

Tunable laser diode system for noninvasive blood glucose measurements

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ABSTRACT

Tight control of blood glucose levels has been shown to dramatically reduce the long-term complications of diabetes. Current invasive technology for monitoring glucose levels is effective but underutilized by people with diabetes because of the pain of repeated finger-sticks and the cost of reagent strips. Optical sensing of glucose could potentially allow more frequent monitoring and tighter glucose control for people with diabetes. The key to a successful optical non-invasive measurement of glucose is the collection of an optical spectrum with a very high signal-to-noise-ratio in a spectral region with significant glucose absorption. Unfortunately, the optical throughput of skin is very small due to absorption and scattering. To overcome these difficulties, we have developed a high-brightness tunable laser system for measurements in the 2.0-2.5 μm wavelength range. The system is based on a 2.3 micron wavelength, strained quantum-well laser diode incorporating GaInAsSb wells and AlGaAsSb barrier and cladding layers. Wavelength control is provided by coupling the laser diode to an external cavity that includes an acousto-optic tunable filter. Tuning ranges of greater than 110 nm have been obtained. Because the tunable filter has no moving parts, scans can be completed very quickly, typically in less than 10 ms. We describe the performance of the laser system and its potential for use in a non-invasive glucose sensor.

Keywords: non-invasive, in vivo, near-infrared, glucose, tunable laser, spectroscopy, GaInAsSb

1. INTRODUCTION

The benefits of tight glycemic control in people with diabetes are well-documented.¹⁻³ Hyperglycemia over extended periods is the primary cause of the severe complications associated with diabetes, including premature death, blindness, kidney failure, amputations, heart disease, and stroke. Effective glycemic control requires frequent blood glucose monitoring to provide the information needed to administer the proper amount of insulin while avoiding hypoglycemia. The avoidance of hypoglycemia is critical because diabetic patients who maintain tight glucose control generally experience a greater incidence of hypoglycemia compared to those with less control.¹ Hypoglycemia is potentially life threatening and must be avoided in any viable disease management strategy.

Frequent blood glucose monitoring would be more widely practiced with the availability of an analytical system that operates in a manner that is accurate, painless, sample-free, and easily implemented by the diabetic patient during his/her normal daily routine. State-of-the-art glucose monitoring technology falls considerably short of these requirements. Current test-strip technology requires a blood sample for each measurement. The pain associated with such measurements can inhibit frequent monitoring, especially in children. Frequent monitoring is also discouraged by the need to handle and dispose of the blood sample and by the difficulty of implementing the test in social settings. Current industry-wide efforts to reduce the size of the required blood sample and to shorten the analysis time are beneficial, but they do not address the fundamental limitations of an invasive procedure. Recent instrumental advances have focused on reducing these technological barriers. Examples of next-generation technologies include implantable glucose biosensors,^{4,5} which are capable of continuous glucose monitoring over multiple days, and the GlucoWatch biographer, which provides a new glucose reading every 20 minutes.⁶

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Noninvasive optical sensing of glucose has been proposed by many research groups for the frequent and painless measurement of glucose in people with diabetes.⁷ The concept is to pass a selected band of near-infrared radiation through a vascular region of the body and extract the glucose concentration from the resulting spectral information. Near-infrared spectroscopy is the principal approach for noninvasive sensing because of the unique near-infrared absorption spectrum of glucose and the significant penetration of near-infrared light into human tissue.

The largest difficulty with performing optical absorption measurements in skin is the small optical throughput. In addition to the strong water absorption (0.6 AU/mm at 2.2 μm wavelength), skin is highly scattering. In our measurements, we typically see a peak transmission of approximately 0.1% for a sample with an effective aqueous path length of 0.6 mm. In order to maximize the signal-to-noise ratio of the measurement, it is helpful to have the brightest source possible. We presently use 50 W tungsten filament bulbs that operate at 3050 K. Although higher power bulbs can be obtained, their brightness (optical power per unit radiating area) does not increase with power.

