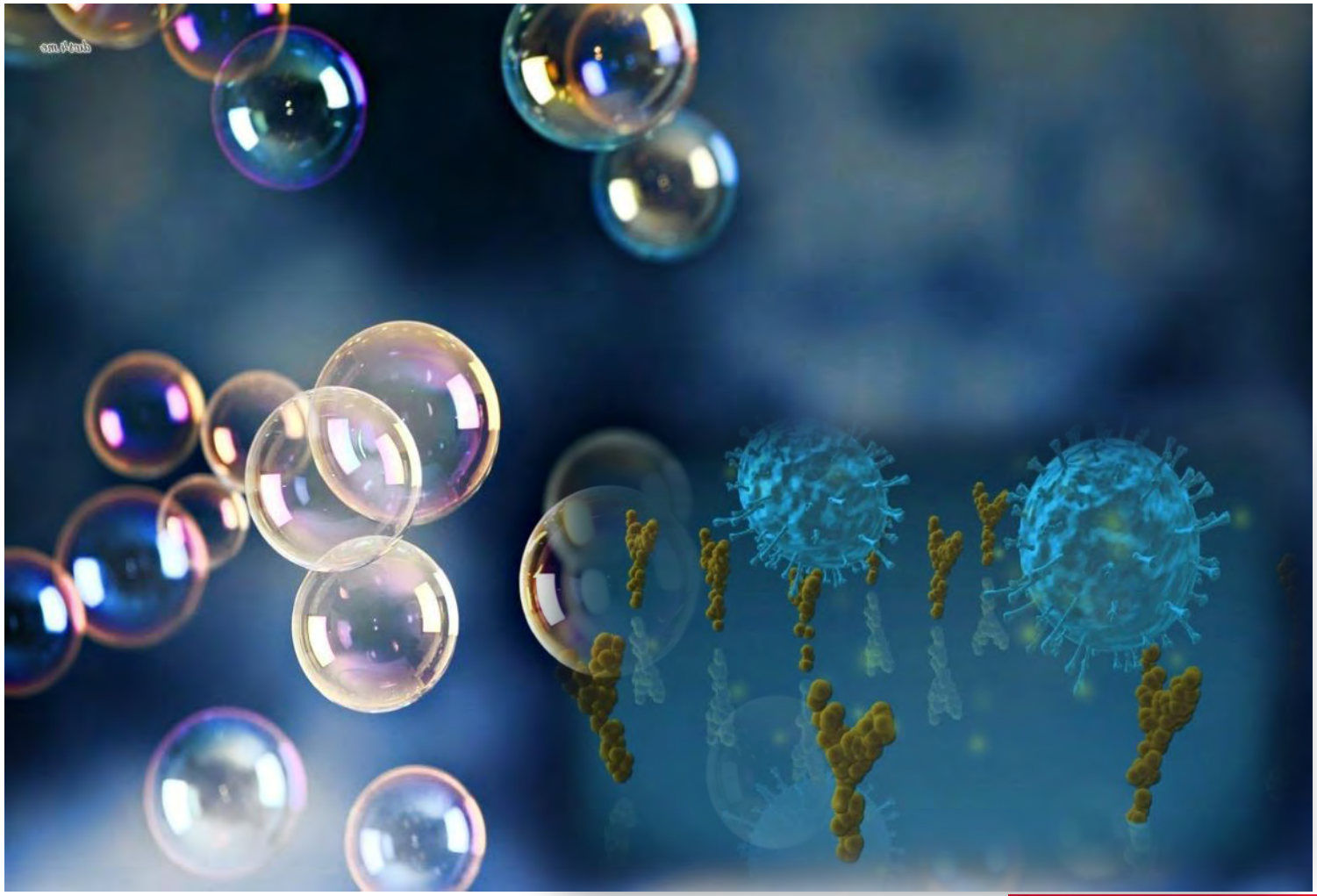
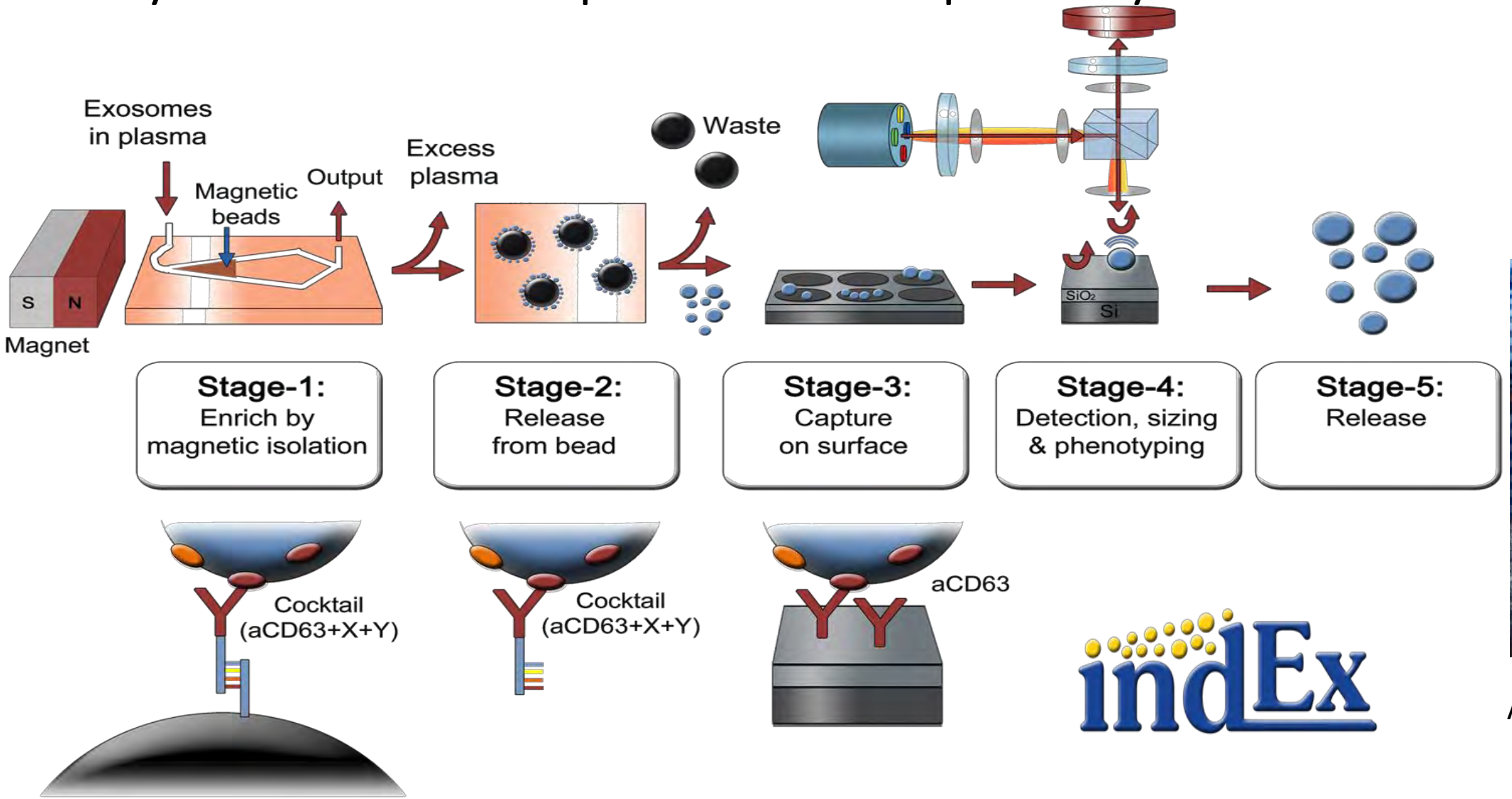
Interferometric microscopy for detection and visualization of biological nanoparticles

M. Selim Ünlü
Electrical Engineering, Physics,
Biomedical Engineering
Graduate Medical Sciences



- Detection vs. visualization/characterization
- Interferometric Reflectance **Imaging** Sensor
- Biological Nanoparticle Detection and Sizing
- Si-based microfluidics
- Pupil function engineering
- Resolution improvement by oblique illumination and reconstruction
- Towards 100nm in label-free visible light microscopy
- miRNA detection

Integrated nanoparticle isolation and detection system for complete on-chip analysis of exosomes



Ayca Yalcin Ozkumur

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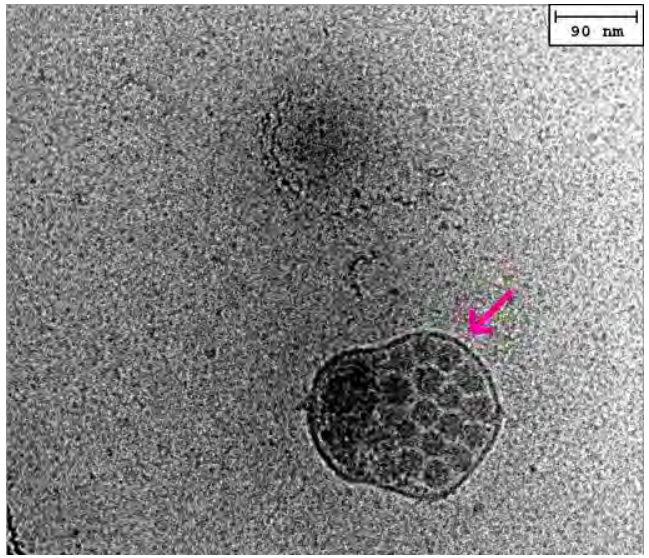
Technologies for bio-nanoparticle characterization

Cryo-TEM

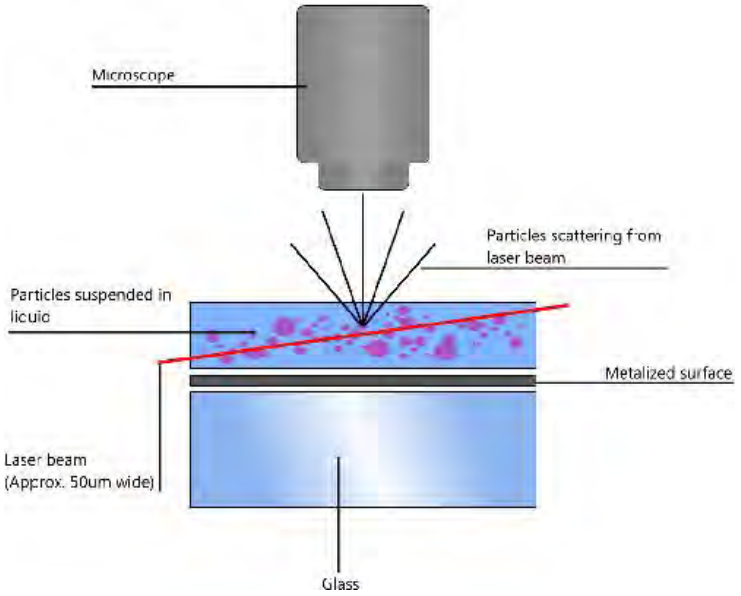
- Fantastic resolution
- Low throughput and difficult



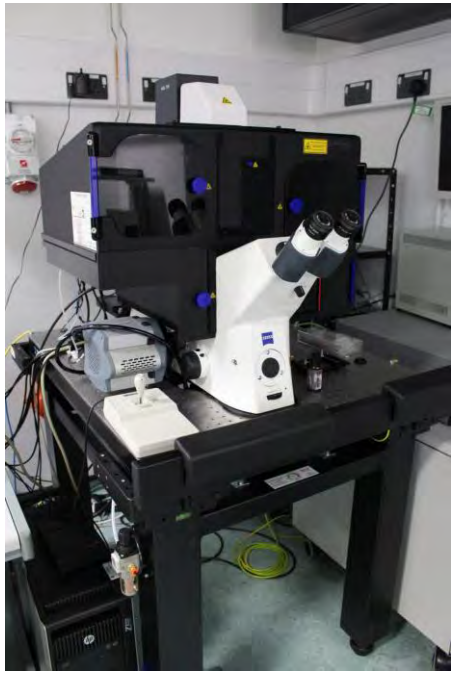
Bullitt Lab, BU MED

Nanoparticle Tracking Analysis

- Estimate size of particles based on Brownian motion
- Little/no molecular information



