Handheld high-throughput plasmonic biosensor using computational on-chip imaging

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We demonstrate a handheld on-chip biosensing technology that employs plasmonic microarrays coupled with a lens-free computational imaging system towards multiplexed and high-throughput screening of biomolecular interactions for point-of-care applications and resource-limited settings. This lightweight and field-portable biosensing device, weighing 60 g and 7.5 cm tall, utilizes a compact optoelectronic sensor array to record the diffraction patterns of plasmonic nanostructures under uniform illumination by a single-light emitting diode tuned to the plasmonic mode of the nanoapertures. Employing a sensitive plasmonic array design that is combined with lens-free computational imaging, we demonstrate label-free and quantitative detection of biomolecules with a protein layer thickness down to 3 nm. Integrating large-scale plasmonic microarrays, our on-chip imaging platform enables simultaneous detection of protein mono- and bilayers on the same platform over a wide range of biomolecule concentrations. In this handheld device, we also employ an iterative phase retrieval-based image reconstruction method, which offers the ability to digitally image a highly multiplexed array of sensors on the same plasmonic chip, making this approach especially suitable for high-throughput diagnostic applications in field settings.

INTRODUCTION

Early detection and effective diagnosis are important for disease screening and preventing epidemics. Most of the current medical technologies are time-consuming and require costly chemical procedures and bulky instrumentation, necessitating an advanced medical infrastructure and trained laboratory professionals. In developing countries, there is an urgent need for cost-effective and easy-to-use diagnostics technologies. Similarly, in developed countries, even though resources are available, the cost of health care is still a concern. For various diseases including Alzheimer’s disease and cancer, expression of certain proteins in the body is up- or downregulated, making them suitable to be used as disease biomarkers. Recent works have also shown that instead of monitoring a single biomarker, screening a panel of proteins could significantly improve the accuracy in medical diagnostics by eliminating false positives.1–3 High-throughput sensing technologies that can enable simultaneous detection of a wide range of proteins might offer a viable solution for medical diagnosis. Therefore, there is a strong need for affordable and high-throughput screening technologies that can effectively monitor and diagnose various medical conditions. As recognition of some of these challenges, international consortiums are calling for innovative solutions toward cost-effective and handheld wireless biosensor devices with a desired list of performance metrics (see, for example, The Qualcomm Tricorder X Prize and Nokia Sensing X Challenge). Similarly, various point-of-care diagnostic devices have been developed4–29 and among them optical imaging and sensing techniques are highly advantageous as they can provide real-time, high-resolution and highly sensitive quantitative information, potentially assisting rapid and accurate diagnosis.30–40 To date, a number of optical techniques have been proposed for point-of-care diagnostics such as in vitro optical devices,41–53 including portable optical imaging systems, optical microscopes integrated to cell phones or in vivo optical devices,54–63 involving confocal microscopy, microendoscopy and optical coherence tomography techniques. Among these approaches, lens-free computational on-chip imaging64 has been an emerging technique that can eliminate the need for bulky and costly optical components while also preserving (or even enhancing in certain cases) the image resolution, field of view and sensitivity. In this
on-chip microscopy platform, computational holographic reconstruction and phase recovery methods are used to partially eliminate diffraction effects, providing higher resolution microscopic images across very large imaging areas, e.g., >20–30 mm² using off-the-shelf CMOS (Complementary Metal–Oxide–Semiconductor) imager chips. Together with the improvements provided by unique sample preparation and self-assembly techniques, lens-free on-chip imaging can even detect single viruses and sub-100 nm particles across a wide field of view, e.g., >20 mm² and provides a high-throughput nano-imaging platform.

