

# Infrared surface plasmon resonance technique for biological studies

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We report on a surface plasmon resonance (SPR) technique based on Fourier-transform infrared spectrometer. In contrast to the conventional surface plasmon technique, operating at a fixed wavelength and at variable angle of incidence, our setup allows the wavelength and the angle of incidence to be varied simultaneously. We explored the potential of the SPR technique in the infrared for biological studies involving aqueous solutions. Using computer simulations, we found the optimal combination of parameters (incident angle and wavelength) for performing this task. Our experiments with physiologically important glucose concentrations in water and in human plasma verified our computer simulations. Importantly, we demonstrated that the sensitivity of the SPR technique in the infrared range is not lower and, in fact, is even higher than that for visible light. We emphasize the advantages of infrared SPR for studying glucose and other biological molecules in living cells. © 2008 American Institute of Physics. [DOI: 10.1063/1.2828162]

## I. INTRODUCTION

In recent years, in the fields of biochemistry and pharmacology, there has been a rigorous and extensive search for label-free techniques capable of quantitatively monitoring biomolecules and their interaction with living cells.<sup>1,2</sup> This can be achieved by measuring the refraction index of solutions with biomolecules. The surface plasmon resonance (SPR) technique is extremely sensitive to small variations in refractive index. SPR is usually excited in the regime of the attenuated total reflectance when a *p*-polarized electromagnetic wave is incident on a metal-coated prism at a certain angle (Kretschmann's geometry).<sup>3</sup> The reflectivity displays a sharp minimum at certain angles/wavelengths that strongly depend on the refraction index of the dielectric medium in contact with the metal. By measuring this angle/wavelength, one can monitor in real time the concentration of a chemical substance in solution<sup>4-7</sup> and in the cell culture as well.<sup>2,8</sup> Most of the SPR techniques utilize glass-based optics, which limits its operation to the visible and near infrared (NIR) range.<sup>2,4,9-11</sup> Here, we examine the advantages offered by the SPR technique in the midinfrared range, up to 12  $\mu\text{m}$ . These advantages are as follows:

- Fast multiwavelength measurements. The ability to detect SPR at varying wavelengths and/or varying angles allows "tuning" the surface plasmon resonance to any desired spectral range in order to achieve the highest sensitivity.
- Since many biomolecules have specific absorption bands in the infrared (so-called "fingerprints"), the tuning of SPR to this spectral range allows these biomolecules to be identified.
- The relatively large penetration depth of the surface plasmon into a dielectric medium (a few microns in the infrared range, which is on the order of the cell

height, as compared to 0.5  $\mu\text{m}$  in the visible range) is beneficial when studying cell cultures.

The main disadvantage of the IR range when using the SPR technique is the large water absorption and lack of convenient laser sources. At first glance, this may result in a lower sensitivity with respect to biomolecules in aqueous solutions. However, we demonstrate here that by clever choice of parameters (wavelength, angle of incidence, and conducting film thickness), one can achieve high enough sensitivity. To determine the sensitivity of our SPR-Fourier-transform IR (FTIR) technique, we chose glucose in water as a test case. Briefly, we measured small and physiologically important glucose concentrations (1–50 mM) in water as well as in human plasma. We achieved a sensitivity that is comparable or even higher than that for the visible range. This may suggest that the SPR-FTIR technique is an excellent tool for studying biomolecules and living cells in aqueous solutions.

## II. SENSITIVITY CONSIDERATIONS: OPTIMAL PARAMETERS FOR SENSITIVE DETECTION OF GLUCOSE IN AQUEOUS SOLUTION USING SPR IN THE INFRARED

