IPRO 308

DEVELOPMENT OF AN ARTIFICIAL PANCREAS

FINAL REPORT - FALL 2008

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	Adam Smith (Arch)
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Abstract

Our team was asked to come up with an innovative and non-invasive means of extracting and measuring glucose levels in the body as well as administering insulin back into the body, also by non-invasive means. Our research lead us to several reports on the effectiveness of ultrasound in expanding pore opening diameters. We decided to approach the problem with a device that would administer ultrasonic vibration to the surface of the skin thus expanding the pore openings. Once expanded a combination of vacuum and reverse iontophoresis would then extract a small amount of interstitial fluid. The fluid would be measured for glucose concentration using impedance spectroscopy. Once a glucose concentration was found, a proper amount of insulin would then be administered back through the skin by means of pressure and iontophoresis.

Our experiments were conducted on harvested porcine skin. Sonic vibration at or around 10kHz served as a substitute for ultrasound. Vacuum was administered to the surface of the skin after a set amount of time of sonic vibration. Although results at first seemed promising, further investigation into the behavior of harvested skin yielded that our results were not as they seemed. Impedance spectroscopy was explored by first trying to find the resonant frequency of glucose. Earlier attempts at this were unsuccessful do to frequency limitations of measuring devices. Our team learned of a device that could measure 10 times higher frequencies than what had previously been recorded, but unfortunately was unable to solidify a concrete resonant frequency for glucose.

Background

21 million Americans are currently battling diabetes, and 54 million adults and children in the U.S. are on the verge of being diagnosed with diabetes. The United States spend approximately 132 billion on diabetes-related issues per year. Diabetes alone represents 11% of the U.S. health care expenditure.

Diabetes is an illness that is becoming more prevalent around the world and is linked with either

abnormal insulin production, or utilization or both in the body. Diabetes may be classified into two groups: Type 1 and Type 2 In an individual with Type 1 diabetes, the pancreatic ß cells that normally produce insulin are nonexistent as they have been destroyed due to autoimmune response. In an individual with Type 2 diabetes there is tissue-wide resistance to insulin and usually some impairment of ß cells as well. Therefore, although insulin production may be present its functionality is impaired. Type 1 diabetes is typically treated with frequent extraneous insulin injections, depending on the prevailing blood glucose levels of the individual; however, in order to determine the glucose levels individuals subject themselves to periodic finger pricks throughout the day which is often uncomfortable and stressful.

Mechanical devices for insulin delivery, also known as “artificial pancreases” or “insulin pump” are currently available in the marketplace. Those devices are more convenient than traditional way which people have to inject insulin 5-10 times a day. However, these devices are not only highly invasive and painful, but also must be sanitized frequently to prevent infections. Most people who using those machines says they don’t need to stick a needle many times a day, but now the needle and tube is in there all the time. So it can't be removed for more than a few minutes at a time (bathing, etc.). Also they still need to check the glucose level with needles in the glucose monitor. As a result, they are inconvenient and many diabetic patients still have complained about that. The goal of IPRO 308 is to develop an automated, non-invasive artificial pancreas that will be capable of determining blood glucose levels and administering an appropriate amount of insulin into the blood stream while causing minimal discomfort to the individual.

Insulin is a necessary hormone to sustain metabolic activity; however, excessive amounts may be fatal. Therefore, we have a responsibility to ensure that our product maintains the highest safety standards. Ultimately an algorithm based upon the measured interstitial glucose concentration recorded will have to be written to output a calculated dose of insulin to the individual without compromising their safety.

The past IPRO groups made great strides in researching various extraction techniques, measuring techniques, and also in documenting their successes and problems. For example previous semesters have identified the optimal frequency at which to operate sonophoresis, established a relationship to acquire porcine skin for testing, and also established connections at UIC to perform impedance spectroscopy. Due to their documentation we were able to approach this semester's topics much more efficiently. In order to optimize our group's resources we have divided into three major subcommittees: the Closed-Loop, Glucose Measurement, and Research subcommittees.

In the process of developing the artificial pancreas, the members of our team study the basic biological mechanisms of the pancreas, sugar chemistry and glucose metabolism, product design and implementation, economics, marketing, patent laws and regulations, and psychosocial factors. The major problems we face include time and space constraints. With only two and a half months to focus on the project it is necessary to limit the team vision. Additionally, it has proven difficult to find laboratory space and supplies and instruments needed to carry out our research.

