Sensors

DOI: 10.1002/anie.201206804

Surface Plasmon Resonance Chemical Sensing on Cell Phones**

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Decentralized chemical sensing for environmental or medical diagnostic uses is an emerging field, which can be approached from diverse perspectives. Dedicated instruments constitute the classical solution,[1–3] but are hampered by limited deployment, common to market introduction of new appliances. An alternative strategy capitalizes on the widespread dissemination and versatility of standard consumer electronic devices (CEDs) as measuring platforms, since chemical sensing devices can be adapted for interrogation by flatbed scanners,[4,5] DVD/CD drives,[6] radio frequency identification (RFID) systems,[7] compact cameras,[8] and cell phones.[9–13] Cell phones offer the most ubiquitous CED infrastructure, and their extensive features and continuously increasing capabilities entail residual resources for chemical sensing functions.

CED sensing ubiquity is restricted by the availability of the chemical sensing element and accessories rather than the CED platform itself. Hence, the critical requirements for cell phone applications are: the development of chemical sensing interfaces deployable at a comparable scale and the formulation of solutions, which demand neither permanent modifications nor additional peripherals.

Disposable devices can satisfy these requirements, if the measurement principle can accommodate the desired analytical performance. In this work, surface plasmon resonance (SPR), which is an established label-free detection method,[14] is examined, because of its performance and compatibility with cell phone capabilities.

Herein we demonstrate the first angle-resolved surface plasmon resonance (SPR) detection system that is based on a single disposable device, which is configured to use conditioned illumination and optical detection from cell phones.

The SPR coupler central to this implementation is compatible with regular lab-on-a-chip (LOC) technology and temporarily adheres to the phone screen surface during the measurement; it couples and conditions the illumination from the screen and directs the SPR image to the phone camera. After the measurement the device can be detached and disposed of, thereby leaving the phone intact.

SPR detection is illustrated with a commercial assay for β_2 microglobulin (β_2M),[15] which is an established marker[16,17] for cancer, inflammatory disorders, and kidney disease, which are deemed candidates for complementary monitoring in decentralized conditions; moreover SPR detection is also illustrated with a custom-made chip including embedded calibration.

In SPR, illumination is configured to excite a plasmon at the surface of a thin metal film;[14,18] the effect of the plasmon is observed as a characteristic dip in the reflected light as a function of the illuminating angle and energy. Changes in the optical properties at the metal surface are sensitively transduced as changes in the coordinates of the dip and can be used for sensing purposes.[14] SPR is a reference method for the study of biomolecular interactions and label-free biosensing, and measurements are frequently implemented with laboratory instruments, although compact devices aimed at point-of-care applications have also been developed.[19,20]

SPR is remarkably well-suited to the light sources and cameras available in commercial cell phones, tablets, and laptops, by contrast with fluorescence measurements, which demand intense light sources, usually secured by accessory permanent parts.[10,11] Cell phone displays, typically between 300 and 500 nits in current models, are sufficient to illuminate SPR experiments. Moreover, the displays naturally provide the wide-angle illumination required to configure angle-resolved SPR experiments, and, depending on the display technology, the linear polarizer may also be embedded.

The dynamic range of cell phone cameras is rather limited, which can impair accurate intensity detection, whereas for angle-resolved SPR experiments a moderate contrast pattern is produced, which suffices to register the angular position of the SPR dip, since response quantification is here related to the spatial resolution of the detector. Modern front cell phone cameras are typically of VGA resolution (640×480 pixels or 0.3 MP) and currently progressing to 2 MP, whereas intensity measurements are limited to 256 levels/channel. Hence, most phone cameras can capture angle-resolved SPR images, once fitted with a suitable optical coupler.

In the experimental arrangement used in this work (Figure 1 a), the light source is supplied by an image displayed in the cell phone screen, in this case a red rectangle, and a white frame outlines the placement of the optical coupler. The coupler is a disposable optical element made of polydimethylsiloxane (PDMS) rubber and epoxy with a refracting index that matches that of glass (EPO-TEK 301-1, $n = 1.5$). The epoxy is needed to attain the necessary illuminating angles to capture the SPR dip for an Au/water interface under red illumination.

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[**] This work has been supported by a grant from the Linköping Centre for Life Science Technologies (LIST), Sweden, and a PhD scholarship from Thammasat University of Thailand for P.P.)

