

## Spring 2005 FINAL REPORT

### IPRO-331 Non-Invasive Blood Glucose Monitoring System

#### Team Members:

|                        |                         |
|------------------------|-------------------------|
| Leland Barnard         | Yio-Fan (Deborah) Hsu   |
| Ben Freemire           | Jude Kieltyka           |
| Wadzanayi Maketiwa     | Stephen Mullins         |
| Mehjabeen (Maje) Nazim | Veeral Oza              |
| Prabhav Patil          | Quratulann (Annie) Riaz |
| Vidya Shivakumar       | Daniel Young            |

**Professor:** Dr. Emmanuel Opara

**Consultants:** Ray Deboth, Dr. Gottlieb, Keith Brembaugh

#### **Background:**

Numerous blood glucose-monitoring devices on the market today, require pricking of the finger to draw a sample of blood in order to obtain blood glucose readings. As it would be imagined, multiple piercing of the finger with a lancet daily is highly uncomfortable and undesirable for any individual. This also leads to sore fingers and is especially difficult for children. In addition, more than 10% of the population is also afflicted with Aichmophobia –the fear of needles.

In contrast to the current devices in the market that cause discomfort and pain, our device offers a superior alternative. This device does not involve piercing of the finger or even drawing up blood. It simply uses interstitial fluid drawn up by a light suction vacuum from the skin to obtain an accurate glucose reading by measurement of electrical impedance. To facilitate the sampling of the interstitial fluid, ultrasound waves are used to disrupt the bio-lipid layer of the skin. This method creates pores in the skin to permit extraction of interstitial fluid without the pain and hassle of drawing blood. It is hoped that this new technology will relieve diabetic patients of painful piercing lancets and expensive glucose monitoring strips. There will be no pricking and bleeding involved; all patients, especially pediatric patients, will be sure to prefer the non-invasive glucose monitor as it will eliminate the hassle and fear of the conventional methods, making finger pricking look archaic. Future modifications in the development of the final device will include incorporating an insulin delivery system into the device.

#### **Problem Objective Statement**

The objective of this IPRO project is to investigate, research, and develop methods of non-invasive blood glucose monitoring, with a view towards continuing the work of the previous two IPRO 331 teams (Spring 2004, Fall 2004). In addition to the technical aspects of this project, a direction towards marketing and patenting our novel idea has also been a goal of this year's IPRO.

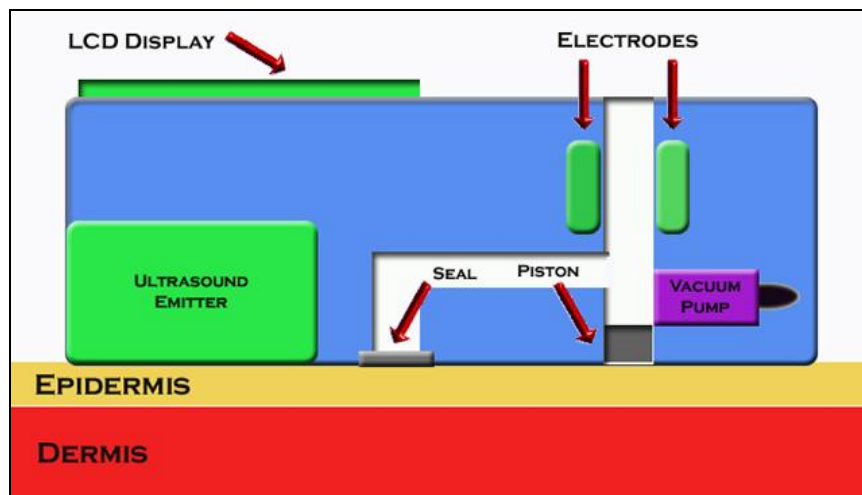
#### **Documentation of the final design**

