MEMS Fabricated, Flexible Glucose Sweat Sensor

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May 4, 2023

I. Abstract

Type 1 Diabetes is a growing epidemic across the world, and without a cure currently available sophisticated means of administering insulin and monitoring blood glucose levels are needed to ensure that diabetics are healthy and have quality of life. Current glucose monitors are: invasive, have a lot of waste, expensive, and need to be replaced, on average, every fourteen days. The invasiveness of the current sensors causes excessive scar tissue development which reduces effective insulin absorption and require regular injections for diabetics. The majority of Type 1 diabetics are diagnosed in the juvenile stage of life; resulting in juveniles having to constantly use needles causing a severe impact of quality of life. This project successfully proposed and show successful glucose measurements of a MEMS fabricated, flexible sweat sensor. This sensor is coated with adhesives making it able to be applied to many areas and generate sweat efficiently; it is also not limited to a short enzyme life span which allows it to be used for an above average time frame. The overall design and results from this project reflect on the next generation of glucose monitors that brings diabetics one step closer to having an autonomous and minimally invasive way of managing their diabetes.

II. Introduction

Diabetes Mellitus has affected hundreds of millions of people across the world; it is reported, as of June 29, 2022, that 11.3% of the United States of America has diabetes and 23% of adults are undiagnosed diabetics [1]. Internationally, it is expected that by 2045 there will be 783 million people with diabetes across the world [2]. Many international companies have begun to see rises in the number of people who need insulin and self-monitoring systems for maintaining blood glucose. While North America is the global leader in type 1 diabetes (T1D) and insulin consumption, Europe has become the second largest consumer region in the insulin market with Asian Pacific, Middle East, and Latin America having significant rises in need for insulin amongst their populations [3]. During Covid, the need became vitally apparent which has forced many companies like Eli Lilly, Eva Pharma, Sanofi, and Astra Zeneca to invest in both Type 1 and Type 2 diabetes treatment therapies and insulin production.

Diabetes Mellitus has seen a major spike in the Type 2 diabetes (T2D) market in North America due to a rising obesity epidemic sparked by the number of processed foods consumed. Type 1 diabetes has also had a rise, in 2019 it was reported that 1.9 million Americans have T1D [4]. Type 1 diabetes is also called juvenile diabetes since it develops in children, which means a majority of the people with T1D would have been diagnosed with the disease before they turn 20 and will live with the disease for the rest of their lives [5]. With 1.4 million people being diagnosed with diabetes every year and with diabetes being the seventh leading cause of death in the United States alone, typically from ketoacidosis, it is imperative to understand both what is causing this disease and how to manage the disease effectively on an individualized platform [5], [6].

T1D is caused by an immune response where T lymphocyte cells attack the beta cell mass, found in the pancreas. The beta cell mass in responsible for producing insulin, which is the hormone responsible for controlling blood sugar levels, formally the glucose levels. Glucose is the fuel source used by cells throughout the body, especially the brain. Any imbalance, low blood sugar, hypoglycemia, or high blood sugar, hyperglycemia, can be deadly for a person. Once the beta cell mass is destroyed it does not regenerate; many attempts are currently being pursued for stem cell treatments to help the beta cell mass regenerate [7]. While these attempts have worked

in lab settings, it is difficult to implement them due to the immune system still destroying the beta cells, and making a patient live on immunosuppressants can create many more complications. This is why T1D is typically treated by regular intervals of insulin therapy and glucose monitoring [2].