In parallel to these advancements in computational imaging, current trends for health-care technologies aim to utilize high-throughput and massively multiplexed detection methods that can be used to rapidly extract a wide range of diagnostic data. One way of such multiplexing is fluorescence imaging. However, this approach suffers from cross-interference of labels with other molecular binding interactions, a limited number of fluorophore labels and additional labeling steps that increase the sample preparation time. Recently, various high-throughput optical detection methods have been investigated to overcome these problems as they offer strong advantages by being compatible with physiological solutions, not affected by the variation in the ionic strengths of biosolutions, and reducing sample contamination allowing remote transduction of the biomolecular binding signal. Among optical biosensors, surface plasmon resonance (SPR)-based platforms are one of the most favored. Surface plasmons (SPs) are waves propagating at a metal/dielectric interface associated with the collective electron oscillations. This feature makes SPs highly suitable for investigation of near-field variations of a specimen due to absorption of specific molecules onto the metal surface, enabling label-free detection of binding events. In fact, SPR is considered as the gold standard for label free biodetection. Strong sensitivities of SPR sensors allow detection of small proteins with molecular weights down to tens of kDa without the use of any lenses under uniform illumination by a single nano-aperture. In this system, the plasmonic sensor chip, the LED-based excitation source and the compact CMOS image sensor are automatically aligned in a dark environment, without the need for any bulky optical instruments or mechanical microstages. Unlike existing multiplexed biodetection systems, this on-chip biosensing technology is ultracompact and lightweight (~7.5 cm tall and 60 g), making it highly suitable for field medicine and diagnostic needs. Our biosensor detects protein monolayers down to 3 nm thickness without any labels and enables quantitative analysis of protein binding events over a wide range of biomolecule concentrations. The multiplexing capability of our lens-free computational sensing system is demonstrated by simultaneous identification of protein mono- and bilayers on the same plasmonic chip. Employing a computational image reconstruction method that is based on iterative phase retrieval, our device provides a promising platform for high-throughput biosensing of for example over 150,000 sensors on large-scale plasmonics chip through a CMOS imager with an active area of 5.7 mm × 4.3 mm.

As shown in Figure 1a and 1b, our on-chip biosensing platform is comprised of the following components: (i) a plasmonic chip containing microarray pixels composed of periodic nanoholes fabricated on a thin gold film to detect the variations in the surface conditions (near-field) due to the specific binding of molecules on the chip surface. Scanning electron microscope (SEM) image of 6 plasmonic sensor pixels containing nanohole arrays is provided in Figure 1c; (ii) an LED source that significantly overlaps with the plasmonic modes of the nanostructured surface of the chip. These plasmonic nanohole arrays, when illuminated by an LED (peak wavelength: ~683 nm, bandwidth: ~26 nm), excite a plasmonic mode which supports electromagnetic fields strongly localized around the rims of the nanoholes at the top surface. The fields extend into the sensing medium, together with ~550 times intensity enhancement of as verified by our finite-difference time-domain simulation (FDTD) results shown in Figure 1d (see Supplementary Information for details); and (iii) a CMOS imager chip that records the diffraction patterns of the plasmonic nanoapertures, modulated by molecular binding events on the aperture surface. Design and fabrication details of this platform are presented in the next section, which is then followed by the section on ‘results and discussion’.

MATERIALS AND METHODS

The presented computational biosensing platform combines wide-field nanoplasmic arrays with a lens-free on-chip imaging, where a CMOS imager chip records the diffraction patterns of the plasmonic structures without the use of any lenses under uniform illumination provided by a LED that overlaps with the plasmonic modes of the nanoapertures. Integrating the plasmonic sensor chip, the LED-based excitation source and the compact image sensor in a lightweight handheld unit, this biosensor platform can monitor multiple protein binding events without any labels at the point of care or in field settings.

