From Telecommunication to Cancer Detection: New Applications of Fiber Optics Technology

Bahram Jalali
jalali@ucla.edu
www.photonic.ucla.edu

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Stanford University
UCLA – Relevant Facts

• **Engineering School & EE Department**
  - Ranked #7 in US among all Engineering Schools – US News & World Report
  - **Ranked #1 in U.S. according to Microsoft Research H-index**
  - Ranked among top 10 in the nation according to National Research Council ranking
  - Top 3 in terms of research funding per faculty (UCLA in top 5)
  - **Top 7 in terms of impact (Times Higher Education)**

• **UCLA Medical Center**
  - Ranked #1 in the western U.S. for 19th consecutive year
  - Ranked top 3 hospitals in the United States
  - Ranked top 2 in United States in terms of research funding

• **California Nano-Systems Institute**
  – $170M State initiative
  – New 180,000 square foot facility
  – Focus: Bio-technology, nanotechnology
1. Silicon Photonics
   - Dispersive Elements, EO Modulators
2. Real-time Instruments
   - Digitizer, Spectrometer, Camera

First silicon laser pulses with life

Mark Penlow

Published online: 26 October 2004; doi:10.1038/news041025-10
Today’s talk

• Link between communication and blood screening

• How to create Real-time fast instruments with fiber optics

• Imaging & blood screening
Bits vs. Cells

- Blood volume ~ 5 Liters
- Cell density: ~ $5 \times 10^9$ cells per mL
- Number of cells in blood: ~ $25 \times 10^{12}$ cells
  - 25 Tera Cells!

Fiber Optics can help
<table>
<thead>
<tr>
<th>Blood Component</th>
<th>Concentration (cells / mL of blood)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Erythrocytes</td>
<td>5,400,000,000</td>
</tr>
<tr>
<td>Thrombocytes</td>
<td>350,000,000</td>
</tr>
<tr>
<td>Neutrophils</td>
<td>6,000,000</td>
</tr>
<tr>
<td>T Lymphocytes</td>
<td>1,500,000</td>
</tr>
<tr>
<td>CD4+ T cells</td>
<td>1,000,000</td>
</tr>
<tr>
<td>B Lymphocytes</td>
<td>600,000</td>
</tr>
<tr>
<td>Monocytes</td>
<td>500,000</td>
</tr>
<tr>
<td>Eosinophils</td>
<td>250,000</td>
</tr>
<tr>
<td>Natural Killer Cells</td>
<td>200,000</td>
</tr>
<tr>
<td>Basophils</td>
<td>50,000</td>
</tr>
<tr>
<td>Dendritic Cells</td>
<td>20,000</td>
</tr>
<tr>
<td>Hematopoietic Stem Cells</td>
<td>2,000</td>
</tr>
<tr>
<td>Antigen-Specific T Cells</td>
<td>1,000</td>
</tr>
<tr>
<td>Circulating Endothelial Cells</td>
<td>500</td>
</tr>
<tr>
<td>Fetal Cells in Maternal Blood</td>
<td>500</td>
</tr>
<tr>
<td>Endothelial Progenitor Cells</td>
<td>200</td>
</tr>
<tr>
<td>Circulating Tumor Cells</td>
<td>10</td>
</tr>
<tr>
<td>Unknown Cell Types</td>
<td>?</td>
</tr>
</tbody>
</table>
**Photodetection**  
**Quantum Efficiency**  
**Dark Noise**  
**Shot Noise**

**Rare Cell Detection**  
**Capture Efficiency**  
**False Positive Events**  
**Statistical Accuracy**

### Analogy

<table>
<thead>
<tr>
<th>Photodetection</th>
<th>Rare Cell Detection</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>SNR</strong> = ( \frac{\text{Signal}}{\text{Shot Noise}} = \frac{N}{\sqrt{N}} = \sqrt{N} )</td>
<td></td>
</tr>
<tr>
<td><strong>SNR</strong> = Detected Number of Photons / Rare Cells</td>
<td></td>
</tr>
</tbody>
</table>

### Requirements for rare cell detection

The instrument must be

1. High throughput
2. Continuous real-time
3. Able to analyze massive data

*Goda et al., PNAS 2012*
Time Stretch Amplified Dispersive Fourier Transform

Origin: 1994 project on designing 2 Gsample/s 8bit electronic A/C converter

Modulation $\rightarrow$ Transmission $\rightarrow$ Detection

Time stretch is a modified optical communication link
Captures fast time series then slows it down so it can be digitized in real-time
Amplifies the signal to overcome thermal noise
We make real-time instruments