Supporting information for this article is available on the WWW under http://dx.doi.org/10.1002/anie.201206804.

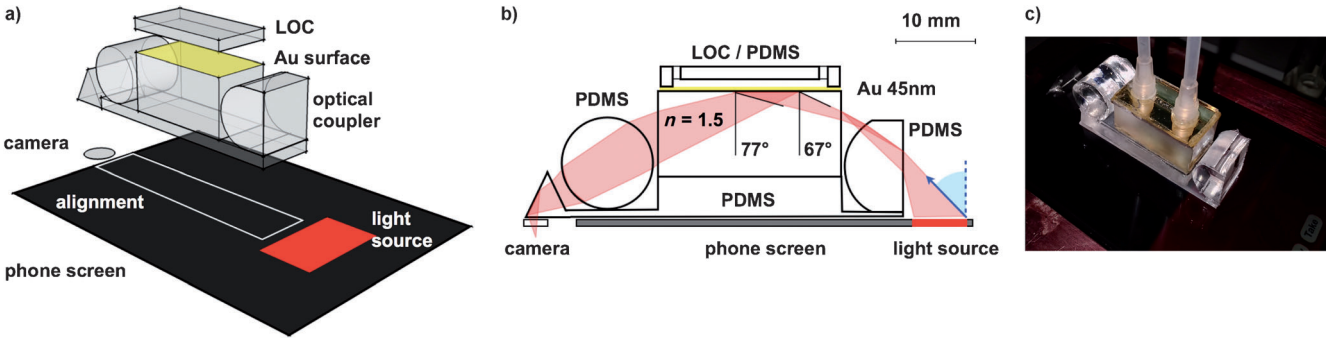

Figure 1. a) 3D Scheme of a representative setup for angle-resolved SPR using screen illumination and front camera detection optically coupled by a disposable device. b) 2D raytrace of the experimental arrangement showing the light path from screen to camera. c) Picture of the actual experimental arrangement.

The polymer surface is terminated by a glass that is coated by 45 nm of thermally evaporated gold. The glass simplifies fabrication, since Au needs to be deposited only once, independently of the coupler; however, for scalable fabrication, direct Au deposition on the epoxy surface is also possible. The PDMS base of the structure gently adheres to the screen surface, thus providing adequate optical and mechanical coupling, and leaves the screen intact upon removal.

On the Au surface simple fluidics or more advanced lab-on-a-chip devices, which are compatible with regular fabrication technologies, can be used for sample conditioning.

To configure the necessary illuminating angular range, the PDMS plano-cylindric element collects screen illumination and directs it to an 8 mm long region at the Au interface (raytrace Figure 1 b). Phone screens are composed of numerous pixels (units of three elements below eye resolution; these units emit red, green, and blue light of controlled intensity to generate millions of colors). Each pixel emits with a particular angular distribution (the light-blue area in Figure 1 b indicates half of the symmetric emission from one pixel) and covers an angular range by its relative position with respect to the PDMS plano-cylindric element, which selects the illuminating range for the Au interface.

Although different phones differ in screen, pixel pitch, and pixel design, wide view angle screens are a common feature, which easily complies with SPR illumination requirements. Main results of this work correspond to an iPod Touch/iPhone-type platform, but other screens deliver equivalent performance using the same coupler (Figure S2 in the Supporting Information).

Light reflected from the Au interface carries the angle-resolved SPR signal, but the signal requires conditioning for acquisition by the phone front camera; this conditioning is provided by a PDMS cylindrical element with a final deflection by total internal reflection in a PDMS prism (Figure 1 b). The complete setup on an iPod Touch (4th generation, 960 × 640 pixel screen resolution, 640 × 480 pixel camera resolution; equivalent to iPhone 4 and 4S devices) is illustrated in Figure 1 c.