The SPR sensitivity is limited by conductor losses and by absorption and scattering in the dielectric. In water, optical absorption in the visible range is low and the sensitivity of the SPR technique is limited by conductor loss in the metallic film. Silver is the best metal for the SPR technique in the visible range. In the infrared range, however, the situation is different. Indeed, the imaginary part of the SP wave vector is determined by the conductor loss,  $k_{\text{sp}}'' \sim \varepsilon_m''/2(\varepsilon_m')^2$ , where  $\varepsilon_m'$  and  $\varepsilon_m''$  are real and imaginary parts of the metal dielectric constant. The dielectric constant of the gold is  $\varepsilon_{\text{Au}} = -238.8 + i37.35$  at  $\lambda = 2.48 \mu\text{m}$  and  $\varepsilon_{\text{Au}} = -9.895 + i1.05$  at  $\lambda = 0.652 \mu\text{m}$ .<sup>12</sup> The conductor losses in the infrared are lower,  $k_{\text{sp}}'' = 0.00033$  and  $0.0054 \mu\text{m}^{-1}$ , at 2.48 and 0.652  $\mu\text{m}$ , correspondingly. The best choice of a metal for  $\lambda > 1.5 \mu\text{m}$  is gold, although other metals, such as

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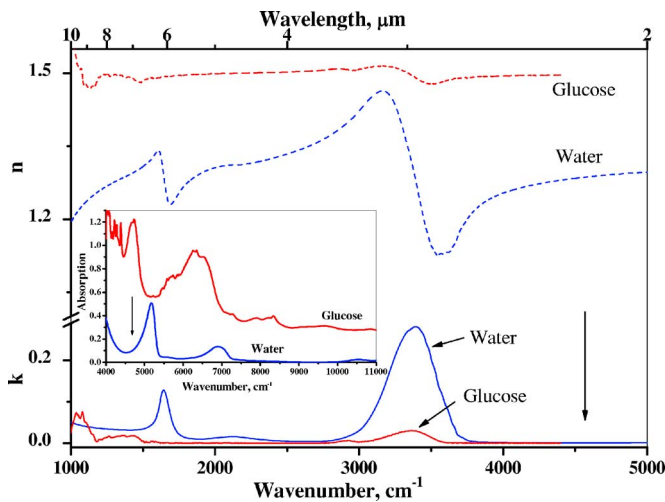


FIG. 1. (Color online) Real ( $n$ ) and imaginary ( $k$ ) parts of the refractive index of water and of the dry D-glucose (based on data of Refs. 12 and 13). Inset shows FTIR absorption spectra of water (our measurements) and dry D-glucose (Bruker, Inc. database). The arrow shows our working point (SPR minimum) that corresponds to the glucose absorption peak (see inset) and the maximum difference between the refractive indices  $n$  for water and glucose.

silver and copper should also work well. However, the sensitivity of the SPR technique in the infrared range is limited by the dielectric losses in water. Therefore, to achieve high sensitivity for a certain type of biomolecule (glucose in our present work), one should carefully choose the wavelength range where water absorption is not high enough.

Figure 1 shows the real and imaginary parts of the refraction index  $n+ik$  of pure water and dry glucose calculated based on the data of Refs. 12 and 13. We note that across the wavelength range from 2 to 10  $\mu\text{m}$ , the water absorption is high, compared with that of glucose. Therefore, absorption spectroscopy is inefficient in measuring glucose in water. However, note the large differences in the real part of the refraction indices of water and glucose, especially in the range of 2.5–3  $\mu\text{m}$ . By measuring the difference in the real part of the refraction indices of pure water and of the water-glucose solution, we can measure the glucose concentration. The sensitivity of the SPR technique to small variations in the refractive index depends in a complicated way on conductor thickness  $d$ , wavelength  $\lambda$ , incident angle  $\Theta$ , and the average refraction index of solution  $n_{\text{solution}}$ ,<sup>9,10,14,15</sup> so choosing the most sensitive configuration represents a serious task. In the following paragraphs, we discuss how to find the optimal combination of  $\lambda$  and  $\Theta$  in order to achieve the highest sensitivity to glucose in water. A similar strategy can be applied to biomolecules other than glucose.

