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Possible correlation between blood glucose concentration and the reduced scattering coefficient of tissues in the near infrared

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Tissue glucose levels affect the refractive index of the extracellular fluid. The difference in refractive index between the extracellular fluid and the cellular components plays a role in determining the reduced scattering coefficient (μ_s') of tissue. Hence a physical correlation may exist between the reduced scattering coefficient and glucose concentration. We have designed and constructed a frequency-domain near-infrared tissue spectrometer capable of measuring the reduced scattering coefficient of tissue with enough precision to detect changes in glucose levels in the physiological and pathological range.

Millions of diabetics around the world measure their blood glucose concentration several times a day. Essentially, all the current methods for glucose determination require patients to obtain blood by lancing a finger. They then perform a quantitative analysis of blood sugar by monitoring a chemical reaction with the blood sample. Reference 1 provides a brief review of the diverse minimally invasive approaches to monitoring blood glucose. Other ideas include sensors implanted subcutaneously,² direct measurement of plasma index of refraction,³ and noninvasive chemometric analysis of tissue effective absorption spectra.⁴

In this Letter we investigate modifications of light transport through tissues as a result of changes in glucose concentration. We focus our attention on near-infrared light because tissue absorption in this spectral region is low, leading to harmless penetration of light deep into the tissue. Recently we developed a sensitive frequency-domain near-infrared tissue spectrometer capable of separately measuring reduced scattering (μ_s') and absorption (μ_a) coefficients in tissues.⁵ Using this instrument, we can independently assess the effect of glucose concentration on the absorption and scattering properties of tissues. The method is based on measurement of the product of the reduced scattering coefficient and the mean index of refraction of tissue (n) at a single wavelength (850 nm). We propose a model that correlates this product ($n\mu_s'$) to changes in the refractive indices of the blood plasma and interstitial fluid [together known as the extracellular fluid (ECF)].

Light scattering occurs in tissues because of the mismatch of index of refraction between the ECF and the membranes of the cells composing the tissue. The index of refraction of ECF (n_{ECF}) varies with dissolved sugar concentration, whereas the index of the cellular membranes (n_{cell}) is assumed to remain relatively constant. In the near infrared the index of refraction of the ECF is $n_{\text{ECF}} \sim 1.348\text{--}1.352$,^{6,7} whereas the index of refraction of the cellular

membranes and protein aggregates is in the range $n_{\text{cell}} \sim 1.350\text{--}1.460$.^{7,8} Adding glucose to blood will raise the refractive index of the ECF, which will cause a change in the scattering characteristic of the tissue as a whole. Our approach is based on the principle that physiological changes in the glucose concentration in the ECF can cause measurable changes in the product of the reduced scattering coefficient of the tissue and the mean refractive index of the tissue ($n\mu_s'$).

The *in vitro* experiment is described as follows: we measured the product $n\mu_s'$ at 850 nm of a Liposyn-glucose suspension (1.5% lipid solid content) as a function of glucose concentration, using a previously described frequency-domain technique.⁹ Briefly, this technique involves placing an intensity-modulated light source deep in the medium to be studied. The phase and the intensity of the photon-density wave generated by this source are measured with high precision at several source-detector separations. These measurements are combined with equations analytically derived from linear transport theory to yield the ratio of the absorption coefficient to the mean refractive index (μ_a/n) and the product of the mean refractive index and the reduced scattering coefficient ($n\mu_s'$) characteristic of the medium.¹⁰

The light source was a light-emitting diode with a peak wavelength of 850 nm. Its intensity was modulated at a frequency of 120 MHz. Over the course of the experiment we incrementally added to the Liposyn suspension a previously prepared solution with a glucose concentration of 140 g/L and the same Liposyn concentration as the suspension. The results are shown in Fig. 1, in which the experimental data are plotted against glucose concentration (lower axis) and the refractive index of the water-glucose mixture (upper axis).

To compare the above experimental results with an appropriate model, we consider the reduced scattering coefficient $\mu_s' = \mu_s(1 - g)$, where μ_s is the microscopically derived scattering coefficient and g

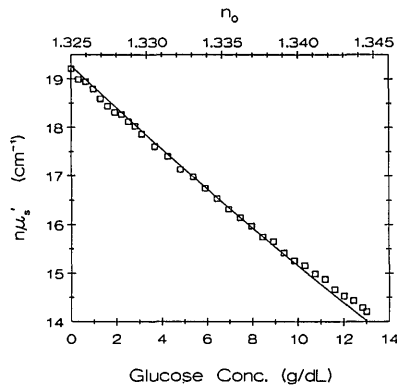


Fig. 1. Product of the refractive index n and the reduced scattering coefficient μ_s' of the Liposyn–glucose suspension as a function of the glucose concentration (lower axis) and the index of refraction (upper axis) of the solution suspending the lipid droplets. This solution consists of water with a varying concentration of dissolved glucose to change the refractive index. The open squares indicate measured values, whereas the curve is a theoretical prediction based on the Rayleigh–Gans scattering model of Eq. (1) with $n_1 = 1.465$ and $K = 1.30 \times 10^3 \text{ cm}^{-1}$. The experimental errors in the data points are of the order of the dimensions of the open squares.