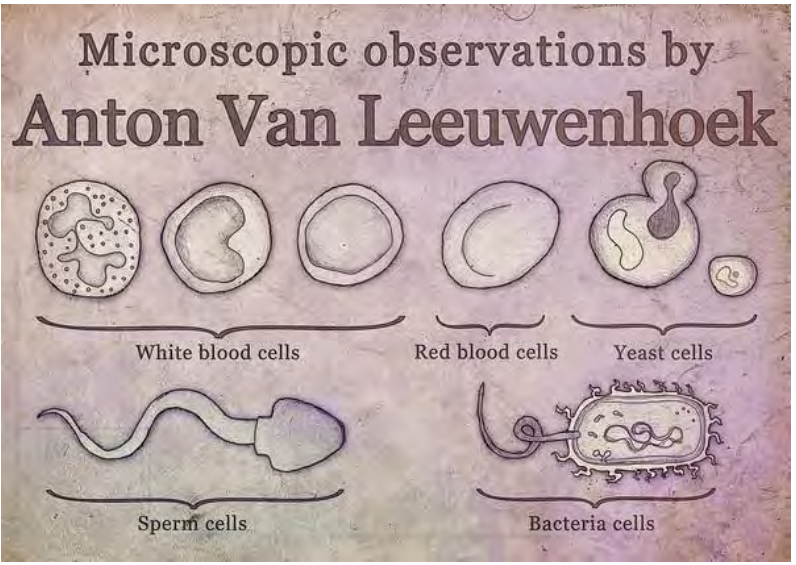
Fluorescence microscopy (STED/PALM)

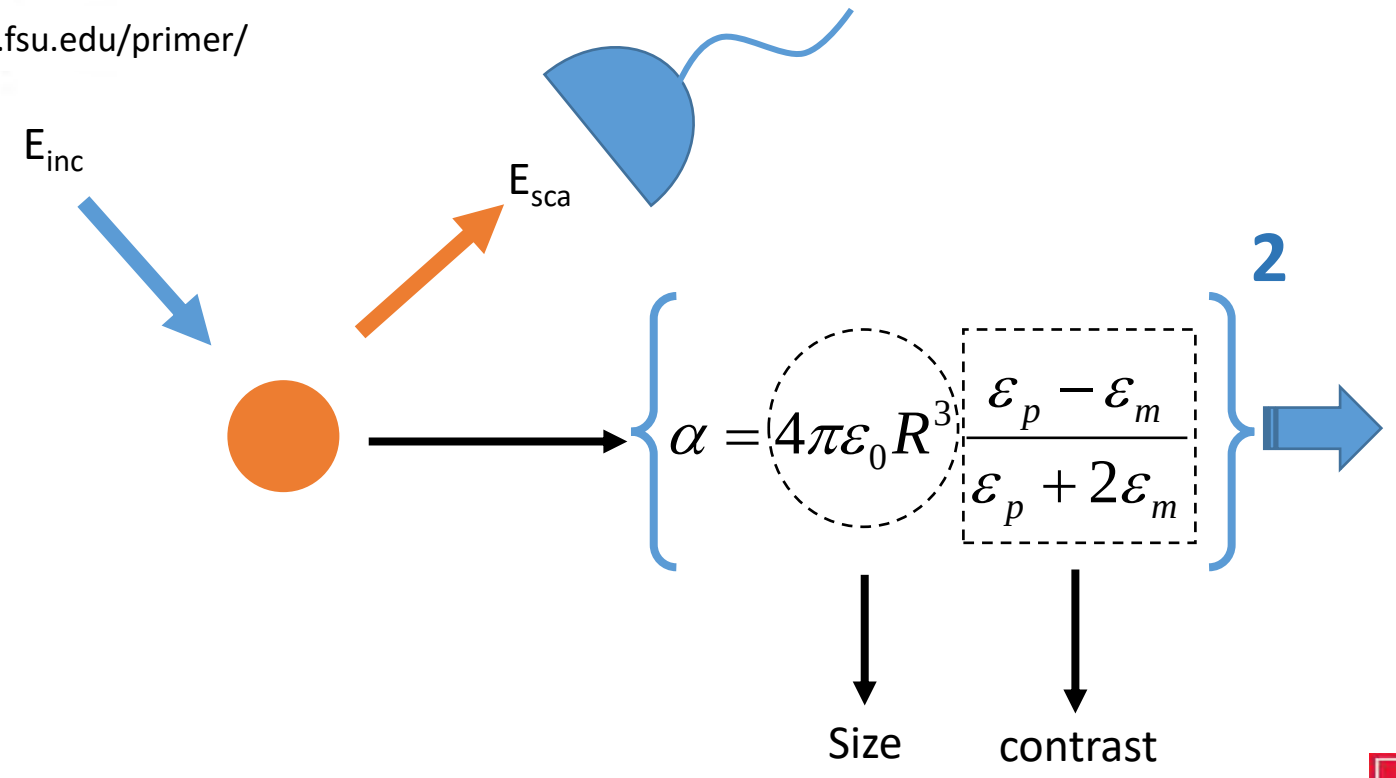


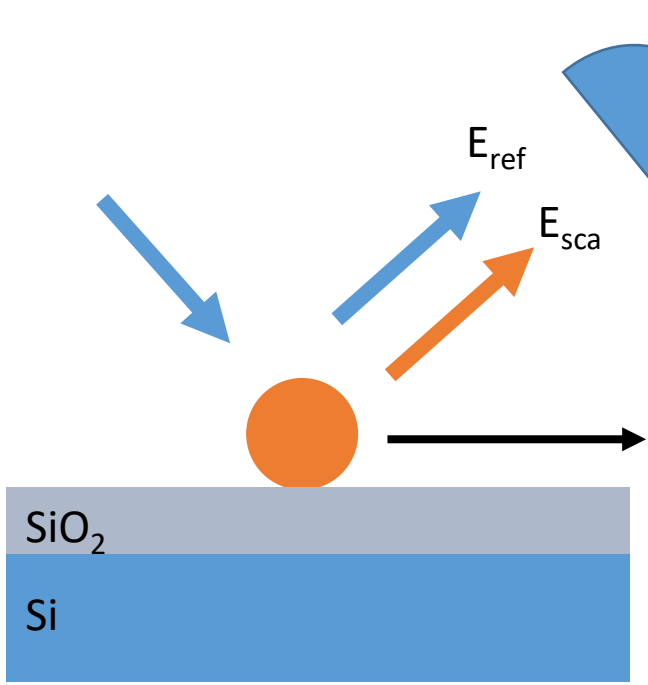
Needed: High-throughput methods to measure the **size, shape** and **molecular profile** of biological nanoparticles

Optical microscopy can see small – but …

micro.magnet.fsu.edu/primer/







$$I_{det} \propto |E_{ref}|^2 + |E_{sca}|^2 - 2|E_{ref}||E_{sca}|\sin\theta$$

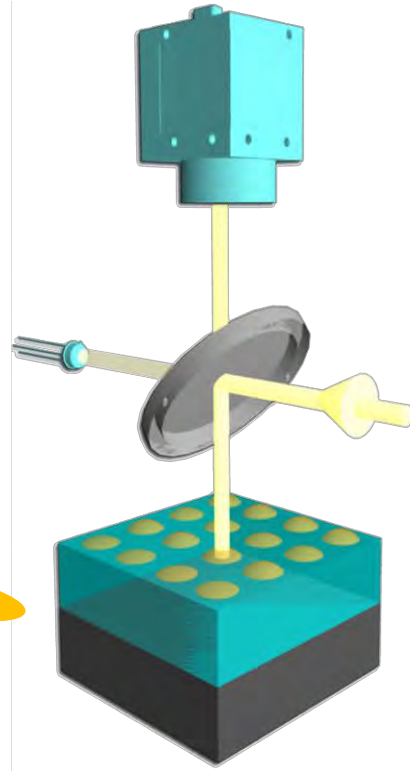
$$\alpha = 4\pi\varepsilon_0 R^3 \frac{\varepsilon_p - \varepsilon_m}{\varepsilon_p + 2\varepsilon_m}$$

Size

Material

Signal ~ R^3

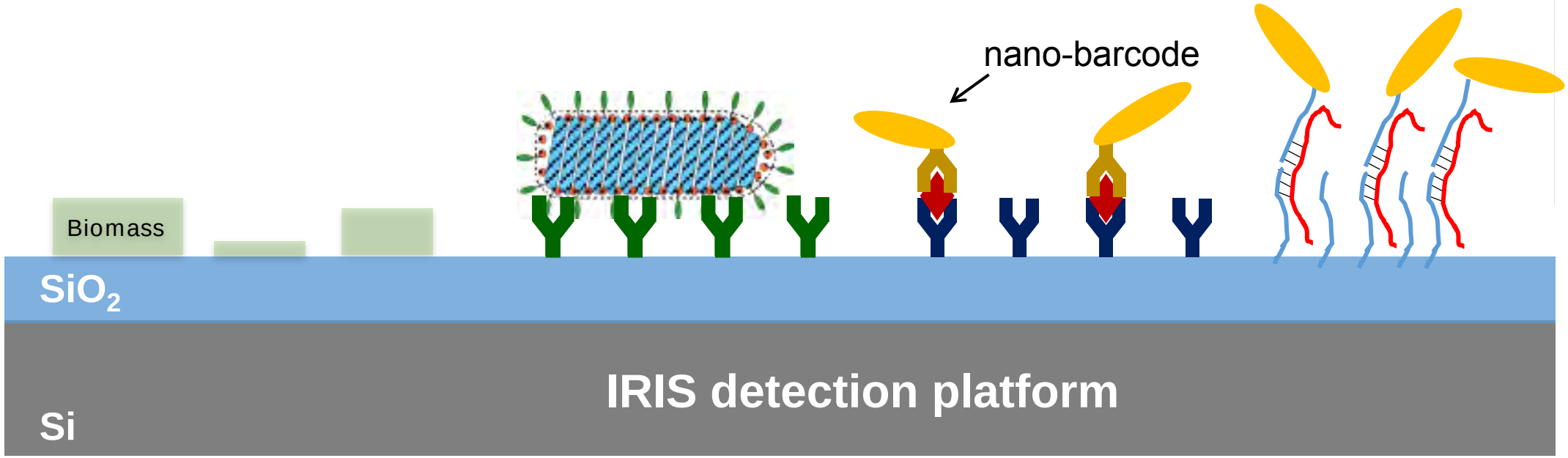
A versatile biosensing technology platform for microarrays



Ensemble Molecular Binding (label–free)

Single BNP Detection (label–free)

Single Molecule Detection of Antigen proteins and DNA/RNA



- Label-free molecular binding
- Label-free direct sensing of individual viruses
- Digital Detection: Single molecule level detection of Nucleic Acids and Proteins

