

# APPLICATIONS OF LONG-WAVELENGTH SOURCES AND DETECTORS FOR MEDICAL MONITORING

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There are many potential applications of optical sensing of biological molecules for medical monitoring. Optical monitoring of body chemistry offers several advantages over conventional chemical techniques. Long-wavelength semiconductor source and detector technology will likely play a key role in making these applications possible and practical. Although development of optical blood glucose sensors has been pursued aggressively for several years, there are still no commercially available instruments. This is due to a combination of factors, including extremely high signal-to-noise requirements and the difficulty of properly interpreting spectral absorption information. The factors required for successful noninvasive biochemical monitoring, especially as they relate to the potential impact of the development of semiconductor source and detector technology in the 2.0-10  $\mu\text{m}$  wavelength range, will be discussed.

## INTRODUCTION

Chemical sensors based on infrared spectroscopy can quantify the concentration of multiple chemical analytes within complex chemical matrices in a reagentless, non-intrusive, and non-destructive manner.<sup>1-3</sup> This makes infrared chemical sensing technology ideally suited for applications in clinical chemistry and biomedical research where accurate, *in situ* chemical measurements are needed. Optical sensing has the potential to replace standard chemical-based assays in situations where direct access to the sample is not desirable, or where repeated (or continuous) measurements make invasive techniques unattractive.

The potential impact of noninvasive biosensing technology is particularly significant in the area of clinical treatment because of the potential for performing *in situ*, reagentless, and continuous measurements. Sample-free clinical measurements can be envisioned in numerous health care settings. Noninvasive biosensing is ideally suited for patient testing in physician offices, operating rooms, emergency rooms, critical care units, neonatal clinics, and other sites in the traditional acute care hospital. As health care delivery moves increasingly to a managed care environment, even more opportunities for noninvasive biosensing will emerge outside the hospital in rehabilitation centers, skilled nursing facilities, and the home. The principle utility of this technology will be the ability to monitor *in vivo* chemistry in a point-of-care fashion. Such a capability has the potential to impact all areas of medical science and all clinical specialties.

Several important applications of infrared chemical sensing technology have been identified where infrared chemical sensors can provide valuable and potentially life saving analytical information. Examples of applications include 1) lactate measurements to monitor stress and shock, 2) urea measurements in individuals with kidney failure for the purpose of optimizing the life saving process of hemodialysis, 3) ethanol measurements in people to combat alcohol abuse, and 4) glucose, lactate, and glutamine measurements in bioreactor system to control the chemical environment for fundamental *in vitro* experiments in life sciences and to optimize production of biotechnology products.

## NON-INVASIVE GLUCOSE SENSING

The best-known example of non-invasive optical monitoring, however, is the measurement of blood glucose for individuals with type-I or type-II diabetes. Diabetes is a chronic, incurable disease that causes an array of serious medical complications and premature death. The Center for Disease Control and Prevention reports that each year an estimated 12,000 to 24,000 people with diabetes become blind, more than 100,000 receive treatment for kidney failure, and 86,000 require amputations. In addition to pain and suffering, these complications are costly.<sup>4</sup> The American Diabetes Association estimates that, in 1997, the total cost of diabetes in the United States was \$98 billion dollars. This amount corresponds to both direct healthcare costs (\$44 billion) and the indirect costs (\$54 billion) associated with disability, premature mortality and loss of work.<sup>5,6</sup>

The prevalence of people with diabetes is growing at an alarming rate. A recent report from the Centers for Disease Control and Prevention shows that the incidence of diabetes in the United States has increased by 33% from 1990 to 1998. More startling is the estimate that, over this period, the incidence of diabetes increased by 70% for people in their 30's.<sup>7</sup> The World Health Organization warns of a diabetes epidemic on the basis of a tremendous increase in the incidence of diabetes worldwide. Their figures indicate that the number of people with diabetes increased from 30 million in 1985 to 135 million in 1999. They project that 300 million people will have diabetes by 2025.<sup>8</sup>

