Molecular Sensors Based on Raman Scattering and Fiber Technology

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Multidisciplinary Collaboration

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- Tiziana Bond (LLNL)

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Outline

- **Raman Scattering and Surface Enhanced Raman Scattering (SERS)**
  - Molecular specificity & extremely high sensitivity
  - SERS Substrate: Au or Ag nanoparticle aggregates
  - Chemical and biomedical applications

- **Optical Fibers**
  - Side-polished (D-shaped) fibers
  - Tip-coated multimode fibers
  - Photonic crystal fibers

- **Conclusions**
Motivation-Biomedical Application of Nanomaterials: Cancer Detection (e.g. lung and ovarian)

Some Disturbing Statistics on Cancer

<table>
<thead>
<tr>
<th>Cancer</th>
<th>New cases (2000)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1. Lung</td>
<td>1,238,861</td>
</tr>
<tr>
<td>2. Breast</td>
<td>1,050,346</td>
</tr>
<tr>
<td>3. Colorectal</td>
<td>944,717</td>
</tr>
<tr>
<td>4. Stomach</td>
<td>876,341</td>
</tr>
<tr>
<td>5. Liver</td>
<td>564,336</td>
</tr>
<tr>
<td>...</td>
<td>...</td>
</tr>
<tr>
<td>15. Kidney</td>
<td>189,077</td>
</tr>
</tbody>
</table>

Over 10 million people diagnosed per year
Causes 6 million deaths per year
12% of worldwide deaths
Cancer rate is *increasing*, could be 15 million by 2020
Biomedical Applications of Nanomaterials: Cancer Cell and Biomarker Detection with PL and SERS

Cancer is one of the most commonly fatal diseases: e.g. lung and ovarian
Early detection is key to survival but challenging
Sensitive detection of cells and biomarkers (antigens, e.g. CA125) with molecular specificity is highly desired
Semiconductor quantum dots (SQD) and metal nanoparticles (MNP) hold great promise for cancer detection
General applications in chemical, biological, and environmental detection
What is Spectroscopy?

Spectroscopy is the study of the interaction between radiation and matter.
What is a Spectrum?

- The results of Spectroscopy analysis is a *spectrum*: a plot of the response as a function of *wavelength*.
Raman Scattering

- The light may be reflected, absorbed or scattered.
- Most of the scattered light retains the frequency of the source, which is Rayleigh.
- Some of the scattered light changes frequency, based on the vibrational state of the molecule. That is Raman.
Raman Energy State
Raman Spectrum of Methane
What is Raman Spectroscopy?
Raman Detection

It’s Methane!
It’s Useful

- **Fingerprint** of Molecule!
- Has application in medicine, food safety, environmental protection and millitary applications.
Raman Scattering

Advantage: Molecule specific

Disadvantage: very small signal (QY=10^-6-10^-8)
SERS (Surface Enhanced Raman Scattering)

Roughened metal surface:
Enhancement=$10^{6-8}$

Metal nanoparticles or aggregates:
Enhancement=$10^{8-15}$

Nie, Emory, Science, 275, 1102, 1997;
Kneipp, et al. PRL, 78, 1667, 1997
Electromagnetic Field Enhancement Near Sharp Edges and Small Particles

Contour plot of the potential around a metal sphere
Mechanism of SERS

- Local Field Enhancement
  Enhancement of the local excitation field
  Enhancement of the local Raman scattering field

\[ P_{sers}(\nu_s) = N \cdot I(\nu_i) |A(\nu_i)|^2 |A(\nu_s)|^2 \sigma_{ads}^2 \]

- Increase of the Raman scattering cross section
  Electronic coupling between molecule and metal (chemical effect)

HRTEM and AFM of Au Particles

Lattice matches Au, not Au$_2$S

Evidence of Au aggregate
SERS Spectra of DNA Base and Amino Acids on Au NP Aggregates

SERS of Adenine on a single aggregate

Schwartzberg, et al., JPCB, 108, 19191, 2004
SERS of Polyclonal Antibodies: Donkey Anti-Goat IgG

Au - d anti g with actin g poly added (9/10/04)