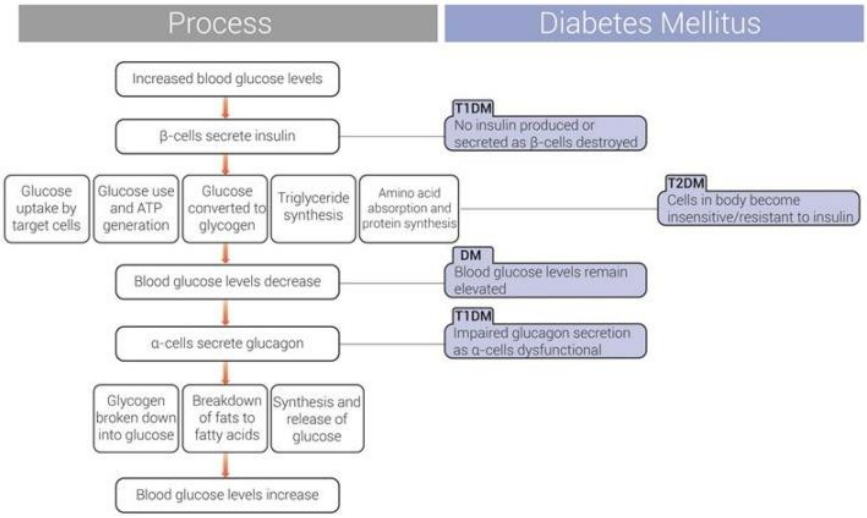

Figure 1: Biological process for natural glucose monitoring and insulin secretion compared to glucose monitoring and secretion in diabetes mellitus [2].

T2D is caused by obesity and seen primarily in overweight adults. The excess build-up of fat in the body reduces the body's ability to absorb insulin which causes glucose imbalances. In severe cases, the body will stop producing insulin, but it is not linked to an immune response [4]. T2D is reversible through improved diet and other treatment systems, but, similar to T1D, it is imperative that blood glucose levels be monitored regularly and accurately.

Many attempts have been made and are continuing to progress in the area of closed loop management for diabetes, specifically T1D, on the treatment side and research side. Traditionally, diabetics have an insulin pump that boluses insulin dosages based on an inputted glucose reading from a blood glucose reading or a constant glucose monitor (CGM). These systems have delays and work in a reactive based system; if a person is already showing high blood sugar, then administering insulin will have a delay before it is able to control the blood sugar level [2]. Many commercial systems have a direct link between a CGM and insulin pump, termed the artificial pancreas, allowing data to be sent and approved by the diabetic. The FDA has not given approval nor has there been a commercial development in an automatic system. This is for patient safety incase an inaccurate reading occurs. As sensor development progresses and reliability increases, many treatment possibilities will be developed to drastically increase quality of life for diabetics.

Insulin absorption is a major issue faced by diabetics despite the developments that have been made. As with any drug, the effectiveness from person to person will vary, and the effectiveness overtime from a chronic user will also change [8]. This means the same amount of insulin needed to treat a glycemic spike will not be the same for everyone. Insulin is typically administered via subcutaneous injection in order to be circulated throughout the body. Due to the limited number of areas approved for insulin administering, scar tissue will develop; insulin cannot be absorbed as effectively through scar tissue which affects how well an insulin bolus is at controlling glucose levels [9].

This project seeks to address many of the complications that are seen in day-to-day life for diabetics by developing a sweat sensing glucose monitoring. The sensor is flexible and easily worn, allowing for it to bring quality of life to diabetics by reducing the number of injections needed on a daily basis and allowing for a comfortable way to monitor glucose levels when compared to other

systems. In addition to being cost-effective, the sensor also has a long lifespan due to the materials used in its fabrication. Platinum and titanium offer good stability and corrosion resistance [10],[11],[12],[13], whereas tungsten is known for its hardness and excellent electrical conductivity [14]. This makes it a sustainable and reliable option for long-term monitoring of glucose levels compared to counterparts available in the market.

III. Background and Significance

All of these factors that control the delicate process of glucose balance make diabetes a difficult disease to treat and cure. Currently, research is pursuing a bionic pancreas which would allow insulin administration and glucose management without needing the patient's input every time a decision is made. This would be made possible by a unique algorithm that takes into account individual factors that normally would not be considered in commercial closed loop systems [15], [16]. Other algorithm research is being done into predictive analysis of patient behavior in an effort to bolus insulin before a glycemic event can occur. RocketAP is a clinical trial that sought to bridge the gap in current hybrid closed loop systems and the goal of a fully automated closed loop system via a unique Control-IQ algorithm. This study was focused around adolescents and predicting untimed meals [17]. Research is also pursuing unique ways to test closed loop systems without needing human studies. Human clinical trials can be costly and time consuming; the Padova T1D model is an FDA approved in silico model for simulating daily usage and providing CGM data that can be used to test new algorithms [18].

