Final Report Fall 2004
IPRO 331: Non-invasive Blood Glucose Monitoring

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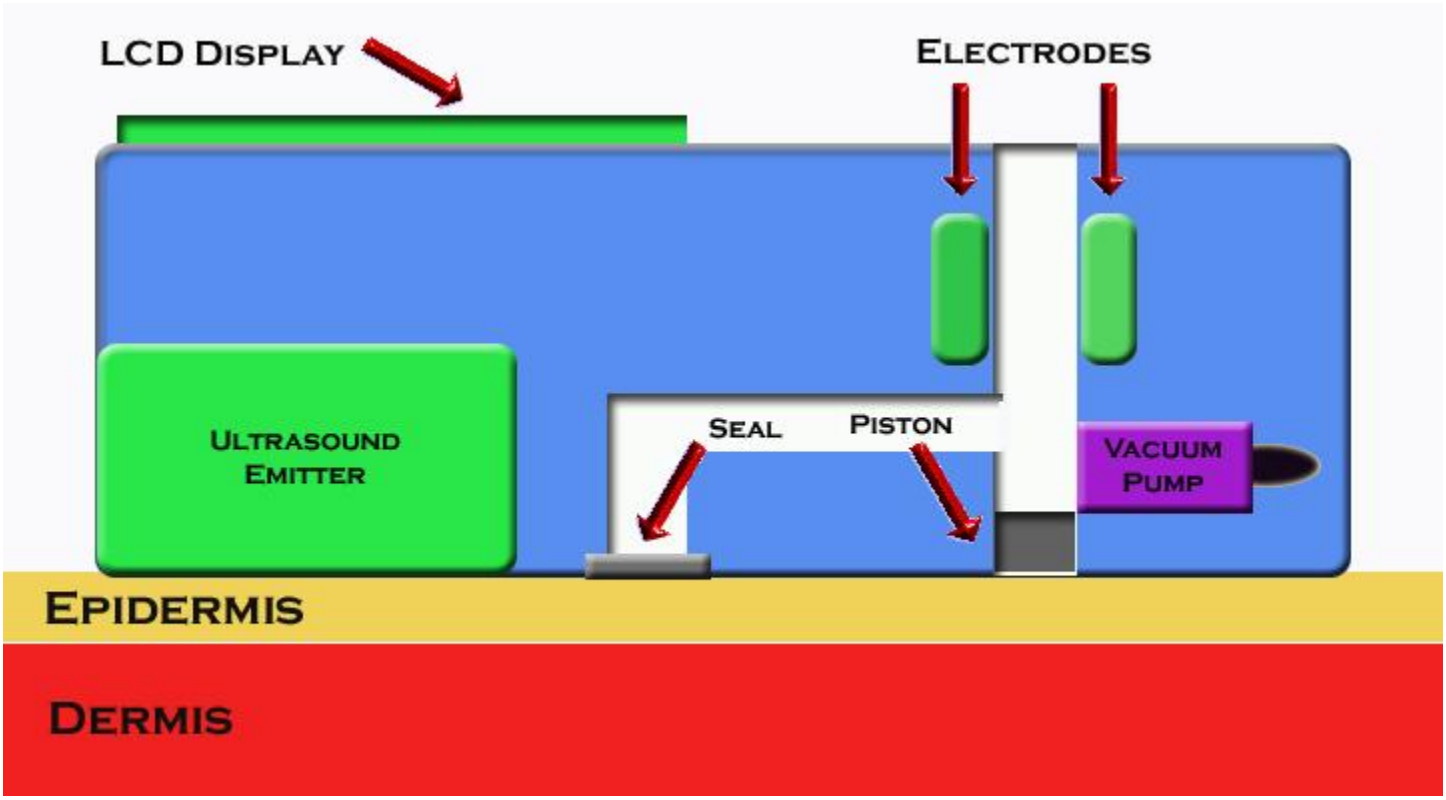
Purpose of project:

The objective of this Interprofessional Project is to develop a non-invasive blood glucose monitoring technique. Currently, invasive techniques such as venepuncture are used to monitor blood glucose levels in patients. Unfortunately, because diabetics must constantly monitor their blood sugar level, venepuncture is an undesirable procedure because it requires multiple needle punctures a day. Not surprisingly, this process is uncomfortable for patients, so there is a need for new technology. Many other techniques that involve measuring blood glucose concentration have been developed, but they require blood samples. Our purpose is to develop a method that measures glucose level without extracting blood. Therefore, our IPRO has developed a non-invasive design where glucose concentration is measured in hopes of potentially alleviating the discomforts associated with current invasive methods.