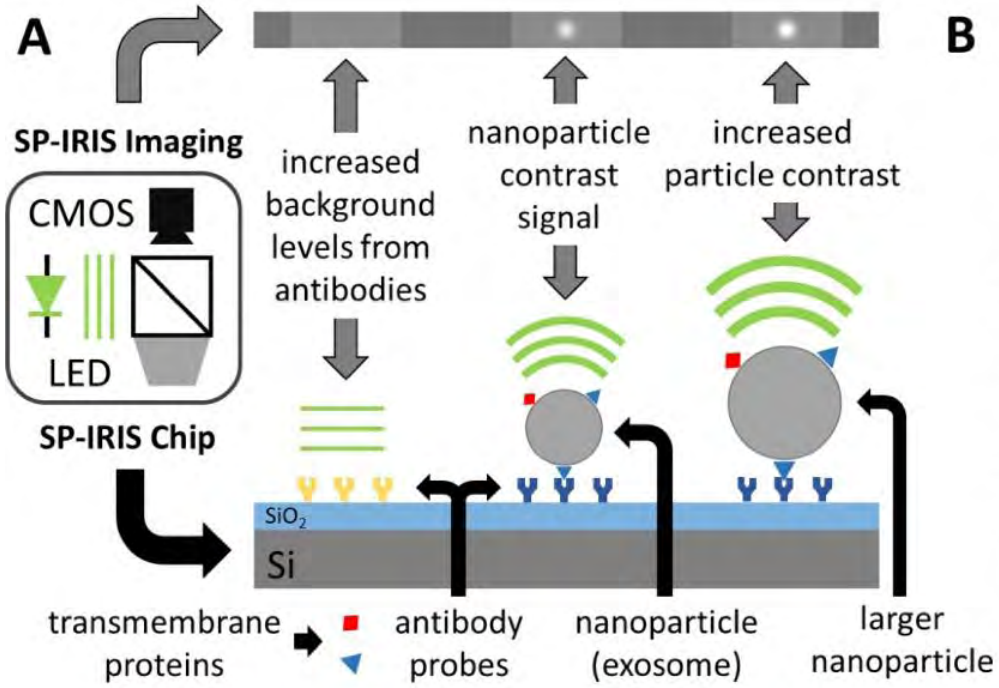
Single Nanoparticle Detection

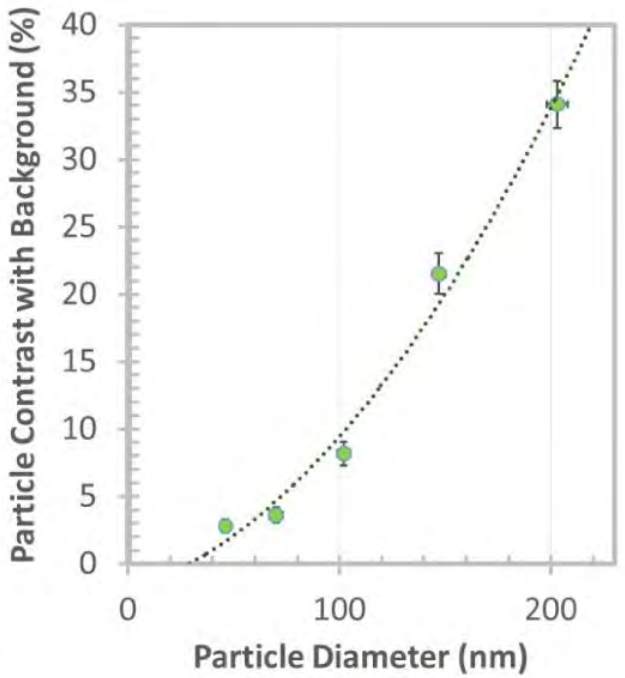
SCIENTIFIC REPORTS

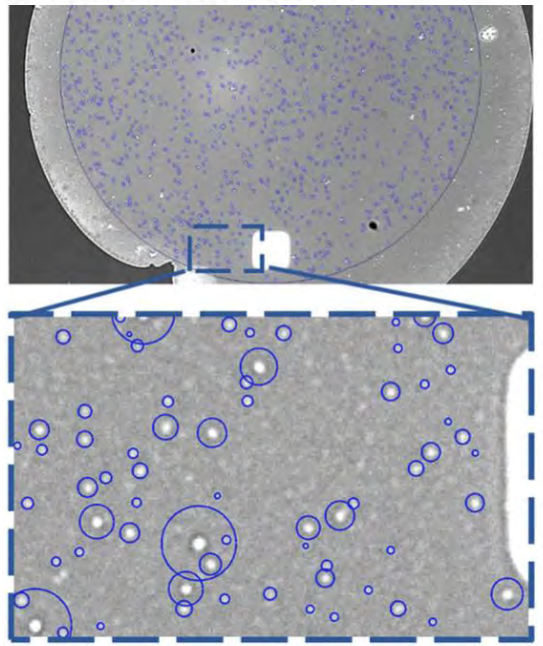
OPEN

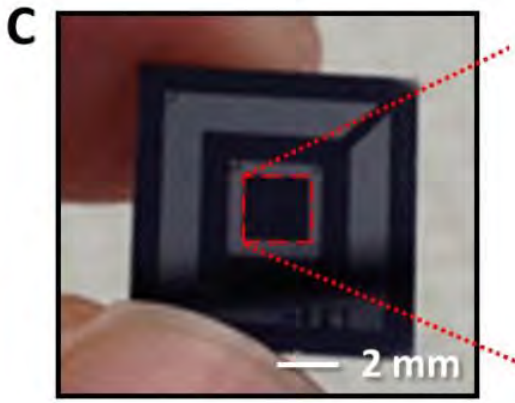
Digital Detection of Exosomes by Interferometric Imaging

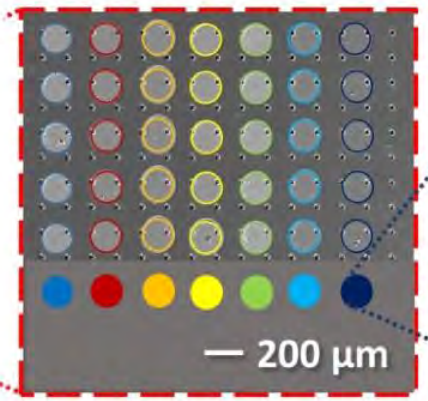
George G. Daaboul[1,*], Paola Gagni[2,*], Luisa Benussi[3], Paolo Bettotti[4], Miriam Ciani[3], Marina Cretich[2], David S. Freedman[1], Roberta Ghidoni[3], Ayca Yalcin Ozkumur[5], Chiara Piotto[4], Davide Prosperi[6], Benedetta Santini[6], M. Selim Ünlü[7] & Marcella Chiari[2]

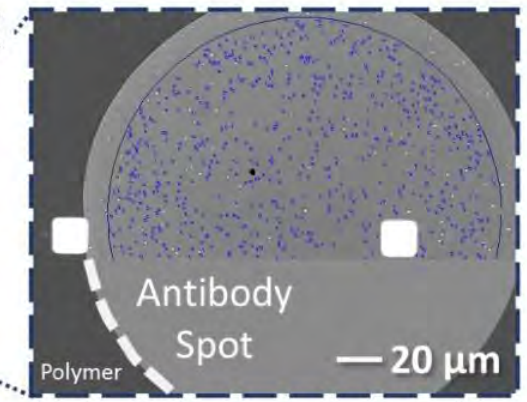




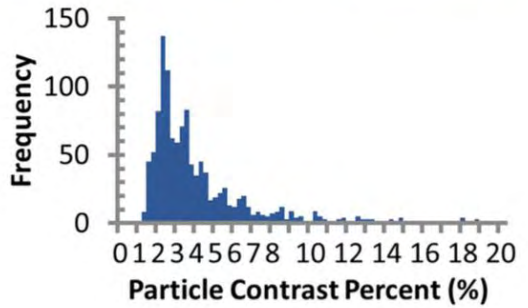




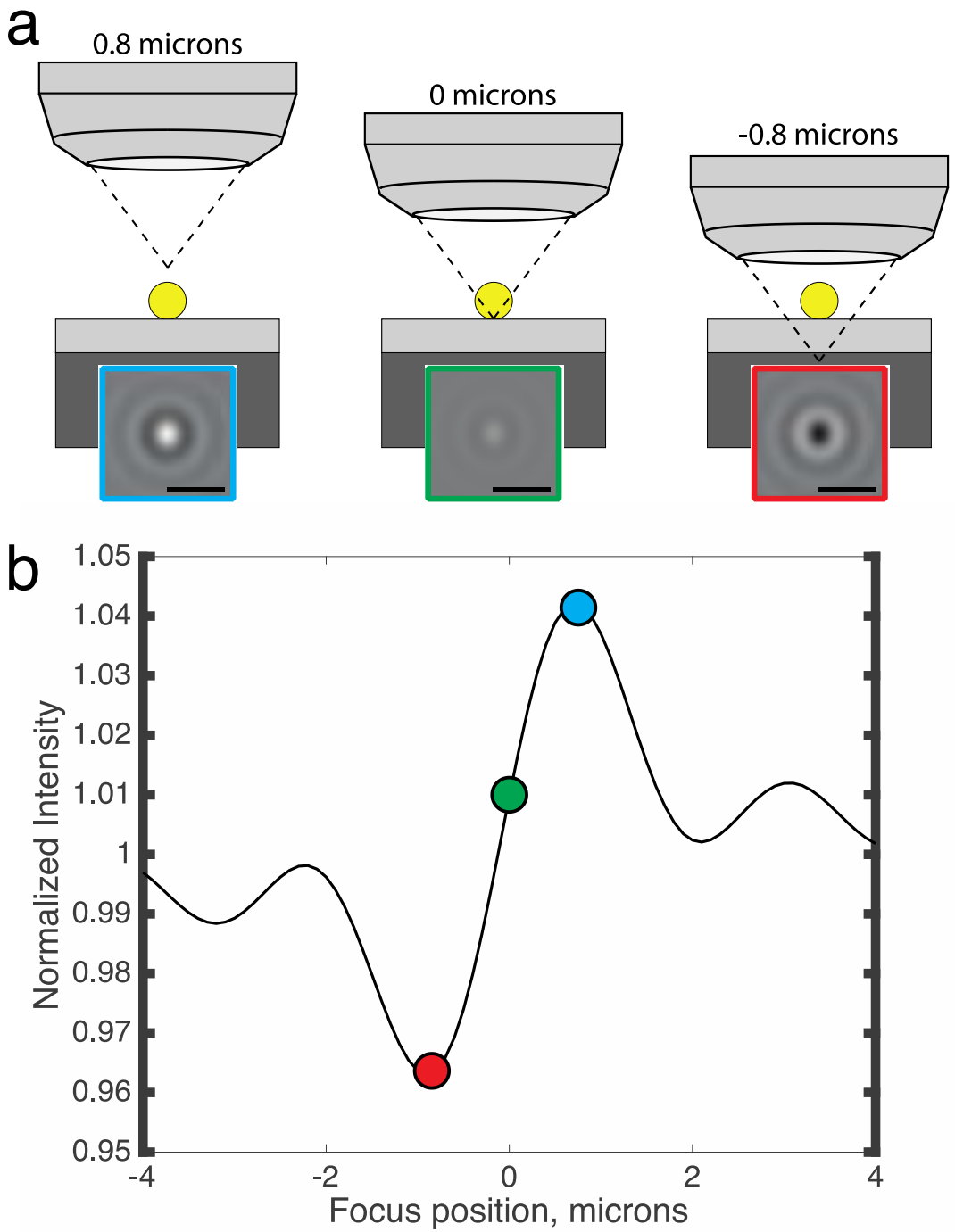




Daaboul '13



Accurate Sizing – defocus profile



$$I_{det} \propto |E_{ref}|^2 + |E_{sca}|^2 - 2|E_{ref}||E_{sca}|\sin\theta$$

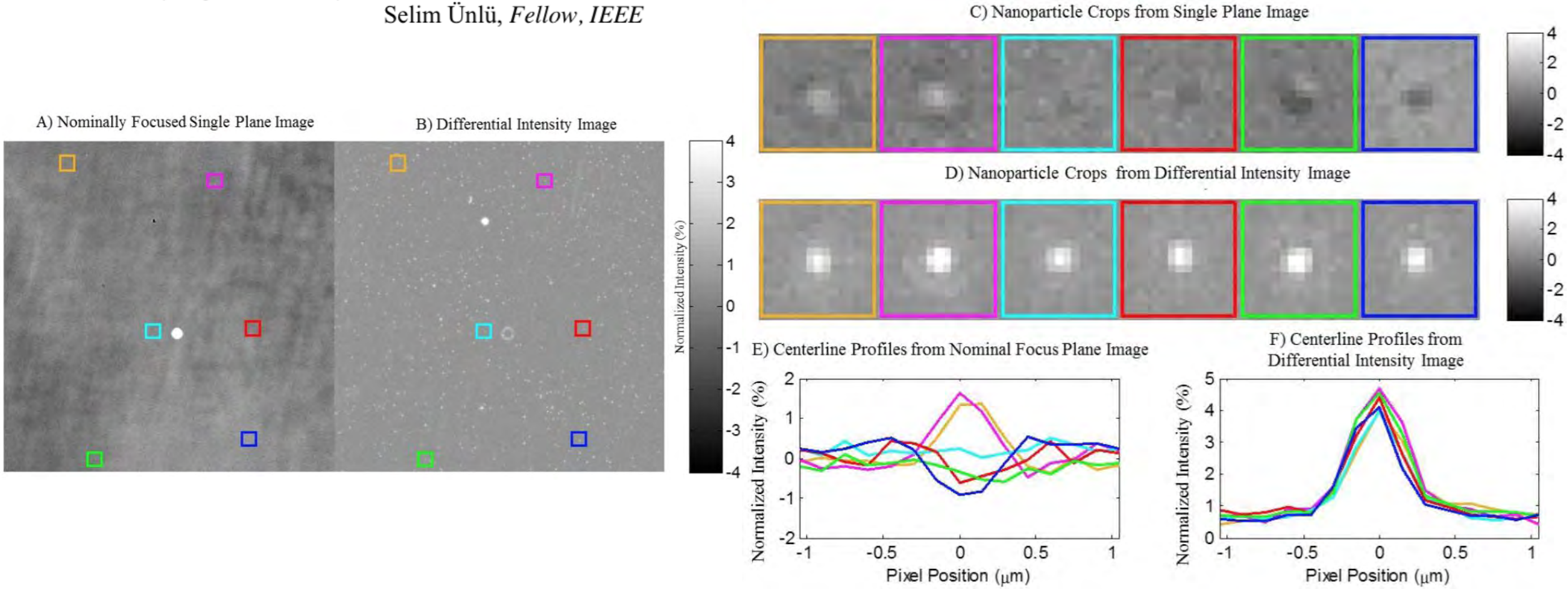
Changing the focus position changes the path length to the detector differently for reference reflection and scattered light