The final design (Figure 1) uses ultrasound to disrupt the skin's bio-lipid layer, followed by reverse-iontophoresis to facilitate the suction of interstitial fluid. The

suction of interstitial fluid is performed with a pressure differentiated vacuum in which the low pressure is used to remove sweat which is evaporated, and the higher pressure suction is used to draw-up interstitial fluid. Electrical impedance is then used to obtain a glucose reading, which is displayed on a digital screen. The digital screen will display a history of glucose readings including the current glucose concentration. As a result, the user will know the trend of his or her blood glucose concentration whether it has decreased or increased from the previous reading. This will enable the user to act and deliver insulin accordingly from the readings. Our device has not entered testing phase, as its funding is still pending. However, various published research articles have proven the validity of the individual components of our device.

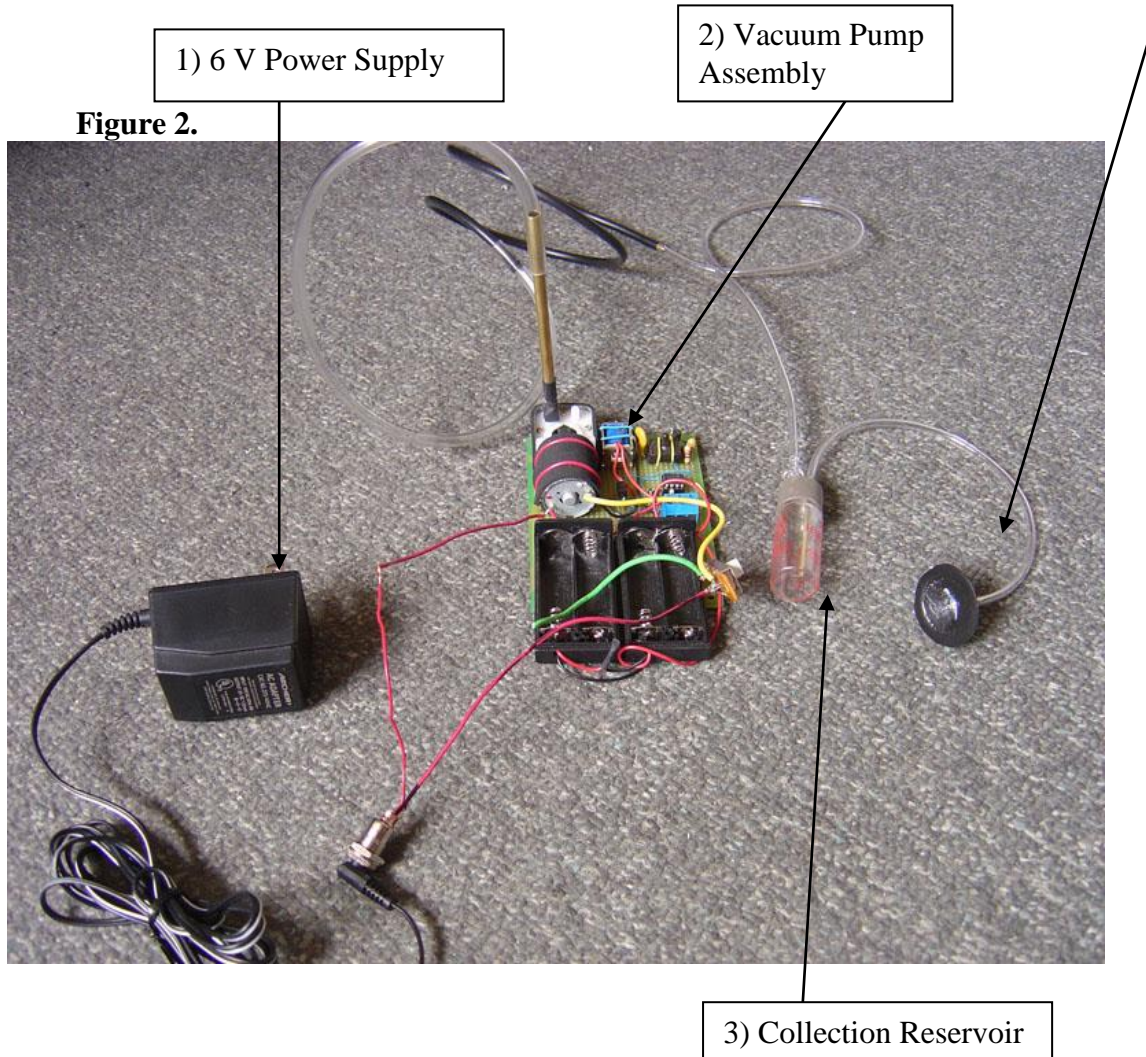
The standard frequency used for ultra-sound is 20 kHz, and the reverse-iontophoresis needs to be at a low current of roughly  $0.3\text{mA}/\text{cm}^2$  with a small warm-up period required to reflect the systematic readings. The vacuum should be of differentiated pressure, and the electrical impedance of the sensor depends on impedance changes within human skin and underlying tissue. Radio wave impedance spectroscopy measures how changes in blood composition affect the impedance pattern of the skin and underlying tissue. Usually, the dielectric spectrum is measured over a range of frequencies from 100Hz to 100MHz. Previous studies have shown that impedance sensor signals correlated with changes in blood glucose.<sup>1</sup> The device will be optimized to measure the effects of glucose molecules on the impedance pattern. These measurements are then correlated to glucose concentrations.

