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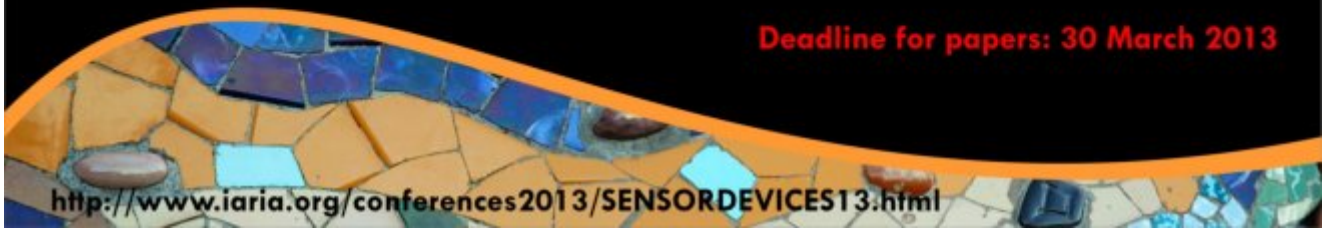

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Development of a Non-invasive Micron Sized Blood Glucose Sensor Based on Microsphere Stimulated Raman Spectroscopy

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Abstract: We proposed a new method for Non-invasive measuring of blood glucose levels by using microsphere Stimulated Raman scattering. We show that this method can be used to measure biological glucose levels with low power lasers. The field enhancement due to the resonance condition of high quality factor microsphere causes to reduce stimulated Raman scattering thresholds of its surrounding media (glucose) and hence observing stimulated Raman scattering with low power. The results from theoretical studies indicate that the stimulated Raman signal amplitude levels produced from the very low Glucose concentrations. By measuring the changes of the signal intensity in output of fiber, we can determine small amount of glucose with a low power. *Copyright © 2012 IFSA.*

Keywords: Blood glucose, Microsphere, Non-invasive, Stimulated Raman scattering.

1. Introduction

Diabetes mellitus is a disease in which cells fail to take up glucose either due to a lack of insulin (Type I) or insensitivity to insulin (Type II) [1]. This abnormality in prolonged periods of time can cause a number of problems including retinopathy, nephropathy, neuropathy, and heart disease [1]. A typical care regimen for diabetics are done by pricking a finger and extracting a drop of blood for testing with any glucometer that all based on the electroenzymatic oxidation of glucose. Since, current blood (finger-stick) glucose tests are painful and inconvenient due to disruption of daily life, cause fear of

hyoglycemia resulting from tighter glucose control and maybe difficult to perform in long term diabetic patients due to calluses on the fingers, a non-invasive method of blood glucose measurement would allow for a significant increase in the quality of life for the 180 million diabetics worldwide and a reduction of the yearly much higher health care costs [2]. In recent years many techniques are being investigated to reach this goal, e.g. near infrared (NIR) [3], Raman spectroscopy [4], fluorescent [5], polarimetric [6], photonic crystal [7], optoacoustic [8], and optical coherence tomography (OCT) [9].

The major challenge in analysis of turbid media such as human skin is the presence of numerous low-concentration components, all with weak signals that are further distorted by the strong light absorption and scattering caused by other components. Raman spectroscopy, by generating a distinct spectrum for each analyte, can resolve the individual components of this complex mixture.

Raman spectroscopy such as spontaneous Raman spectroscopy and stimulated Raman spectroscopy are widely used in physics, chemistry and biology fields for investigations of vibrational modes. In medicine, Raman spectroscopy has been applied to determine the diagnosis of several diseases, such as skin cancer [10], atherosclerosis [11], and diabetes [12].

The concentration of human blood glucose is as low as ~0.7-1.1 $\times 10^{-3}$ g/ml for normal persons and $>1.1\times 10^{-3}$ g/ml for diabetes. The spontaneous Raman intensity from such low concentration glucose is too weak. A group at MIT showed that it is not possible to measure the blood glucose concentration with spontaneous Raman scattering [13], so stimulated Raman spectroscopy is employed. Stimulated Raman scattering can be described by the third order nonlinearity and need high power laser pump fluency which is not suitable for the in-vitro and in-vivo diagnostic purpose. To overcome this problem silica microsphere is chosen.

Silica microspheres act as high-Q small-volume optical resonators owing to the properties of whispering gallery modes (WGM's). Light in such modes is trapped internally by continuous reflections at the surface and provide a high-Q resonators system for use in studying a number of interesting of optical effects such as low threshold lasers [14] and high-sensitivity sensors for biochemical detecting [15].