D. D. Sevenler, O. Avci, and M. S. Ünlü, **"Quantitative interferometric reflectance imaging for the detection and measurement of biological nanoparticles,"** *Biomedical Optics Express*, 2017

O. Avci, et al., **"Physical Modeling of Interference Enhanced Imaging and Characterization of Single Nanoparticles,"** *Optics Express*, 2016

Robust Visualization and Discrimination of Nanoparticles by Interferometric Imaging

Jacob Trueb ‡, Oguzhan Avci ‡, *Student Member, IEEE,* Derin Sevenler, John H. Connor, and M. Selim Ünlü, *Fellow, IEEE*



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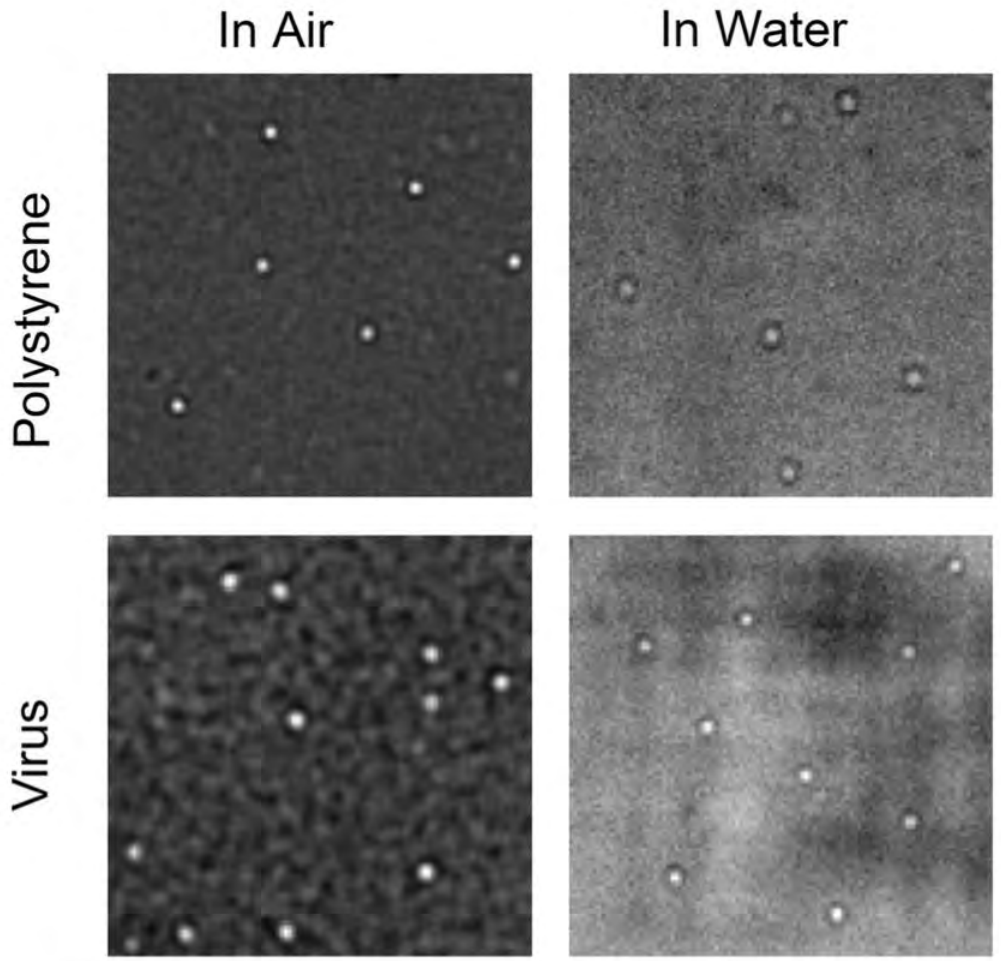
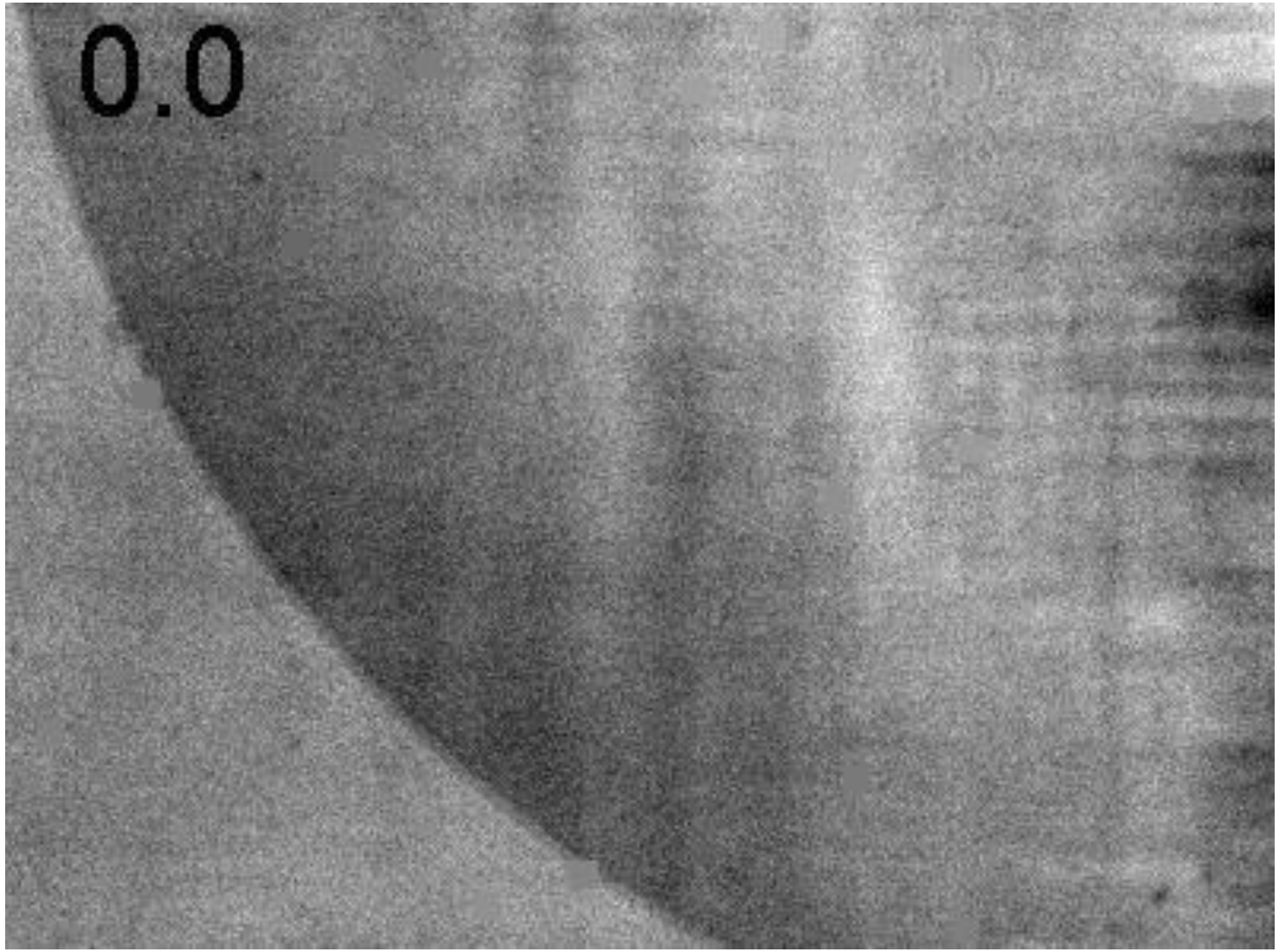
In-liquid detection for a more versatile assay



