Topics in Nano-Biophotonics: Fabrication of Plasmonic Metasurfaces that Attract and Spectroscopically Interrogate Cancer Cells

2018 CNF REU Intern: Vivek Anil

2018 CNF REU Intern Affiliation: Engineering Science, Physics, The Pennsylvania State University

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CNF REU Principal Investigator: Professor Gennady Shvets, School of Applied and Engineering Physics, Cornell University

CNF REU Mentors: Dr. Steven He Huang, School of Applied and Engineering Physics, Cornell University; Dr. Maxim Shcherbakov, School of Applied and Engineering Physics, Cornell University

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Contact: vivek3anil@gmail.com, gs656@cornell.edu, hh623@cornell.edu, mrs356@cornell.edu

Website: http://www.cnf.cornell.edu/cnf_2018reu.html

Primary CNF Tools Used: E-beam resist spinners, JEOL 9500, Anatech resist strip, AJA ion mill, Zeiss Ultra SEM, Zeiss Supra SEM, Even-Hour evaporator, P10 profilometer

Abstract:

Current methods for detecting cancer rely heavily on imaging or tumor markers that are often inaccurate and inefficient. Meanwhile, Fourier transform infrared spectroscopy (FTIR) has been widely studied as a method for label-free biosensing because the characteristic vibrational modes of most biomolecules oscillate at mid-IR frequencies [1]. More recently, plasmonic metasurfaces have drawn interest because they can be engineered to have a resonant electromagnetic response over a broad range of frequencies. Their unique properties enable them to confine light to nanoscale regions (high local field concentration) and have a wavelength-specific response, which is ideal for molecular sensing by spectroscopy [2]. Infrared (IR) plasmonic metamaterials are particularly useful for biosensing: the resonant response of these materials can be tuned to match that of the vibrational modes in biomolecules so that biomolecules can be sensed via surface-enhanced IR spectroscopy. We investigated the use of plasmonic metasurfaces for detection of selected vibrational modes by fabricating gold metasurfaces on an infrared-transparent calcium fluoride (CaF_2) substrate; the metasurfaces were patterned using electron-beam lithography. We successfully fabricated three different types of structures: Fano resonant asymmetric metamaterials (FRAMMs), nanoantennae, and nanoslits, and validated the presence of resonance peaks by performing FTIR on the metasurfaces to obtain reflectance spectra. By adjusting the structures' dimensions, the resonances (quality factor Q~10) seen in each structure's reflectance spectra were tuned to match the amide I (~ 1650 cm^{-1}) and carbohydrate (~ 2900 cm^{-1}) molecular resonances, which are present in cells. Our results demonstrate the potential to develop an improved method of cancer detection via surface-enhanced IR spectroscopy with engineered plasmonic metasurfaces.

Summary of Research:

Introduction. Biomolecular components in cells possess characteristic vibrational modes in the IR, which can be spectroscopically probed to obtain information from cells [1]. The signals from these vibrational modes are often weak, and so we propose using a plasmonic metasurface to enhance these signals. The dimensions and spatial arrangements of the structures were chosen such that the metasurface resonated at frequencies similar to cellular vibrations. Each set of structures with the same dimensions were fabricated together, with consistent spacing between structures, in squares, called pixels. This was done for the sake of testing simplicity: each pixel could be probed as an individual metasurface, and so we could assess how well each set of dimensions enabled us to tune to a particular resonance.

Fabrication. For the FRAMMs and nanoantennae, the fabrication process was as follows: CaF_2 wafers were washed and dried thoroughly, and then ~ 240 nm PMMA was spin-coated onto the wafers. The wafer was then baked at 170°C. We patterned the metasurface using the JEOL 9500 electron-beam lithography system. We developed the PMMA from the patterned areas using a methyl isobutyl ketone-isopropanol developer (MIBK:IPA 1:3). We evaporated 10 nm Cr and 70 nm Au onto the substrate at 1 A/s each. Remaining PMMA was lifted-off in an overnight acetone bath. The process for fabricating nanoslits was similar, except that we evaporated Au between cleaning and spin-coating, and added an extra ion mill etching step after development and before lift-off.

FTIR Experiment. The metasurface was integrated into a polydimethylsiloxane microfluidic chamber; a solution — phosphate buffer saline (PBS), ethanol, or DI water — was injected into the chamber, and an IR spectroscopy was done on the metasurface (probing pixel by pixel) in the chamber using a Bruker-Hyperion FTIR-microscope system.

Results and Conclusions:

We were able to successfully tune our FRAMM (pi structure) and nanoantenna resonances to the desired frequencies, as seen in Figure 1 — where the "Pi_5" (d = *225.1 nm* and L = *1.727 μm* as in Figure 2a) and "Nanoantenna_2" (w = *234.8 nm* and L = *1.693 μm* as in Figure 2b) pixels resonate at the amide I frequency (~1650 cm^{-1}) and the "Pi_3" (d = *66.19 nm* and L = *0.9555 μm* as in Figure 2a) and "Nanoantenna_1" (w = *238.3 nm* and L = *0.9624 μm* as in Figure 2b) pixels resonate at the carbohydrate frequency (~2900 cm^{-1}). In general, we saw that as we increase the size of FRAMM structures, we decrease the position of the resonant frequency (Figure 3); this relationship proved useful for tuning resonances.