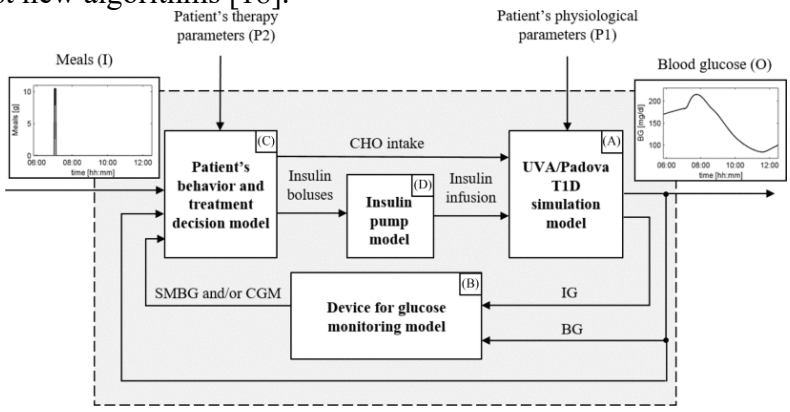

Figure 2: Block diagram for UVA Padova in silico model for CGM testing [18].

While advances in closed loop management and insulin delivery are being made, a reliable system is still dependent on an accurate sensor. Industry currently uses subcutaneous fluid-based sensors due to their reliability. Companies such as Dexcom, Medtronic, and Abbott have a large number of users and trusted sensors, but they are costly and produce a large amount of waste due to their packaging and lack of reusability.

Table 1: Comparing current CGM specifications on market [19], [20], [2], [21], [22].

Company	Sensor	Life Span	Average Life Span	Closed Loop Integration Ability
Dexcom	G6	14 Days	10 Days	Tandem t:slim insulin pump
Medtronic	Guardian 4	7 Days	7 Days	Medtronic 670g hybrid Insulin Pump
Abbott	Freestyle Libre 3	14 Days	14 Days	None
Eversense	Eversense E3	90 Days	90 Days	None

Company	Sensor	Water resistance	Calibration	Sensing Frequency
Dexcom	G6	8 feet (24 hours)	Factory Calibrated	5 Min
Medtronic	Guardian 4	7.5 feet (10 minutes)	Factory Calibrated	5 Min
Abbott	Freestyle Libre 3	3 feet (30 minutes)	Factory Calibrated	1 Min
Eversense	Eversense E3	3.2 feet (30 minutes)	Requires Daily Calibration	5 Min

Company	Sensor	MARD	Average Monthly Cost
Dexcom	G6	9.00%	$520
Medtronic	Guardian 4	8.70%	$541
Abbott	Freestyle Libre 3	7.9% - 9.7%	$135
Eversense	Eversense E3	8.50%	$466

Additionally, companies like Senseonics are undergoing new clinical trials for a long-term implantable glucose sensor. They have completed one study for a 180-day implantable sensor for the next generation of Eversense CGM. They also have begun their first pediatric study for an implantable glucose sensor [22], [23]. Aside from implantable sensor development and initial fluid sensing, other methods of glucose sensing are being considered as well. Microgels are being developed to release insulin in response to blood glucose, just as a closed loop system would work. They work by using a pH sensitive matrix and enzymes to react with glucose and release insulin that is stored within the microgel [24]. Insulin patches are also being developed; proof of concepts have been done by utilizing microneedle array patches that are coated with a glucose responsive matrix. Depending on the glucose surrounding the microneedle array, the openings will swell or shrink allowing insulin to pass [25]. Hydrogels doped with insulin and a reactive element that responds to glucose have also been used, but hydrogels have a certain amount of leakage which can lead to undesired release [26]. There have been many attempts to make diabetes management completely hands off, but the issues arise with keeping the drug delivery in check. This is why no matter how developed the science gets on drug management, have a sensing system that is easy to use, comfortable, and reliable is vital for any application.

Sweat sensing can answer the call that many methods of sensing cannot and future developments for insulin delivery need. Sweat sensing is non-invasive, easy to replace, and relatively cheap to produce. It can also be connected wirelessly to any modern drug delivery system, or provide a more comfortable way to monitor blood glucose in the event an insulin pump is replaced with a more hands off system. As mentioned previously, a majority of T1D patients are adolescents who do not like needles. Having a noninvasive way for them to track their blood glucose will drastically improve their quality of life. Additionally, the development of scar tissue in the select areas for CGM and insulin injections would drastically decrease over a diabetic's life

time if the number of needle insertions can be eliminated from daily life. Sweat sensing has been around, but has not become a major competitor in commercial settings. Other areas have also been pursued but are not feasible for many reasons, mainly relating to reliability or ease of use [27].

