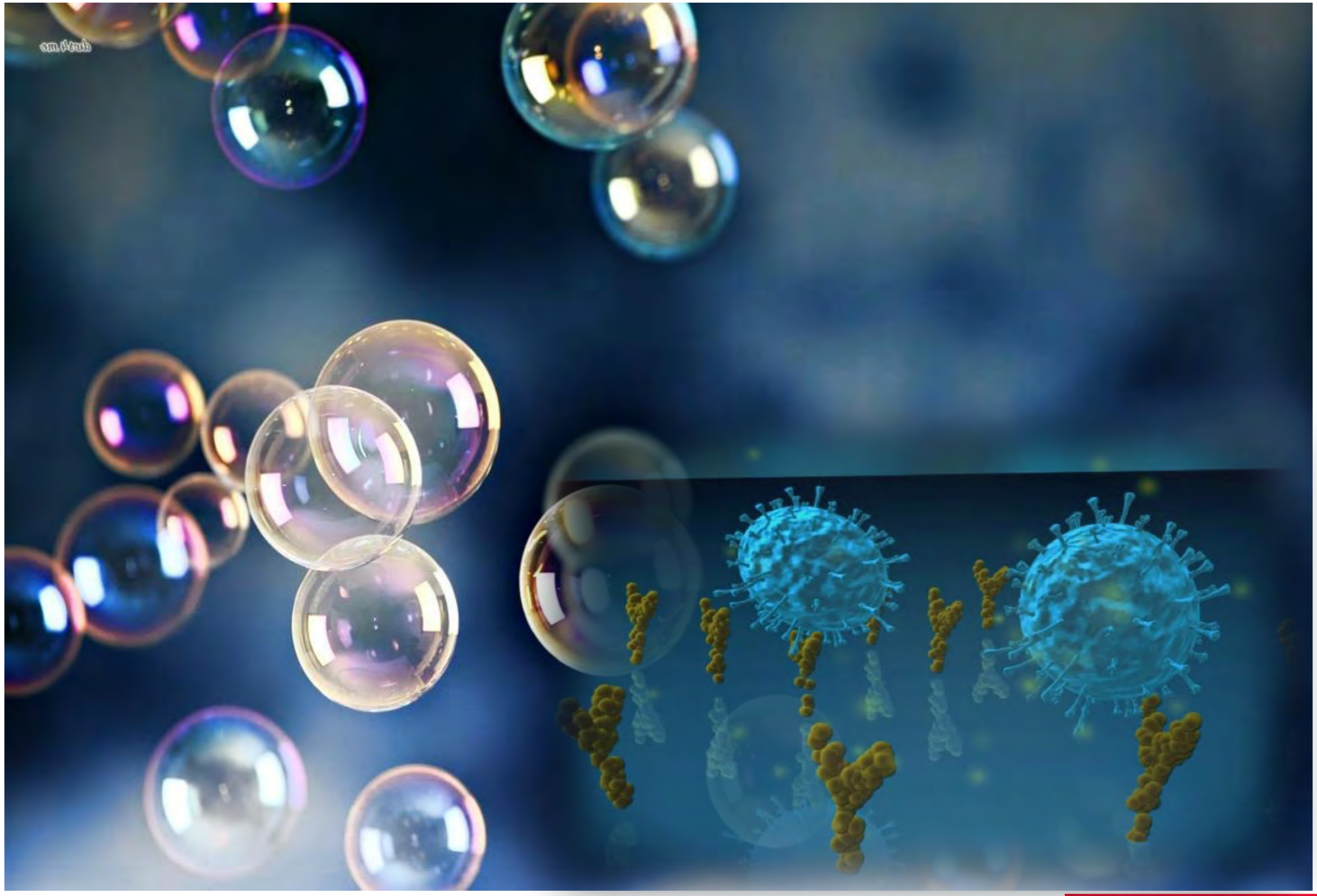
Interferometric Microscopy for Detection and Visualization of Biological Nanoparticles



M. Selim Ünlü

Electrical Engineering,

Physics,

Biomedical Engineering

Graduate Medical Sciences

BUNano

Photonics Center

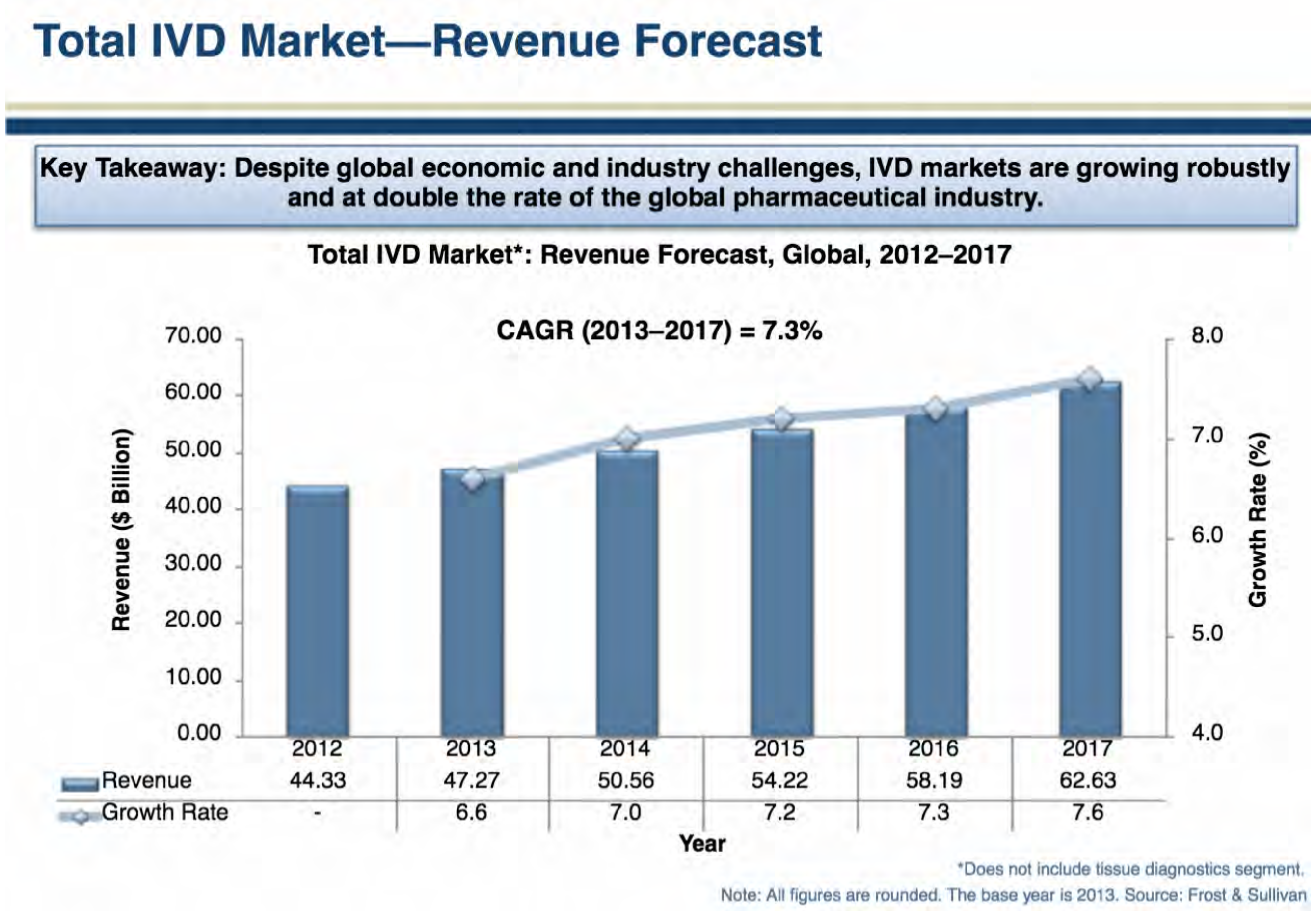
BOSTON UNIVERSITY

OUTLINE

- A bit of philosophy – some history of optics
  - Optical Interference
- Interferometric Reflectance Imaging Sensor (IRIS)
  - Principles
  - Requirements and technology
- Kinetic measurements of molecular binding
- Single bio-nanoparticle detection
  - Exosomes
  - Viruses
  - Bacteria
- Super-resolution imaging
- Single Molecule Detection

MOTIVATION

Enjoy curiosity driven research to make the world a better place for all.
Training / transforming students.



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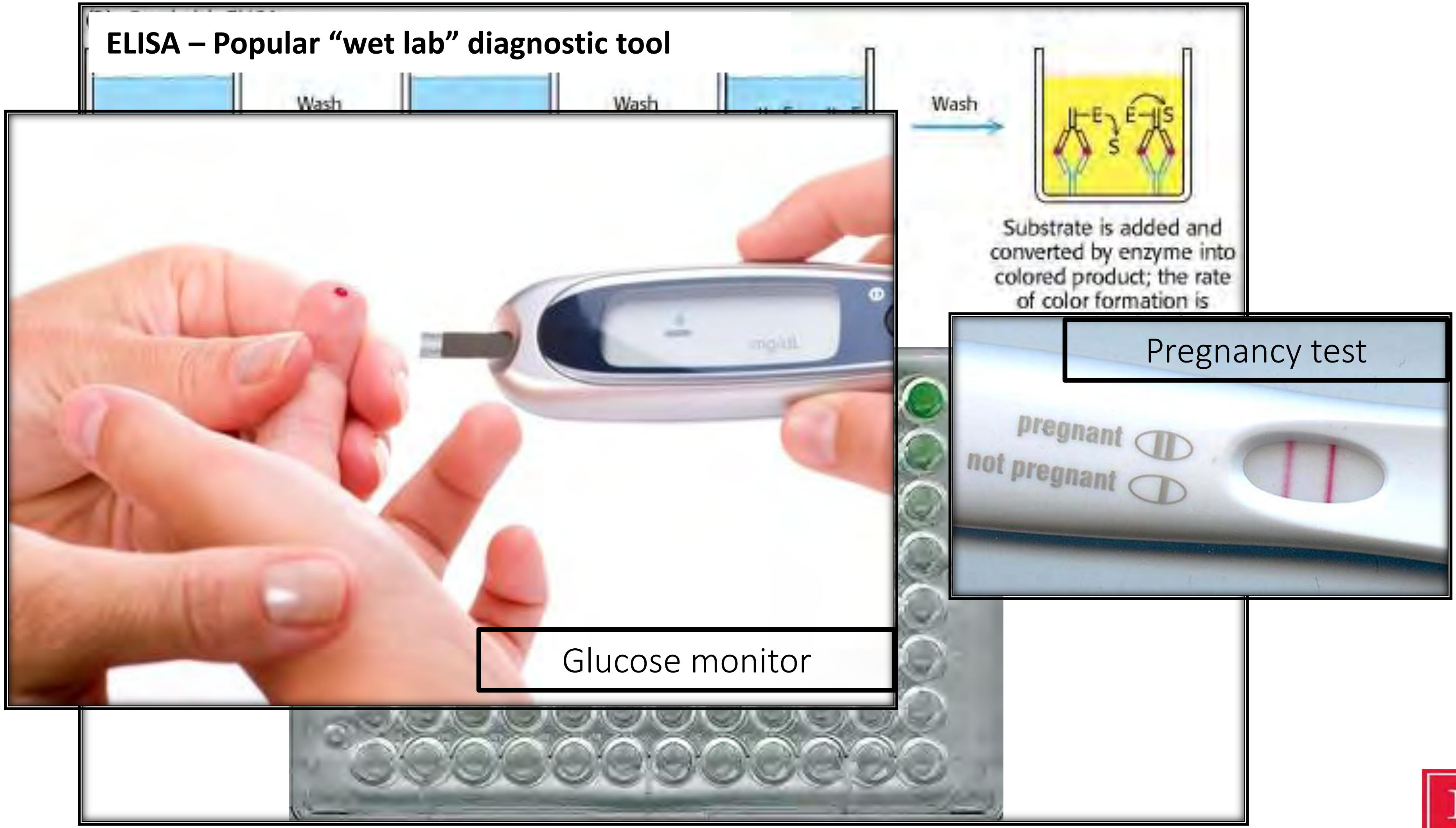
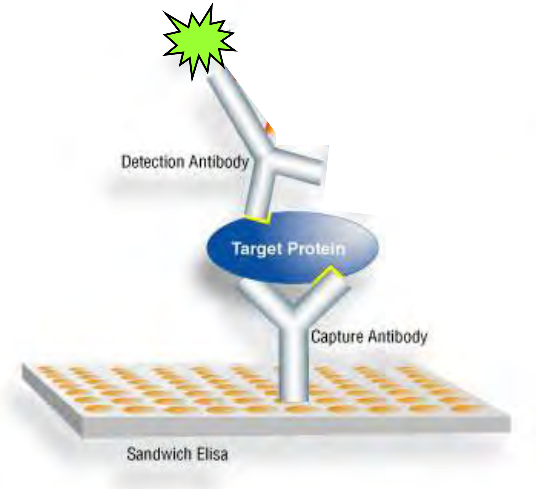
Conventional *in vitro Dx* (IVD)

- Biomarkers indicate state of disease
- Point of care (POC) diagnostics would expedite clinical decision making



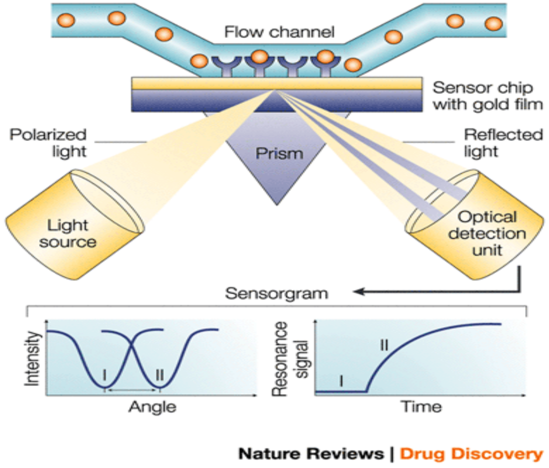
Diagnostics/detection

ELISA
(Enzyme-linked immunosorbent assay)



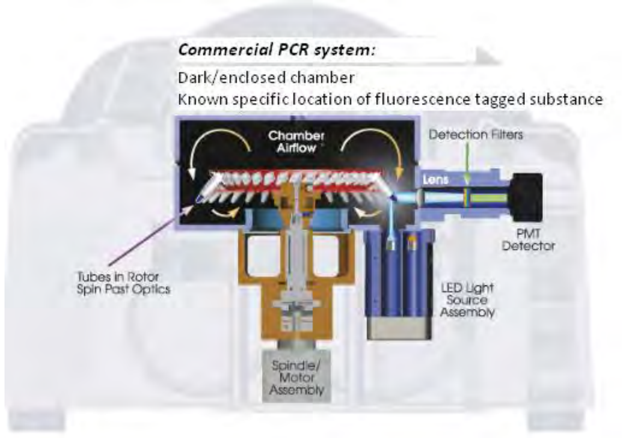
- Uses secondary labeling for detection
- Requires laboratory and skilled technicians
- Time-consuming process

SPR
(Surface Plasmon Resonance)

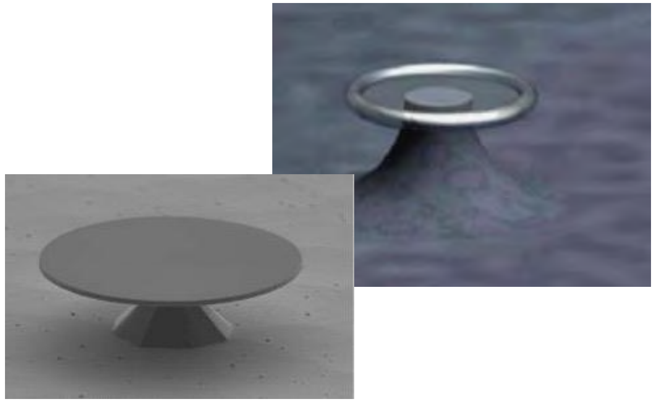


- Label-free optical detection
- Large, expensive equipment
- Requires laboratory environment

PCR
(polymerase chain reaction)

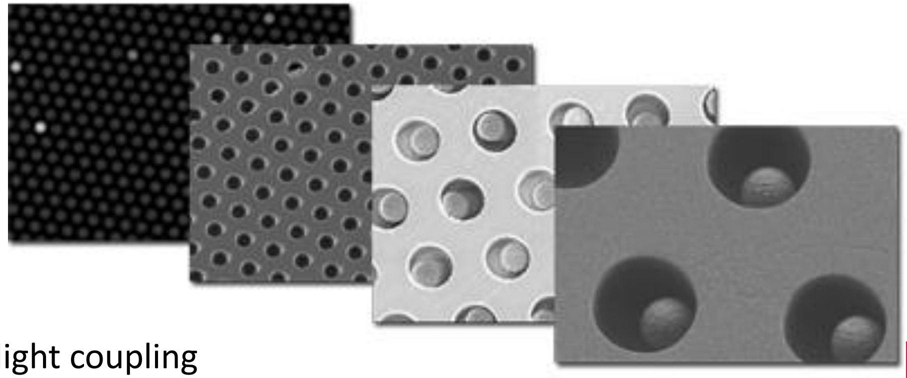


- Sample preparation,
- Dark/enclosed chamber,
- Known specific location of target



Single particle detection
- High-Q Resonators
- Digital PCR, Simoa

- Small interaction volume
- Fragile/complex devices, difficult light coupling



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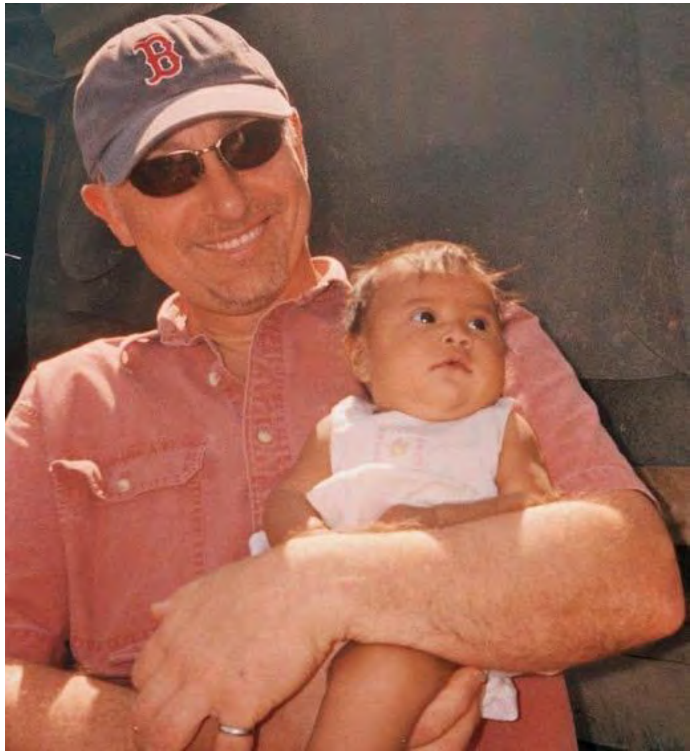
Altruistic - MOTIVATION

Global access to state-of-the-art diagnostics



March 2011, Nicaragua
Field trip with 14 BU-ENG undergraduate students.
Global health / limited resource settings

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Optics in 17th-century Europe

Rene Descartes

Descartes reasoned that light must be like sound.

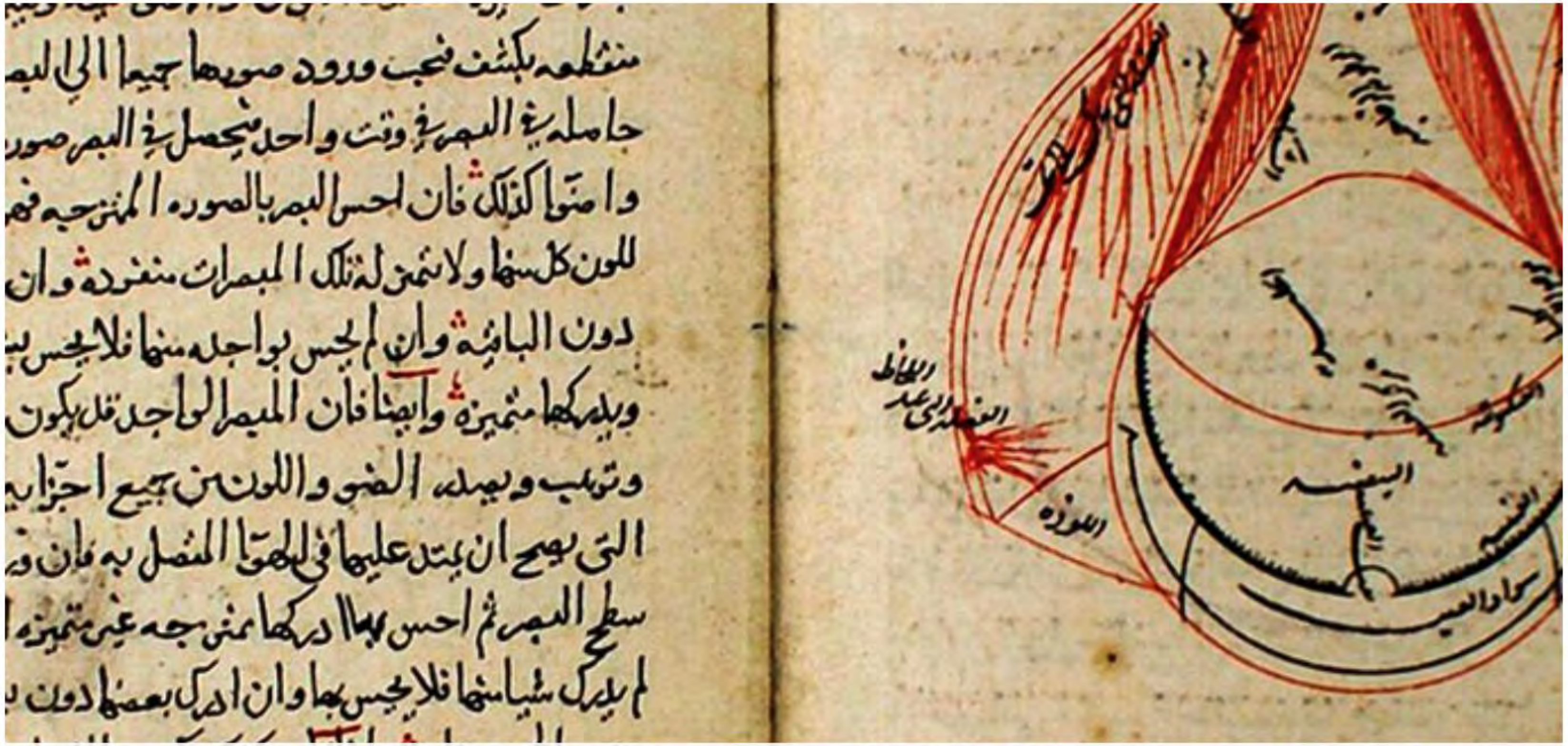
Is light a WAVE then ?

So he modeled light as pressure variations in a medium (aether or ether).

Descartes (1596-1659)

Kamāl al-Dīn al-Fārisī
فـارسى كمال الدين

Farisi is known for giving the first mathematically satisfactory explanation of the rainbow, and an explication of the nature of colors that reformed the theory of Ibn al-Haytham Alhazen



Kamal al-Din al-Farisi's Tanqih al-Manazir, a revision of Ibn Al-Haytham's book of optics (708 H.E./1309 A.D.) Adilnor Collection.

Farisi also "proposed a model where the ray of light from the sun was **refracted twice** by a water droplet, **one or more reflections occurring between the two refractions**." He verified this through extensive experimentation using a transparent sphere filled with water

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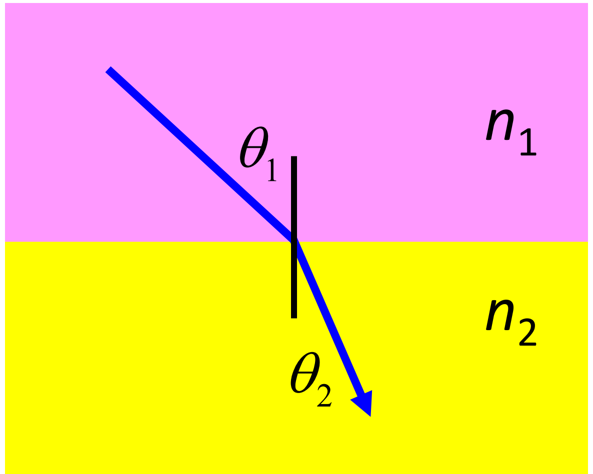
Optics in 17th-century Europe

Willibrord Snell discovered the Law of Refraction, now named after him.



n_i is the refractive index of each medium.

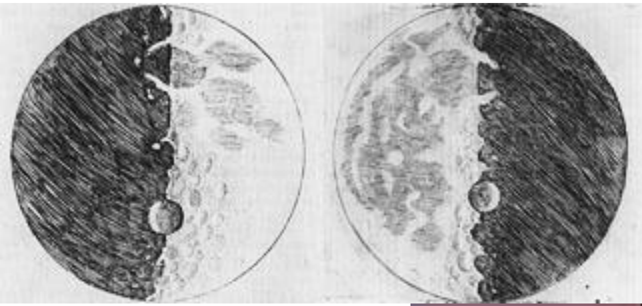
$$n_1 \sin(\theta_1) = n_2 \sin(\theta_2)$$

Willibrord Snell (1591-1626)

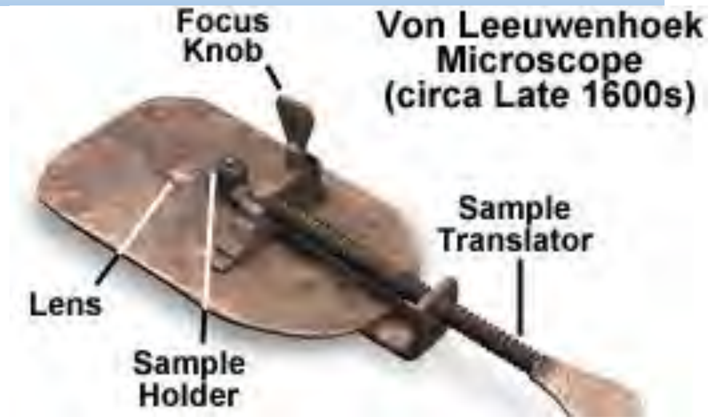
The person who did discover the Law of the Sines, was Willebrord Snell, about 1621; but the law was first published by Descartes, who had seen Snell's papers'. Descartes does not acknowledge this law to have been first detected by another; and after his manner, instead of establishing its reality by reference to experiment, he pretends to prove *à priori* that it must be true', comparing, for this purpose, the particles of light, to balls striking a substance which *accelerates* them.

Optics in 17th-century Europe

Galileo (1564-1642) used Galilean telescope to look at our moon, Jupiter and its moons, and the sun.



Galileo's drawings of the moon



Optics in 17-18th-century Europe

"I procured me a triangular glass prism to try therewith the celebrated phenomena of colours." (Newton, 1665)

Isaac Newton
(1642-1727)

Light was one of Newton's many areas of research. After remaining ambivalent for many years, he eventually concluded that it was evidence for a <u>particle theory of light</u>.

THE

LONDON AND EDINBURGH

PHILOSOPHICAL MAGAZINE

AND

JOURNAL OF SCIENCE.

CONDUCTED BY

SIR DAVID BREWSTER, K.H. LL.D. F.R.S. L. & E. &c.

RICHARD TAYLOR, F.S.A. L.S. G.S. Astr. S. &c.

AND

RICHARD PHILLIPS, F.R.S. L. & E. F.G.S. &c.

"Nec aranearum sane textus ideo melior quia ex se fila gignunt, nec noster vilior quia ex alienis libamus ut apes." Just. Lips. *Monit. Polit.* lib. i. cap. 1.

VOL. II.

NEW AND UNITED SERIES OF THE PHILOSOPHICAL MAGAZINE AND JOURNAL OF SCIENCE.

JANUARY—JUNE, 1833.

LONDON:

PRINTED BY RICHARD TAYLOR, RED LION COURT, FLEET STREET, *Printer to the University of London.*

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Philosophical magazine

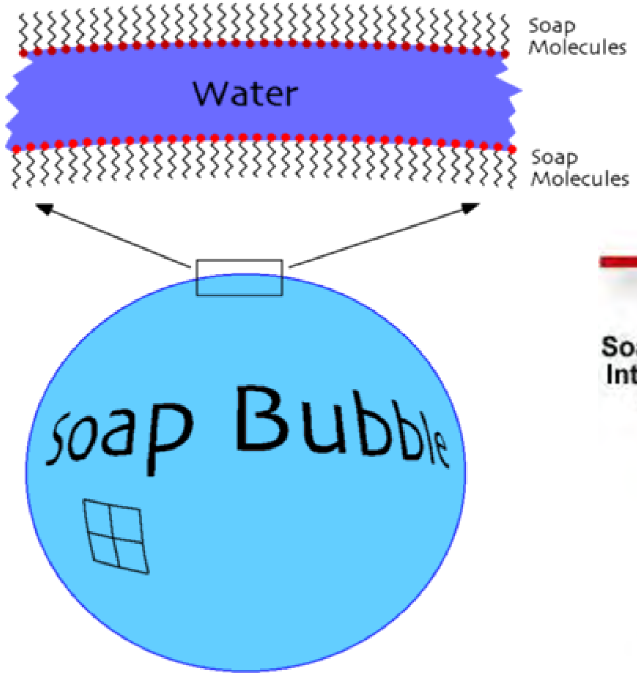
VI. *On the Phænomena of* Newton's *Rings when formed between two transparent Substances of different refractive Powers. By* G. B. Airy, *M.A. F.R.A.S. F.G.S. Late Fellow of Trinity College, and Plumian Professor of Astronomy and Experimental Philosophy in the University of Cambridge**.

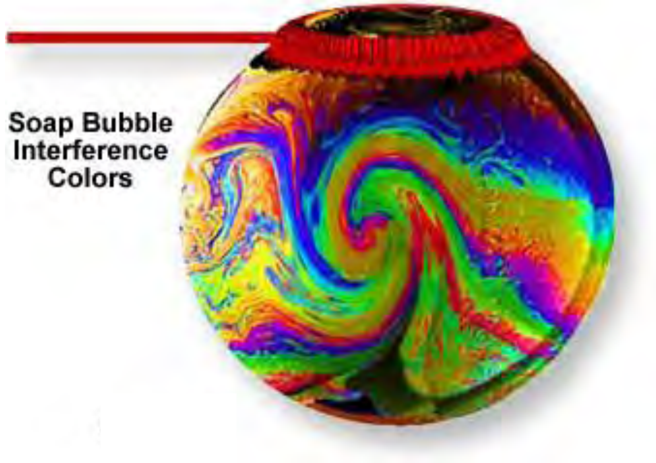
IN a paper comm... since, I stated m... that if a lens of a... plane surface of a l... ized in the plane p... incident upon it, t... less than the polar... or greater than tha... rings would be se... incidence was gre... second, Newton's... I have now to ann...

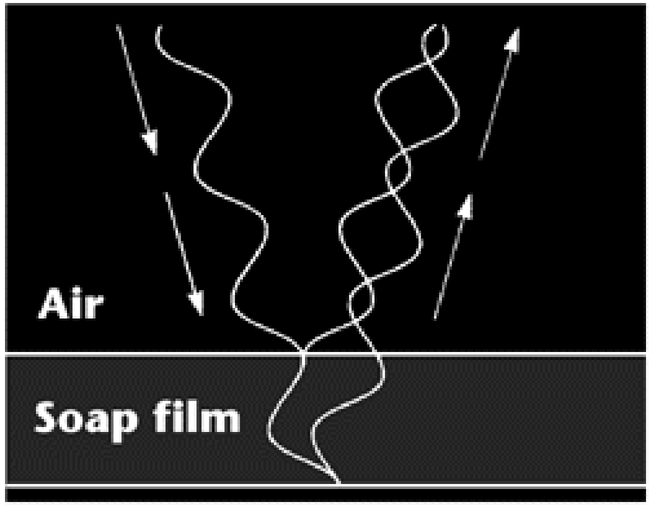
Before describi... in the examinatio... give a theoretical... rings; as without t... will not be sufficie...

Conceive two nearly parallel plates of different media to be separated by a plate of air whose thickness is T; and let the vibration in the plane of reflexion, of an incident stream of light within the first medium, be represented by $a \sin \frac{2\pi}{\lambda}(vt-x)$ where x is the equivalent in air to the actual distance of a particle from some fixed point, (the light being supposed polarized in a plane perpendicular to the plane of reflexion). Let ι be the angle of incidence on the last surface of the first medium; ι' the angle of refraction, which is the same as the angle of incidence on the first surface of the second medium; and ι'' the angle of refraction in the second medium. A part of the light will be reflected at the last surface of the first medium; a part will reach the first surface of the second medium, where it will be subdivided; and one portion will be reflected to the surface of the first medium, where it will be again divided; and one of its parts will enter in the same direction as that which was reflected at first. In this the phase of the undulation will be *behind* that which was first

Optical Interference: from basic to the ultimate







~ 10 nm thickness change can be visually observed

>10 orders of magnitude

0.1 atto-m displacement

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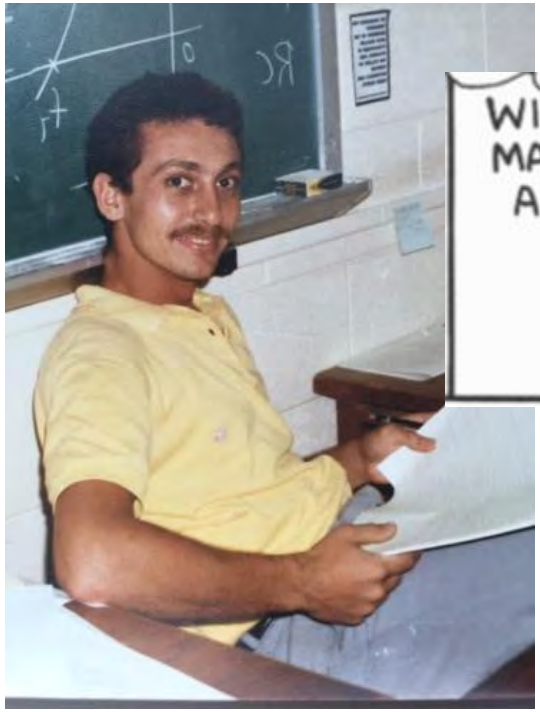
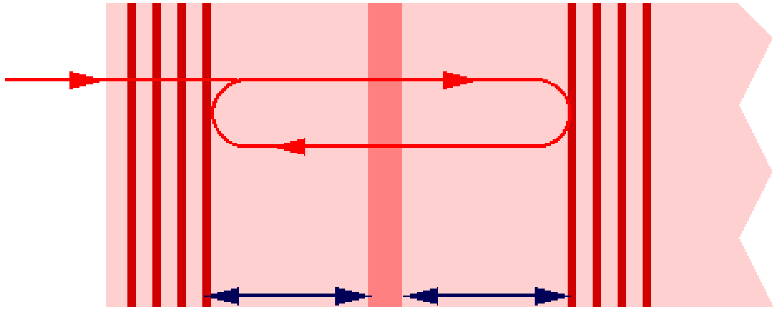
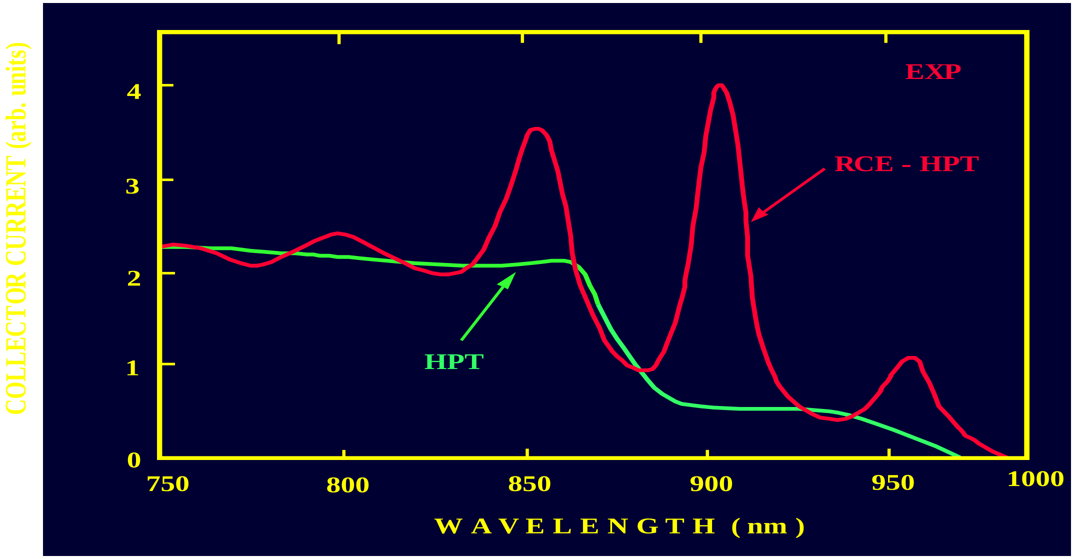
PhD years - semiconductor devices



Let's incorporate a reflector at the bottom

Prof. Kishino
Sophia Univ





In my comfort zone from undergrad
Waves – EM
PhD on Resonant Cavity Detectors
and on to BU in 1992


'98


'01


'01


'03


'05

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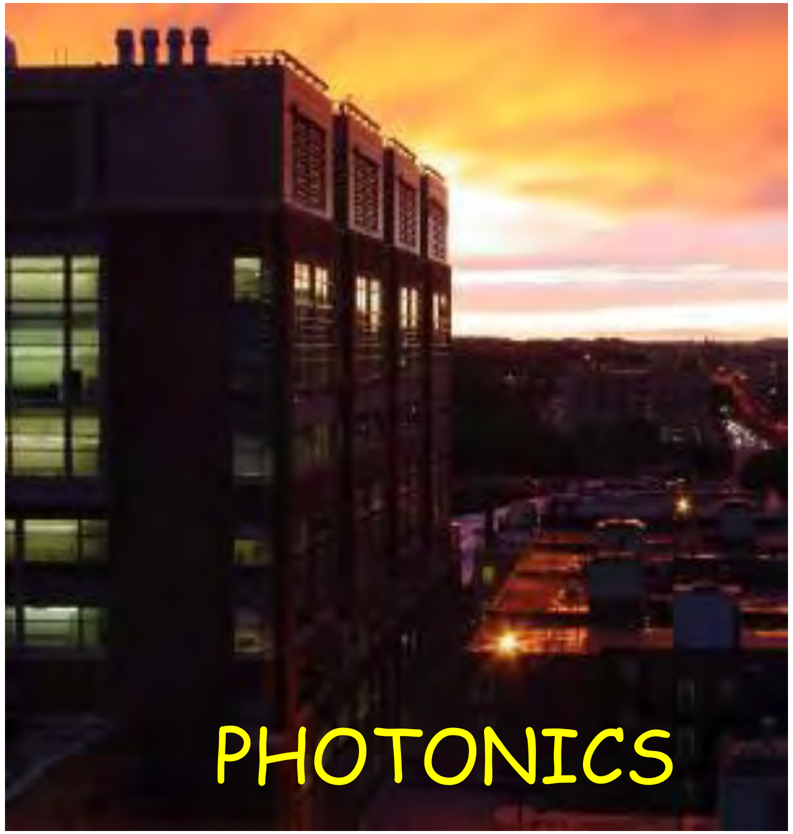
BOSTON UNIVERSITY

@ BU

LIFE SCIENCE AND ENGINEERING



EMERGING INFECTIOUS DISEASES

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OUTLINE

- A bit of philosophy – some history of optics
  - Optical Interference
- **Interferometric Reflectance Imaging Sensor (IRIS)**
  - **Principles**
  - **Requirements and technology**
- Kinetic measurements of molecular binding
- Single bio-nanoparticle detection
  - Exosomes
  - Viruses
  - Bacteria
- Super-resolution imaging
- Single Molecule Detection