[Graph showing Raman shift (cm⁻¹) with count values]
SERS Detection of an Ovarian Cancer Biomarker: LPA

LPA: A unique ovarian cancer marker

![SERS Detection of an Ovarian Cancer Biomarker: LPA](image)

**Diagram:**
- LPA: A unique ovarian cancer marker
- Diagram showing SERS detection of 18:0 LPA with various samples:
  - Pure 18:0 LPA Crystal
  - Ag/LPA #1
  - Ag/LPA #2

**Chemical Structure:**
- Diagram of LPA molecular structure

**Raman Shift and Intensity Graph:**
- X-axis: Raman Shift
- Y-axis: Intensity
- Graph comparing SERS intensities for different samples

**Notes:**
- LPA is a lipid that is unique to ovarian cancer.
- SERS is used to detect LPA in various samples.
Optical Fiber Endoscope

http://www.mayoclinic.com/health/medical/IM04428

Ultra-sensitive Compact Fiber Sensor Based on Nanoparticle Surface Enhanced Raman Scattering
A Compact Platform for D-Shaped Fiber-Based SERS/Raman Sensor and Molecular Imaging Device

Non-invasive optical technique with unique combination of molecular specificity and extremely high sensitivity
Light Propagation and Coupling Inside a Side-Polished Fiber Covered with a Metal Overlay
SERS Results for D-shaped Fibers with Side Detection

Excitation light
Side-polished fiber
Raman spectrometer
SERS substrate
Objective
Raman signal

Tip Coated Multimode Fiber

![Diagram of Tip Coated Multimode Fiber]

- **Laser**
- **Beam Splitter Objective**
- **Raman spectrometer**
- **Fiber with silver nanoparticles coated on the tip**
- **0.1mM R6G solution**

**Graphs**
- **Raman Shift (1/cm) vs. A.U.**
  - Sample Detection
  - Fiber
  - Background

**Data Points**

<table>
<thead>
<tr>
<th>Raman Shift (1/cm)</th>
<th>A.U.</th>
</tr>
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<tbody>
<tr>
<td>600</td>
<td>-5000</td>
</tr>
<tr>
<td>800</td>
<td>0</td>
</tr>
<tr>
<td>1000</td>
<td>5000</td>
</tr>
<tr>
<td>1200</td>
<td>10000</td>
</tr>
<tr>
<td>1400</td>
<td>15000</td>
</tr>
<tr>
<td>1600</td>
<td>20000</td>
</tr>
</tbody>
</table>
Double SERS Substrate “Sandwich” Fiber Probe — Tip-coated multimode fiber SERS probe

Synthesis of Silver nanoparticles (SNPs) in the sample solution

- Using a synthesis method from Lee and Meisel
- A concentration of $3.77 \times 10^{-11}$ M
- Average diameter is 25 nm
- Solvent is water
- UV-vis absorbance curve exhibited a plasmon peak at 406 nm
Silver nanoparticles on the tip

Using a synthesis method from modified Brust method and solvent is tetrahydrofuran (THF).
Results and Discussion

(a) $10^{-5}$M

- TCMMF
- MMF in sample solution
- Direct sampling

(b) $10^{-6}$M

- TCMMF
- MMF in sample solution
- Direct sampling

Uncoated MMF in sample solution

Direct sampling
Results and Discussion

(c) $10^{-7}$M

(d) $10^{-8}$M

![Graphs showing Raman shift vs. intensity for TCMMF and direct sampling at 10^{-7}M and 10^{-8}M concentrations.](c) and (d) show the intensity (a.u.) on the y-axis and Raman shift (cm^{-1}) on the x-axis for TCMMF and direct sampling.
Results and Discussion

(e) $10^{-9}$M
Comparison

1. The lowest detectable concentration for MMF, direct sampling and TCMMF are $10^{-6}$ M, $10^{-8}$ M, $10^{-9}$ M respectively.

2. TCMMF sensor has a higher sensitivity than other methods at the same concentration.

3. It demonstrated the stronger SERS activity with the TCMMF due most likely to stronger EM field enhancement as a result of the unique sandwich structure.