The acquired SPR image for red illumination, as well as the region of interest (ROI) selected for analysis (white frame) and the ROI images for red and green illuminations are illustrated in Figure 2 a. The images show contrast patterns darkening proportionally to the dip in reflected light, as a function of illuminating angle. Different illuminat-

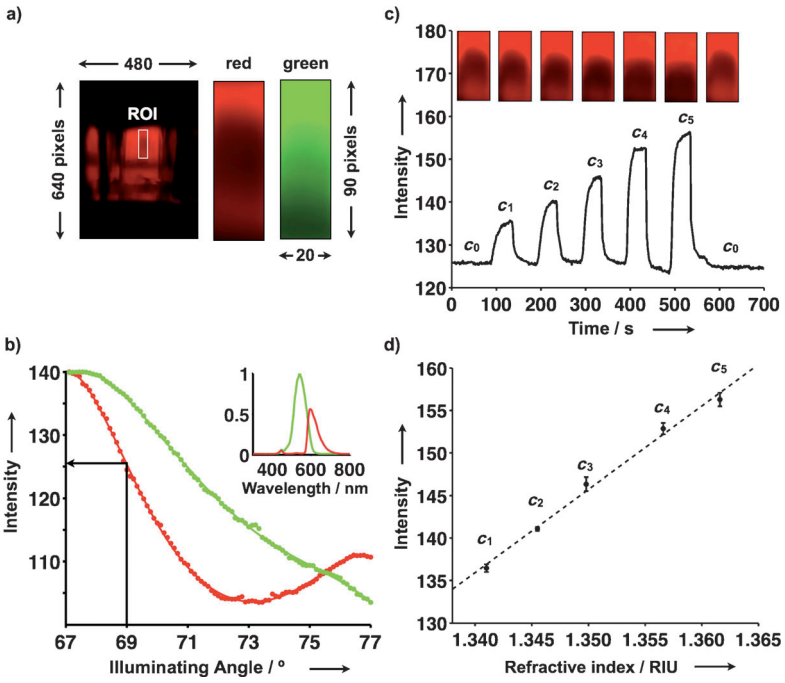

Figure 2. a) Angle-resolved SPR image measured under red illumination, and regions of interest (ROIs) used for evaluation under red and green illuminations. b) Angle-resolved SPR signals extracted from the ROIs in (a) and measured in a 2 mm × 50 µm cross-section channel. The inset shows the spectral radiance of the red and green illuminations used in this experiment. c) Time response at constant angle (indicated in (b)) for solutions of known refractive index measured under red illumination. d) Steady-state SPR response vs. refractive index units (RIU) from which the sensitivity and resolution is calculated. c_0–c_5 indicate five different concentrations of ethanol in water.

ing colors probe the energy dependence to provide a simple rendition of spectroscopic SPR. As predicted by theory[21] the SPR under green illumination has its dip shifted towards higher angles. The screen illumination does not supply monochromatic bands but rather wide spectral radiances in the red and green regions of the visible spectrum (inset Figure 2b and Figure S2 in the Supporting Information for comparison with Nokia and Android devices). This feature widens the dip with respect to monochromatic illumination but remains usable for detection nonetheless, as demonstrated elsewhere.[22]

The resulting angle-resolved SPR signals for red and green illumination bands are shown in Figure 2b. A 10° range covering the SPR dip in the red band is represented by 90 pixels in the acquired image, thus resulting in an angular resolution of 0.111°/pixel. This resolution is attainable with almost any cell phone with a VGA front camera. Increased resolution, emerging in new phone models, will improve this feature.

Appropriate software is required to command image acquisition while displaying the desired light source (Figure 1a). In the case of the iPhone/iPod Touch platforms this configuration was implemented with an application developed for Apple's mobile operating system (iOS 5), which enables to set and lock the camera exposure (exposure time and ISO number) to measure all signals in identical conditions—an important requirement for SPR sensing and optical chemical sensing in general.