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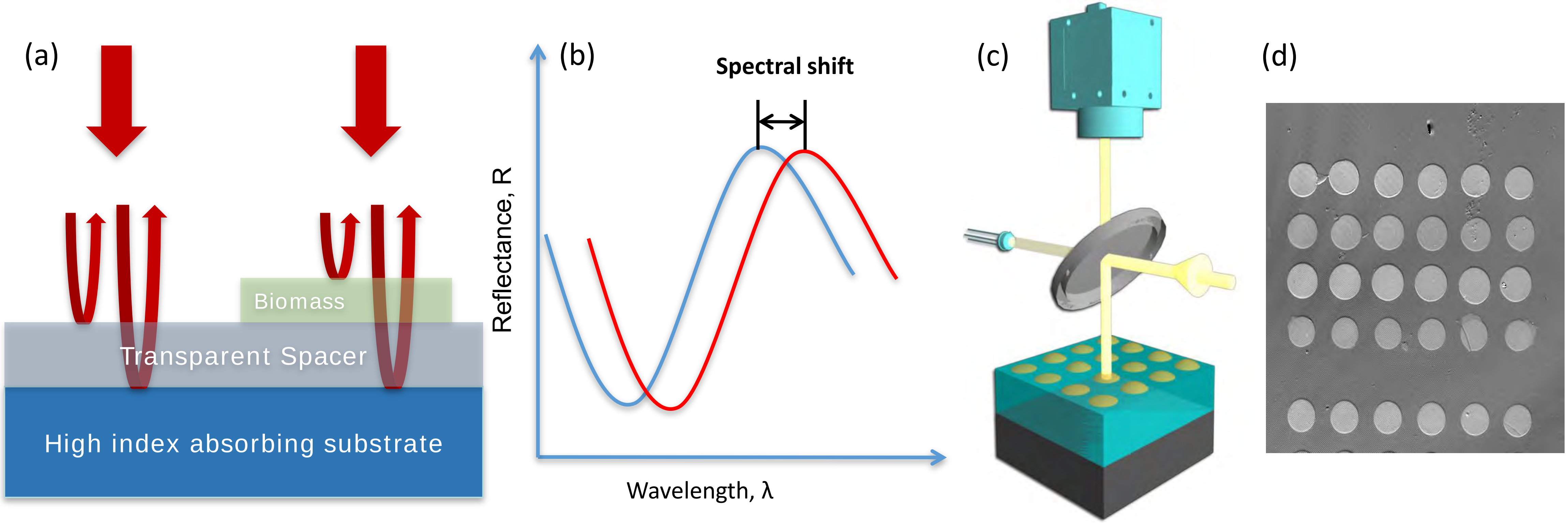
Interferometric Reflectance Imaging Sensor (**IRIS**)



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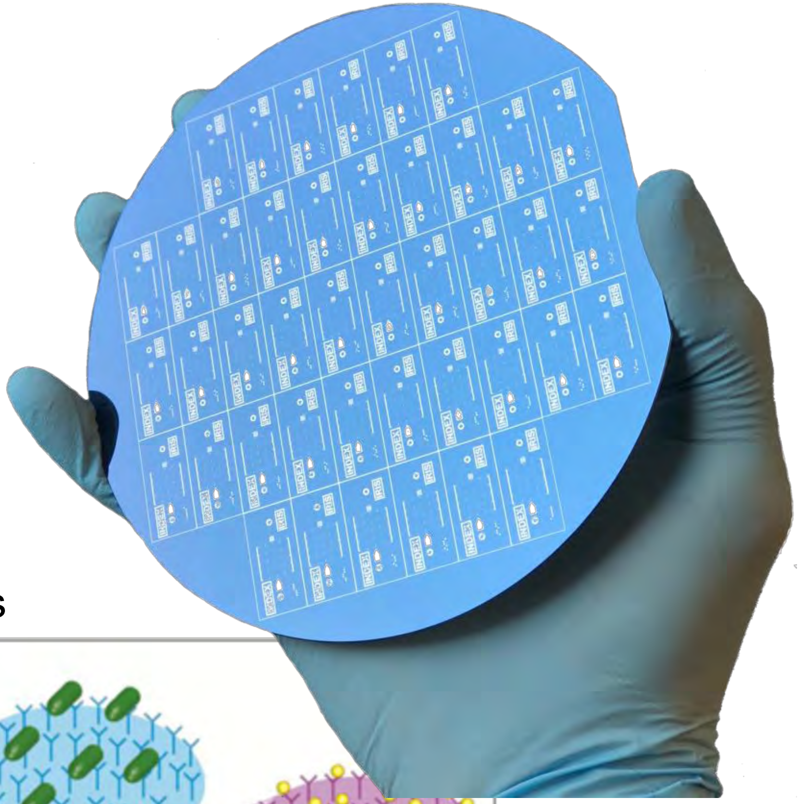
Sensor Chip Requirements

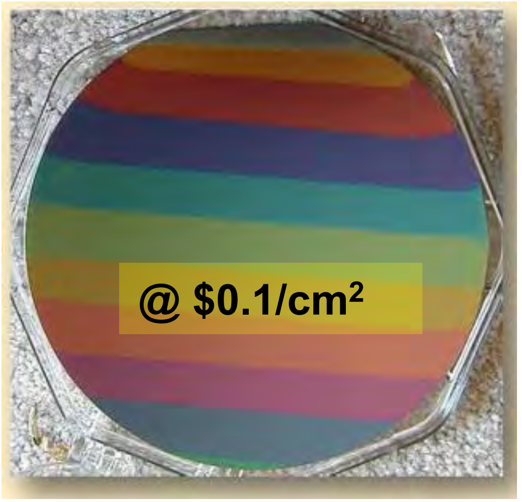
- Multilayer reflector with no stray light
- Flat and smooth surface
- Chemical functionalization / glass
- Manufacturable and scalable

Transparent Spacer
High index absorbing substrate



soap film

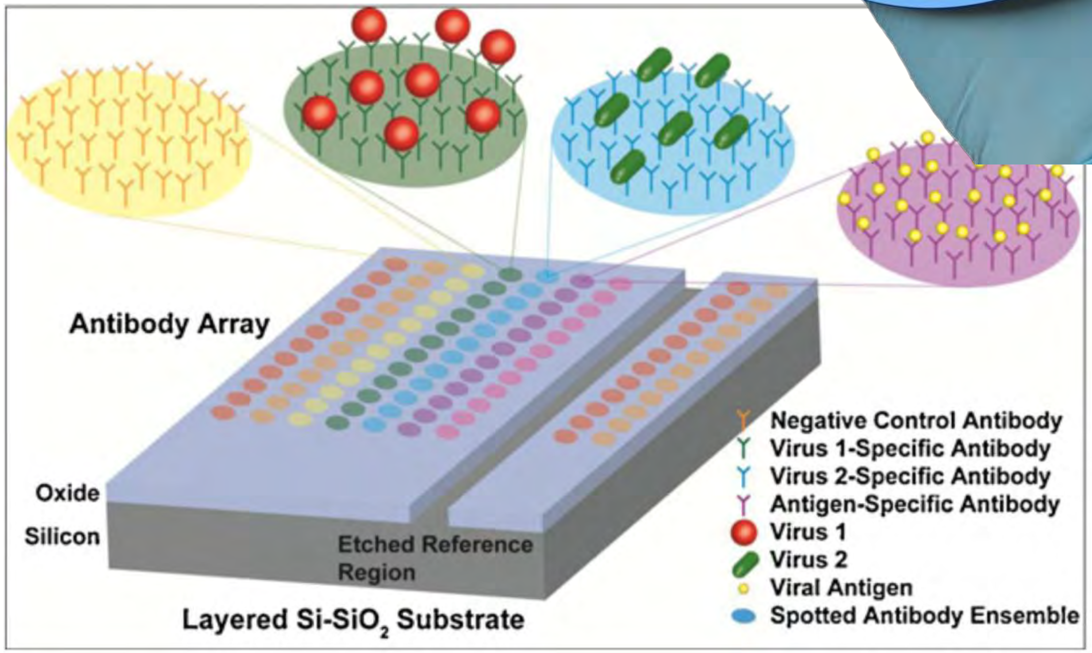
Oxide coated Si



Ünlü et al, "STRUCTURED SUBSTRATES FOR OPTICAL SURFACE PROFILING,' US Patent No: 9599611, 2017

pg/mm² sensitivity 1,000s of spots

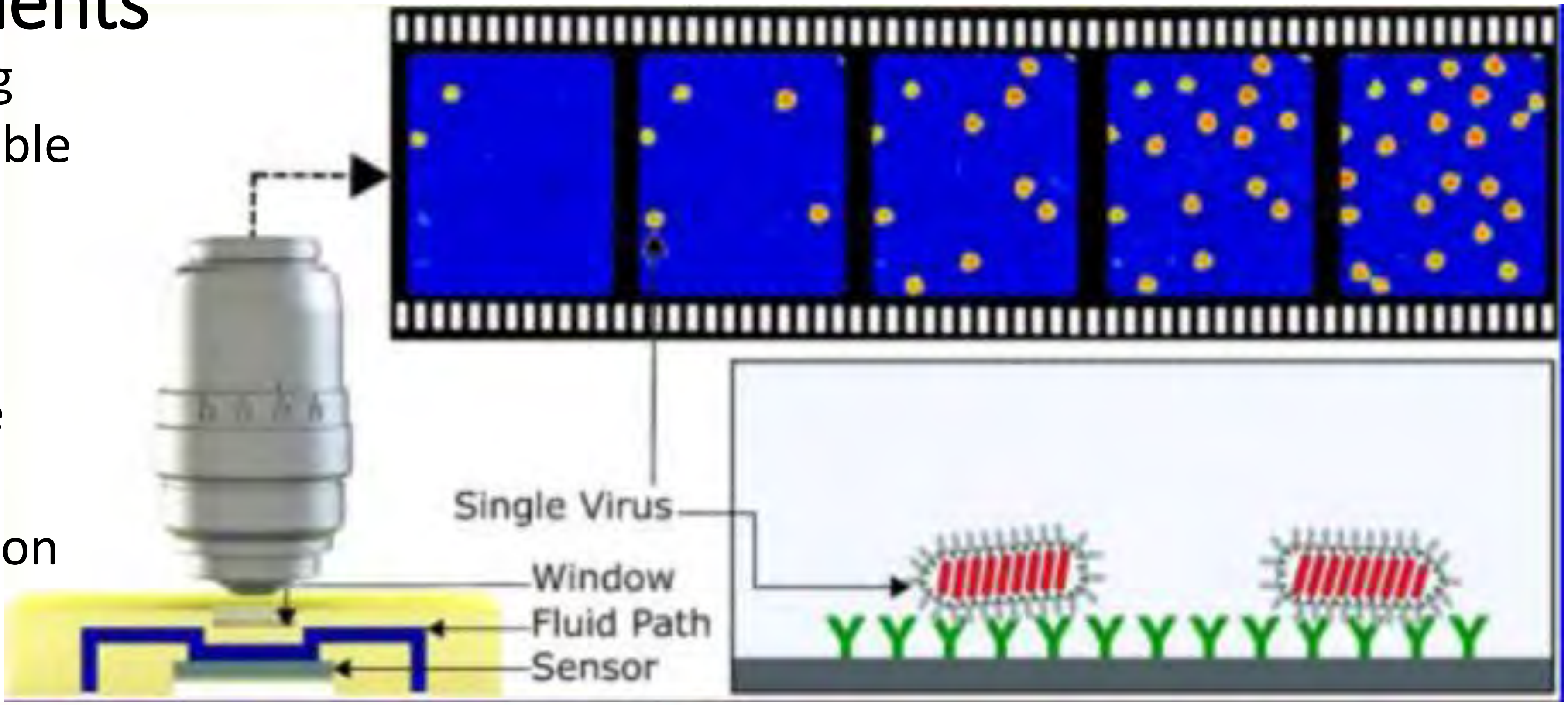
Protein microarray chips with 100s to 1,000s of probe spots

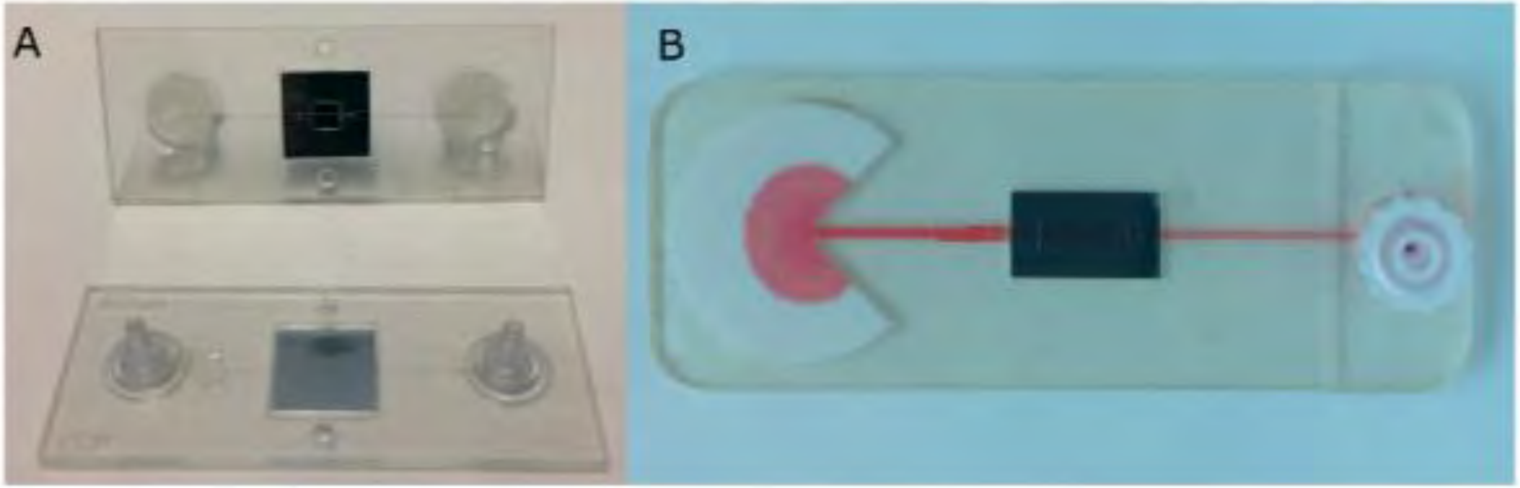


Cartridge Requirements

- Optical quality for imaging
- Manufacturable and scalable
- Easy assembly with chip
- Cost

- Multi-layer polycarbonate laminates (7 layers)
  - Good prototype solution
  - Cost remains high for medium volume





Scherr et al, *ACS Nano* 10 (2016)
Scherr et al, *Lab on a Chip* (2017)

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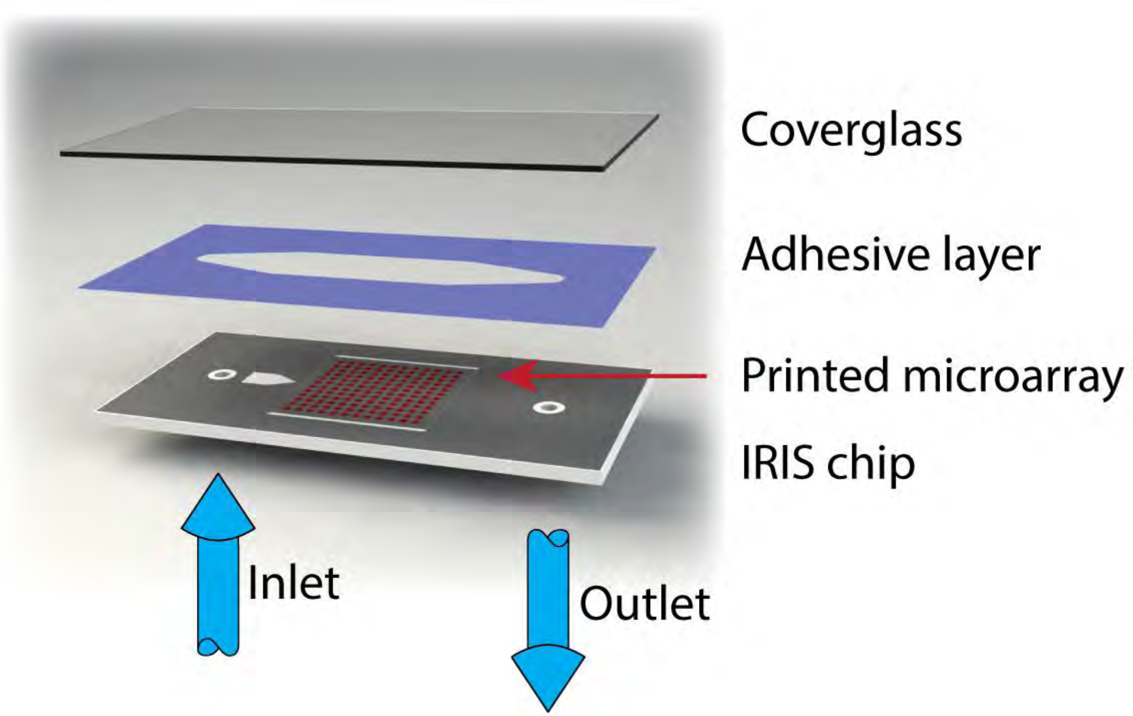
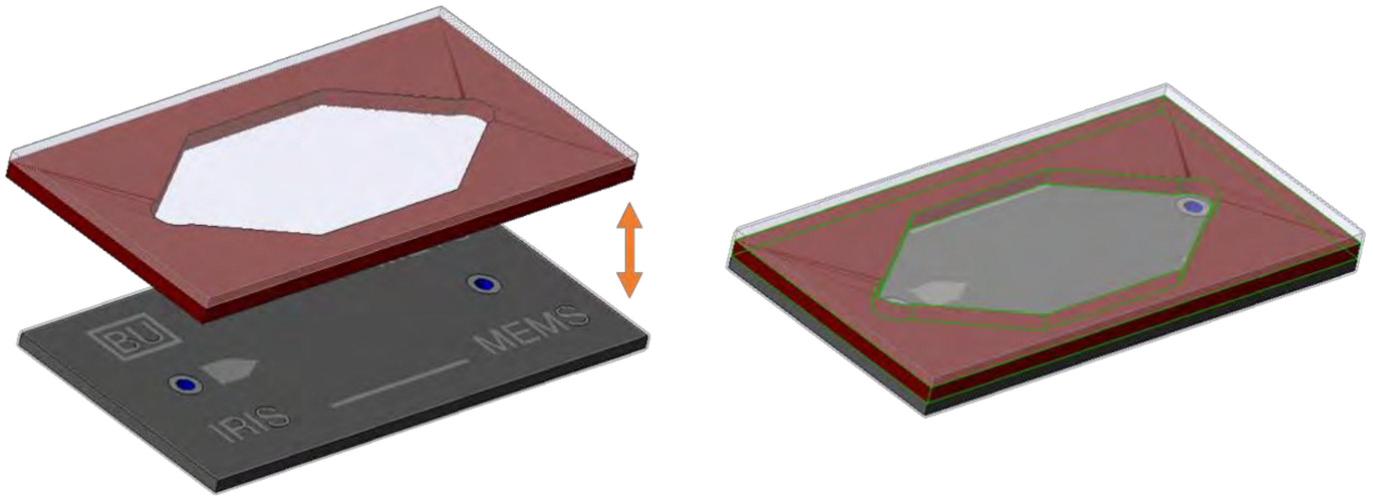
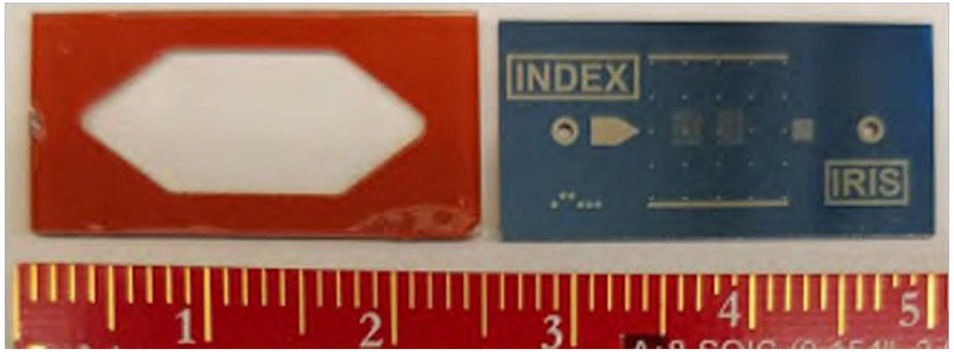
Si-based Microfluidics solution

- Fluidics through Si
- Manufacturable / scalable – established infrastructure
- Top window can be separately optimized
  - AR coating
  - Polarization preserving







Yalcin-Ozkumur, JSTQE (2018)

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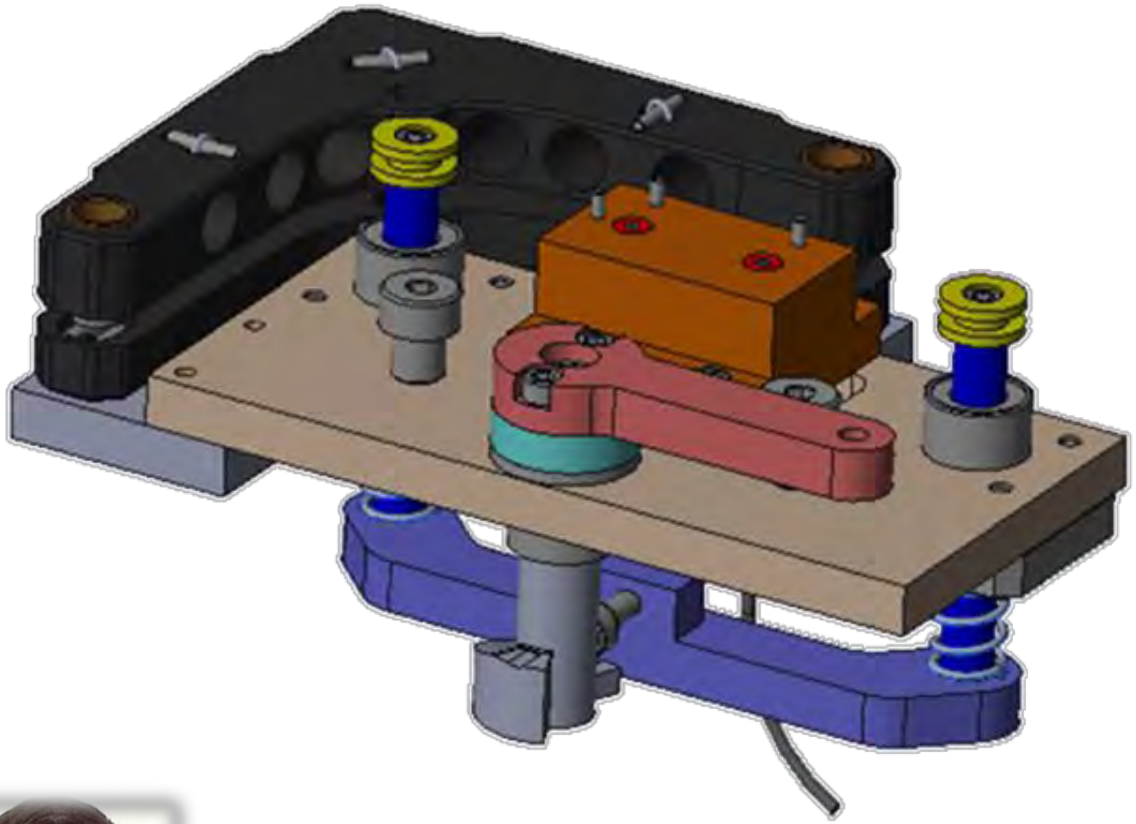
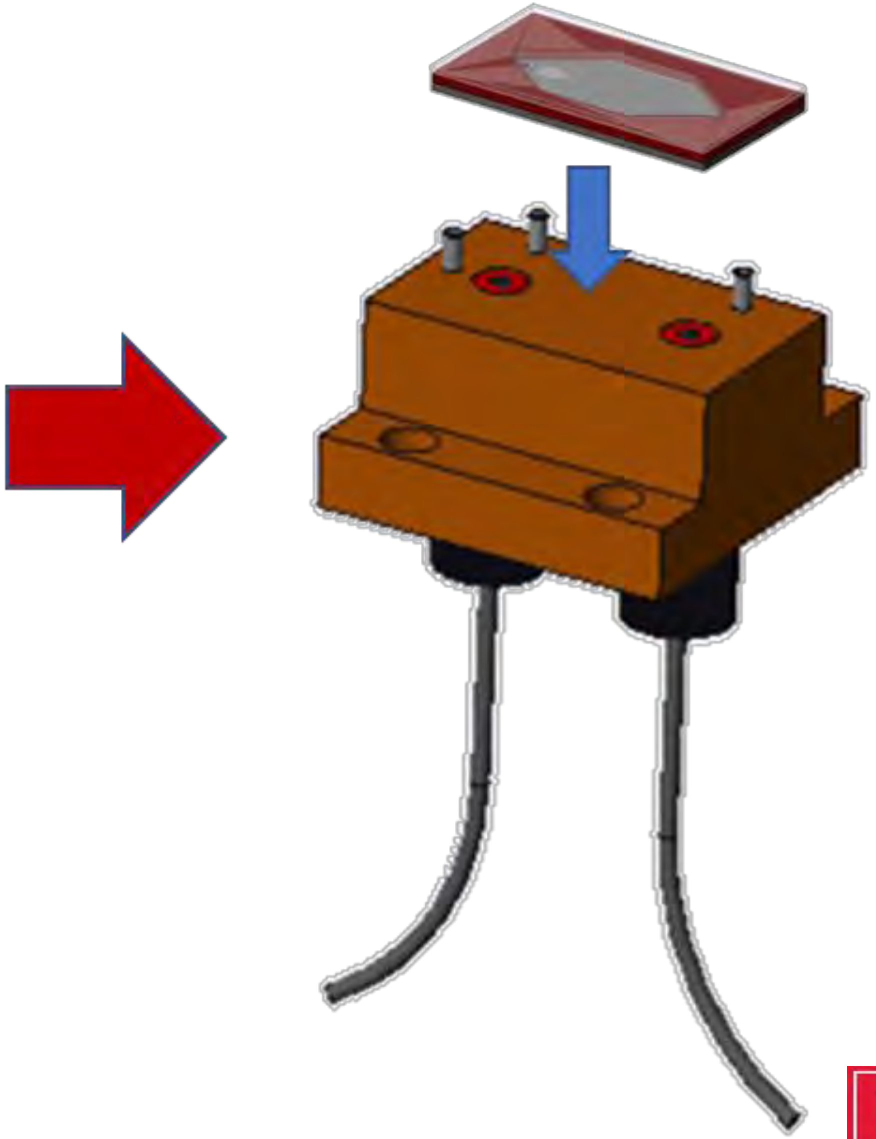
Mechanical Fixture



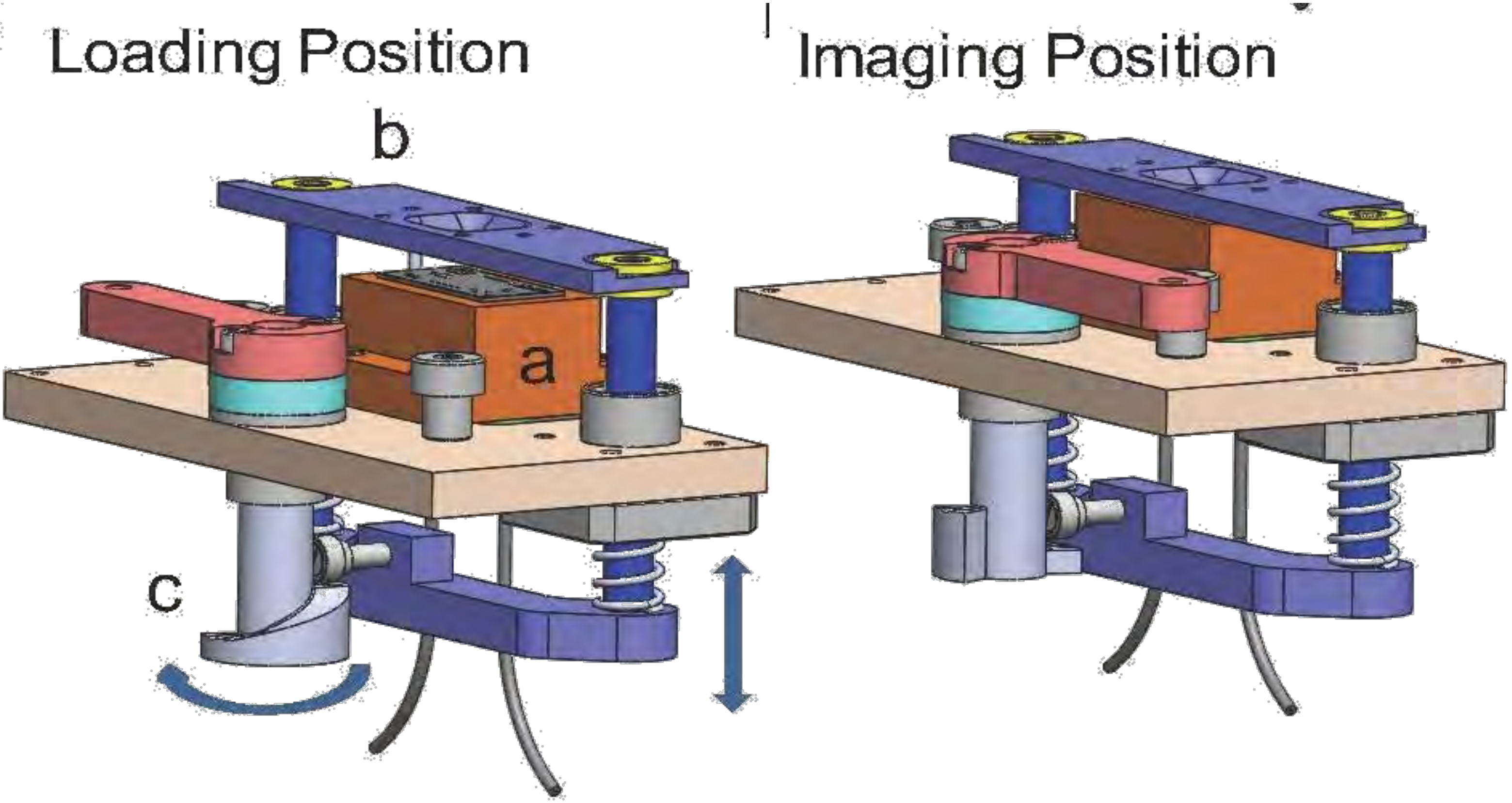


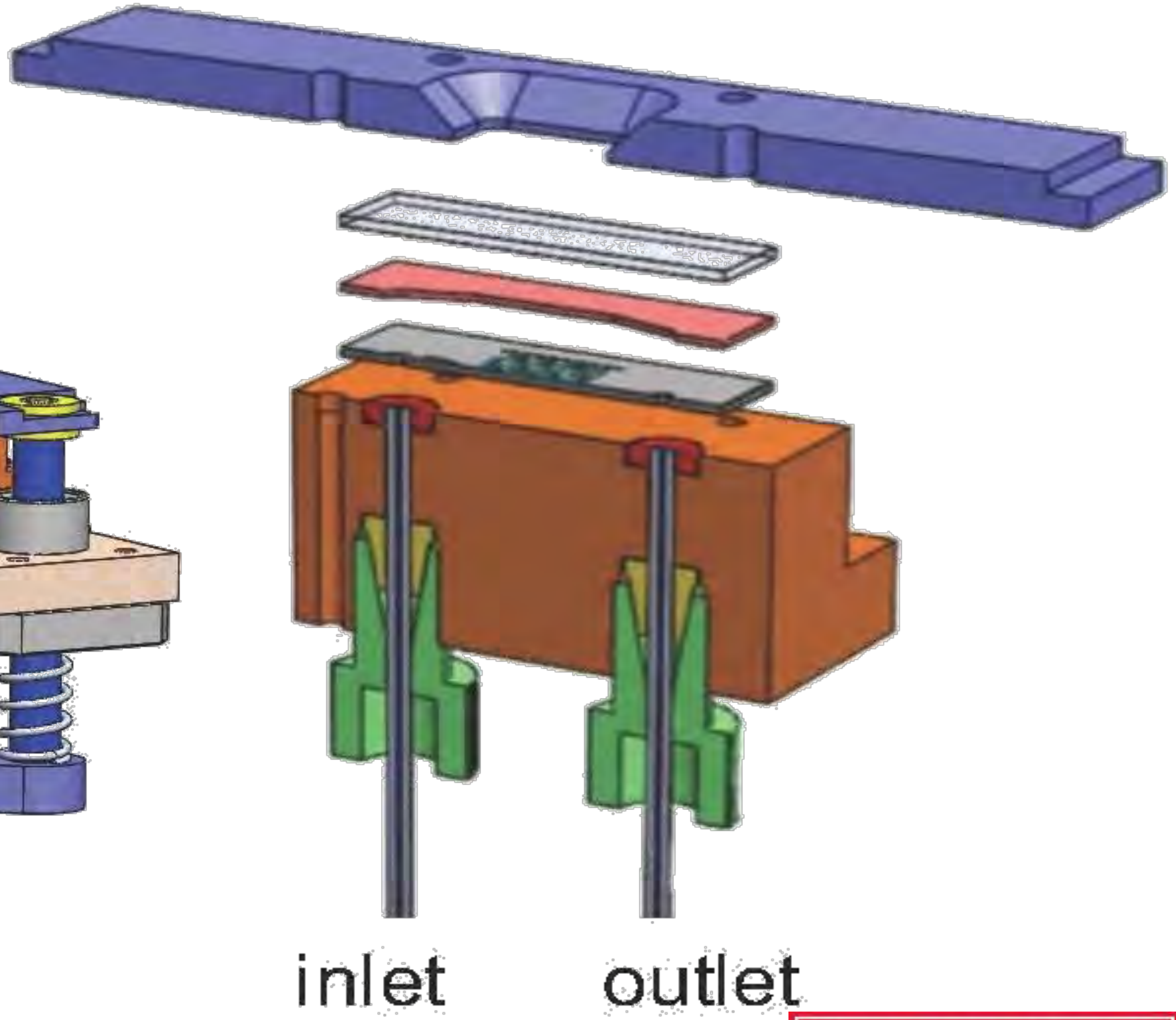

'18

Cam Operation

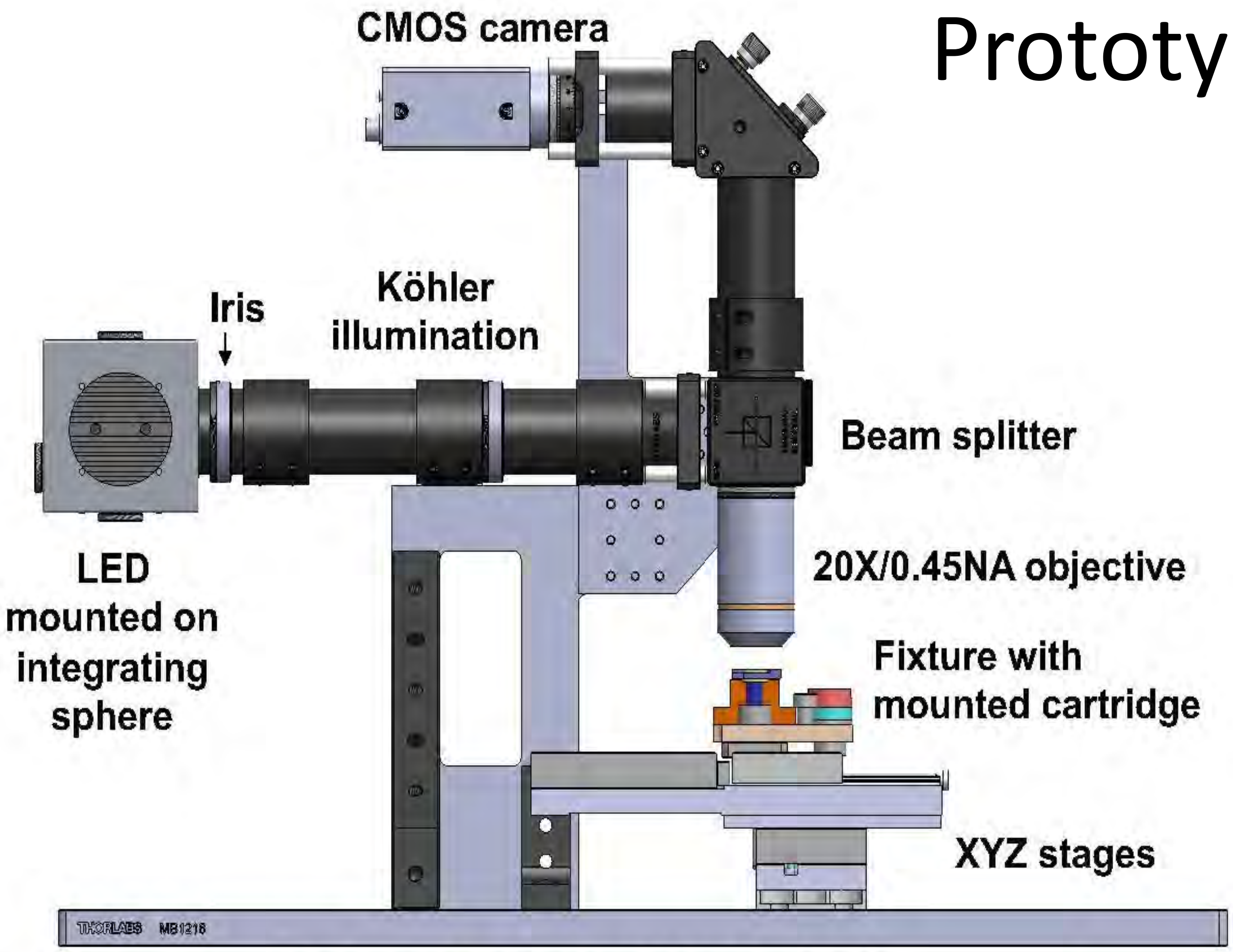
Interferometric Detection and Enumeration of Viral Particles using Si-based Microfluidics

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





Prototype Instrument



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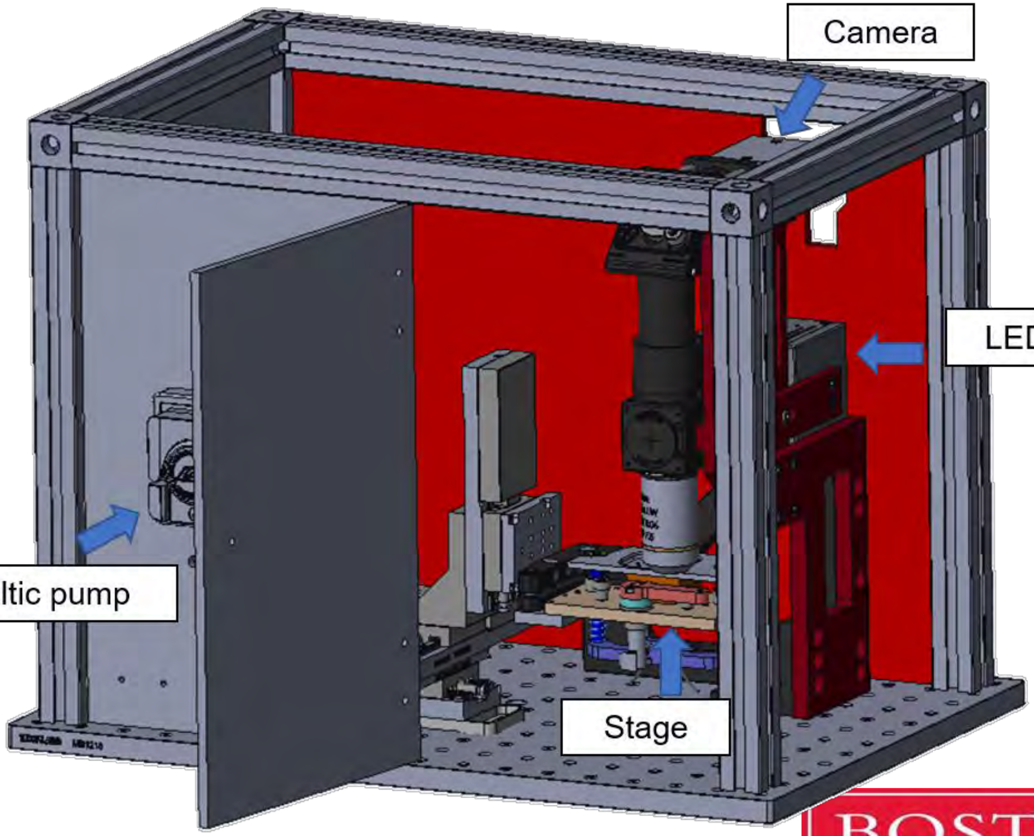