The long photon lifetimes and small volume of ultra-high-Q microspheres in the resonance condition, allow to significantly reducing the threshold for nonlinear phenomena such as stimulated Raman scattering [16]. Stimulated Raman sources based on silica have required very high pump power, and are macroscale devices. The field enhancement due to the resonance condition of microspheres cause to reduce the stimulated Raman scattering thresholds of its surrounding media and hence observing stimulated Raman scattering with low power. So silica microspheres are good candidates for next-generation Raman sources. This device enables a large reduction in the necessary threshold pump power, while fiber- coupling notably improves overall efficiency and provides a convenient method of optical filed transport [17]. The lasing threshold occurs when cavity round-trip gain equals round-trip loss.

In this paper, we demonstrate the use stimulated Raman spectroscopy, for non-invasive monitoring of biological glucose concentrations. By using ultralow-threshold stimulated Raman lasing in microspheres, we have tried to measure biological glucose levels with low power lasers, which is not above the safety limitation for human body applications. The pump and probe powers are coupled through a tapered optical fiber to the microsphere. In the presence of glucose, the evanescent fields of pump and probe cause stimulated Raman scattering from the glucose and amplification of the probe signal.

2. Preliminaries

2.1 Fingerprint Raman Spectrum of Glucose

We have explored the use of Raman spectroscopy to accomplish this end. This inelastic scattering, discovered by Raman and Krishna [18], gives information about fundamental molecular vibrational by measuring the wavelength shift of a photon at any excitation wavelength. Each molecule has its own distinct vibrational frequencies. The Raman spectrum of solution glucose is shown in Fig. 1 [13]. The eight Raman modes of 436.4, 525.7, 854.9, 911.7, 1065.0, 1126.4, 1365.1, and 1456.2 are considered as the fingerprint Raman lines of blood glucose. Spontaneous Raman spectroscopy is not a useful technique for sensing molecules in extremely low concentrations such as glucose because its cross section is on the order of 10-30 cm, which is lower than the typical fluorescence cross section. Therefore stimulated Raman spectroscopy is employed. In this method a low-power CW pump and a low power CW probe are employed. When the difference between the pump and probe frequencies is coincident with a Raman vibrational mode frequency of glucose, the weak spontaneously Raman light will be amplified by several orders of magnitude (10 to 10^4) due to the pump photon flux. The mode of 1126.4 cm-1 which have high Raman cross-section and narrow bandwidth are expected to be enhanced with lager gain factors. Hence we chose this fingerprint mode in our investigation.

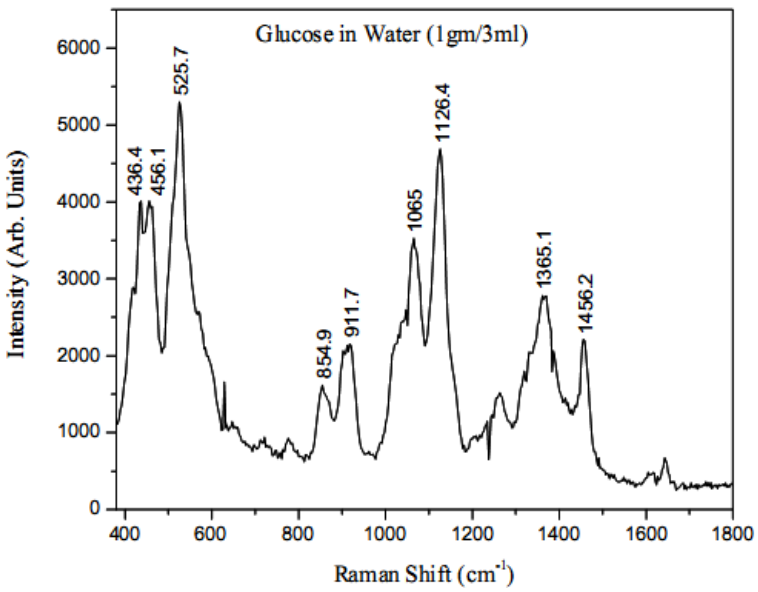


Fig. 1. Raman spectrum of aqueous glucose solution [13].

2.2. Silica Microsphere

In the past decades, the advances in micro-fabrication techniques have made it feasible to consider optical resonators having physical dimensions of the order of optical wavelength. As a particular mode of microcavity resonances, the whispering-gallery-mode (WGM) is a morphology-dependent resonance. WGM occurs when light travels in a dielectric medium of circular geometries. After repeated total internal reflections at the curved boundary, the electromagnetic field can close on itself and give rise to resonances. Of all geometries studied for confining light, silica microspheres have attained the highest optical quality-factor (Q) about 10^9-10^{11}, and are of interest for a number of fundamental and applied studies [19-21].

Our own interest in such microsphere resonators arises within the realm of Stimulated Raman laser, in which they have both small-cavity mode volumes (for large electric fields per photon) and ultralow resonator losses (for long photon-storage times).