Although diabetes is a potentially devastating disease, early diagnosis and tight glycemic control can greatly diminish its medical complications and cost. The goal of tight control is to maintain blood glucose levels within a physiologically acceptable range. Tight control requires frequent blood glucose measurements, which provides the information needed to properly administer insulin or glucose in order to avoid chronic hyperglycemia and acute hypoglycemia. The benefits of tight control are well-documented<sup>9-11</sup> and stem from a delay in the onset of the medical complications caused by chronic hyperglycemia. Unfortunately, early diagnosis and tight glycemic control are not often achieved. The NIH reports that of the 15.7 million Americans with diabetes, 5.4 million people remain undiagnosed (34%). In addition, recent studies indicate that a vast majority of Americans with type-I diabetes only measure their blood glucose levels once per day, which is insufficient to maintain tight control.<sup>6</sup> The pain, cost and inconvenience of state-of-the-art glucose monitoring technology impede frequent

monitoring and are primarily responsible for the failure of patients to maintain tight control.

One solution for non-invasive monitoring of glucose would involve a sensor that could be attached to a body site for either occasional or continuous measurement. Infrared light would be passed through a tissue sample where it would interact with glucose. The emerging light would then be analyzed to quantify the concentration of glucose in the tissue sample. Instrumentation for this scenario could potentially be table-top size and utilize normal AC wall power.

It has been recognized for several decades, though, that the ideal treatment of diabetes would involve a closed-loop insulin delivery system that is implanted within the patient's body. The so-called artificial pancreas consists of an insulin delivery pump coupled with some type of glucose-sensing technology. Insulin is delivered continuously in response to detected changes in the blood glucose concentrations. For this to work, the glucose-sensing component must be able to provide accurate and rapid blood glucose values to a micro-processing unit, which computes the amount of insulin required and then controls insulin delivery. From a practical standpoint, the sensing unit must function reliably for a minimum of one year with minimal operator intervention. The key limitation to the successful development of an artificial pancreas is the implantable glucose sensing technology.

## WAVELENGTH REGIONS OF INTEREST

Biomolecule absorption in the infrared is due to interaction of the optical field with vibrational modes of the molecules. In this regard, infrared optical sensing is much more difficult than the measurement of hemoglobin oxygenation in pulse oxymetry, which utilizes much stronger electronic transitions in the hemoglobin molecule. The most intense vibrational interactions are due to bonds involving hydrogen atoms, such as, O-H, C-H, and N-H bonds. Fundamental vibrational modes exist in the 4-10  $\mu\text{m}$  wavelength range. Weaker nonlinear combinations of fundamental modes exist in the 2.0-2.5  $\mu\text{m}$  wavelength range, and yet weaker overtones exist in the 1.5-1.8  $\mu\text{m}$  and 0.8-1.2  $\mu\text{m}$  ranges.

Any measurement in a biological material must deal with the presence of water. Water has significant absorption throughout the long-wavelength infrared, requiring the selection of wavelength regions lying in water absorption windows. The dominant water transmission windows in the long-wavelength infrared occur between 2.0-2.5  $\mu\text{m}$ , 3.3-5.9  $\mu\text{m}$ , and 6.2-11  $\mu\text{m}$ . The transmission spectrum of 1 mm water in the 1-2.5  $\mu\text{m}$  wavelength range is shown in Figure 1. Transmission in the 2.0-2.5  $\mu\text{m}$  range has a peak value just over 10%. In a sample of tissue, the transmission would be significantly lower than this due to the large amount of scattering. These factors limit the thickness of sample that can be probed to less than 2 mm total thickness. Figure 2 shows the transmission spectrum of water across the 2.5-14  $\mu\text{m}$  wavelength range. Note that the path length in this case is only 40  $\mu\text{m}$ .