The risk involved with using ultrasound to facilitate the suction of interstitial fluid is minimal according to previous studies. There is no pain associated with ultrasound during the procedure and there is no visible damage to the skin.<sup>2</sup> However, further studies assessing the safety of ultrasound after repeated extractions are still required. Next, the risk involved with reverse-iontophoresis is that in very few cases, it has caused minor burns and some skin irritation. In addition, the vacuum suction should not be at too high a pressure to cause redness or discomfort to the patients' skin. For electrical impedance, measurements are also affected by factors other than glucose. These factors include the concentration of electrolytes in the blood and body temperature.<sup>1</sup> The effects of these factors will be studied further. Electrical impedance has no apparent risks and is also used in breast cancer scanning for early detection of cancer.



**Figure 1.** The above diagram indicates the rough schematic design of our proposed prototype.

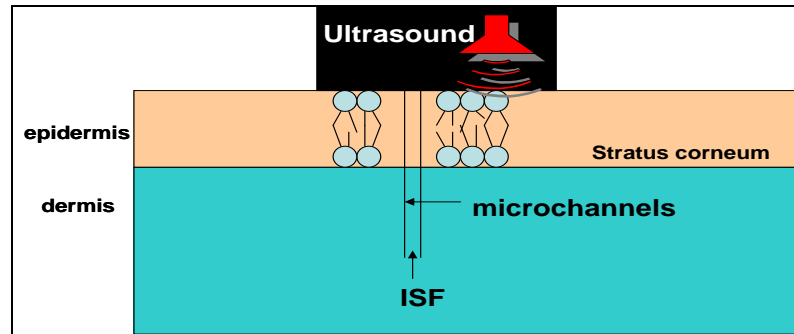
**Prototype of the final design**



As shown in Figure 2, the current prototype has the capability to draw up fluid into a small glass reservoir (3) through the plastic vacuum formed cone (4). The vacuum pump (2) is powered by a 6 V power supply (1), or it can alternatively be powered by four AA batteries. Eventually, an ultrasonic speaker (at approximately 20kHz) will be used to speed up the liquid withdrawal process. Reverse iontophoresis will also be implemented in the near future. Impedance spectroscopy will be used across the collection reservoir to measure the glucose content of the interstitial fluid.

In order to draw up the interstitial fluid, the suction cone will first be applied to the skin. An ultrasonic speaker will be used to dilate the pores of the skin, disrupting the lipid bilayer and forming more channels for the interstitial fluid to escape the body (as show in Figure 3 below).