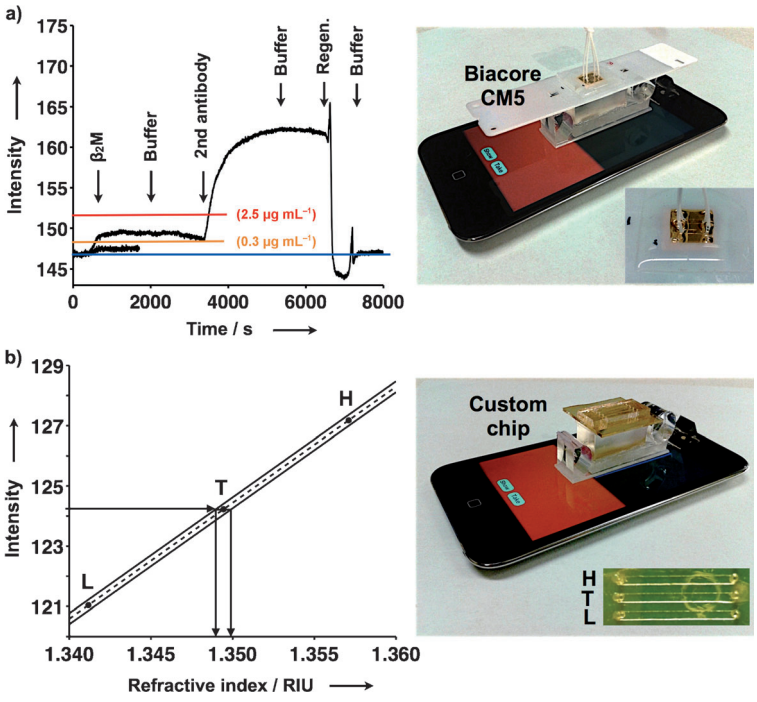

Figure 3. a) Interaction analysis of a commercial Biacore CM5 test chip functionalized for β_2 microglobulin detection and tested at 1.32 $\mu g\,mL^{-1}$ and 0.132 $\mu g\,mL^{-1}$ concentrations. The baseline of the measurement is indicated with a blue line, while red and orange lines indicate normal serum ($<2.5\ \mu g\,mL^{-1}$) and urine ($<0.3\ \mu g\,mL^{-1}$) levels, respectively. b) Test chip with embedded calibrations (H and L for high and low references) providing direct quantification of the unknown test value (T). The two solid lines in (b) indicate the error margin.

Typical sensitivity and resolution are characterized by the results of Figure 2c,d. A single-channel PDMS chip is attached to the Au surface and solutions of known refractive index are circulated at constant flow rate. The intensity at constant angle (indicated in Figure 2b) is measured from the curve fitting of the angle-resolved SPR acquired at a rate of 1 photo/s. Steady-state values and three-σ error bars from these measurements show a linear behavior (Figure 2d) from which a sensitivity of 11×10^{-3} RIU/° can be calculated, which compares favorably with established compact SPR instruments[19] also rated at 11×10^{-3} RIU/°. For the measured noise level in the primary signal (red channel intensity) of 0.31%, the platform has a resolution of 2.14×10^{-6} RIU, which is again comparable with compact SPR devices (1×10^{-6} RIU), while using an ROI that is just 90 pixels long. Considering the representation of the SPR in 640 pixels (total use of VGA resolution), the ultimate resolution for VGA cameras would be 2.96×10^{-7} RIU.

The performance of the SPR system with a commercial test chip (Biacore sensor chip CM5) is illustrated in Figure 3a. In this example, the chip was functionalized with a monoclonal mouse-anti-human β_2 microglobulin. Figure 3a shows the interaction analysis with β_2 microglobulin (1.32 $\mu g\,mL^{-1}$ and 0.132 $\mu g\,mL^{-1}$). The response indicates useable signals even for the lowest concentration without the need of the enhancement antibody (polyclonal rabbit-anti-human β_2 microglobulin), thus simplifying the implementation. Very little nonspecific binding and bulk contribution is expected for this analyte concentrations,[15] and the results fairly reflect the platform performance and a limit of detection of about 0.1 $\mu g\,mL^{-1}$ of β_2M. This performance is adequate for detection in the clinical range, which identifies as normal levels[23] values below 2.5 $\mu g\,mL^{-1}$ (red line in Figure 3a) in serum and 0.3 $\mu g\,mL^{-1}$ in urine (orange line in Figure 3a). Numerous other targets are known to be detectable in relevant concentrations with SPR methods and consequently compatible with this concept (see the Supporting Information for details).

The use of embedded calibrations is crucial in ubiquitous instrumentation systems,[4,8,9] hence the final example (Figure 3b) involves a custom-made chip including calibration channels integrated in the device, and represents a simpler format closer to autonomous lab-on-a-chip instrumentation, which could capitalize decentralized uses of this platform. In this approach the reference and test channels are simultaneously imaged. From the calibration channels (with known high (H) and low (L) values) the range of the linear response is measured, and the test concentration can thus be directly determined. In this case, the test resulted in a value of (1.3494 ± 0.0005) RIU, properly containing the $n=1.3498$ true value of the solution.