Off-the-shelf components
Parts cost (BOM) under $10K

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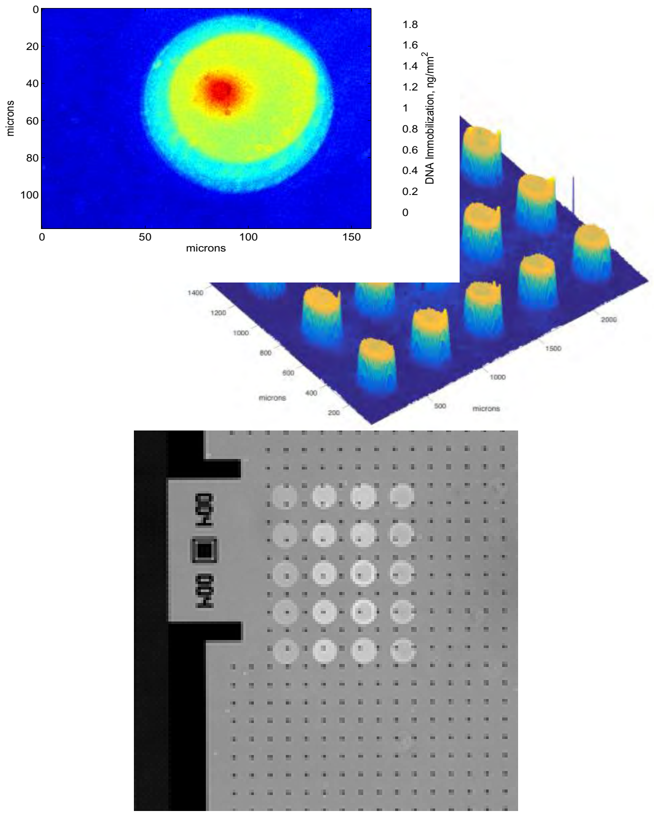
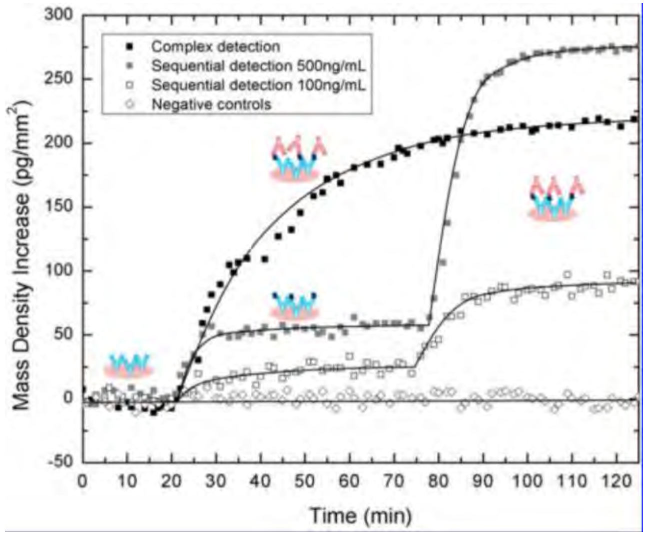
IRIS – a versatile biosensing technology platform for microarrays

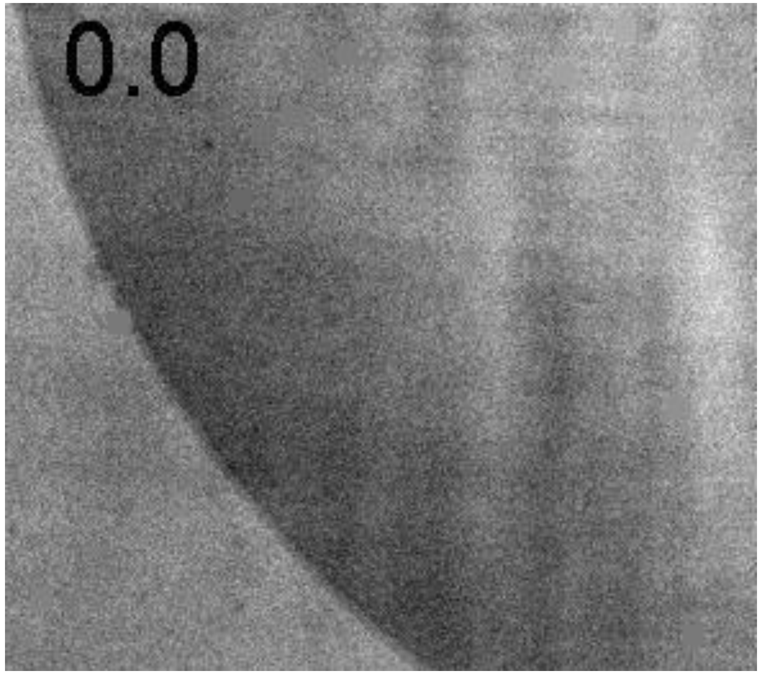
Quantitative / QC



Dynamic Measurements



Single virus/exosome



- decade long R&D
- various applications demonstrated.
  - From QC to single exosome/virus detection
  - pg/mm^2 sensitivity
  - Single biological nanoparticle detection and characterization
  - attoM sensitivity for protein and nucleic acid detection

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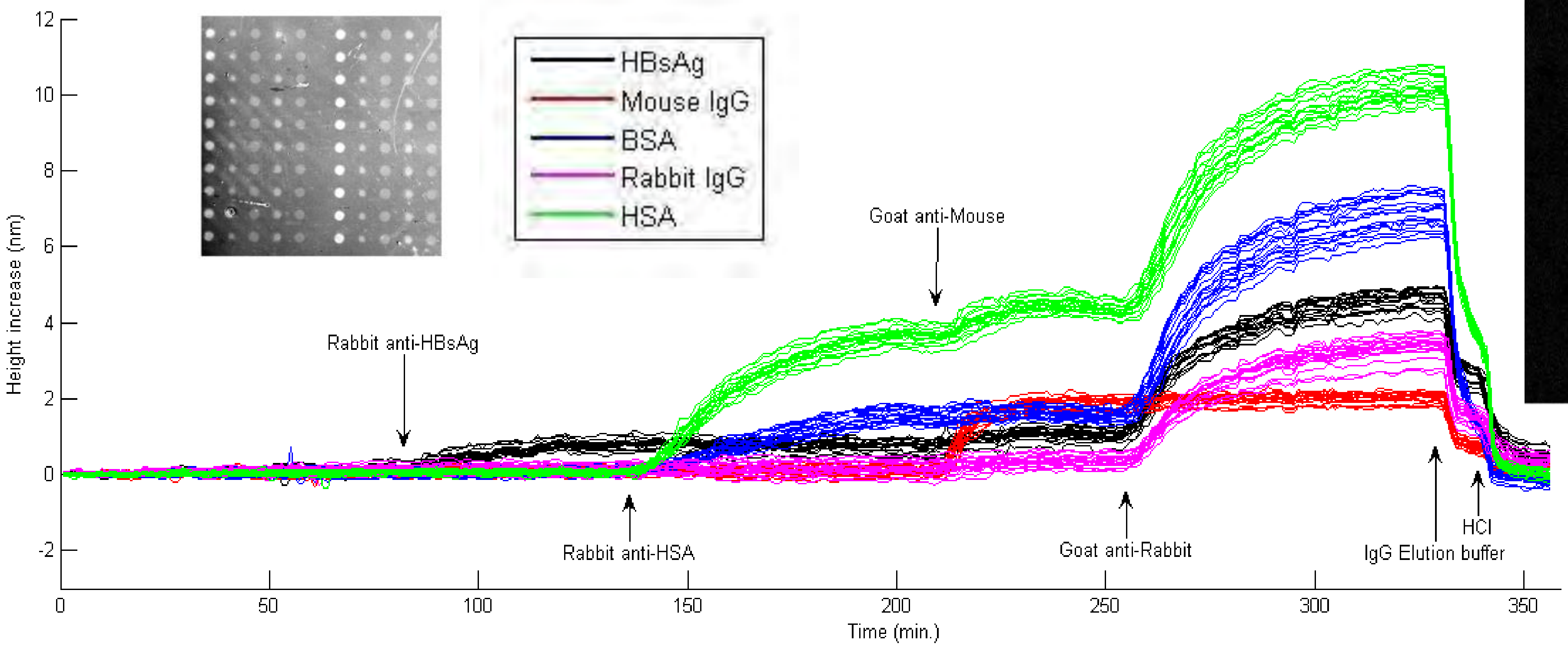
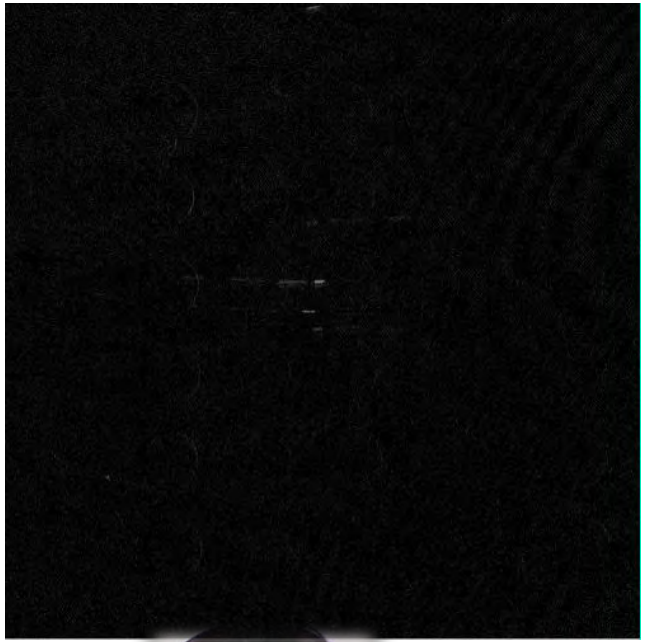
Dynamic - Quantitative Microarrays





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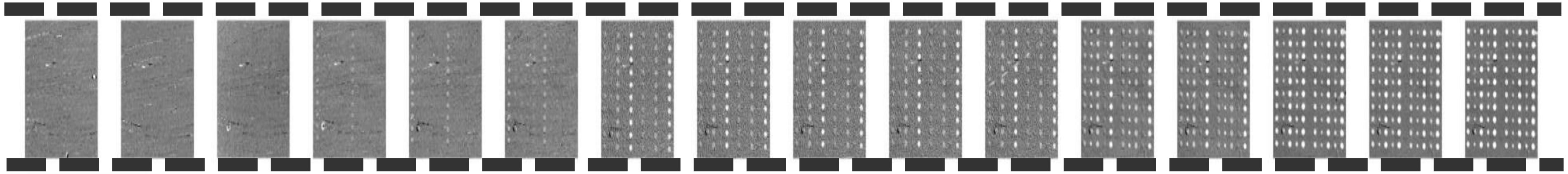

’09

Ozkumur et al, “Label-free and dynamic detection of biomolecular interactions for high-throughput microarray applications,” *PNAS*, 2008

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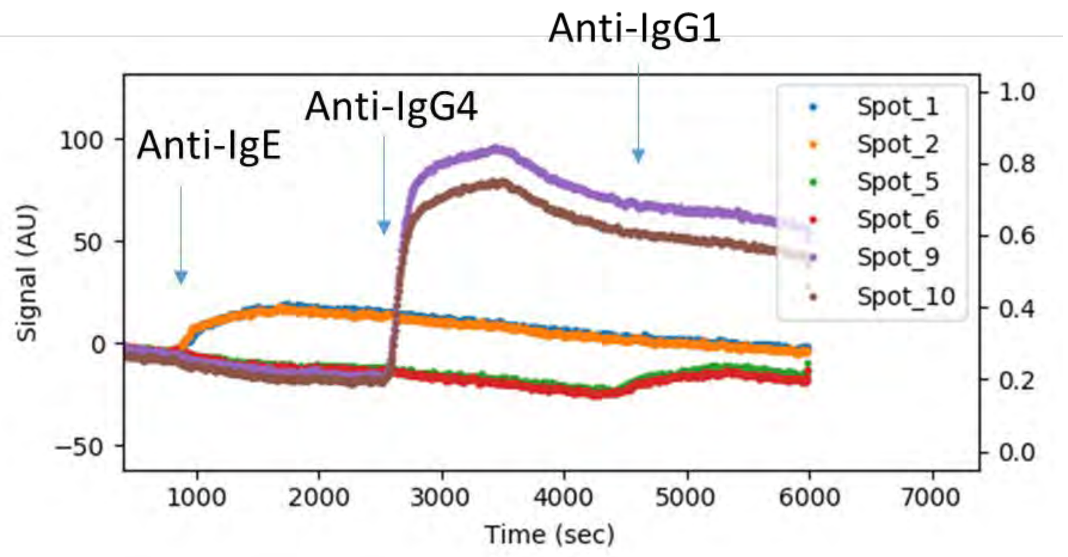
1. Molecular binding Kinetic Measurements



- Multiplexed (100s to 1000s of probes)
- Quantitative
- Glass surface
- Inexpensive instrumentation and disposables
- ng/ml target sensitivity
- ~kDa molecular weight

’21

OUTLINE

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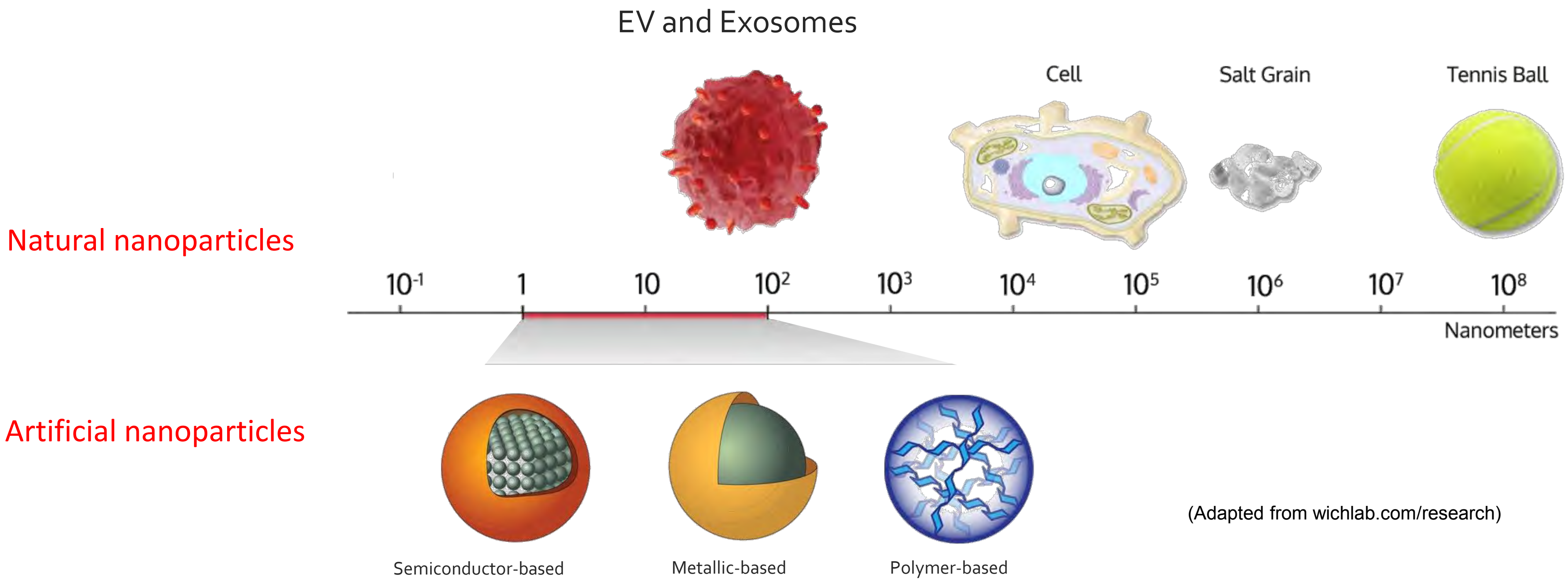
Motivation - Nanoparticles



(Adapted from wichlab.com/research)

Artificial nanoparticles

- Optically & physically engineered
- Used as labels or vehicles in diagnostics, therapeutic applications
- Gold, polystyrene NPs, QDs

Natural nanoparticles

- Low-index, complex-shaped
- Hard to detect without labels
- *Virus* – infectious diseases and cancer
- *Exosome* – secreted from cancer cells

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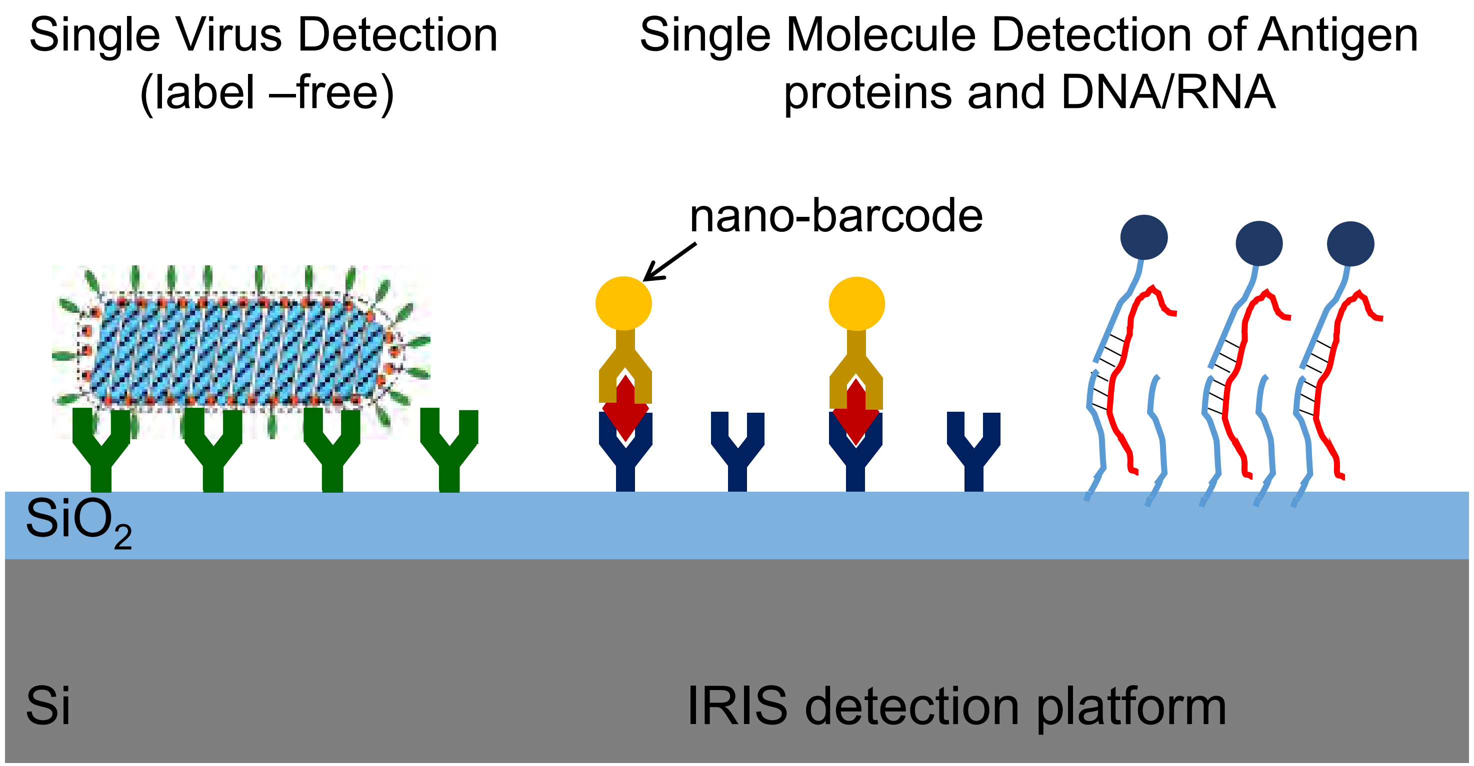
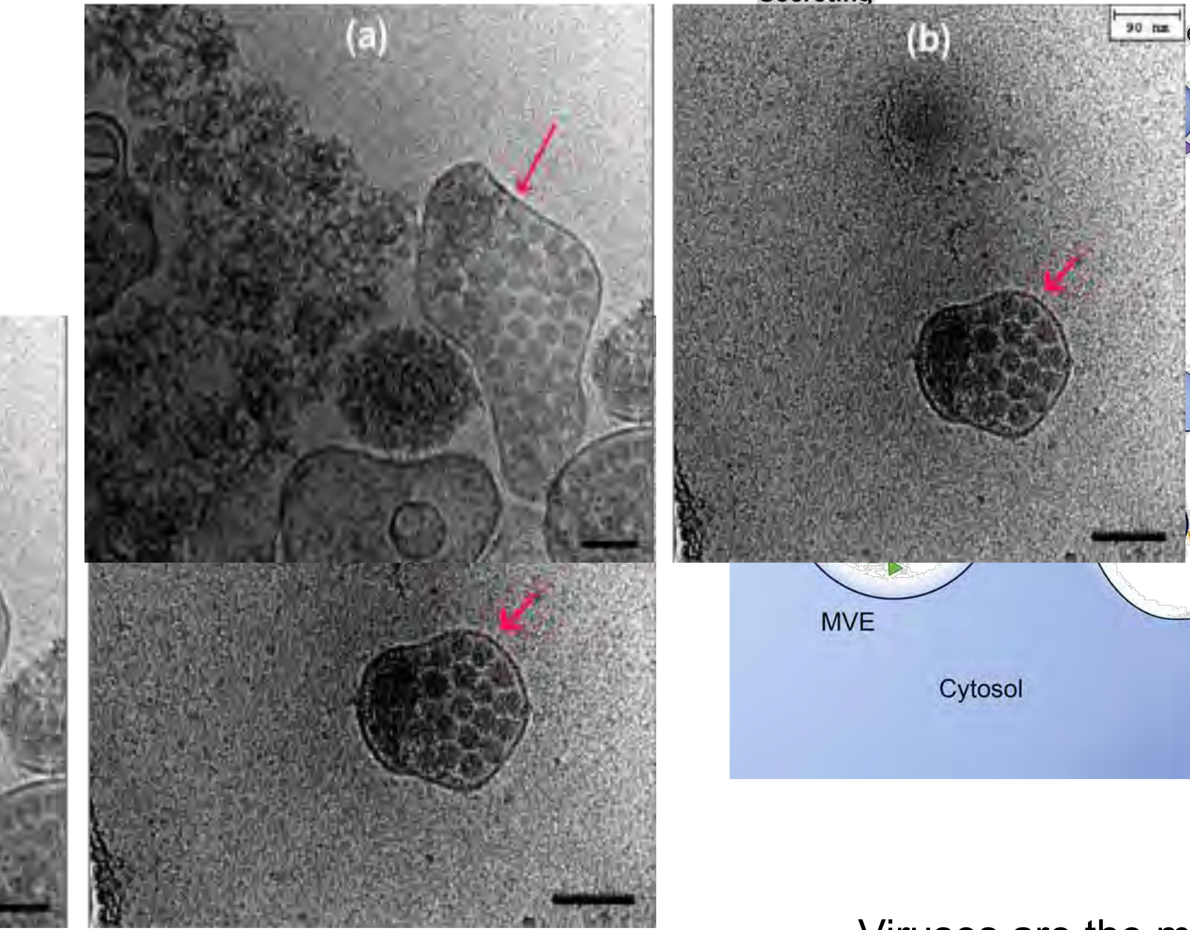
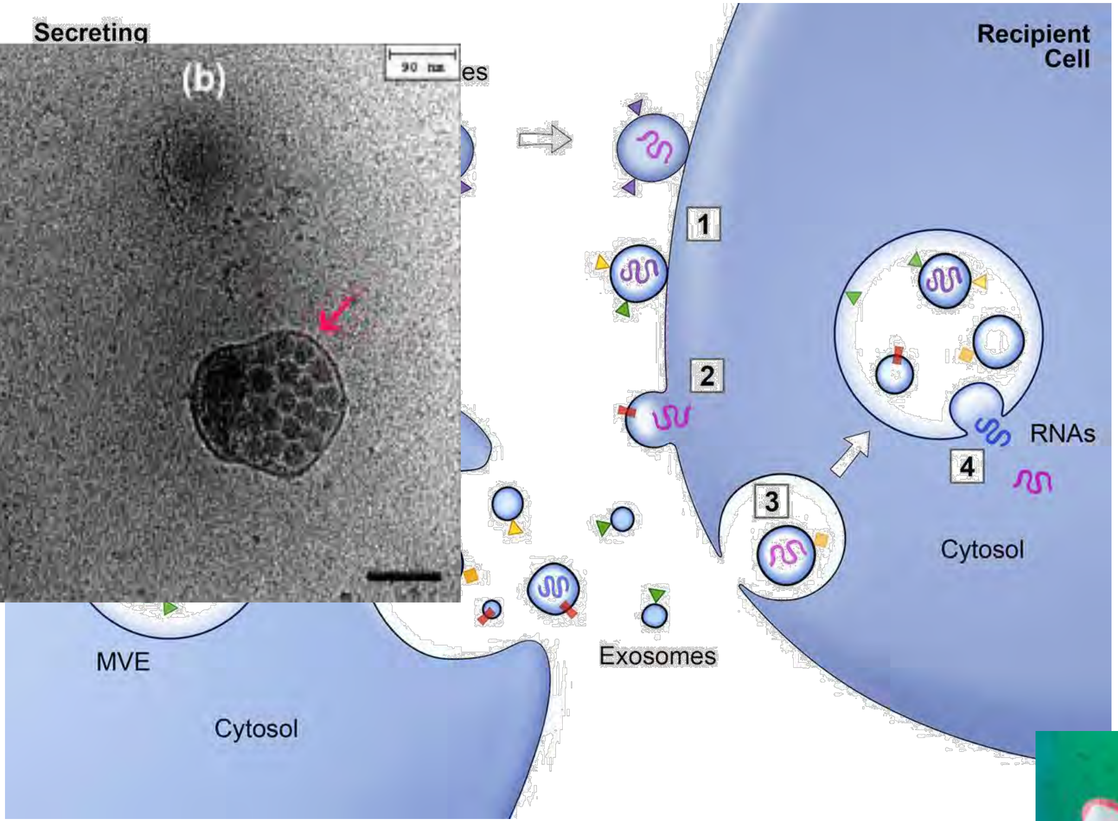
Single Particle - IRIS : Digital Detection



- Label Free direct sensing of individual viruses
- Digital Detection: Single molecule level detection of Nucleic Acids and Proteins
- ULTIMATE BIODETECTION PLATFORM?

Extra cellular vesicles, exosomes, and viruses





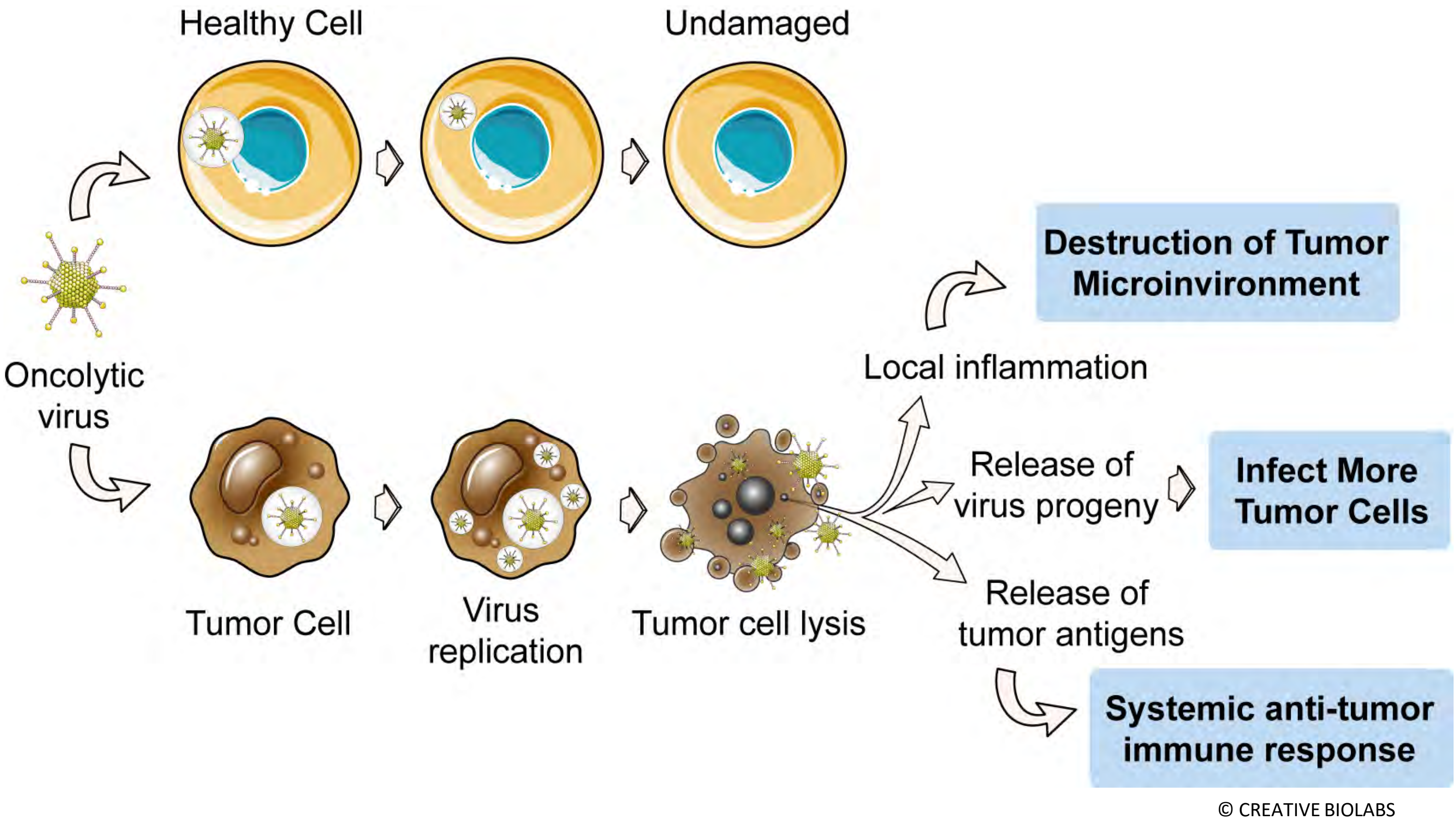
Example cryo-EM images of infectious extracellular vesicle (Bullitt Lab – BU MED)

SEM image of Ebola virion

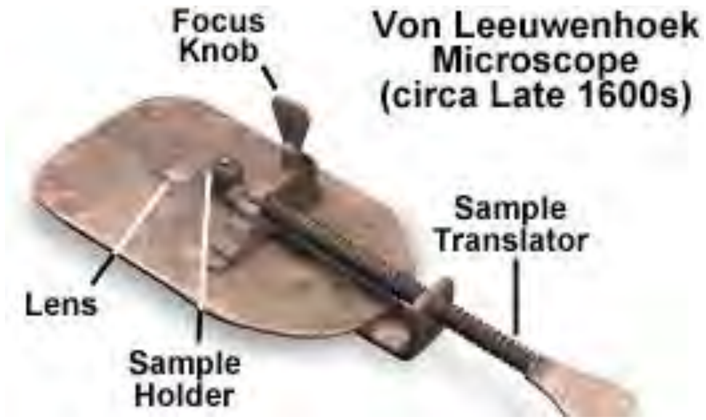
Viruses are the most abundant species on earth.
$>10^{31}$ phages in the biosphere
$\sim10^{7}$ viruses on average in a mL of seawater

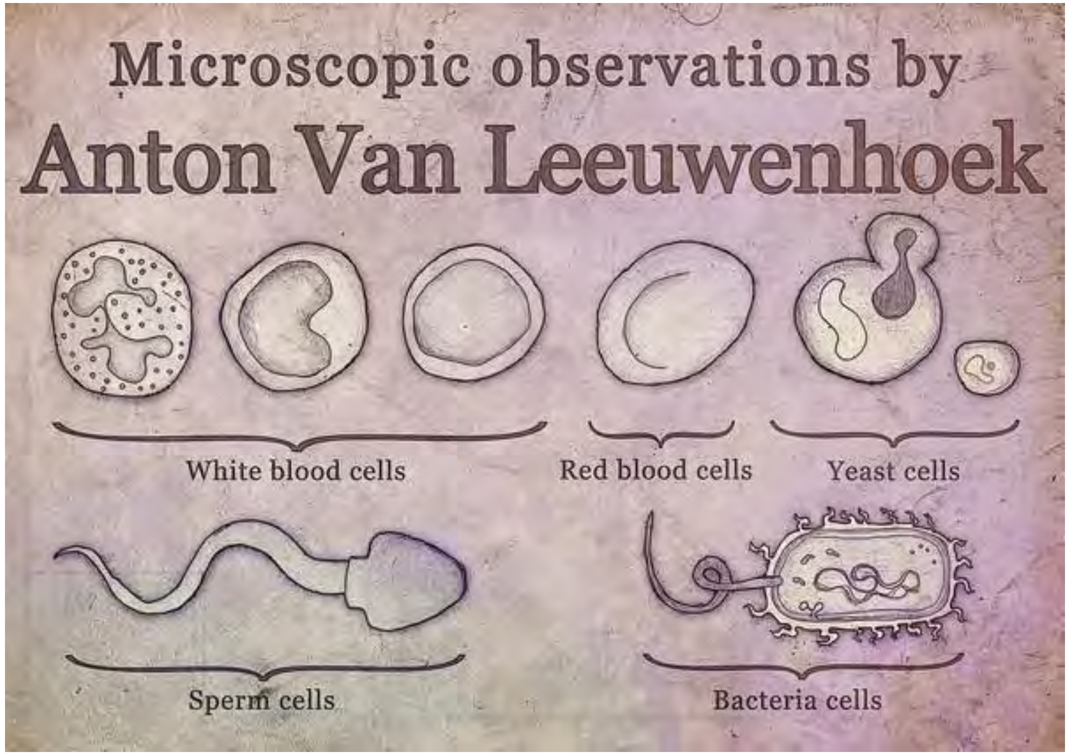
Compare to $\sim10^{23}$ stars in the known universe

Example: Engineered viruses for cancer therapy



Optical microscopy can see small – but …





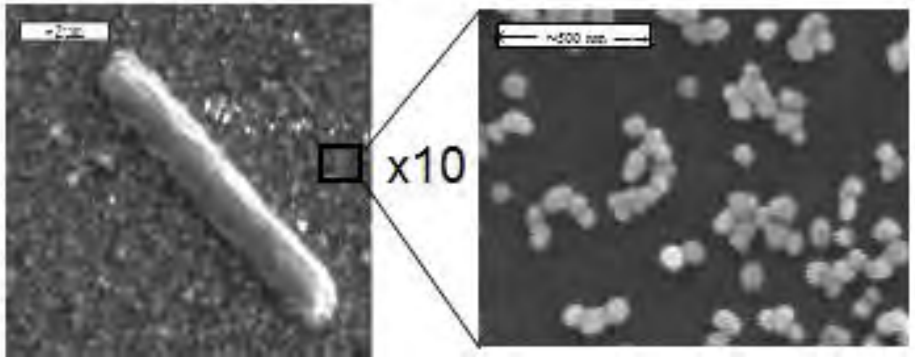
micro.magnet.fsu.edu/primer/

Nanoparticle Detection and Sizing

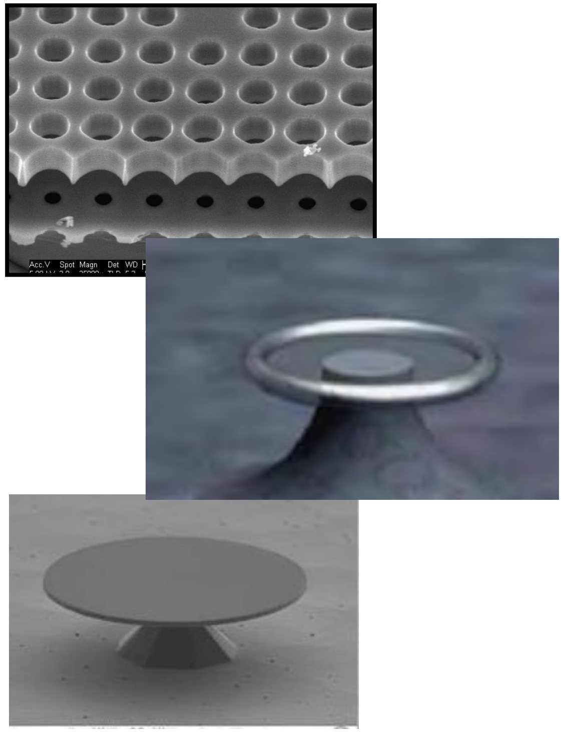
Why difficult and how we make it easy

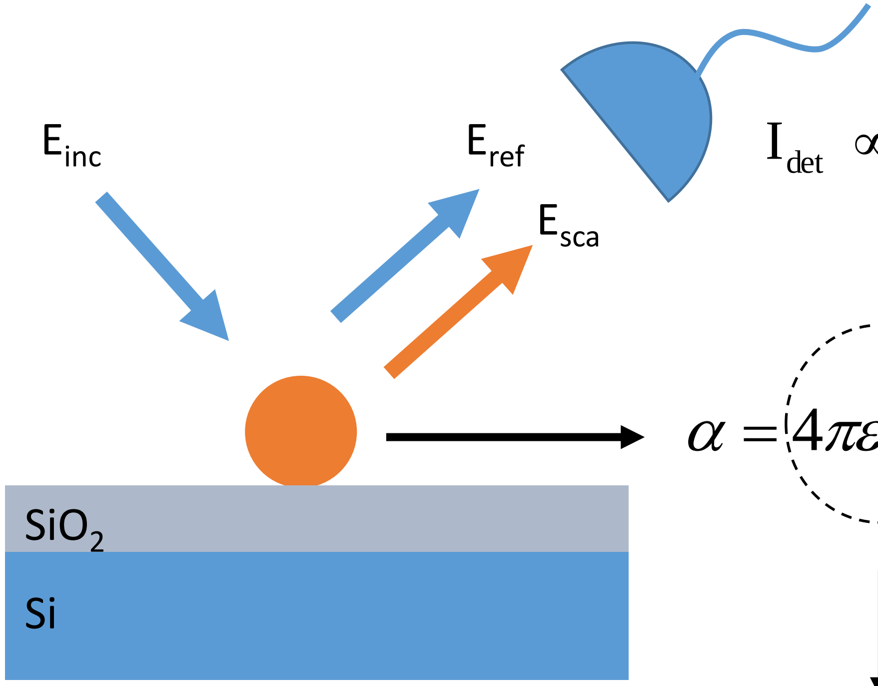
Resonators provide very high sensitivity
- Photonic Crystals
- Toroids/Disks/Spheres

