Biophotonic Nano-Satellites: Toward Real-time Cellular Galaxy Exploration & Gene Regulations in Living Cells

Luke P. Lee
Department of Bioengineering
QB3 Institute & BSAC
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  - Ben Ross
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  - Jason Silver
  - Brittany Nielson
  - Edwin Li
  - Andrew Tran
  - Sylvia Qi
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  - Philip Jeng
  - Liyi Xu

• Collaborators:
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Motivations of *BioPOETS*

*Biologically-inspired* Optical Systems:

Biophotonic Nano-Satellites: *Euvirus*

Photonic Gene Circuits

Summary

*Biomolecular Photonics-Optofluidics-Electronics Technology & Science*
Dow Jones Industrial Index


IBM 701 Calculator, 1952

1963 - CMOS invented

Intel, Microsoft

IBM

Large scale Applications

Microtechnology Fundamentals

Microtechnology Applications

http://finance.yahoo.com
The BioPOETS
Technology, Quo Vadis?

- Quantitative Medicine
- Predictive Medicine
- Preventive Medicine
- Personalized Medicine
- Regenerative Medicine

- Bionanoscience Fundamentals
- Bionanoscience Applications
- Nature Technology Fundamentals

- Biologic Microprocessor
- Biomarker Discovery
- iMDs

- iMDs

Quantitative Biology & Medicine

Biological Model

Parameter Fitting

Experimental Data

Refine Model

Concentration Gradient

Sample Collection

Continuous Live Cell Microscopy
Quantitative Biomedical Science

Fundamental Concepts:

- Rapid collection of large experimental data sets
- Intelligent consolidation of quantitative values
Computer Chip vs. BioChip

- **Quantitative Biology & Quantitative Medical Science**
- **Repeatable, Predictive, & Precision Biology on CMOS Camera on a Chip**
- **High-content & High-speed Biologic Microprocessor**

**Jack S. Kilby @ TI (BSEE, 1947):** Nobel Prize in Physics (2000)
Quantitative Biomedicine by BioPOETS*

*Biomolecular Photonics-Optofluidics-Electronics Technology & Science

Nanocrescent for In-vivo Molecular Imaging

Optofluidics for Biophotonic LOC

Cellular BioASICs: Biologic Application Specific Integrated Circuits

Biologically Inspired Optical Systems for Imaging & Manipulations

Nanoplasmonic SERS for In-vitro Diagnostics
Quantitative Cell Biology

- **Patch Clamp Array**

- **Dynamic Cell Culture**

- **Single Cell Analysis**

- **Artificial Liver**
  - Lee et al., *Biotechnology & Bioengineering* (2007)

- Lab-on-a-chip
- POC Diagnostics
- Molecular Diagnostics
Optical MEMS for Biophotonics

Biologically-inspired Optical Systems

for new paradigm of biophotonics, quantitative biology, molecular imaging, and photonic gene circuits
Learn from Nature
Biologically Inspired Optical System for Advanced Photonic Systems

(Science, Nov. 2005)
Nature-inspired Optics

Biolab on a chip
In vitro Diagnostics

To see the Nature,
See the Nature!!

Trilobites Eye

Descartes’ lens design

Jeong et al.,
Optics Express (2004)
Self-powered Integrated Microfluidic Blood Analysis System (SIMBAS)
Whole Blood In

Extracted Plasma

Flow Direction

Filter Trench 300 µm
OASIS

Optofluidic Application Specific Integrated Systems for Label-free Detection

Anti-Nanocrescent

Optical Antennas in OASIS

EM Enhancement

Polarization Effect

E-field Distribution
Optofluidic SERS

(a) PDMS SERS chip
Ag/PDMS Nanowells

Biomolecules
Glass Microfluidic Chip

Laser Excitation
Dichroic Mirror
Objective Lens

Raman Filter
SERS Spectrum
Spectrometer

(b) 1mM R6G on Ag/PDMS nano well
1mM R6G on Smooth Ag/PDMS

Raman Shift [cm⁻¹]

Intensity [a.u.]

Adenosine

1 μM
10 nM
100 nM
10 pM
1 pM
10 fM
DI water
10 μM on smooth Ag/PDMS surface
Personalized Preventive Medicine

Information Technology  Biotechnology  Nanotechnology

*IMDs: Integrated Molecular Diagnostic Systems
Nano-Satellites for Exploring the Cellular Galaxy
Can We Capture e-motions in Living Cells?

Need for Satellite Nanoscopes

Read out e-motions:
Electronic states
Vibration states

- Monitoring & Regulating Cellular Signaling Pathways
- Understanding Electron Transfer Mechanism in Living State
- Observation of In Vivo Electron-Transport Dynamics
Nano-Satellites

Nano-Satellites are micro-nano objects designed to perform specific tasks in specific areas. These objects are engineered to be lightweight, small, and highly specialized, allowing them to carry out specific missions. The diagram illustrates the scale of these objects, from the size of small molecules to the size of large animals and trees, showcasing the range of applications and capabilities of nano-satellites.
Satellite Telescopes
Satellite Nanoscopes

Time to Study the Inner Life

Fiat Lux!
Surface Plasmon Polariton

- Longitudinal coherent charge oscillation localized to a metal/dielectric boundary.
- Surface plasmon associated with evanescent electromagnetic mode.