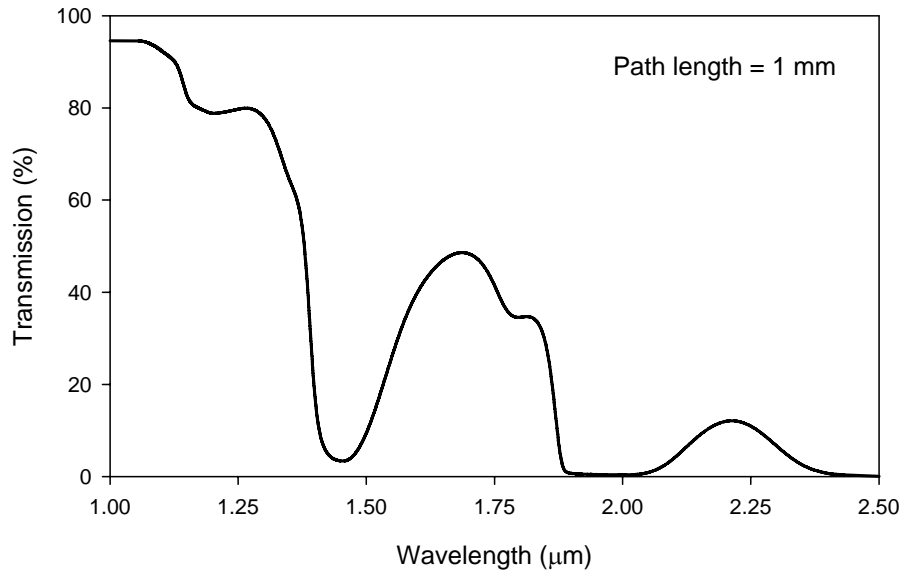


Figure 1: Transmission spectrum of 1 mm of water.

Much of the work in noninvasive sensing has utilized short wavelength regions of the infrared (0.8-1.8  $\mu\text{m}$  wavelengths) because of the large penetration depth of water and the abundance of well-developed source and detector technology. However, the optical interaction strength of light with glucose is very weak in these ranges. The field of biochemical sensing will be greatly aided by advances in device technology in the 2.0-2.5  $\mu\text{m}$  and 6-10  $\mu\text{m}$  wavelength ranges.

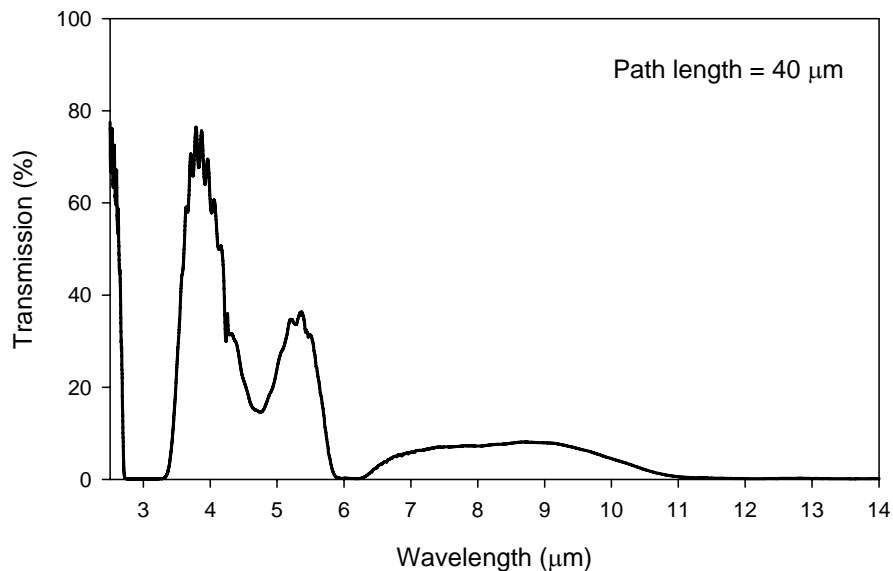


Figure 2: Transmission spectrum of 40  $\mu\text{m}$  of water between 2.5-14  $\mu\text{m}$ .

## KEY FACTORS FOR NON-INVASIVE SENSING

The requirements for biomolecule sensing in aqueous environments are very different from gas sensing, where absorption lines are narrow. Figure 3 shows a comparison of the absorption spectra of gas-phase CO and aqueous glucose. A common strategy in gas sensing is to scan across one of the rotational fine-structure modes. In an aqueous environment, however, the absorption features are broad. In the 2.0-2.5  $\mu\text{m}$  wavelength band, feature widths are approximately  $25\text{ cm}^{-1}$  (3 meV, or 15 nm at 2.4  $\mu\text{m}$ ); in the longer-wavelength infrared they are approximately  $20\text{ cm}^{-1}$  (2 meV, or 200 nm at 10  $\mu\text{m}$ ), as illustrated in Figure 4. Because the dominant absorption features of biomolecules arise from only 3 bond types (C-H, N-H, and O-H bonds), absorbance features are highly overlapped. This is illustrated in Figure 5, where the extinction spectra of several biomolecules are shown along with the extinction spectrum of glucose. Fortunately, though, the absorption spectrum of each chemical species is unique because the exact structure of the absorption bands depends on the chemical environment surrounding the active bonds. But absorption measurements must be made at several wavelengths in order to provide enough degrees of freedom to identify glucose in the presence of other interfering compounds.