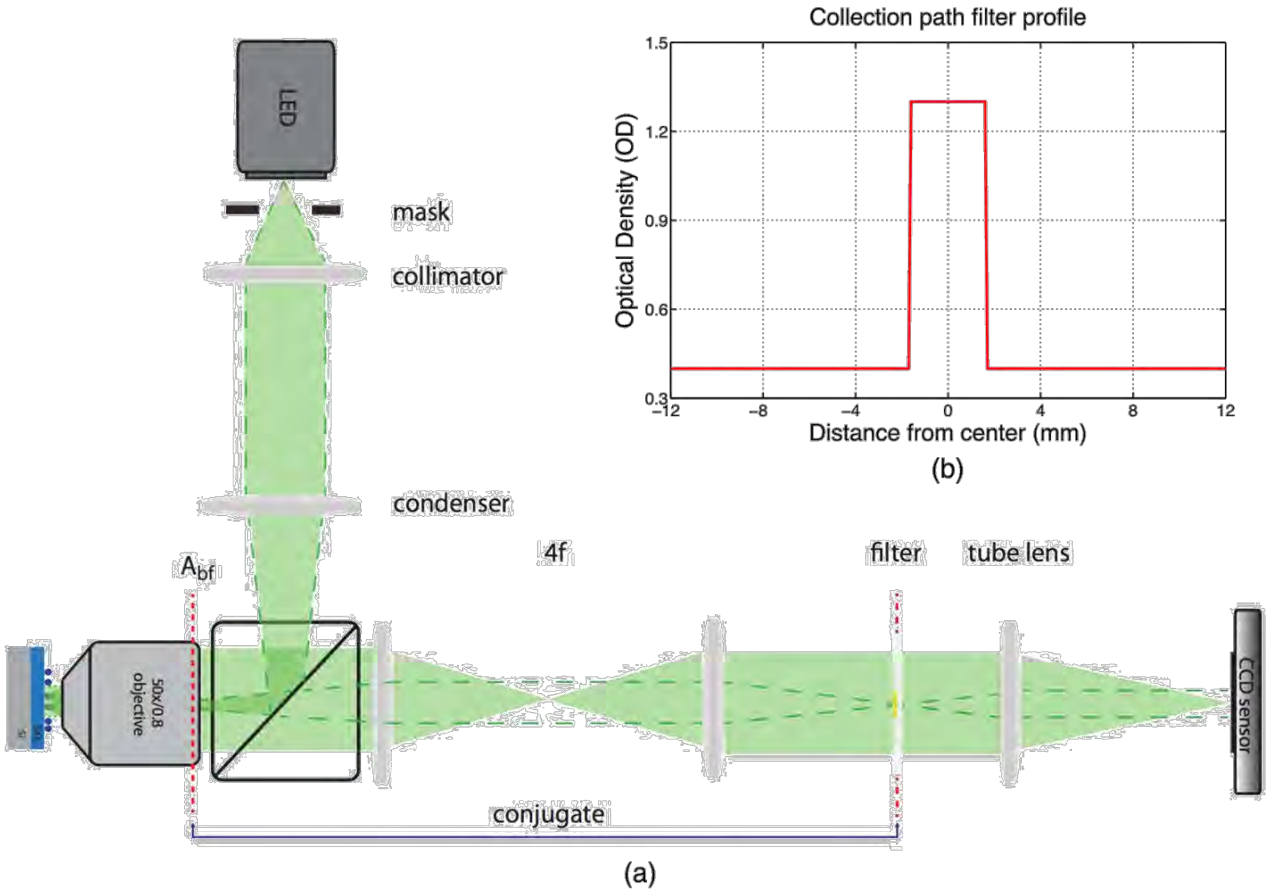


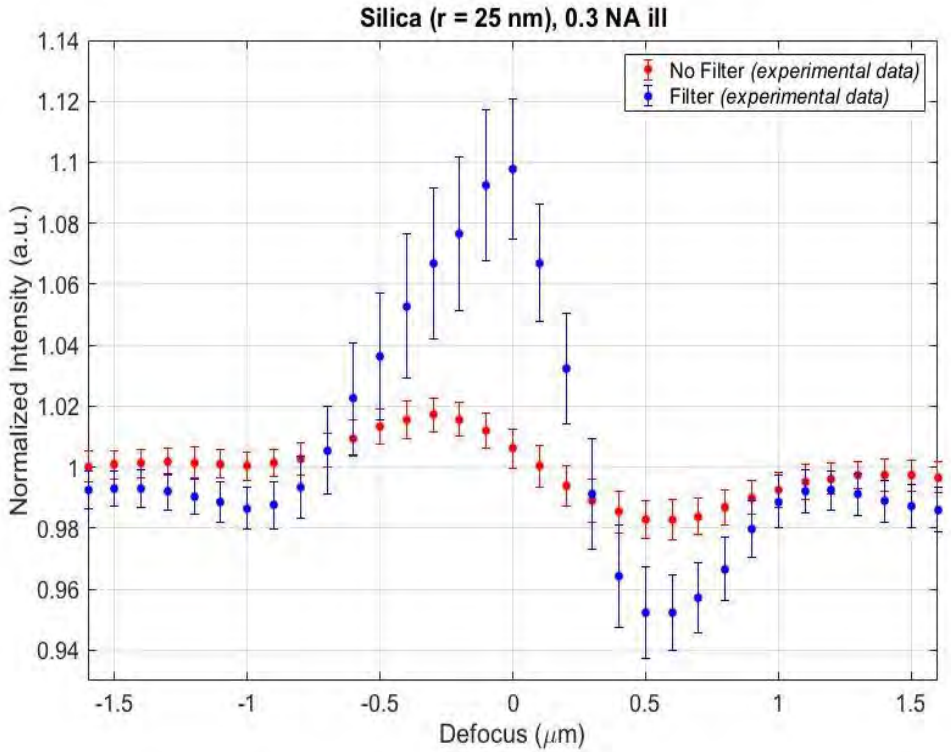
Research Article Vol. 4, No. 2 / February 2017 / Optica 247

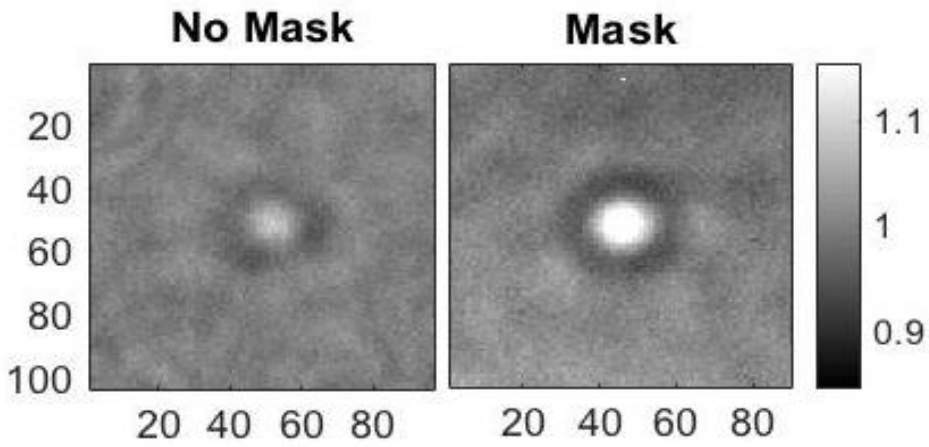
optica

Pupil function engineering for enhanced nanoparticle visibility in wide-field interferometric microscopy

Collection Path – Apodization and Reference Attenuation

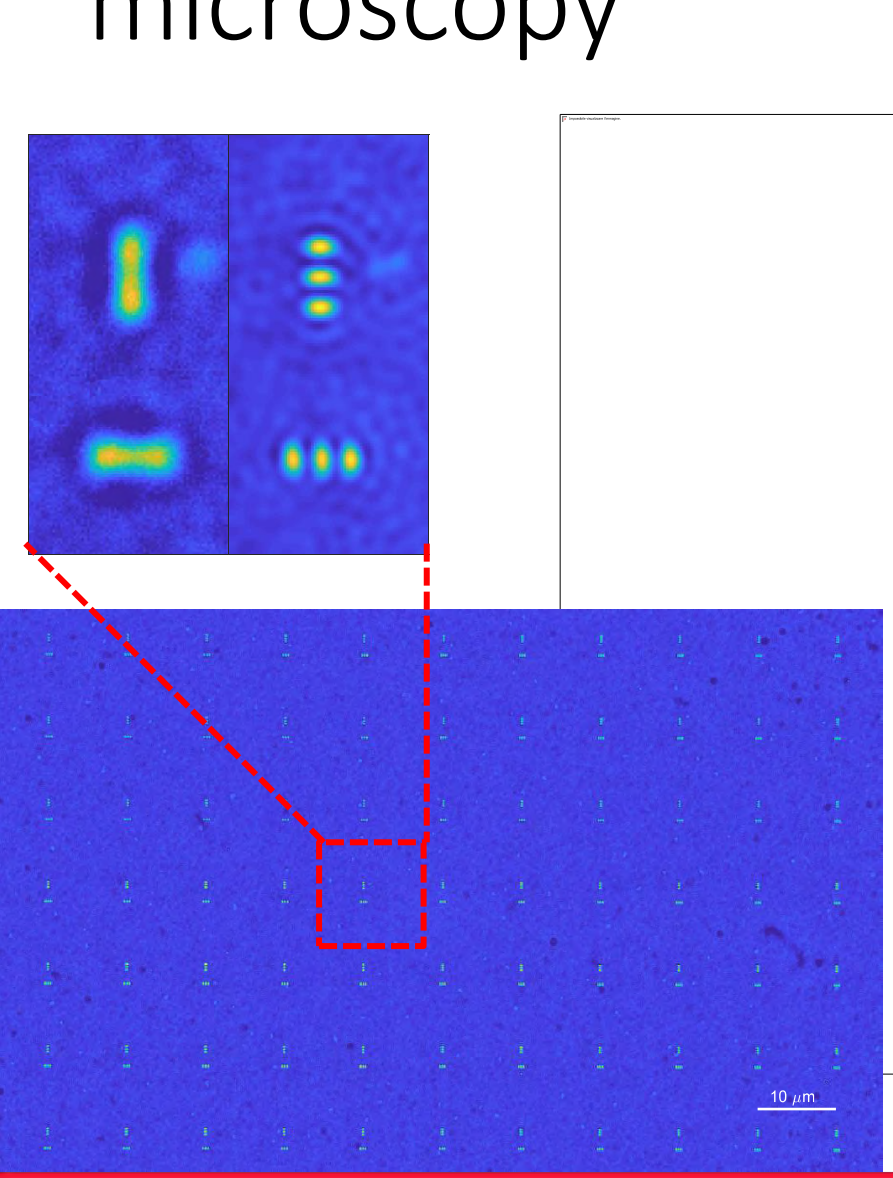


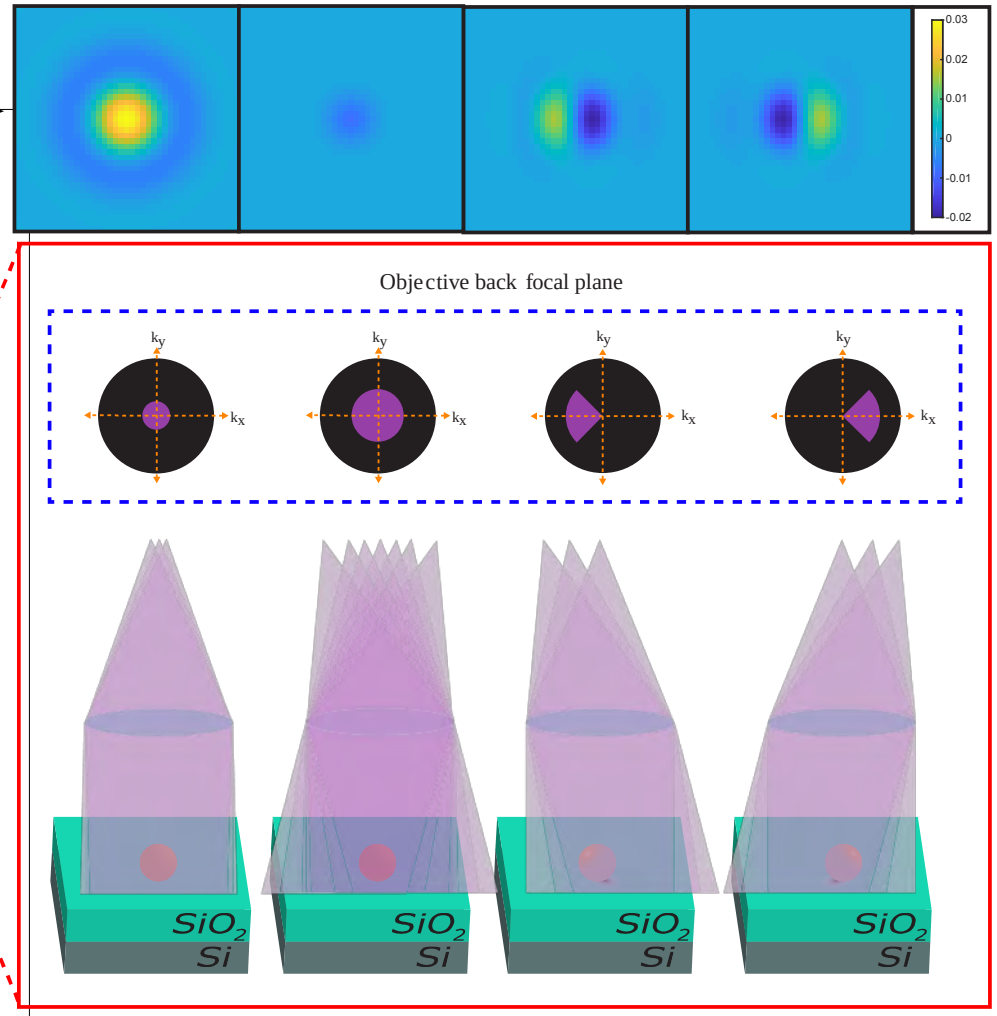




Contrast enhancement of Silica particles with r=25 nm using pupil function engineering.