Laser diodes would be a very useful tool for tissue spectroscopy because of their brightness, which enable large optical powers to be collected onto a small, low noise detector. Laser diodes, being solid-state devices, could lead to more compact and rugged spectrometer compared to a system that requires a sensitive interferometer. In order to be useful for noninvasive spectroscopy, however, a laser diode system must be capable of acquiring a spectrum consisting of measurements at a number of wavelengths. The need for a spectrum rather than measurements at one or two discrete wavelength is a consequence of the broad and highly-overlapped nature of near-infrared absorbance bands.

There are at least two ways to collect a spectrum using laser diodes: the first is to use a set of diodes, each operating at a fixed wavelength. To be useful for transcutaneous spectroscopy, however, this would require at least 12–18 devices, each of which is locked at a particular wavelength using, for example, a distributed feedback grating. This arrangement represents a straightforward but cumbersome solution. The second way to obtain a spectrum is to use a single tunable device.

With regards to spectroscopy, tunable laser diodes have been used across both near-infrared^{8–12} and mid-infrared^{13–15} wavelengths. The vast majority of spectroscopic work performed using tunable laser diodes has been directed at gas sensing. The requirements for noninvasive aqueous sensing, however, are very different from those of gas sensing because of the difference between gas-phase and condensed-phase absorption spectra. Gas-phase absorbance spectra are comprised of several sharp features that correspond to the rotational modes of the gas molecule. By contrast, the aqueous glucose spectrum is composed of three features with widths on the order of 50–200 cm^{-1} (25–100 nm). A tunable laser diode system designed to measure gas will typically scan across a single rotation line to quantify the species (0.3 cm^{-1} of tuning). For aqueous spectra, however, much broader tunability is required (500–700 cm^{-1}). While gas sensing requires very narrow laser line-widths to resolve the sharp features, narrow line-widths are not required for aqueous sensing. The typical spectral resolution utilized in our transcutaneous measurements is 16 cm^{-1} .

Several tuning strategies have been employed with tunable laser diode systems. The most convenient systems involve only electronic wavelength control. For example, current can be injected into regions of the device in order to modify the index of refraction of the material, which leads to a small shift in wavelength. Alternatively, the current used to drive the device can be ramped in order to rapidly vary the device temperature, which causes a shift in wavelength. Both of these approaches provide tunability that is sufficient for gas sensing but not for aqueous spectroscopy. Tuning can also be achieved by directly modifying the temperature of the device heat-sink, but this provides limited tuning range and is slow. A third strategy is to employ an external cavity, which provides the widest tuning range. Tuning ranges of up to 1170 cm^{-1} have been reported in the literature.^{16, 17} An external cavity laser diode spectroscopy system can potentially provide a powerful and compact platform for transcutaneous spectroscopy.

2. EXPERIMENT

The work described here was performed with coated Fabry-Perot laser diodes fabricated at the Fraunhofer Institute for Applied Solid-State Physics. These devices are based on an active region with three strained

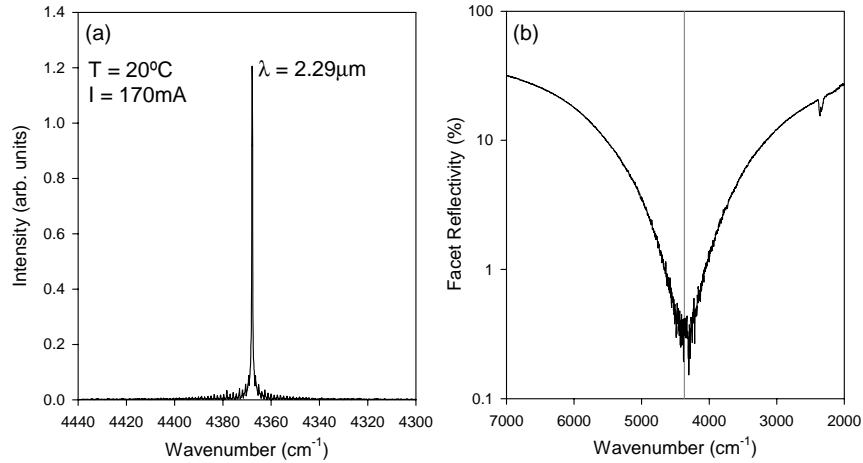


Figure 1. (a) Free lasing spectrum of the anti-reflection coated laser diode operated just above threshold. (b) Reflectivity of the antireflection coated facet. The vertical line shows the free lasing wavelength of the device.