In the microsphere stimulated Raman scattering can occur when both energy and momentum conservation among the pump photon, scattered photon and phonon are obeyed. Momentum conservation is intrinsically satisfied, due to the essentially flat dispersion relation of optical phonons. Due to the broad nature of the Raman gain spectrum, the resonance condition (i.e. energy conservation) for a Raman mode is strongly relaxed [16].

A crucial point of these studies is that one needs to be able to couple light into and out of the microsphere. Light must be coupled into the sphere without disturbing the high characteristics. Evanescent coupling, in which an exterior field tunnels into the sphere, appears to be the most promising approach. Numerous coupling devices, such as prisms [22], half-block fibers [23], and tapered optical fibers [24], have been developed by several research groups. Among these, the tapered fibers have been shown to provide the most efficient coupling to the WGMs without degrading the qualities of the microspheres [25]. So in this paper, trapped fiber coupling was employed.

2.3 Optics of Living Tissues

Skin presents a complex heterogeneous medium where blood and pigment content are spatially distributed variably in depth. Skin consists of three main visible layers from surface: epidermis (50–200 μm thick, the blood-free layer), dermis (1–4 mm thick, vascularized layer) and subcutaneous fat (from 1 to 6 mm thick depending on the body site) [26]. The randomly inhomogeneous distribution of blood and various chromospheres and pigments in skin produces variations of average optical properties of skin layers.

Fibrous tissues, such as sclera, dermis and cerebral membrane (Dura mater), show similar structure and, consequently, similar optical properties. The optical model of fibrous tissue can be presented as a slab with a thickness containing scatterers (collagen fibrils)–thin dielectric cylinders with an average meter of 100 nm, which is considerably smaller than their lengths. The refractive index of the collagen fibrils (n_c) and ISF (n_I) can be written as [27]:

$$n_c(\lambda) = 1.439 + \frac{15880.4}{\lambda^2} - \frac{1.48 \times 10^9}{\lambda^4} + \frac{4.39 \times 10^{13}}{\lambda^{13}} \quad (1)$$

$$n_I(\lambda) = 1.351 + \frac{2134.2}{\lambda^2} + \frac{5.79 \times 10^8}{\lambda^4} - \frac{8.15 \times 10^{13}}{\lambda^6}, \quad (2)$$

where λ is the wavelength, nm.

The temporal dependence of the refractive index of the ISF caused by the clearing agent permeation into a tissue can be derived using the law of Gladstone and Dale as [28]:

$$n_I(t) = [1 - C(t)]n_{base} + C(t)n_{osm} \quad (3)$$

$$n_{osm}(\lambda) = n_w(\lambda) + 0.1515C \quad (4)$$

$$n_w(\lambda) = 1.3199 + \frac{6.878\times10^3}{\lambda^2} - \frac{1.132\times10^9}{\lambda^4} + \frac{1.11\times10^{14}}{\lambda^6}, \quad (5)$$

where n_{base} is the refractive index of the tissue ISF at the initial moment, n_{osm} is the refractive index of an agent solution, $n_w(\lambda)$ is the wavelength dependence of the refractive index of water, C is the glucose concentration, g/ml, and C(t) is volume fraction of agent solution.

In a first-order approximation, for a slab with a thickness l at the moment t with $C(0,t)=C(l,t)=C_0=$const, as boundary and C(x,0)=0 as initial conditions ,C(t) will have the form[28-29]:

$$C(t) \approx C_0(1-\exp(-t\pi^2 D / l^2)) = C_0(1-\exp(-t/\tau)) \quad , \quad (6)$$

where $\tau = l^2(\pi^2 D)$ is the characteristic diffusion time and D is the diffusion coefficient. The diffusion coefficient measured in vivo for the human skin, is $2.56\pm0.13\times10^{-6}$ cm^2/s [30].

In a good approximation, the mean values of refractive indices of tissue, blood and their compounds can be presented as following [31]:

$$n_{tissue}(\lambda) = \phi n_c(\lambda) + [1-\phi] n_I(\lambda) \, , \quad (7)$$

ϕ is the volume fraction of the tissue scatters. For fibrous tissues ϕ is usually equal to 0.3 [32].

An important ability of glucose is to change the tissue scattering coefficient. Changes in tissue scattering are more specifically attributed to glucose than changes in tissue absorption spectra due to the presence of glucose in the NIR spectral range [33].