In our experiments, the surface plasmon is excited using Kretschmann's geometry based on a ZnS prism coated with a 12 nm thick gold film. To optimize the sensitivity of this setup, we studied numerically how the reflectivity of the ZnS/Au/water interface,  $R_{\text{water}}$ , depends on the wavelength and incident angle. The simulations were based on the Fresnel reflectivity formulas.<sup>3</sup> Figure 2 shows computed reflectivity versus wavelength and incident angle. The surface plasmon resonances correspond to black regions. The angle where the SP resonance occurs is determined by the water

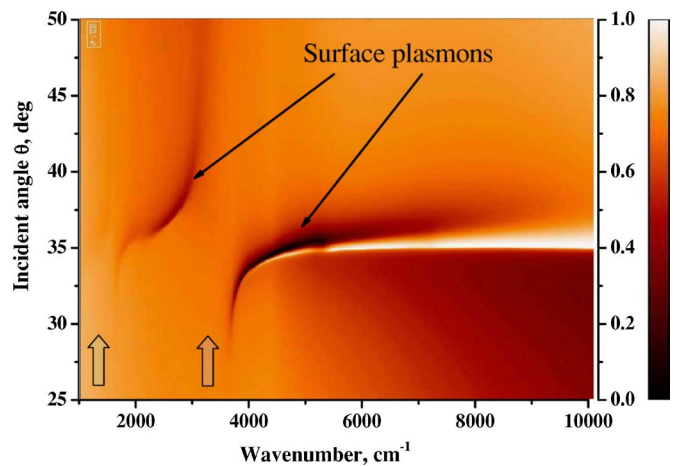


FIG. 2. (Color online) Computer simulation based on the Fresnel reflectivity formulas of the reflectivity from the ZnS/Au/water interface vs wavelength and angle of incidence,  $\Theta$  (this is the angle between the beam direction in the ZnS and the normal to the ZnS-water interface). The narrow dark areas correspond to the surface plasmon resonance. Thick arrows indicate water absorption peaks. The Au film thickness is 12 nm.

refraction index. The gaps in Fig. 2 where surface plasmon resonance disappears (note thick arrows in Fig. 2 at 1600 and 3400  $\text{cm}^{-1}$ ) correspond to the regions of anomalous dispersion in Fig. 1.

To estimate the optical reflectivity of the water-glucose solution, we need to know its complex refractive index over a wavelength range of 2–12  $\mu\text{m}$ . Our estimate is based on effective-medium approximation,<sup>16</sup>

$$\varepsilon_{\text{solution}} = \varepsilon_{\text{water}} \left( 1 + 3c_{\text{glucose}} \frac{\varepsilon_{\text{glucose}} - \varepsilon_{\text{water}}}{\varepsilon_{\text{glucose}} + 2\varepsilon_{\text{water}}} \right). \quad (1)$$

Here,  $c_{\text{glucose}}$  is the volume concentration of glucose and  $\varepsilon$  is the complex dielectric constant (which is wavelength dependent). The complex refractive index was found from the equation  $n_{\text{solution}} = (\varepsilon_{\text{solution}})^{1/2}$ .

In the limit of small concentrations,  $c < 15\%$  (that corresponds to 83.3 mM), Eq. (1) yields a linear dependence on concentration. In particular, at  $\lambda = 2.5 \mu\text{m}$ , the refraction index is  $n = 1.25 + 4.2 \times 10^{-5}c$ , whereas at  $\lambda = 0.586 \mu\text{m}$ , it is  $n = 1.33 + 2.57 \times 10^{-5}c$  (here,  $c$  is in mM). This linear dependence for the visible range has been verified experimentally in several works;<sup>5,6,17</sup> hence, we believe that Eq. (1) is valid for the infrared range as well.