Wearability	Biofluid Type	Sampling Method	Benefits
Eyeglasses sensor	Sweat	Exercise	Continuous monitoring of sweat glucose. Integration with wireless electronics.
Wearable patch with multimodal glucose sensor	Sweat	Exercise	Controlled sweat uptake. Improved accuracy of glucose sensing using multimodal sensing array and correction with sweat pH value.
Graphene-based stretchable patch	Sweat	Exercise	Accurate monitoring by combination of pH, temperature, and humidity. Nanomaterials-based sensitive glucose sensor.
Wearable patch coupled with induced sweating	Sweat	Iontophoresis (stimulated)	Integration of iontophoresis sweat generation with glucose sensing.
Multiplexed wearable, flexible array patch	Sweat	Exercise	Simultaneous multiplexed sweat sensing. Integration of customized wireless electronics.
Temporary tattoo	ISF	Reverse iontophoresis	Cost effective, easy to wear, and no skin irritation.
GlucoWatch	ISF	Reverse iontophoresis	FDA approved, provide continuous monitoring and electronics for measurement.

Figure 3: Table comparing various sweat and interstitial fluid sensing methods [27].

The advancements in MEMS have made sweat sensing expand rapidly in many ways. Many sweat sensors utilize lab on chip designs and electrochemical detection for sensing [28], [29], [30], [31]. Utilizing microfluidics and reverse iontophoresis allows for small concentration of analytes such as: cortisol, uric acid, lactate, and interleukin-6 to be analyzed [32]. Another major step in sweat sensing is multianalyte sensing; since sweat has many analytes, understanding how to obtain specificity is vital. Additionally, making sure a device is comfortable to wear is important and why many people are pursuing sweat sensing that is flexible or able to be integrated into wearable sensing like clothing or bands [33]. Methods utilizing microfluidic channels or clothing integration are advantageous since they allow for repeatable sensing by collecting and removing sweat from the sensor [34]. Clothing embedded MEMS must be flexible, able to withstand cleaning, and effective with movement. These challenges have been studied by making the sensor woven into the textile and fixing sensing elements on the inside. Once integrated into clothing, the sensor can be worn over many parts of the body and are almost unnoticeable [35]. Depending on the sensing analyte and desired life span, sweat sensors can also be made to adhere to skin with medical adhesive. The advantage of a reusable adhesive is relocation of the sensor if desired [32]. Sweat sensors can also be used for many scenarios that are not focused on disease management; by using MEMS and sweat sensing, alcohol consumption can be measured [36]. This could replace traditional breathalyzers that are easily interfered with by substances, like mouth wash containing alcohol.

Glucose sensors have come a long way from their original development in 1962. The current generation of glucose sensors, commercially, are in the 3rd and 4th generation of sensors. These are based on enzymatic reactions that cause glucose oxidation to occur resulting in a change that can be detected by an amperometry measurement [20], [27], [37], [38]. This enzyme immobilization design for a glucose sensing mediator has been used in many glucoses sweat sensors [39], [40], [41], [38]. Using enzymes as a mediator has great reliability, but is susceptible to a shorter life span for users who have consistently higher blood sugars. This is due to the enzyme layer being used up faster than anticipated and a build up of other interfering molecules at the sensor, such as triglycerides, oxygen, and uric acid [42]. Direct oxidation at the electrode is a form

of electrochemical sensing that is being used in the next generation of glucose sensors. It used a modified electrode, typically electrical deposition or other surface deposition, to undergo an oxidation reaction that can be measured [41], [43]. This method does require enzymes which could reduce cost and time needed to fabricate a sensor. If the specificity of a nonenzymic based glucose sensor can be enhanced then a noninvasive, long-term sensor could be developed and greatly benefit the world of diabetes management.