Project background:

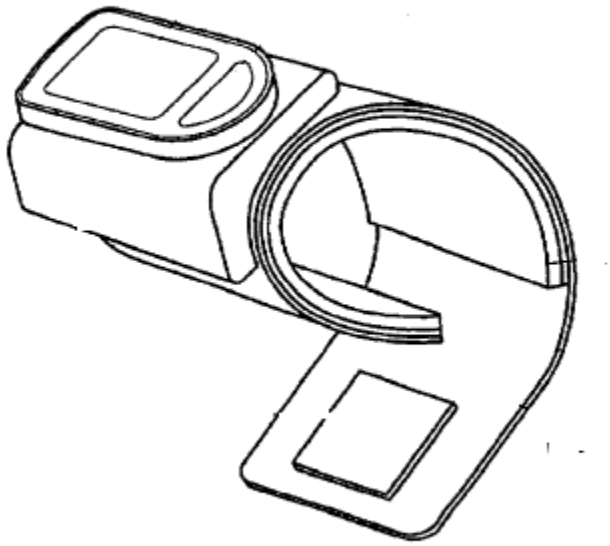
Diabetes mellitus is a group of devastating metabolic diseases caused by insufficient insulin synthesis, increased insulin destruction or ineffective insulin action. Its metabolic effects are due to a failure to acquire glucose from the blood. The metabolic imbalances that occur have serious, if not life-threatening, consequences. In insulin-dependent diabetes mellitus (IDDM), also called type 1 diabetes, low amounts (if any) of insulin are secreted because the beta-cells of the pancreas have been destroyed (endocrine disease). Because IDDM usually occurs before the age of 20, it has been referred to as juvenile-onset diabetes. Non-insulin-dependent diabetes mellitus (NIDDM), also called type 2 or adult-onset diabetes, is caused by the insensitivity of target tissues to insulin (metabolic disease).

Overview of design:



The ultrasound emitted permeates the skin, and the vacuum proceeds to draw any superficial fluids on the skin. The piston expels the fluid from the device through a one-way valve and returns to its initial position. A second stronger vacuum pulls approximately 5 microliters of interstitial fluid. The piston pushes the interstitial fluid between the two electrodes and discrete frequencies are aimed at the sample. The electrodes measure the impedance of the interstitial fluid which is then used to calculate the glucose concentration. The concentration is displayed on the LCD screen. The interstitial fluid is also expelled through the one way valve. The sensor is self cleaning when illuminated with UV. The piston is restored to its initial position.

Model Picture:



Cost of Non-invasive Glucose Blood Monitoring Device:

Equipment needed:

- **Ultrasound**
    1. **Transducer**
    2. **Amplifier**
- **Vacuum unit**
    1. **Batteries**
    2. **Vacuum pump**
- **Impedance device**
- **Titanium oxide film**
    1. **UV source**
    2. **Water storage**

50 test strips – $ 30 (replaced every 25 days or less)
Testing equipment $ 20- $ 50

Our technology:

Item	Cost Range ($)
Ultrasound components	**25-100**
Vacuum device including batteries	**15-20**

Total cost will be between $ 40 to $ 120
No replenishing of supplies : One time purchase

Findings:

Interstitial fluid can be drawn from the skin non-invasively. The glucose concentration in interstitial fluid can then be correlated with that of blood, removing the need to extract blood. The research conducted by the groups within the IPRO is presented below with the reasoning that led to the development of the final proposed design.