In the next step, we calculated the reflectivity for a similar system, but we replaced the pure water with a 0.3% D-glucose solution. We analyzed the difference,  $\Delta R = R_{\text{water}} - R_{\text{solution}}$ , and found that it is most pronounced at the wavelength-angle range, which corresponds to the surface plasmon resonances (black areas in Fig. 2). The highest  $\Delta R$  was achieved for  $\theta = 34^\circ$  and  $\lambda \sim 3700\text{--}5000 \text{ cm}^{-1}$ . In principle,  $\Delta R$  can be further increased by the proper choice of Au film thickness.<sup>9</sup>

Next, we estimated the SPR sensitivity to refractive index variation. Note that under conditions of surface plasmon resonance, the dependence of the reflectivity on the refraction index is a nonlinear function that can be linearized only in a very small range of refraction index variations. To esti-

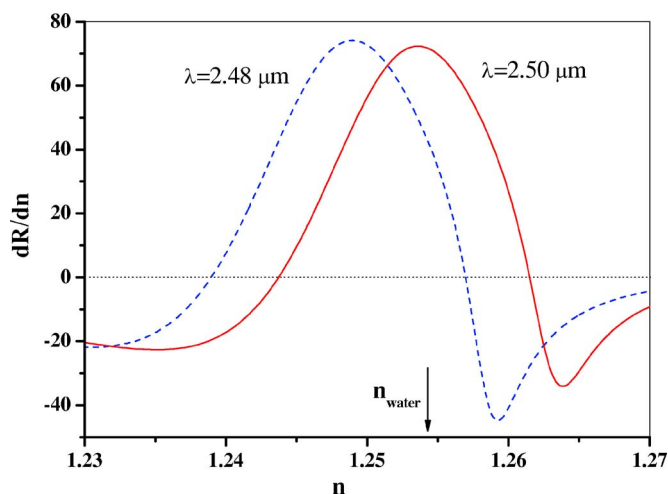


FIG. 3. (Color online) Calculated sensitivity of the SPR technique to refractive index variations (based on Fig. 2).  $\theta=34^\circ$ . The continuous line stands for  $\lambda=2.50\ \mu\text{m}$ ; the dashed line stands for  $\lambda=2.48\ \mu\text{m}$

mate the sensitivity, we calculated the reflectivity of a hypothetical solution that has the same loss tangent as water but whose refractive index is slightly different. Figure 3 shows that  $S=dR/dn$  (at a fixed angle where  $\theta=34^\circ$ ) strongly depends on the average refractive index. The maximum sensitivity is  $S_{\text{max}}=75\ (\text{RIU})^{-1}$ ; where RIU stands for refractive index unit for pure water, this is achieved at  $\lambda=2.49\ \mu\text{m}$ . When the average refractive index of the solution deviates from that of the water by more than 0.5%, the sensitivity decreases by a factor of 2, which defines the dynamic range of the SPR technique. In the context of glucose in water, this means that if we wish to measure the glucose concentration in water by measuring infrared reflectivity under surface plasmon resonance and using the linear relation  $R=R_0+S_{\text{max}}c\,dn/dc$ , we are limited to glucose concentrations of less than  $c_{\text{glucose}}<50\ \text{mM}$ . If we wish to measure higher glucose concentrations or to measure glucose in media with a slightly different average refractive index (for example, human plasma), we must use a different angle of incidence or a different wavelength ( $\lambda=2.48\ \mu\text{m}$  in our case).

### III. EXPERIMENTAL

Figure 4 schematically shows our experimental setup. A tungsten lamp of the Bruker Equinox 55 FTIR spectrometer, equipped with the KBr beam splitter, served as our light source. Briefly, the infrared beam is emitted from the external port of the spectrometer and passes through a collimator, consisting of a 1 mm diameter pinhole mounted between two gold-coated off-axis parabolic mirrors with focal lengths of 76.2 and 25.4 mm, correspondingly. The diameter of the collimated beam is 4 mm. This beam passes through the grid polarizer (Specac, Ltd.) and is reflected from the right-angled gold-coated ZnS prism (ISP Optics, Inc.) mounted on a rotating table. Another parabolic mirror focuses the reflected beam onto the liquid-nitrogen-cooled HgCdTe (MCT) detector that is mounted on a separate rotating table. A temperature-stabilized flow cell with a volume of 0.5 mL is in contact with the gold coating. The gold film thickness is  $d_{\text{Au}}=12\text{--}18\ \text{nm}$ .

