

ARTIFICIAL PANCREAS

1. Describe the problem to be solved

Diabetes is a serious disease that affects millions of Americans and it is known to be the sixth leading cause of death in the United States. The regimen most often prescribed to patients with Type 1 diabetes by their health care provider includes multiple daily insulin shots with frequent monitoring of blood glucose. If the blood glucose is not monitored frequently during intensive insulin treatment, a diabetic individual is prone to hypoglycemia (low blood sugar), which is a life-threatening condition.

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. 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. The need for a non-invasive device that not only monitors glucose but also delivers insulin in an automated way is greater than ever.

2. Problem objective statement

The objective of this project is to develop an artificial pancreas, which will not only incorporate a non-invasive blood glucose monitoring technique, but also a noninvasive insulin delivery method. Currently, invasive techniques, such as venepuncture, are used to monitor blood glucose levels and deliver insulin in patients. The three main features of a desirable artificial are to make it non-invasive, automated and user-friendly so as to give diabetic patients more flexibility and freedom.

3. Documentation of the final design, including applicable standards and risk analysis

The focus of this semester's team is to develop and test the prototype for determining the measurement of glucose using non-invasive means and design a simultaneous transdermal insulin delivery system. The first step to developing the device is the extraction of interstitial fluid to test the blood glucose level. Several technologies are being incorporated into the device; mainly, iontophoresis and ultrasound.

Extraction:

The IPRO team conducted several experiments to test the application of the processes of vacuum, ultrasound and reverse iontophoresis in the extraction of interstitial fluid. It was determined that when ultrasound (used to open the pores) is applied with vacuum (used to break the meniscus formed by the skin), time of interstitial fluid extraction reduces from 6 hours to 6 minutes. The procedure involved the application of vacuum and ultrasound on a warm porcine skin of thickness 0.052/0.056 inches, at a voltage of 3V, using a pump of 0.75 hp power at a frequency in the range of 17 kHz-20 kHz. The results included an increase in pore size as shown by the figure 1 and extraction of liquid in micro liter range. The addition of reverse iontophoresis to this process, which

reduces the time of extraction to less than minute, was tested at a voltage of 14V in the absence of current limiting resource. This led to the burning of the skin and hence its application could not be favorably concluded.

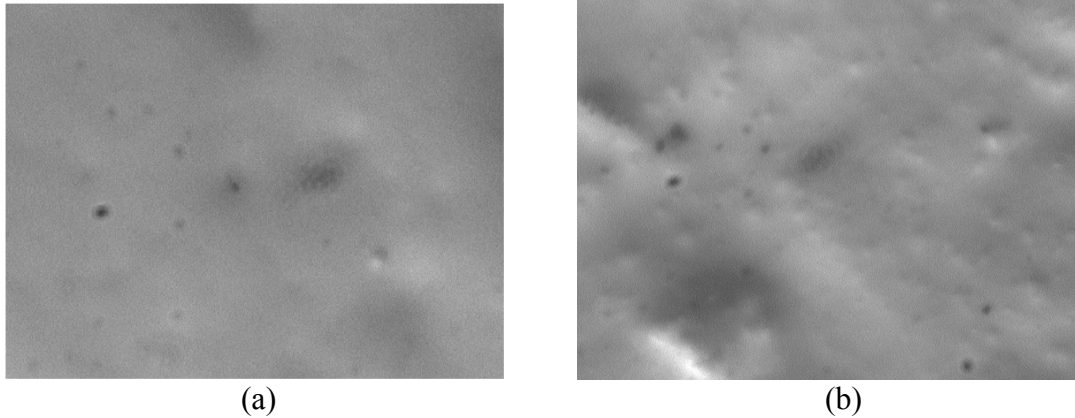


Figure1: The pictures display microscopic images of porcine skin before and after the application of vacuum and ultrasound. **(a)** The microscopic image of regular skin at 20x magnification. **(b)** The microscopic image of skin after the experiment at 20x magnification.

Glucose Measurement:

The next step of the process is glucose measurement. Two techniques were researched to incorporate the least time and effort consuming and accurate method into the device- impedance spectroscopy and absorbance spectroscopy.

Impedance Spectroscopy:

In the first method, the experiment was designed to test for the resonance frequency of glucose and if resistance values of the solution changed with increasing glucose concentrations using Krebs Ringer buffer at a pH of 7.41 on Electric Cell-Substrate Impedance Sensing (ECIS Model 1600R Biophysics) with ECIS 8 Software (Biophysics). Although the resonance frequency for the glucose was not clearly displayed, different concentrations appeared to be clearly distinguishable between \log_3 and \log_4 Hz and a downward trend was visible. The plot of concentration versus resistance in figure 2 shows that on average there was an increasing trend of resistance with increasing glucose concentration with measurements taken at approximately 3000Hz. The possible sources of error include variable temperature and extensively used gold electrodes. Upon fixing these variables, greater accuracy can be obtained.

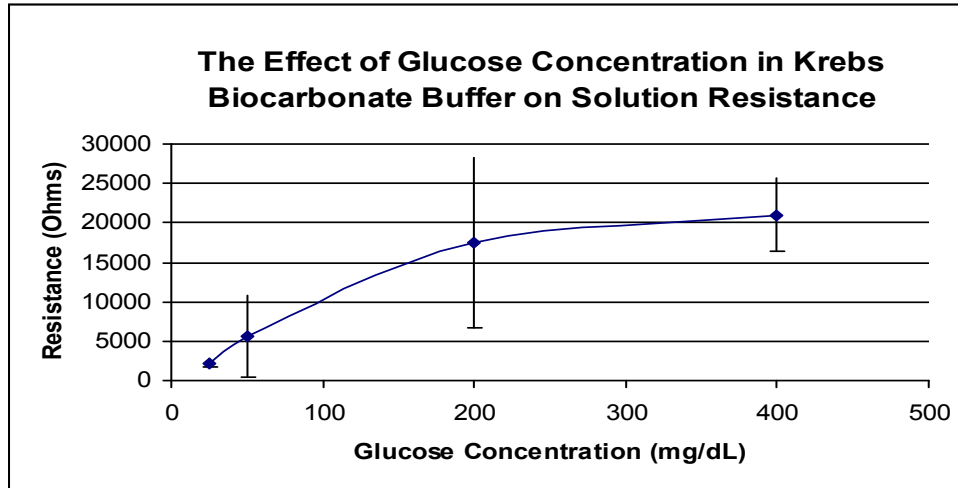


Figure 2: Resistance appears to increase with increasing glucose concentrations

Absorbance Spectroscopy:

The purpose of the experiment is to obtain a mathematical relationship between glucose concentration and optical absorbance. Once a mathematical relationship is found, the device can be programmed to record the system glucose level and calculate the amount of insulin needed to bring the glucose levels to normal. The tests were run at a wavelength of 1000nm and the limit of detection was found to be around ~12.5mg/dL of glucose. An FTIR spectroscopy showed that the optimum wavelength for the measurement of glucose is 6850nm. It can be observed from figure 3 that the glucose concentration is directly proportional to the absorbance. The accuracy of the results was compromised as the wavelength of the instrument used reached a maximum at 1100nm, which played an important role in the measurement. Hence, this method can be successfully applied at the appropriate wavelength to obtain accurate results with concentrations as low as 10mg/dL.

