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Towards an Integrated Chip-Scale Plasmonic Biosensor

Biosensing allows researchers to detect tiny amounts of harmful chemicals before they become major threats. It is used to help diagnose diseases and to identify biohazards in the environment. These researchers are using advanced optical technologies to develop the biosensor of the future—a plasmonic-based chip-scale device that will allow for compact, inexpensive, ubiquitous and sensitive detection.

In the world of biosensing, researchers are accustomed to looking for the proverbial needle in a haystack—a very, very large haystack. Often the quantity of the chemical of interest is present in the range of parts per billion or less. Imagine, for example, a few anthrax spores hidden in a box of baking soda—certainly enough to be dangerous, but very difficult to detect. Or, in the medical realm, picture a patient with slightly raised blood levels of tumor necrosis factor, which, if detected, could

indicate the beginning stages of cancer. Early detection is critical to addressing the issue, whether it be cancer, disease epidemics or an outbreak due to bioterrorism. Separating the chemical from the surrounding environment represents a great challenge.

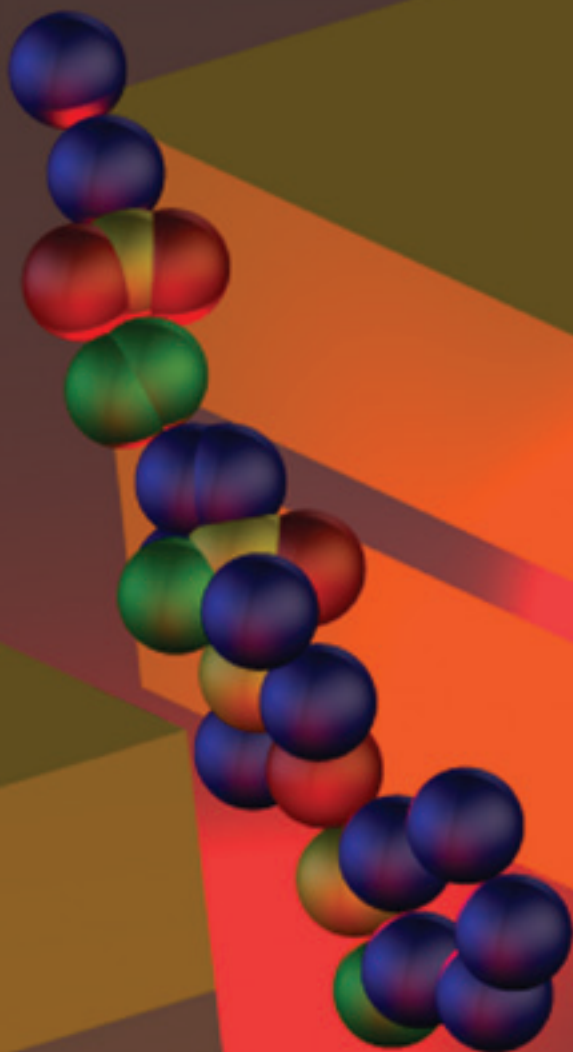
There are two general approaches for addressing this difficulty. The first is to develop techniques that have high sensitivity and specificity, and the second is to create high throughput. A method that can sift through large volumes of

sample material must require minimal preparation and have the capability for fast multiparallel sensing while still being accurate. The end diagnostic tool should be inexpensive, fast, sensitive and ideally portable and noninvasive.

In cancer care, the detection of protein markers is one potentially noninvasive technique that could replace current diagnostic standards. The markers are compounds produced in the body when cancer is present or antibodies that are produced when the body is under

An illustration of a biomolecule in the gap of a metal-dielectric-metal plasmonic antenna integrated onto a quantum cascade laser.

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distress. Current technologies for detecting biomolecules, such as enzyme-linked immune-sorbent assay (ELISA), use time-consuming and complicated pre- and post-processing handling.

Optical spectroscopy is an emerging technology that is fast, sensitive and shows promise as a diagnostic tool for detecting and identifying molecular and biological compounds. Many optical techniques are sensitive enough to detect minute quantities of biomolecules, and many are well researched and mature. Some of the most

well known are surface-enhanced Raman spectroscopy (SERS), coherent anti-Stokes Raman spectroscopy (CARS), UV/Vis absorption spectroscopy, two-photon nonlinear spectroscopy and photoemission spectroscopy.