SP wavelengths can reach nanoscale at optical frequencies! SPPs are “X-ray waves” with optical frequencies.
Nanoplasmonic Optics

Advantages:

- *Nano-focusing of Light*
- *Strong Optical Cross Section*
- *Metamaterial Nano-Optics*
- *Directional Control of Light*
  - Optical antennas
- *Transformational Optics*
- *Precision Temperature Control*
Satellite Nanoscope

**Microscope**

**Nanoscope**

**Molecular Spectroscopic Imaging**

**sub 10 nm Resolution**

Conventional Lens Focusing

Plasmonic Lens Focusing

Highly focused EM field

High Sensitivity Spatial Resolution
Nanoplasmonic Effect: \textit{LFE}

\textbf{Lightning Rod Effect (LRE)} (a.k.a. “tip effect”)

- Highly localized field enhancement (LFE)
  - Dramatic increase in near-field intensity due to the accumulation of surface charge at sharp structures
  - Field enhancement localized at the apex
Ultrasensitive Biomolecular Detections by Local Electromagnetic Field Enhancement Effect

Nanocrescent Optical Antennae
Wireless Cellular Communication

External Optical Signals

Cellular Galaxy: Nova Biology

“Cell” Phone Optical Antennas
Nanocrescent SERS Probes

Multiple particles with dispersed SERS hot spots

Single nanocrescent with multiple SERS hot spots

TEM image of nanocrescent

(c)
Magnetic Nano-Crescent SERS

G. L. Liu, Y. Lu, J. Kim, J. C. Doll, and L. P. Lee

Advanced Materials (2005)

Raman Peak Intensity at 637 cm$^{-1}$

Rotation angle [degree]

N  S  N  S  N  S  N  S

Rotating Permanent Magnet

Intensity [a.u.]
Plasmonic Resonance Energy Transfer (PRET)

Nanospectroscopic Imaging

Quantized Nanoplasmonnic Dip Spectroscopy by PRET
Multiplexed PRET for Functional Cellular Imaging
Monitoring Dynamics of Intracellular Aβ Induced Apoptosis in AD*

Single Protein Imaging in Living Cells

Internalized GNPs

*AD: Alzheimer Disease
Real-Time Observation of Intracellular Cyt c Release Induced by AβO

Incubated with AβO (2.5 μM) for 3 hours
Selective Metallic Ion Detections by PRET for

*In vivo* Cellular Imaging of Metalloproteinase Activity & Environmental Monitoring

GNP Donor & ML Acceptor

Metal ion

Highly selective metal-ligand complexation

Plasmonic Resonance Energy Transfer (PRET)

split d - orbital

White light illumination

d - orbital

Accepter

Donor
Selective Metal Ion Detection

The graph shows the change in intensity ($\Delta I/I_0$) for different metal ions at various concentrations: 100 nM, 1 $\mu$M, 10 $\mu$M, and 100 $\mu$M. The ions include Cu$^{2+}$, Mg$^{2+}$, K$^+$, Na$^+$, Ca$^{2+}$, and Ni$^{2+}$. The intensity change is more pronounced for Cu$^{2+}$ at all concentrations compared to other ions.
Molecular Ruler for Measuring Nuclease Activity & DNA Footprinting

G. L. Liu et al. (Nature Nanotechnology, 2006)
DNA Footprinting of the Binding Position of EcoRI Mutant

Plasmon Resonance Detection of EcoRI Mutant Position on the dsDNA

DNA length ↓ Negative charges ↓ Plasmon Resonance Shift
NanoSatellites in Medicine

Targeting
Sensing
Gene Delivery
Drug Delivery
Mutifunctional Nanocorals: Targeting
ONCOS*

Oligonucleotides on Nanoplasmonic Carrier Optical Switch & Photonic Gene Circuits

Precise Temporal and Spatial Controls of Localized Gene Regulation and Protein Translation

Lee et al., Nano Letters (2009)
Gene Regulation

Transcription

Antigene DNA, Decoy DNA

Translation

Antisense DNA, siRNA, microRNA

Protein
Molecular Optogenetics

Precise Temporal & Spatial Temperature Controls
Selective Photothermal Control

\[ PTE = \frac{\text{Resistive heat}}{\text{Incident energy in cross section}} \]
Selective NIR Activation of ONCOS
Photonic Gene Circuits: Molecular Optogenetics

Precise controls of antisense DNA, siRNA, & microRNA delivery
Summary of NanoSatellites

- Targeting
- Sensing
- Delivery
- Controls

Cellular Galaxy: Precision Biology

Molecular Imaging

Gene Therapy

Biologic Regulation

Basis of Quantitative Nova Biology & Nanomedicine
Summary

• **Biophotonic nanosatellites** are developed for targeting, imaging, and delivery of genes in living cells.

• **Integrated optofluidic devices** with optical antenna provide a solution for *label-free* *in vitro* molecular diagnostics platforms.

• **Biophtonic gene circuits** allow precision gene regulations with nanoscale spatial resolution and localized molecular controls in living cells.

• **Exploring inner space of living cells** can be accomplished by nanosatellites and might open up a new paradigm of studying living cellular dynamics.