Objectives

- ## Closed Loop

The objective of the Close loop section in IPRO 308 is to build on the work done by the previous IPRO team by accomplishing the task list below:

1. Verify the result obtained from previous IPRO group using the previous extraction device and a modified extraction device
2. Minimize the bulkiness of the prototype by eliminating unnecessary components.
3. Modify the extraction technique in order to extract a micro-volume of interstitial fluid.
4. Modify the extraction technique to decrease time needed to extract required amount of interstitial fluid for glucose measurement.
5. Research and design a device to obtain interstitial fluid from the user in a non-invasive

manner.

- **Measurement**

The objective of the measurement subgroup in IPRO 308 is to continue work done by the previous IPRO team by accomplishing the task list below:

1. Determine how to use the AUTOLAB in a two electrode measurement.
2. Create the comb pattern capacitor to amplify the signal and put the glucose solution into.
3. Obtain data over the frequency range for the capacitor with no dialectic (air as dielectric).
4. Obtain data over the frequency range for the capacitor with distilled water as the dielectric
5. Obtain data over the frequency range for the capacitor with different concentrations of glucose in distilled water as the dielectric.
6. Compare the results of the difference concentrations and find a way to determine the concentration based on the data obtained.

Methodology

- **Closed Loop**

A presentation was made to our team by one of the Previous IPRO team member to give us a better understanding of the work done by the previous IPRO group. He explained the details of the non-invasive extraction device designed by his group and the results obtained at the end of their project. Based on our assessment of their accomplishment and their methodology, we created and implemented a methodology that we believed will help in expediting the achievement of our objectives and they are listed below:

- Designed separate devices for sonophoresis and extraction of interstitial fluid
- Designed and calibrated a hollow centered speaker (sonophoresis device) in order to

achieve an optimum skin pore enlargement during sonophoresis.

- Ensured that the speaker (Sonophoresis device) touches the porcine skin during sonophoresis
- Observed and compared initial and final pore sizes after sonophoresis.
- Skin samples were soaked after sonophoresis in a colored saline solution at a level just below the surface of the skin to provide visibility for extraction experiments.
- Extraction using Vacuum tube was done at a vacuum pressure of 20inHg.
- Extraction process, using vacuum tube was done with and without sonophoresis, at different frequencies and time ranges and the results were recorded in a lab notebook.
- Final prototype was modified by Center-mounting the vacuum tube in the improved prototype.
- An outer chamber with vacuum suction was also incorporated in order to hold the new prototype tight to the skin while the device is in operation.

- Search for existing patent on non-invasive method and possible reproduction of the claims was made after an inference was drawn from observation made during the extraction sessions.

Based on the results of the experiments conducted in the lab, the following was documented into a formal report:

- The type of skin used and the thickness was recorded within a lab notebook.
- The detailed procedure of the processes used was recorded within a lab notebook.
- Pore sizes before and after sonophoresis was recorded within a lab notebook.
- Efficiency measurement of interstitial fluid using vacuum was recorded in a lab notebook.

Measurement

Last semester's measurement team concentrated on using the glucose oxidase method to measure glucose levels. This semester we decided to concentrate on using impedance spectroscopy to measure glucose concentration for several reasons including.

- Data obtained using the glucose oxidase method over the previous two semesters showed conflicting and inconsistent results.
- The previous semester's IPRO group did some work with impedance spectroscopy at the end of the semester that showed some promising looking results.
- Unlike the glucose oxidase method, Impedance spectroscopy does not require a chemical that would need to be replaced, making it cheaper and easier to miniaturize.

The following is a list of steps that we took towards completing our objective in chronological order.

- Determine how to use the AUTOLAB in a two electrode measurement.
- Design a capacitor that can use the glucose solution as a dielectric.
- Test the capacitor using air as the dialectic.
- Test the capacitor using DI water as the dielectic.
- Use a solution of DI water saturated with glucose as the dielectric and scan the whole frequency range available (1Hz-1MHz) to look for a resonant frequency.
- Make solutions of glucose with 200g/dL, 400g/dL, 800g/dL, and a saturated solution of glucose to use as a dielectric.
- Measure the different solutions of glucose between 250KHz and 500KHz and try to find a feature that can be used to identify the concentration of glucose from the graph.