However, most of these use two or more photon processes and as a result they are not as inherently sensitive as a single-photon interaction. To increase sensitivity, they often require complex surface treatments, large cumbersome optical components and equipment, and

complicated chemical sample treatments to add tags or labels to the targets. All of these modifications add to the complexity of the detection technology and, more important, they reduce the throughput capabilities.

Since these compounds are usually proteins or other large biomolecules, they have very strong and unique vibrational characteristics in the 10 to 100 THz range. Optical energy that matches a natural molecular mode in this frequency range will be absorbed and converted

into a mechanical vibration or rotation. Unfortunately, this frequency range corresponds to free-space optical wavelengths in the mid- to long-infrared, which is akin to throwing a rock at an ocean wave and hoping for an interaction.

The nanoscale molecules are washed over by the huge optical waves without any significant interaction. Therefore, direct optical spectroscopy often requires a large number of molecules to produce reliable detection. In order to sense just a few molecules with good reliability, one needs to address the critical issue of increasing the interaction strength by many orders of magnitude.

Portability is the most challenging component for any diagnostic device. It is extremely important for next-generation tools, and it could very well revolutionize medicine. If we could build a highly sensitive and portable biosensing device, health care professionals would have a new arsenal for combating disease—both in the developed world and in more impoverished areas. In addition, first responders would be able to measure acute toxicity levels of their environment, and law enforcement would know whether to evacuate a building due to a chemical threat.

This method could also be used to track levels for at-risk individuals of a specific disease, so that their doctor would know if something was wrong. Our motivation is to address some of the above issues by applying our understanding of plasmonics, infrared semiconductor lasers and microfluidics to produce a

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chip-scale, potentially inexpensive and portable diagnostic tool.

For any system to be made portable, the pieces and parts must all be miniaturized and integrated. It has not been until recently that a mid- to long-infrared source has been developed that is compact and that works at room temperature. With the invention of the quantum cascade laser (QCL)—a semiconductor inter-subband laser first demonstrated in 1994 at Bell Labs—we have such a source.

And with further development in design and fabrication, it has shown enough performance in terms of wall-plug efficiency to begin thinking about using it not just as an infrared source, but rather as the power center for a more application-oriented device. Hui Chun Liu of the Institute for Microstructural Sciences at the National Research Council in Canada believes that, when discussing the QCL, “ultimately, the success of any semiconductor device is measured by its applications. Having high wall-plug

efficiency will undoubtedly attract interest from those in application areas such as chemical and environmental sensing and biomedical diagnostics.”

Unlike SERS, this device relies on exciting the natural vibrational frequencies of molecules, and, as such, it does not require large optical spectrometers (filters). Note that the spectrometer size is inversely proportional to its resolution due to the uncertainty principle, and hence chip-scale SERS systems face a fundamental limit.

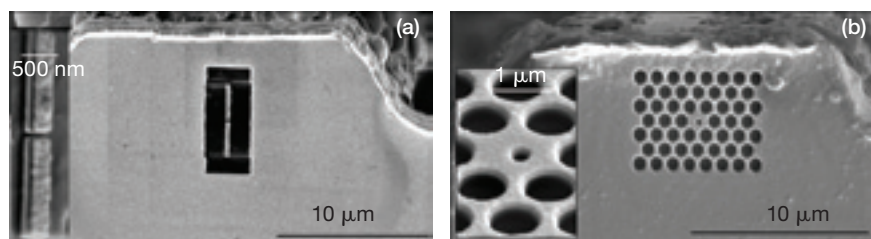
Optical antennas for biosensing

With the source decided on, we looked at solutions to the low interaction efficiency that plagues infrared spectroscopy. For inspiration, we looked to the field of microwave and radio frequency and to a little piece of metal that has completely revolutionized our world—the antenna. In almost every technology we use, from those integral to saving lives to others that we can't fathom living without, there exists an antenna. This piece of wire has, for more than 100 years, allowed us to use electromagnetic waves with wavelengths of centimeters to interact with devices that have been becoming more miniature with each generation.