**Figure 3.**



A weak electric current will be applied across the skin to draw up charged particles, again enhancing the withdrawal of fluid. Figure 1 briefly explains the process, assuming the drug is interstitial fluid.

### **Accomplishments:**

Our IPRO group has accomplished all of the goals that we have set for ourselves this semester. We have researched and improved the technical aspects of our design, looked into and determined the patentability and analyzed the market appeal of our product. In addition we applied for funding from numerous companies and organizations and entered the highly recognized BME idea competition sponsored by the National Collegiate Inventors and Innovators Alliance as well as the Whitaker Foundation. The competition will be held over the summer and the prize is \$10,000.

#### **1. Proof that the design is functional and will solve the problem**

Each component of this device has been tested individually and reported in various prestigious medical journals. The paper by Mitragotri et. al.<sup>3</sup> describes the analysis of ultrasonically extracted interstitial fluid. It was reported that low frequency ultrasound rapidly increased skin permeability for up to 15 hours. Furthermore, it was shown that low frequency ultrasound at around 20kHz increased the permeability of skin by many orders of magnitude, much better than using high frequency ultrasound. “Reverse Iontophoresis for Non-Invasive Transdermal Monitoring” by Benoit Leboulanger, et al<sup>4</sup>, describes the mechanism of reverse-iontophoresis and shows that reverse-iontophoresis may be used to extract interstitial fluid. In reverse-iontophoresis, a small electric current is applied and the sodium ions ( $\text{Na}^+$ ) move towards the cathode. Sodium ion is the major charge carrier in iontophoresis, and much like sodium, calcium ion ( $\text{Ca}^{2+}$ ) performs the same function towards the anode. The uncharged particles such as glucose are carried by electro osmosis to the cathode.

Electro osmosis describes the movement of molecules through a porous membrane by an electric field. Reverse-iontophoresis, which also induces electroosmosis, is used to extract interstitial fluid with a vacuum. The vacuum should have a differentiated pressure in which the lower pressure is used to remove sweat which is later evaporated, and the higher pressure is used to extract interstitial fluid. The extra pores created by the ultrasound facilitate the extraction of the interstitial fluid with ease.

Next, the accuracy and precision of using electrical impedance to measure glucose concentrations through interstitial fluid is proven by many papers including the article by Caduff et. al.<sup>5</sup> A number of clinical-experimental studies were performed on healthy subjects in order to prove the applicability of electrical impedance in measuring glucose concentration. In most cases, the experiments showed a good correlation between changes in blood glucose and sensor recordings. These experiments can be considered as proof of the validity of this concept.<sup>5</sup>

When all the separate components are integrated into a functional prototype, further steps in its final development include miniaturization of the prototype and incorporating insulin delivery. Our device will solve the problem of using invasive techniques for measuring blood glucose concentration, because the device will be a non-invasive and painless way of accurately measuring blood glucose concentration.

## **2. Results of a patent search**

There are a number of approved patents already in existence describing techniques for noninvasive blood glucose monitoring. The majority of them are based on spectrophotometry processes, however some incorporate aspects of our own design. These are as follows:

*US patent number 6 522 903: Glucose Measurement Utilizing Non-invasive Assessment, February 2003.*

This is a somewhat broad patent which claims a process which includes a number of different techniques for collecting interstitial fluid and measuring the glucose content therein. Of particular interest, it describes collection via suction, iontophoretic extraction, and sonophoretic extraction, among a number of other extraction methods. These are precisely the methods our device utilizes for collection of fluid. Furthermore, this patent claims the use of electrochemical impedance spectroscopy, among a number of other techniques, as a means to measure the glucose content in the interstitial fluid, once collected. This is also a technique which we have incorporated into our design. The patent does not describe with any amount of specific detail how the inventors intend to accomplish any of the claims they've made, and as such if we can determine a highly detailed methodology for our claims, this particular patent should not obstruct attainment of our own patent.