High Q / Small interaction volume
Evanescent optical field



Ziegler





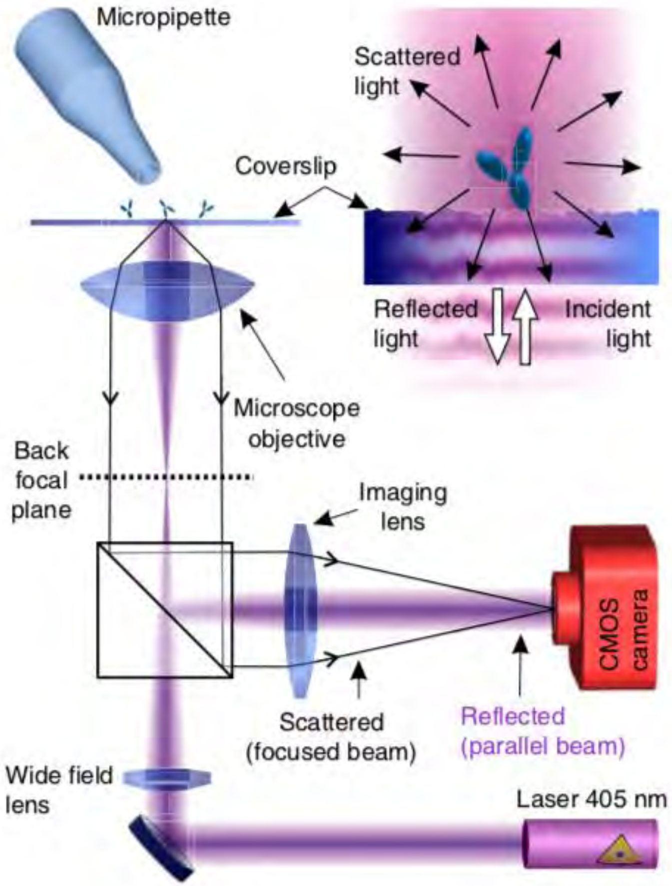
$$I_{det} \propto |E_{ref}|^2 + |E_{sca}|^2 - 2|E_{ref}||E_{sca}|\sin\theta$$

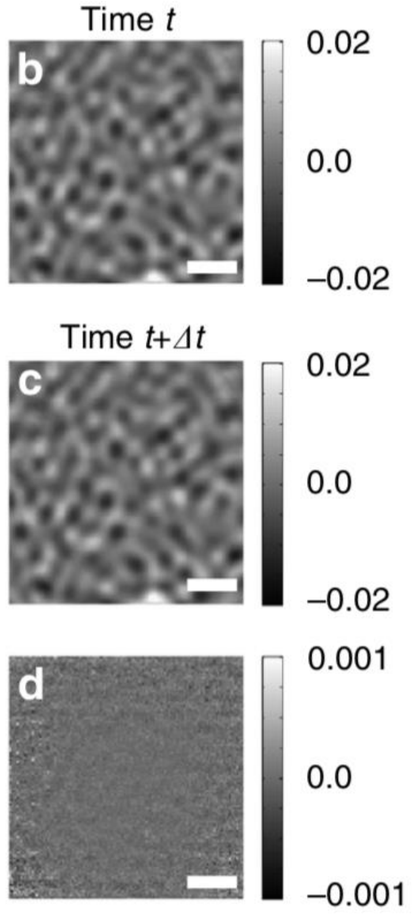
Phase Term

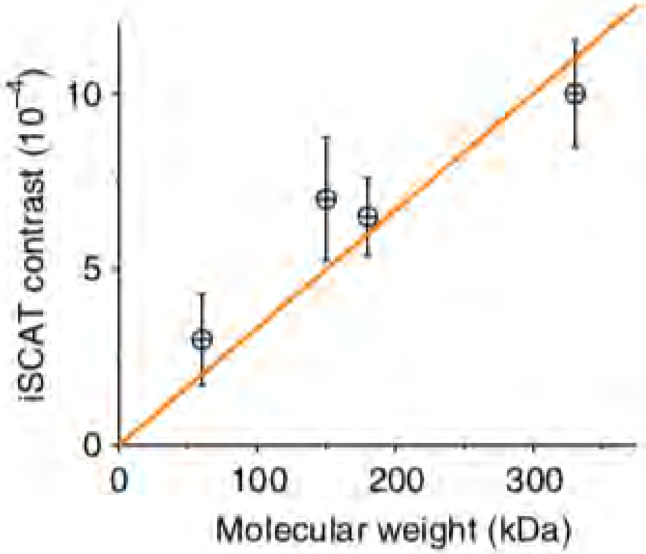
$$\alpha = 4\pi\varepsilon_0 R^3 \frac{\varepsilon_p - \varepsilon_m}{\varepsilon_p + 2\varepsilon_m}$$

Size — Material

Interferometric measurements of single molecules



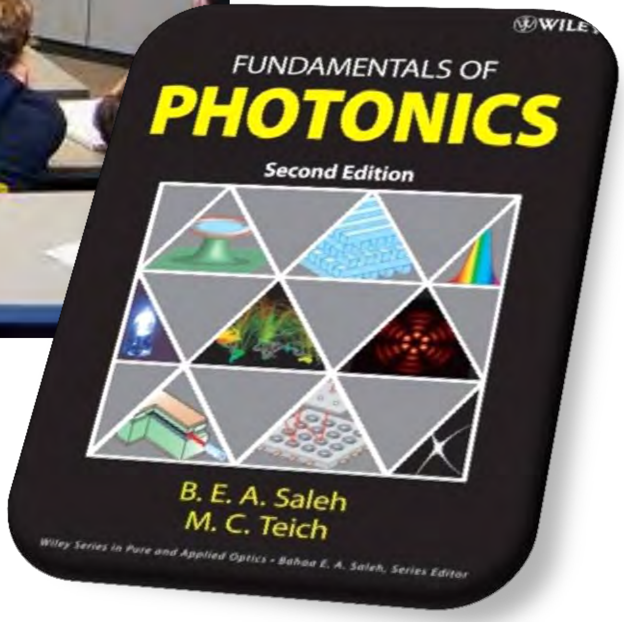




Pikiarik and Sandogdar, *Nature Communications* 5 (2014)

Teaching Introduction to Electronics – recruiting PhDs

Rahul Vedula(MD) and George Daaboul, PhD ‘13



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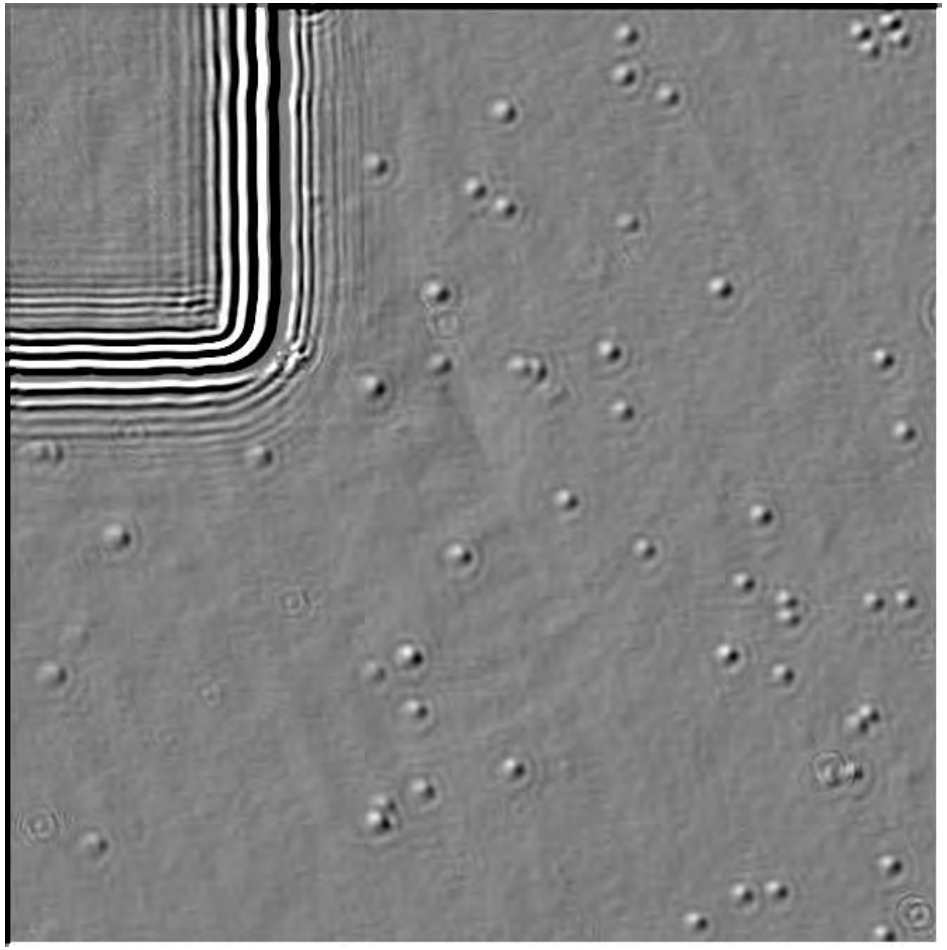
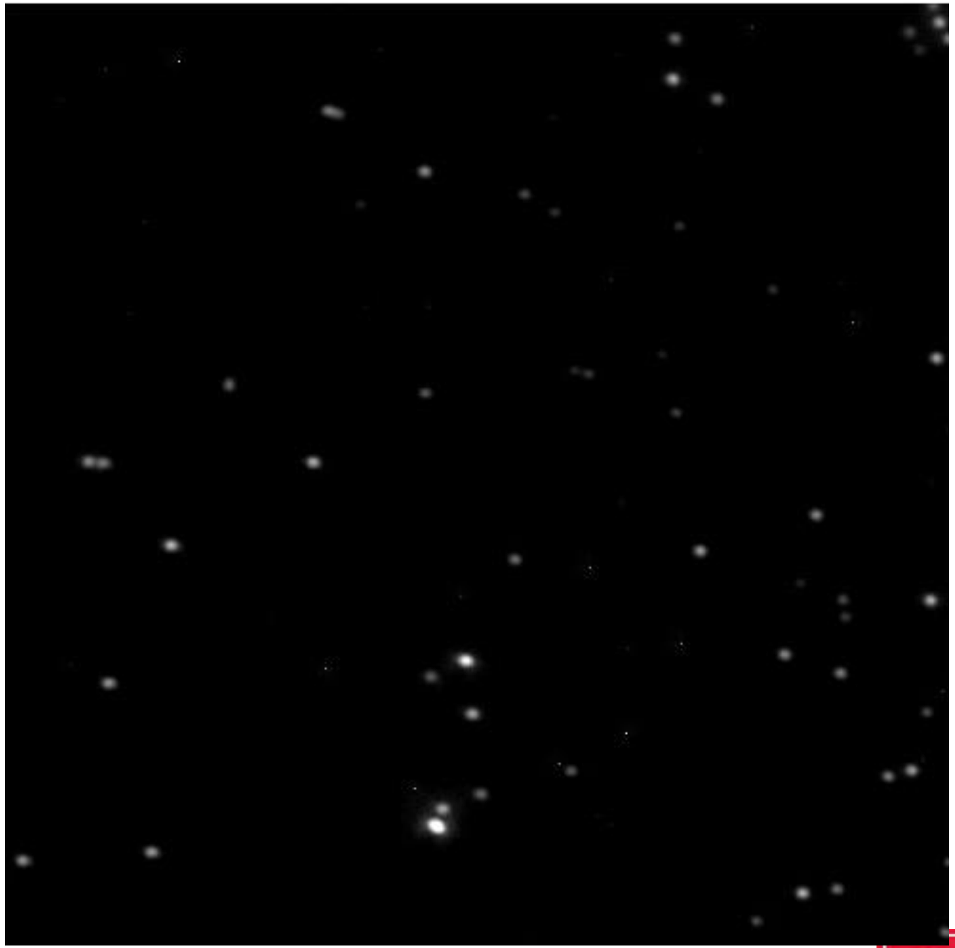
Simple Particle Detection

Fluorescent 100nm Carboxyl modified beads immobilized on Lysine surface. Incubation time 15min





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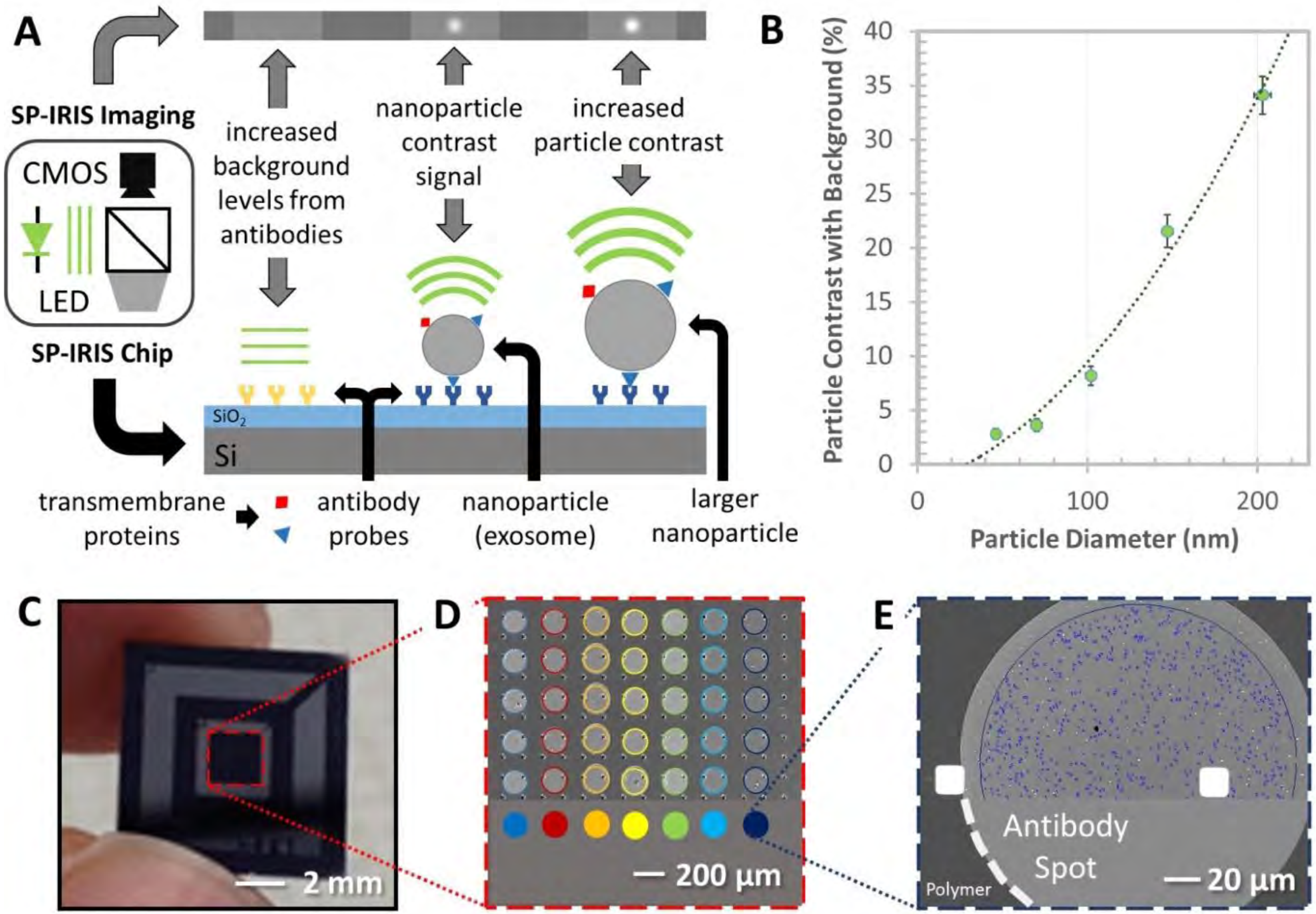
SP - IRIS – a simple, compact Nano particle sensor



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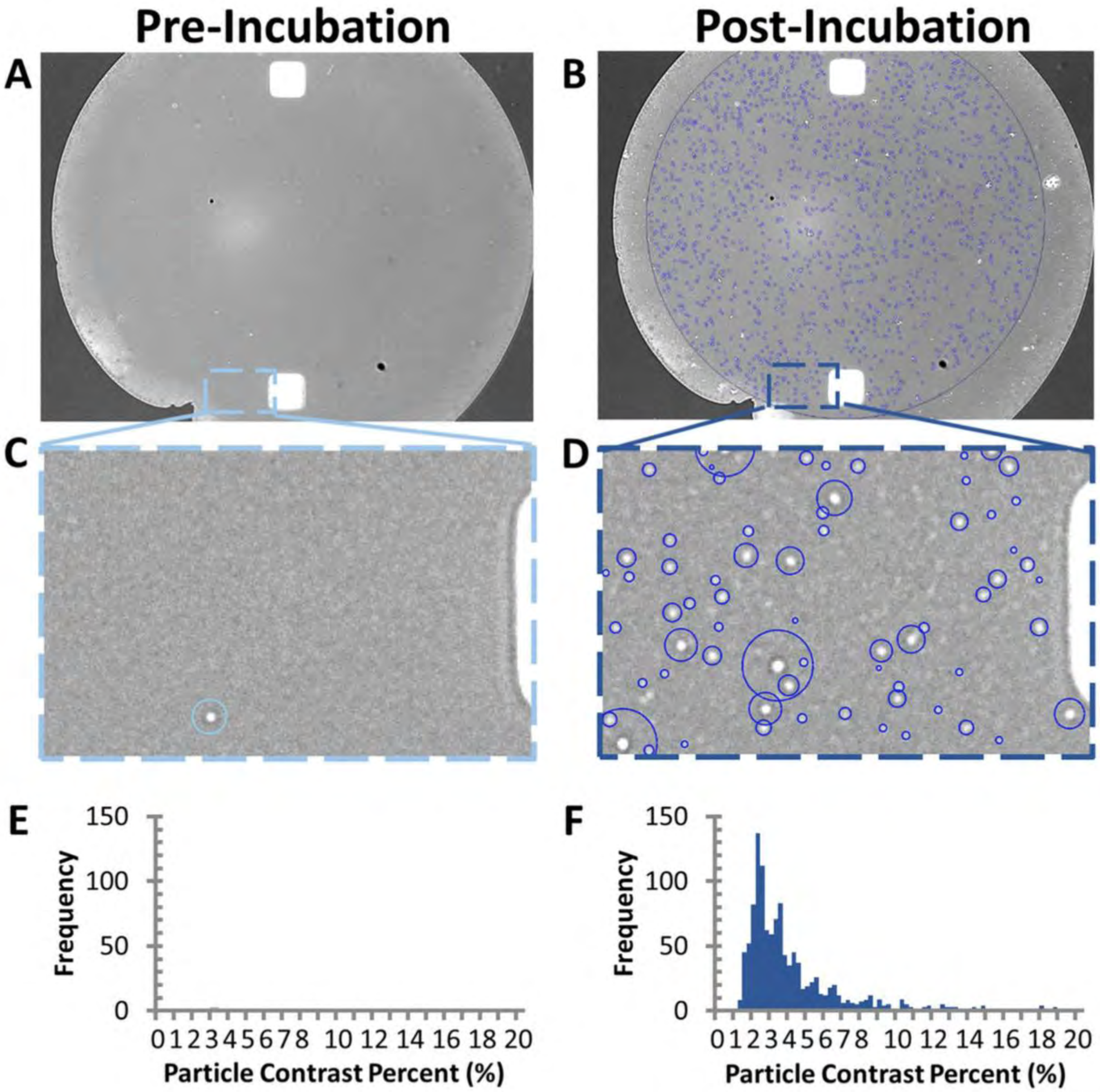
Exosome detection



Anti-CD81 capture probe image acquired before and after incubation with purified HEK293 cells derived exosomes.

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]

Received: 20 June 2016

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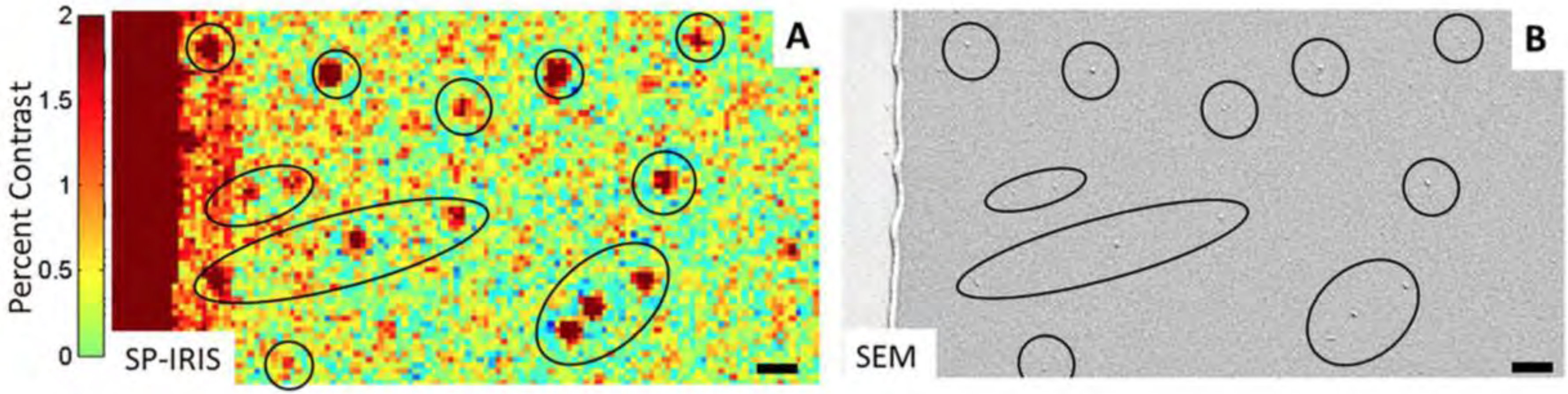
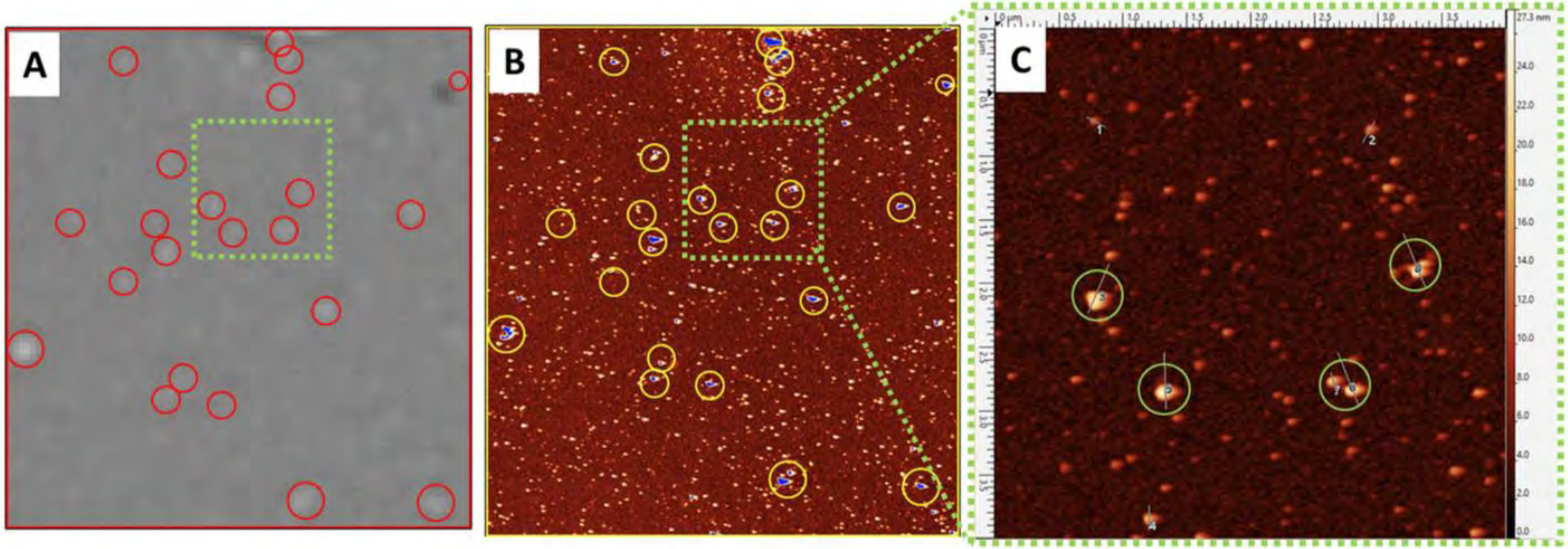
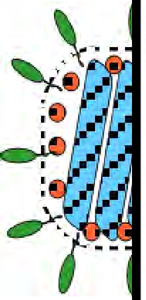
Verification by SEM and AFM – down to r=30nm dry

