A Review on Non-Invasive Blood Glucometer Based on Photoacoustic Method

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Abstract

Diabetes is one of the biggest health challenges in human beings in 21st century. Determination of blood glucose level is a frequently occurring procedure in diabetes care. As the most common method involves collecting blood drops for chemical analysis, it is invasive and liable to afflict a degree of pain and cause a skin injury. To eliminate these disadvantages, this project focuses on pulsed photo acoustic techniques, which have potential ability in non-invasive blood glucose measurement. The fundamental theory of photo acoustics in liquid and soft tissue will be studied systematically. The distributions of photo acoustic sources in a near-infrared optical skin model can be simulated by the Monte Carlo method. Expansion coefficient and specific heat of glucose solution will be measured by thermodynamic method, while the sound velocity in it can be determined by photo acoustic approach.The effect of glucose on blood optical scattering can be studied by a picosecond pulsed laser. A photo acoustic apparatus comprising a pulsed laser diode and a piezoelectric transducer can be built and applied to measure glucose concentration in water and scattering media. Moreover, this apparatus can be used to non-invasive experiment on human fingers.
Keywords: Photo Acoustic Measurement, Glucose Determination, Tissue Optics, Acoustic Detection, PVDF, Pulsed Dye Lasers

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I. INTRODUCTION

Diabetes mellitus is a serious disease that affects not only the patient’s internal organs, circulation system and eyesight, but also his entire life. There are reportedly more than 120 million diabetic people in the world at the moment, and this figure is expected to double within the next ten years. The first step in diabetes care is to monitor the patient's blood glucose level 24 hours a day. Knowing the glucose level assists in determining the right diet and medical treatment.

Current methods of measuring blood glucose concentrations require the diabetic patient to puncture a finger to collect a drop of blood, whose chemical composition is then analysed by a glucose meter. As the procedure is not totally painless and harms the skin, diabetics are often unwilling to check their glucose level as frequently as doctors would wish. During the last fifteen years, this has resulted in the proliferation of non-invasive measurements based often on optical methods. These are particularly suitable for the purpose, because they utilize non-ionizing radiation to examine the human body, they do not generally require consumable reagents and they provide fast responses. Moreover, the availability of low cost, sophisticated lasers and optical detectors add to the list of attractive characteristics.

All non-invasive optical methods utilize a beam of light to irradiate some selected part of the human body, such as a finger, the forearm, tongue, lip, thigh or abdomen and so on. Light that is transmitted through, reflected or scattered out of the skin comprises information about the composition of the illuminated tissue. This light is then received by optical detectors and analysed to determine the concentrations of certain analytes, such as oxygen or haemoglobin. The analysis, however, is inherently complex because the received signal is often very faint and easily interfered with not only by a number of analytes in blood, but also by other factors including the variability and inhomogeneity of the human skin and the constantly changing human physiology. Other non-invasive methods take advantage of the correlation that exists between glucose content in the interstitial fluid and capillary blood. From the clinical point of view, the main flaw in these otherwise excellent methods is that they are time consuming. Furthermore, they only provide an indirect measure of glucose concentration which is, unfortunately, also time-delayed.

The technique of laser photo acoustic (PA) spectroscopy has been used in trace detection due to the high sensitivity it offers. In this method, a high-energy laser beam is used to irradiate the matter under study. The beam produces a thermal expansion in the matter, thereby generating an acoustic wave. The characteristics of the wave are determined not only by the optical absorption coefficient of the matter, but also by such thermal physical parameters as thermal expansion, specific heat and sound velocity. In addition, the acoustic wave may also be affected by optical scattering which influences the distribution of light in the matter. Accordingly, relative to optical absorption spectroscopy, the PA technique offers an inherently higher degree of sensitivity. In the 1970s, PA spectroscopy made great progress in the trace analysis of gases and condensed matter. Its application range quickly embraced the food industry, atmospheric inspection, semiconductor process, materials testing and in the oil industry, with a particular emphasis on the study of powders, gels, emulsions, suspensions and other highly scattering or opaque materials. The method allows a range of measurements, including *in vitro* and *in vivo* non-invasive online measurements. Unlike ordinary acoustics, sound waves produced by the PA method carry information about the material properties of the substance in which they are generated. Thus, they can be used to study both the propagation medium and the substance excited directly by the energy radiation. Since the 1990s, the pulsed PA technique has found frequent use in biomedicine, where it has achieved great progress in the non-invasive measurement of the optical properties of tissue, tissue diagnostics and imaging. However, the method faces similar difficulties as the aforementioned optical approaches in non-invasive blood glucose measurements.