**Spectroscopy**

- Optical Rogue waves
  - *Nature 2007, PRL 2008*

**Cameras**

- STEAM camera, *Nature 2009*

**Vibrometric cameras**

- Rare cancer cells detection, *PNAS 2012*

**Core Technology:**

*Time stretch with simultaneous amplification*

**“Amplified Dispersive Fourier Transform”**

*Review: Nature Photonics Feb 2013*

**Real-time Spectrometry,**

*Nature Photonics, 2008*
10 Tera-sample/s Real-time Transient Digitizer

- J. Mallari et al, (GigOptix - UCLA) OFC 2010

- Real-time digitization of 95 GHz millimeter wave
- Quantization at 100 fs intervals
- Input bandwidth limited to 110 GHz by EO modulator
12.5 Gbit/s data eye diagram
NI-5154 powered with fronted time stretch

Before
12.5 Gbps

After
12.5 Gbps

40 Gbps

1 GHz digitizer with TiSER

NI 5154 without TiSER

NI 5154 with TiSER

UCLA – Jalali Lab

www.photonics.ucla.edu
How to find rare cells?

Current State-of-the-Art

Flow Cytometry
Detecting Rare Cells with STEAM
Automated Flow-through Microscope

Flow Cytometer (High Speed)

Microscope (High Precision)

STEAM Flow Cytometer: Goda, Tsia, Jalali, Nature 2009
Real-time Screening of Cells or Bacteria

Goda, Tsia, Jalali, Nature 458, 1145 (2009)
The STEAM Flow Cytometer

- Imaging Optics
- Blood In
- Blood Out
- Microfluidic Chip
The **real-time image processor** performs image-based classification of a large population of cells in real time.
Rare Cell Detection Experiment

Can we detect the rare cancer cells?

3 mL of Lysed Blood
(N = ~24,000,000)

Breast Cancer Cells
(N = ~10)

STEAM Flow Cytometer
The real-time image processor enables **real-time cell classification**

After screening by presence of metal beads (N = ~10)

After size-based screening (N = ~100)

After removing empty images (N = ~30,000,000)

After selecting images (N = ~100,000,000)
The STEAM flow cytometer provides extremely low false positive rate, yet with high throughput & high sensitivity.

Goda et al., PNAS, July 2012, doi/10.1073/pnas.1204718109
Applications of Detection of Circulating Tumor Cells (CTCs)

1. Minimally-invasive, low-cost detection of cancer and metastasis

   - Blood Draw CTC Test
   - Medical Imaging (MRI, CT, PET)

   - Breast Cancer: 2 – 3 months
   - Prostate Cancer: 1.5 – 2 months


2. Monitoring efficacy of chemo & radiation therapy

Temporal Resolution in Diagnosis of Response to Chemotherapy

<table>
<thead>
<tr>
<th></th>
<th>Medical Imaging (MRI, CT, PET)</th>
<th>CTC Count</th>
</tr>
</thead>
<tbody>
<tr>
<td>Breast Cancer</td>
<td>2 – 3 months</td>
<td>3 – 4 weeks</td>
</tr>
<tr>
<td>Prostate Cancer</td>
<td>1.5 – 2 months</td>
<td>2 – 4 weeks</td>
</tr>
</tbody>
</table>
Summary

- Real-time Instruments for capturing rogue cells in flow
- *Photonics Time Stretch: a practical system that* has established many benchmarks
- Imaging based blood screening
- Record false positive rate
- Many other applications
JALALI-LAB @ UCLA

- Affiliations: EE Dept, CNSI Institute, School of Medicine
- Research:
  - Silicon Photonics
  - High throughput Instruments

Postdoctoral Fellows and Research Associates

Graduate Students

Undergraduate Students

K. Goda, E. Diebold, N. Sarkhosh, C. Wang, J. Adam, Zhongwei Tan, Robert Rice, Monte Khoshnevisan, Vish Upadhye, Daniel Solli

A. Fard, A. Ayazi, P. DeVore, A. Weidel, Philipp Metz, A. Mahjoubfar, K. Hon, B. Buckley, J. Sadasivam, C. Lonappan

A. Quach, E. Chen, G. Fu, N. Brackbill, O. Malik

Bahram Jalali, jalali@ucla.edu
Thank You
jalali@ucla.edu
Outlier Cells

Very rare (less than 0.1% subpopulations), but important

- Circulating tumor cells
- Fetal cells in maternal blood
- Hematopoietic stem cells
- Antigen-specific T cells