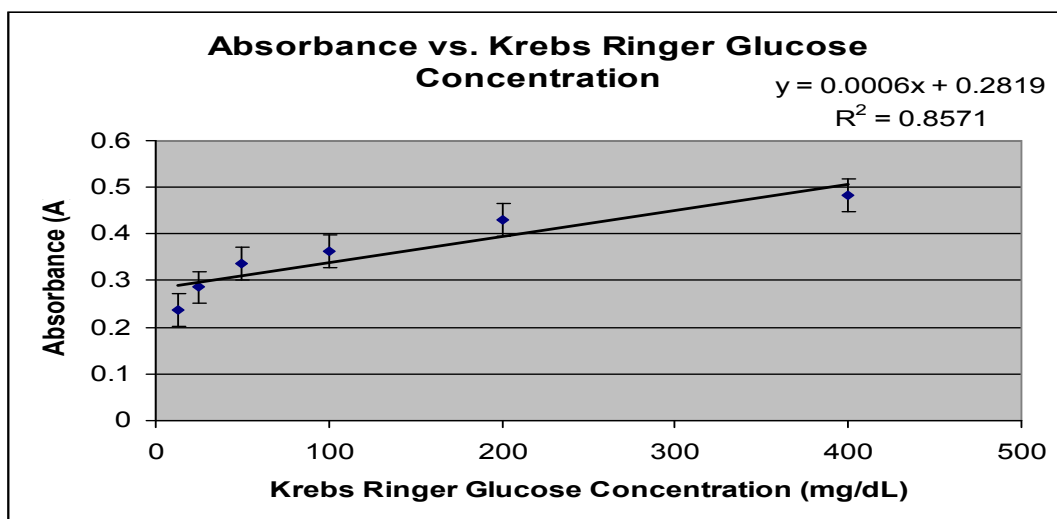


Figure 3: The plot displays the direct relationship existing between absorbance and glucose concentration.

Insulin Delivery:

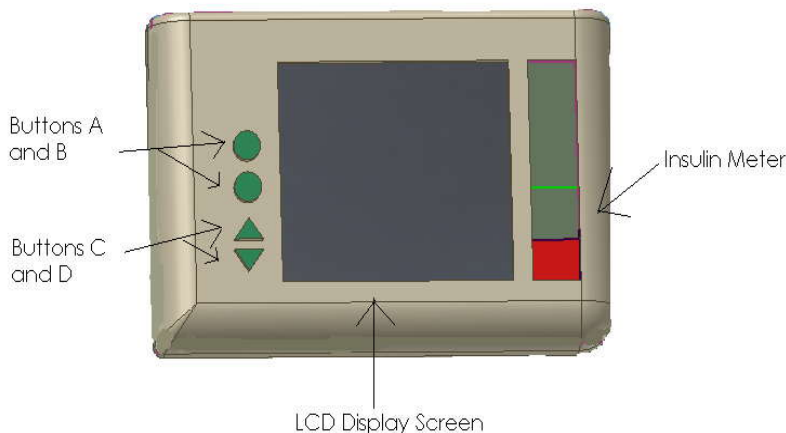
The second part of the artificial pancreas is insulin delivery, which is also noninvasive. The main idea behind delivery of insulin into the body is to reverse the extraction method so it moves the fluid in the opposite direction. Instead of a vacuum, pressure will be applied for delivery via the same pump through the pressure port. A pseudo code has been developed that will allow to control the amount and frequency of insulin injections depending glucose measurements. By frequent blood glucose measurements, the insulin pump will provide the necessary amount of insulin on-demand and keep the blood glucose levels close to normal. Work was also done on the aesthetics of the design and a tentative model as shown in image 5 was created.

4. Prototype of the final design



Figure 4: The design of the prototype

Front View



Back View

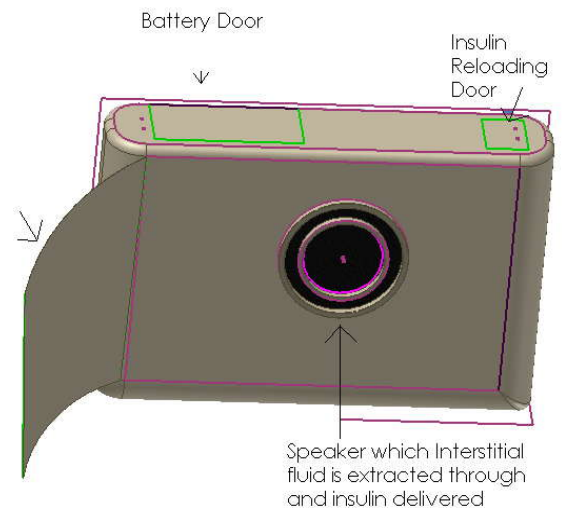


Figure 5: Aesthetics of Artificial Pancreas

5. Proof that the design is functional and will solve the problem

Through research and patent documents, all the information necessary was combined towards making a prototype. These topics considered for information included the advantages of choosing iontophoresis for our insulin delivery scheme over other noninvasive methods, the extent of skin permeability under ultrasound, ionic properties of glucose, dimers and polymers that insulin naturally converts into, properties of interstitial fluids and how it can be used to determine glucose concentration in blood, as well as using impedance spectroscopy as a method of measuring glucose concentration in interstitial fluid. After evaluating the advantages and disadvantages of the researched topics, we decided to use ultrasound and a two-way vacuum system to extract interstitial fluid. Also we have two options for determining blood glucose level. We could use absorbance or impedance spectroscopy. In the insulin delivery system, we decided to use iontophoresis in introducing insulin into the blood stream non-invasively. We thus, came up with the concept of a continuous insulin delivery system that works solely on the glucose levels just like a real pancreas does without any external monitoring required.