Take peak 1514 cm$^{-1}$ as an example.
TCMMF with Oppositely Charged NPs for protein detection

- Oppositely charged double-substrate “sandwich” structure
- Larger silver nanoparticles (SNPs) coated on the fiber tip (25 nm vs. 5 nm)
- Easy and reproducible synthesis and coating

TCMMF SERS probe operating in aqueous lysozyme detection

Similar to the detection limit in the literature\(^*\) (5 µg/mL)


- One magnitude lower detection limit
- Average enhancement of 10 times but with variation for different peaks
- Advantages over dried-film strategy: higher reproducibility, flexibility and potentially in-situ remote sensing capability.
- Integration with a portable Raman spectrometer
TCMMF SERS probe operating in aqueous cytochrome c detection

Some new peaks are observed at 821, 1197, and 1330 cm\(^{-1}\) and can be attributed to Tyr; Tyr and Phe; and Trp, respectively. In addition, the sensitivity enhancement varies for different peaks, with an average enhancement factor of 7.
Liquid core photonic crystal fiber (LCPCF) Probe

Alpha-synuclein detection using LCPCF sensors

- (a) (b) were collected with the 633 nm laser at 3 mW and a scanning period of 10 s.
- With the introduction of the silver binding peptides, the detectable concentration reached $10^{-4}$ M ~ $10^{-5}$ M.
Tryptophan-W

W-dry film
W drop of solution detected through PCF

Same laser power
Additional Sensitivity Enhancement
Liquid core photonic crystal fiber SERS probe

LCPCF SERS probe for aqueous bacteria detection


- Gram-negative facultative anaerobe
- Extracellular electron transfer capability
- Various applications:
  - bioremediation of contaminated soils
  - heavy metal detoxification
  - microbial fuel cells
  - microbial reduction of graphene oxide

1) F. Qian et al., Nano Lett. 10, 4686-4691 (2010)
2) F. Qian et al., Biores. Technol. 102, 5836-5840 (2011)
3) G. Wang et al., Nano Res. 4, 563-570 (2011)
LCPCF SERS probe for aqueous bacteria detection

Control experiments for aqueous bacteria detection

Control experiment with lactate medium and SNPs but without MR-1 cells (a) in bulk detection and (b) using the LCPCF SERS probe.
Liquid-filled PCF Raman probe for glucose detection

Glucose Detection with SERS

Fig. 1 (Left) Illustration of interaction of BBV with AuNP-ZnONWs without (top) and with (bottom) glucose (G). Formation of a complex between BBV and glucose is expected to increase SERS of BBV. (Right) SEM image of AuNP-ZnONWs. The large elongated structures are ZnONWs (~500 nm in length and 50 nm in diameter) and the smaller spherical particles are AuNPs (~10 nm in diameter).

Fig. 2 (Left) SERS spectra of BBV using AgNPs as substrate with varying concentrations of glucose (from bottom to top): (a) 0 mM, (b) 0.5 mM, (c) 2.5 mM, (d) 10 mM, (e) 20 mM, and (f) 30 mM. (Right) SERS intensity of 1004 cm$^{-1}$ peak of BBV as a function of glucose concentration.
Integrating the TCMMF SERS probe with a portable Raman spectrometer

- TCMMF provides 2-3 times stronger SERS signal than direct sampling, similar to the result under the bulky Renishaw Raman system
- Flexible and alignment free
- The SERS probe is reusable.

SERS signals obtained using the portable-TCMMF system and that obtained using direct sampling, when the R6G concentration is $10^{-5}$ M
Reusability of the TCMMF SERS probe

SERS signals obtained using the portable-TCMMF system after washing procedures.
Portable LCPCF SERS Sensor System

- No optical table or breadboard
- Real-time adjustment
- Portable
- Sensitivity enhancement (59 times stronger SERS signal than direct sampling)
SERS signals obtained using (a) direct sampling, and (b) the portable-LCPCF system, when the R6G concentration is $10^{-6}$ M.
Conclusion

Fiber-based SERS sensors provide a compact, low-cost, non-invasive optical technique with unique combination of molecular specificity and extremely high sensitivity for potential chemical and biomedical applications.