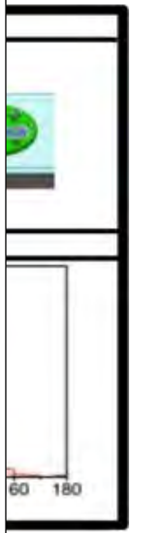




indEx

NTEGRATED NANOPARTICLE ISOLATION AND
)ETECTION SYSTEM FOR COMPLETE ON-CHIP
\NALYSIS OF EXOSOMES

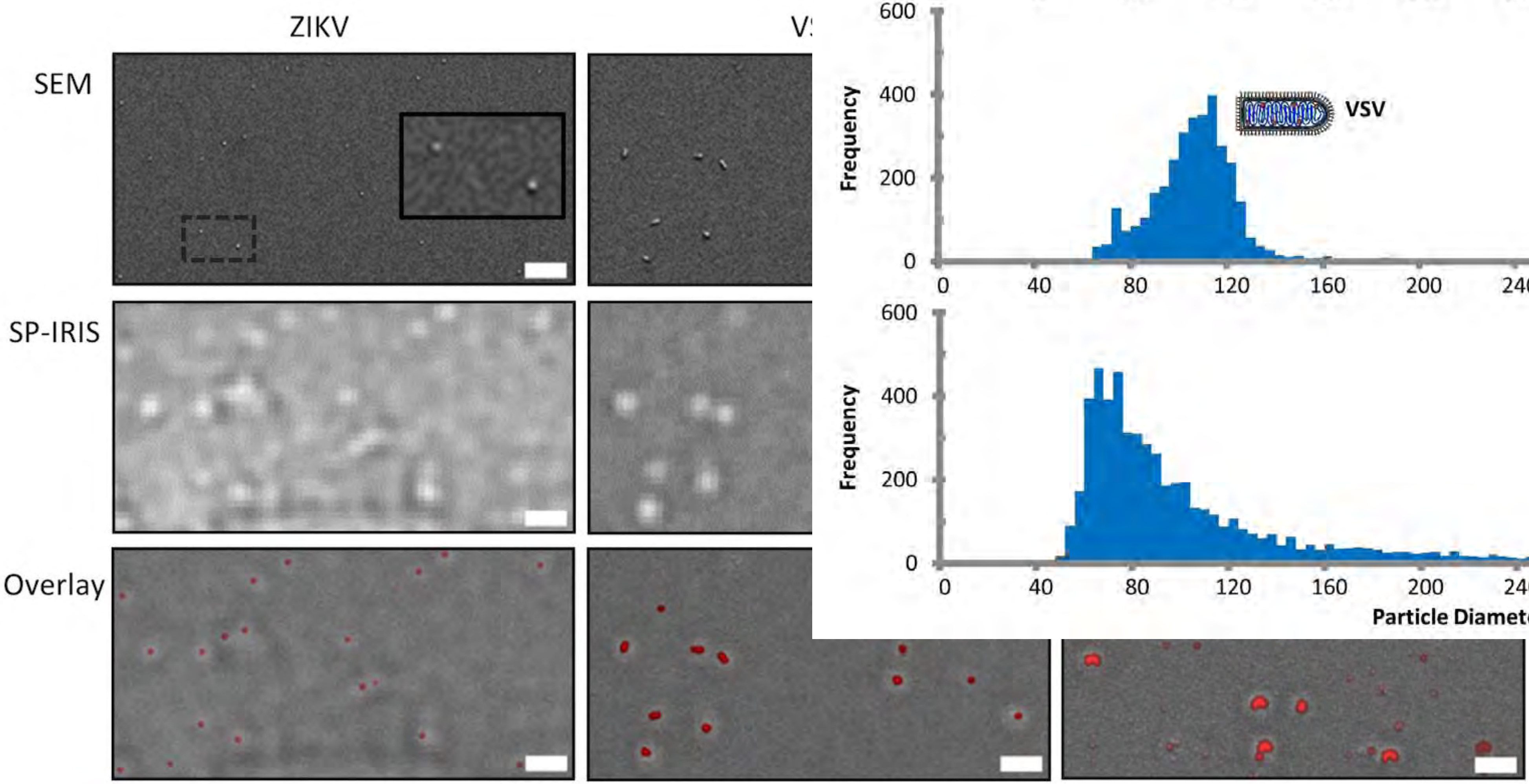


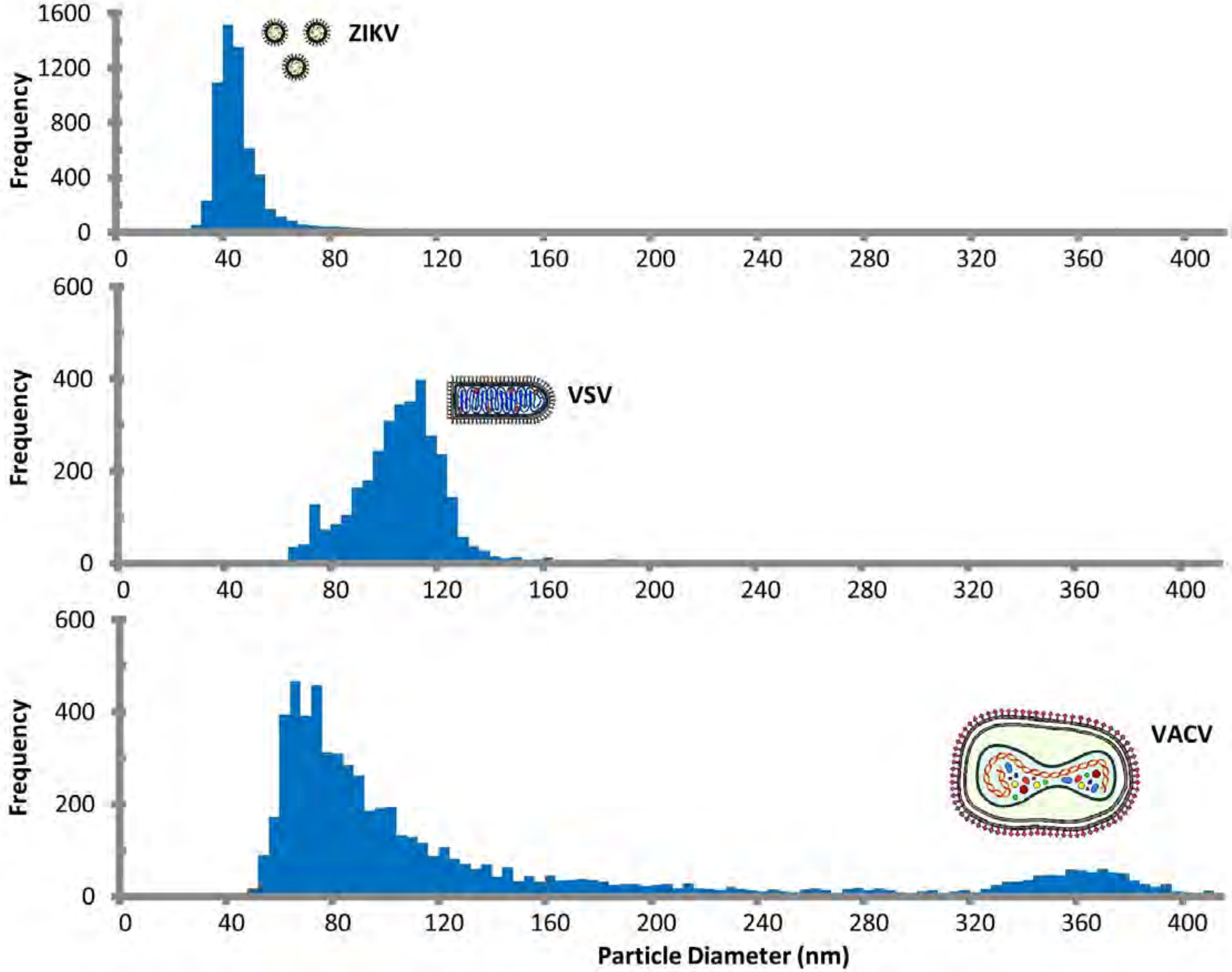


rometric
virons

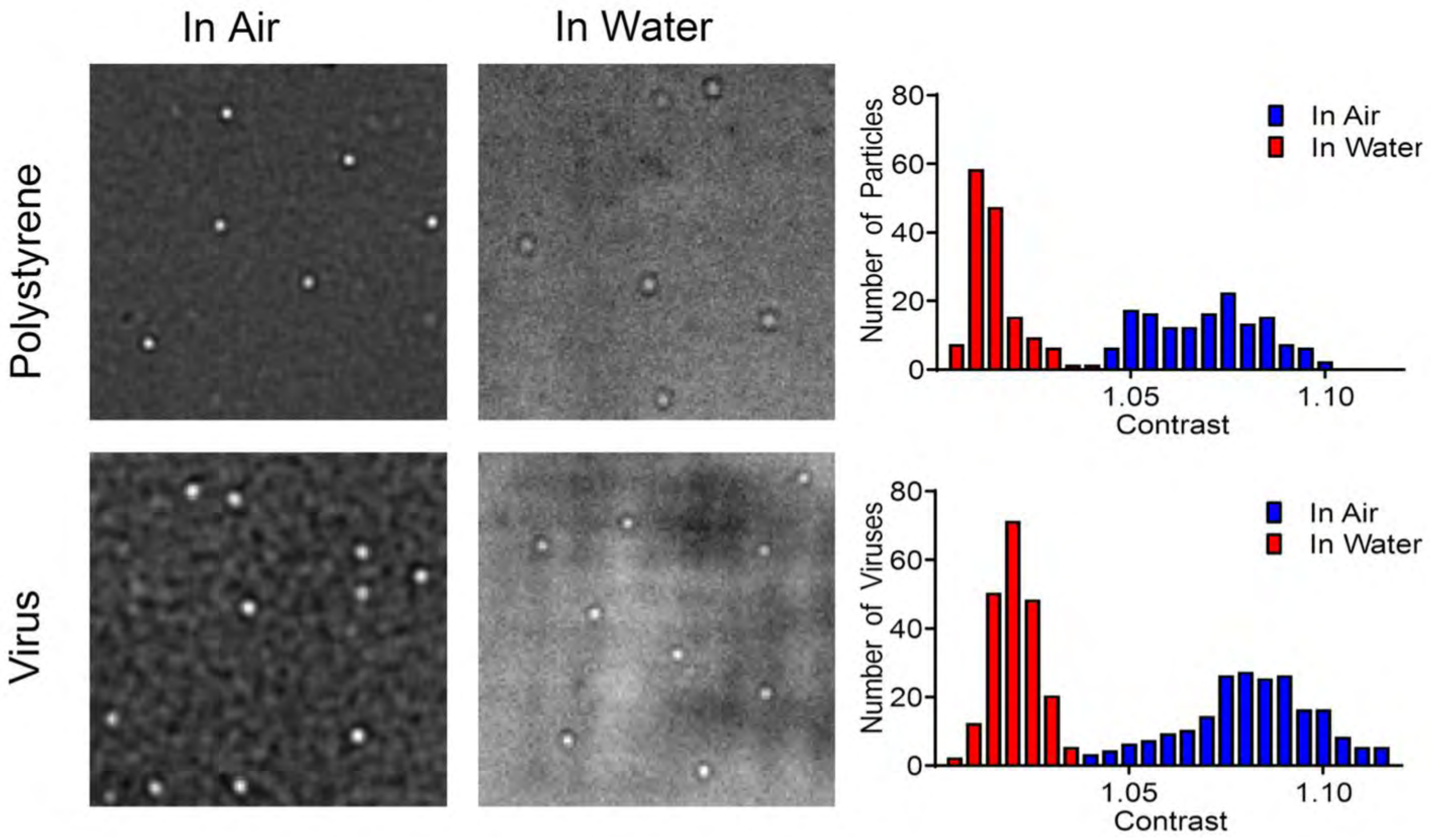
RIAPA

Various viruses

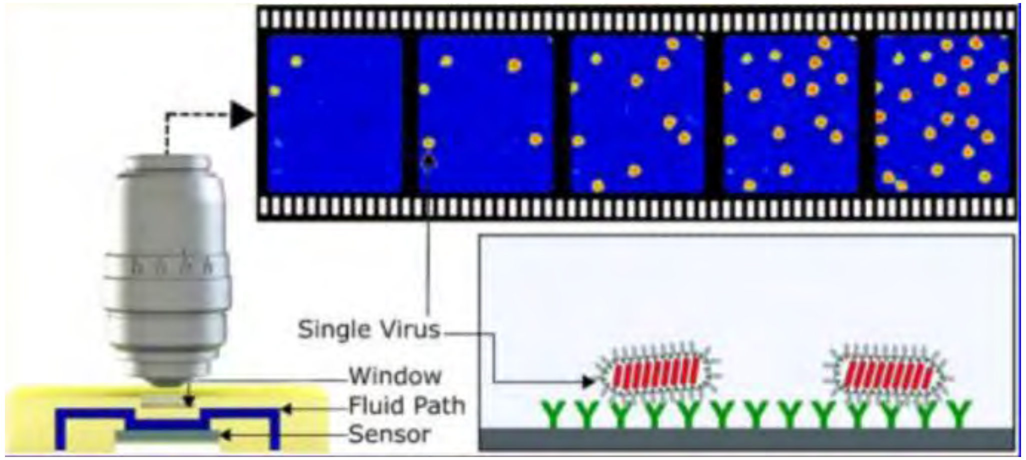


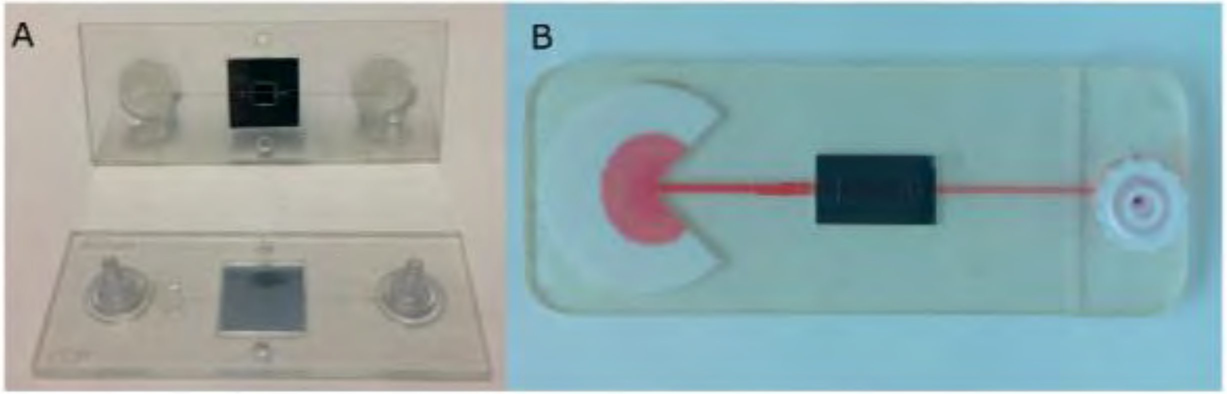


In-liquid detection to simplify the assay

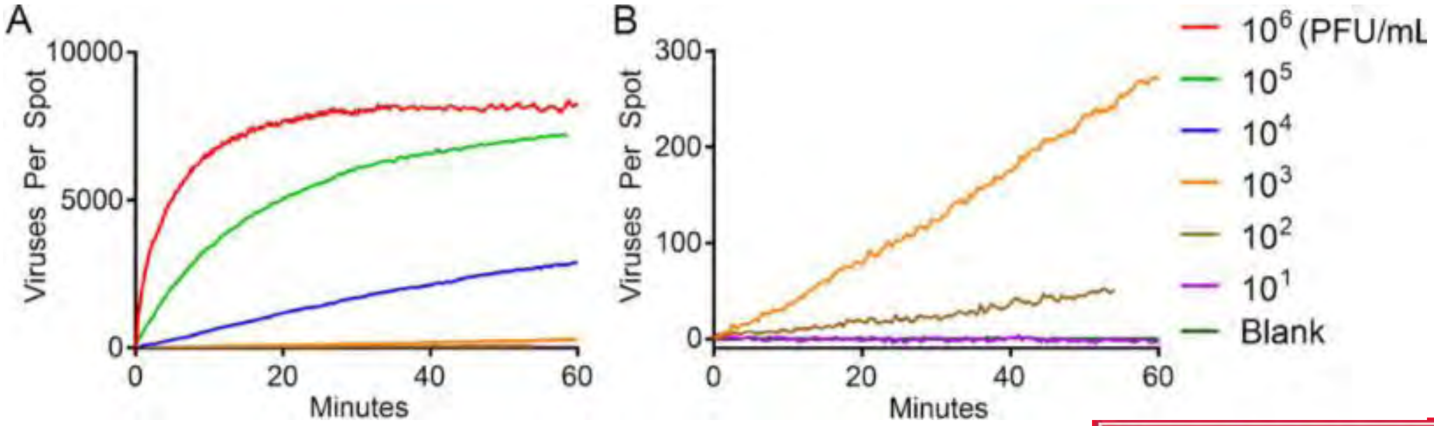


Virus detection for diagnostic applications



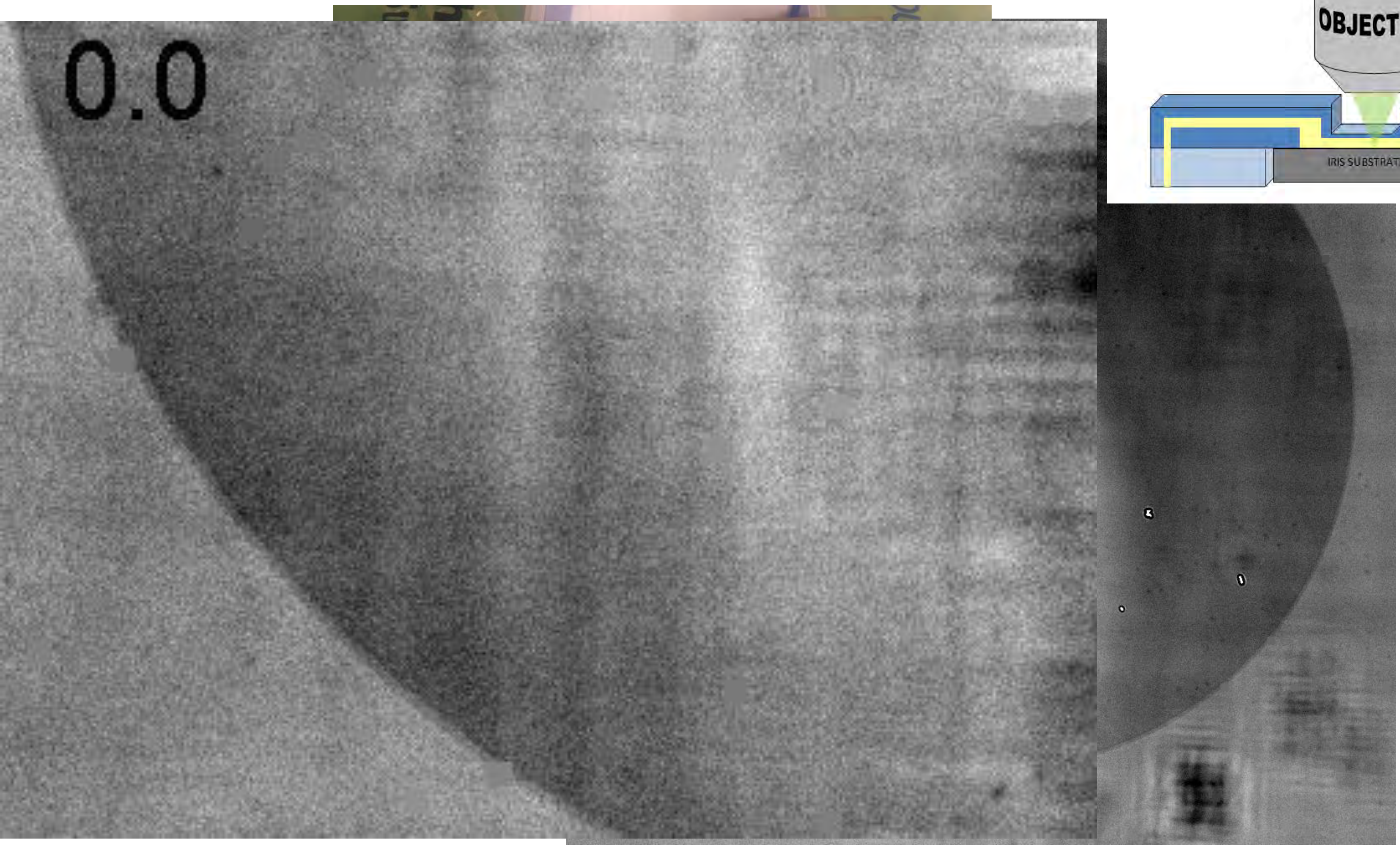


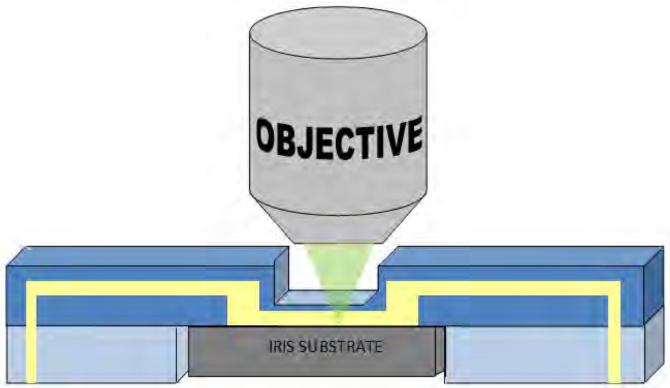
Highly-sensitive virus detection directly from blood serum



Scherr et al, *ACS nano* 10 (2016) and Scherr et al, *Lab on a Chip* 17 (2017)

Real-Time in-liquid Virus Detection



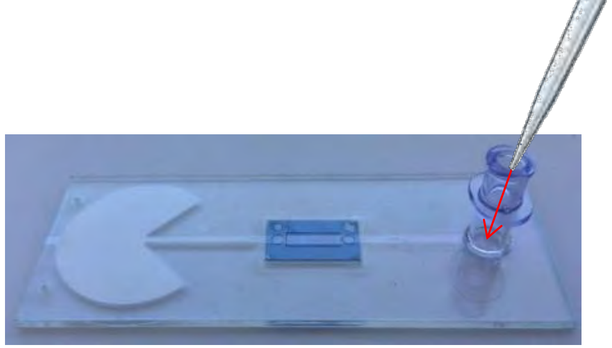


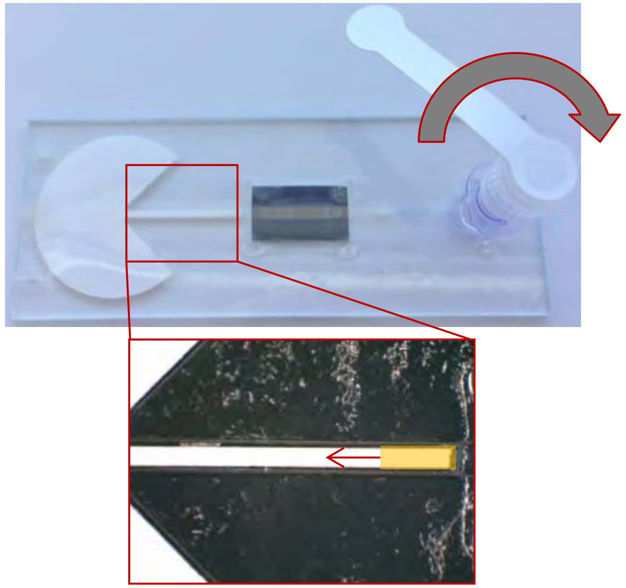

'17

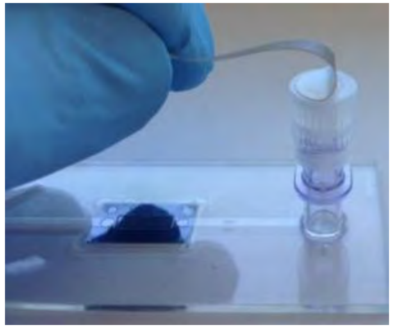

'15

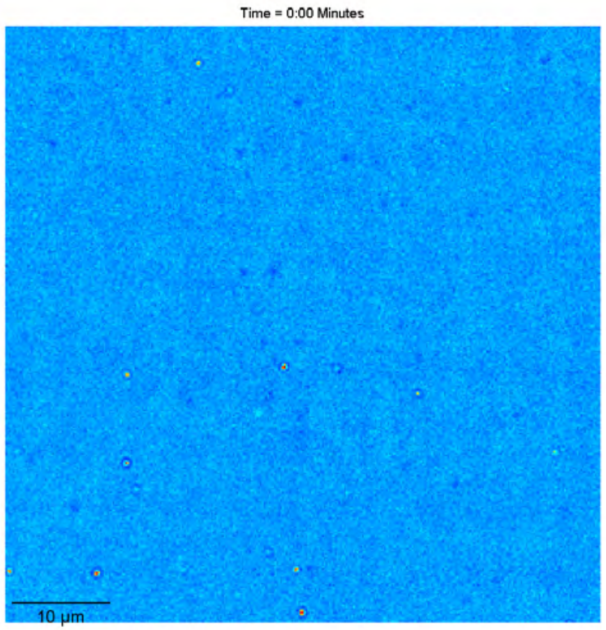
Passive Cartridge - Simple Workflow

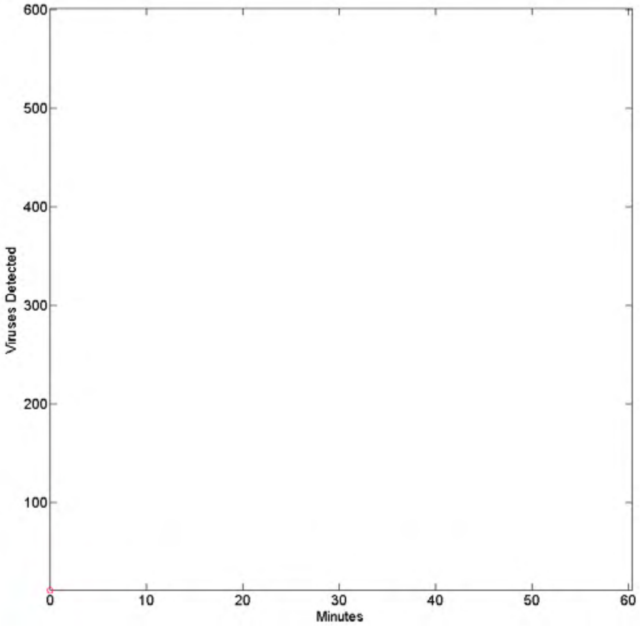
1. Remove cartridge from package just prior to use
2. 100 uL of sample is pipetted into the bottom of the reservoir (*care needs to be taken not to introduce bubbles)
3. Luer cap (sealed with adhesive strip) is screwed down finger tight
4. When liquid reaches the pad, the luer cap is vented (adhesive strip removed)
5. Cartridge is placed in the instrument to begin acquiring data











Lab on a Chip

ROYAL SOCIETY OF CHEMISTRY

PAPER

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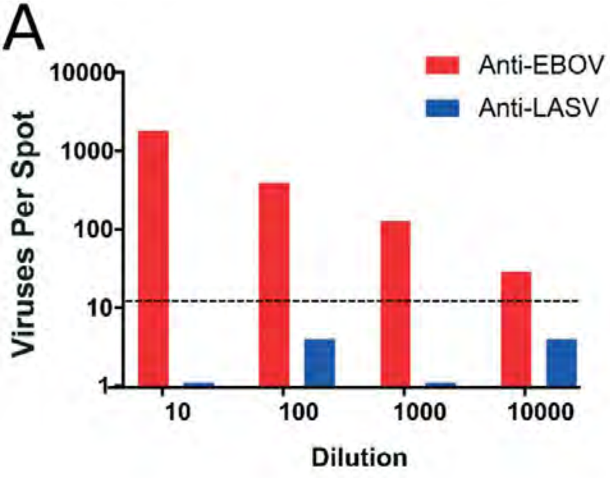
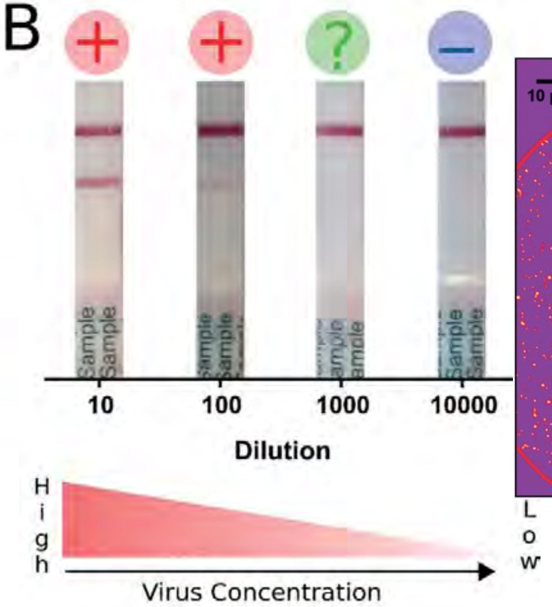
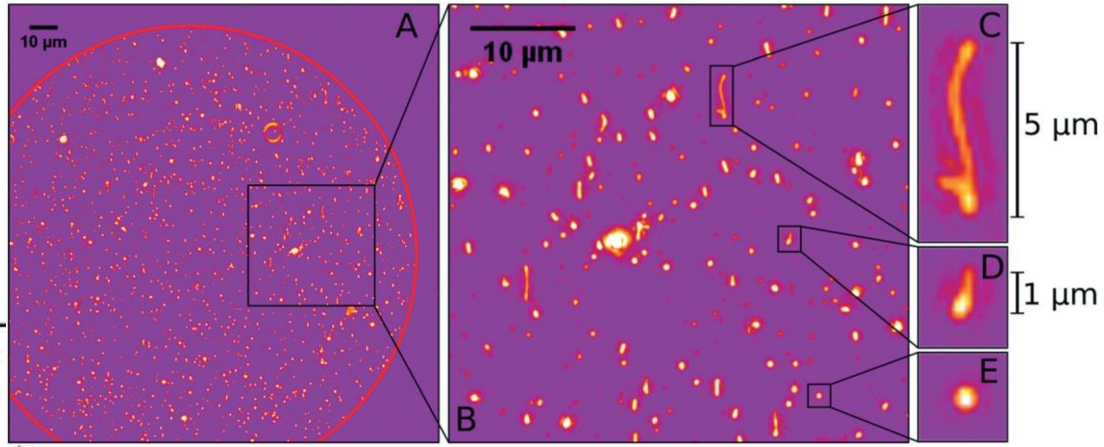
Cite this: DOI: 10.1039/c6lc01528j

Disposable cartridge platform for rapid detection of viral hemorrhagic fever viruses†

Steven M. Scherr,[a] David S. Freedman,[b] Krystle N. Agans,[cd] Alexandru Rosca,[b] Erik Carter,[e] Melody Kuroda,[f] Helen E. Fawcett,[a] Chad E. Mire,[cd] Thomas W. Geisbert,[cd] M. Selim Ünlü[ghi] and John H. Connor*[eh]







Dilution	SP-IRIS Anti-EBOV (Viruses Per Spot)	SP-IRIS Anti-LASV (Viruses Per Spot)	ReEbov Test Strip
1:10	1824	**	+
1:100	393	4	+
1:1000	126	-4	?
1:10000	29	4	-

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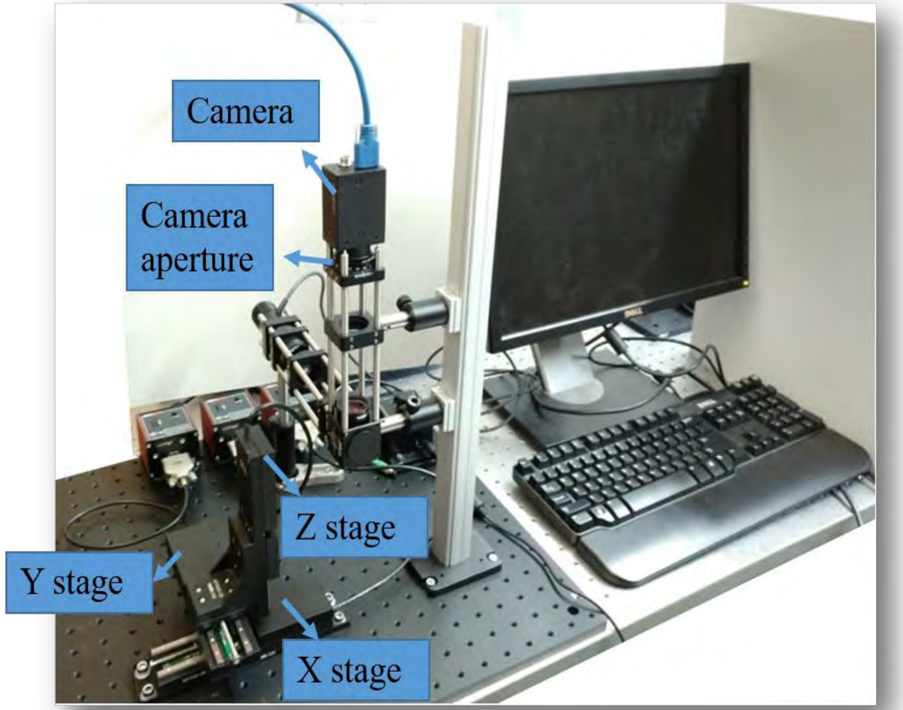
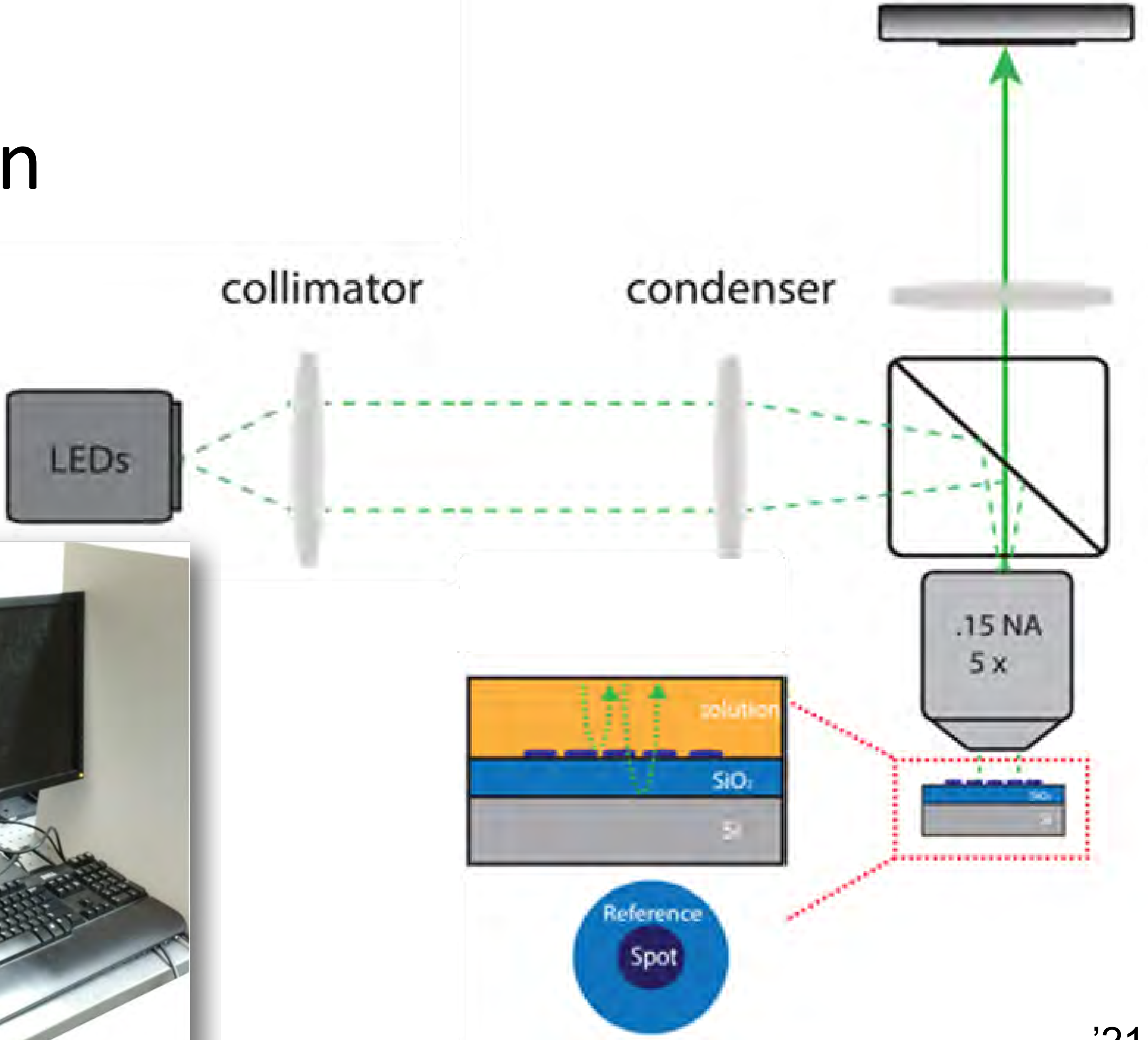
E-coli Detection





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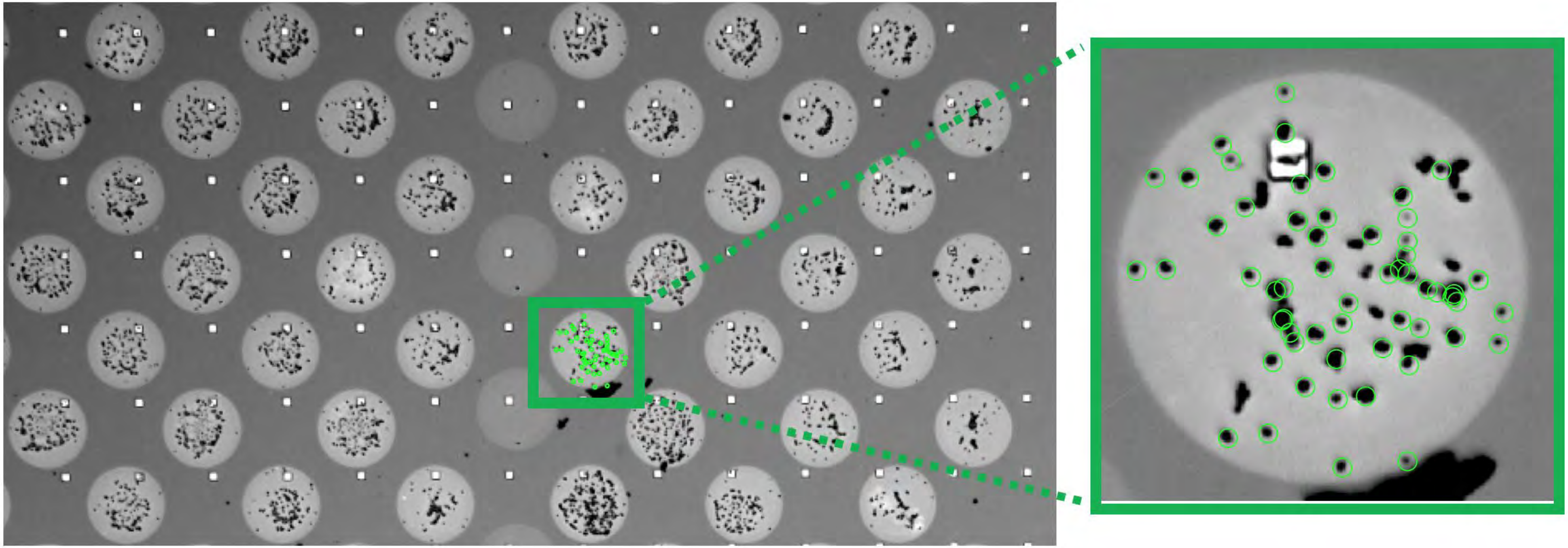
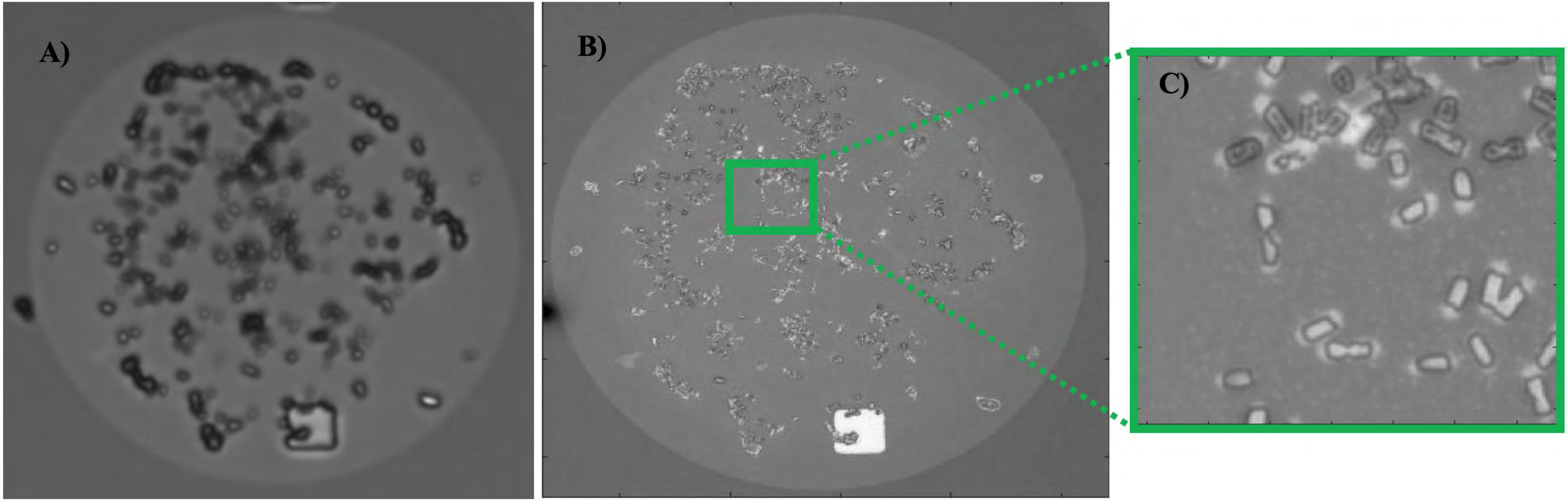
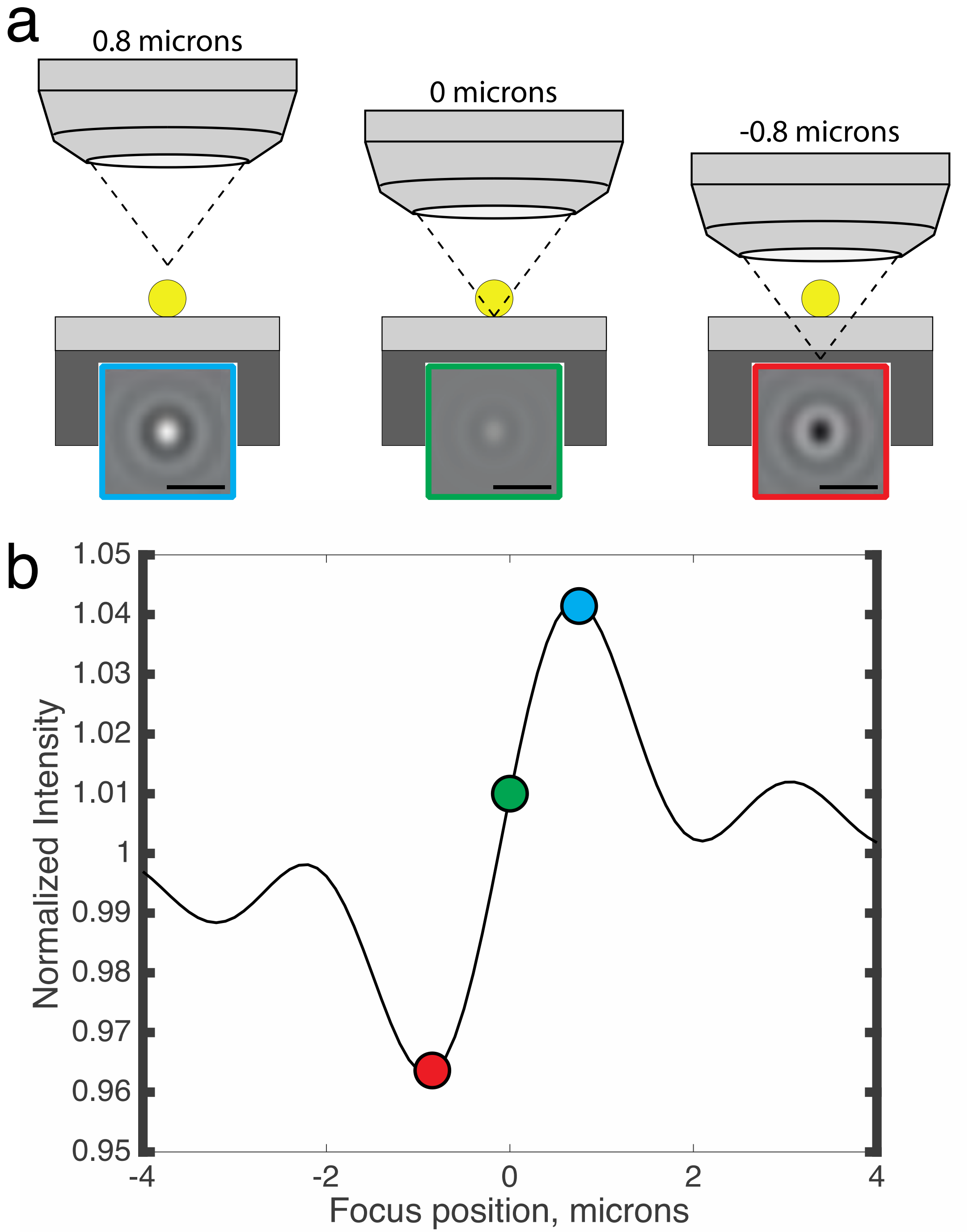
5X objective imaging and processing



LOD of ~50CFU/ml.   with 1000X concentration -> 1 CFU/20 ml

Detection and Verification





Interferometric fringes – defocus profile

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

'17

D. Sevenler et al, **"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

O. Avci, et al. **"Pupil function engineering for enhanced nanoparticle visibility in wide-field interferometric microscopy,"** *Optica*2017

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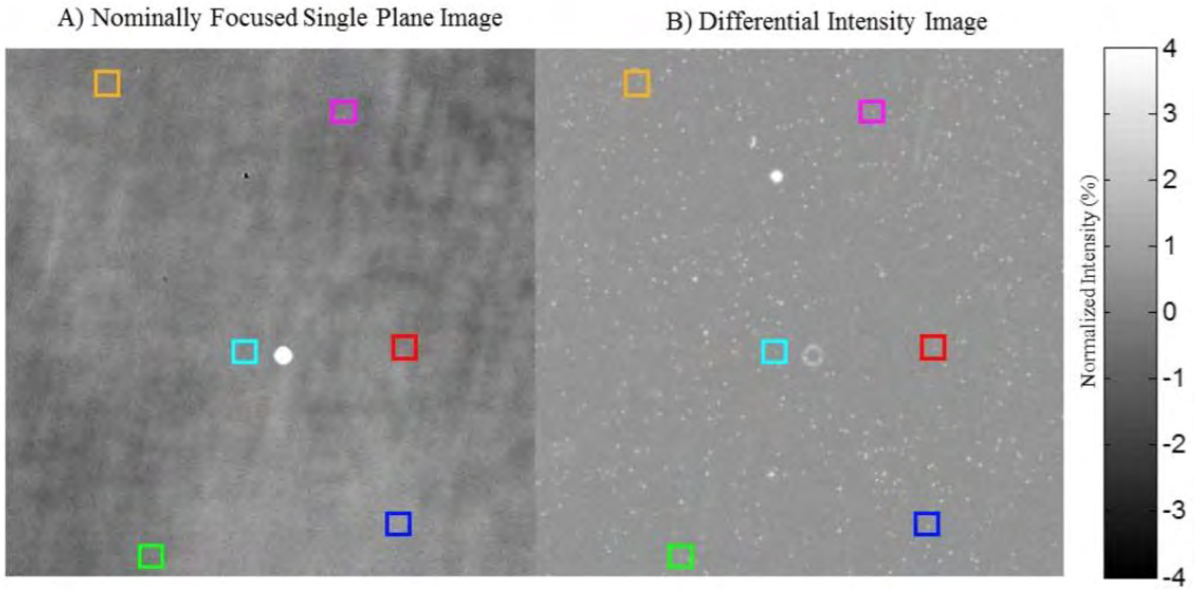
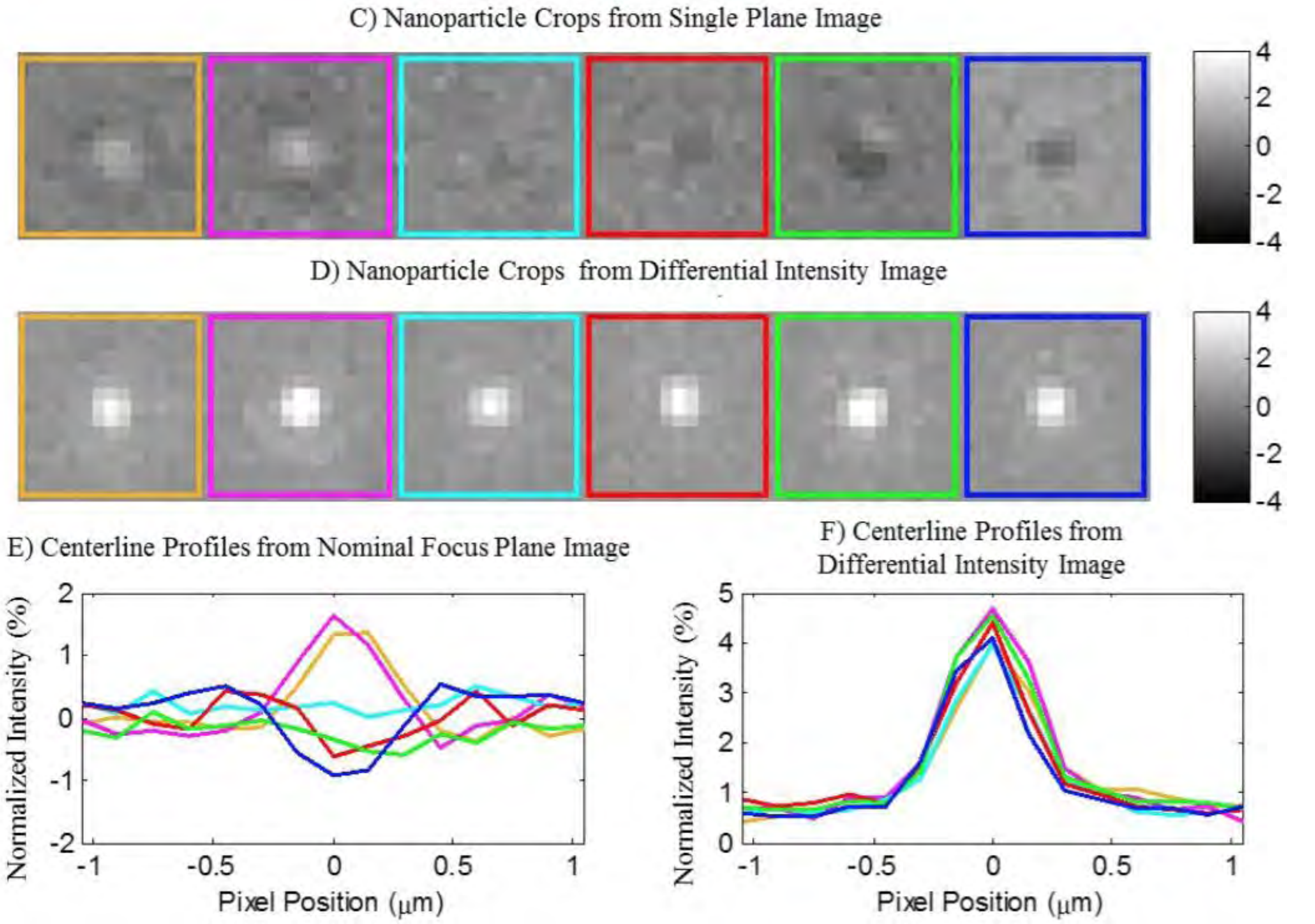
Robust Visualization and Discrimination of Nanoparticles by Interferometric Imaging

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





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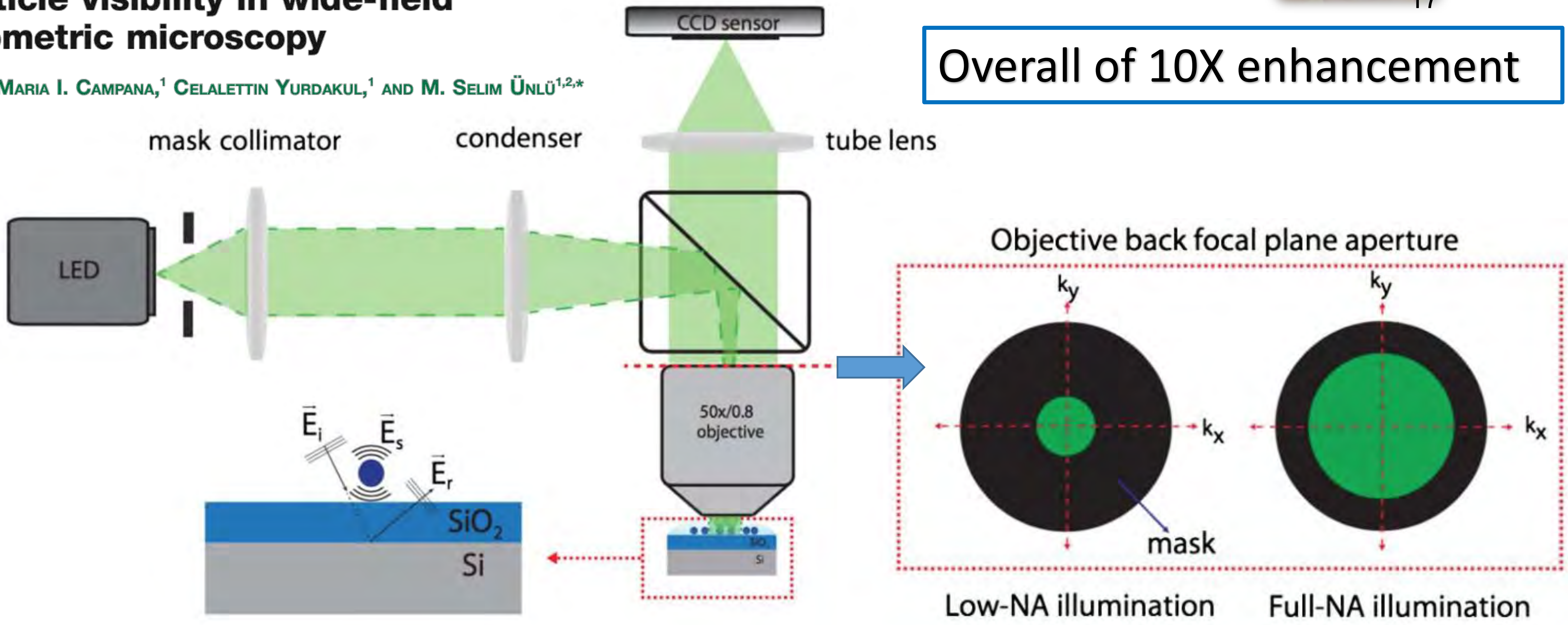
Research Article
Vol. 4, No. 2 / February 2017 / Optica 247
optica

