Ultrasensitive plasmonic sensors mold the flow of light and fluidics

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Novel plasmonic biodetection systems enable ultrasensitive biomolecular studies for early disease detection and treatment.

Detection of large numbers of proteins and determination of their functions may enable early diagnosis of complex diseases such as cancer and Alzheimer’s, as well their treatment, by discovering effective drugs. Although large-scale studies of proteins are significant because of such potentially far-reaching implications, their realization is challenging owing to the limitations of current detection techniques. In particular, label-free, ultrasensitive, real-time, and high-throughput on-chip biosensing systems are urgently needed.

Over the last decade, electrical, mechanical, and optical surface biosensors used to explore novel science at nanoscale dimensions have attracted significant attention. Several highly multiplexed, ultrasensitive nanobiosensors offering detection with single-particle sensitivity have been proposed. Concurrently, researchers are integrating sensitive and compact biosensors with microfluidics for automation and improved throughput. However, the performance of surface nanosensors operating in fluidic environments is strongly limited by the efficiency of analyte delivery to the sensing surface rather than by the sensors’ intrinsic detection capabilities. Relying only on passive diffusion for mass transport can severely limit sensor performance. At low concentrations, this ‘mass-transport problem’ causes impractically long detection times for nanosensors, from days to weeks.

To overcome this fundamental limitation, we recently demonstrated a biosensing system that merges photonics and fluids. By efficiently delivering analytes to the device surface, our system dramatically increases the response time of ultrasensitive sensors. Thus far, one of the main conceptual constraints was that biosensors and microfluidics are always considered as different parts of the sensor platform, completing each other rather than forming a fully merged single entity. We merge both components by employing suspended nanohole arrays: see Figure 1(a). The nanoholes, by resonantly transmitting light through the extraordinary-light-transmission effect, are...
Figure 3. Efficiencies of conventional (triangles) and targeted (squares) delivery of the analytes based on real-time measurements. A 14-fold improvement in the mass-transport rate is observed for the targeted delivery scheme. DI: Deionized (water).

instrumental for sensing. In addition, they also transport the flow by connecting the fluidic chambers. We engineered multiple in- and outlets on both sides of the top/bottom chambers to actively control the fluid flow in three dimensions: see Figure 1(b). As a result, unlike conventional approaches, our platform enables targeted analyte delivery to the sensor surface.

To demonstrate the advantage of our approach, we performed microfluidic simulations, solving the steady solution of the incompressible Navier-Stokes equations. For performance quantification, we define the ‘transfer rate,’ i.e., the ratio of the perpendicular to the inlet flow. For conventional delivery, we introduce the solution from the bottom inlet, keeping the other in- and outlets open. The laminar flow mainly covers the bottom channel: see Figure 2(a). Even though the top outlets are open, we observed only 0.3% transfer of the input flow to the top channel. This indicates that diffusion is ineffective in transporting the analytes to the sensor surface. In our proposed flow scheme, on the other hand, we actively direct the stream toward the sensor surface through the nanohole openings: see Figure 2(b). In this case, the transfer rate is 100%, indicating very effective analyte delivery.

To experimentally compare the efficiencies of analyte delivery to the sensor surface, we performed time-dependent spectral measurements. Initially, both chambers are filled with deionized (DI) water. We then introduced a higher-index analyte solution from the bottom inlet. By slowly replacing the DI water, the analyte solution increases the effective refractive index and redshifts the resonance as time evolves. Figure 3 shows that our proposed scheme results in a much larger resonance shift over a much shorter period of time. To quantify the efficiency, we fitted experimental data to a sigmoid function and obtained a 14-fold improvement in the diffusion-rate constants. Such improvements in the exponential term indicate a superior mass-transport capability of our approach.

Finally, using plasmonic nanoantennas, we recently demonstrated an ultrasensitive IR absorption-spectroscopy method that enables detection of molecular signatures of even single protein layers: see Figure 4(a). IR spectroscopy, which can directly access the vibrational fingerprints of the biomolecular structures, particularly in the mid-IR spectral region, is an important tool for functional studies of proteins. However, because of the Beer-Lambert law, its sensitivity has been limited for single-molecule/monolayer studies. We overcome this limitation by specifically arraying tailored nanorod antennas: see Figure 4(b). Upon assembly of the nanorods, we showed that radiative losses can be manipulated to create plasmonic excitations with spectrally narrower far-field resonances and much stronger near-field enhancements than those achievable with an individual nanoantenna. With this strong control over electromagnetic radiation, we achieved up to 100,000-fold enhancements of backbone signatures of proteins and demonstrated detection of absorption signals at zeptomole sensitivity. Because it is adaptable to enhance the IR fingerprints of other biomolecules, our method can be a general-purpose toolkit for ultrasensitive bio-analysis and identification. Recently, we also introduced an inexpensive and high-throughput fabrication method to produce these IR plasmonic substrates. Currently, we are integrating these novel detection platforms for complete analysis of biomolecules for fundamental studies and field applications.

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