Each component of this device has been tested individually and reported in various prestigious medical journals. The paper by Mitragotri et. al. ³ 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 al⁴, describes the mechanism of reverse-iontophoresis and shows that reverse-iontophoresis may be used to extract interstitial fluid. A patent document by Flower et. al.⁶ discusses the voltage needed for iontophoresis. He describes that around 20 to 30 DC volts is necessary to reduce the millamperes of the skin to 0.6 from the desired drug delivery current of 2 milliamperes. The average impedance of the skin is around 15,000 ohms. Flower et. al.⁶ also describes a DC-DC converter circuit that maintains a consistent voltage across the skin accordingly to the skin’s change in impedance.

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. ⁵ 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. ⁵ we also have experimental results of using an absorbance spectroscopy. The experiment also showed a good correlation between glucose levels and sensor readings. We have practically evaluated these various techniques in our laboratory and can confirm their validity for various purposes in the final prototype.

6. Results of a patent search and assessment of patentability

Based on the accomplishments of the previous team, we knew that a number of patents existed which described techniques for non-invasive glucose monitoring. We felt it necessary however, to expand this search both in terms of identifying relevant issued patents, as well as current patent applications. The results of our expanded search confirmed that while some devices may utilize some of the same components as our prototype, no other single device combines all the aspects of the artificial pancreas into their design. Some of the most prominent features of our device are listed below (Reference the full patent report for details regarding differences between our prototype and individual patents or applications):

- Combines continuous glucose monitoring *and* insulin delivery in the same device
- Extraction of interstitial fluid combines vacuum, ultrasound, and reverse iontophoresis.
- Measurement of glucose levels takes place outside the body, *not* through the skin, which may confound results.
- Glucose measurement occurs directly from extracted interstitial fluid without the requirement of an additional chemical reagent or chemical reaction.

7. 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. In 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.

8. Estimated manufacturing costs

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 labor for manufacture of the initial working prototype will utilize student workers.

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 ~\$10,600.

9. 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. 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.

As of now, only two non-invasive blood glucose monitoring devices have been approved by the U.S Food and Drug Administration. The Gluowatch 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. 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 Gluowatch 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. 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, also more precise than the previous two, and cheaper for users. Apart from the one time expense to purchase the sonifier and the iontophoresis apparatus, we estimate <\$1,000 to be the non-recurrent cost of purchase of our device. Other comparison with top competitors is listed below:

Features	Deltec	MiniMed	Artificial Pancreas
Non-invasive	No	No	Yes
Glucose Monitoring & Insulin Delivery	Can be attached to the pump	Yes	Yes
Waterproof	Yes	No	Yes
Can be used in airplanes	Yes	No	Yes

	MiniMed's Paradigm	MiniMed's Guardian	Dexcom STS	Artificial Pancreas
Batteries for monitor	No separate monitor	2 AAA batteries	Chargeable batteries	Lithium ion rechargeable
Communicates with insulin Pump	Yes, with Paradigm 522 & 722	No	No	Yes

10. Business plan detailing strategy for commercialization and opportunity statement

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. The ultimate goal in the commercialization plan is to sell the final technology to a large corporation for large-scale production and marketing.

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 enable 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 noninvasive 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.
6. Flower R., Devine J. Iontophoretic drug delivery device having high-efficiency DC-to-DC energy conversion circuit. *United States Patent* .61

ARTIFICIAL PANCREAS

1. Describe the problem to be solved

Diabetes is a serious disease that affects millions of Americans and it is known to be the sixth leading cause of death in the United States. The regimen most often prescribed to patients with Type 1 diabetes by their health care provider includes multiple daily insulin shots with frequent monitoring of blood glucose. If the blood glucose is not monitored frequently during intensive insulin treatment, a diabetic individual is prone to hypoglycemia (low blood sugar), which is a life-threatening condition.

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. 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. The need for a non-invasive device that not only monitors glucose but also delivers insulin in an automated way is greater than ever.

2. Problem objective statement

The objective of this project is to develop an artificial pancreas, which will not only incorporate a non-invasive blood glucose monitoring technique, but also a noninvasive insulin delivery method. Currently, invasive techniques, such as venepuncture, are used to monitor blood glucose levels and deliver insulin in patients. The three main features of a desirable artificial are to make it non-invasive, automated and user-friendly so as to give diabetic patients more flexibility and freedom.

3. Documentation of the final design, including applicable standards and risk analysis

The focus of this semester's team is to develop and test the prototype for determining the measurement of glucose using non-invasive means and design a simultaneous transdermal insulin delivery system. The first step to developing the device is the extraction of interstitial fluid to test the blood glucose level. Several technologies are being incorporated into the device; mainly, iontophoresis and ultrasound.

Extraction:

The IPRO team conducted several experiments to test the application of the processes of vacuum, ultrasound and reverse iontophoresis in the extraction of interstitial fluid. It was determined that when ultrasound (used to open the pores) is applied with vacuum (used to break the meniscus formed by the skin), time of interstitial fluid extraction reduces from 6 hours to 6 minutes. The procedure involved the application of vacuum and ultrasound on a warm porcine skin of thickness 0.052/0.056 inches, at a voltage of 3V, using a pump of 0.75 hp power at a frequency in the range of 17 kHz-20 kHz. The results included an increase in pore size as shown by the figure 1 and extraction of liquid in micro liter range. The addition of reverse iontophoresis to this process, which

reduces the time of extraction to less than minute, was tested at a voltage of 14V in the absence of current limiting resource. This led to the burning of the skin and hence its application could not be favorably concluded.