Super-resolution in wide-field interferometric microscopy





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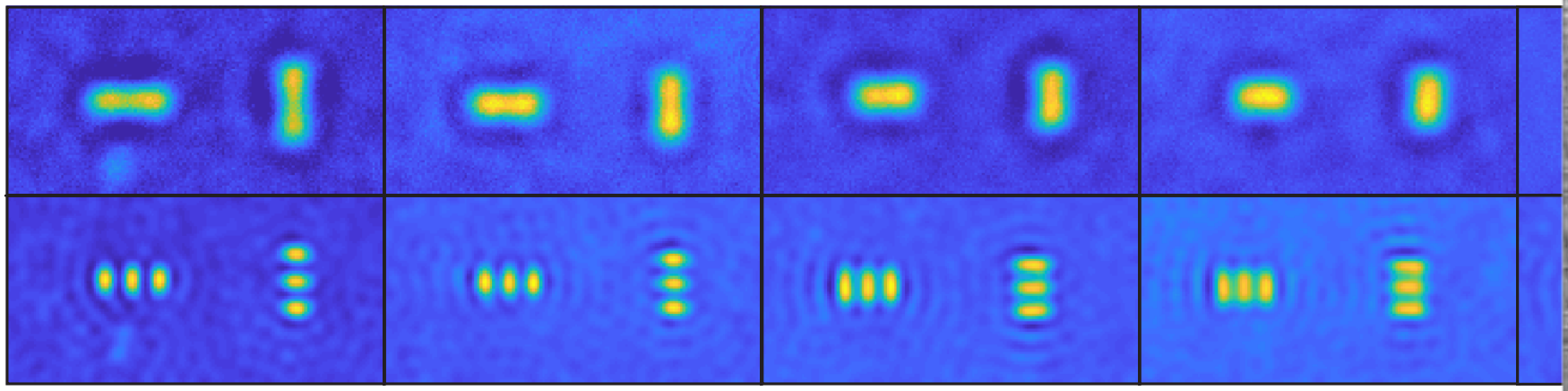
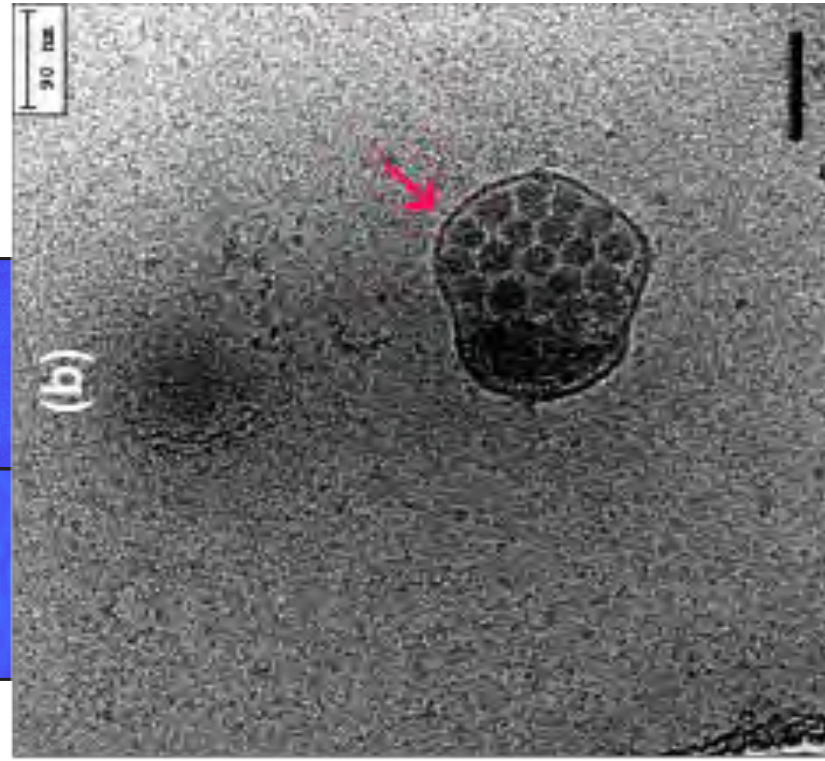
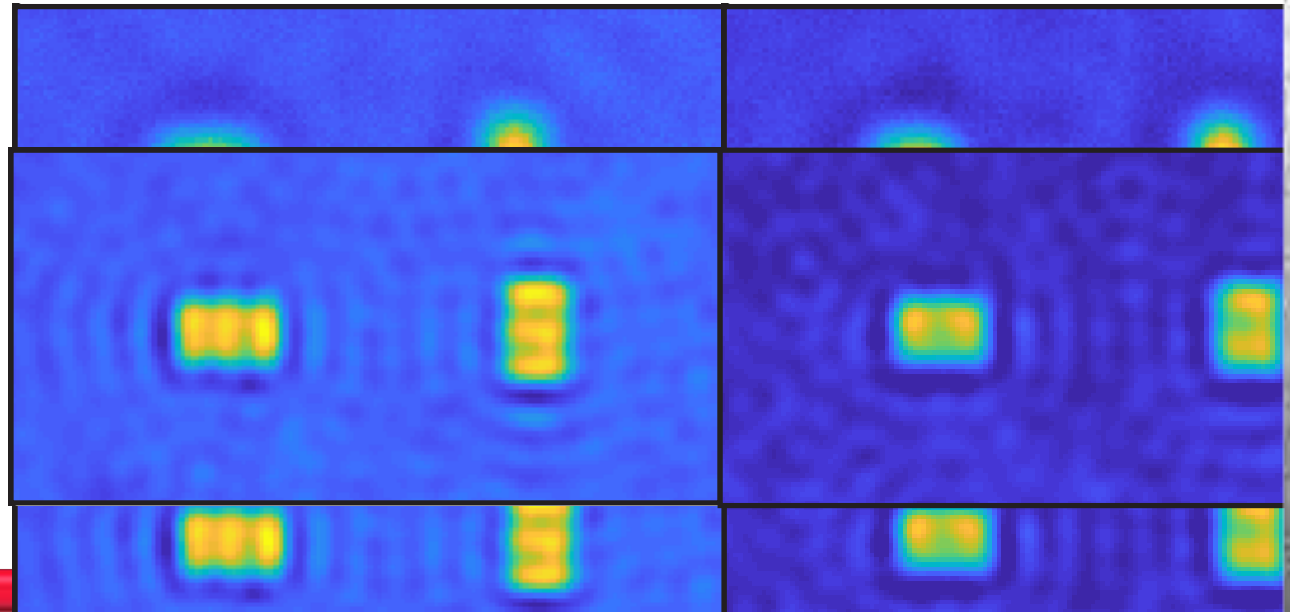
Reconstructed resolution targets