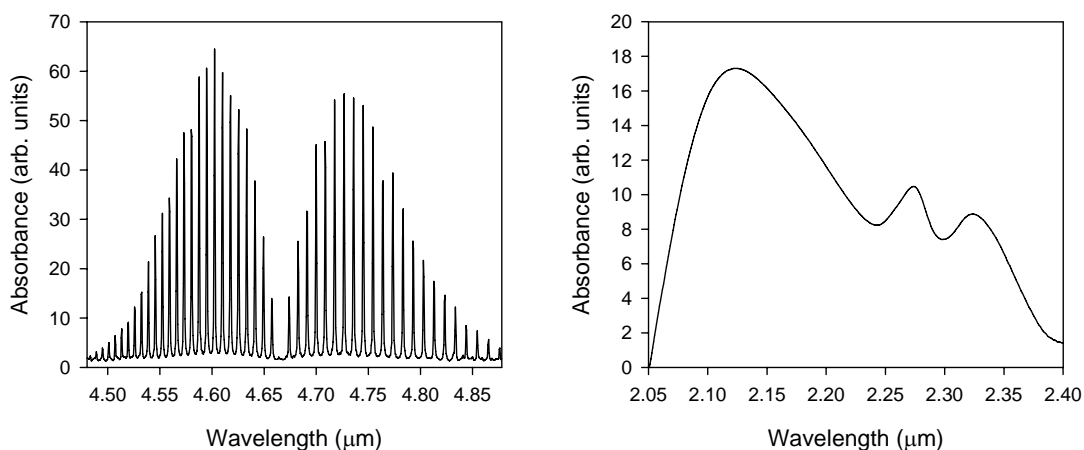


Figure 3: Comparison of the absorption spectra of gas-phase CO and aqueous glucose.

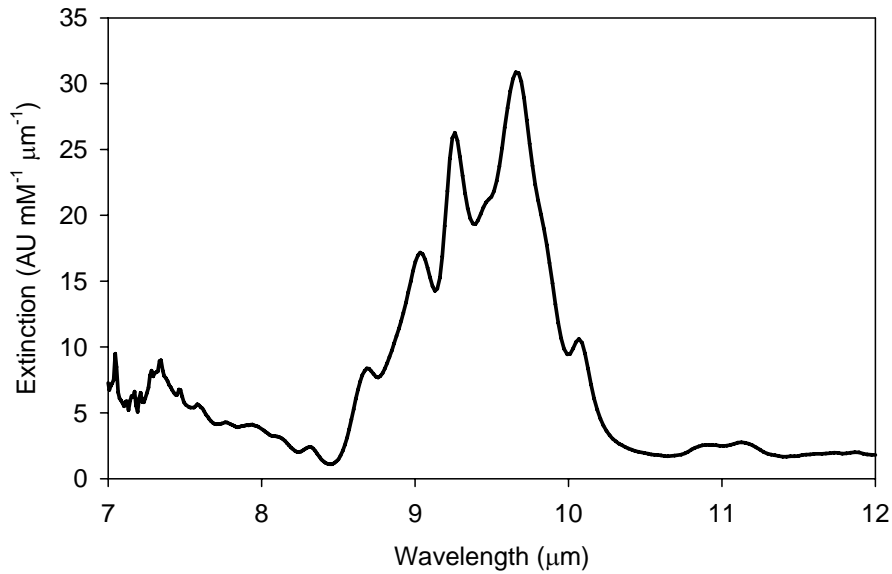


Figure 4: Absorption spectrum of aqueous glucose between 7-12  $\mu\text{m}$ .

