Metasurfaces for Infrared Spectroscopy of Live Cells in a Microfluidic Chamber

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Primary CNF Tools Used: JEOL 9500, CVC SC4500 evaporator, ZEISS Supra SEM, PDMS casting station

Abstract:

Non-invasive and label-free identification of different cell types allows for early stage diagnosis and leads to more efficacious potential treatment of various human diseases. For example, early stage cancer detection enables many more treatment options and potential cure as compared to detection in the later stage of cancer. In this respect, circulating tumor cells (CTCs) in the blood stream have been shown to be a strong indicator of early stage of various cancers. However, separation, capturing and identification of CTCs still possess significant challenges with regarding to their extremely low concentration as well as the inability of traditional methods to characterize them accurately. Other diagnostic techniques, such all-optical diagnostics of aspiration biopsies, have similar requirements for rapid capture and identification of cancer cells. The following approach is pursued in our lab: simultaneous capture and spectral cytopathology using a combination of dielectrophoresis (DEP) and metasurface-enhanced infrared reflection spectroscopy (MEIRS).

Summary of Research:

Mid-IR spectroscopy is one of the prominent ways of identifying different materials via their fingerprint molecular vibrations. In the past, this has been used for spectroscopically distinguishing cancerous versus non-cancerous tissue. Typically, at least a complete monolayer of cells is required for performing such a characterization. This limitation on the number of cells is a large hindrance for adapting this technique for the detection of CTCs, due to their inherently low concentration in blood. It has been previously shown by our group that mid-IR spectroscopy performed using plasmon resonant metasurfaces (Figure 1) allows one to enhance the sensitivity of this technique significantly and we used this approach to accurately characterize a single protein layer [1]. The increase in sensitivity arises from the highly enhanced optical electric fields created near the structures. Furthermore, the metasurface only probes a small region close to the cell membrane due to the rapid decay of the enhanced fields away from the metasurface.

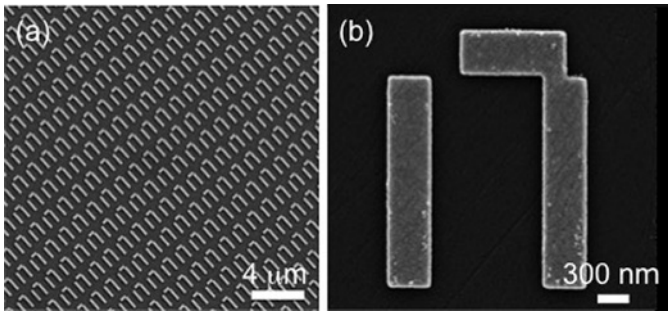

Figure 1: SEM micrographs of the plasmonic metasurface sensor used for MEIRS. (a) Low magnification image showing the periodic plasmonic microstructures. (b) SEM image of a single unit cell of the metasurface. The metasurface is designed to exhibit very high electric fields in the vicinity of the structure. Depicted unit cells are repeated on the substrate plane to form arrays 500 × 120 $(\mu m)^2$ in size. These metasurfaces are made of gold and fabricated on CaF_2 substrates using electron beam lithography.

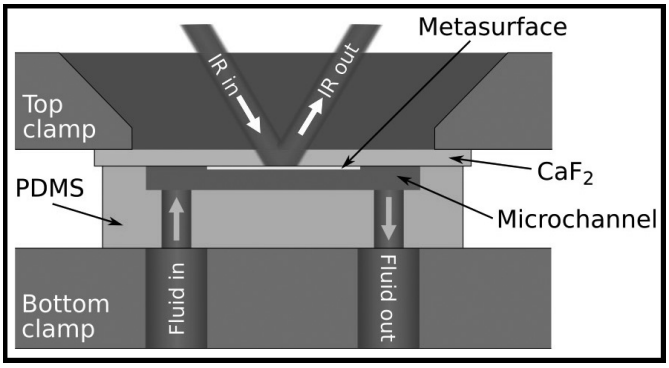

Figure 2: Schematic of a microfluidic device for capturing cells onto the metasurface sensor and measuring their mid-IR spectra. CaF_2 substrate is coupled to a PDMS microchannel allowing cell solution to flow over the sensor surface. PDMS and CaF_2 are fixed together with acrylic clamps compatible with standard microscope slide mounts. Cell solution is pumped through the channel with a syringe pump and voltage is applied on the wire electrodes within the metasurface using a function generator (not shown).