Vacuum

A vacuum can be used to pump up interstitial fluid after the skin permeability increases through ultrasound treatment. Two vacuums of different pressure will be used. The first pumping action will be of lower pressure to remove sweat and other secretions on the skin. This will clear the skin for our next step. A second pump will use a higher pressure to extract interstitial fluid. A more detailed discussion follows in the section labeled "ultrasound."

Iontophoresis

In this method, a low level electric current (0.3 mA/cm^2, square wave, bipolar, direct current) is passed through the skin between an anode and cathode. The current is carried by sodium ions (Na^+) to the cathode. Uncharged particles (such as glucose) are carried by electroosmosis to the cathode as well. Electroosmosis is the movement of a molecule through a porous membrane by an electric field.

The reason iontophoresis is effective is because the skin is naturally negatively charged, so Na^+ are easy to pull out of the skin towards the cathode. Interestingly, Na^+ concentration is relatively constant in the body, so it can be used to determine a ratio of the flux of glucose and the flux of sodium and eventually the glucose concentration (using Faraday's law).

Unfortunately, there are a number of drawbacks in iontophoresis. They include long duration of measurement time and cracking of the skin in the treated area. Most patients reported a tingling sensation and mild pain especially at the beginning of the treatments. Weighing the setbacks of this method, the group agreed to use an alternate technique to extract glucose and measure its concentration.

Ultrasound

Ultrasonic energy applied on the skin disorganizes the lipid-bilayer of the stratum corneum, and creates reversible microchannels in the skin through which fluids and analytes can be extracted and large molecules delivered. The transport permeability of the skin increases 100 fold after ultrasonic skin permeation. The skin is then left permeable for approximately 15 hours. Ultrasound thus presents a non-invasive way of obtaining interstitial fluid.

The next issue to address was how to draw up the interstitial fluid out of the skin. Since interstitial fluid comes up via the microchannels created by the ultrasound, we decided to use a vacuum to draw it up.

An airtight seal would be formed on the skin. There will be an internal piston within the device that will be controlled by a button. Once activated it will cause the piston to draw back, thus increasing the volume and reducing the pressure in the sealed space. This will cause the interstitial fluid to be drawn out of the microchannels and fill the space within the sealed area. The interstitial fluid will be directed in a collection device for glucose measurement.

The previous IPRO group determined that residual sweat on the skin interferes with accurate glucose measurement. The issue of getting rid of the residual sweat on the skin was addressed by researching the following methods:

a) Evaporate the water from sweat.
b) Treat salts in sweat with reagents, and then evaporate the water.
c) Use an alcohol rub to remove the sweat.
d) Use a vacuum to pull up both sweat and interstitial fluid.

After researching the above options, the team decided that the best solution would be to use the vacuum to pull both the sweat and interstitial fluid through the skin. The concept was to use pressure to pull up the sweat first, and then apply greater pressure to pull up the interstitial fluid. (The vacuum was described above as well.)

Self-Cleaning Sensors

After deciding to use the vacuum option the next step was to determine how to clean out the vacuum chamber after a sample was taken. As a result, the group looked into cleaning the vacuum chamber through self-cleaning sensors. Self-cleaning sensors are produced by the company TOTO. They are working on a film made of titanium oxide (TiO_2) which oxidizes organic compounds when illuminated with UV light. Another great feature of the titanium oxide film is that it is super hydrophilic. This means that when water is added to the TiO_2 and it is exposed to UV light, the water spreads to form a very thin layer because of its high affinity for water. If a contaminant is present on the surface of

the TiO_2, and water and UV are added, the water replaces the contaminants' positions on the film and the contaminants are oxidized. There is no need for detergents to clean the film. We are still deliberating how to incorporate UV and/or a water storage and application system to the protocol.

Determining Glucose Concentration with Impedance Spectroscopy

The last step in the process is to measure the glucose concentration. Various methods of measuring glucose concentration were researched such as Near Infrared Spectroscopy (NIR), Far Infrared Spectroscopy (FIR), and impedance spectroscopy. It was determined that dielectric impedance spectroscopy is the most favorable.