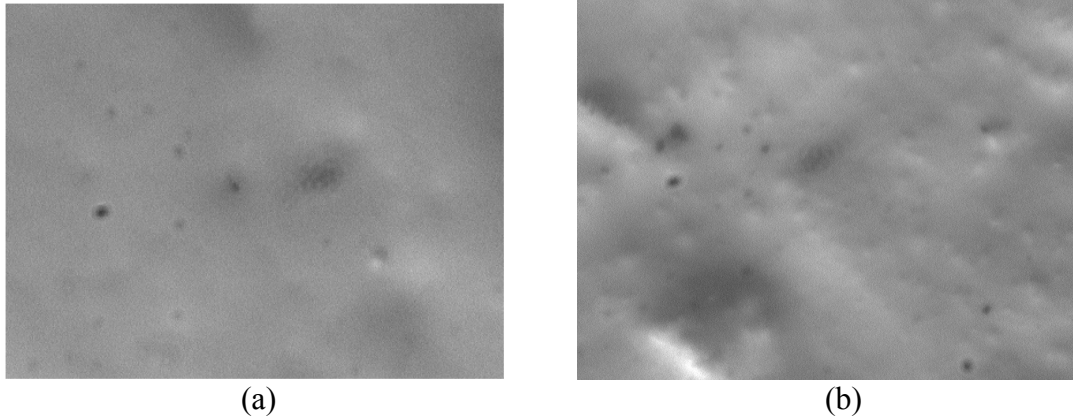


Figure1: The pictures display microscopic images of porcine skin before and after the application of vacuum and ultrasound. **(a)** The microscopic image of regular skin at 20x magnification. **(b)** The microscopic image of skin after the experiment at 20x magnification.

Glucose Measurement:

The next step of the process is glucose measurement. Two techniques were researched to incorporate the least time and effort consuming and accurate method into the device- impedance spectroscopy and absorbance spectroscopy.

Impedance Spectroscopy:

In the first method, the experiment was designed to test for the resonance frequency of glucose and if resistance values of the solution changed with increasing glucose concentrations using Krebs Ringer buffer at a pH of 7.41 on Electric Cell-Substrate Impedance Sensing (ECIS Model 1600R Biophysics) with ECIS 8 Software (Biophysics). Although the resonance frequency for the glucose was not clearly displayed, different concentrations appeared to be clearly distinguishable between \log_3 and \log_4 Hz and a downward trend was visible. The plot of concentration versus resistance in figure 2 shows that on average there was an increasing trend of resistance with increasing glucose concentration with measurements taken at approximately 3000Hz. The possible sources of error include variable temperature and extensively used gold electrodes. Upon fixing these variables, greater accuracy can be obtained.

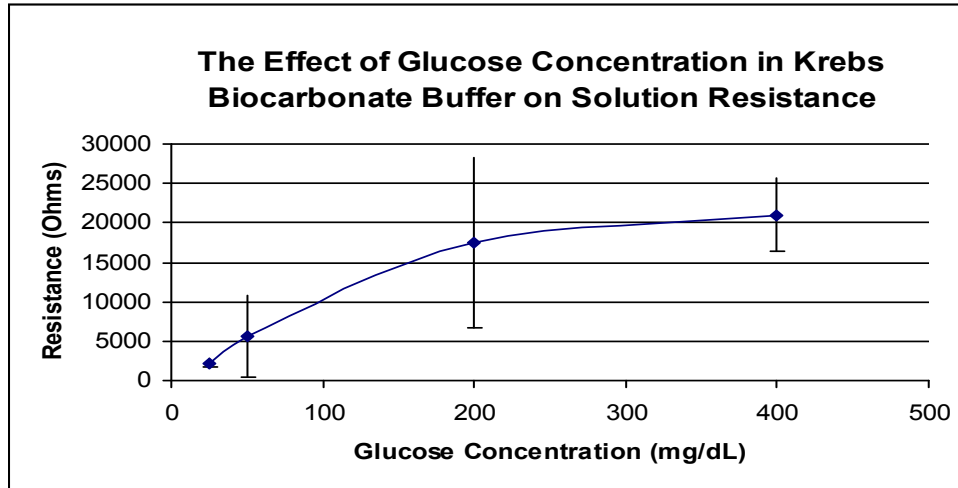


Figure 2: Resistance appears to increase with increasing glucose concentrations

Absorbance Spectroscopy:

The purpose of the experiment is to obtain a mathematical relationship between glucose concentration and optical absorbance. Once a mathematical relationship is found, the device can be programmed to record the system glucose level and calculate the amount of insulin needed to bring the glucose levels to normal. The tests were run at a wavelength of 1000nm and the limit of detection was found to be around ~12.5mg/dL of glucose. An FTIR spectroscopy showed that the optimum wavelength for the measurement of glucose is 6850nm. It can be observed from figure 3 that the glucose concentration is directly proportional to the absorbance. The accuracy of the results was compromised as the wavelength of the instrument used reached a maximum at 1100nm, which played an important role in the measurement. Hence, this method can be successfully applied at the appropriate wavelength to obtain accurate results with concentrations as low as 10mg/dL.

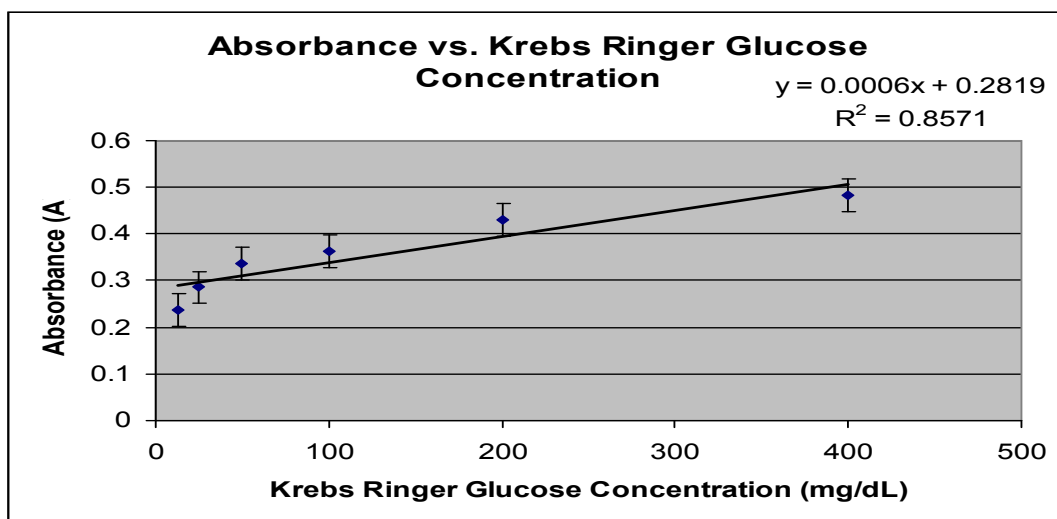


Figure 3: The plot displays the direct relationship existing between absorbance and glucose concentration.