Design of the wide-field plasmonic microarrays

In our platform, we utilize microarray pixels composed of nanoapertures in the form of nanohole arrays exhibiting multiple spectral points of extraordinary light transmission due to the excitation of SP waves at different grating orders (see Supplementary Information for the theory of the SP excitation through periodic structures and Supplementary Fig. S1 for the fabrication of nanohole arrays). For our analysis, we focus on the SP(−1,0) mode (indicated by a black arrow in experimental spectrum taken by an optical spectrum analyzer shown in Figure 2a), since it supports large transmission intensity which can be easily detected by our lens-free imaging device. Inset in Figure 2a shows...
the calculated distribution of the \( y \)-component of the magnetic field intensity, \(|H_y|^2\). Here, the standing field pattern along the \( x \)-direction is due to the propagating SP excitation and the hot spots around the rims of the nanoholes along the \( y \)-direction are due to the localized SP waves.\(^{112,113}\) For the SP(\(-1,0\)) mode, the local excitations have dipolar character allowing the light to strongly couple to localized SPs resulting in an extraordinary light transmission. Localized SPs also lead to large near-field enhancements around the nanoapertures. Accordingly, our plasmonic aperture system shows high sensitivities to surface conditions by enabling strong overlap between analytes in the vicinity of the sensor surface (near-field) and the local fields. Upon biofunctionalization of the microarray pixels with a protein bilayer, containing 0.5 mg mL\(^{-1}\) protein A/G and 0.5 mg mL\(^{-1}\) protein IgG, which increases the local refractive index around the sensor surface, the plasmonic mode shifts to longer wavelengths by \( \sim 19 \) nm (from 683 nm to 702 nm).\(^{91,92}\) Protein A/G is a recombinant fusion protein constituting binding domains of proteins A and G. Protein A/G has a molecular weight of 50.46 kDa and the thickness of protein A/G layer is approximately 3 nm.\(^{93}\) Protein IgG is immobilized on protein A/G due to the high affinity of protein A/G to the Fc regions of protein IgG. Molecular weight of protein IgG is 160 kDa and the thicknesses of this layer is approximately 5 nm (see Supplementary Information for methods on protein chemistry and sample preparation techniques).

### Characterization of the lens-free on-chip sensing platform

In our lens-free plasmonic sensing platform, the spectral shift in response to molecular binding is determined by monitoring the intensity changes captured by the CMOS imager (Figure 1). In order to reliably detect the red shift in the transmission resonance, the selection of the LED peak wavelength is critical, and it should ideally match to 683 nm. As shown in Figure 2c, our LED response spectrally overlaps with the transmission resonance of the nanohole array located at 683 nm. Figure 2b illustrates that the presence of the protein binding events leads to a redshift in the transmission resonance, detuning it from the LED peak wavelength. Consequently, the total transmitted signal of the acquired lens-free image drops considerably; thus enabling to detect presence of biomolecular layers with a thickness down to 3 nm (refer to the section on ‘results and discussion’ for further details).

In our on-chip detection platform, the vertical distance between the plasmonic microarray pixel (with an individual pixel size of 100 \( \mu m \times 100 \mu m \)) and the CMOS active area is \( \sim 1 \) mm. Therefore, even if the plasmonic interaction occurs in the near-field of the sensor chip, evanescent wave contribution is negligible during the detection or sampling of the lens-free diffraction patterns of the nanoapertures. For an accurate calculation for the diffraction pattern, we utilize an approach based on convolution and Fresnel kernel (see Figure 2d and Supplementary Fig. S2 for details of the field transmission calculations).
through our plasmonic chip). It is also important to note that since we utilize circular-shape apertures which have azimuthal symmetry in the aperture plane, the transmission response is the same for different linear polarization components (see Supplementary Fig. S3 for the near-field analysis of polarized vs. unpolarized light sources for our nanoaperture design). This behavior is highly advantageous for our lens-free computational detection system since a simple LED without a polarizer can be used for partially coherent illumination of the nanoaperture plane.

**Computational reconstruction method for multiplexed plasmonic microarrays**

To get multiplexed and high-throughput read-out, using a large number of sensor pixels into the same chip area results in a significant spatial overlap of diffraction patterns at the detector plane due to the lens-free operation. As illustrated in Figure 3a, the transmitted fields propagate ~1 mm before being captured by the CMOS imager chip. To address this spatial overlap problem for especially high-density microarrays, we employ a numerical approach that is based on a phase recovery technique to digitally backpropagate the diffraction patterns onto the exit aperture of the nanohole array.