This dissertation reports a set of studies involving photo acoustics, tissue optics and glucose measurements in vitro. The findings are also useful for certain other forms of trace detection as well. In addition, the experiences acquired during the study may also serve the future development non-invasive blood glucose determination methods.

II. METHODOLOGY

A. Laser Sources

PA waves can be generated by any radiation energy source with a short duration. Thermo elastic generation, however, requires a high power radiation source, due to the low efficiency (< 0.0001) of optical to acoustic transformation. Pulsed laser sources have some advantages over continuous-wave modulating sources in terms of PA techniques. First, pulsed lasers offer higher detection sensitivity owing to their high output power producing a correspondingly strong PA signal. The high frequency PA signals produced by pulsed lasers are easy to separate from the low frequency noise in the environment, resulting in a low noise level. Furthermore, the use of timing gates is a very efficient technique for getting rid of noise signals produced by the absorption and light scattering from other parts of apparatus. Secondly, in spite of their high output power, pulsed lasers are free of convection currents and, owing to their low duty cycle, they are immune to the spurious effect caused by sample heating. Avoiding sample heating is an important consideration for some applications. Thirdly, unlike continuous-wave lasers, PA signals generated by pulsed lasers exhibit no complex dependence on the thermal diffusion length and chopping frequency. And, finally, narrow banding the laser with intra-cavity etalons enables high-resolution studies.

Various kinds of gases, solids, semiconductors and dye lasers have been used in PA spectroscopy and photo acoustics. In recent years, near-infrared laser sources such as the Nd: YAG laser and the diode laser have been widely used in PA research in biomedicine and environmental protection. These devices allow the study of the internal properties and structure of weakly absorbing materials in the near-infrared region, including aqueous substances and most bio-tissues.

1) *Q-switched Nd: YAG laser*

In the Nd: YAG laser, Nd3+ ions are embedded in the solid matrix of an yttrium aluminium garnet (Y3Al5O12). Laser action is induced by the level transitions of the Nd3+ ions. Usually, a flash lamp is used for pumping the laser in the high power pulsed operation at a transition wavelength of 1.06 μm. If the peak power of the pulse is sufficiently high, a suitable crystal can be used to generate the second and third harmonic at 532 nm and 355 nm, respectively. The output energy is usually on the order of mJ and can reach the order of sub-Joule, where the pulse duration ranges from a few nanoseconds to a few hundreds of nanoseconds. Moreover, other wavelengths, for examples, 436nm and 461 nm, can be produced by applying a Raman shifter to the output of the laser. Based on the correlation between the reduced scattering coefficient and the glucose concentration of the tissue, the time-resolved PA measurement of tissue optical parameters may be used in non-invasive glucose measurements. The main advantage is improved detection sensitivity (-3%/mM).

2) *Pulsed diode lasers*

The diode laser is based on the recombination of electrons and holes in semiconductors and in the associated release of energy in the form of light radiation. The wavelength of the radiated emission is determined by the band gap of the active semiconductor layer. Although the diode laser has some disadvantages such as relatively low output energy and poor directionality, it has a wide application range, due to its lightweight, small volume, high efficiency, low price and easy compaction. With wavelengths in the near infrared and middle-infrared region, current diode lasers can be very useful in biomedical applications and environmental monitoring.