Radio wave impedance spectroscopy measures how changes in blood composition affect the impedance pattern of the skin and underlying tissue. The device itself is the size of a wrist watch and is fixed with an open resonant circuit which lies against the skin. This circuit performs the impedance measurement. The device is optimized to measure the affects of glucose molecules on the impedance pattern, these measurements are then correlated to glucose concentrations.

The components for a device using this technology will be inexpensive because they will be off-the-shelf and not custom-miniaturized versions of bench-top equipment. However, there are a few disadvantages of using impedance. Measurements are also affected by factors other than glucose, which must be accounted for to determine the relationship between impedance and blood glucose concentration. These factors include the concentration of electrolytes in the blood and body temperature.

Research methodology:

Over the course of the semester we divided ourselves into different groups. We began by learning about last semester's research on non-invasive glucose monitoring and decided to take the previous IPRO's ideas further. Each group researched topics that were necessary for developing a non-invasive technique. These topics included determining skin permeability, ionic properties of glucose, as well as infrared spectroscopy, iontophoresis, and impedance as methods of measuring glucose concentration. After evaluating the advantages and disadvantages of the researched topics, we decided to use ultrasonic energy and a two-way vacuum to extract interstitial fluid, and impedance spectroscopy to determine blood glucose concentration. A self cleaning titanium oxide film will be utilized to line the interior of the device.

Team organization & Assignments:

There were different groups assigned every time there was a new task at hand. Everyone in the class got to know each other during these smaller group sessions. Research assignments were conducted by the groups individually and subsequently presented in class.

Here is a listing of the research groups.
Ultrasound: Researched the ultrasound affect on the skin and the methods of the previous IPRO team.
Impedance spectroscopy: Researched what it was and how it operated. Also demonstrated if it could be used on interstitial fluid and not just blood.
Photoacoustics groups: Researched competing technology to ascertain a better alternative to the proposed device.
Infrared Spectroscopy (IR): Verified advantages and disadvantages of using IR.
Vacuum: Researched the pressure at which water evaporated off the skin at body temperature and what vacuum size would be needed.
Cleaning: Researched a way to clean the sensor area after a first reading was taken
Basic research on permeability: Researched the problems with the skin and all the different issues with sweat and how to eliminate it.

Obstacles and barriers:

The team faced several obstacles. These included how to split the research assignments and deliberating the course of action to take after conducting research. Generally, several students took leadership roles in the group to create focus so issues were resolved within a class period.

Other obstacles encountered were during the developmental process. The first major complication was sweat. Sweat posed a problem to all proposed methods because the salt content of sweat skewed measurements. Sweat also contains water which would dilute the sample if mixed with interstitial fluid. This was resolved by pulling a vacuum to suck up the sweat and expel it out of the chamber before interstitial fluid was extracted. The second problem was vacuum pressure. A relatively large vacuum is required to pull interstitial fluid from the skin and can lead to bruising and other skin damage. The problem was solved by researching how much pressure can pull the fluid body temperature. The use of ultrasound on the skin also helped to make the skin permeable so that a less powerful vacuum can remove the fluid. The final barrier was determining how to clean the chamber. The chamber would hold residual fluid from the previous measurements of the glucose and the sweat and this needed to be cleaned out. The solution to this obstacle the group found was a piston to eject the fluid from the chamber. There were also self cleaning sensors that would get rid of any residue on the walls of the chamber through the application of UV.

There were also misunderstandings regarding the possibility of a patent and who should be on it. Dr. Gottleib and Dr. Anderson graciously met with the whole group and several team members, respectively, to discuss the subject, so this is not an obstacle anymore.

Recommended next steps:

A primary objective is to obtain an intellectual patent for our design. We would also like to build a working prototype and have a display for it. We want future IPRO's to continue working on our concept and actualize a working model. Additionally, we are hope to enter our idea in NCIIA competition for biomedical engineering innovation, design and Entrepreneurship award. As a long term (and lofty) goal we would a company to use the idea and replace current methods of glucose monitoring.

References and Resources:

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