Insulin Delivery:

The second part of the artificial pancreas is insulin delivery, which is also noninvasive. The main idea behind delivery of insulin into the body is to reverse the extraction method so it moves the fluid in the opposite direction. Instead of a vacuum, pressure will be applied for delivery via the same pump through the pressure port. A pseudo code has been developed that will allow to control the amount and frequency of insulin injections depending glucose measurements. By frequent blood glucose measurements, the insulin pump will provide the necessary amount of insulin on-demand and keep the blood glucose levels close to normal. Work was also done on the aesthetics of the design and a tentative model as shown in image 5 was created.

4. Prototype of the final design

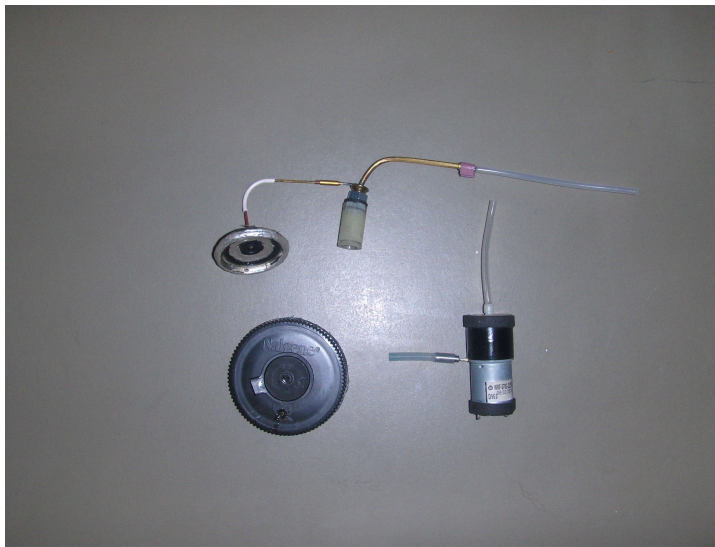
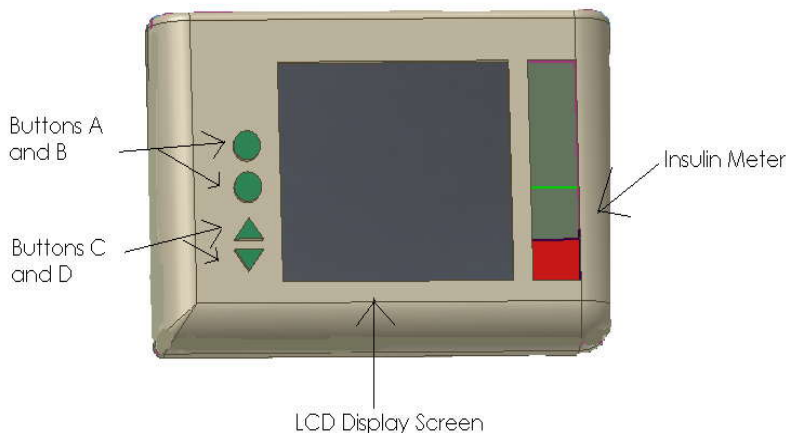


Figure 4: The design of the prototype

Front View



Back View

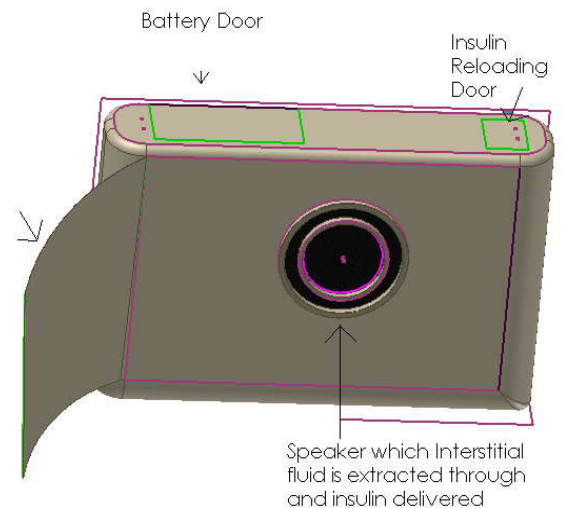


Figure 5: Aesthetics of Artificial Pancreas

5. Proof that the design is functional and will solve the problem

Through research and patent documents, all the information necessary was combined towards making a prototype. These topics considered for information included the advantages of choosing iontophoresis for our insulin delivery scheme over other noninvasive methods, the extent of skin permeability under ultrasound, ionic properties of glucose, dimers and polymers that insulin naturally converts into, properties of interstitial fluids and how it can be used to determine glucose concentration in blood, as well as using impedance spectroscopy as a method of measuring glucose concentration in interstitial fluid. After evaluating the advantages and disadvantages of the researched topics, we decided to use ultrasound and a two-way vacuum system to extract interstitial fluid. Also we have two options for determining blood glucose level. We could use absorbance or impedance spectroscopy. In the insulin delivery system, we decided to use iontophoresis in introducing insulin into the blood stream non-invasively. We thus, came up with the concept of a continuous insulin delivery system that works solely on the glucose levels just like a real pancreas does without any external monitoring required.

Each component of this device has been tested individually and reported in various prestigious medical journals. The paper by Mitragotri et. al. ³ 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 al⁴, describes the mechanism of reverse-iontophoresis and shows that reverse-iontophoresis may be used to extract interstitial fluid. A patent document by Flower et. al.⁶ discusses the voltage needed for iontophoresis. He describes that around 20 to 30 DC volts is necessary to reduce the millamperes of the skin to 0.6 from the desired drug delivery current of 2 milliamperes. The average impedance of the skin is around 15,000 ohms. Flower et. al.⁶ also describes a DC-DC converter circuit that maintains a consistent voltage across the skin accordingly to the skin’s change in impedance.

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. ⁵ 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. ⁵ we also have experimental results of using an absorbance spectroscopy. The experiment also showed a good correlation between glucose levels and sensor readings. We have practically evaluated these various techniques in our laboratory and can confirm their validity for various purposes in the final prototype.

6. Results of a patent search and assessment of patentability

Based on the accomplishments of the previous team, we knew that a number of patents existed which described techniques for non-invasive glucose monitoring. We felt it necessary however, to expand this search both in terms of identifying relevant issued patents, as well as current patent applications. The results of our expanded search confirmed that while some devices may utilize some of the same components as our prototype, no other single device combines all the aspects of the artificial pancreas into their design. Some of the most prominent features of our device are listed below (Reference the full patent report for details regarding differences between our prototype and individual patents or applications):

- Combines continuous glucose monitoring *and* insulin delivery in the same device
- Extraction of interstitial fluid combines vacuum, ultrasound, and reverse iontophoresis.
- Measurement of glucose levels takes place outside the body, *not* through the skin, which may confound results.
- Glucose measurement occurs directly from extracted interstitial fluid without the requirement of an additional chemical reagent or chemical reaction.