$\text{Ga}_{0.70}\text{In}_{0.30}\text{As}_{0.06}\text{Sb}_{0.94}$ quantum wells, $\text{Al}_{0.28}\text{Ga}_{0.72}\text{As}_{0.02}\text{Sb}_{0.98}$ barriers and separate confinement region, and $\text{Al}_{0.85}\text{Ga}_{0.15}\text{As}_{0.07}\text{Sb}_{0.93}$ waveguide cladding layers.^{18–21} The devices were 1 mm long with a 16 μm wide stripe. The devices were mounted epilayer-side down on a copper C-mount heat-sink. The optimal device for wavelength tuning had a 95% high-reflective coating on one end and a 0.2% anti-reflection coating on the other. The device operates with a natural wavelength of 2.29 μm with a threshold current of 150 mA at a heat-sink temperature of 20° C. Figure 1(a) shows the natural lasing spectrum of the device at a current of 170 mA. Shown in Figure 1(b) is a measurement of the reflectivity of the anti-reflection coated facet, which is designed to reach a minimum reflectivity at the natural lasing wavelength.

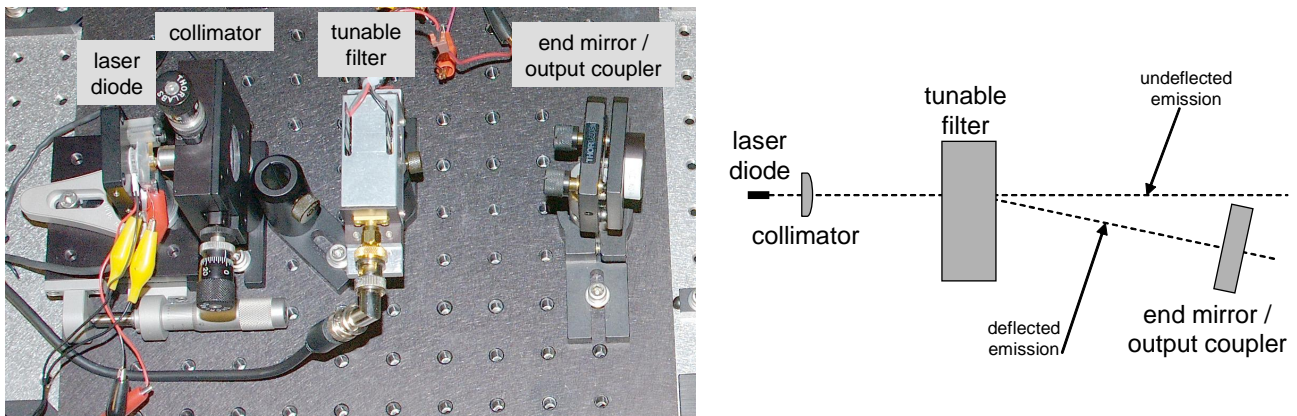


Figure 2. Photograph of the present external cavity system and a simplified schematic.

The laser diode was mounted on a thermoelectric temperature-controlled mount and coupled into an external cavity arrangement. A photograph and simplified schematic of the system are shown in Figure 2. The laser output from the end with the anti-reflection coating was collected with a high numeric aperture asphere (NA=0.55 and $f=4.51$ mm) and imaged onto an end-mirror (which also serves as an output coupler) 20 cm away. A beam-splitter could optionally be inserted in the cavity in order to pick off a small portion of the beam during alignment. An acousto-optic tunable filter was placed between the collimating lens and end-mirror. The tunable filter is based on a temperature-stabilized TeO_2 crystal and optimized for the 2.0–2.5 μm wavelength range with a pass-band

width of 24 cm^{-1} . The tunable filter causes a 6° horizontal deflection of the selected wavelength range, which requires that the end-mirror be rotated by 6° off-normal with respect to the output from the laser diode. The tunable filter is driven by a custom-designed radio-frequency (RF) driver based on an Analog Devices AD9854 direct-digital-synthesis signal generator chip. The synthesizer chip is controlled by a microcontroller which programs the synthesizer to generate a chirped sine-wave with frequencies running from 40–45 MHz. The chirp is amplified by a 4 watt RF power amplifier and delivered to the tunable filter. A small portion of the system output is picked off using a pellicle beam splitter and delivered to an extended-wavelength InGaAs detector to provide a reference channel. The system as a whole is mounted on a 12 in optical breadboard so that the system can be moved and positioned as a unit.