An antenna can, in a sense, help us to break the diffraction limit. Using conventional geometrical lenses, light cannot be focused beyond half its wavelength. This was discovered and theorized by Abbe in 1873, and it defines the fundamental limit of diffraction. Optical antennas can guide the signal to a spot that is orders of magnitude smaller than the operating wavelength and thereby in a sense overcome this limit. Going well past this limit is essential in the area of molecular detection. Maria F. Garcia-Parajo, a professor of optical science in the Optical Science group at the University of Twente in the Netherlands, states that “key multimolecular interactions that dictate functionality occur at the nanometric scale, a size regime not accessible by the classical optical techniques owing to the diffraction of light.”

For many years, most researchers thought of gold as a light killer up to

[Metal-dielectric-metal antennas]



Scanning electron micrograph (SEM) image of (a) the Au-SiO₂-Au (70/30/70 nm) coupled nanorod antenna and (b) plasmonic photonic crystal integrated on the facet of a quantum cascade laser. Magnified SEM images of the structure are shown on the lefthand side of each SEM image.

the near-infrared portion of the electromagnetic spectrum. Optical antennas therefore were not considered practical because they are too lossy. However, at the mid- and long-wave infrared part of the spectrum, gold becomes a good conductor, and the propagation length and lifetime of the surface plasmon increases enough to mitigate its lossy nature. These surface plasmons, which are collective oscillations of electrons at the interface between a metal and a dielectric, even played an integral role in the development of long-wavelength and THz QCLs. The gold contact layer was deposited near the active region so they wouldn't have to grow tens of microns worth of active material. Luckily gold is also nonreactive to most solvents, specifically those that are biocompatible and so it is the ideal material for our antenna.

We know the material of our antenna. However, in order to develop the design, we would need to use another technique developed in the early 1970s, which has become popular recently. The advent of high-capacity, high-power computer systems has made accurate, full, three-dimensional simulations possible even with memory-intensive highly dispersive material. Finite difference time domain (FDTD) simulations are important to the understanding of many optical devices. This computation method provides researchers with the ability to test device designs and optimize those designs quickly, inexpensively and safely. In this way, we know the experimental parameters should work and can fabricate to those specifications.