In the case of unchangeable scatterer size, all changes in the tissue scattering are connected with the changes of the refractive index of the ISF. The increase of the refractive index of the ISF provides the decrease of the relative refractive index of the scattering particles and, consequently, the decrease of the scattering coefficient. For noninteracting particles the scattering coefficient of a tissue is defined by the following equation [34].

$$\mu_s(t) = \frac{\phi}{\pi a^2}\sigma_s(t)\frac{(1-\phi)^3}{1+\phi} \, , \quad (8)$$

where a is the cylinder radius, ϕ is the volume fraction of the tissue scatters, and $\sigma_s(t)$ is the time-dependent cross-section of scattering.

For a thin dielectric cylinder in the Rayleigh-Gans approximation of the Mie scattering theory the scattering cross-section $\sigma_s(t)$ for un polarized incident light is given by [35]:

$$\sigma_s = \frac{\pi^2 a x^3}{8}(m^2-1)^2\left(1+\frac{2}{(m^2+1)^2}\right), \quad (9)$$

where $m=n_c/n_I$ is the relative refractive index of the scattering particle, and x is the dimensionless relative scatterers size which is determined as $x = 2\pi a n I/\lambda$, a is the cylinder radius.

Attenuation of light intensity for ballistic photons, in a medium with scattering and absorption is described by the Beer-Lambert law [33]:

$$I = I_0 e^{-\mu_t z}, \tag{10}$$

where $\mu_t=\mu_s+\mu_a$ is the attenuation coefficient of ballistic photons, μ_s, μ_a are the scattering and absorption coefficients, respectively, and I0 is the incident light intensity. Since absorption in tissues is substantially less than scattering (μ_a μ_s) in the NIR spectral range, the exponential attenuation of ballistic photons in tissue is dependent mainly on the scattering coefficient:

$$I = I_0 e^{-\mu_s z} \quad , \tag{11}$$

Since the tissue scattering coefficient changes with glucose concentration, the exponential profile of light attenuation in tissue is dependent on glucose concentration. Therefore, one can monitor glucose concentration by measuring the exponential slope of light attenuation in tissue.

3. Basic of the Microsphere Non-invasive Glucose Sensor

Fig. 2. shows the schematic of the glucose Raman microsphere sensor.

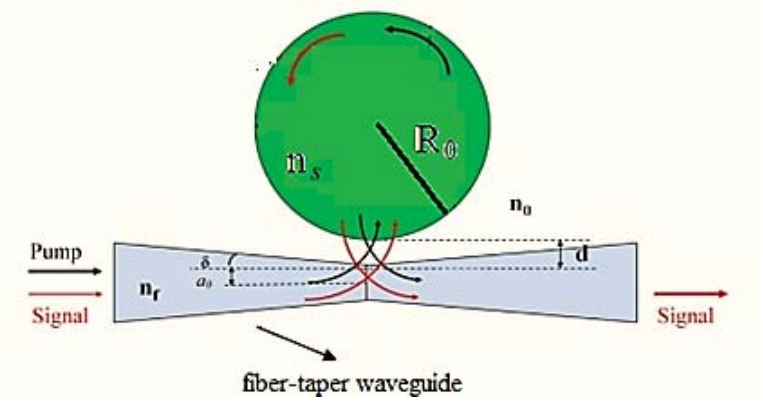
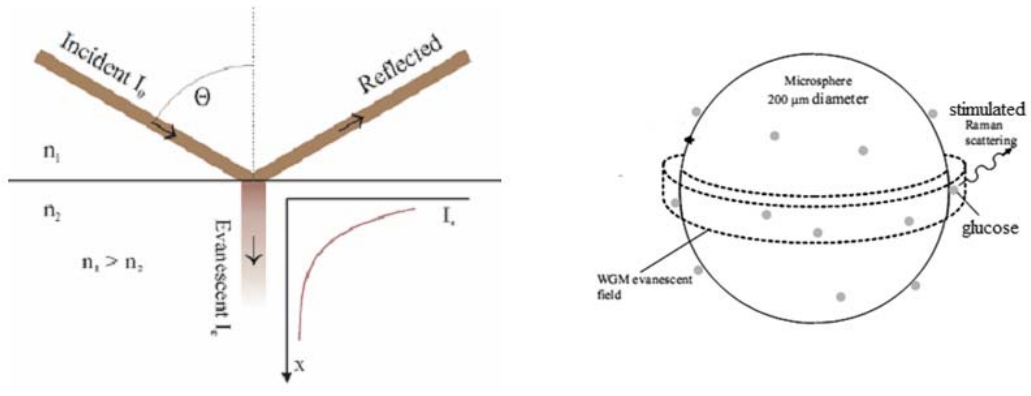


Fig. 2. Microsphere stimulated Raman spectroscopy system. The pump and probe signals are coupled to the microsphere through tapered optical fiber.