We also successfully fabricated nanoslits and adjusted structure dimensions (w ~ *50 nm* and L ~ *700 nm* for "slit_1" and w ~ *50 nm* and L ~ *1500 nm* for "slit_2") such that we observed the interference between the nanoslit peaks and the deionized (DI) water (~1660 cm^{-1} and 3400 cm^{-1}) and ethanol (~3000 cm^{-1} and 3400 cm^{-1}) resonances (Figure 4). Figure 4 suggests the potential for biosensing by tuning resonances to observe similar interference between biomolecular vibrations in cells and our metasurfaces' resonances. Furthermore, integrating our metasurface into the microfluidic chamber shows even more promise for developing a device for biosensing by surface-enhanced spectroscopy.

Future Work:

Future work will include refining nanoslit fabrication and resonance tuning, attaching cancer cells to the metasurface and performing FTIR to obtain biomolecular information from cells, comparing nanoantennae and nanoslits to determine which shows greater near field enhancement, and analyzing spectra to understand how we can use them to distinguish between healthy and cancerous cells.

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References:

[1] Baker, M. J., et al. (2014). Using Fourier transform IR spectroscopy to analyze biological materials. Nature Protocols,9, 1771-1791.

[2] Wu, C., et al. Fano-resonant asymmetric metamaterials for ultrasensitive spectroscopy and identification of molecular monolayers. Nature Materials,11(1), 69-75.

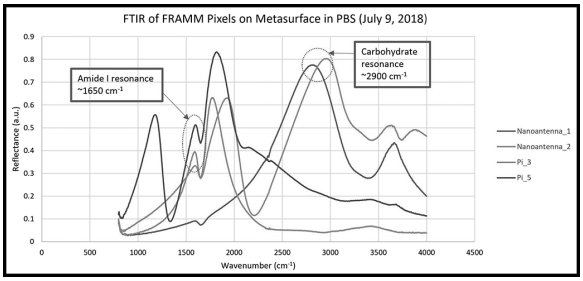

Figure 1: Reflectance spectra of FRAMM and nanoantenna pixels in PBS, tuned to match amide I and carbohydrate resonances.

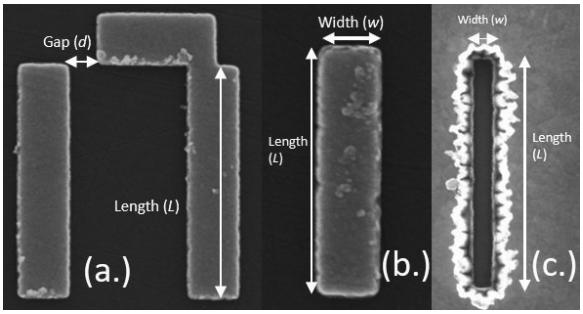

Figure 2: Scanning electron microscopy images (taken at 20.00 kV) of (a) FRAMM (pi), (b) nanoantenna, and (c) nanoslit structures.

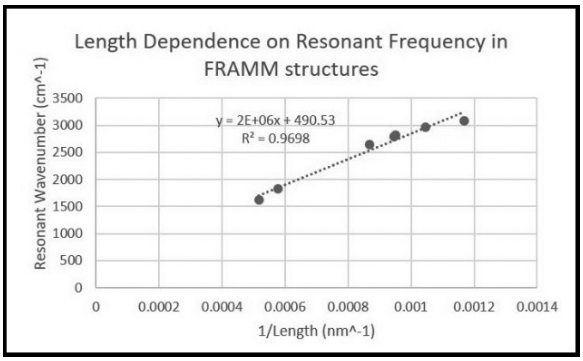

Figure 3: Relationship between length and position of the resonance seen in reflectance spectra for FRAMMs in PBS.

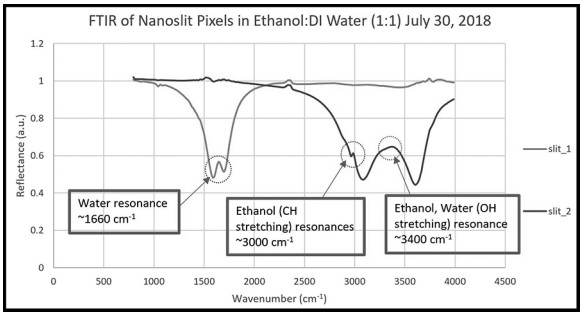

Figure 4: Reflectance spectra for 50 nm wide nanoslits in ethanol-DI water mixture showing water and ethanol resonances.