7. 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. In 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.

8. Estimated manufacturing costs

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 labor for manufacture of the initial working prototype will utilize student workers.

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 ~\$10,600.

9. 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. 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.

As of now, only two non-invasive blood glucose monitoring devices have been approved by the U.S Food and Drug Administration. The Gluowatch 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. 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 Gluowatch 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. 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, also more precise than the previous two, and cheaper for users. Apart from the one time expense to purchase the sonifier and the iontophoresis apparatus, we estimate <\$1,000 to be the non-recurrent cost of purchase of our device. Other comparison with top competitors is listed below:

Features	Deltec	MiniMed	Artificial Pancreas
Non-invasive	No	No	Yes
Glucose Monitoring & Insulin Delivery	Can be attached to the pump	Yes	Yes
Waterproof	Yes	No	Yes
Can be used in airplanes	Yes	No	Yes

	MiniMed's Paradigm	MiniMed's Guardian	Dexcom STS	Artificial Pancreas
Batteries for monitor	No separate monitor	2 AAA batteries	Chargeable batteries	Lithium ion rechargeable
Communicates with insulin Pump	Yes, with Paradigm 522 & 722	No	No	Yes

10. Business plan detailing strategy for commercialization and opportunity statement

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. The ultimate goal in the commercialization plan is to sell the final technology to a large corporation for large-scale production and marketing.

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 enable 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 noninvasive 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.
6. Flower R., Devine J. Iontophoretic drug delivery device having high-efficiency DC-to-DC energy conversion circuit. *United States Patent* .61

ARTIFICIAL PANCREAS

1. Describe the problem to be solved

Diabetes is a serious disease that affects millions of Americans and it is known to be the sixth leading cause of death in the United States. The regimen most often prescribed to patients with Type 1 diabetes by their health care provider includes multiple daily insulin shots with frequent monitoring of blood glucose. If the blood glucose is not monitored frequently during intensive insulin treatment, a diabetic individual is prone to hypoglycemia (low blood sugar), which is a life-threatening condition.

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. 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. The need for a non-invasive device that not only monitors glucose but also delivers insulin in an automated way is greater than ever.

2. Problem objective statement

The objective of this project is to develop an artificial pancreas, which will not only incorporate a non-invasive blood glucose monitoring technique, but also a noninvasive insulin delivery method. Currently, invasive techniques, such as venepuncture, are used to monitor blood glucose levels and deliver insulin in patients. The three main features of a desirable artificial are to make it non-invasive, automated and user-friendly so as to give diabetic patients more flexibility and freedom.

3. Documentation of the final design, including applicable standards and risk analysis

The focus of this semester's team is to develop and test the prototype for determining the measurement of glucose using non-invasive means and design a simultaneous transdermal insulin delivery system. The first step to developing the device is the extraction of interstitial fluid to test the blood glucose level. Several technologies are being incorporated into the device; mainly, iontophoresis and ultrasound.

Extraction:

The IPRO team conducted several experiments to test the application of the processes of vacuum, ultrasound and reverse iontophoresis in the extraction of interstitial fluid. It was determined that when ultrasound (used to open the pores) is applied with vacuum (used to break the meniscus formed by the skin), time of interstitial fluid extraction reduces from 6 hours to 6 minutes. The procedure involved the application of vacuum and ultrasound on a warm porcine skin of thickness 0.052/0.056 inches, at a voltage of 3V, using a pump of 0.75 hp power at a frequency in the range of 17 kHz-20 kHz. The results included an increase in pore size as shown by the figure 1 and extraction of liquid in micro liter range. The addition of reverse iontophoresis to this process, which

reduces the time of extraction to less than minute, was tested at a voltage of 14V in the absence of current limiting resource. This led to the burning of the skin and hence its application could not be favorably concluded.

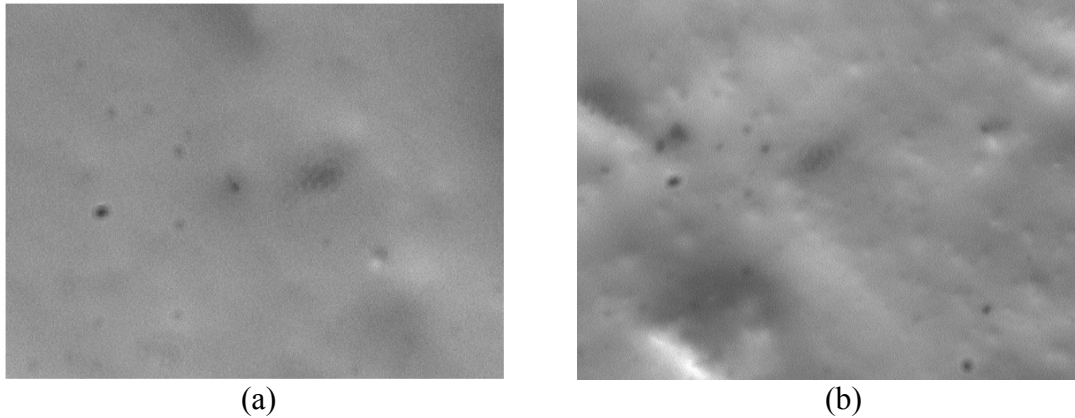


Figure1: The pictures display microscopic images of porcine skin before and after the application of vacuum and ultrasound. **(a)** The microscopic image of regular skin at 20x magnification. **(b)** The microscopic image of skin after the experiment at 20x magnification.

Glucose Measurement:

The next step of the process is glucose measurement. Two techniques were researched to incorporate the least time and effort consuming and accurate method into the device- impedance spectroscopy and absorbance spectroscopy.

Impedance Spectroscopy:

In the first method, the experiment was designed to test for the resonance frequency of glucose and if resistance values of the solution changed with increasing glucose concentrations using Krebs Ringer buffer at a pH of 7.41 on Electric Cell-Substrate Impedance Sensing (ECIS Model 1600R Biophysics) with ECIS 8 Software (Biophysics). Although the resonance frequency for the glucose was not clearly displayed, different concentrations appeared to be clearly distinguishable between \log_3 and \log_4 Hz and a downward trend was visible. The plot of concentration versus resistance in figure 2 shows that on average there was an increasing trend of resistance with increasing glucose concentration with measurements taken at approximately 3000Hz. The possible sources of error include variable temperature and extensively used gold electrodes. Upon fixing these variables, greater accuracy can be obtained.