In this method two laser sources are employed. A low-power continuous pump and a low-power continuous probe beams. The frequency of the pump beam is changed, while the frequency of the probe beam is fixed. The pump beam is used to induce the Raman emission, while the probe beam serves to reveal the Raman modes. An adiabatic fiber taper is then used to couple laser beams into and out of the microsphere. The quality factor of microsphere is on the order of 10^9. The field enhancement due to the resonance condition of high quality factor microsphere causes to reduce stimulated Raman scattering thresholds of its surrounding media and hence observing stimulated Raman scattering with low power. When the difference between the pump and probe frequencies is coincident with a Raman vibrational mode frequency of glucose, the evanescent fields of the pump and probe that exist in the outside of microsphere cause stimulated Raman scattering from the glucose and the weak spontaneously Raman light will be amplified by several orders of magnitude (10 to 10^4) due to the pump photon flux (see Fig. 3).

Increased glucose in the blood is proportional to an increase in the stimulate Raman scattering from the glucose molecules and thus the signal intensity changes. Signal intensity will increase with increased glucose in the blood. The blood glucose concentration can be determined by analyzing the spectral information contained within the signal changes in the output of tapered fiber.



(a) (b)

Fig. 3. (a) Reflection of a plane wave from a microsphere interfaces, (b) Stimulate Raman scattering from glucose molecules on the surface of a microsphere.

4. Governing Equations

4.1. Raman Gain

Raman gain is optical gain (amplification) arising from stimulated Raman scattering. It can occur in transparent solid media (e.g. optical fibers); liquids and gases under the influence of intense pump light, and is used in Raman amplifiers and Raman lasers. Its magnitude depends on the optical frequency offset between pump and signal wave, to some smaller extent on the pump wavelength, and on material properties [36]. Stimulated Raman scattering governed by the third-order susceptibility $\chi(3)$ is a nonlinear optical phenomenon in the sense that it occur when the response of a material system to an applied optical field depends in a nonlinear manner on the strength of the optical field [37].

A semiclassical model can be used to determine the gain, g_s, in which the electromagnetic fields are treated classically, and the medium is treated quantum mechanically [38]. Probe wave's equation can be written as:

$$\frac{\partial^2 E_s}{\partial z^2} + \mu_0 \varepsilon_0 n_g^2 \omega_s^2 E_s = -\mu_0 \omega_s^2 P_s^{(3)} \quad , \tag{12}$$

where n_s is the refractive index, ω_p and ω_s are frequency of pump and probe. Assuming plane wave solutions to the wave equation, the electric field at the probe frequency, ω_s is:

$$E_s = \frac{1}{2}(E_{0s} \exp\left[i(k_s z - \omega_s t)\right] + \text{c.c.}) \quad , \tag{13}$$

here E_s is a vector constant and k_s is the propagation constant. By substituting E_s in equation (12) and solving for the propagation constant, k_s will yield:

$$k_s \approx \frac{n_s \omega_s}{c}\left(1 + \frac{\mu_0^2 c^3}{2 n_s^2 n_p} \chi(\omega_s)^{(3)} I_p\right) , \qquad I_p = \frac{1}{\mu_0}\frac{n_g}{c}\left|E_p\right|^2 \tag{14}$$

where $\chi^3(\omega)$ is third susceptibility and in the resonance condition can be broken down into its component parts, $\chi^3(\omega)=(\chi'+i\chi'')_R+\chi_{NR}$, χ'_R and χ''_R are the real and the imaginary part of the resonant contribution, χ_{NR} is a term accounting for the nonresonant background.

Now by substituting this expression in equation (14) and k_s in equation (13), E_s can be rewritten as:

$$E_s(z)=\frac{1}{2}E_{0z}\exp\left[-\kappa_s\frac{\mu_0^2c^3I_p}{2n_g^3}\chi_R''z\right]\times \exp\left[i\kappa_s\left(1+\frac{\mu_0^2c^2I_p}{2n_g^2}(\chi_R'+\chi_{NR})z\right)\right]\exp[-\omega_s t] \quad , \tag{15}$$

Now $I_s(z)$ can be written as:

$$I_s(z)=\frac{n_g}{\mu_0 c}|E_s|^2=I_s(0)e^{g_s/I_p z} \quad , \tag{16}$$

where $I_s(0)$ is the initial intensity of the probe wave. On the other hands, in the resonance condition($\omega_0=\omega_p-\omega_s$), can be expressed in terms of the spontaneous Raman scattering cross section, $d\sigma/d\Omega$, as:

$$\chi_R''=-\frac{\pi N\Delta c^4}{\omega_s^4 h\Gamma}\frac{d\sigma}{d\Omega}(4\pi)^3\varepsilon_0^2 \quad , \quad \Delta=1-\exp(\frac{hc(\Delta k)}{KT}) \quad , \quad \Gamma=2\pi c(30cm^{-1}) \tag{17}$$

where N is the density of molecules, and h is Planck's constant. Substituting equation (17) into (15) for the stimulated Raman gain leads to:

$$g_s=\frac{16\pi N\Delta c^2}{\omega_s^3 n_{tissue}^2 h\Gamma}\frac{d\sigma}{d\Omega} \quad , \tag{18}$$

But this is not the effective Raman gain because only the evanescent pump and probe fields that are located outside the cavity interact with glucose. Therefore it should be averaged on the radial component of filed.