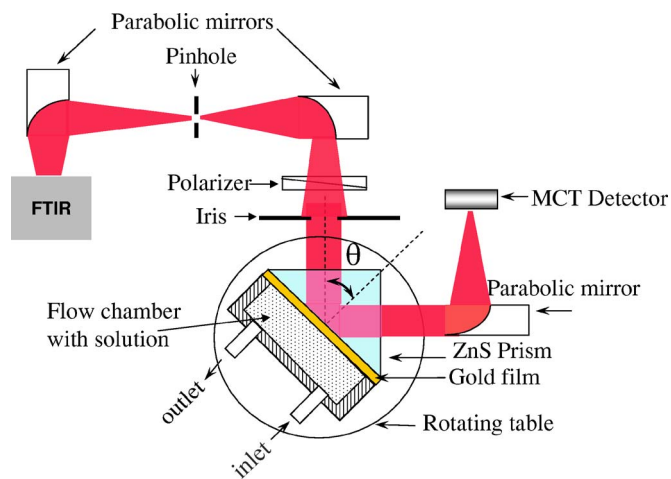


FIG. 4. (Color online) FTIR-based surface plasmon resonance technique. We measured the reflectivity spectrum from the ZnS/Au/solution interface at different angles using a FTIR source and MCT detector. The angular and wavelength ranges correspond to the excitation of the surface plasmon resonance.

To operate this setup, first, we choose the optimal conditions (incident angle, wavelength, and gold film thickness) to achieve maximum sensitivity for a given task. Then, we fill the flow cell with a solution that includes the biomolecules (glucose), and we measure the reflectivity spectrum first for the  $s$ - and then for the  $p$ -polarization. The FTIR collects the data with the  $4\ \text{cm}^{-1}$  resolution and averages the data over 16 scans. The reflectivity of the  $s$ -polarized beam is used as a background, in such a way that the output of our experiment is the ratio of reflectivities for  $p$ - and  $s$ -polarizations. We perform the series of measurements for ascending glucose concentrations, followed by a measurement for pure solvent, and then analyze the difference,  $\Delta R=R_{\text{solution}}-R_{\text{solvent}}$ .

### IV. EXPERIMENTAL RESULTS AND DATA PROCESSING

Figure 5 compares reflectivity spectra for the double-distilled water and for the 55.5 mM D-glucose solution in water. The surface plasmon resonance for the gold/water interface manifests itself as a deep minimum at  $\sim 4350\ \text{cm}^{-1}$ . (The shallow minimum at  $5173\ \text{cm}^{-1}$  corresponds to a weak absorption band of water.). For the glucose solution, the reflectivity minimum is slightly shifted. Generally, to quantify the changes in the SPR spectra, one considers the SPR shift.<sup>6,14,18</sup> Although this is well justified for those measurements at constant wavelengths and variable angles where the SPR dip is rather sharp, such a procedure is less justified for those measurements with variable wavelengths, where SPR is wide and the variation in the SPR width is appreciable. In this case, the whole SPR reflectivity curve should be analyzed.<sup>9,10,19</sup> Therefore, we analyzed the differential spectra  $\Delta R=R_{\text{solution}}-R_{\text{solvent}}$  (Fig. 6).

The differential spectra for small glucose concentrations are very similar and, in fact, can be scaled (see inset to Fig. 6). The scaled spectrum is a fingerprint of glucose in water, whereas the scaling factor is a measure of the glucose con-