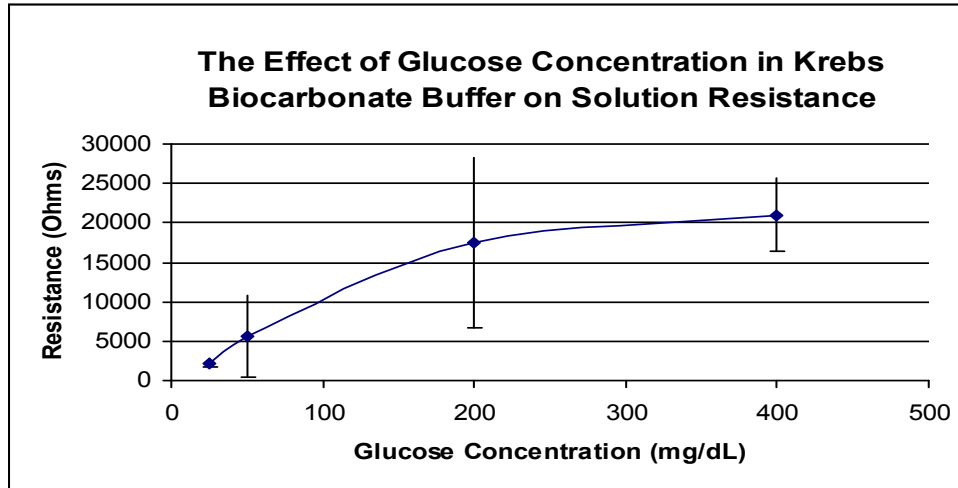


Figure 2: Resistance appears to increase with increasing glucose concentrations

Absorbance Spectroscopy:

The purpose of the experiment is to obtain a mathematical relationship between glucose concentration and optical absorbance. Once a mathematical relationship is found, the device can be programmed to record the system glucose level and calculate the amount of insulin needed to bring the glucose levels to normal. The tests were run at a wavelength of 1000nm and the limit of detection was found to be around ~12.5mg/dL of glucose. An FTIR spectroscopy showed that the optimum wavelength for the measurement of glucose is 6850nm. It can be observed from figure 3 that the glucose concentration is directly proportional to the absorbance. The accuracy of the results was compromised as the wavelength of the instrument used reached a maximum at 1100nm, which played an important role in the measurement. Hence, this method can be successfully applied at the appropriate wavelength to obtain accurate results with concentrations as low as 10mg/dL.

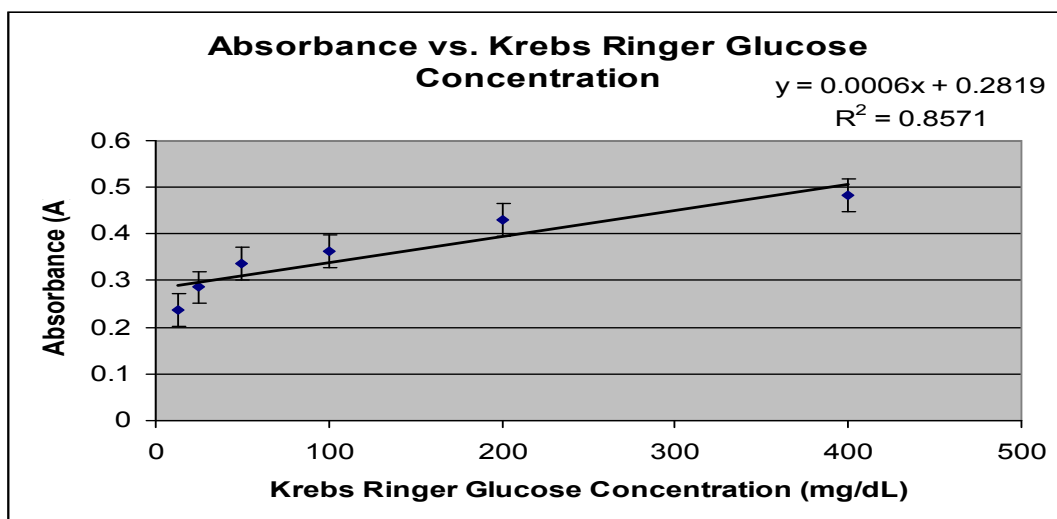


Figure 3: The plot displays the direct relationship existing between absorbance and glucose concentration.

Insulin Delivery:

The second part of the artificial pancreas is insulin delivery, which is also noninvasive. The main idea behind delivery of insulin into the body is to reverse the extraction method so it moves the fluid in the opposite direction. Instead of a vacuum, pressure will be applied for delivery via the same pump through the pressure port. A pseudo code has been developed that will allow to control the amount and frequency of insulin injections depending glucose measurements. By frequent blood glucose measurements, the insulin pump will provide the necessary amount of insulin on-demand and keep the blood glucose levels close to normal. Work was also done on the aesthetics of the design and a tentative model as shown in image 5 was created.

4. Prototype of the final design

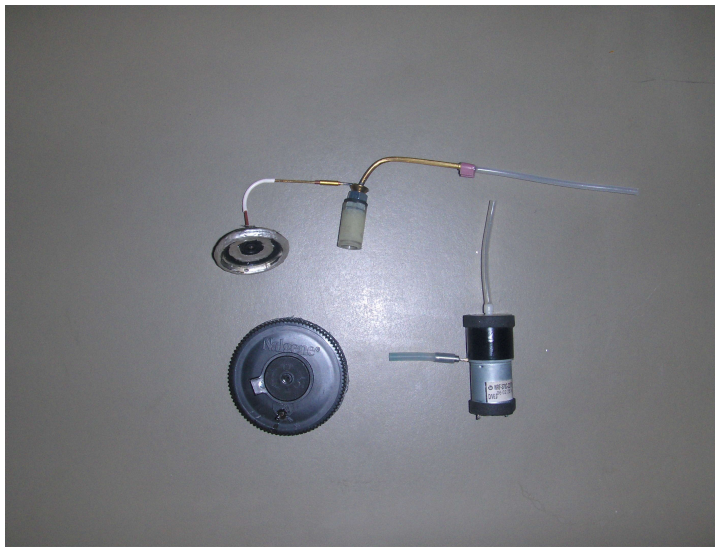
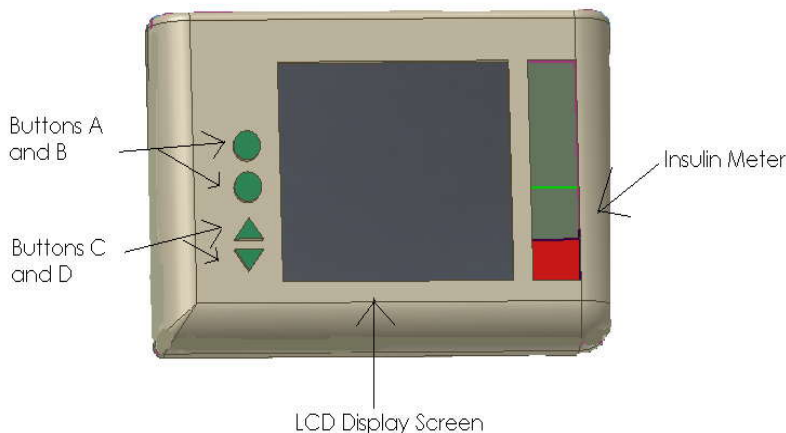