3. RESULTS

The present system is capable of tuning over a wavelength range of 220 cm^{-1} (110 nm), as is illustrated by the spectra in Figure 3, which were collected at a series of fixed RF drive frequencies using an FTIR spectrometer. The external cavity system begins to lase at a threshold current of 105 mA and obtains optimal tunability at a drive current of 200 mA. At higher currents, the output power increases although the tuning range narrows slightly due to carrier loss to internal cavity lasing. Note however, from the schematic in Figure 2, that the internal lasing signal is not collinear with the external cavity output and can be eliminated with a beam-stop. With a 90% reflective output coupler, the optical power at 200 mA is 0.5 mW. Powers of 5 mW should be obtainable with improved antireflection coatings and waveguide geometries. Optical power levels as high as 1 watt have been obtained with near-infrared external cavity systems.²² The optical power available presently with our broad-band source is approximately 0.05 mW, when integrated over the 2.0–2.5 μm wavelength range. Thus an output of 5 mW from the tunable laser system will represent more than a factor of 100 improvement in available signal.

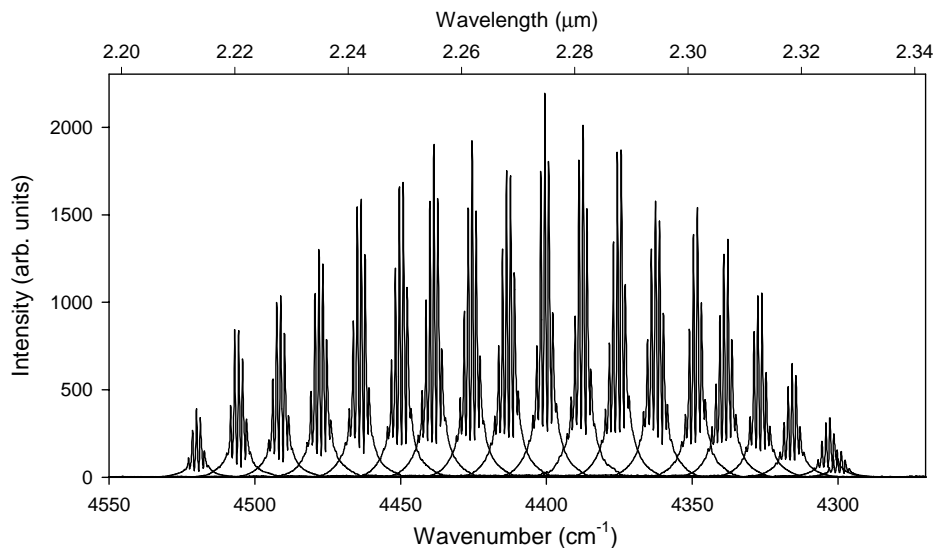


Figure 3. Tuning spectra obtained with the present external cavity system. The fringes are due to feedback from the internal laser diode cavity.

In Figure 3, fringes are visible in each of the lasing spectra. These fringes are due to significant feedback from the anti-reflection coated facet of the device. The presence of the fringes indicates that the laser is operating in a coupled-cavity regime, which is undesirable.^{23–25} The coupling of the internal and external cavities can be reduced by decreasing the feedback from the anti-reflection coated facet.

Spectra of four chemical components were measured using the tunable laser system and an FTIR spectrometer to test the tunable laser system’s ability to accurately quantify small spectral changes. Solutions of glucose, urea,