*US patent number 5 458 140: Enhancement of transdermal monitoring applications with ultrasound and chemical enhancers, October 1995.*

This patent specifically deals with the use of ultrasound to increase the permeability of the skin to aide in the collection of an analyte transdermally (sonophoresis). Contained within are the results of extensive research and a detailed methodology, describing the precise sound frequencies and power levels which are optimal for the extraction of fluid through the skin. This patent very clearly claims the sonophoretic collection technique employed by our device.

*US patent number 6 792 982: Vacuum device for substance extraction, September 2004.* This patent claims specifically a device, which is used to extract a fluid. It does not claim the extraction of interstitial fluid specifically, and the device described is highly specialized. The patent employs highly detailed schematic drawings of the prototype. A patent claiming an alternative device specifically for extracting interstitial fluid through the skin should not infringe on this patent.

That some of the key concepts in our design have already been explored and employed with some degree of success has two important implications. First, it suggests that our design concepts are solid and can likely be made to work. Second, certain aspects of our design are already protected by patents, which may adversely affect the patentability of our device. Our device is however the first to explicitly incorporate iontophoresis, sonophoresis, and vacuum suction together into a single unit for collection of interstitial fluid, along with the use of impedance spectroscopy as a means to measure the glucose content of the fluid. Thus our device may be patentable in its entirety; however, it remains to be seen if we have to seek licensing from any inventor(s) of relevant technology to incorporate any technique(s) into specific aspects of our prototype design.

### **3. Anticipated regulatory pathway**

Before entering the commercial market, our product will first have to undergo a series of stringent regulation tests to make sure that the product is safe and effective. Such regulatory pathways are usually carried out by the Food and Drug administration in the manner described as follows. Our product, falling under the category of “medical devices” would undergo several more specific areas.

The first criteria to be rated would be risk management. This is the process by which a product is assessed for potential risks or harmful effects that a consumer may experience while utilizing the product. To analyze risk management, three separate tests could potentially be run, two of which would be relevant to our design. The first, “Pre-market Approval” describes the methods by which the product is self analyzed by its producers/sponsors. This analysis is then reviewed by FDA officials, before its safety is verified. “Pre-market Acceptance” is a process that looks at current trends. This is only relevant if the product is similar to a model already in existence. Using “Pre-market Acceptance”, administrators can gauge public acceptance of the product, as well as known positive and negative aspects currently associated with it.

For the second criteria, a legalistic approach is taken as the FDA consults with other government agencies to come to a consensus on the safety of the product. Discussed here are regulations between different branches and sects to make sure that no rules are broken and that the product, once released, will cause as few legal issues as possible in the future. Also discussed are further definitions of safety risks and precautions associated with use of the product.

### **4. Estimated manufacturing cost**

Our research will require several resources. In order to test our device, we will require CD-rats that are 60 days old. Each rat costs \$30 (\$900 / 30 rats). Maintaining the rats in lab conditions for the duration of the experiment(s) (~30 days) will require an additional \$500. As mentioned earlier, our prototype will be using the concept of reverse iontophoresis. The reverse iontophoresis unit has been quoted at \$1500. In order for the experiment to be a success, it is essential that interstitial fluid can be withdrawn via the extra cellular membranes on the surface of the skin. This step requires a sonifier to disrupt the biological membranes. Branson digital Sonifiers are some of the best cost-

effective units in the market, and it has been priced at \$3200. A cylindrical horn, a piece of equipment that is a necessary peripheral device to the Sonifer has been priced at \$320. The students who will be performing the research and completing the prototype will be paid a stipend of ~\$1500 each (\$4500). Thus, the total budget of our development of this project is estimated at ~\$12000.