We should emphasize that even using an LED, the spatial coherence diameter at the sensor chip surface can be fine-tuned between 0.2 mm and 1 mm by for example adjusting the vertical distance between the LED and sensor chip or changing the pinhole diameter in front of the LED. This partial spatial coherence ensures that each element of the plasmonic microarray effectively faces a quasimonochromatic and spatially coherent plane wave, such that we can frame the entire reconstruction process around phase recovery. The workflow of our iterative phase retrieval method (Figure 3b) can be summarized as follows: (i) lens-free diffraction images of the plasmonic microarrays are recorded using a CMOS imager chip; (ii) the raw diffraction images are then upsampled typically by a factor of 4–6, using cubic spline interpolation method before the iterative reconstruction procedure. Note that this upsampling step does not increase the information content of the diffraction images; however, it helps to achieve faster phase recovery; (iii) the square root of the diffracted field intensity, calculated from the measured transmission signal and (inset) corresponding diffraction patterns of a plasmonic microarray pixel before and after the addition of the protein bilayer acquired by the CMOS imager. (c) Spectral curve demonstrating the overlap of the LED spectrum (blue dashed line) and the transmission response of the bare nanohole array (black solid line) measured by an optical spectrum analyzer. (d) 3D intensity plot of the simulated transmission pattern for the bare and the biofunctionalized nanohole array calculated at a propagation distance of 1 mm from the nanohole array structure to the sensor plane at the peak wavelength of the LED spectrum. CMOS, Complementary Metal–Oxide–Semiconductor; 3D, three-dimensional; FDTD, finite-difference time-domain; LED, light-emitting diode.

**Figure 2** Working principle of our on-chip computational biosensing platform. (a) Experimental transmission spectra of the bare nanohole array (black solid line) and the plasmonic substrate covered with protein bilayer containing 0.5 mg mL$^{-1}$ A/G and 0.5 mg mL$^{-1}$ IgG (red solid line). (Inset) FDTD simulation result showing the intensity distribution of the $y$-component of the magnetic field ($|H_y|^2$) calculated for a bare aperture array at 683 nm. (b) 3D intensity plot of the experimental transmission signal and (inset) corresponding diffraction patterns of a plasmonic microarray pixel before and after the addition of the protein bilayer acquired by the CMOS imager. (c) Spectral curve demonstrating the overlap of the LED spectrum (blue dashed line) and the transmission response of the bare nanohole array (black solid line) measured by an optical spectrum analyzer. (d) 3D intensity plot of the simulated transmission pattern for the bare and the biofunctionalized nanohole array calculated at a propagation distance of 1 mm from the nanohole array structure to the sensor plane at the peak wavelength of the LED spectrum. CMOS, Complementary Metal–Oxide–Semiconductor; 3D, three-dimensional; FDTD, finite-difference time-domain; LED, light-emitting diode.
intensity image;\(^6\) and (iv) this complex field can then be backpropagated to the object/aperture plane, providing the reconstructed images of the plasmonic microarrays at the nanoaperture plane. To demonstrate the success of the above outlined phase recovery-based image reconstruction process, Figure 3c illustrates the diffraction patterns of six different neighboring plasmonic sensor pixels (separated by 25 \(\mu\)m edge-to-edge distance) that are detected by the CMOS imager chip at a propagation distance of 2 mm from the nanostructures to the sensor plane, exhibiting partial spatial overlaps due to our lens-free operation. Employing the iterative reconstruction procedure discussed above, the diffracted lens-free images of the plasmonic sensor pixels can now be digitally focused onto the nanoaperture plane, removing the spatially overlapping parts of these images. This lens-free image reconstruction process is quite valuable especially for highly dense arrays of nanoapertures for increased multiplexing. However, we should also note that quantitative sensing information of the binding events could also be extracted from only the diffraction patterns of the same nanoapertures in case the physical separation between neighboring aperture regions is large, minimizing the intensity overlap at the detector/sampling plane.\(^6\) Using this phase recovery approach procedure, we can reduce the distance between individual sensory pixels even down to 2 \(\mu\)m.\(^6\) A single sensor with a size of 10 \(\mu\)m \(\times\) 10 \(\mu\)m, consisting of more than 200 nanoholes (hole diameter=200 nm and array period 600 nm) should result in sufficient transmitted signal to be captured by the CMOS imager.\(^6\) Based on these numbers, employing a CMOS imager with an active area of 5.7 mm \(\times\) 4.3 mm, we could image 170,000 sensor pixels all in parallel, which is highly promising for high-throughput applications.