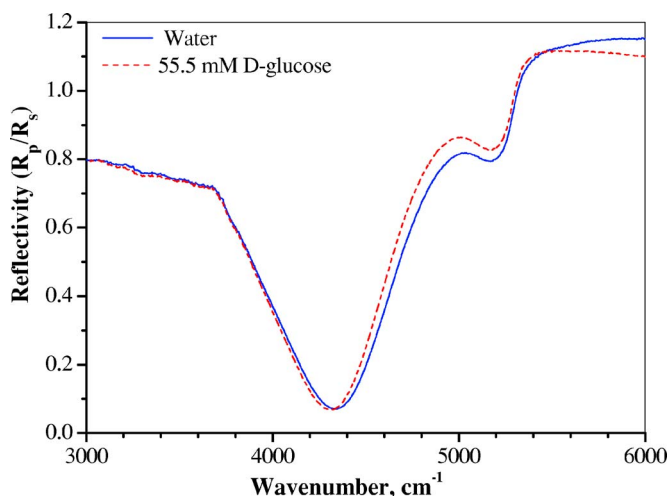


FIG. 5. (Color online) Measured reflectivities of the water and water-glucose solution. The minimum at  $4330\text{ cm}^{-1}$  corresponds to the surface plasmon resonance. Upon addition of the glucose, the peak shifts and broadens.

centration. We calculate this scaling factor at two points in the differential spectra to achieve better accuracy in glucose concentrations. One of them is the minimum itself and another point is at  $4900\text{ cm}^{-1}$ . The corresponding data are plotted in Fig. 7. The differential reflectivity is linearly proportional to the glucose concentration with very high accuracy. We performed similar measurements at several angles of incidence ( $32^\circ$ – $36^\circ$ ) and found a linear dependence on concentration as well, whereas the highest sensitivity was achieved at  $\Theta=34^\circ$ . From the slope of the linear dependence in Fig. 7, we found sensitivity,  $S_{\text{exp}}=|dR/dc|=3\times 10^{-5}\text{ mM}^{-1}$ . This is in good agreement with the value  $(S_c)_{\text{sim}}=3.2\times 10^{-5}\text{ mM}^{-1}$  found in our computer simulations that take into account imaginary parts of the dielectric permittivity of all media. Homola *et al.*<sup>20,14</sup> developed analytical expression for the sensitivity of the wavelength-dependent SPR that does not account for the imaginary part of the dielectric permittivity. While the formula of Ref. 14 accounts fairly well for the

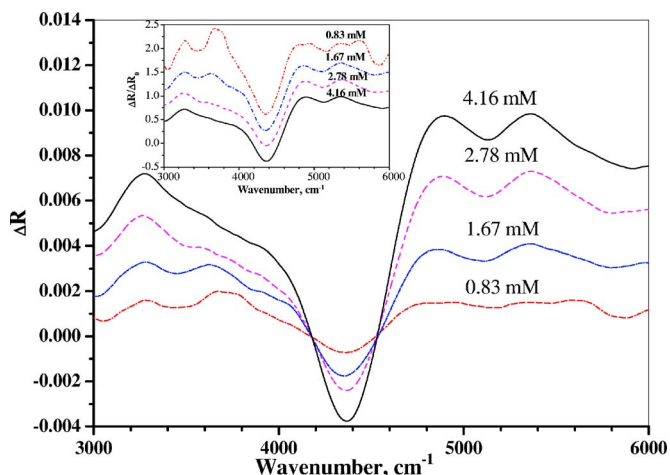


FIG. 6. (Color online) Differential reflectivity,  $\Delta R=R_{\text{water}}-R_{\text{water+glucose}}$ , under the surface plasmon resonance regime. The numbers at each curve indicate the D-glucose concentration in mM. When the glucose concentration is varied, the shape of the spectra undergoes only a very slight change.