## **5. Market Analysis**

It is estimated that the United States spends over \$100 billion dollars annually for the direct and indirect treatments for diabetes. The home blood glucose monitoring sales worldwide are currently almost \$5 billion and the market is expected to expand to almost \$8 billion by 2007.

The regimen most often prescribed to patients with diabetes by their health care provider includes daily monitoring of blood glucose and insulin shots. If the blood glucose is not monitored multiple times a day as prescribed by a doctor, a diabetic individual could suffer hypoglycemia or hyperglycemia in which health complications such as high blood pressure, kidney failure, nerve damage, adult blindness, and a coma to name the few may result.

Numerous blood glucose monitoring devices on the market today involve pricking of the finger to draw a sample of blood in order to obtain blood glucose readings. There are over 25 different meters in the market today that vary in different ways; however they all still require the primitive technique of pricking of the skin. As it would be imagined, multiple piercing of the finger with a lancet daily is highly uncomfortable and undesirable for any individual; this would result in the discouragement of the proper monitoring of blood glucose levels. "Physicians who treat diabetes agree that continuous non-invasive monitoring of blood glucose will greatly improve compliance to frequent testing, which has been shown to significantly reduce severe complications related to diabetes and lead to reduced health care costs" (diabeteshealth.com). As a result of frequent glucose testing, the administration of insulin treatment can be tightly juxtaposed, which has been shown to reduce diabetes-related complications.

"A noninvasive device that's reliable, accurate, user-friendly, and not sensitive to environmental stresses would be a miracle," says Stephen Clement, MD, Director of Georgetown University Medical Center's Diabetes Center and Chair of the FDA Clinical Chemistry and Clinical Toxicology Devices Panel. "It will help patients make critical decisions in the moment, such as whether it's safe to exercise or drive a car."

As of now, only two non-invasive blood glucose monitoring devices have been approved by the U.S Food and Drug Administration. The Glucowatch G2 powered by Cygnus incorporated is worn on the arm like a wristwatch. It pulls up interstitial fluid every twenty minutes for up to 20 hours in order to detect levels of glucose in the blood; however, it may not be used as the sole source of glucose detection. It is meant to show patterns of the levels of glucose in the blood, and is supposed to be used in conjunction with the previous and trite methods of pricking the skin for blood. It is also only meant for those that are 18 years and above. The second monitor, which is manufactured by

Minimed is a catheter placed underneath the skin and detects glucose concentrations from the fluid that it traps. Just like the Glucowatch G2, it is not supposed to be used as a single device for monitoring the levels of sugar; however, it is used to monitor trends in the blood and must be downloaded to a reader in order to obtain the results.

There are many more prototypes that are being designed; however, many of them must first meet FDA requirements before they can be marketed. Many of the devices fall into a “high risk” category and must require more clinical and analytical studies. One device that has a good chance of making it into the market is the Pendra by Pendragon Medical. This device uses radio-wave impedance to measure the sugar levels, which has been known to be sufficiently accurate. This device is also just a supplement to the old-fashioned ways of finger pricking.

There is a desperate need for devices that are non invasive and can reliably monitor blood glucose levels. Since there are only two that have been FDA approved, our device has a high chance of being approved as both of the previous devices use different methods to ascertain the levels of sugar in the blood as compared to our device. Our methods will hopefully provide a device that is quicker at reading and also more precise than the previous two. Apart from the one time expense to purchase the sonifier and the iontophoresis apparatus, we estimate around \$200 - \$ 250 to be the cost of purchase of our device.

## **6. Business plan detailing strategy for commercialization and opportunity statement**

Our business plan is to work towards creating business, marketing and facilitation plans. We will also work on our risk assessments and sales program.

### *Funding*

The first step towards commercializing our product is to identify funding sources and to acquire funding. Currently, we are working on grant proposals to different agencies such as American Diabetes Association, Diabetes’ Wellness etc., to obtain funding to further our research and optimize the prototype.

### *Research Collaboration*

A team will be organized to perform extensive research, make a comprehensive prototype and to test our device. When this is completed, we will work on the miniaturization of our completed prototype.