RESULTS AND DISCUSSION

Multiplexing performance of the lens-free detection platform
To evaluate the performance of our computational biosensing platform, we demonstrate multiplexed detection of protein mono- and bilayers. Figure 4a and 4b show the schematic view and the diffraction patterns of the analyzed microarray pixels, respectively. Here, the microarray pixels enumerated from ‘1’ to ‘6’ correspond to the bare sensors, and ‘M’ and ‘B’ correspond to the same sensors after introducing protein monolayer (M) containing bovine serum albumin (BSA, 0.5% v/v), and protein bilayer (B) containing 0.5 mg mL\(^{-1}\) protein A/G and 0.5 mg mL\(^{-1}\) protein IgG, respectively.\(^9\) Here, approximately 150 pL protein solution is precisely introduced on the individual sensor pixel using a protein nanospotter.\(^1\) BSA has a molecular weight of 66 kDa and forms a very thin layer on our plasmonic substrate, approximately 3 nm.\(^1\) Figure 4c shows the transmission spectrum of our nanohole array before and after the presence of the protein layers. Initially, for the 6 bare pixels, the plasmonic mode has an average resonance wavelength of \(\sim\)690.3 nm, with a standard deviation (s.d.) of 0.74 nm. For the 3 pixels that are covered with protein monolayer, the plasmonic mode shifts to 696.5 nm (s.d.=0.21 nm) and for the remaining 3 pixels with protein bilayer, it shifts to 707.4 nm (s.d.=0.77 nm). As clearly seen by the lens-free diffraction pattern images in Figure 4b, monolayer spotted sensors look brighter than the bilayer spotted ones due to the additional 11 nm shift from the LED peak wavelength. Figure 4d shows the statistical analysis of our plasmonic pixels, demonstrating a good correlation between the resonance wavelength shift and the relative intensity difference corresponding to mono- and bilayers.
Quantitative analysis of binding events using lens-free on-chip detection

Our on-chip plasmonic biosensing platform can also be utilized for quantitative analysis of binding events, providing precise concentration of target biomolecules bound to the plasmonic substrates. Towards this end, we demonstrate the quantification of a single-type of protein in a large variety of concentrations, spanning from microgram per milliliter to milligram per milliliter range. Furthermore, we image reference and target plasmonic microarray pixels simultaneously on the same chip to quantify the binding events on the target sensors, engineering a robust self-calibrated biodetection system that operates independent of the LED intensity variations from measurement to measurement. To illustrate this, Figure 5a shows lens-free diffraction patterns of six different sensors where (i) the pixels denoted by ‘M’ are the reference sensors and their spectral responses stay constant through the whole concentration experiment; and (ii) the pixels denoted by ‘B’ are the target sensors used for our concentration analysis. In these measurements, reference sensors are initially covered with BSA to block nonspecific binding events on these pixels, and the target sensors are covered with protein A/G (≈ 4 mg mL⁻¹) for capturing protein IgG on the sensor surface. In more complex sample matrices, custom designed blocking agents can also be used, in a similar fashion, to reduce nonspecific molecular bindings. Note that the BSA and A/G pixels provided comparable level of spectral shift and transmitted signal intensity, indicating that similar amount of biomass bound to the reference and target pixels. Target pixels have then been processed with 8 different IgG concentrations, ranging from 3.9 µg mL⁻¹ to 1000 µg mL⁻¹. Figure 5b shows the average spectral response, measured by an optical spectrum analyzer, of the reference and the target sensors for different protein concentrations demonstrating that the plasmonic mode consistently shifts to longer wavelengths as the concentration increases. The statistical analysis calculated from the optical spectrum analyzer measurements in Figure 5c shows that the difference in the average resonance shift value for the target pixels spanning a range from 2.95 nm to 27.1 nm. In the figure inset, we show the relationship between the spectral shift in the plasmonic mode and the IgG concentration. In the low concentration range (e.g., 3.9–100 µg mL⁻¹), the plasmonic mode red-shifts linearly with increasing IgG concentration, whereas it shows minor variations at high concentrations (250–1000 µg mL⁻¹) due to saturation of binding sites. Calculated from the lens-free images, the corresponding intensity difference analysis in Figure 5d reveals a minimum detectable intensity difference of 0.024 (a.u.) as denoted by the red curve which corresponds to a minimum detectable wavelength shift of 3 nm for the transmission resonance from its initial position. Note that this 3 nm limit of detection can also be converted into a refractive index sensitivity of 621 nm RIU⁻¹, corresponding to a minimum detectable refractive index change of ~4×10⁻⁵ RIU (see Supplementary Figs. S4 and S5 for the same analysis conducted using an optical spectrum analyzer). These results summarized in Figures 4 and 5 confirm that our plasmonic biosensing approach is highly promising for simultaneous detection of different biomolecules over a wide range of concentrations using the same field-portable and cost-effective handheld platform.