The demonstrated concept operates as a disposable single element, which does not require additional accessories and is capable to operate on varied cell phones. Thus, the optical coupler is a generic support to run diverse SPR experiments, from classical affinity assays with commercial chips, to custom-made tests oriented to autonomous LOC operation.

Current cell phones provide the performance required for chemical sensing, thereby rendering this platform viable to develop tests that may complement routine monitoring. The fact that this technology is based on a single disposable element that can operate on unmodified ubiquitous cell phones makes it an attractive possibility to implement decentralized chemical sensing on a wide scale.

Received: August 22, 2012
Published online: October 16, 2012

Keywords: analytical methods · cell phone · sensors · surface plasmon resonance

[1] P. Yager, T. Edwards, E. Fu, K. Helton, K. Nelson, M. R. Tam, B. H. Weigl, *Nature* **2006**, *442*, 412 – 418.
[2] C. D. Chin, V. Linder, S. K. Sia, *Lab Chip* **2007**, *7*, 41 – 57.
[3] D. S. Boyle, K. R. Hawkins, M. S. Steele, M. Singhal, X. Cheng, *Trends Biotechnol.* **2012**, *30*, 45 – 54.
[4] N. Rakow, K. Suslick, *Nature* **2000**, *406*, 710 – 712.
[5] S. H. Lim, L. Feng, J. W. Kemling, C. J. Musto, K. S. Suslick, *Nat. Chem.* **2009**, *1*, 562 – 567.
[6] R. A. Potyrailo, W. G. Morris, A. M. Leach, L. Hassib, K. Krishnan, C. Surman, R. Wroczynski, S. Boyette, C. Xiao, P. Shrikhande, A. Agree, T. Cecconie, *Appl. Opt.* **2007**, *46*, 7007 – 7017.
[7] R. A. Potyrailo, A. Burns, C. Surman, D. J. Lee, E. McGinniss, *Analyst* **2012**, *137*, 2777 – 2781.
[8] D. Filippini, A. Alimelli, C. D. Natale, R. Paolesse, A. D'Amico, I. Lundström, *Angew. Chem.* **2006**, *118*, 3884 – 3887; *Angew. Chem. Int. Ed.* **2006**, *45*, 3800 – 3803.
[9] A. W. Martinez, S. T. Phillips, G. M. Whitesides, *Proc. Natl. Acad. Sci. USA* **2008**, *105*, 19606 – 19611.
[10] D. Breslauer, R. Maamari, N. Switz, W. Lam, D. Fletcher, *PLoS One* **2009**, *4*, e6320.
[11] H. Zhu, O. Yaglidere, T. Su, D. Tseng, A. Ozcan, *Lab Chip* **2011**, *11*, 315 – 322.
[12] P. Preechaburana, S. Macken, A. Suska, D. Filippini, *Biosens. Bioelectron.* **2011**, *26*, 2107 – 2113.
[13] B. Y. Won, H. G. Park, *Angew. Chem.* **2012**, *124*, 772 – 775; *Angew. Chem. Int. Ed.* **2012**, *51*, 748 – 751.
[14] J. Homola, *Chem. Rev.* **2008**, *108*, 462 – 493.
[15] Biacore 3000 Getting Started Kit.
[16] B. A. Cunningham, J. L. Wang, I. Bergga°rd, P. A. Peterson, *Biochemistry* **1974**, *12*, 4811 – 4822.
[17] M. Pignone, D. Nicoll, S. J. McPheke, *Pocket guide to diagnostic tests*, McGraw-Hill, New York, **2004**, p. 191.
[18] H. Raether, *Surface Plasmons on Smooth and Rough Surfaces and on Gratings*, Springer, Berlin, **1988**, p. 11.
[19] T. M. Chinowsky, J. G. Quinn, D. U. Bartholomew, R. Kaiser, J. L. Elkind, *Sens. Actuators B* **2003**, *69*, 1 – 9.
[20] X. D. Hoa, A. G. Kirk, M. Tabrizian, *Biosens. Bioelectron.* **2007**, *23*, 151 – 160.
[21] K. Kurihara, K. Suzuki, *Anal. Chem.* **2002**, *75*, 696 – 701.
[22] D. Filippini, F. Winquist, I. Lundström, *Anal. Chim. Acta* **2008**, *625*, 207 – 214.
[23] D. Latt, J. B. Weiss, M. I. V. Jayson, *Ann. Rheum. Dis.* **1981**, *40*, 157 – 160.