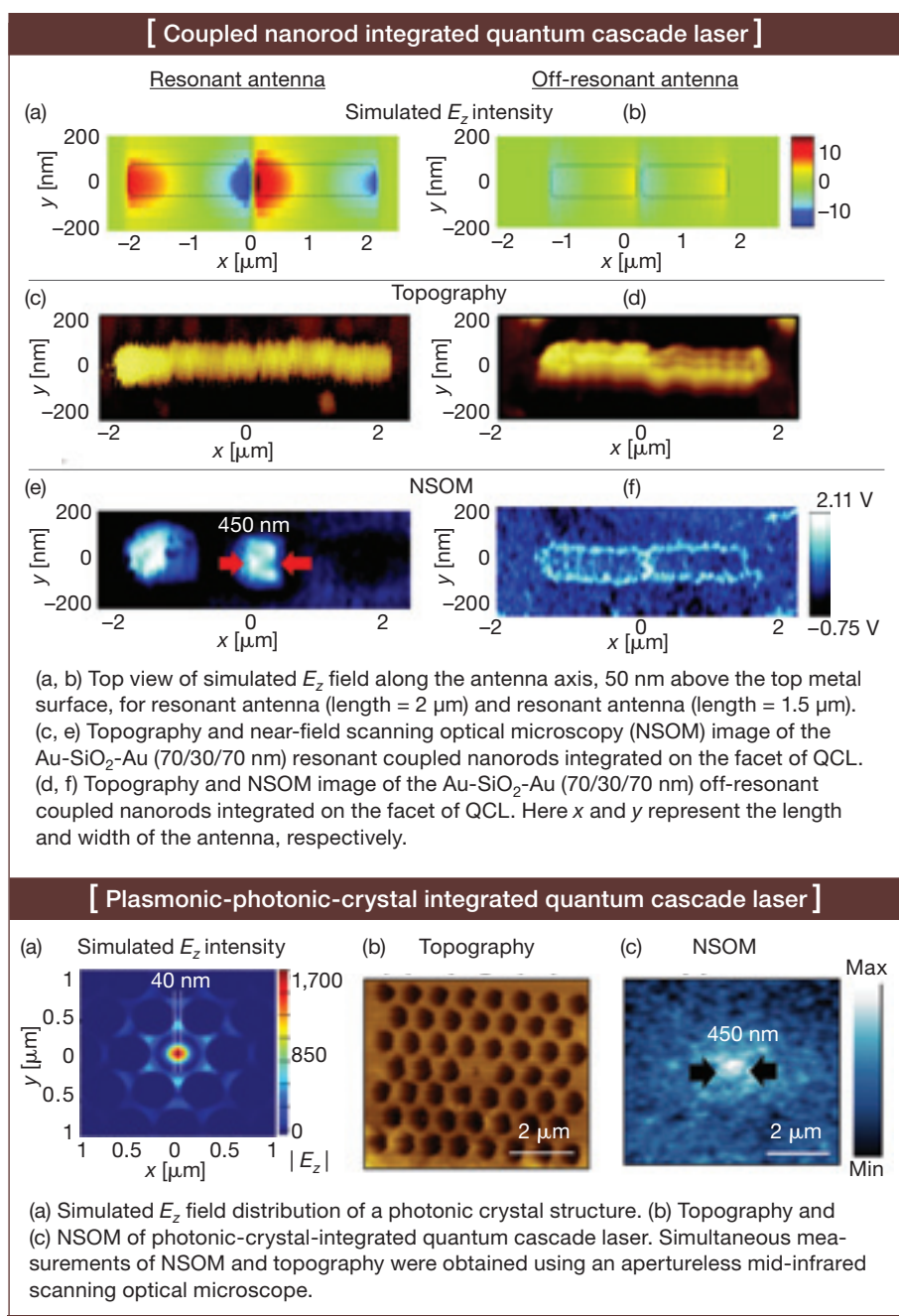
We have studied two optical antenna designs that are fabricated directly onto the facet of a QCL. The first is two closely spaced metal-dielectric-metal (MDM) coupled nanorods and the second is a plasmonic photonic crystal (PPC) with a cavity defect. For the coupled nanorods, we use the MDM geometry instead of just a single metal layer because the simulations show an increase in the coupling between the two inner metal dielectric interfaces, which results in a stronger optical confinement in the cavity. The volume of the squeezed mode is approximately

200 nm³, which is 6,000 times less than the incident mode volume from a free space wavelength of 6.1 μm (the working wavelength of our QCLs).

The PPC is an MDM sandwich with a very thin dielectric region (10-40 nm) and a photonic crystal drilled through the three layers. The central hole is made very small and acts as a cavity defect, wherein the light can be squeezed more than 300,000 times less than the volume of the free space wave. The excited gap mode

resonates through the middle dielectric layer, where, because of the extremely high refractive index, it propagates very slowly, giving itself every opportunity to interact with a molecule. The cavity defect hole also serves as a conduit, allowing molecules to freely flow in and out.

Our simulation data certainly support the notion that an optical antenna can be a powerful tool for overcoming the fundamental limit of diffraction. The squeezing of optical modes using an optical antenna



has far-reaching consequences in bio-sensing. To be able to detect a biomolecule, the primary condition is to achieve a detection volume as small as the size of the individual analytes.

But this squeezing does not come without a cost; we must sacrifice a high quality (Q) factor cavity to achieve such small modal volumes. In fact, the Q -factor for a typical plasmonic cavity is only somewhere between 10 and 100. But all is not lost because the important parameter for a cavity can be characterized by Purcell's Factor (F_p). Normally a measure of the interaction strength between photons and an emitter, by reciprocity this factor is also the interaction strength between photons and an absorber. Exactly the kind of system we want to explore.

Here, F_p is proportional to the Q -factor divided by the mode volume, V_{mode} , of the optical excitation. Therefore, if we want to maximize F_p , we can reduce V_{mode} and not have to rely on extremely large Q -factors. Furthermore, since the Q -factor is inversely proportional to the linewidth, it becomes possible to construct a *broadband* cavity that will be resistant to manufacturing variances and environmental changes such as temperature or humidity. More important, this broadband capability allows us to sweep over a range of wavelengths to hit the molecular resonances around that excitation. Because not all molecules will have

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identical spectral responses, this sweeping will dramatically improve the specificity.