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

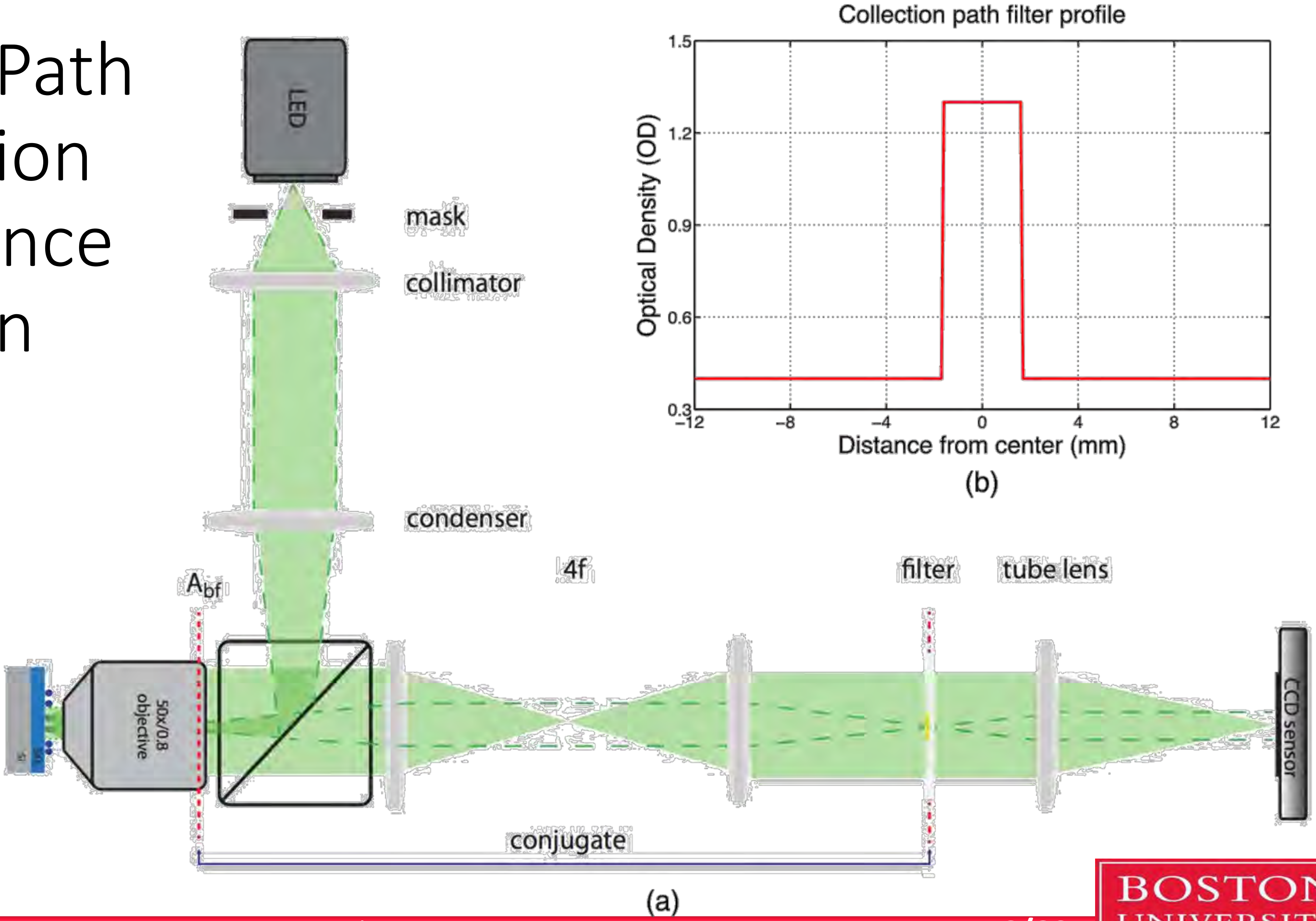
Oguzhan Avci,[1] Maria I. Campana,[1] Celalettin Yurdakul,[1] and M. Selim Ünlü[1,2,*]

'17

Overall of 10X enhancement



Collection Path – Apodization and Reference Attenuation



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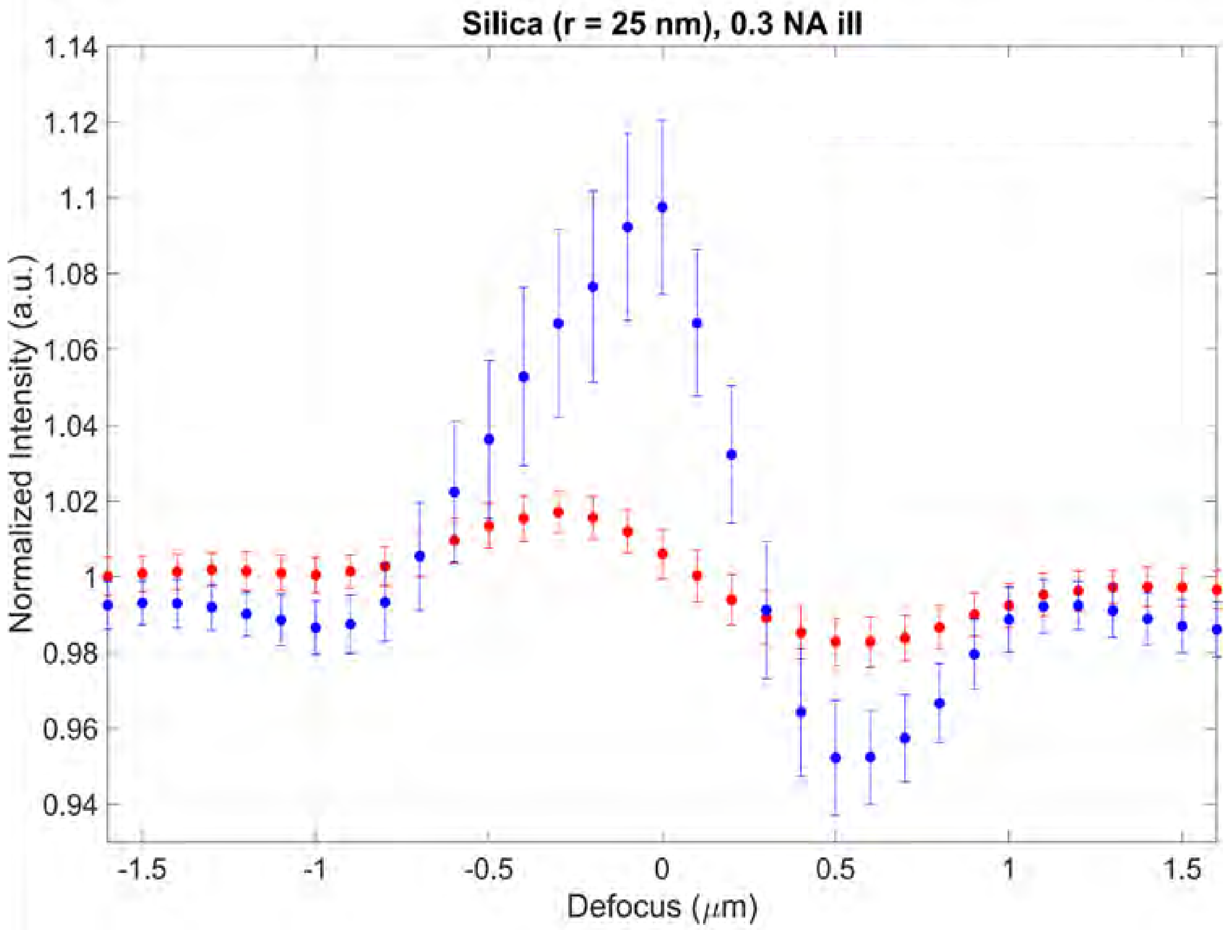
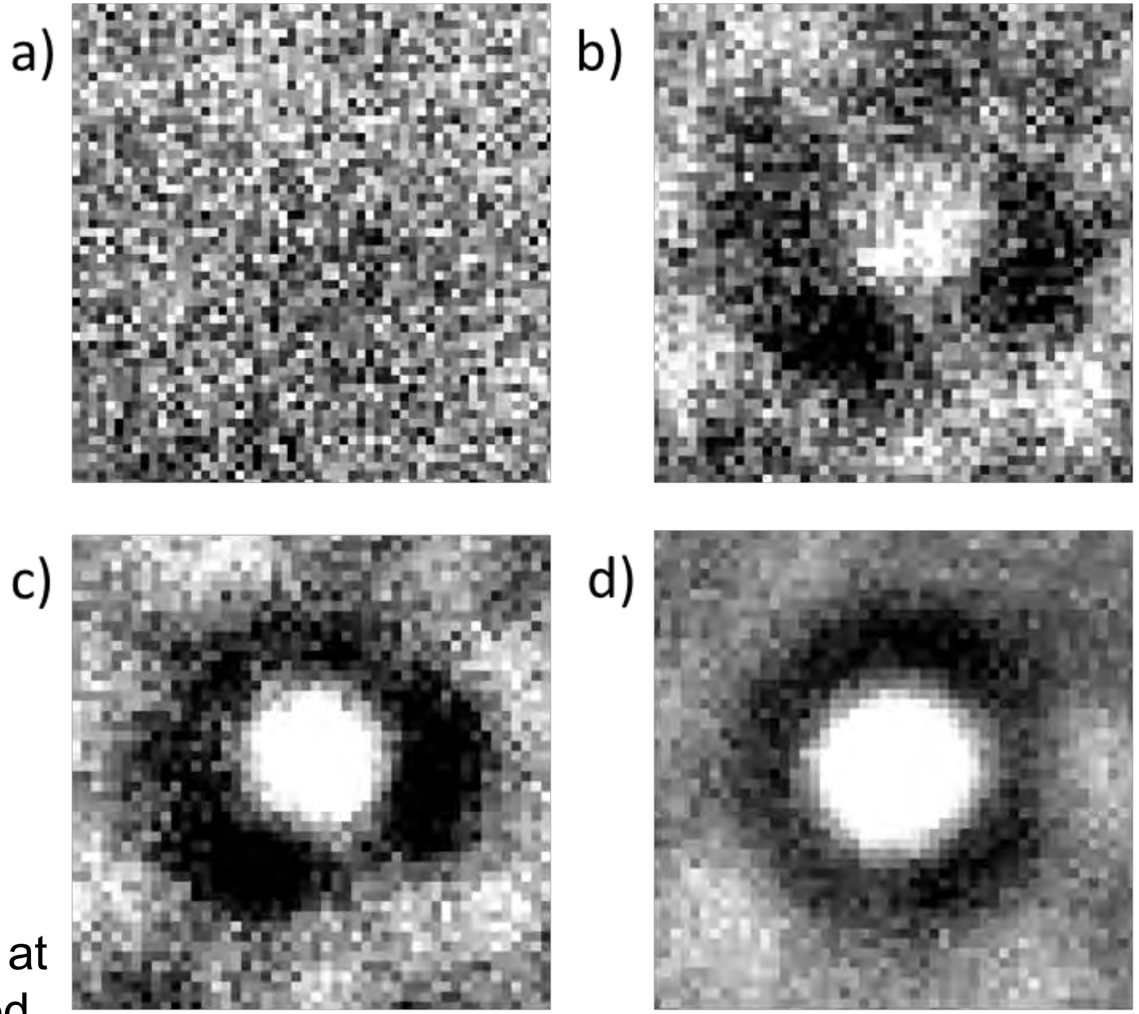
Silica particles defocus curve **~5X enhancement (3% → 15%)**





a) full-NA illumination at λ=530 nm, b) apodized illumination at λ=530 nm, c) apodized illumination at λ=460 nm, d) apodized illumination with amplitude filter in the collection path at λ=460 nm.

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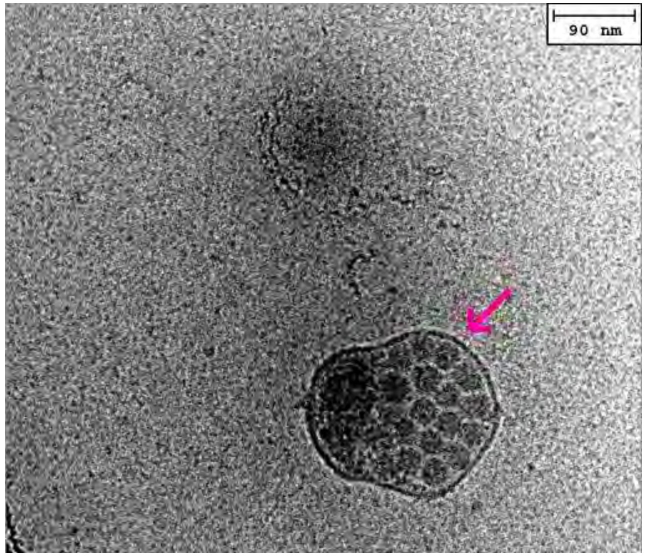
OUTLINE

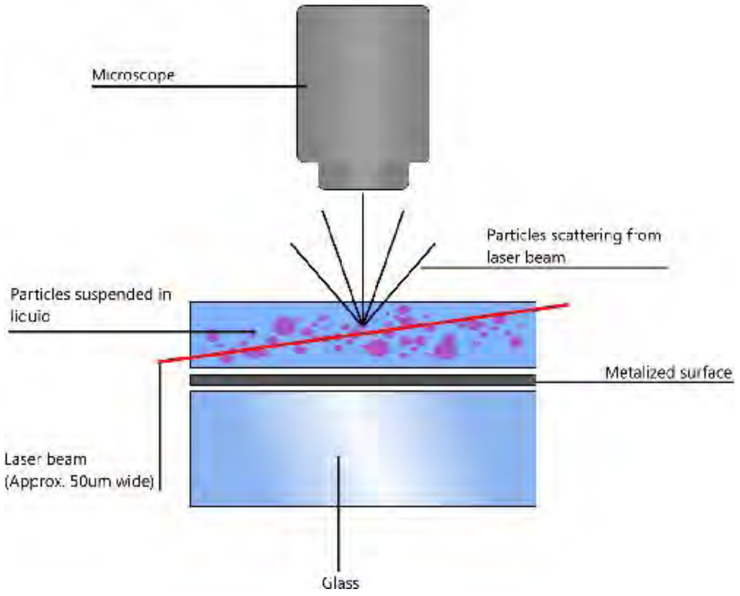
- A bit of philosophy – some history of optics
  - Optical Interference
- Interferometric Reflectance Imaging Sensor (IRIS)
  - Principles
  - Requirements and technology
- Kinetic measurements of molecular binding
- **Single bio-nanoparticle detection**
  - **Exosomes**
  - **Viruses**
  - **Bacteria**
- **Super-resolution imaging**
- Single Molecule Detection

Technologies for bio-nanoparticle characterization

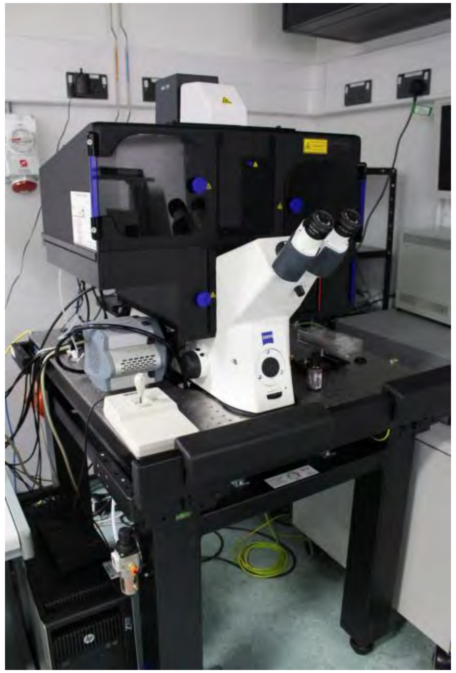
Cryo-TEM
- Fantastic resolution
- Low throughput and difficult



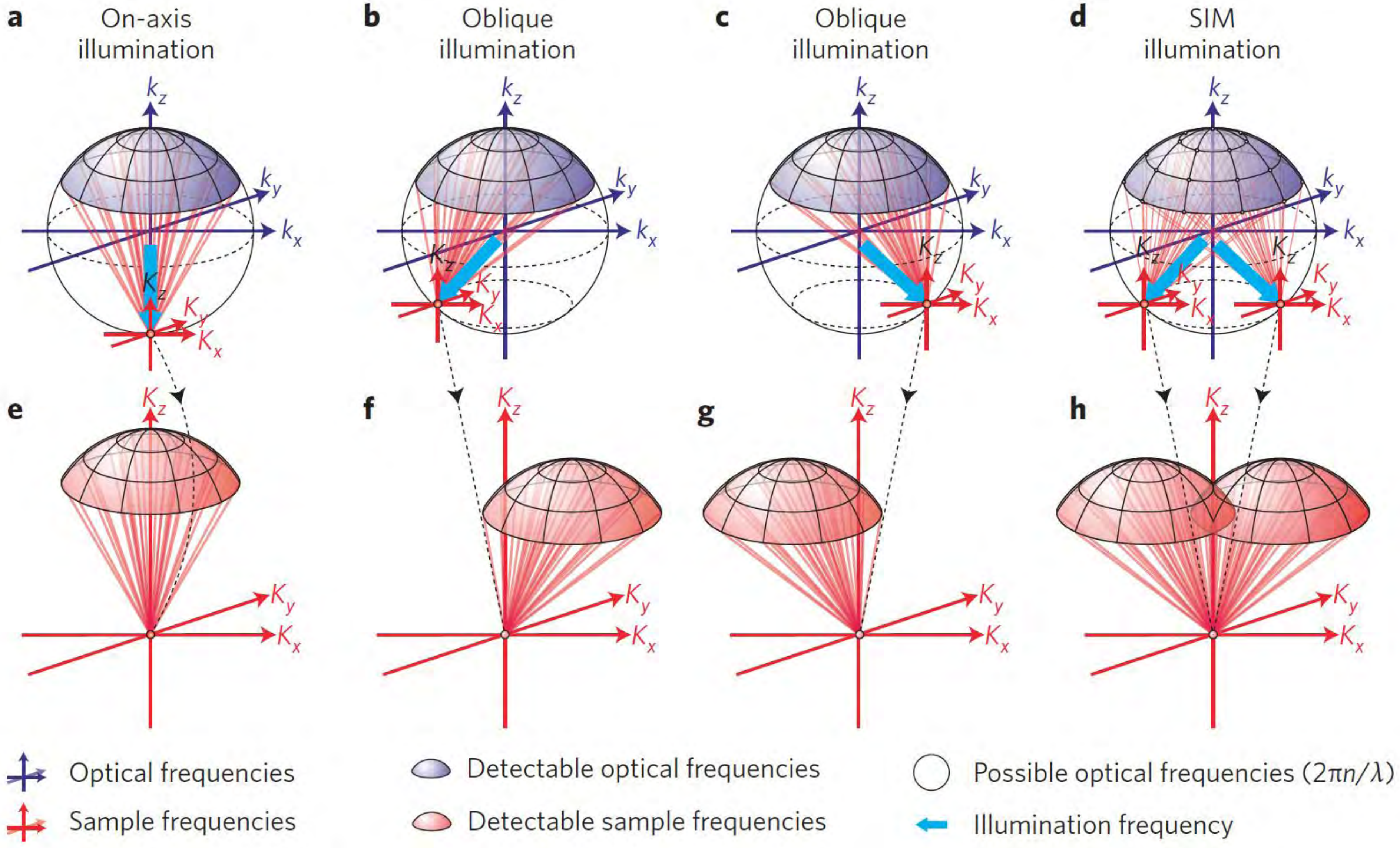
Nanoparticle Tracking Analysis
- Estimate size of particles based on Brownian motion
- Little/no molecular information



Fluorescence microscopy (STED/PALM)



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



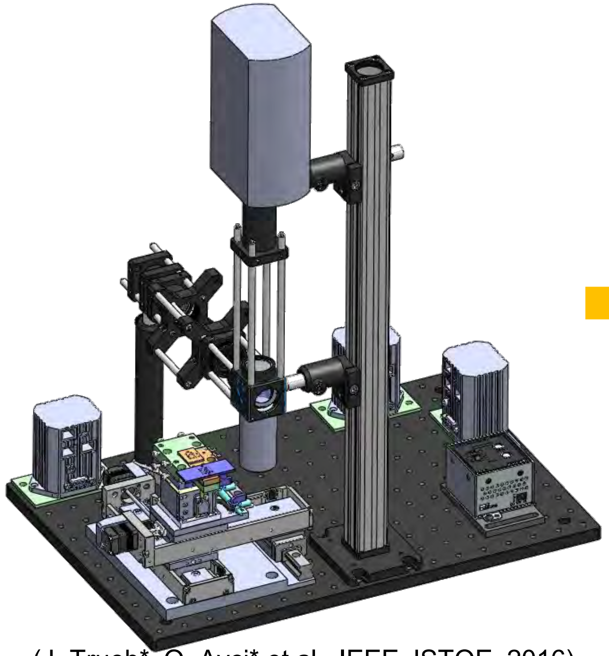
NATURE PHOTONICS | VOL 8 | MAY 2014 |

Reconstruction in Interference Microscopy

imaging system

object

in



out

observation

(J. Trueb*, O. Avci* et al., IEEE JSTQE, 2016)

$$y = Ax + e$$

observation ← y

system response
convolution matrix ← A

object ← x

noise ← e

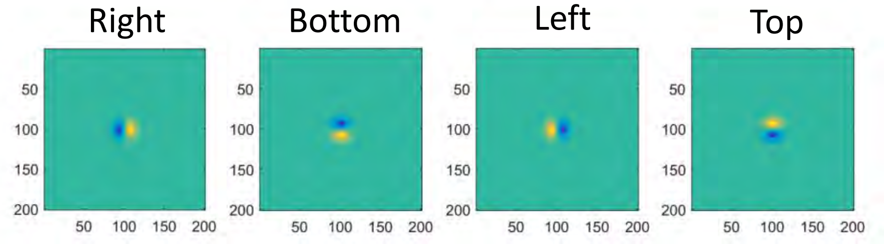
Super-resolution in wide-field interferometric microscopy

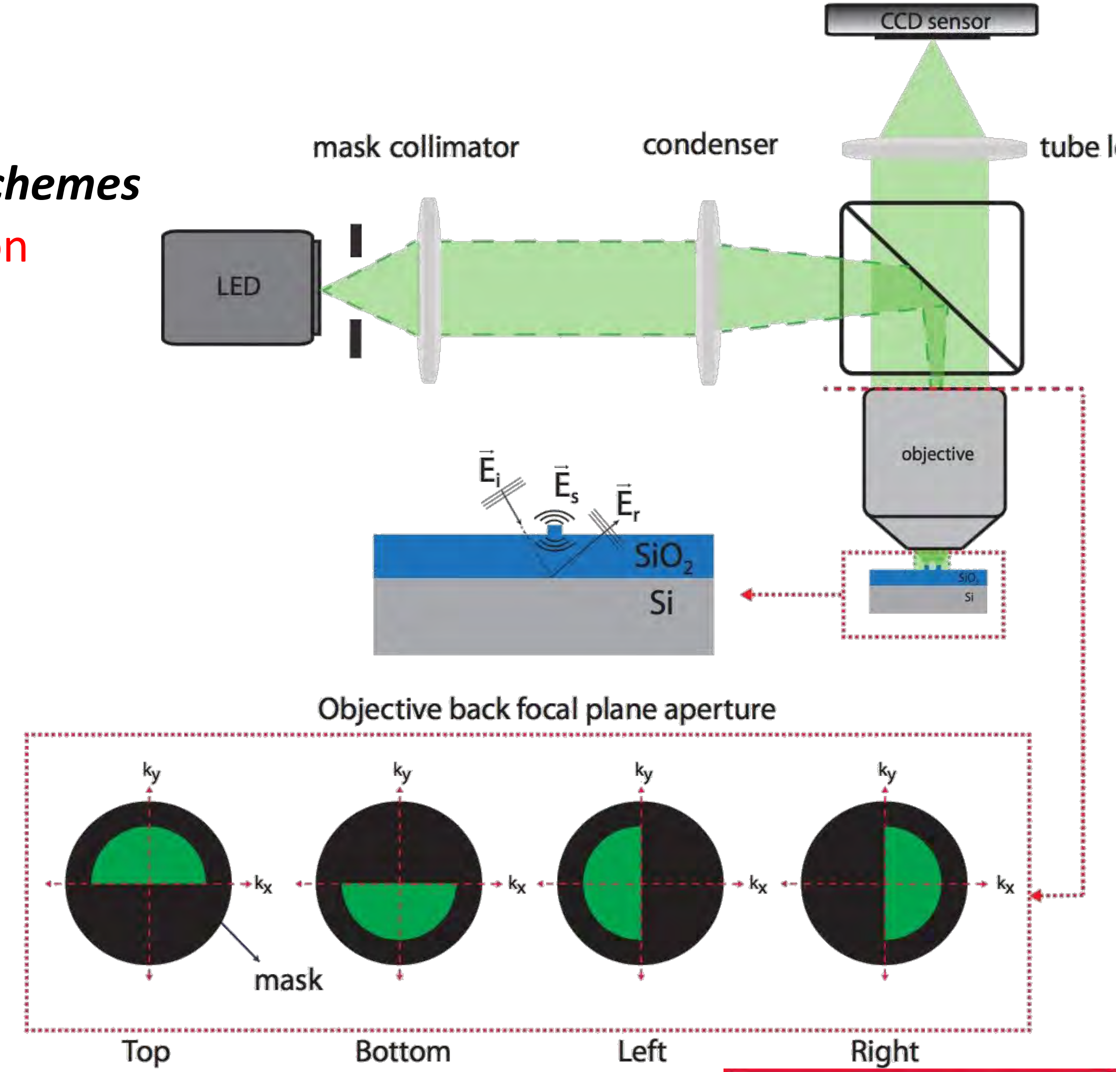
- ***Enhancing low-index nanoparticle resolution via reconstruction schemes***
  Asymmetric illumination based reconstruction for super resolution
  (with Lei Tian)

$$\min_{x} \sum_{j=1}^{N} \|A_j x - y_j\|_2^2 + \alpha \|x\|_2^2$$

$$x = \mathcal{F}^{-1}\left\{ \frac{\sum_{j=1}^{N} H_j^* y_j}{\sum_{j=1}^{N} |H_j|^2 + \alpha} \right\}$$

Fourier transforms of the transfer functions (H) for each asymmetric illumination configuration

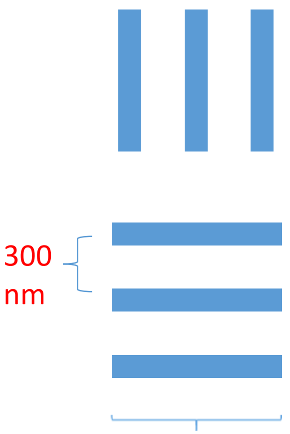




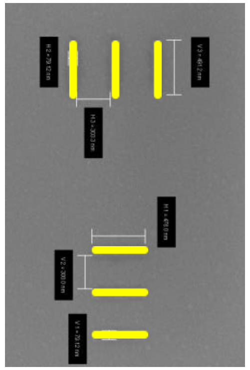
Experimental Results

Sample – E-beam fabricated

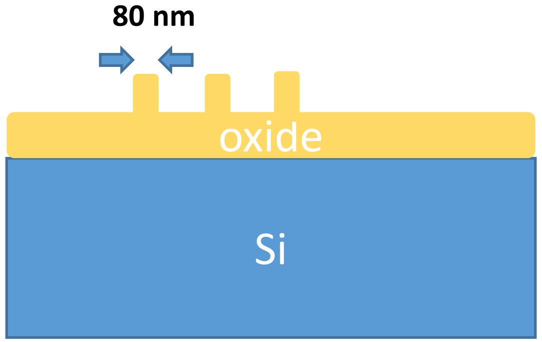
Sketch



SEM

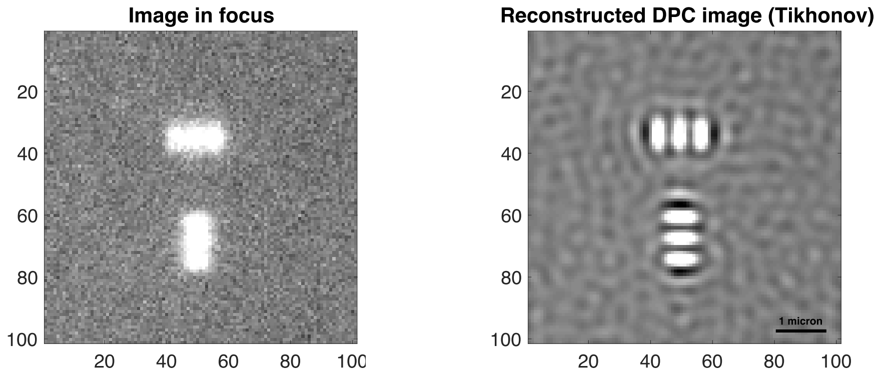


SEM

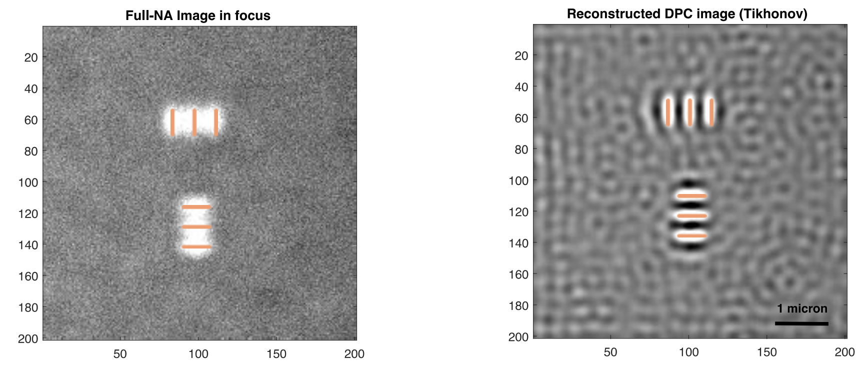


raw

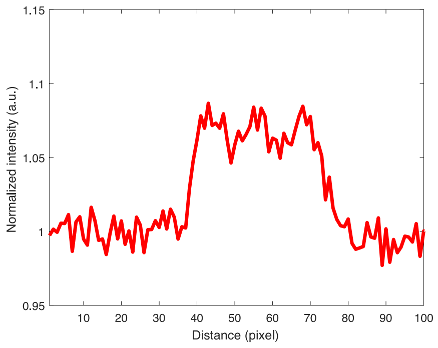
reconstruction

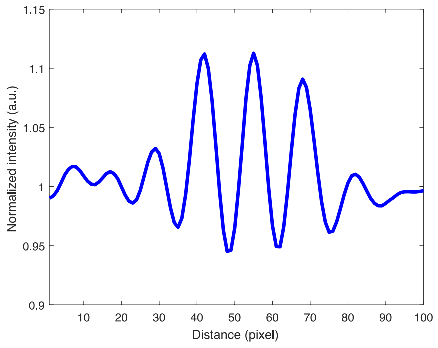


50x/0.8NA 525nm

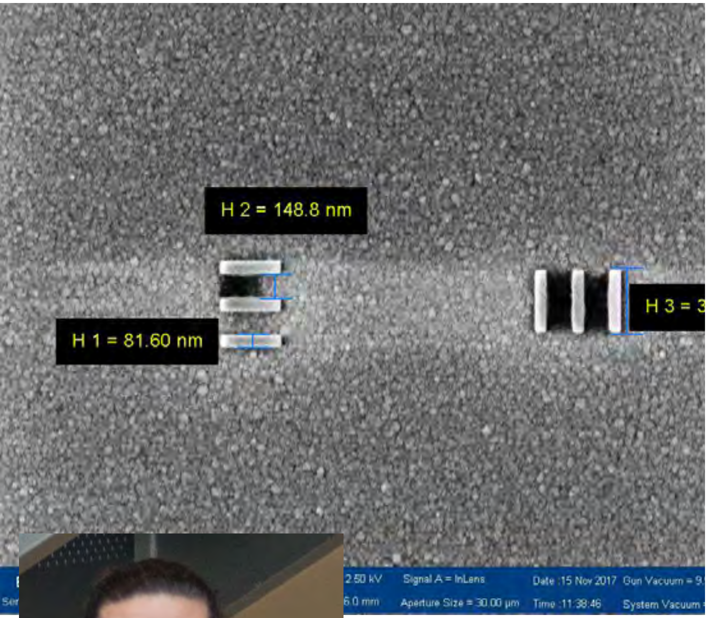


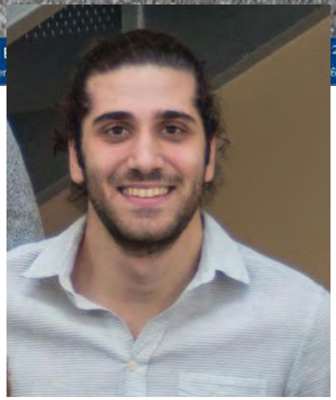
100x/0.9NA 525nm





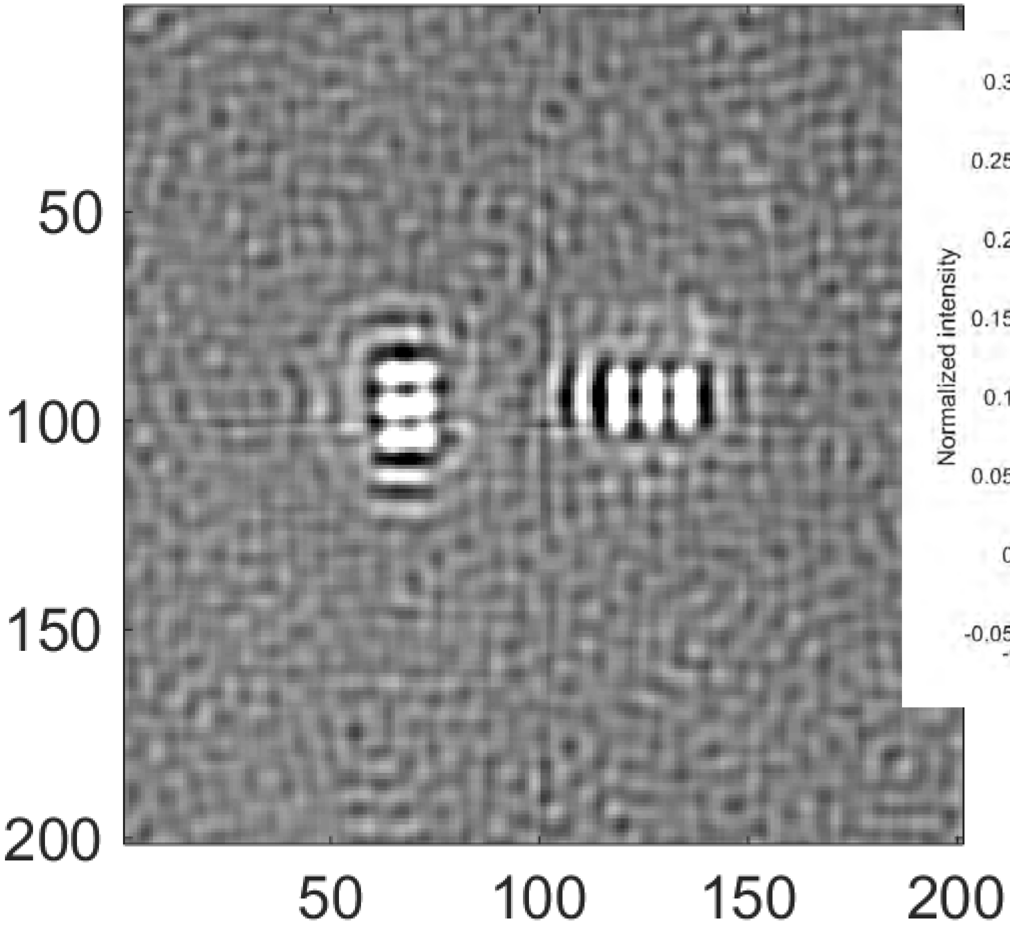
150 nm separation, 0.9 NA, λ=420nm

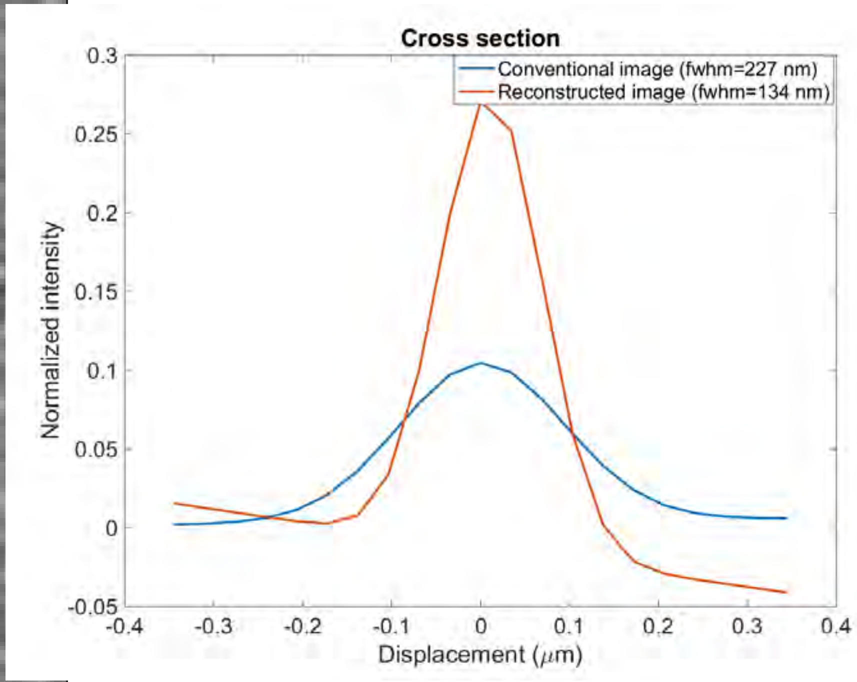




'20

Reconstructed DPC image (Tikhonov)





FWHM ~ 130nm < (λ / 3)