Team Structure and Assignments

Closed-Loop Team Develop a viable option to extract interstitial fluid and administer insulin.		
Name	**Role**	**Concentration**
William Wakeman	Closed-Loop Team Leader	Vacuum, Sonophoresis, and Iontophoresis
Adam Kuuspalu		Vacuum, Sonophoresis, and Iontophoresis
Olufemi Sonoiki		Vacuum, Sonophoresis, and Iontophoresis
Anju Naveenan		Vacuum, Sonophoresis, and Iontophoresis
In Seok		Vacuum, Sonophoresis, and Iontophoresis

Measurement Team Develop a system to measure interstitial fluid for glucose concentration		
Name	**Role**	**Concentration**
Allen Klug	Measurement Team Leader	Impedance Spectroscopy
Adam Kuuspalu		Impedance Spectroscopy
Adam Smith		Impedance Spectroscopy

Patent/Research Team Responsible for IPRO deliverables as well as patent research		
Name	**Role**	**Concentration**
Adam Smith	Research Team Leader	Tech Research, Patent Research, Deliverables
In Seok Sin		Patent Research
Olufemi Sonoiki		Patent Research

DESIGNATION OF ROLES

Meeting Roles

Minute Taker- Anju Naveenan

Agenda Maker- Dr. Opara, William Wakeman

Expected Results

Research Subcommittee:

- Patent information will be obtained

Closed Loop Subcommittee:

- Extracting interstitial fluid using vacuum
- Finding time to extract using only vacuum
- Extracting interstitial fluid using vacuum and sonophoresis
- Discovering larger pore sizes after applying sonophoresis
- Finding time to extract using vacuum and sonophoresis
- Extracting 5 - 10 µL of interstitial fluid using vacuum, sonophoresis, and iontophoresis
- Finding time to extract using vacuum, sonophoresis, and iontophoresis
- A new prototype designed through findings in lab

Measurement Subcommittee:

- Producing and analyzing different concentrations of glucose by using the spectrophotometers
- Confirm the results and also look for practical methods of miniaturizing spectrophotometry to fit a prototype

Budget

Subcommittee	Item	Quantity	Price	Total
Closed Loop	Miniature speaker	2	$5.00	$10.00
Closed Loop	Portable Ultrasonic Device	1	$300.00	$300.00

Closed Loop	Clear Vinyl Tube (1ft)	1	$2.35/ft	$2.35
Closed Loop	Mini Vacuum Pump	1	$15.00	$15.00
Closed Loop	Flexible pvc tube 1” diameter	1	$2.14/ft	$2.14
Closed Loop	Stiff pvc tubing 1” Diameter	1	$2.51/ft	$2.51
Closed Loop	Iontophoresis Device (Existing device for injecting medicines) → Used for reverse engineering the working → Useful to study adaptations with sonophoresis	1	$330	$330.00
Closed Loop	Miscellaneous Equipment (Speakers, tubing, coating, capacitors, resistors, …)	1	$100.00	$100.00
Closed Loop	Rats & Related Expenses	10	$15.00	$150.00 + $200 (shipping & per diem)
Measurement	D-(+)-Glucose	500g	$64.00	$64.00
Measurement	Cuvettes	100	$21.50	$21.50
Measurement	Kreb’s Ringer’s Solution	2	$16.80	$33.60
Measurement	Sodium Bicarbonate 500g	1	$9.20	$9.20

Measurement	Benedict's Reagent	1	$99.90	$99.90
Measurement	Glucose-oxidase	1	$27.00	$27.00
Overall Total				**$1367.20**

Results

- ## Closed Loop

Upon performing our experiments visible changes in the appearance of the skin were noticeable. Green spots were seen on the surface of the skin on more than one occasion. Also, in some of our experiments green spots were seen only on the sonicated skin and not on the skin subjected to vacuum alone. Also, there were times where the length of time of sonophoresis application seemed to directly correlate to concentration, saturation and overall amount of green spots. However, these results were soon proven false positives as described in the obstacles section below. No significant results were obtained this semester.

- ## Measurement

Data was saved in the format used by the FRA software that the computer used to communicate with the AUTOLAB. The following data was collected and uploaded onto the igroups website.