The advance direction of a diode laser is toward to reduce the threshold current density and the line width of the lasing emission. A typical structure comprises a double hetero structure and a buried hetero structure in which the active layer takes the form of a narrow stripe of semiconductor material. Many diode lasers have been developed for the needs of optical communications, with wavelengths corresponding to the absorption minima of optical fibbers (880 nm, 1300 nm and 1550 nm). Diode lasers emitting at other wavelengths have also been made available in recent years. However, the output energy of most laser diodes is too weak for PA generation, although some high power pulsed laser diodes listed in Table 10 below are capable of producing a detectable PA signal. These high power laser diodes, driven by peak currents of several Amperes, have are relatively large volume active region. The output pulses have the duration of one hundred microseconds or more.

Table – 1
Commercial Pulsed Laser Diodes with High Output Energy

λ (nm)	Manufacturer	Model	Pulse Energy (μJ)	Emitting area (μm × μm)	# of diodes
810	SDL	2100	0.1		1
850	Northem Telecom	LP8M10C	0.2		1
880	Hamamatus	L4356	4.0		1
904	LDP Inc.	LD-163	5.0		3
905	EG&G	PGAS1S24	4.0	600 × 1	1
905	EG&G	PGAF5S16	16.0	400 × 450	5
1300	EG&G	C86045	1.0		1
1550	EG&G	C86091E	0.8	150 × 1	1

B. Acoustic Detectors

Several different types of acoustic detectors are available for PA detection. They include microphones, piezoelectric transducers, capacitance transducers, fibre-optic sensors, noncontact optical detectors, and so on . The choice of detector for a particular application is mainly based on factors such as detection style, sensitivity, response time, bandwidth, impedance matching, noise, size and ruggedness. In the PA study of condensed matter, the most common detectors are the piezoelectric transducer and the non-contact optical detector. The former has a good acoustic impedance match while the latter can requires no contact with the object of study or form all optical devices.

1) *Piezoelectric detection*

The piezoelectric effect is based on an electric charge produced on the surface of a material when deformed by pressure. This effect was first observed in natural crystals and is caused by a certain type of asymmetry in the crystal's structure. Any pressure change will distort the crystal, leading to a redistribution of charged elements in the lattice. The net result of this redistribution shows on the surfaces of the crystal. The voltage response of a thin piezoelectric element to a normal incidence plane pressure wave increases linearly as a function of the element's thickness, and is also proportional to its piezoelectric constants. However, if the thickness of the element exceeds the acoustic wavelength, a further increase in thickness does not result in a proportional increase in output voltage. If the acoustic waves are not planar in shape, the cross-sectional area of the element becomes an important consideration, since the pressure exerted may not be uniform over its entire area. The rise time of a piezoelectric element is equal to the ratio of the element's thickness and the acoustic velocity in the element.

Table - 2
Properties of Commonly Used Piezoelectric Materials.

	$LiNbO_3$ (z-cut)	PZT-5A	PVDF
Piezoelectric constant			
d_{33} (10^{-12} C/N)	6	374	-39 ~ -44
g_{33} (Vm/N)	0.023	0.025	- 0.32
Mechanical Q factor	100	75	5 ~ 10
Density (g/cm^3)	4.64	7.7	1.78
Sound velocity (m/s)	7316	4500	2260
Acoustic impedance (10^6 kg/(m^{2}s))	33	35	4
Work temperature (^{o}C)	< 1100	< 300	< 60
Advantages	wideband, rugged	high sensitivity, inexpensive	wideband, inexpensive
Disadvantages	expensive	narrowband, ringing	non-rugged

In the reception of PA waves, commonly used piezoelectric materials include single crystals (quartz, lithium niobate), polycrystalline ceramics (lead zirconate titanate, Barium titanate, lead metaniobate) and polymer materials (PVDF, Teflon and

Mylar). The most important properties and parameters of lithium niobate (LiNbO3), lead zirconate titanate (PZT-5A) and PVDF are listed in Table 2.