In microsphere, the propagation equation for the pump and probe signal in the presence of Raleigh Scattering can be rewritten as follows [16]:

$$\frac{dI_s(z)}{dz}=-(\alpha-g_R I_p(z))I_s(z)+2G\sqrt{I_s(z)I_s(L-z)}\cos[nk(L-2z)] \quad , \tag{19}$$

$$\frac{dI_p(z)}{dz}=-(\alpha+g_R(I_s(z)+I_s(L-z)))I_p(z) \quad , \tag{20}$$

where I_s, I_p are the intensity of the signal and pump modes of the resonator and denotes the input wave. G and α are scattering coefficient of both modes to each others and intrinsic loss respectively and g_R is Raman gain coefficient which is proportional to the glucose concentration.

The boundary condition in coupling region of fiber and microsphere for pump and probe beam can be written as [17]:

$$I_p(0)+r^2 I_p(L)-2r\sqrt{I_p(0)I_p(L)}=\chi^2 I_{in_p}, \tag{21}$$

$$I_s(0)+r^2 I_s(L)-2r\sqrt{I_s(0)I_s(L)}=\chi^2 I_{in_s}, \tag{22}$$

Here r and χ are transmission and coupling coefficient and satisfy the relation $r^2+\chi^2=1$, I_{in} is incident field, I(0) is coupled intensity and I(L) is intensity after one circulation in the microsphere ($L=2\pi R_0$).

Outside of the sphere but very close to the surface, the fields decay exponentially in the radial direction. Because of the rapid decay in field amplitude, the pump and probe intensity for high azimuthal modes (m >>1) can be approximated as [39]:

$$\begin{cases} I_s = I_s(a,z)\exp(-\alpha_s(r-R_0)) \\ I_p = I_p(a,z)\exp(-\alpha_p(r-R_0)) \end{cases}, \tag{23}$$

where

$$\alpha_s=\sqrt{\beta_l^2-k_s^2 n_{sphere}^2} \quad , \quad \alpha_p=\sqrt{\beta_l^2-k_p^2 n_{sphere}^2}$$
$$k_s=\frac{2\pi}{\lambda_s} \quad , \quad k_p=\frac{2\pi}{\lambda_p}$$
$$\beta_l=\sqrt{l(l+1)}/R_0 \quad , \quad |m|\le l$$

By substituting equation (23) into equation (20) and after simplification will be achieved:

$$\frac{dI_p(a,z)}{dz}= -\left(\alpha - g_s \frac{\left[\frac{1}{(\alpha_s+\alpha_p)^2}+\frac{R_0}{\alpha_s+\alpha_p}\right]}{\left[\frac{1}{\alpha_s^2}+\frac{R_0}{\alpha_s}\right]} \right) I_p(a,z) \times (I_{cw}(z)+I_{cw}(L-z)), \tag{24}$$

$$g_R = g_s \frac{\left[\frac{1}{(\alpha_s+\alpha_p)^2}+\frac{R_0}{\alpha_s+\alpha_p}\right]}{\left[\frac{1}{\alpha_s^2}+\frac{R_0}{\alpha_s}\right]}, \tag{25}$$

where g_R is the effective Raman gain in the presence of glucose and R_0 is the radius of microsphere.

4.2. Optimal Wavelength Region

Raman shifts are independent of excitation wavelength and thus Raman spectroscopy offers the flexibility to select a suitable excitation wavelength for a specific application. The NIR spectral region

is commonly used in most reported methods. It has several spectral windows where hemoglobin, melanin, and water absorption band intensities are low enough to allow light to penetrate in the tissue, which enables noninvasive spectral measurements. The choice of NIR excitation for probing biological tissue is justified by three advantageous features: low-energy optical radiation, deep penetration, and reduced background fluorescence [40]. Fig. 4 illustrates the absorption spectra of major endogenous tissue absorbers, [41]. As shown the "diagnostic window," in which a group of minima exists, is outlined over 830-1000 nm.