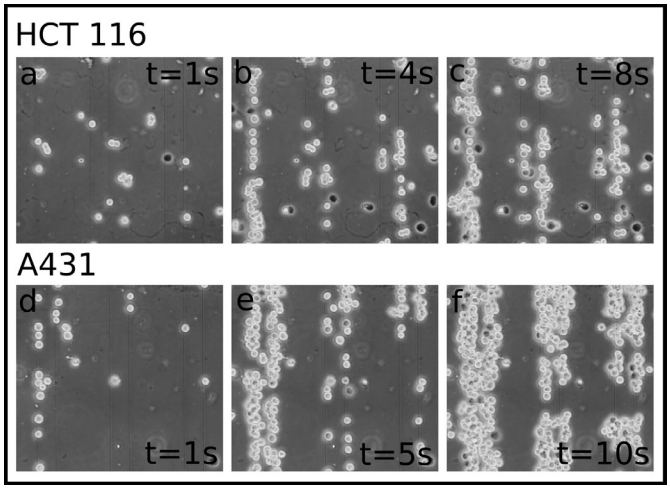

Figure 3: Cells captured on the sensor surface using DEP at different times. (a)-(c) Colon cancer cells (HCT 116). (d)-(f) Skin cancer cells (A431). Three metasurfaces are visible on each image, with two wire electrodes embedded in each metasurface. The DEP force is strongest on the wires, causing cells to form lines on them.

Deposition of cells directly onto the metasurface sensor is achieved with the use of dielectrophoresis. Since cells are essentially dielectric particles, a nonuniform AC electric field can be set up around the metasurface by applying voltage on electrodes embedded in the sensor design, causing cell movement due to DEP force (proportional to electric field gradient). IR spectra of the cells captured and immobilized on the metasurface can then be simultaneously collected under an IR microscope. A schematic of a device constructed to capture cells and collect their mid-IR spectra is shown on Figure 2.

Attachment of cells onto the sensor surface can be further improved by covering the sensor with antibodies. By tuning the frequency of AC signal applied to the electrodes, it is also possible to capture specific cells while repelling other kinds of cells in a multi-species cell solution. Separation of different cell types is especially important while working with blood samples that have very low concentration of CTCs. In the case of CTCs, the separation of tumor and blood cells with DEP is very effective, since those cell types have very different dielectric properties and therefore the frequency of the electric field can be chosen such that CTCs move to the sensor while pushing the blood cells away from it.

Examples of cells captured onto the wires on the sensor surface are depicted in Figure 3. The device can be mounted on a standard IR microscope, allowing instantaneous collection of cell mid-IR spectra for their identification. We have shown that different cell types (e.g., cancerous and non-cancerous) have different mid-IR fingerprints. The difference in the spectral features between various cell types can thus be used for identifying them. The spectra are acquired in an aqueous environment during flow, which is generally not the case in most of the studies in literature. As the whole experiment is performed within a flow chamber enclosing the metasurface sensor, and over the course of just a few minutes, it paves the way for automated and rapid identification and characterization of cells.

References:

[1] Fano-resonant asymmetric metamaterials for ultrasensitive spectroscopy and identification of molecular monolayers. Chihhui Wu, Alexander B. Khanikaev, Ronen Adato, Nihal Arju, Ahmet Ali Yanik, Hatice Altug, Gennady Shvets; Nature Materials 11, 69-75 (2012).