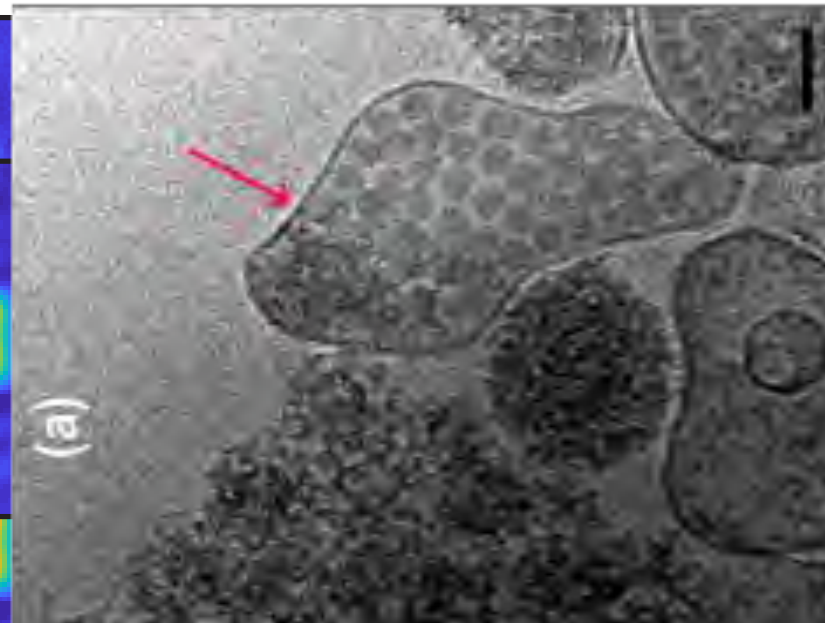
h = 300nm 200nm 175nm 150nm

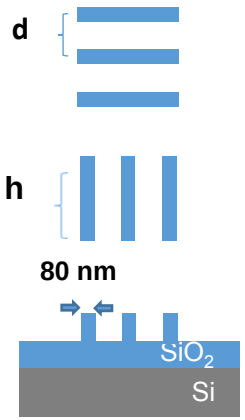


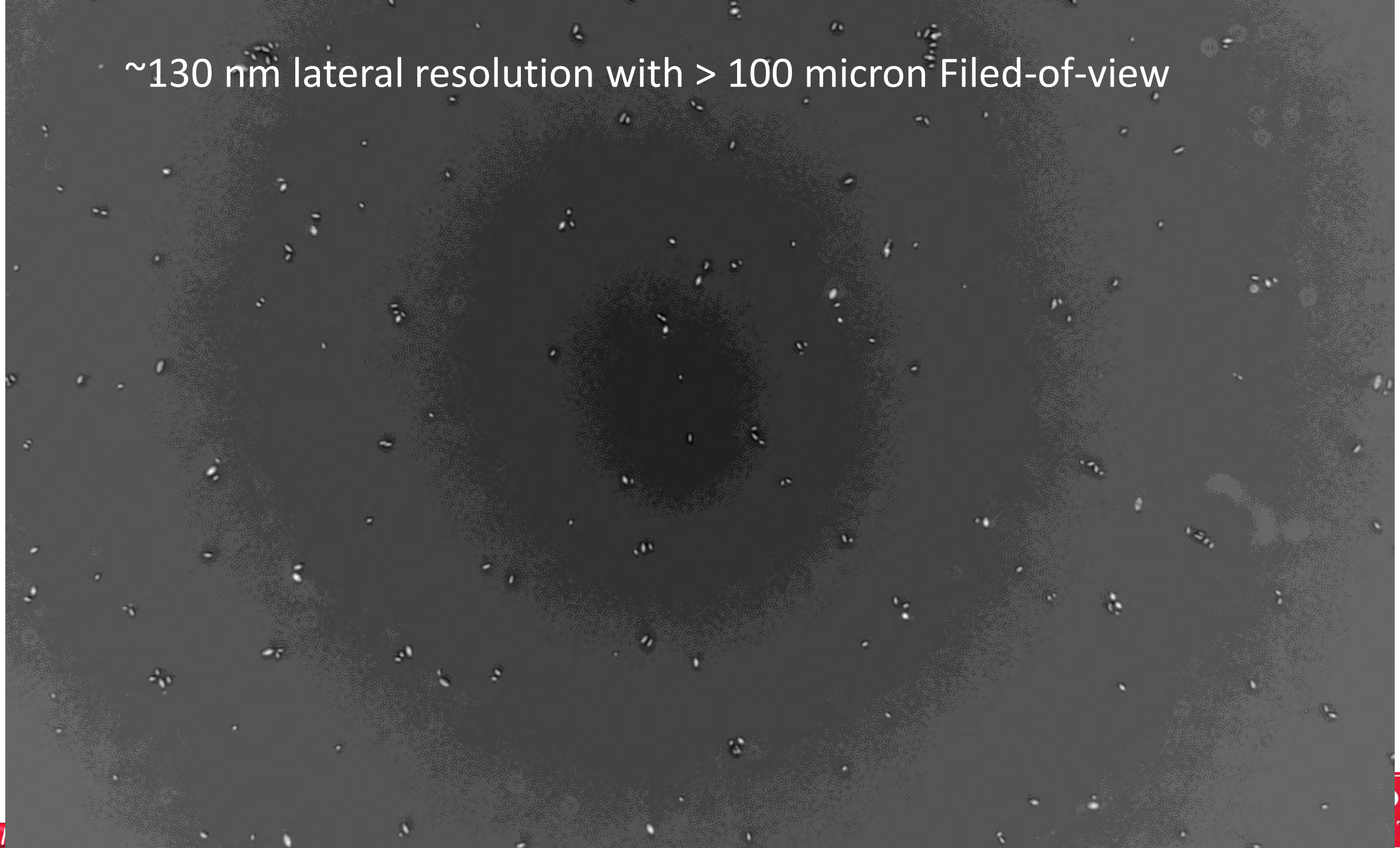


d = 125nm 100nm

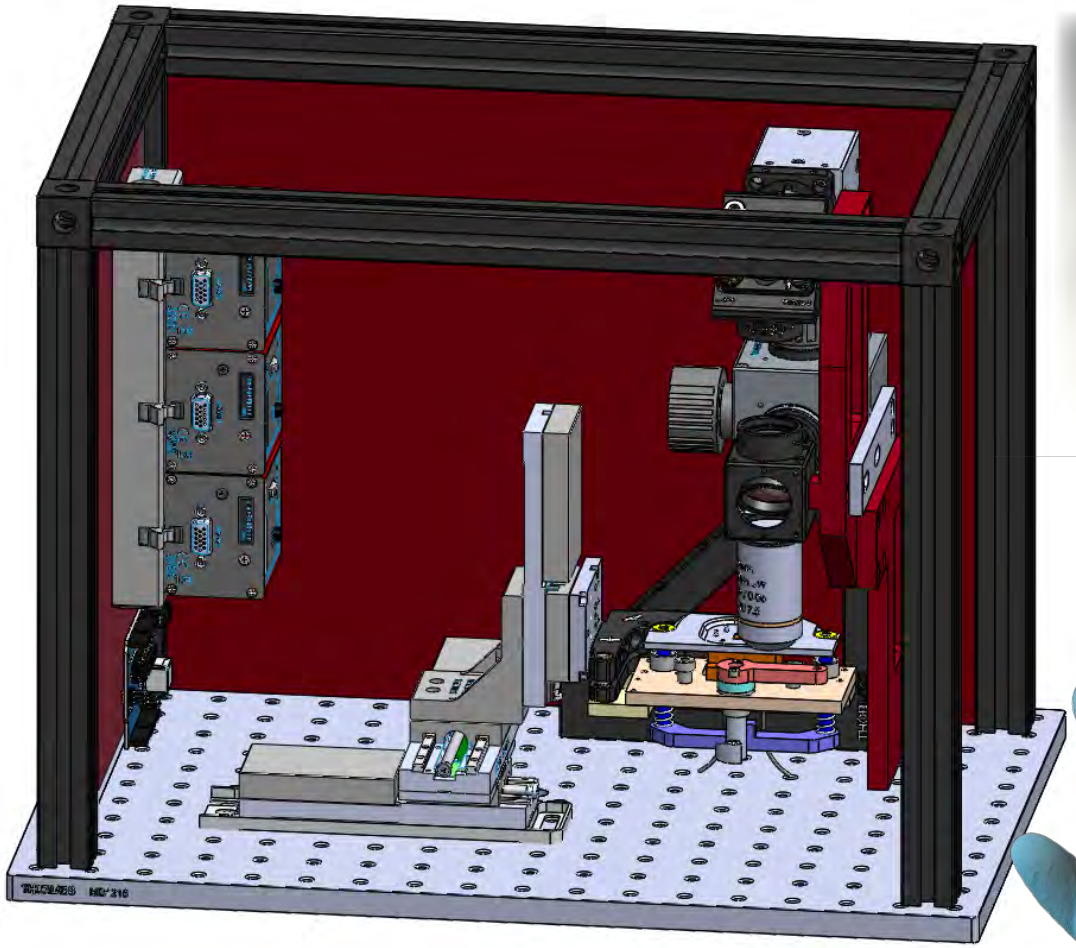


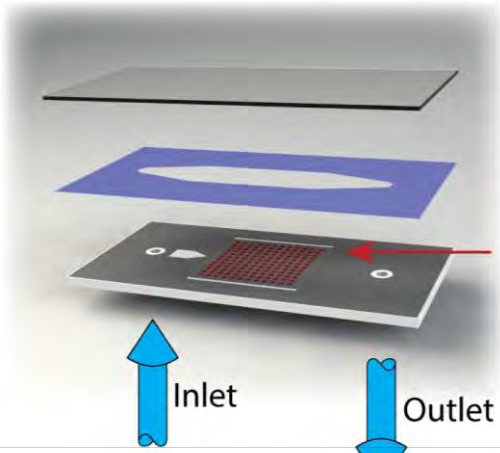


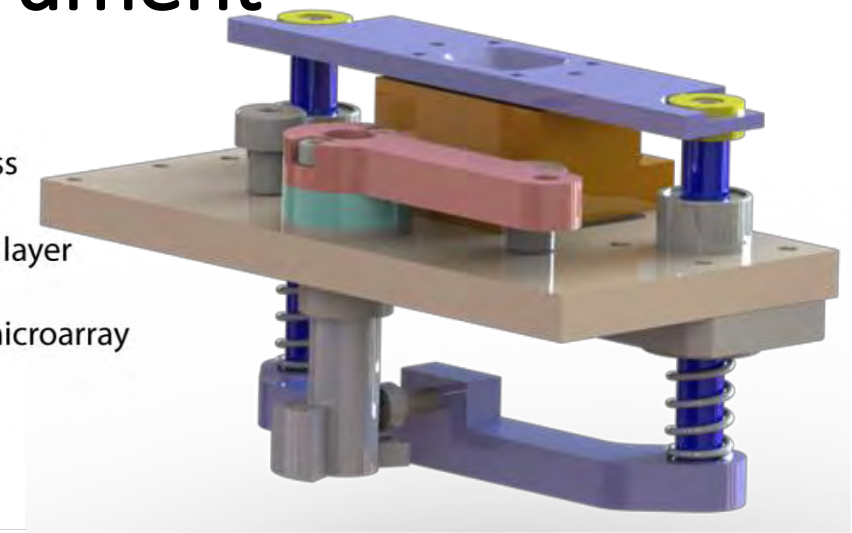


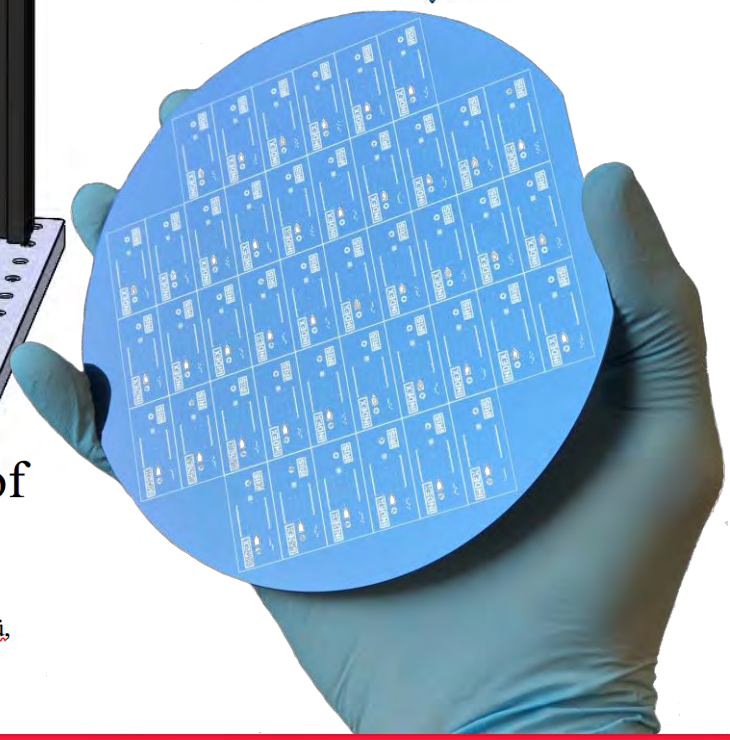

~130 nm lateral resolution with > 100 micron Filed-of-view

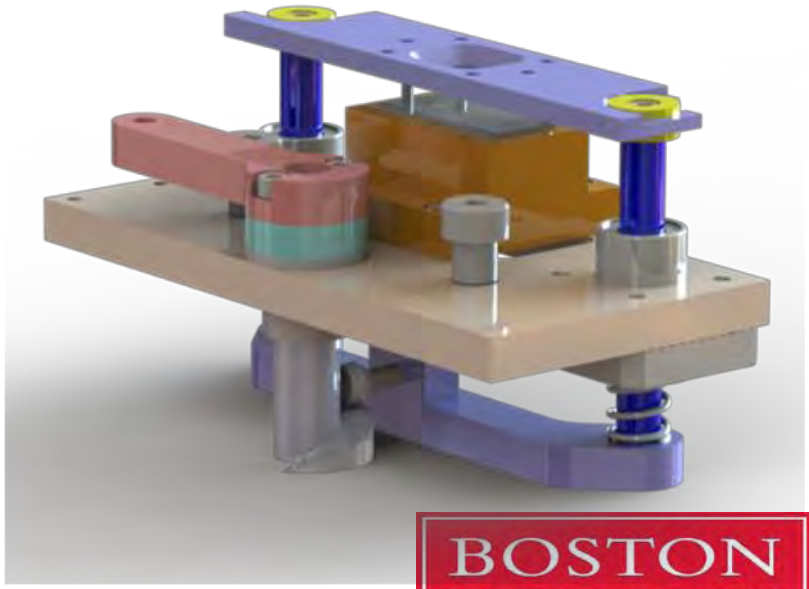
Chips, Si-based Microfluidics, Prototype Instrument











Interferometric Detection and Enumeration of Viral Particles using Si-based Microfluidics

Ayca Yalcin Ozkumur, Fulya Ekiz Kanik, Jacob Trueb, Celalettin Yurdakul, and M. Selim Ünlü,

IEEE JSTQE 2019

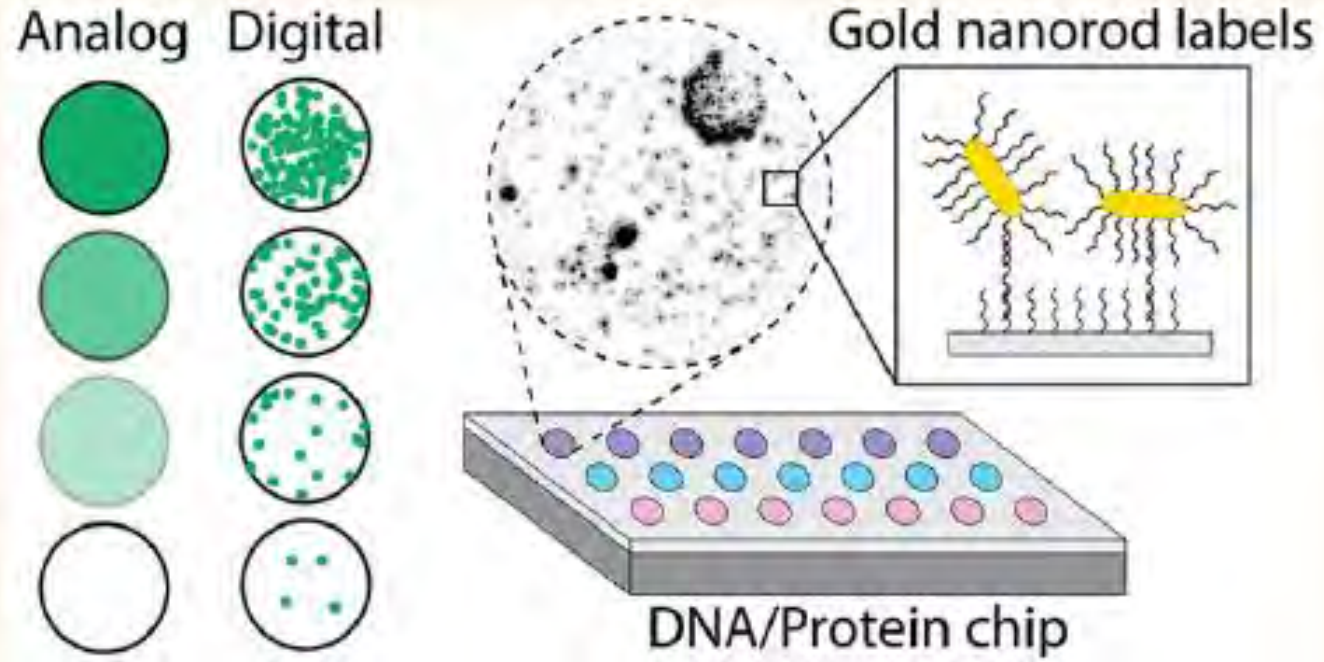
ACS NANO
Cite This: ACS Nano XXXX, XXX, XXX–XXX
www.acsnano.org