  - With Air as the dielectric:
    - 1kHz to 1 MHz logarithmic scan
    - 1kHz to 10kHz linear scan
    - 20kHz to 50kHz linear scan
  - With DI water as the dialectic
    - 10KHz-1MHz logarithmic scan

        - 250KHz-500Khz linear scan
    - With 200g of glucose per deciliter of DI water as the dielectric
        - 250KHz-500Khz linear scan
    - With 400g of glucose per deciliter of DI water as the dielectric
        - 250KHz-500Khz linear scan
    - With 800g of glucose per deciliter of DI water as the dielectric
        - 250KHz-500Khz linear scan
    - With a saturated solution of glucose and DI water as the dielectric
        - 250KHz-500Khz linear scan
        - 100KHz-1MHz linear scan

Obstacles

- **Closed Loop**

Some of the obstacles experienced during the course of achieving our objective include

- Inability to extract colored saline solution through a dead porcine skin. The porcine skins, used during extraction and sonophoresis, for this project were obtained approximately 4hrs after the death of the pig. This made sonophoresis and extraction of little effect.
- Micro sieves of approximately 50 microns (human pore size) and 100 microns (enlarge pore size due to sonophoresis) were bought to standardize the operating condition of our equipment (vacuum pump and acoustic speakers), the amount of fluid that can be obtained from the normal human pore size and the enlarge pore size due to sonophoresis.

- **Measurement**

Some of the obstacles experienced during the course of achieving our objective include

- There was no one at UIC, including the owner of the machine, that knew how to operate it for the experiment that we were trying to conduct. We were able to obtain an instruction manual from the company that produced the machine after a lot of time on the phone. After experiencing some more problems with getting the machine to work correctly we got in contact with the regional representative of the company. After sever weeks of troubleshooting, made more difficult by the fact that the basement that the machine was located in did not get any cell phone signal and didn't have a working land line, we got the machine to start taking data.

References

Emiliano Maione, K. **Kirk** Shung, Richard J. Meyer Jr.**, Jack** W. Hughes, Robert E. Newnham and Nadine Barrie Smith. "Transducer Design for a Portable Ultrasound Enhanced Transdermal Drug-Delivery System." **IEEE** Transactions on Ultrasonics, Ferroelectrics, and Frequency Control, VOL. 40, NO. 10. OCTOBER *2002.*

A. Boucaud, L. Machet, M.A. Garrigue, L. Vaillant and F. Patat. "A Practical Use of Low Frequency Ultrasound For Rapid and Reproducible Transdermal Delivery of Insulin." 2001 IEEE ULTRASONICS SYMPOSIUM-1327

Dachao Li, Xian Huang, Haixia Yu, Xiaotang Hu, and Kexin Xu, Dachao Li, Robert C Roberts and Norman Tien. "Analysis of Glucose Concentration in Interstitial Fluid by Micro Surface Plasmon Resonance Sensor." IEEE Xplore.

M. Gourzi, A. Rouane, R. Guelaz, M. S. Alavi, M. B. Mchugh, M. Nadi and P. Roth. "Non-invasive glycaemia blood measurements by electromagnetic sensor: Study in static and dynamic blood circulation." IEEE Xplore.

Dachao Li, Xian Huang, Haixia Yu, Xiaotang Hu, Kexin Xu, Roberts, R.C. and Tien, N. “Analysis of glucose concentration in ***interstitial fluid*** by micro surface plasmon resonance sensor.” 2007, pp., pp. 106-9, *Publisher:* IEEE *Country of Publication:* USA.

Raffi Karshafian, Peter D. Bevan, Sanya Samac and Peter N. Burns. “The Effect of Acoustic Exposure Parameters on Cell Membrane Permeabilisation by Ultrasound and Microbubbles.” CP911, *6th International Symposium on Therapeutic Ultrasound* edited by C.-C. Coussios and G. ter Haar © 2007 American Institute of Physics.

Custer , et al. Patent 7,066,884, June 27, 2006. *System, method, and device for non-invasive body fluid sampling and analysis.*

Hakky , et al., Patent 6,503,209, January 7, 2003. *Non-invasive focused energy blood withdrawal and analysis system.*

Bruce K. Redding, Jr. “HUMAN SKIN PORE ENLARGEMENT A RESULT OF ULTRASONIC TREATMENT.” Encapsulation Systems, PO Box 759, Broomall, PA. 19008 USA November 30, 2003

“Structure of Skin.” Nanomaterial Science Lab, National Chung Cheng University, 06-Dec-2002 <http://www.nmsl.chem.ccu.edu.tw/tea/SKIN_910721.htm>

Stuart Alan Weinzimer, M.D. “Analysis: PENDRA: The Once and Future Noninvasive Continuous Glucose Monitoring Device?” Diabetes Technology & Therapeutics Volume 6, Number 4, 2004

Resources

- University of Chicago Neuropsychiatric Institute and Dr. Patrick J. *Rousche* Associate Professor, Dept. of Bioengineering
- Illinois Institute of Technology, Wishnick Hall Instrumentation Lab
- Autolab PGSTAT302N

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- Echo Therapeutics

  Echo's Symphony™ tCGM System