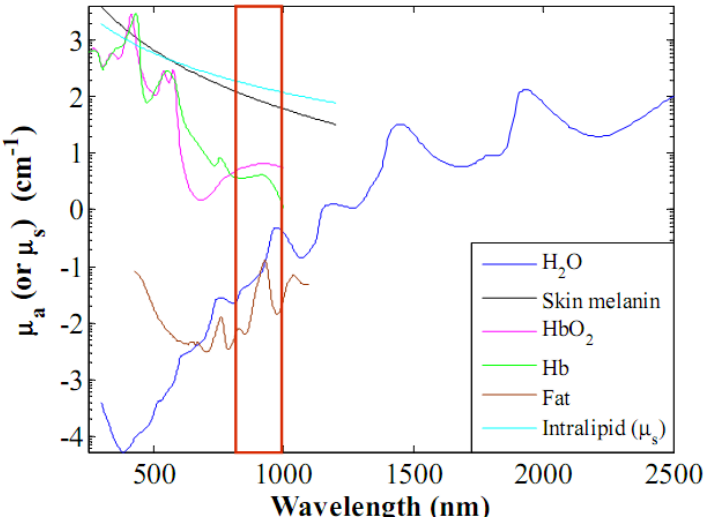


Fig. 4. Absorption spectra of water, skin melanin, hemoglobin, and fat. Also shown is the scattering spectrum of 10 % intralipid, a lipid emulsion often used to simulate tissue scattering [41].

5. Results and Discussion

For excitation of microsphere whispering-gallery modes, the probe and pump laser beam must circle the interior of the sphere through multiples of total internal reflections and returns in phase. The approximate condition for optical resonance of microsphere can be presented as [42]:

$$2\pi R_0 n_1 = m\lambda \qquad \text{m=1,2,3,...,} \tag{26}$$

where, R_0 and n_1 are the sphere radius and refraction index, λ is the wavelength of light, and m is an integer.

The microsphere in this work is approximately 200 nm in diameter and 1.5 in refractive index. When the pump and probe laser wavelengths are on resonance with the microsphere cavity and difference between the pump and probe frequencies is coincident with a Raman vibrational mode frequency of the glucose, the evanescent pump and probe fields illuminates nearby glucose and produces stimulated Raman signal.

As a result and with the respect of equation (26), our NIR Raman studies of biological tissue employ 834 nm as the excitation [49].

Pump wavelength can be achieved as:

$$\frac{1}{\lambda_p} - \frac{1}{\lambda_s} = \Delta k_{glucose}(cm^{-1}) \ , \tag{1}$$

pump wavelength must satisfy the resonance condition are shown with equation (26).By tuning the pump wavelengths from 740.5 nm to 800.9 nm, and measuring the Raman gain at the probe wavelength of 834 nm, the excitation Raman peaks from 436.4 cm to 1456.2 cm should be observed. The mode of 1126.4 cm-1 which has high Raman cross-section and narrow bandwidth are expected to be enhanced with lager gain factors. So in this mode, Stimulated Raman measurements were conducted with the following configurations, shown in Table 1.

Table 1. Parameters in microsphere stimulated Raman detector.

Symbol	Quantity	(SI)
λ_p	Pump wavelength	762.5 nm
λ_s	Probe wavelength	834 nm
I_p	pump intensity	10^3 W/cm^2
I_s	probe intensity	10^{-3} W/cm^2
R_0	Radius	100 μm
α	Interstice loss	10^{-4}
χ	coupling coefficient	0.01

By numerical solving of equations (19)-(20) and corresponding boundary conditions have been employed in equations (21) - (22), for mode of 1126.4 cm-1 with respect of equation (26) and (27),the variation of pump and signal power are obtained and presented by Fig. 5 and Fig. 6 respectively.

These results show in the presence of glucose, pump frequency converts to signal frequency and the amplification of probe intensity will occur. Probe intensity changes are proportional to blood glucose levels. So blood glucose levels can be determined with measuring of probe intensity in the output of fiber after using a suitable calibration method.

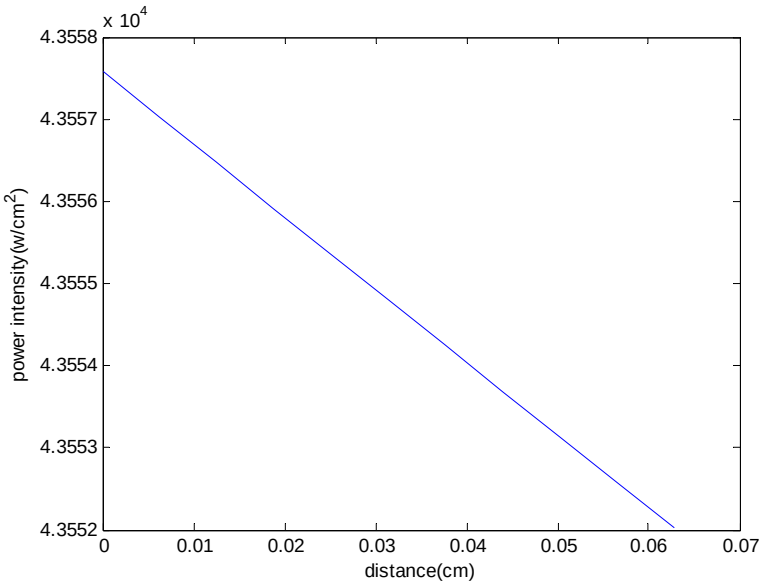


Fig. 5. Variation of the pump intensity versus the distance traveled by light on microsphere circumference.