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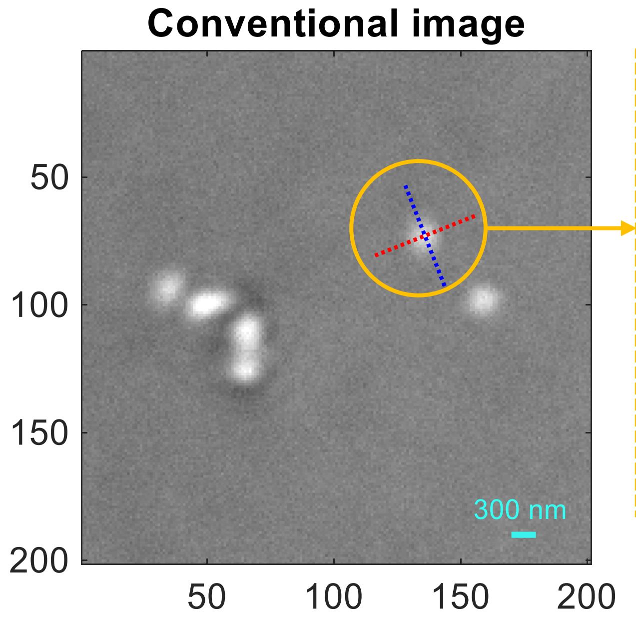
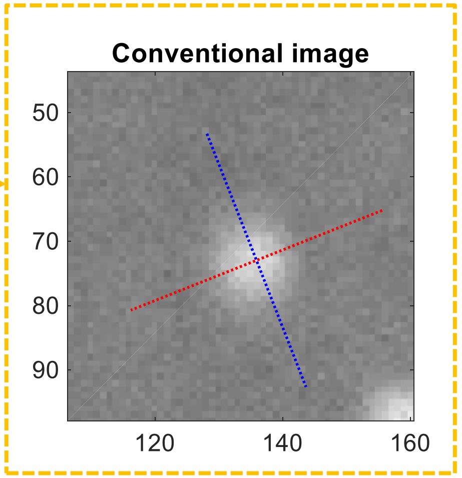
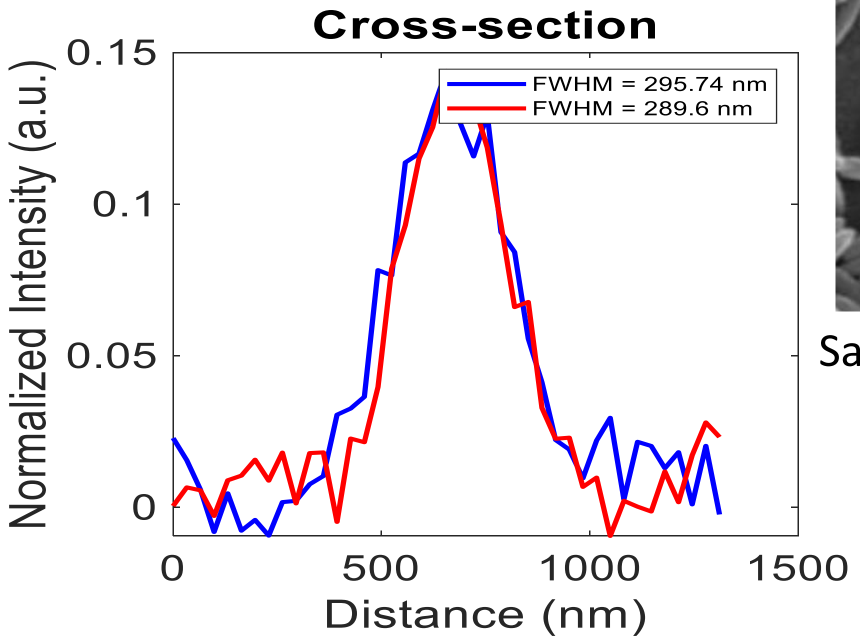
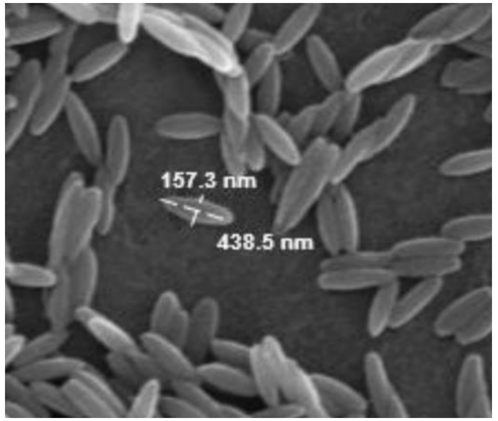
Elongated polystyrene rods



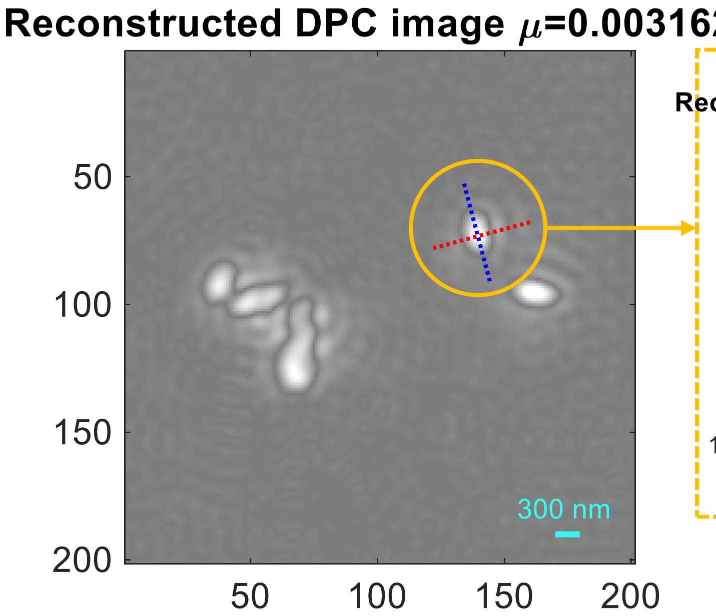


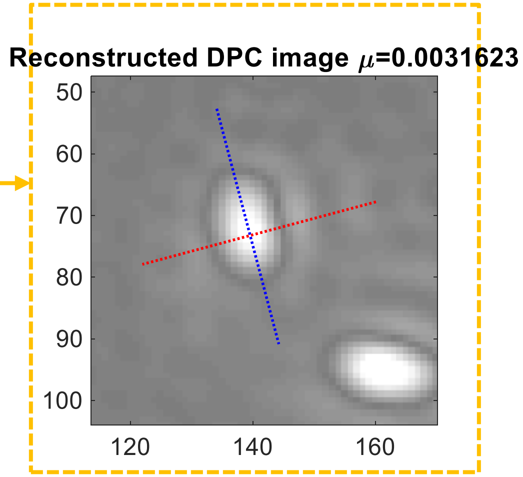


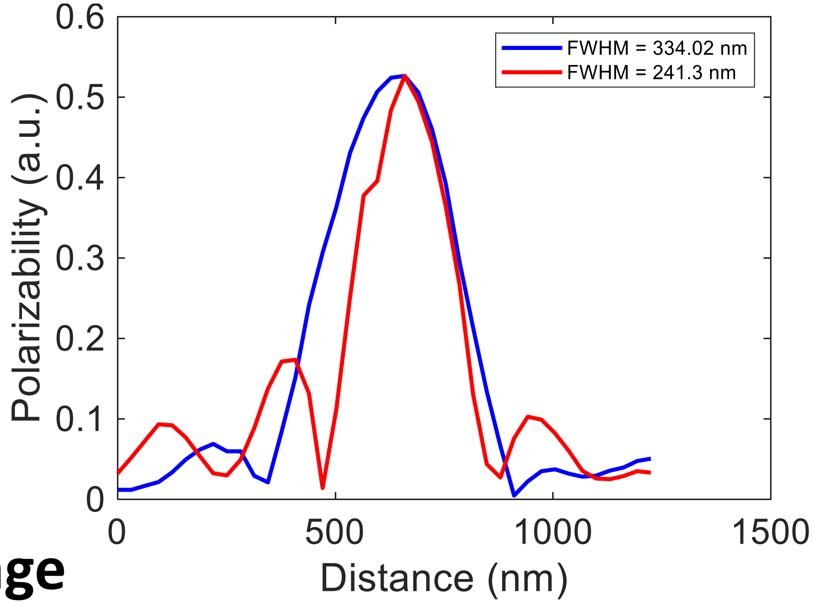


Samir Mitragotri (Harvard)

Full NA







Reconstructed image

OUTLINE

- A bit of philosophy – some history of optics
  - Optical Interference
- Interferometric Reflectance Imaging Sensor (IRIS)
  - Principles
  - Requirements and technology
- Kinetic measurements of molecular binding
- Single bio-nanoparticle detection
  - Exosomes
  - Viruses
  - Bacteria
- Super-resolution imaging
- **Single Molecule Detection – Digital Microarrays**

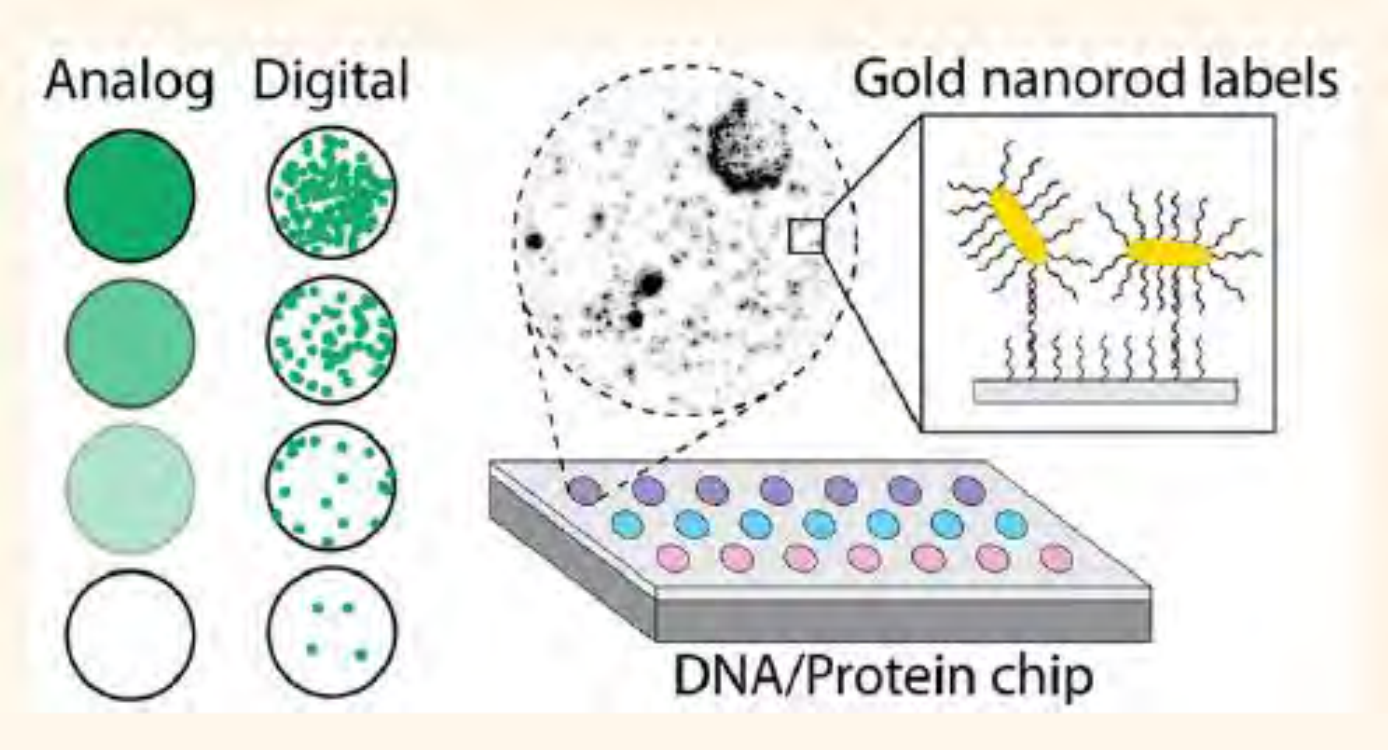
ACS NANO
Cite This: ACS Nano XXXX, XXX, XXX−XXX
www.acsnano.org

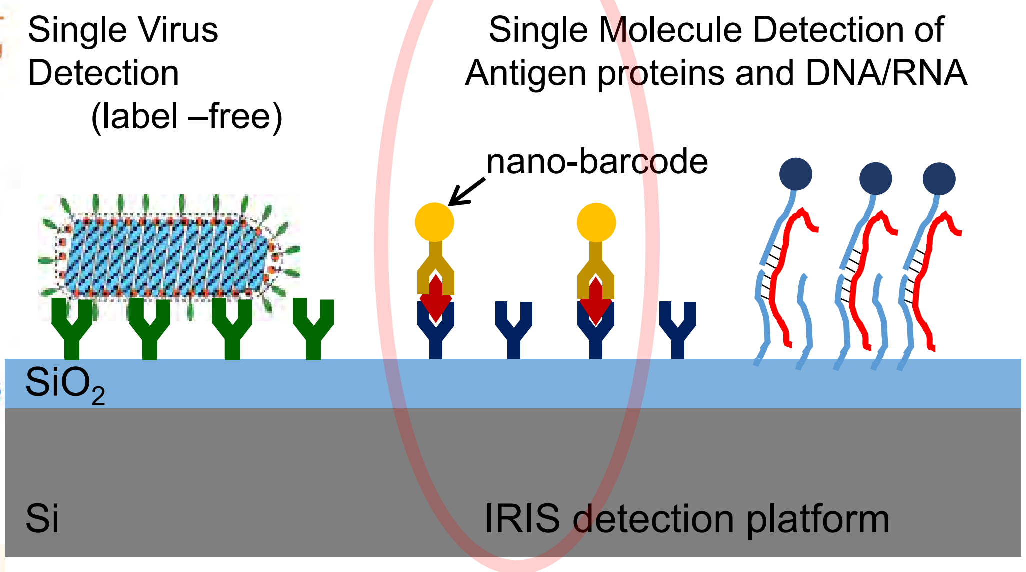
Digital Microarrays: Single-Molecule Readout with Interferometric Detection of Plasmonic Nanorod Labels

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

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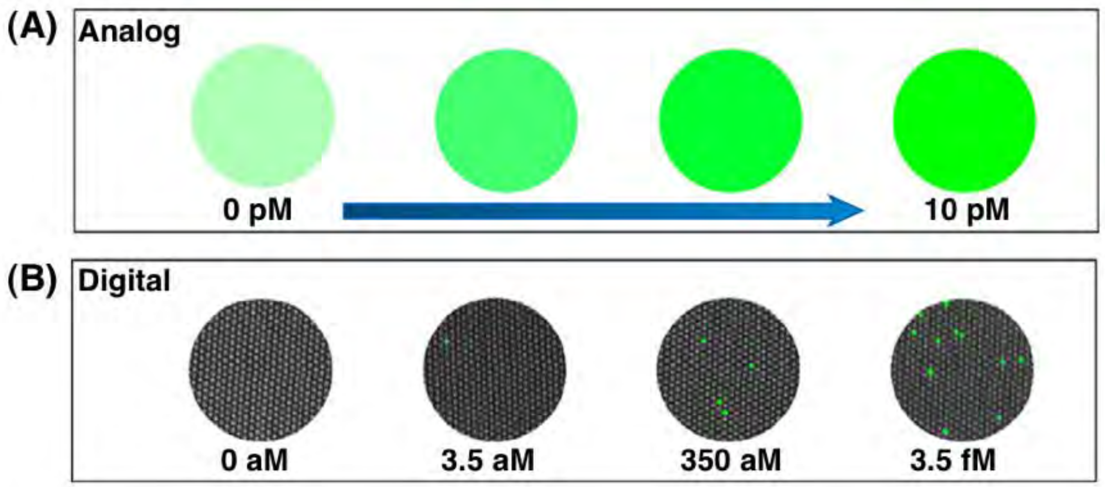
Analog vs. Digital



From David Walt @ Tufts
Quanterix

Wikipedia and twitter

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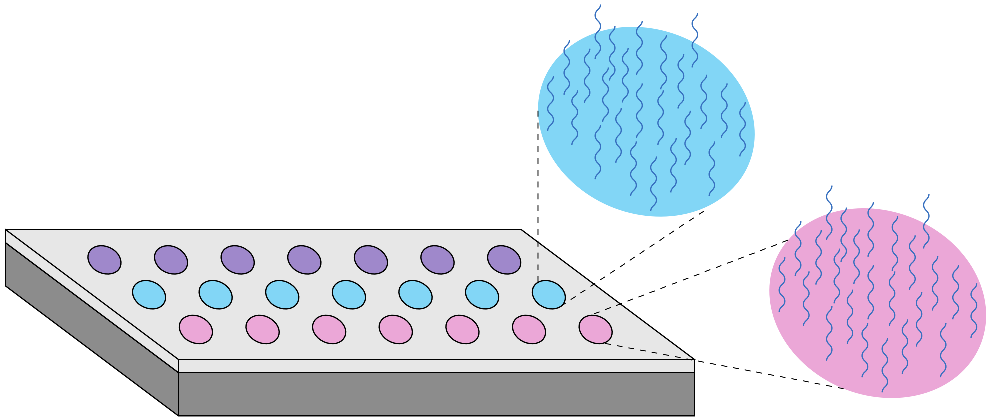
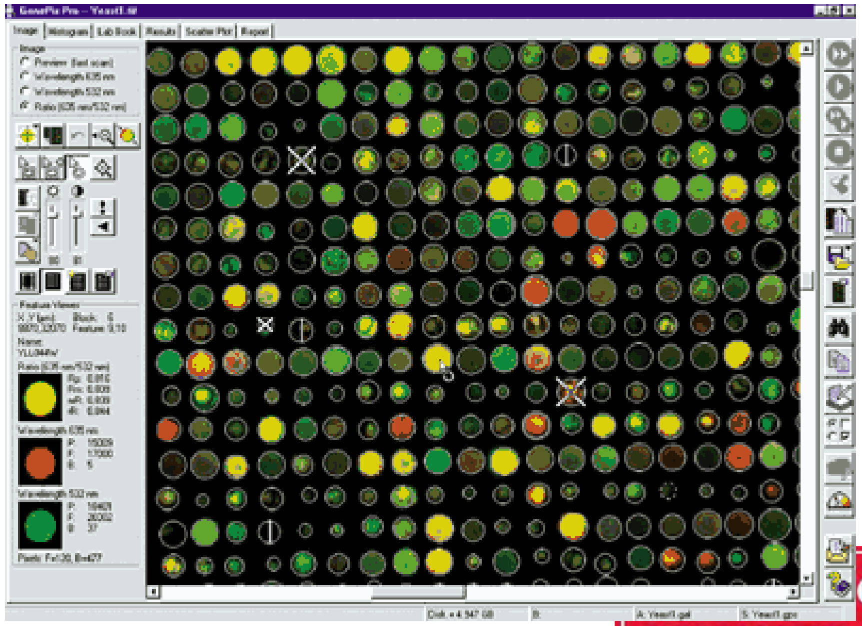
Fluorescence DNA microarrays

1. DNA chip: 100 – 40,000 of unique probes
2. Incubate with sample – RNA targets hybridize
3. Stain with a fluorescent reporter
4. Measure the fluorescence of each spot



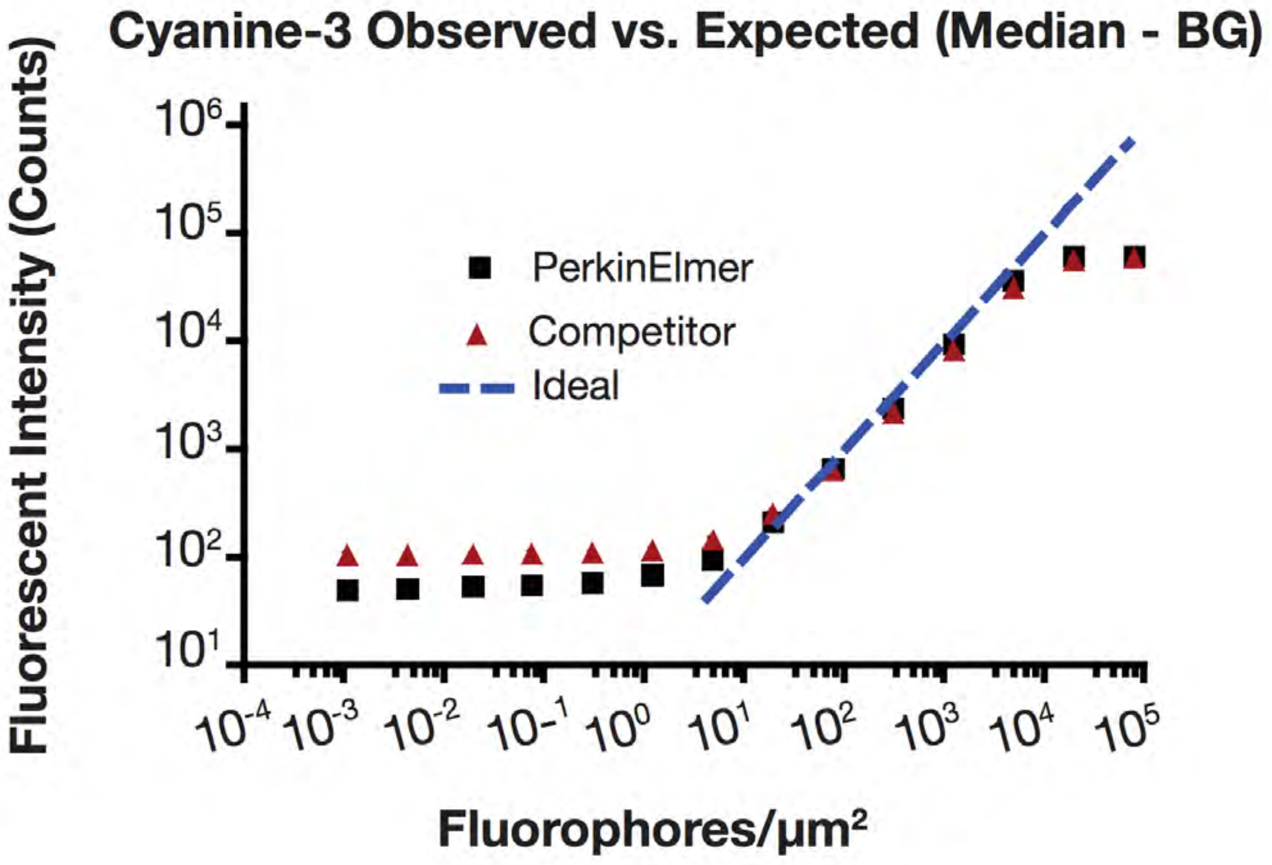


Performance limits of fluorescence

- Sensitivity limit: 10 fluorophores/um^2
- Dynamic range: 100-1000

… but microarray spots are 10,000 um^2

~100 µm diameter



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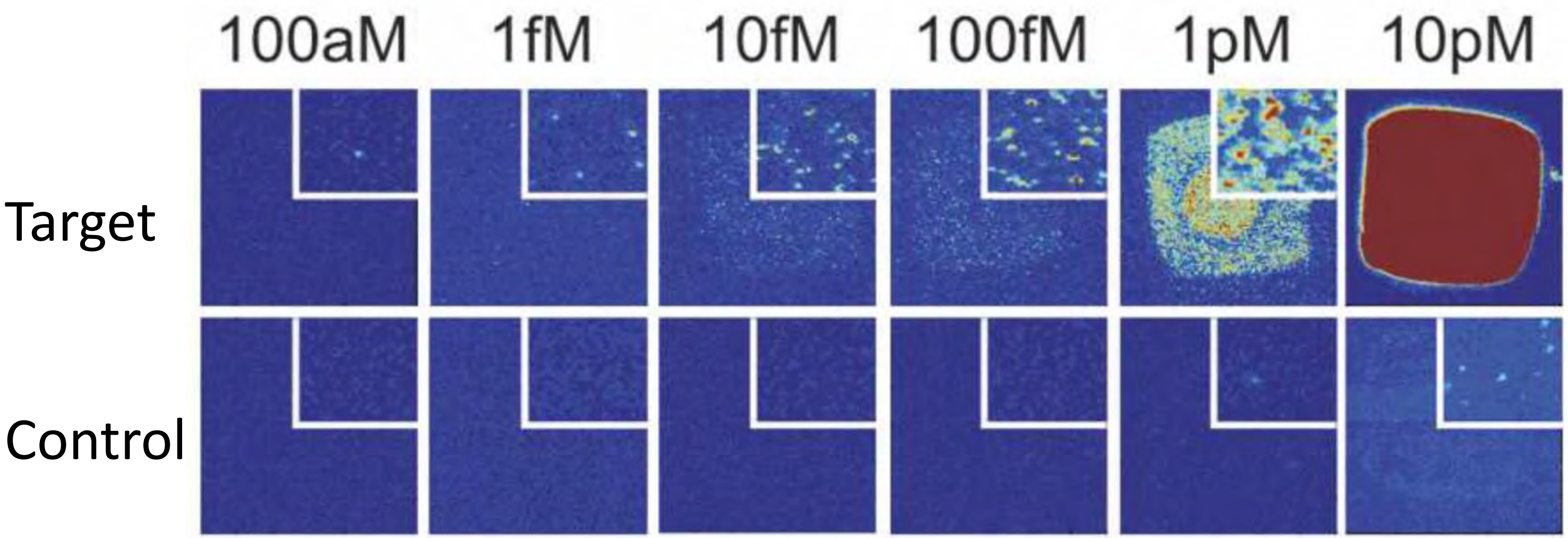
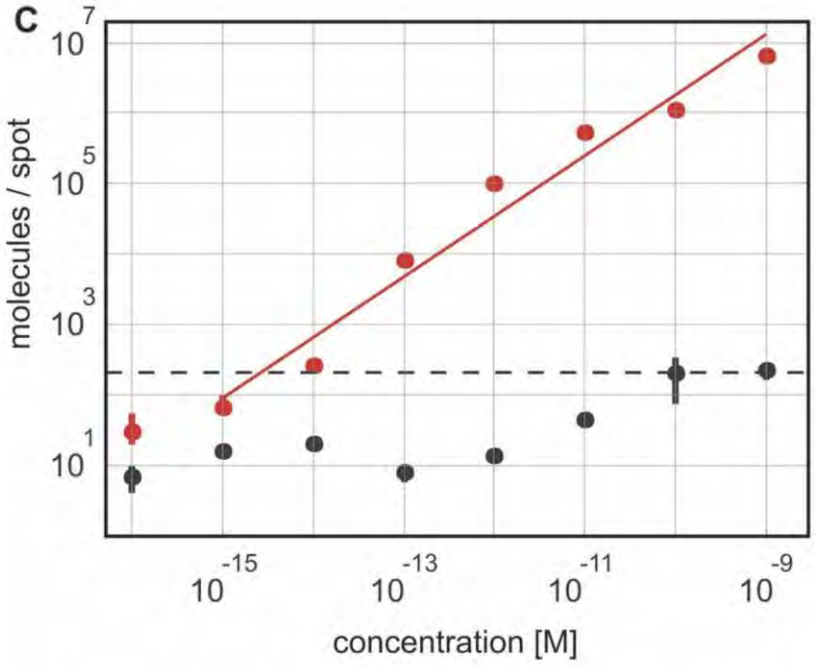
Digital microarray concept



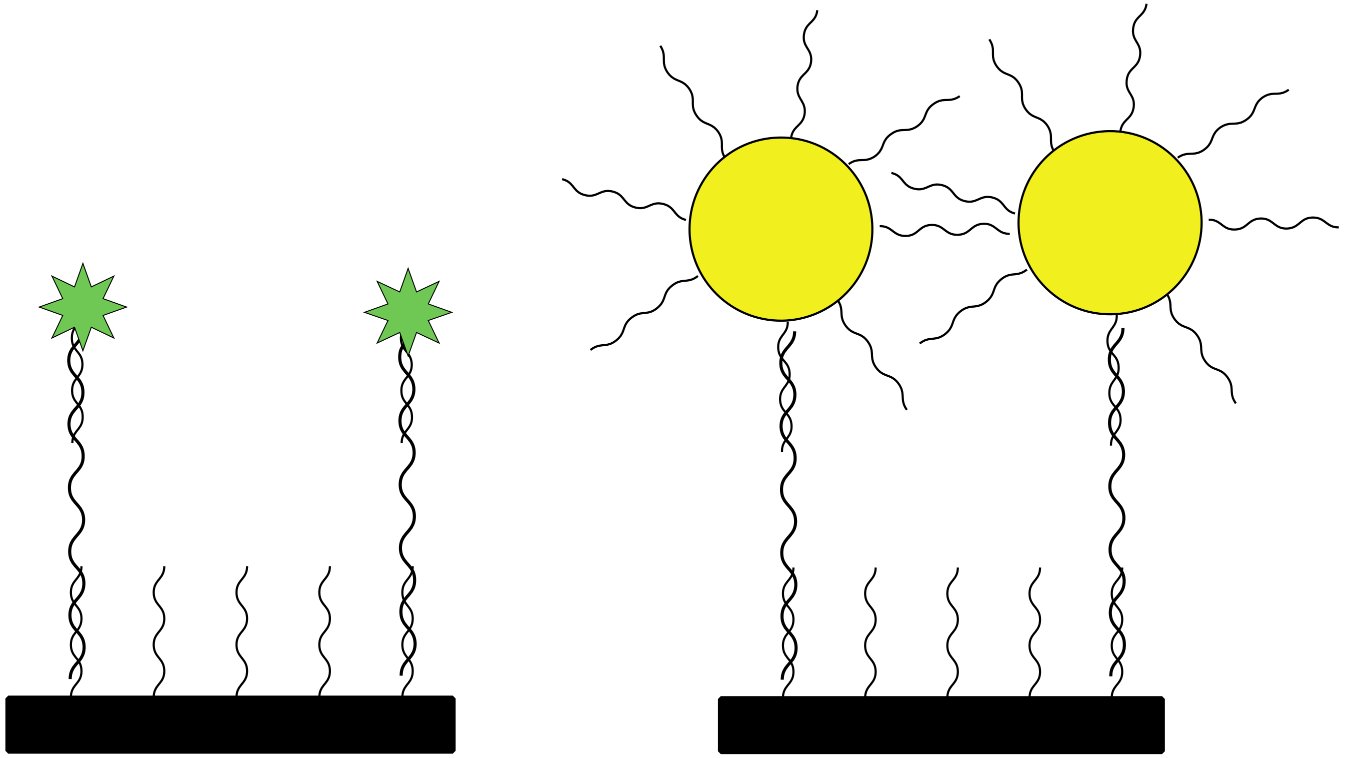


Hesse et al, *Genome Research* 2006

Light scattering

Light scattering is advantageous:

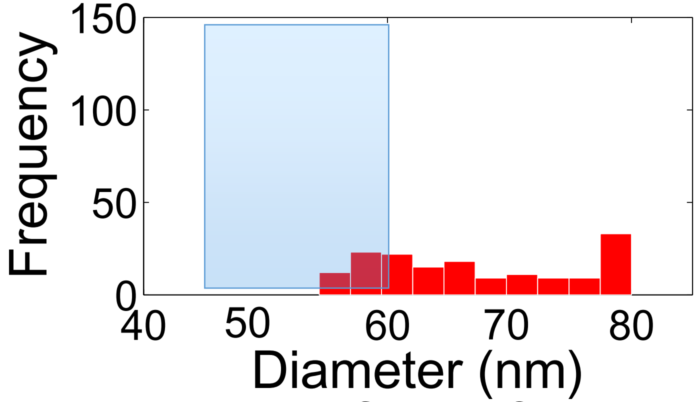
- No saturated emission rate and no photobleaching: only limit to speed is your input light power
- We can use a very simple instrument
- We can do dynamic measurements as well

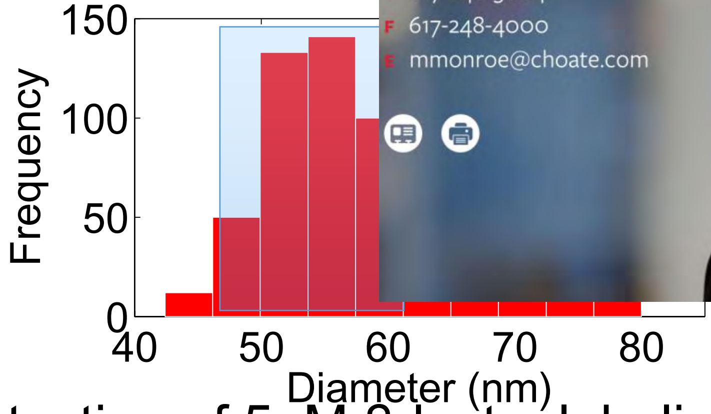


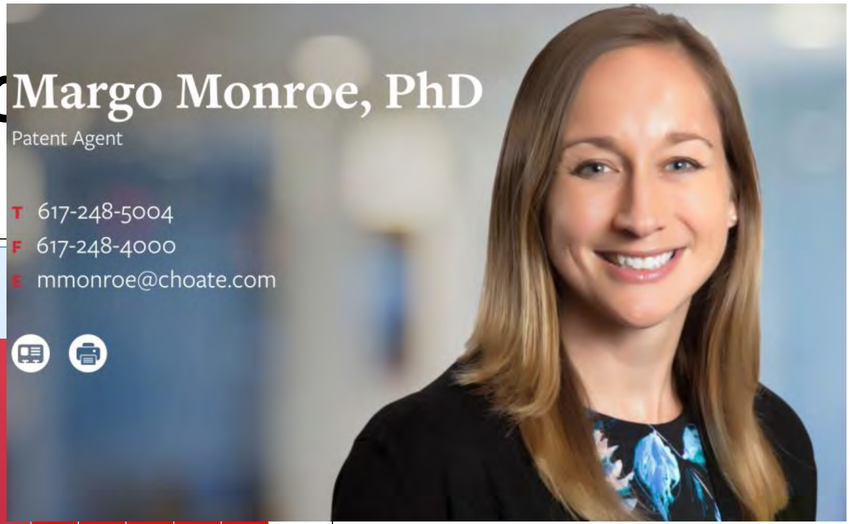
Replace fluorescent reporters with nanoparticle conjugates

Challenge – seeing/detection small nanoparticles

Protein chips by single nanoparticle d





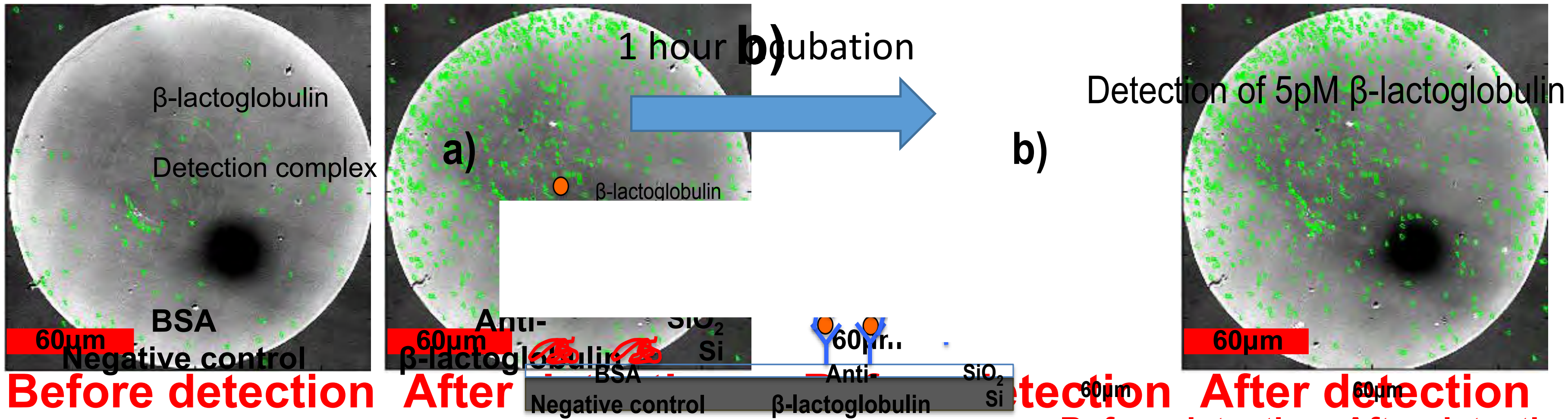


LOD$_{serum}$ < 100aM

LOD$_{blood}$ < 1fM

Detection of 5pM β-lactoglobulin

Detection of 5pM β-lactoglobulin



Before detection complex

After detection complex

After detection complex

c) i) Size discrimination for sensitive, specific detection in complex biological samples

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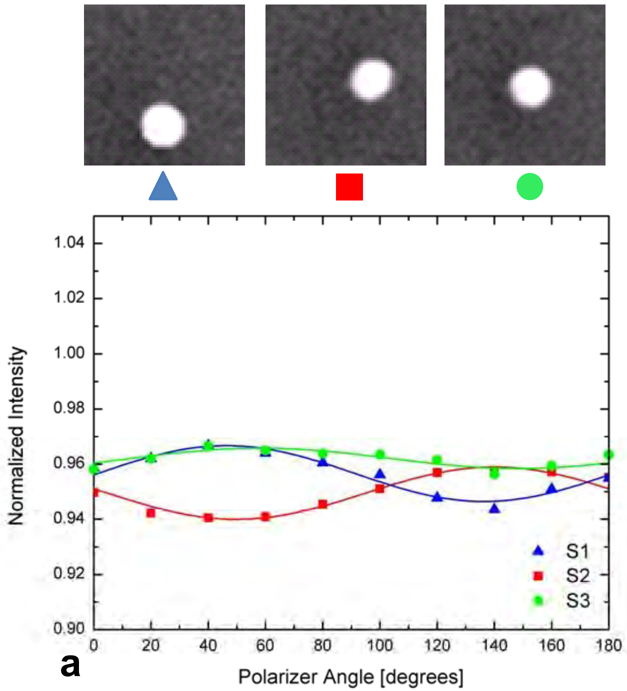
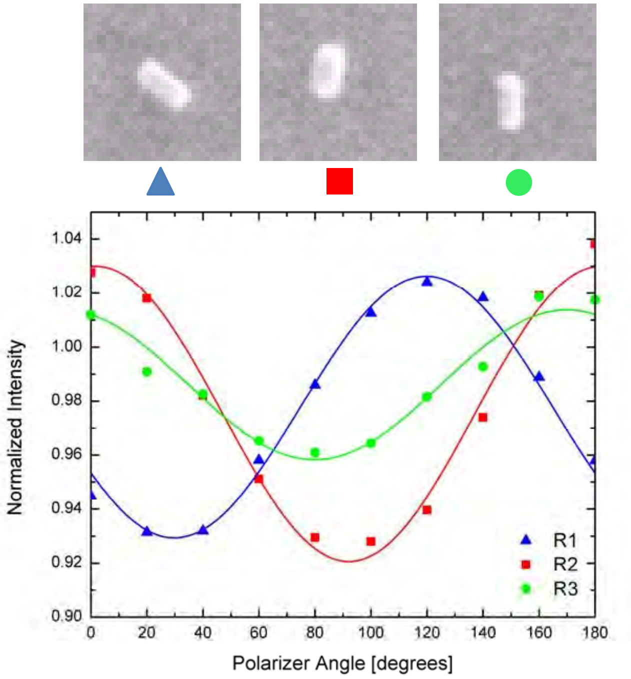
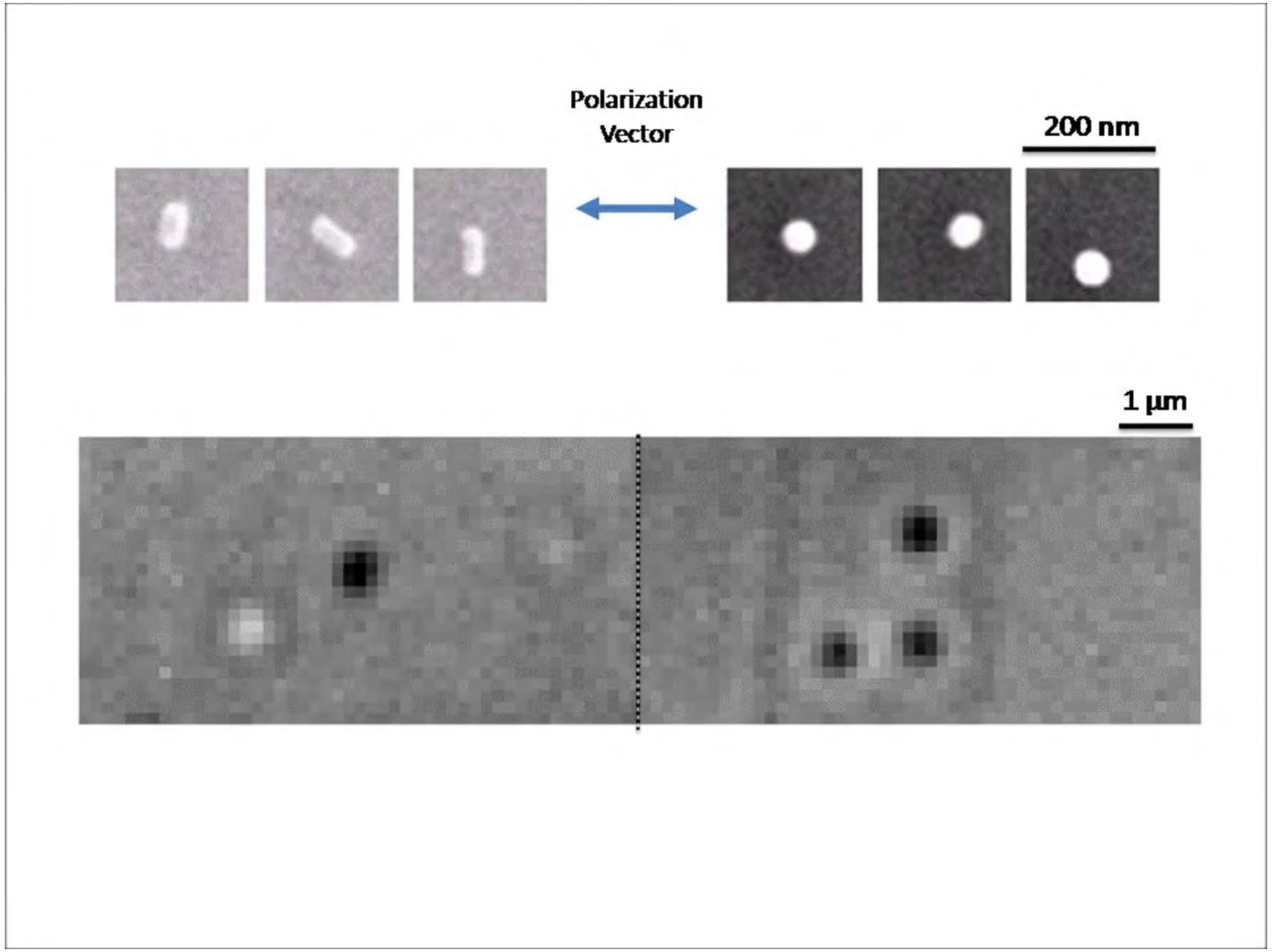
Goal: Larger field of view to scan a larger area