Sensitive signal detection

In order to test the spectral response of our devices, we took inspiration from the group of Federico Capasso at Harvard University. In 2006, Capasso demonstrated the integration of a passive antenna component with an active QCL source. One major difference, however, is that we used metal-dielectric-metal (MDM) structures with much improved mode intensities. We fabricated the devices by evaporating layers of gold and SiO_2 to the facet of an edge-emitting quantum cascade laser operating at room temperature with the device designs drilled in over the active layers by a focused ion beam.

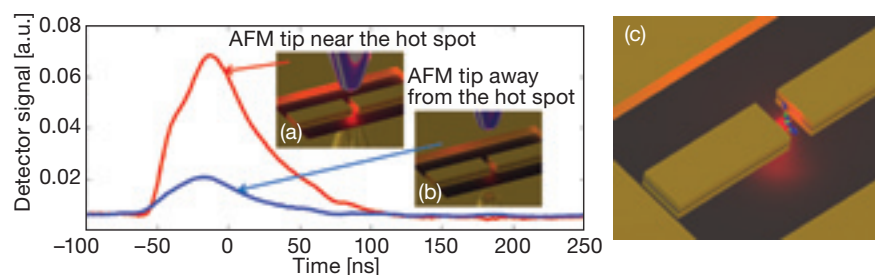
The plasmonic mode that resonates with the antenna exists only in the near field and thus cannot be studied with an ordinary microscope. A special technique, called near-field scanning optical microscopy (NSOM), is required to image the optical modes. So we built a homemade setup based on an atomic force microscope (AFM). The apex of the AFM tip works as a scattering center as we scan the surface of the device in tapping mode.

You cannot get close enough to the surface of the active device using any alternative technique, and, in this non-contact mode, the tip won't damage the laser facet. A frequency lock-in amplification technique—which couples to and accounts for the frequency of the vibrating tip—was used to reduce the noise floor. Using this NSOM approach, we could measure the squeezed mode of the antenna, and we found the optical characteristics of our cavities matched well with our simulation results. We have shown the integration of two antenna designs suitable for biomolecular detection with a QCL that operates at room temperature.

The semiconductor compact detectors that exist at these wavelengths have low sensitivity at room temperature and, as a result, require liquid nitrogen cooling in most conventional setups. However, in our approach, the strong coupling of the antenna's plasmonic modes and the laser cavity's optical modes produces a very large modulation of the laser output from minute scatterings near the hotspot. Since the laser power is quite large, this large modulation can be easily sensed with an uncooled mid-infrared detector, and hence an all-room-temperature sensing platform is feasible.

To demonstrate the above "amplification" mechanism, we use our NSOM setup in a different configuration. Here the AFM tip with about a 50-nm radius oscillating with an amplitude of about 25 nm is located roughly 50 nm above the hotspot. Although this motion is more than two orders of magnitude smaller than the wavelength of the laser, the strong coupling changes the laser intensity by more than a factor of 3. Without the antenna, this interaction

[Intensity modulation of the laser output with an atomic force microscope]



(a) As an AFM tip is brought close enough to the cavity antenna for the laser mode to couple to it, the output intensity will be modulated, and, though the signal itself may be weak, this modulation can be monitored. (b) When the tip is no longer coupled to the cavity antenna, the output intensity of the laser is not modulated as strongly. Thus, as the tip oscillates above the hotspot, the intensity of the laser modulates from weaker to stronger. (c) This intensity modulation can be detected even if the optical signal is very small.

would not produce a detectable signal. In particular, if the laser is operated just near threshold, the tip can turn the laser off by this strong coupling between the two. A molecule that is sitting at or much nearer to the cavity will act as a strong absorber and vibrate at the driven frequency. This will modulate the laser in just the same way the AFM tip did. And thus because we use a source that can excite the natural vibrational frequencies of our large biomolecules, this device can function with a standard infrared photodetector operating at room temperature.