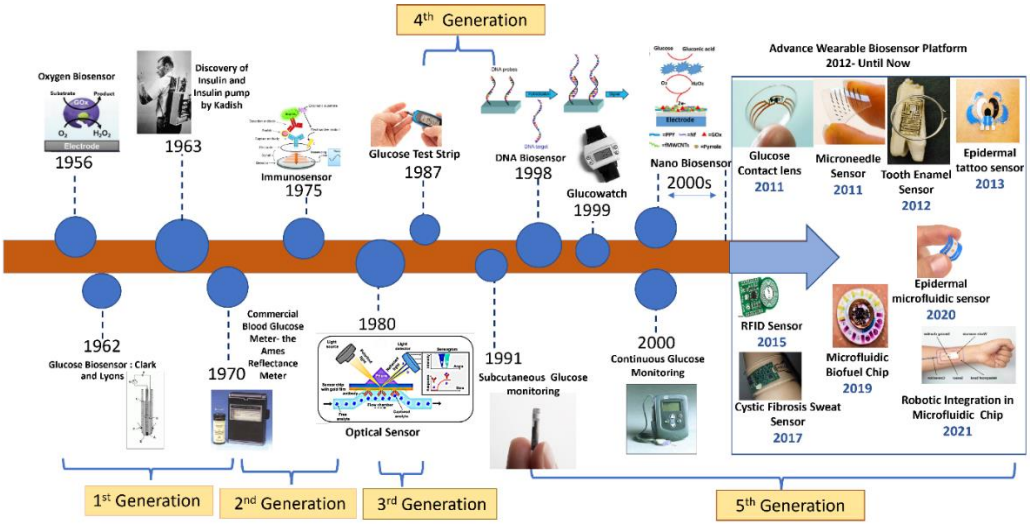

Figure 4: Timeline of Glucose Sensor development from the first discovering of glucose oxidation to current epidermal based sensing [27].

Microelectromechanical systems (MEMS) are devices that integrate electrical and mechanical components on a microscale, generally less than 100 micrometers in size. MEMS have transformed various kinds of industries, including microfluidics, biomedical devices, sensors, actuators, and actuators [44]. There are many benefits for devices on that small scale, including low power consumption, excellent sensitivity and precision, and the capacity to carry out intricate tasks [45]. Smaller, less expensive, and more effective devices have been made possible by MEMS technology and are now employed in a variety of fields, including consumer electronics and medical diagnostics [44], [45], [46].

Moreover, flexible MEMS (FMEMS) are a subset of MEMS that can bend and deform without breaking [47]. Due to their potential to revolutionize a number of industries, including wearable electronics, implantable medical devices, and soft robotics, these devices have attracted a great deal of interest in recent years. FMEMS offer a wide range of possible uses, from managing medication administration to monitoring physiological signals, and their flexibility makes them perfect for usage in unusual settings or on curved surfaces [48], [49].

One of the critical factors that determine the effectiveness of wearable sensors is power consumption. Wearable sensors must consume minimal power to extend their battery life and ensure continuous monitoring of physiological data. It is also limited by the reliability of their power source. Supercapacitors, which have high power density and can store energy for extended periods, have been proposed as an alternative power source for wearable sensors. However, current supercapacitors are still not practical for continuous monitoring activities due to their low energy density and unreliability [50]. Energy harvesting, which converts energy from the environment into electricity, is another potential power source for wearable sensors. However, the development

of practical energy harvesting systems that can generate enough power to sustain continuous monitoring activities is still in its early stages.

IV. Preliminary Results

Sweat sensing is based in electrochemical sensing which is a well-studied field in cross disciplinary sensor research. The proposed sensor in this project will be functionalized by electrodeposition and use a three-electrode configuration for added stability while sensing. For functionalizing the working electrode, the tungsten surface will have platinum deposited onto the electrode. The three-electrode set up utilizes a silver/silver chloride reference electrode and a tungsten counter electrode. The counter electrode should not be functionalized to allow for a constant voltage under normal conditions to be monitored. The silver/silver chloride reference electrode will be fabricated by MEMS techniques. The electrodeposition process does not require a clean room which will significantly lower cost and time to manufacture a sensor. The cyclic voltammetry works by cycling voltage in incremental step values between set voltage values for numerous cycles. This allows the solution containing metal, in this case platinum, to go through reduction and oxidation reactions on the surface of the tungsten electrode. This process will deposit the platinum onto the electrode as more cycles occur. The solution contains potassium Hexachloroplatinate (IV) and perchloric acid [51].

$$(2e^{-3})\ M\ [K_2PtCl_6] + (1e^{-1})M\ [HClO_4]$$

Eqt.1 Chemical solution equation used for platinum deposition.

The deposition process can be altered for desired deposition characteristics. After deposition is done, the impedance can be measured to ensure platinum has been deposited, and images can be taken with an SEM to observe the growth on the electrode. The preliminary deposition shows that it is possible to functionalize the electrode for nonenzymic sensing in a non-clean room environment.