'ower NA – lower contrast

Answer: Nanorods as labels - polarization







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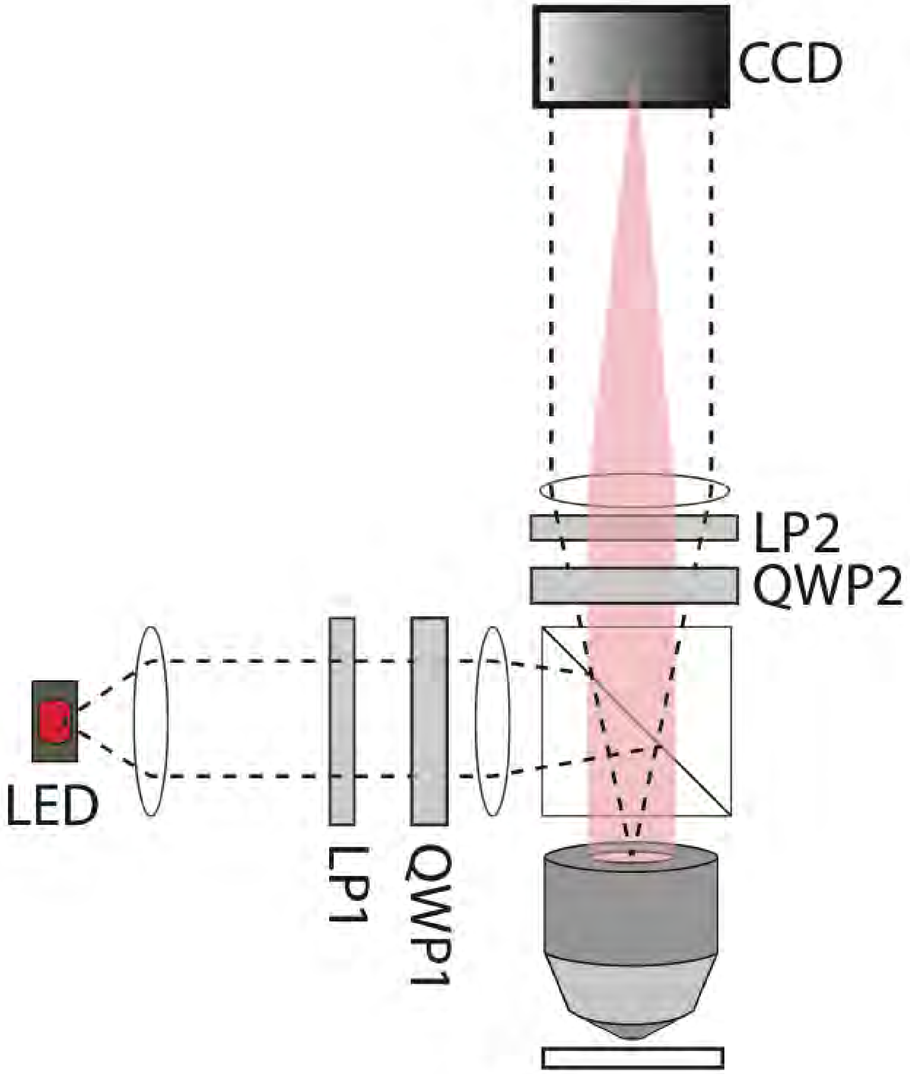
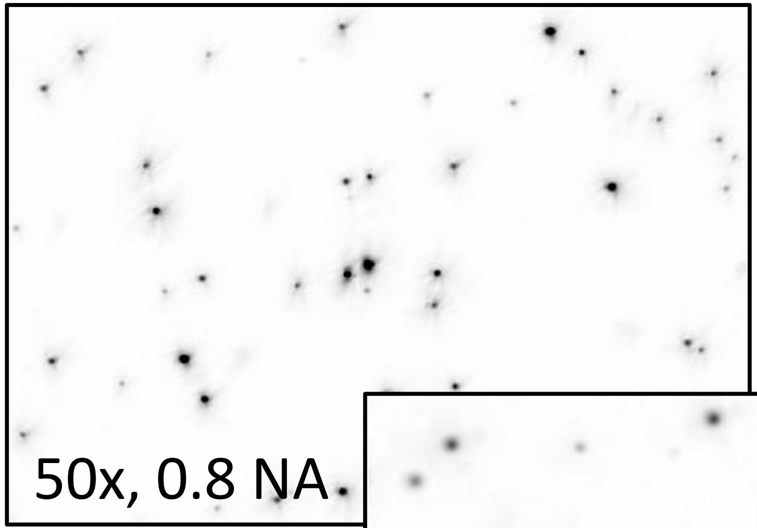
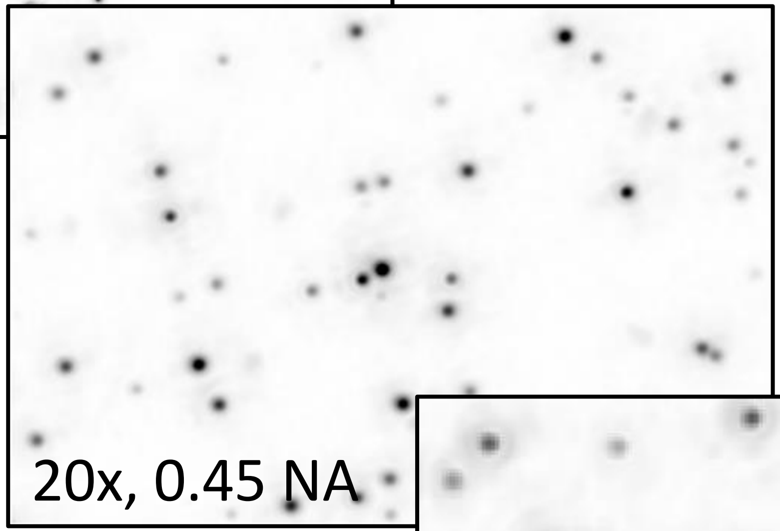
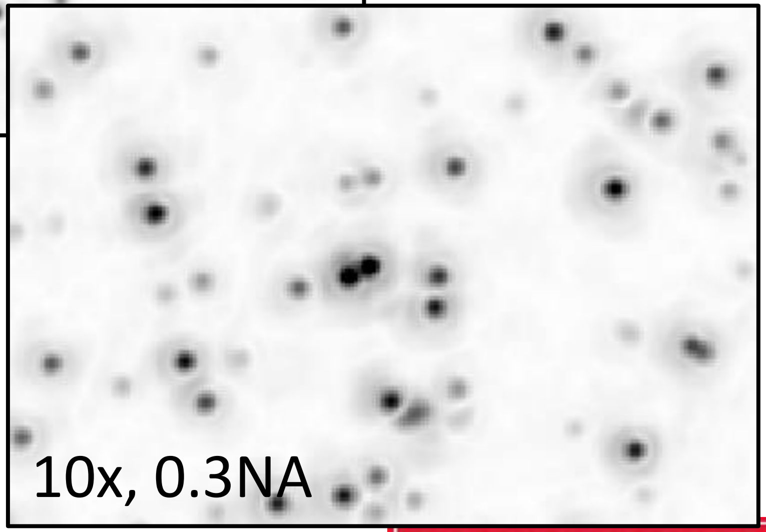
Circular polarization









Polarization enhancement,
real-time DNA detection

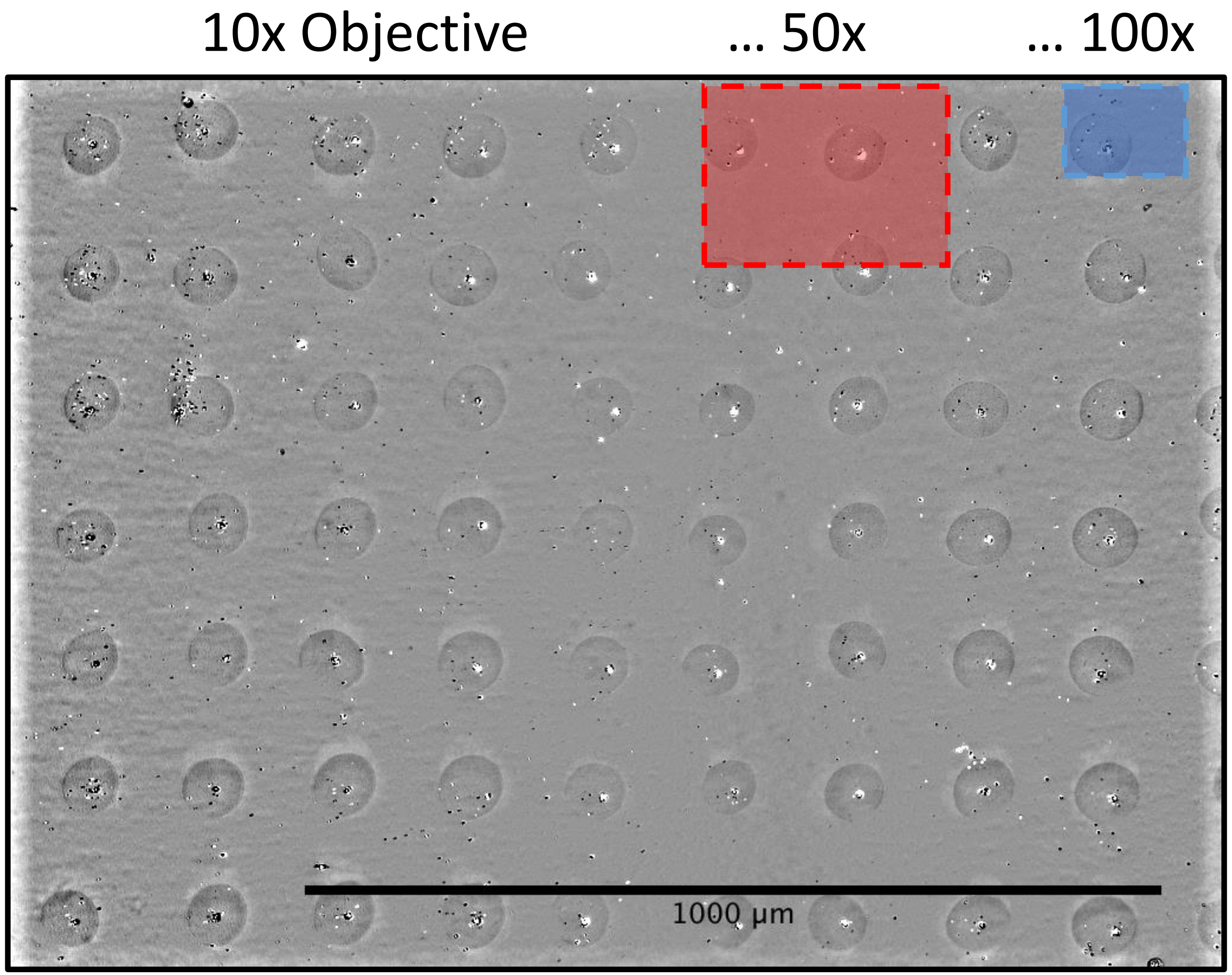
‘17

mRNA detection
AST

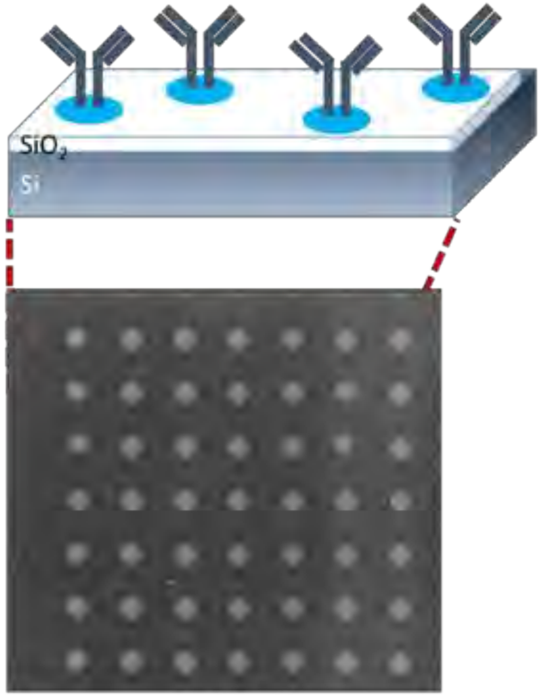
‘19

miRNA detection

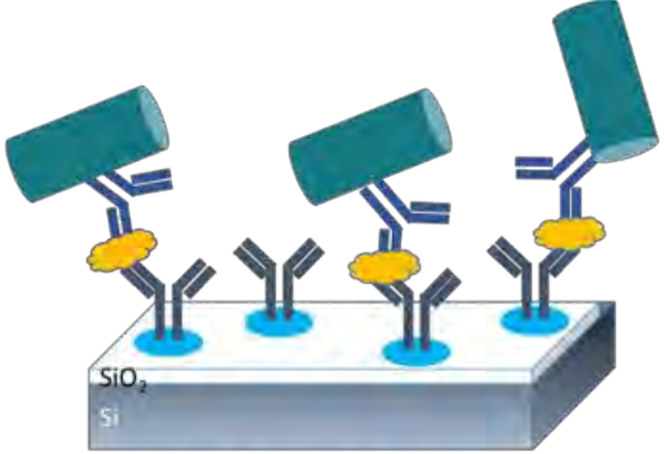
A digital microarray with IRIS



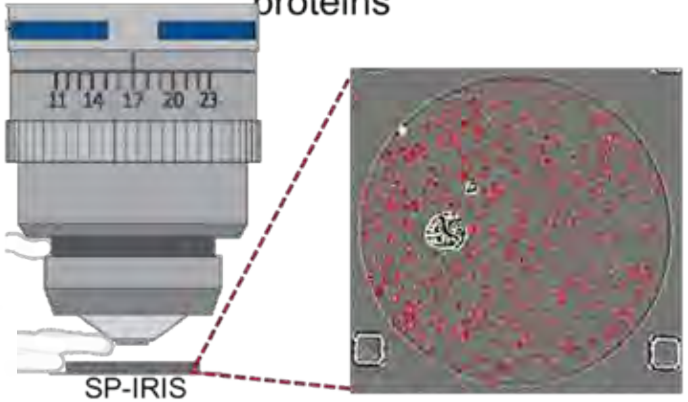
A Typical Assay



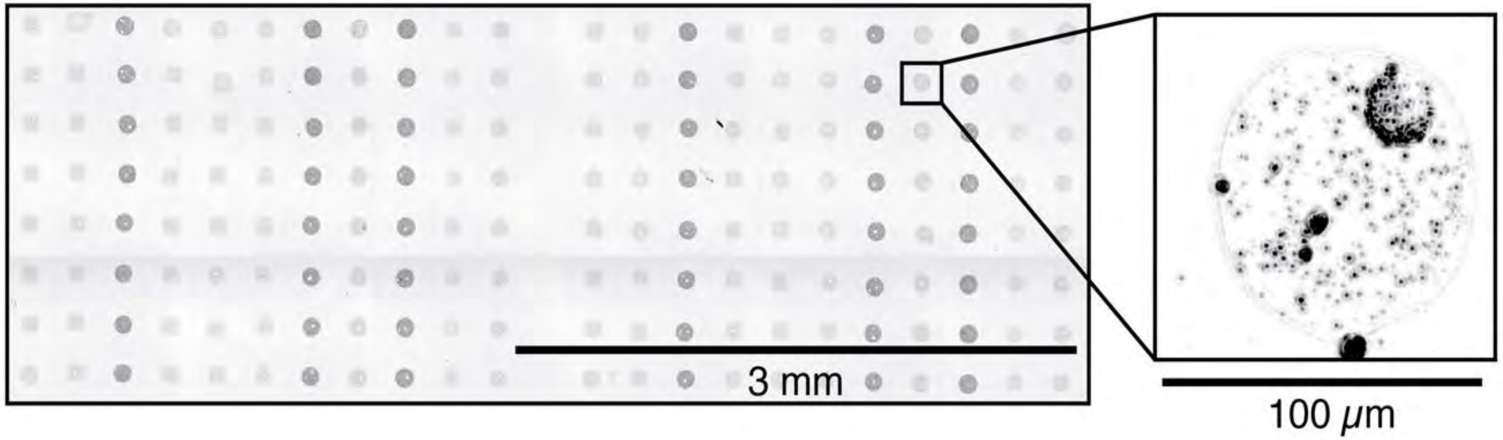
1. Antigen samples
2. Au-nanorod-tagged antibodies flow through the microfluidic array system



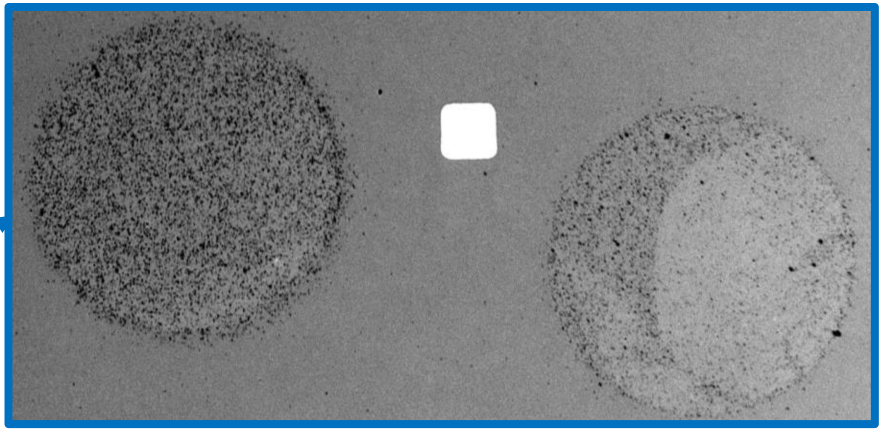
IRIS Single molecule detection and quantification of biomarker HBsAg proteins



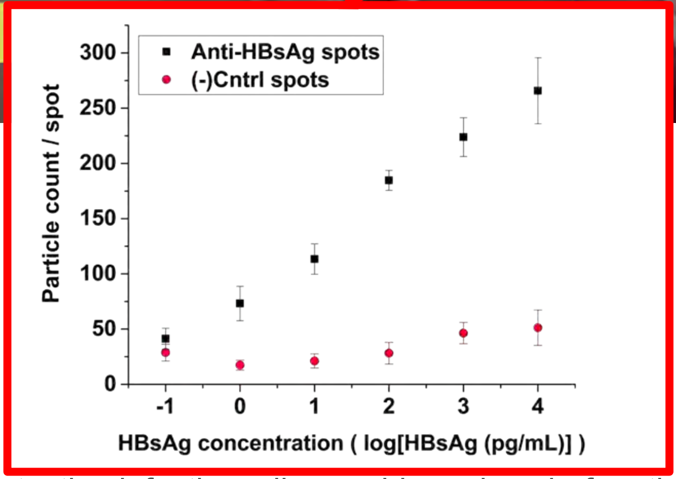
Digitally detected and counted Au-nanorods captured on the spot



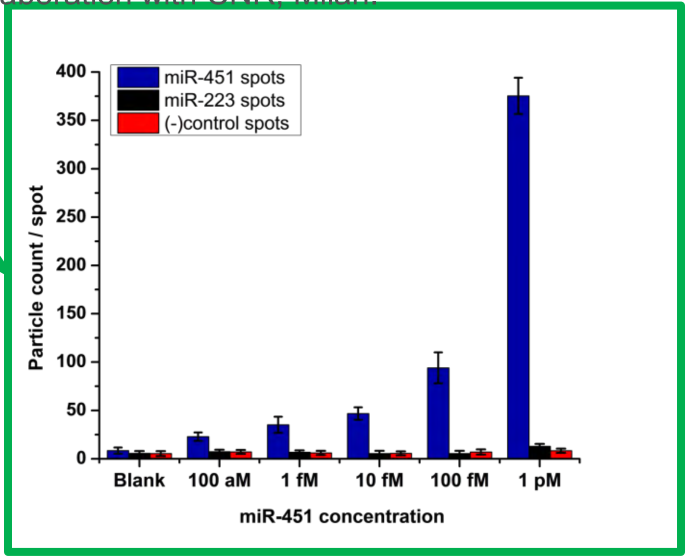
Application Areas



Detecting cancer biomarkers at ultra-low levels and rare mutations - potential to enable new options for diagnostics and treatment in cancer research. KRAS mutation detection (colorectal cancer). Work in collaboration with CNR, Milan.



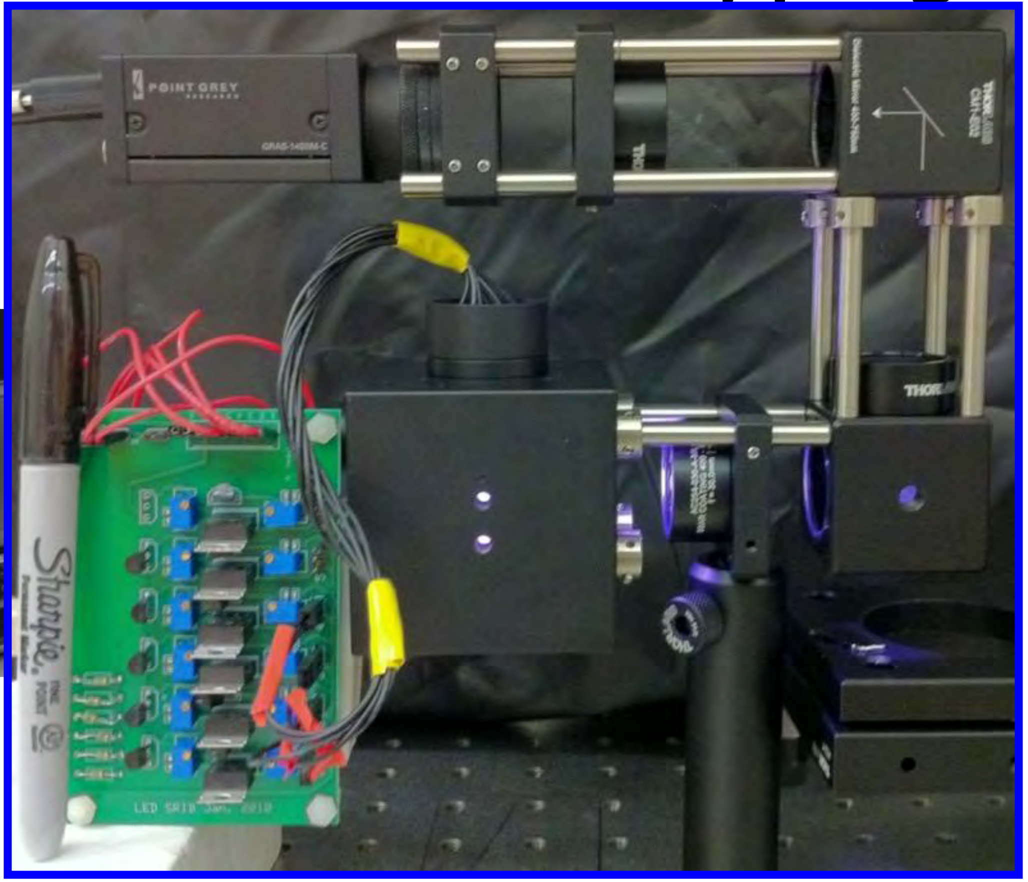
Detecting infectious disease biomarkers before the onset of an immune response. HBsAg detected at 1,000X better sensitivity than commercial assays. Funded by Aselsan.



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.

System Maturation and Prototyping

36”



ELSEVIER

Biosensors and Bioelectronics

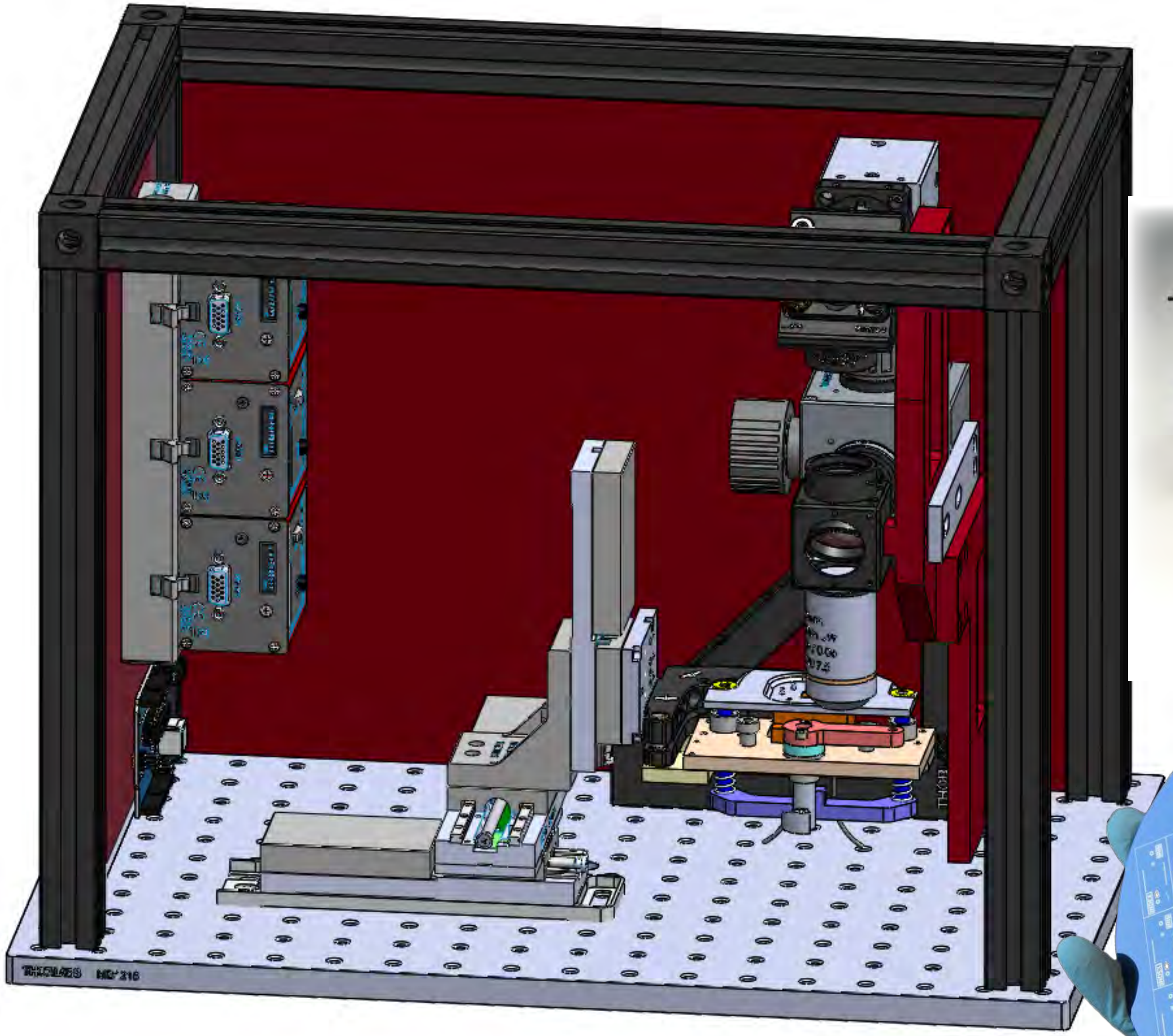
journal homepage: www.elsevier.com/locate/bios

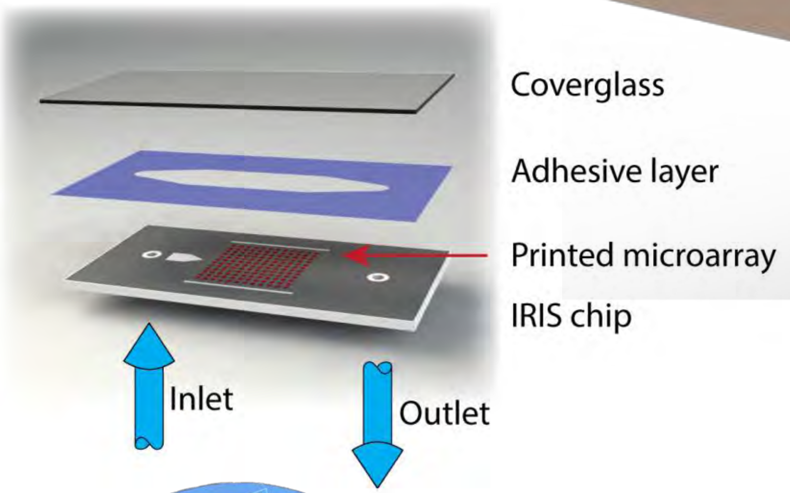
LED-based Interferometric Reflectance Imaging Sensor for quantitative dynamic monitoring of biomolecular interactions

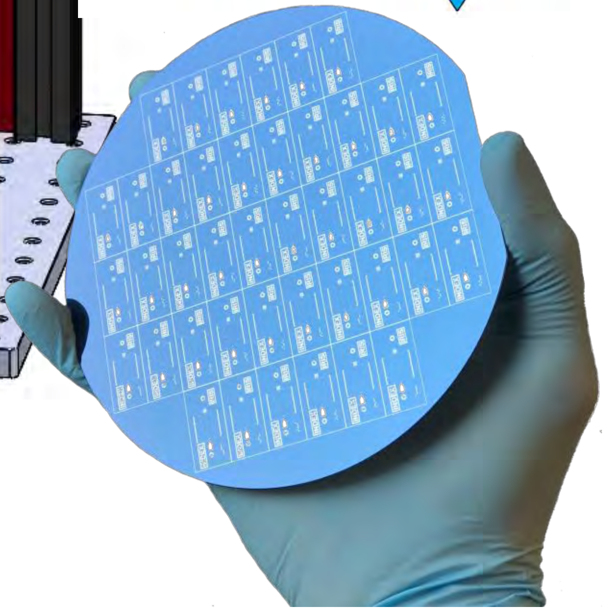
G.G. Daaboul[a], R.S. Vedula[a], S. Ahn[a], C.A. Lopez[b], A. Reddington[b], E. Ozkumur[b], M.S. Ünlü[a,b,c,*]

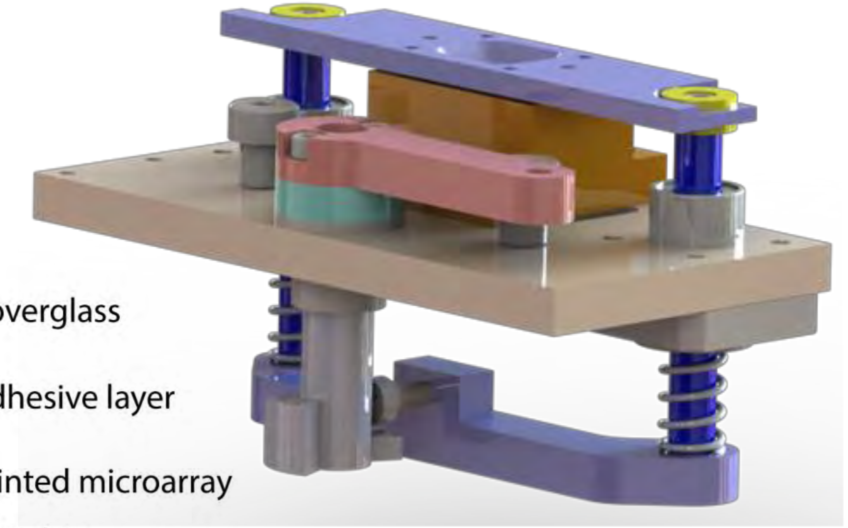
‘08

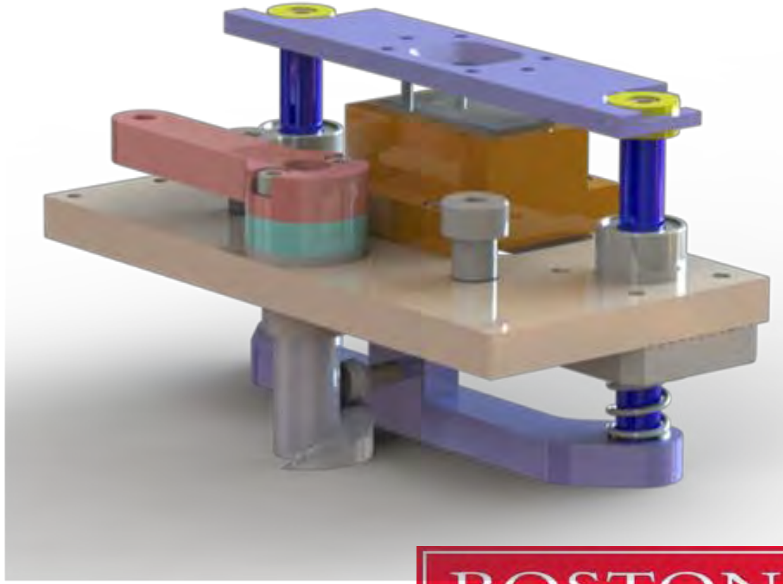
‘14




Coverglass
Adhesive layer
Printed microarray
IRIS chip
Inlet
Outlet







Commercialization

NanoView BIOSCIENCES

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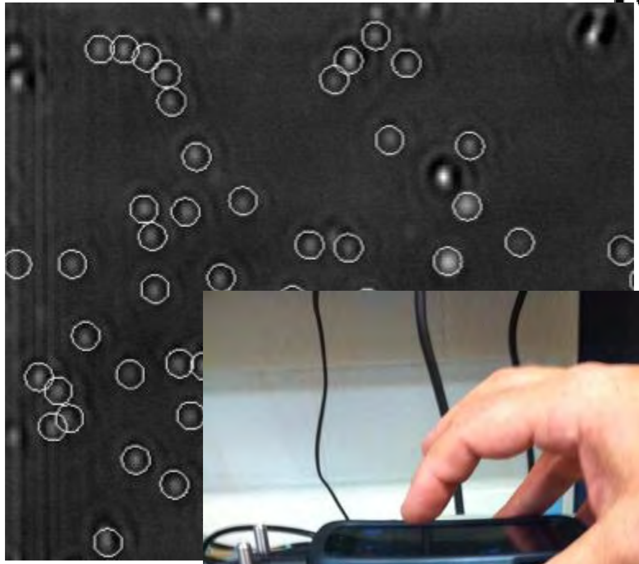
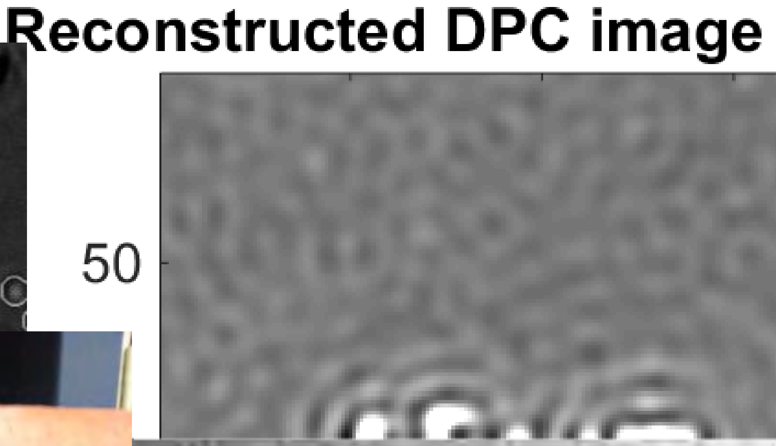
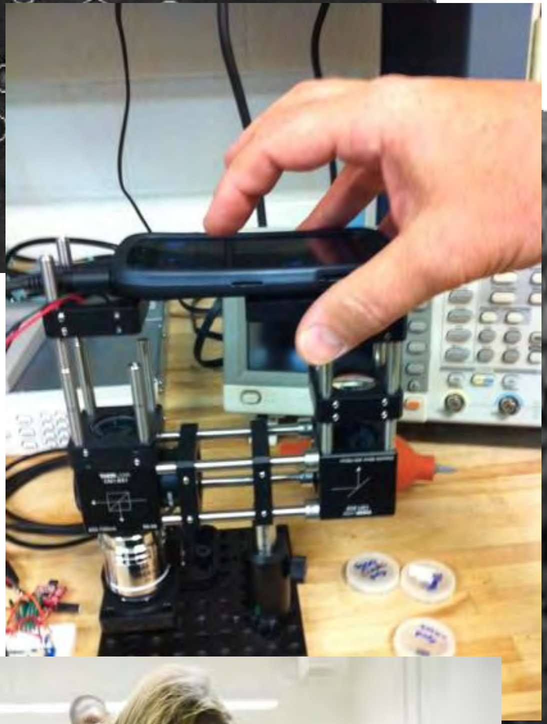
CONCLUSIONS & FUTURE

- Optical interference is a very powerful sensing technique.
- Multi-disciplinary innovation
- Single biological nanoparticle detection / counting / size and shape discrimination / visualization
- **Goals:**
  - Lateral resolution of ~100nm without labeling
  - Sub-fM multiplexed detection of RNA, DNA and proteins







NSF NATIONAL INSTITUTES OF HEALTH indEx aselsan

INTEGRATED NANOPARTICLE ISOLATION AND DETECTION SYSTEM FOR COMPLETE ON-CHIP ANALYSIS OF EXOSOMES