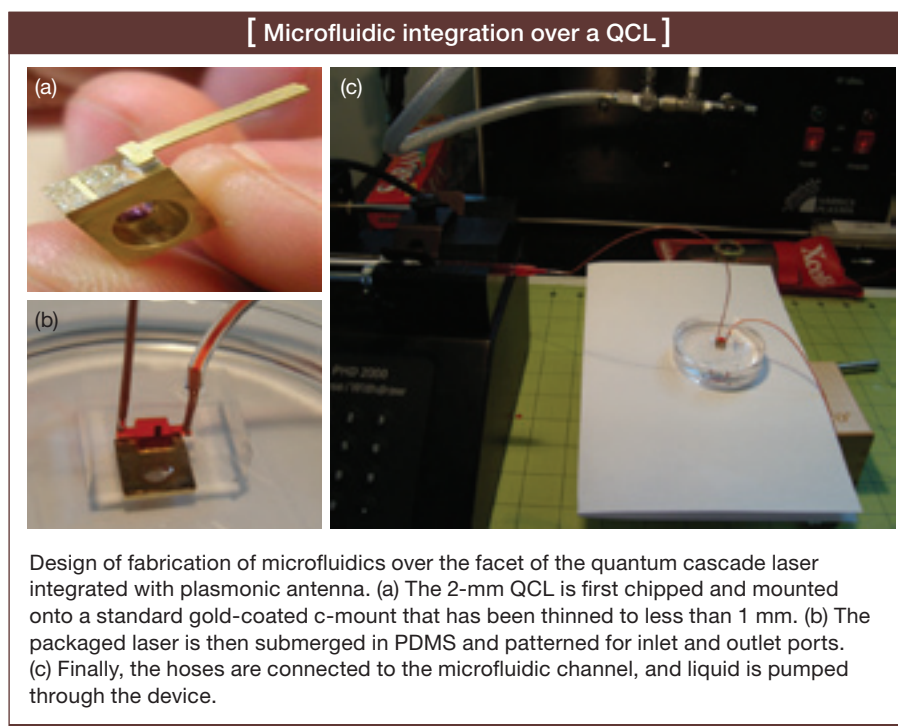
Transport integration

A key challenge in realizing a chip-scale sensor is the delivery of target molecules to the hotspot. As a first step, we have shown the possibility of merging the detector with the laser source. Now we need to integrate this piece with the ability to transport the molecules to the optical antenna. An optofluidic platform is an essential component for such biosensors, as it can be used to control the flow of fluid over the hotspot regions.

Soft lithography, which was first introduced by George Whitesides' research group at Harvard, holds great promise for constructing optofluidic platforms. Polydimethylsiloxane (PDMS) is superior to other elastomeric materials available for soft lithography due to its low cost, rapid prototyping, the reusability of the master molds, its thermosetting nature and its capacity for multilayer fabrication to create complex three-dimensional systems. Fluid flow through the microchannels can be controlled either by external pumps or by microfabricated components integrated on-chip.

And while the pump controls the lateral flow, the targets that are freely swimming in a fluid will pass near enough to the cavity so that the large electromagnetic gradient forces will steer the molecule toward the center. Since Arthur Ashkin's seminal paper on optical trapping in 1970, many research groups have been advancing this technique to ever-smaller particles in ever-smaller volumes.

Recently, many teams have looked at using plasmonics to enhance the force



of the optical trap; a three-dimensional experimental realization was reported in 2008. Although the smallest diameter particle recorded for plasmonic traps is 200 nm, David Grier of the department of physics and the center for soft matter research at New York University, wrote in 2003 that "optical tweezers can trap objects as small as 5 nm and can exert forces exceeding 100 pN ... This is the ideal range for exerting forces on biological and macromolecular systems ...". Combining the technical knowledge of optical trapping with the advances in plasmonic trapping and micro/nano fluidics to realize a single molecule trap on an optofluidic platform will have a

profound impact on the feasibility of the final device operation.

The future certainly holds promise for lab-on-a-chip biosensors, which are noninvasive, portable and accurate. They may trigger a revolution in personalized medicine and the way we look at detection. ▲

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