### *Licensing*

Following the completion of our research, we will work to obtain a license for our completed prototype and idea. We have already performed a patent search and will work towards patenting our completed prototype.

### *Commercialization plans*

We will first perform field experiments and field demonstration and work on market and business assessments. Following this we will establish sales and marketing structures and work on a good sales program. We will then work aggressively to advertise and promote our product which will cost only about a third of what is already available in the market.

## **7. Grant Proposals**

This is a list of the organizations and companies that we applied to for funding of our project.



## **ASSIGNMENTS:**

### **Website group**

Stephen Mullins  
Daniel Young

### **One-page Abstract**

Jude Kieltyka

### **Comprehensive Deliverables CD**

Stephen Mullins  
Daniel Young

### **Sponsorship**

Whole team

### **Midterm Report**

Yio-Fan (Deborah) Hsu  
Quratulann (Annie) Riaz  
Veeral Oza

### **Device Design**

Yio-Fan (Deborah) Hsu  
Prabhav Patil  
Quratulann (Annie) Riaz  
Vidya Shivakumar

### **Patent Work**

Leland Barnard  
Daniel Young  
Stephen Mullins

### **Prototype**

Ben Freemire

Wadzanayi (Wadzi) Maketiwa  
Daniel Young  
Leland Barnard

### **Research**

Jude Kieltyka  
Mehjabeen (Maje) Nazim  
Veeral Oza  
Quratulann (Annie) Riaz

### **Project Plan Report**

Yio-Fan (Deborah) Hsu  
Wadzanayi (Wadzi) Maketiwa  
Mehjabeen (Maje) Nazim

### **Oral Presentation**

Jude Kieltyka  
Veeral Oza  
Prabhav Patil

### **Team Leader**

Jude Kieltyka

### **Team Minutes**

Mehjabeen (Maje) Nazim

### **Team Poster**

Leland Barnard  
Vidya Shivakumar

### **Final Report**

Leland Barnard  
Ben Freemire  
Vidya Shivakumar

## **Process of Working as a Team**

The way in which we operated throughout the semester was by allocating jobs according to expertise and converging our ideas at biweekly meetings. Our meetings provided for an outlet for us to communicate our ideas, positive comments, and constructive criticism. We also conducted peer evaluations as way of alerting group members of the quality of their performance so that improvements could be made and so that tasks could be distributed equally. As a whole our method enabled us to work well as we accomplished all of our goals that we had set in the beginning of the semester.

### **Acknowledgements:**

We would like to especially thank our advisor, Dr. Opara, as well as Mr. Deboth, Dr. Gottlieb, and Keith Brembaugh for their guidance and advice.

### **References**

1. Khalil, O.S. Non-invasive glucose measurement technologies: an update from 1999 to the dawn of the new millennium. *Diabetes Technology & Therapeutics*. 6(#5): 660-697, 2004.
2. Chuang, H, Barman S.P., Farnham H., and Trieu M.Q. Ultrasonic pretreatment enables continuous transdermal glucose monitoring. Presented at the Fourth Annual Diabetes Technology Meeting. Held October 28-30, 2004, Philadelphia, PA.
3. Mitragotri, S., Coleman M., Kost J., and Langer R. Analysis of ultrasonically extracted interstitial fluid as a predictor of blood glucose levels. *Journal of Applied Physiology*. 89(#3):964-966, 2000.
4. Leboulanger, B., Guy R.H., and Delgado-Charro M.B. Reverse iontophoresis for non-invasive transdermal monitoring. *Physiol. Meas.* 25 (#3):R35-R50, 2004.
5. Caduff, A., Hirt E., Feldman Y., Ali A., and Heinemann L. First human experiments with a novel non-invasive, non-optical continuous glucose monitoring system. *Biosensors & Bioelectronics*. 30 (#1):1-9, 2003.