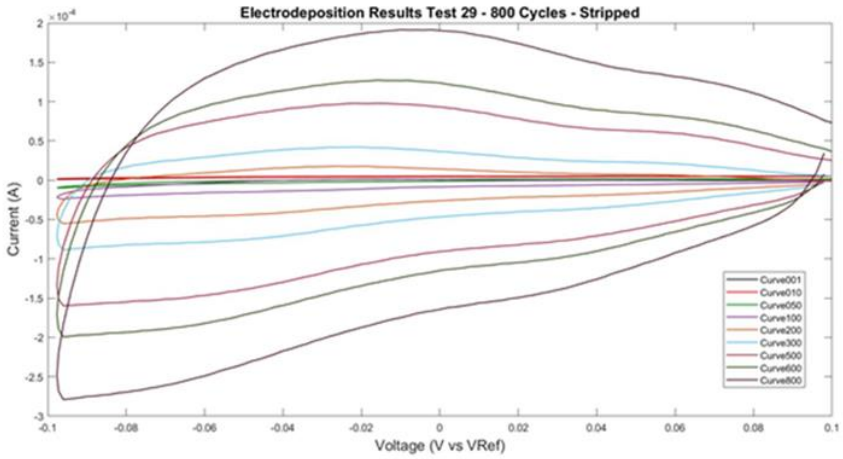

Figure 5: Cyclic Voltammetry Output Graph showing current generated at different scan cycles for electrodeposition of platinum on tungsten electrode.

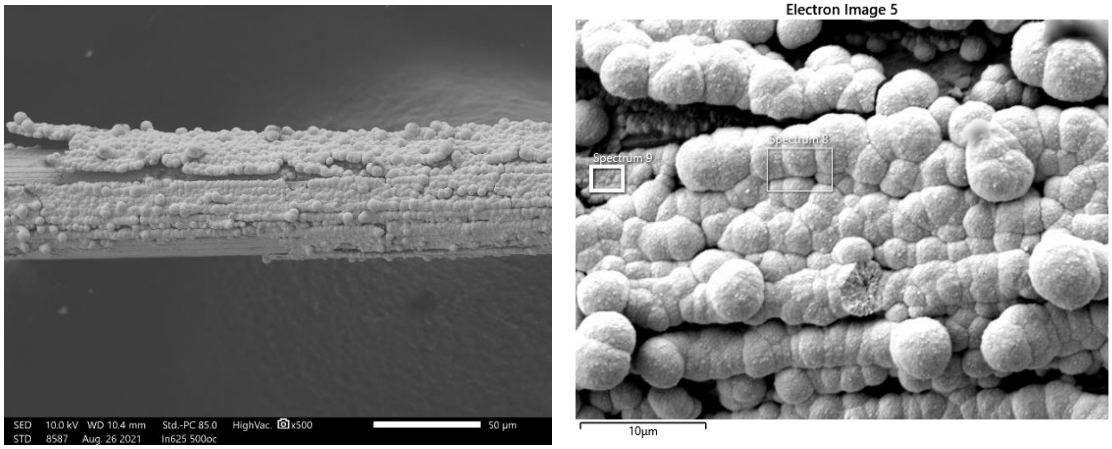

Figure 6: SEM image of platinum particles on tungsten electrode, 50-micron diameter.

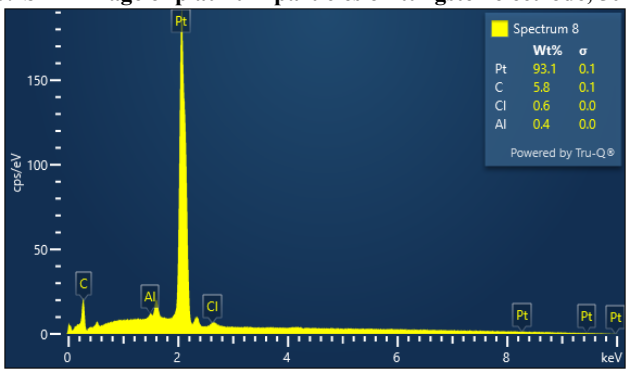

Figure 7: Composition Spectrum showing elements detected in Spectrum 8 of the above SEM image.