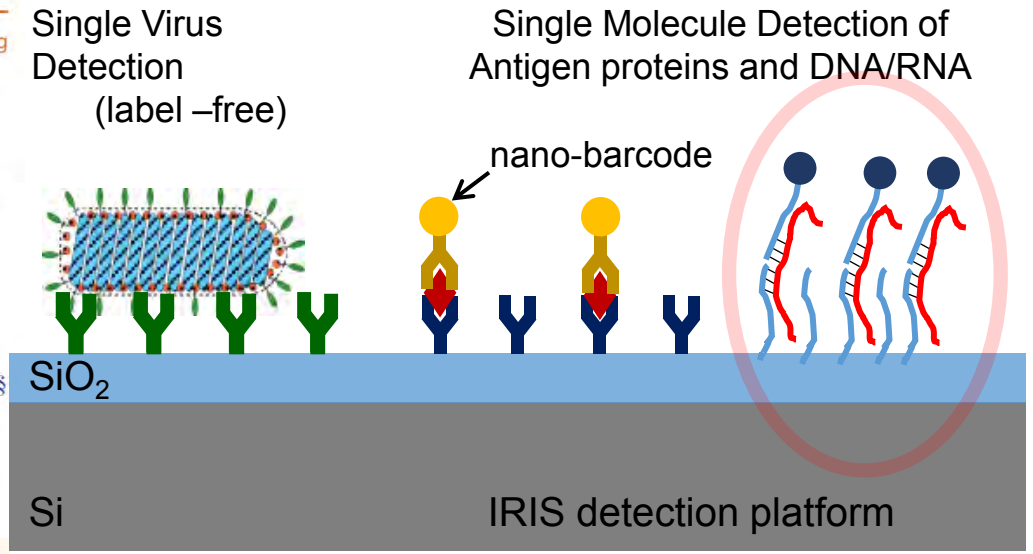
Digital Microarrays: Single-Molecule Readout with Interferometric Detection of Plasmonic Nanorod Labels

Derin Sevenler,*[,†] George G. Daaboul,[‡] Fulya Ekiz Kanik,[†] Neşe Lortlar Ünlü,[§] and M. Selim Ünlü[†,§]

[†]Department of Electrical and Computer Engineering and [§]Department of Biomedical Engineering, Boston University, Boston, Massachusetts 02215, United States

[‡]NanoView Biosciences, Boston, Massachusetts 02215, United States

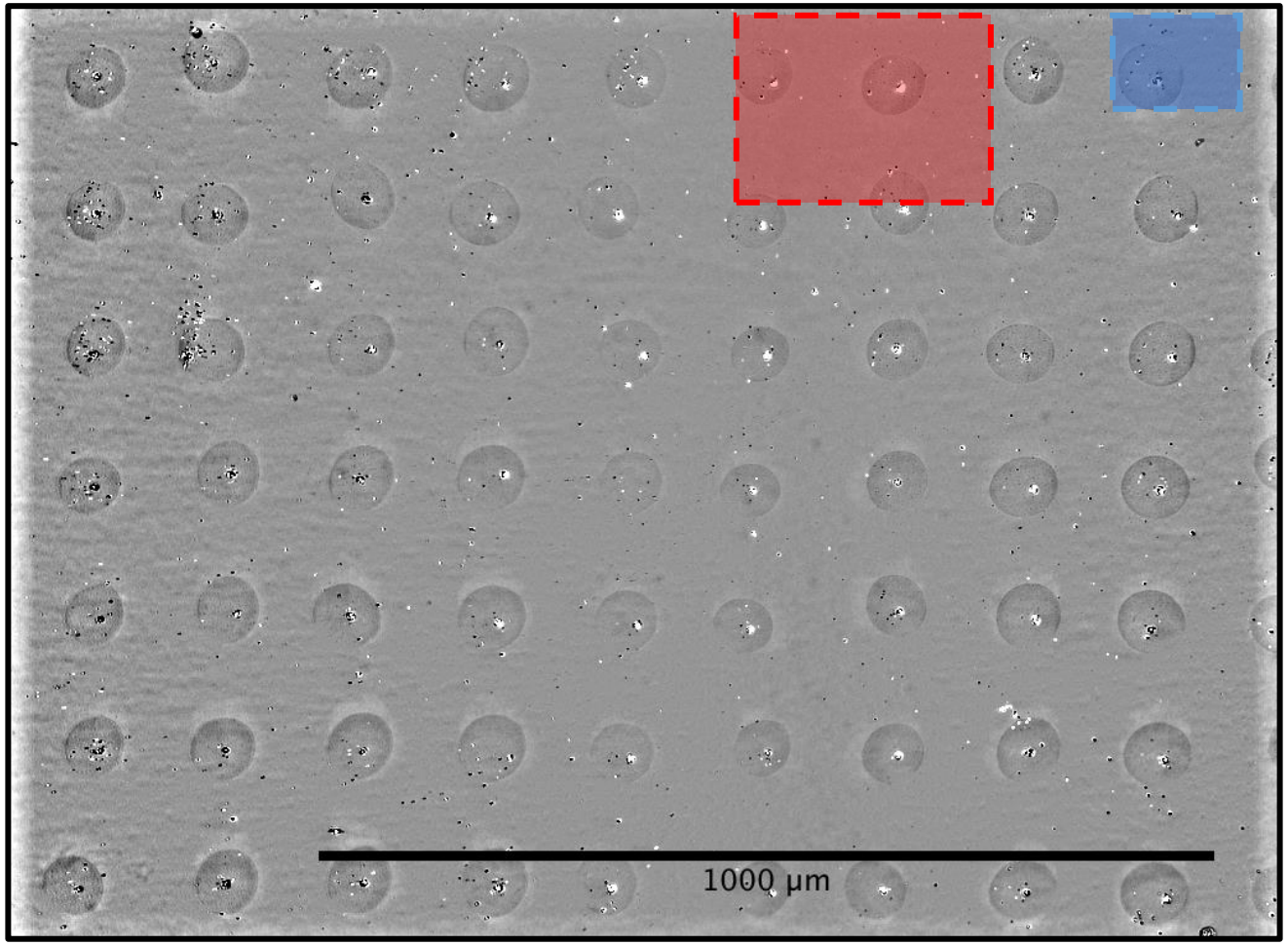


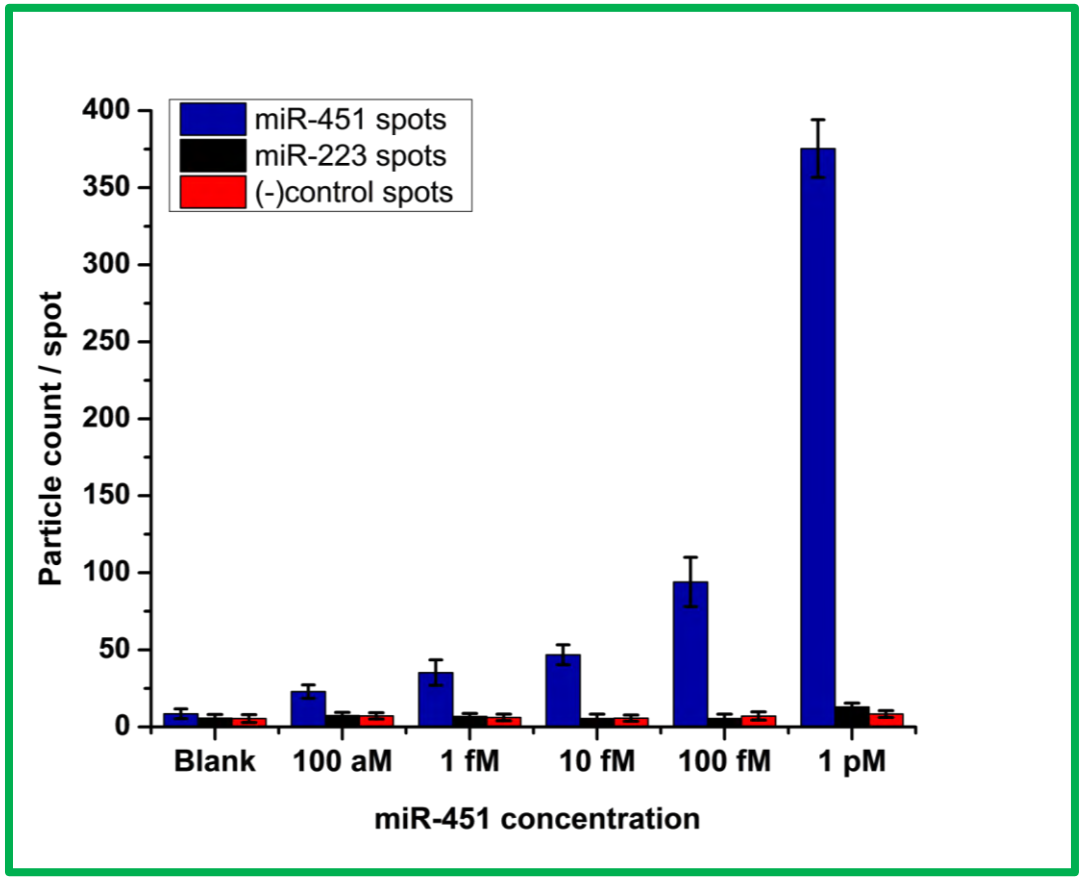


- Digital means counting
- 10,000-fold more sensitive than commercial microarrays, while maintaining all of the advantages:
  1. Highly multiplexed
  2. Low cost
  3. Fast
- Application: molecular diagnostics

A digital microarray with IRIS

10x Objective … 50x … 100x

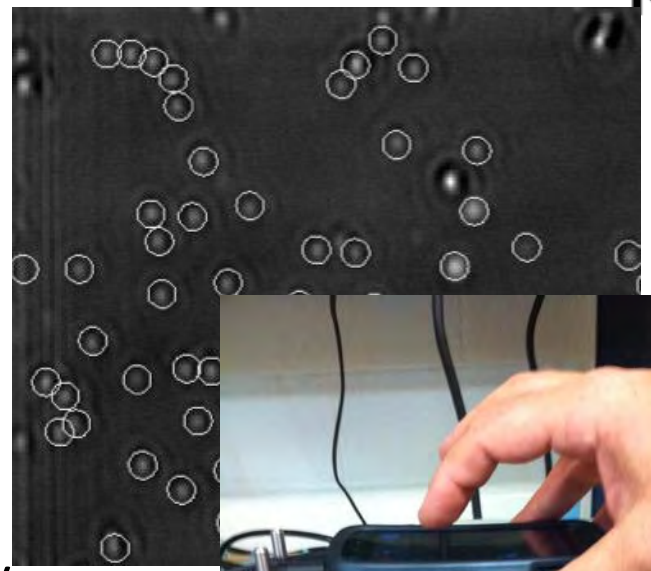


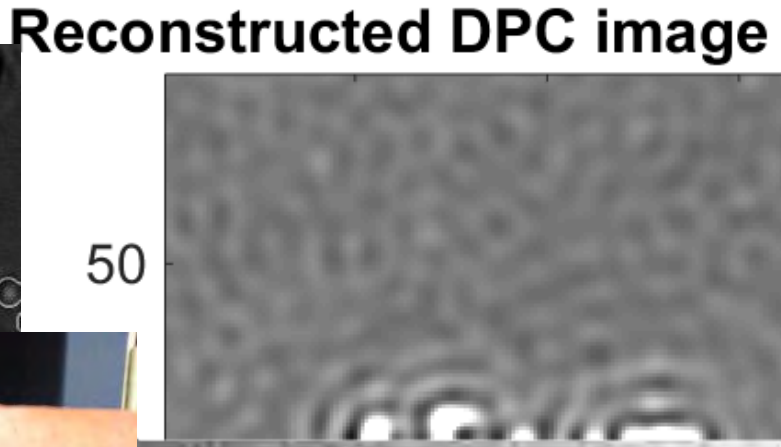


Detecting minute changes in cardiac biomarkers – at-risk patients identified earlier in their disease progression to guide more personalized care. miR-451 is a cardiac biomarker. Work in collaboration with Umass Medical.

CONCLUSIONS & FUTURE

- Optical interference is a very powerful measurement technique.
- Multi-disciplinary innovation
- Single biological nanoparticle detection / counting / size and shape discrimination / visualization
- **Goals:** Down to r=20nm Biological nanoparticle detection in liquid
- Lateral resolution of ~100nm without labeling





NIH – NIAID, NSF
BD Biosciences

Marcella Chiari (CNR, Milan)
Fred Little (MED)
Rhoda Alani (MED)
Caroline Genco (MED)
Charles DeLisi (BME)
Charles Cantor (BME)

UTMB

Questions?