The presented computational high-throughput biosensing platform lends itself to a light-weight and compact point-of-care diagnostic tool that can potentially provide real-time results without the need for any trained professionals. Although such on-chip sensing
platform holds promise as a field-deployable and cost-effective handheld diagnostics device, especially for developing countries, it is important to note that our lens-free imaging platform has relatively higher detection limits (in the order of ~µg mL^{-1}) compared to other plasmonic sensing approaches such as conventional SPR-based platforms. In order to systematically improve our detection limits (down to ng mL^{-1}), we can explore several avenues: (i) spectrally narrow chip-based optoelectronic excitation sources, e.g., laser diodes or resonant-cavity enhanced LEDs can be employed to determine the minute spectral variations in the plasmonic modes; (ii) superior plasmonic designs achieving much sharper plasmonic resonances with stronger near-field enhancements, such as Fano resonant structures, can be implemented; (iii) the spectral shifts in the transmission resonance of the nanoapertures can be more sensitively tracked by acquiring multiple lens-free images (i.e., each with a different color LED). These lens-free frames can then be digitally merged, producing higher contrast differences between the reference and target images; (iv) better CMOS/CCD imagers, equipped with cooling circuits, can be employed in this plasmonic sensing platform achieving higher sensitivities; (v) advanced computational reconstruction approaches, e.g., based on convex optimization, can be applied to the diffractive images of the plasmonic chips; and (vi) nanoparticle based assays can be also functionalized on the same plasmonic substrates improving the binding sites of biomolecules, and further enhancing the contrast of the low-density biomolecules detected through improved lens-free diffraction patterns. A major advantage of using nanoparticles in this on-chip biosensing platform would be to increase the near-field interactions between the biomolecules and the surface plasmon waves up to the penetration depth of evanescent waves (< 200 nm). In our current plasmonic biosensing work, the binding events occur on a planar plasmonic substrate, limiting the near-field interactions only to the surface of the gold layer. Therefore, nanoparticles with diameters of 200–300 nm could provide additional three-dimensional binding sites, increasing the interactions of the biomolecules and surface plasmons. The proof of concept of such an approach is already illustrated in Supplementary Figs. S6 and S7, where streptavidin-coated nanoparticles bound to the plasmonic substrates can be detected using our on-chip biosensing platform, creating an enhanced contrast of the lens-free diffraction images after the binding events. Using a systematic investigation of the avenues
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1 Wei F, Patel P, Liao W, Chaudhry K, Zhang L et al. Electrochemical sensor for multiplex biomarkers detection. Clin Cancer Res 2009; 15: 4444–4452.
2 Oikonomopoulou K, Li L, Zheng Y, Simon I et al. Prediction of ovarian cancer prognosis and response to chemotherapy by a serum-based multiparametric biomarker panel. Br J Cancer 2008; 99: 1103–1113.
3 Kozak RK, Su F, Whitelegge JP, Fauli K, Reddy S et al. Characterization of serum biomarkers for detection of early stage ovarian cancer. Proteomics 2005; 5: 4589–4596.
4 Myers FB, Lee LP. Innovations in optical microfluidic technologies for point-of-care diagnostics. Lab Chip 2008; 8: 2015–2031.
5 Chin CD, Linder V, Sia SK. Lab-on-a-chip devices for global health: past studies and future opportunities. Lab Chip 2007; 7: 41–57.
6 Linder V. Microfluidics at the crossroad with point-of-care diagnostics. Analyst 2007; 132: 1186–1192.
7 Warsinie A. Point-of-care testing of proteins. Anal Bioanal Chem 2009; 393: 1393–1405.
8 Dungchai W, Chailapakul O, Henry CS. Electrochemical detection for paper-based microfluidics. Anal Chem 2009; 81: 5821–5826.
9 Jokster Jv, McDevitt JT. Programmable nano-bio-chips: multifunctional clinical tools for use at the point-of-care. Nanomedicine 2010; 5: 143–155.
10 Chin CD, Linder V, Sia SK. Commercialization of microfluidic point-of-care diagnostic devices. Lab Chip 2012; 12: 2118–2134.
11 Sia SK, Kricka LJ. Microfluidics and point-of-care testing. Lab Chip 2008; 8: 1982–1983.
12 Chin CD, Lakasanopin T, Cheung YK, Steinmiller D, Linder V et al. Microfluidics-based diagnostics of infectious diseases in the developing world. Nat Med 2011; 17: 1015–1019.
13 Peeling RW, Mabey D. Point-of-care tests for diagnosing infections in the developing world. Clin Microbiol Infect 2010; 16: 1062–1069.
111 Artar A, Yanik AA, Altug H. Fabry-Perot nanocavities in multilayered crystals for enhanced biosensing. Appl Phys Lett 2009; 95: 051105.