is the average of the cosine of the scattering angle. Microscopically, Mie theory rigorously treats scattering by spherical scatterers of index of refraction n_1 suspended in a medium of index of refraction n_0 . We employ the Rayleigh–Gans theory as an approximation to Mie theory to find the dependence of the reduced scattering coefficient on the indices of refraction n_1 and n_0 . With this theory, which is appropriate when $|n_1/n_0 - 1| \ll 1$,¹¹ the reduced scattering coefficient has the following dependence on the indices of refraction^{11,12}:

$$\mu_s' = K \left(\frac{n_1 - n_0}{n_0} \right)^2, \quad (1)$$

where K is a proportionality factor related to particle size, wavelength, and particle density and includes g . The curve in Fig. 1 corresponds to a plot of this model for $n\mu_s'$ (we assume that $n \cong n_0$), where n_1 and n_0 are obtained from the *CRC Handbook of Chemistry and Physics* and are based on the type of fat in the suspension (soybean oil) and on the known glucose concentration, respectively.⁷ We set $n_1 = 1.465$ and $n_0 = 1.325 + 1.515 \times 10^{-6} \times [C]$, where $[C]$ is the concentration of glucose in milligrams per deciliter. For the curve in Fig. 1, K is equal to $1.30 \times 10^3 \text{ cm}^{-1}$. We stress that K is the only adjustable parameter in our application of Eq. (1). For a lipid emulsion similar to the one that we employed and in the absence of glucose, an experimentally derived formula verified by Mie theory calculations¹² leads to a similar value for K of $1.25 \times 10^3 \text{ cm}^{-1}$.

For the noninvasive *in vivo* measurement we used a previously described frequency-domain tissue spectrometer.⁵ Four light sources (light-emitting diodes with a peak wavelength of 850 nm) are placed at the skin surface to obtain measurements at several source–detector separations. We measured the

response of a nondiabetic male subject to a glucose load of 1.75 g/kg body weight, as in a standard glucose tolerance test,¹³ by continuously monitoring the product $n\mu_s'$ measured on muscle tissue of the subject's thigh. Instrument acquisition time was 30 s per data point. Informed consent of the subject and institutional review board approval were obtained before the experiment.

Simultaneously, we measured the subject's blood glucose, using a home blood glucose monitor (One Touch, Johnson & Johnson) periodically throughout the experiment. The results of the optical measurement and of the home blood glucose monitor test are shown in Fig. 2. As the subject's blood glucose rose, the reduced scattering coefficient decreased. Figure 3 shows the correlation plot obtained from the data of Fig. 2. A complete explanation of the results in the physiological system requires a sophisticated physical model. However, the simple Rayleigh–Gans model, which explains the *in vitro* experiment, can be used as a first step in the explanation of the *in vivo* results. To this end we assume a suspending medium with refractive index n_{ECF} that is close to the refractive index of the suspended scatterers, n_{cell} . The index of refraction of the fluid changes only slightly [less than 0.05% (Ref. 3)] as a result of physiological changes in glucose concentration. If we let $n_{\text{ECF}}(0)$ be the index of refraction of the ECF at a baseline physiological glucose concentration, we can write $n_{\text{ECF}} = n_{\text{ECF}}(0) + \delta n$, with $\delta n \ll n_{\text{ECF}}(0)$. By replacement of the Rayleigh–Gans parameters K , n_0 , and n_1 with the corresponding tissue parameters K_T , n_{ECF} , and n_{cell} , respectively, Eq. (1) becomes

$$n\mu_s' = \frac{K_T [n_{\text{cell}} - n_{\text{ECF}}(0) - \delta n]}{n_{\text{ECF}}(0)}, \quad (2)$$

where δn is neglected in the denominator because it is much less than $n_{\text{ECF}}(0)$ and we assume $n \cong n_{\text{ECF}}(0)$.