2) *Ceramic transducer*
Piezoelectric ceramics are hard, dense and can be manufactured in almost any given shape or size. Their physical, chemical and piezoelectric characteristics can be tailored to specific applications. They are chemically inert and immune to moisture and other atmospheric conditions. Their mechanical and electrical axes are set during “poling”, and can be precisely oriented in relation to the shape of the ceramic. The geometry and composition of the ceramic element determines its resonant frequencies. If the frequencies of the acoustic waves received match the resonant frequencies of the piezoelectric element, the element will produce a maximum electrical signal.

3) *Polymer transducer*
The PA response of a ceramic transducer is often dominated by the transducer's own frequency characteristics, which usually differ from those obtained with frequency spectroscopy. Hence, the shape of the electrical response produced by a ceramic transducer is not identical to the PA waveform. This is a drawback for applications that require a faithful reproduction of the PA waveform. By contrast, a polymer film transducer is capable of satisfying this requirement, due to its wideband characteristics and flat sensitivity–frequency curve, which is very useful in time-resolved PA detection and medical imaging. Moreover, as polymers are flexible and thin up to a few micro meters, the receiving surface of the transducer can be shaped at will.

The most common type of polymer used in transducers is a PVDF thin film. The transducer could be a fast rise-time (~ 5 ns) and a wide bandwidth (> 100 MHz). Tam has used a PVDF transducer successfully to receive 10 ns acoustic pulses. The acoustic impedance of PVDF is about 4.1 . 106 kg/m2s, closely matching that of soft tissues and water (1.5 . 106 kg/m2s). The mechanical *Q* factor of PVDF is low enough to prevent ringing at the relevant frequencies. Although film thickness is a significant consideration, the film diameter is also important in time-resolved measurements. In reality, the active part of a piezoelectric film integrates the pressure experienced over its entire active area to produce a voltage output. To assure a broad angular response and to preclude diffraction effects from frequency filtering of the transducer's response, the diameter of the active area of a PVDF film is ideally restricted to a quarter of the wavelength at the highest frequency of interest. In medical applications, where many frequency components are typically below 3 MHz, the diameter of the film tends to be 200 ~ 400 μm. If the active diameter is larger than that, the alignment of the transducer relative to the acoustic wave under measurement is of critical importance. In addition, there is a trade-off between the size of the active area and measurement sensitivity.

C. Pulsed Pa Apparatus Based On A Laser Diode - PVDF Transducer
A schematic of the experimental apparatus is shown in Fig. 1. In this set-up, a laser, driven by a laser-driving circuit, outputs light pulses that are projected onto a sample. The acoustic wave produced in the sample is received by an acoustic transducer, which transforms it into an electrical signal. An amplifier enhances the output of the transducer, and the final electrical signal is input to a digital oscilloscope for analysis and storage. In the experiments described in this thesis, the exciting source is a laser diode, because it has a stable optical pulse, which makes energy monitoring and the normalization of the acoustic signal to pulse energy unnecessary.

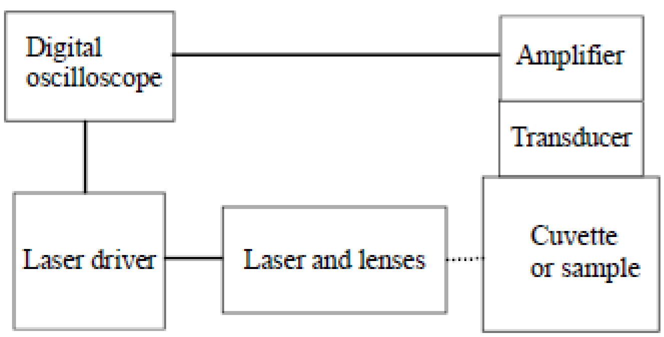

Fig. 1: Schematic of the PA Apparatus

III. CONCLUSION

In India the most popular method for the measurement of the blood glucose is invasive method in which most of these involve drawing blood through a small pinprick and placing a drop on a test strip. This is risk of infection, costly and discomfort for the patients. Our Aim is to provide an innovative idea to solve the existing problems, which patients are facing with the current glucose meter technique. This can be used for continuous monitoring of glucose in home by the patients which is of high accuracy.

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