Figure 4: The design of the prototype

Front View



Back View

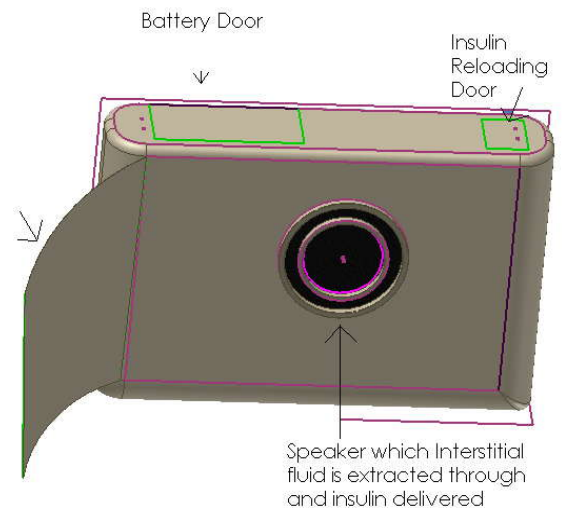


Figure 5: Aesthetics of Artificial Pancreas

5. Proof that the design is functional and will solve the problem

Through research and patent documents, all the information necessary was combined towards making a prototype. These topics considered for information included the advantages of choosing iontophoresis for our insulin delivery scheme over other noninvasive methods, the extent of skin permeability under ultrasound, ionic properties of glucose, dimers and polymers that insulin naturally converts into, properties of interstitial fluids and how it can be used to determine glucose concentration in blood, as well as using impedance spectroscopy as a method of measuring glucose concentration in interstitial fluid. After evaluating the advantages and disadvantages of the researched topics, we decided to use ultrasound and a two-way vacuum system to extract interstitial fluid. Also we have two options for determining blood glucose level. We could use absorbance or impedance spectroscopy. In the insulin delivery system, we decided to use iontophoresis in introducing insulin into the blood stream non-invasively. We thus, came up with the concept of a continuous insulin delivery system that works solely on the glucose levels just like a real pancreas does without any external monitoring required.

Each component of this device has been tested individually and reported in various prestigious medical journals. The paper by Mitragotri et. al. ³ 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 al⁴, describes the mechanism of reverse-iontophoresis and shows that reverse-iontophoresis may be used to extract interstitial fluid. A patent document by Flower et. al.⁶ discusses the voltage needed for iontophoresis. He describes that around 20 to 30 DC volts is necessary to reduce the millamperes of the skin to 0.6 from the desired drug delivery current of 2 milliamperes. The average impedance of the skin is around 15,000 ohms. Flower et. al.⁶ also describes a DC-DC converter circuit that maintains a consistent voltage across the skin accordingly to the skin’s change in impedance.

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. ⁵ 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. ⁵ we also have experimental results of using an absorbance spectroscopy. The experiment also showed a good correlation between glucose levels and sensor readings. We have practically evaluated these various techniques in our laboratory and can confirm their validity for various purposes in the final prototype.

6. Results of a patent search and assessment of patentability

Based on the accomplishments of the previous team, we knew that a number of patents existed which described techniques for non-invasive glucose monitoring. We felt it necessary however, to expand this search both in terms of identifying relevant issued patents, as well as current patent applications. The results of our expanded search confirmed that while some devices may utilize some of the same components as our prototype, no other single device combines all the aspects of the artificial pancreas into their design. Some of the most prominent features of our device are listed below (Reference the full patent report for details regarding differences between our prototype and individual patents or applications):

- Combines continuous glucose monitoring *and* insulin delivery in the same device
- Extraction of interstitial fluid combines vacuum, ultrasound, and reverse iontophoresis.
- Measurement of glucose levels takes place outside the body, *not* through the skin, which may confound results.
- Glucose measurement occurs directly from extracted interstitial fluid without the requirement of an additional chemical reagent or chemical reaction.

7. 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. In 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.

8. Estimated manufacturing costs

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 labor for manufacture of the initial working prototype will utilize student workers.

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 ~\$10,600.

9. 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. 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.

As of now, only two non-invasive blood glucose monitoring devices have been approved by the U.S Food and Drug Administration. The Gluowatch 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. 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 Gluowatch 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. 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, also more precise than the previous two, and cheaper for users. Apart from the one time expense to purchase the sonifier and the iontophoresis apparatus, we estimate <\$1,000 to be the non-recurrent cost of purchase of our device. Other comparison with top competitors is listed below:

Features	Deltec	MiniMed	Artificial Pancreas
Non-invasive	No	No	Yes
Glucose Monitoring & Insulin Delivery	Can be attached to the pump	Yes	Yes
Waterproof	Yes	No	Yes
Can be used in airplanes	Yes	No	Yes

	MiniMed's Paradigm	MiniMed's Guardian	Dexcom STS	Artificial Pancreas
Batteries for monitor	No separate monitor	2 AAA batteries	Chargeable batteries	Lithium ion rechargeable
Communicates with insulin Pump	Yes, with Paradigm 522 & 722	No	No	Yes

10. Business plan detailing strategy for commercialization and opportunity statement

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. The ultimate goal in the commercialization plan is to sell the final technology to a large corporation for large-scale production and marketing.

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 enable 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 noninvasive 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.
6. Flower R., Devine J. Iontophoretic drug delivery device having high-efficiency DC-to-DC energy conversion circuit. *United States Patent* .61