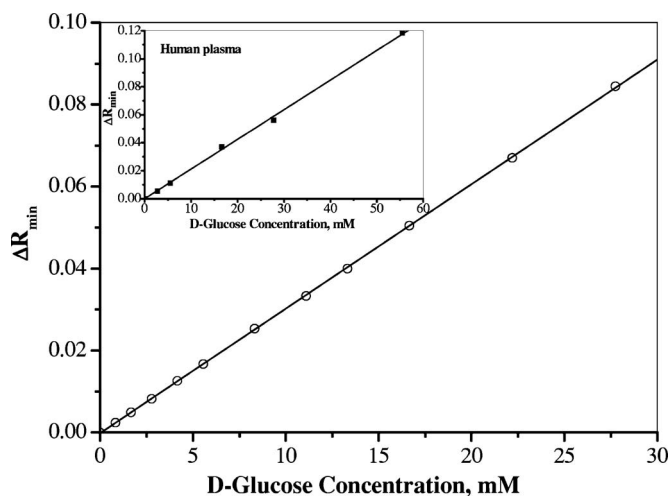


FIG. 7. Differential reflectivity at  $\lambda=4330\text{ cm}^{-1}$  vs glucose concentration in water. Note the linear dependence. Inset shows the corresponding results for glucose in human plasma. Note that at the same angle, the SPR minimum of human plasma is  $200\text{ cm}^{-1}$  redshifted with respect to that of the water because of the numerous solutes that increase the average refraction index of solution.

sensitivity of the surface plasmon resonance in the visible range, it diverges in the infrared and, as noted by Homola *et al.*, it cannot be reliably used there.

We performed similar measurements with the D-glucose solution in human plasma. Here, SPR is  $200\text{ cm}^{-1}$  redshifted with respect to SPR in pure water due to the presence of salts, proteins, and other solutes (not shown here) that affect the average refraction index of solution. Therefore, the optimal wavelength in this case is  $\lambda=4130\text{ cm}^{-1}$ . Clearly, the differential reflectivity linearly depends on the D-glucose concentration (Fig. 7, inset) as well. The slope of the curve, i.e., the sensitivity, is almost the same as for glucose in water.

## V. DISCUSSION

We demonstrate here that FTIR-SPR can be successfully used to measure physiologically important glucose concentrations in water and in human plasma. Next, we compare the sensitivity of our technique to similar techniques that operate in the visible range. The minimal glucose concentration that we were able to measure is  $0.8\text{ mM}$ . This corresponds to a resolution of  $3\times 10^{-7}\text{ RIU}$  at  $\lambda=2.5\text{ }\mu\text{m}$ . This is better than the resolution reported by other groups for aqueous solutions and SPR techniques operating in the visible and NIR range:  $8.6\times 10^{-6}\text{ RIU}$  at  $\lambda=0.9$ – $1.1\text{ }\mu\text{m}$  (Ref. 6) and  $2.8\times 10^{-5}\text{ RIU}$  for the visible range  $\lambda=0.5$ – $0.7\text{ }\mu\text{m}$ .<sup>5</sup> Johansen *et al.*<sup>10</sup> have shown that resolution  $dR/dn$  increases with wavelength and can achieve specified values in the IR range. The ultimate resolution of SPR in air varies from  $5\times 10^{-5}$  at  $\lambda=0.63\text{ }\mu\text{m}$  to  $1\times 10^{-5}$  at  $\lambda=0.85\text{ }\mu\text{m}$ .<sup>15</sup>

We can also compare our FTIR-SPR technique to other label-free methods measuring glucose concentration in water. In particular, optical low-coherence reflectometry<sup>17</sup> measures 2–10 mM glucose concentration with  $\pm 1\text{ mM}$  accuracy at  $\lambda=1.3\text{ }\mu\text{m}$ ; the NIR surface-enhanced Raman spectroscopy measures glucose concentration in the 0.5–44 mM range,<sup>21</sup> although with great uncertainty.