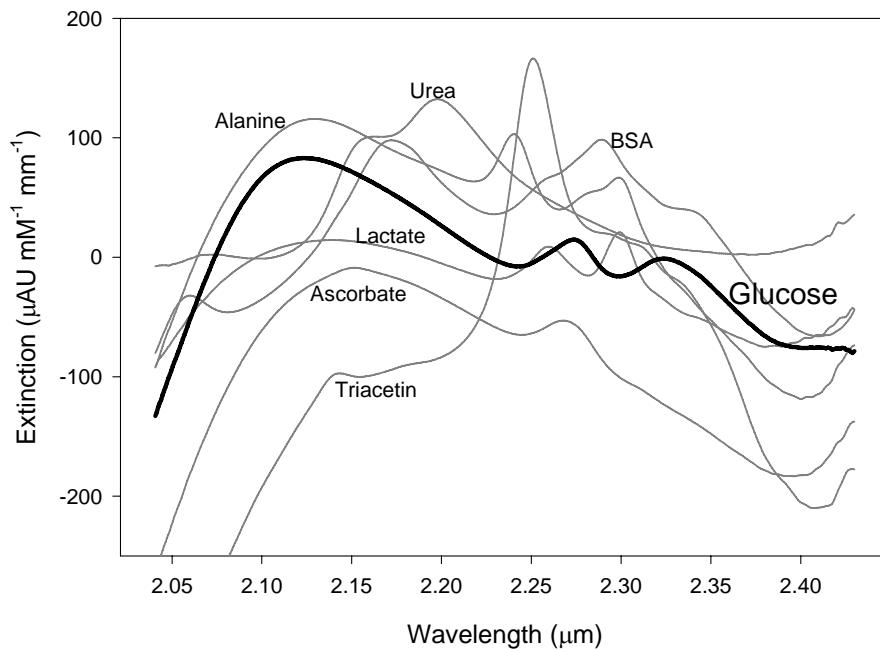


Figure 5: Extinction spectra of glucose and a family of related biomolecules. The glucose spectrum is shown with the bold line.

#### IMPLICATIONS FOR INFRARED SOURCE AND DETECTOR TECHNOLOGY

Much of the current work in non-invasive chemical sensing presently relies on large and delicate interferometric instruments in conjunction with high-power-draw thermal light sources and liquid-nitrogen cooled detectors. This level of technology is clearly insufficient for compact, portable, low-power individual monitoring systems. The

minimum requirements for an infrared biochemical sensor are that it be able to make wavelength-dependent spectral measurements with sufficient signal-to-noise ratios. The precise number of independent wavelength channels required depends on the chemical complexity of the particular site being sampled. It is likely that greater than 12 wavelength channels will be required for measurement in the 2.0-2.5  $\mu\text{m}$  wavelength range; approximately 3-8 are required in the 6-10  $\mu\text{m}$  fingerprint region.

By far the most important requirement of a spectroscopy system is the signal-to-noise ratio. This is because the absorbance of the target analyte (e.g., glucose, lactate, etc.) is several orders of magnitude smaller than absorption due to water. Typical signal-to-noise values required for successful measurement of glucose in a tissue sample are on the order of  $10^5 \text{ Hz}^{1/2}$  for each wavelength channel.

For anything beyond a research prototype, cryogenic cooling is not a practical option, which means source and detector elements must operate within the limits imposed by thermoelectric cooling. For an implantable device (and even for a small portable unit), operation must be possible at room or body temperature.

There are at least three general sensor implementation strategies that can be envisioned. The first would utilize a broadband source (e.g., a light-emitting diode) coupled with a miniature spectrometer, which in turn could utilize a single-element detector or a detector array. The second implementation strategy would utilize a set of single-wavelength sources (e.g., laser diodes) coupled into a single-element detector. A third strategy would be to develop a narrow-wavelength tunable source using a laser diode incorporating electronic tuning or embedded in an external cavity.

The tunable source strategy is attractive in that it utilizes only two devices (the source and a single-element detector). Also, a high-brightness laser source can potentially overcome the low optical throughput caused by water absorption and provide high signal-to-noise ratios even with an uncooled detector. As stated before, the absorption line width of biomolecules in solution are very broad, thus spectral resolution requirements are not stringent. However, a wide tuning range will be required for the multivariate calibration techniques. Depending on the sample matrix, the required tuning range can vary from  $200\text{-}800 \text{ cm}^{-1}$  (25-100 meV).

## ACKNOWLEDGEMENTS

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