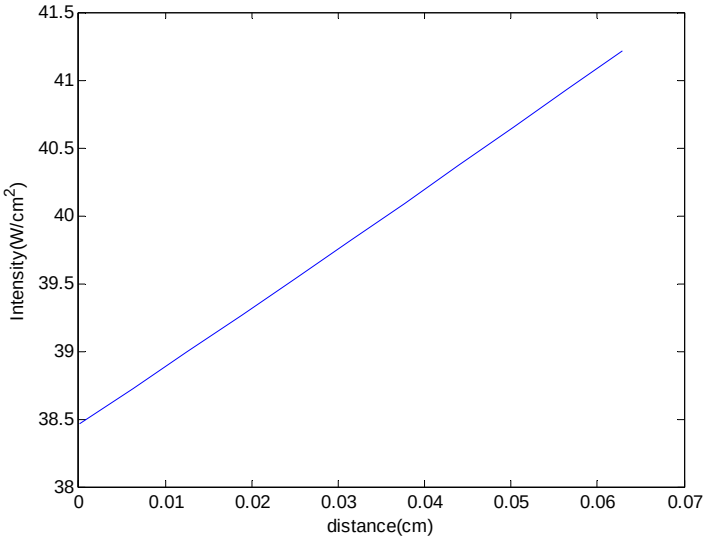


Fig. 6. Variation of the signal intensity versus the distance traveled by light on microsphere circumference.

6. Conclusion

A technique has been devised to non-invasively measure the glucose concentration in the presence of skin. This approach is radically different from conventional non-invasive blood glucose measurement techniques. One of the important problems in determining blood glucose levels without injury based on stimulated Raman scattering technique is high pump power laser fluency which is above the safety limitation for human body application. In order to solve this problem, silica microsphere is employed. Very high quality factor microsphere reduces the thresholds of nonlinear optical effects such as stimulated Raman scattering from its surrounding media. In addition, theoretical studies have been performed to determine the feasibility of the stimulated Raman spectroscopy technique for in-vivo measurements. A low-power CW laser as pump and low-power CW laser as probe are employed. After laser start to work, the existence Pump and probe evanescent fields interact with glucose and cause stimulated Raman scattering. The results from these theoretical studies indicate that the stimulated Raman signal amplitude levels produced from the very low Glucose concentrations. By measuring the changes of the signal intensity in output of fiber, we can determine small amount of glucose with a low power pump in reasonable exposure time. Therefore, this system can be used as a sensitive sensor to measure changes in small amount of analytes.

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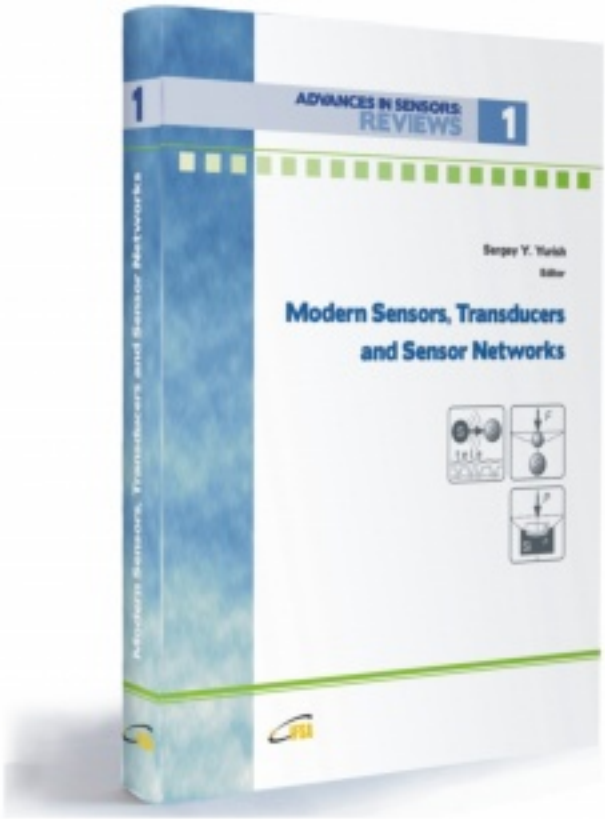

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