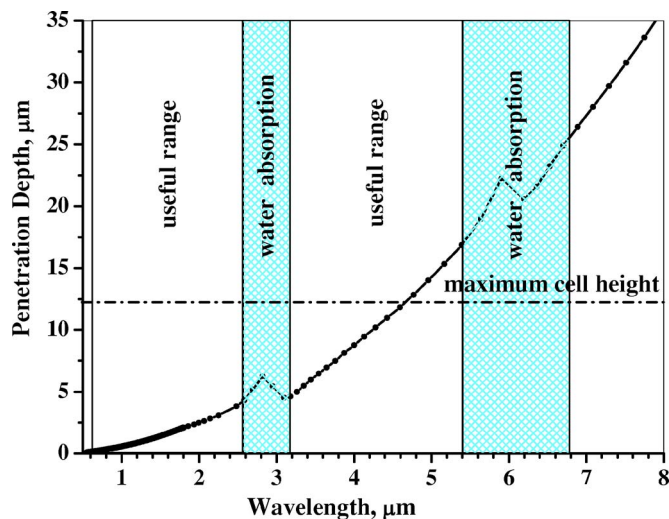


FIG. 8. (Color online) Schematic drawing that illustrates the choice of spectral regions for the SPR-based monitoring of processes in a single layer of cells grown on a gold surface. The requirements are as follows: (i) Surface plasmon penetration depth into biomedium (solid line) is on the order of the cell height (3–12  $\mu\text{m}$ ). (ii) Water absorption bands are excluded. This leaves the regions of 0.5–2.6 and 3.1–4.6  $\mu\text{m}$ .

Finally, we will discuss how our FTIR SPR technique may be applied for studying living cells and their interaction with biomolecules, including glucose. We wish to show that the FTIR-SPR is better suited for this task than the SPR in the visible range. Indeed, the cells can be grown directly on the gold surface and by measuring the SPR reflectivity from the ZnS/Au/cell culture+solution interface, one can study the interaction of cells in a physiological solution with various biomolecules dissolved there. To achieve this goal, the penetration depth of the surface plasmon into dielectric media should be comparable to the cell height. Figure 8 shows the penetration depth of the surface plasmon<sup>3</sup> excited at the gold-water interface. For the visible range,  $\lambda=0.652 \mu\text{m}$ , the SPR penetration length into the water,  $\delta\sim 0.25 \mu\text{m}$  ( $\epsilon_{\text{water}}=1.77$ ,  $\epsilon_{\text{Au}}=-9.895+i1.05$ ), is much smaller than the cell height  $h=3-12 \mu\text{m}$ . Therefore, the surface plasmon in the visible range penetrates the cell membrane but not the cell body. In contrast, for  $\lambda=2.5 \mu\text{m}$ , the penetration length is  $\delta=4 \mu\text{m}$  ( $\epsilon_{\text{water}}=1.583+i0.004$ ,  $\epsilon_{\text{Au}}=-238.8+i37.35$ ), whereas for  $\lambda=4.5 \mu\text{m}$ , it is even higher,  $\delta=12 \mu\text{m}$  ( $\epsilon_{\text{water}}=1.73+i0.0325$ ,  $\epsilon_{\text{Au}}=-784.4+i185.5$ ). This penetration depth is indeed comparable to the cell height. Figure 8 shows that for  $\lambda>4.6 \mu\text{m}$ , SPR penetrates too deep, thereby sensing largely the extracellular environment rather than the cells themselves, whereas the spectral region of 2.6–3.1  $\mu\text{m}$  is characterized by enhanced water absorption and, therefore, is also excluded. The spectral ranges of 0.5–2.6 and 3.1–4.6  $\mu\text{m}$  represent a compromise between water absorption, SPR sensitivity, and penetration depth, as compared to cell height. These ranges are optimal for studying cell cultures grown on gold.

## VI. CONCLUSION

We demonstrated the effectiveness of the FTIR-based surface plasmon resonance technique operating in the mid-IR range. We verified the sensitivity of this technique by monitoring small but physiologically important glucose concentrations in water. The system has a high resolution of  $3 \times 10^{-7}$  RIU, which corresponds to a measurement error of 0.1 mM of glucose in water. The smallest glucose concentration that we have measured is 0.8 mM but it is not our limit of sensitivity, as shown on inset of Fig. 6. Our results suggest that the FTIR-based surface plasmon resonance technique operating in the mid-IR range is an effective optical system for measuring glucose, and this strengthens the possibility of developing a noninvasive blood glucose device based on the SPR effect in the mid-IR range. Clearly, our technique can monitor other biomolecules as well.

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