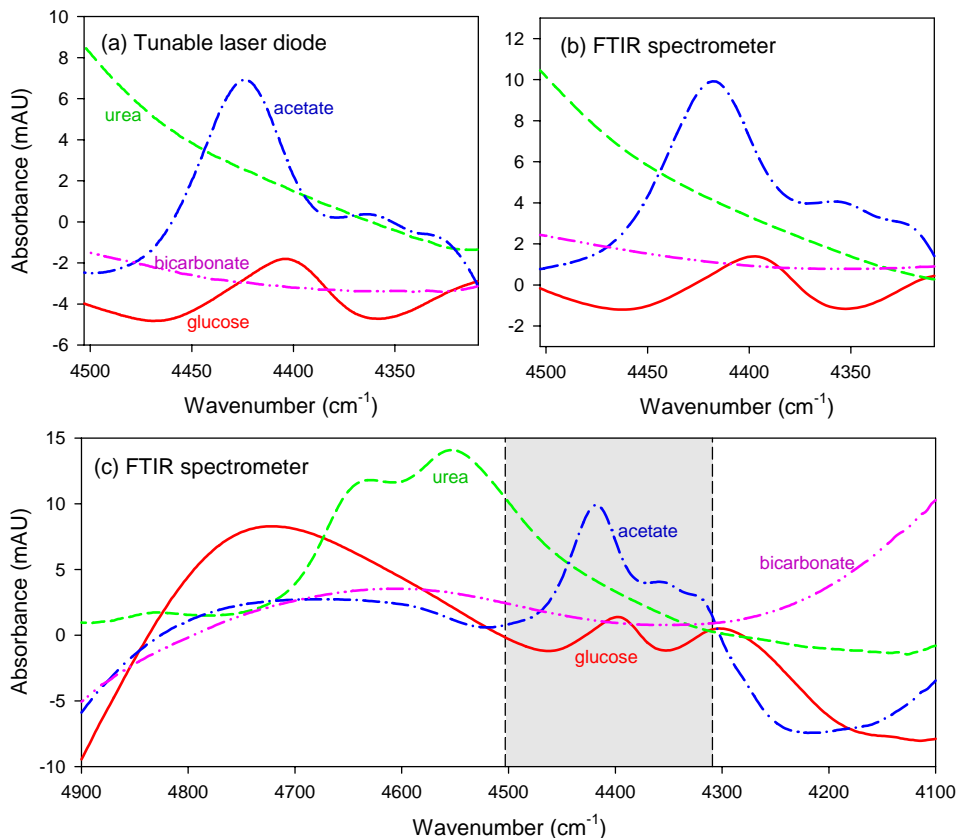


Figure 4. Absorbance spectra of four analytes measured with (a) the present tunable laser diode spectrometer and (b) an FTIR spectrometer. Panel (c) shows the absorbance spectra measured with an FTIR spectrometer over a wider spectral range. The highlighted region is the portion of the spectra shown above. Note that vertical shifts are common in this wavelength range and are not analytically significant.

and acetate were measured in a 1 mm path length cuvette and referenced to water. Absorbance spectra for the solutions are shown in Figure 4 for measurements made using the tunable laser system and a Nicolet Nexus FTIR spectrometer. The spectra recorded using the two systems are very similar in shape and magnitude. Vertical shifts in absorbance spectra are common in the 2.0–2.5 μm wavelength range due to the strong temperature dependence of water absorption and are not analytically significant. Solution temperatures were not controlled during these measurements.

The present performance of the tunable laser system is sufficient for *in vitro* quantification of biological analytes such as glucose in moderately complex samples, (e.g., for quantification of glucose in interstitial fluid or clear effluent from a bioreactor). However, our experience with *in vivo* measurements indicates that a wider spectral range is required for transcutaneous glucose measurements. Based on our preliminary work with animal models, we estimate that a minimum useful tuning range 500 cm^{-1} is required for *in vivo* tissue measurements, whereas 700 cm^{-1} would be ideal. In addition, the present tunable laser implementation has a higher noise level than optimized FTIR instruments. The noise level we observe is beyond what would be expected due to detector noise. Our current system is most likely limited by the nature of coupled-cavity operation.^{23–25} The two key improvements needed to make the present system a powerful spectroscopic tool for non-invasive sensing are extension of the tuning range and the suppression of feedback from the anti-reflection coated semiconductor facet.

4. CONCLUSIONS

We report the initial development of a tunable laser diode spectroscopy system designed for the measurement of glucose in *in vivo* transcutaneous spectra. The high-brightness source provides 0.5 mW of power tunable over the 4300–4520 cm^{-1} range. Further improvements designed to reduce the optical feedback from the anti-reflection coated facet will reduce noise from cavity coupling and extend the tuning range. These improvements will make the system an attractive platform for near-infrared spectroscopy in high optical density samples.

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