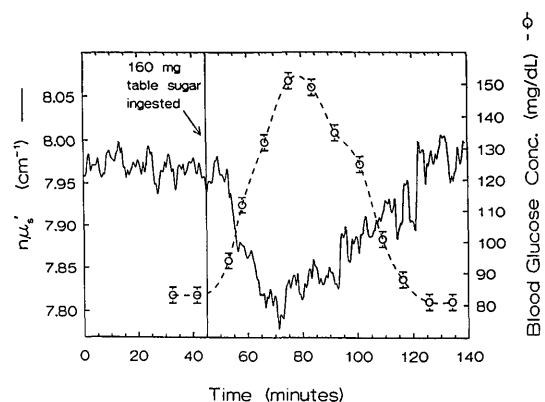


Fig. 2. Glucose tolerance test performed on a human subject. At time $t = 45$ min the subject ingested a glucose load of 160 g of table sugar (1.75 g/kg body weight). The open circles indicate blood glucose concentration as determined by a home blood glucose monitor. A dashed curve joins the circles to aid the eye. The solid curve is the continuous measurement of $n\mu_s'$ on the thigh of the subject made with our portable frequency-domain near-infrared spectrometer. The data acquired every 30 s were averaged in sets of five to produce the plot.

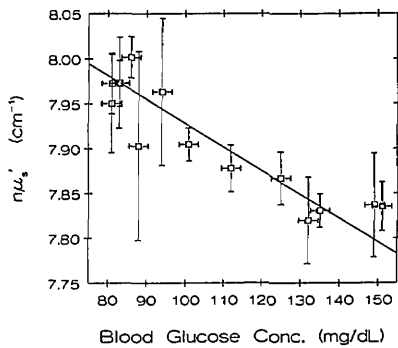


Fig. 3. Correlation plot of the data shown in Fig. 2. The open squares indicate the correlation between the blood glucose as measured with the home blood glucose monitor with the measured product $n\mu_s'$ averaged over a time of 2.5 min centered on the time the finger was lanced for the measurement. The errors in $n\mu_s'$ shown here are the standard deviations of the five measurements averaged to generate a single scattering point. The errors in blood glucose concentration are estimated to be ± 2.5 mg/dL. The curve is the theoretical result according to the Rayleigh-Gans model.

Using the CRC table for the dependence of the index of refraction of water solution on glucose concentration, we obtain $\delta n = 1.515 \times 10^{-6} \times [\Delta C]$, where $[\Delta C]$ is the change in glucose concentration in milligrams per deciliter from the physiological baseline.⁷ For $n_{\text{ECF}}(0)$ and n_{cell} we chose typical values of 1.350 and 1.360. It is not possible to calculate K_T a priori because of the random inhomogeneous nature of tissues. We chose to make K_T equal to the measured value of $n\mu_s'$ at $[C] = 82$ mg/dL multiplied by $\{n_{\text{ECF}}(0)/[n_{\text{cell}} - n_{\text{ECF}}(0)]^2\}$. In this fashion we obtained $K_T = 7.28 \times 10^3 \text{ cm}^{-1}$. The curve in Fig. 3 is the plot of Eq. (2) with these parameters. We found a higher sensitivity of $n\mu_s'$ to changes in glucose concentration for the *in vivo* measurement than that for the *in vitro* measurement.

Our claims for the correlation between blood glucose concentration and reduced scattering coefficient are based on a simple physical model for light transport in tissues. This model accounts for the changes of the reduced scattering coefficient of tissues owing to changes in the refractive index of ECF. The novelty of our method lies in exploiting the better match of index of refraction between ECF and cellular materials caused by an increase in glucose concentration. An increase of glucose concentration in the physiological range decreases the total amount of tissue scattering. Clearly our approach assumes a value for the baseline and, in this sense, can provide only a relative measurement that permits monitoring glucose levels over an extended period of time. Key factors for the success of this approach are the precision of the measurement of the reduced scattering coefficient and the separation of scattering changes from absorption changes, as obtained with our frequency-domain spectrometer. However, we observe that the physical model that we propose is only a possible explanation of the glucose-induced scattering effect.

Other physiological effects related to glucose concentration could account for the observed variations of the reduced scattering coefficient with time.

Because glucose has low absorption at 850 nm relative to other tissue constituents the absorption coefficient is negligibly affected by glucose concentration. This was borne out in both the *in vitro* and the *in vivo* experiments that we conducted. Because the reduced scattering coefficient is more affected by changes of glucose concentration, the fact that scattering dominates the transport properties of near-infrared light in tissues is actually advantageous in refractive-index-based glucose monitoring. Provided that one can separate absorption and scattering effects, the highly scattered slightly absorbed near-infrared light employed in this technique is actually in the spectral region of choice.

During the course of our study we learned that other researchers are developing a similar approach to noninvasive glucose monitoring.¹⁴ Our research is supported by National Institutes of Health grants RR03155 and CA57032 and by the University of Illinois at Urbana-Champaign. We thank Albert Cerussi for help in performing the *in vitro* experiment.

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