112 Lalanne P, Rodier JC, Hugonin JP. Surface plasmons of metallic surfaces perforated by nanohole arrays. J Opt A—Pure Appl Opt 2005; 7: 422–426.

113 Cetin AE, Yanik AA, Yilmaz C, Samu S, Busnaina AA et al. Monopole antenna arrays for optical trapping, spectroscopy and sensing. Appl Phys Lett 2011; 98: 111110.

114 Goodman JW. Introduction to Fourier Optics. New York: McGraw-Hill; 1968.

115 Huang M, Galarreta B, Artar A, Adato R, Aksu S et al. Reusable nanostencils for creating multiple biofunctional molecular nanopatterns on polymer substrate. Nano Lett 2012; 12: 4817–4822.

116 Wright AK, Thompson MR. Hydrodynamic structure of bovine serum albumin determined by transient electric birefringence. Biophys J 1975; 15: 137–141.

117 Figueira VB, Jones JP. Viscoelastic study of the adsorption of bovine serum albumin on gold and its dependence on pH. J Colloid Interface Sci 2008; 325: 107–113.

118 Wu CW, Khankina AB, Adato R, Arju N, Yanik AA et al. Fano-resonant asymmetric metamaterials for ultrasensitive spectroscopy and identification of molecular monolayers. Nat Mater 2012; 11: 69–75.

119 Artar A, Yanik A, Altug H. Directional double Fano resonances in plasmonic hetero-oligomers. Nano Lett 2011; 11: 3694–3700.

120 Kim SJ, Koh K, Lustig M, Boyd S, Gorinevsky D. An interior-point method for large-scale $l_1$-regularized least squares. IEEE J Sel Topics Signal Process 2007; 1: 606–617.

121 Donoho DL. Compressed sensing. IEEE Trans Inf Theory 2006; 52: 1289–1306.

122 Candes EJ, Romberg JK, Tao T. Stable signal recovery from incomplete and inaccurate measurements. Comm Pure Appl Math 2006; 59: 1207–1223.

123 Conchello JA. Superresolution and convergence properties of the expectation-maximization algorithm for maximum-likelihood deconvolution of incoherent images. J Opt Soc Am A Opt Image Sci Vis 1998; 15: 2609–2619.