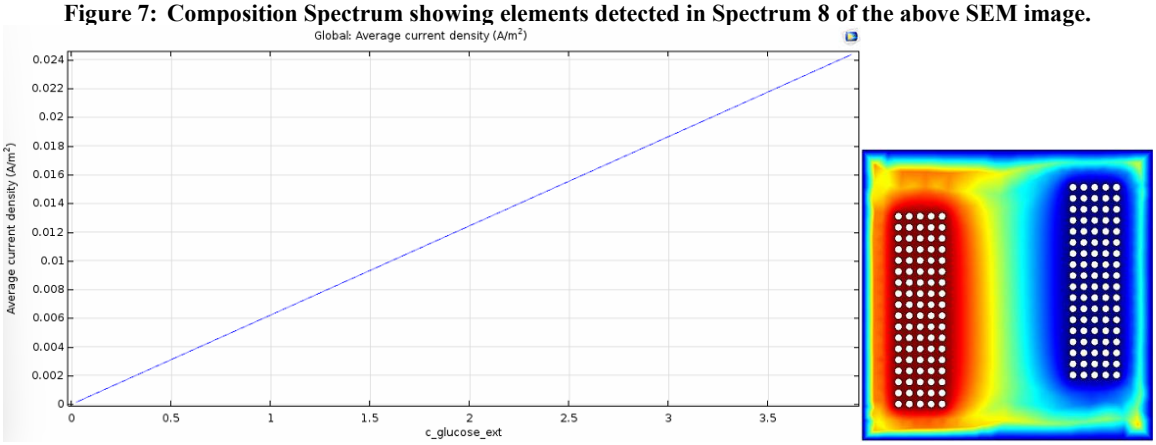

Figure 8: (Left)COMSOL simulation Current density versus glucose concentration. (Right) Glucose concentration in the 2d sensor design.

COMSOL 5.1 software was employed to simulate the sensor response using amperometry, which measures the current for different glucose concentrations, see figure 8. The sensor was modeled using the electroanalysis model and simulated with a parametric sweep in a stationary study. To achieve more accurate results, the simulation involved modeling three species: ferrocyanide, ferricyanide, and glucose. The rate of the reaction in this simulation was described by the Michaelis-Menten law: $R = \frac{c_{glucose} \cdot V_{max}}{1+K_m c_{glucose}}$, where Vmax is the maximum rate of the reaction and Km is the Michaelis constant. In this study, the values of Vmax and Km were set to 1.5×10^ (-5) (mol/L)/s and 0.5 mM/L, respectively. These values were slightly adjusted from the default values provided in the Glucose sensor file from COMSOL's application library, which was used

as a reference for the simulation. However, it is important to note that finding specific Vmax and Km values for the electrodes used in this project was not possible in the literature, and experimental determination is necessary for more accurate results.

V. Proposed Research

Reverse Iontophoresis

One of the biggest factors for the quality of a sweat sensor is its ability to generate enough sweat to obtain a desired measurement. Passive sweat sensing can be easily achieved by monitoring physical activity and begin sensing once sweat is naturally generated by the body. Active sweat sensing involves a process called reverse iontophoresis; iontophoresis is the process of passing current through skin. Reverse iontophoresis utilizes this same concept using an electric field to induce osmosis on the skin. As positively charged particles are moved through the field to either the cathode or anode, uncharged particles, such as glucose, will move toward the cathode and released via sweat [38].

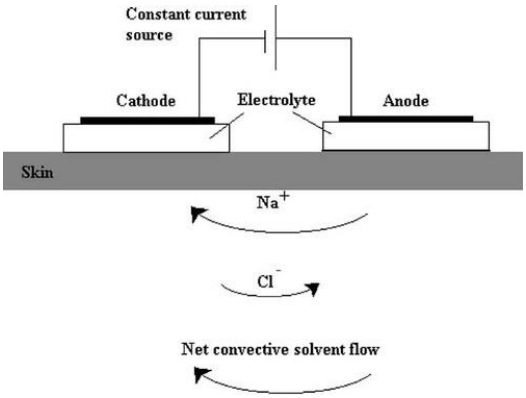

Figure 9: Simplified diagram of reverse iontophoresis and the flow of different sweat analytes once voltage is applied to the electrodes [38].

Sweat generating in volumes greater than 18 microliters is difficult, which means the specificity and accuracy of the sensor has to have a low margin of error. The design presented in this project is similar to the work done by Davis, et. al [43]. The performances is expected to be similar to the results achieved here. The sweat induction is fundamentally a current source coupled with a protection circuit; this ensures that no damage is done to the skin and adequate current is delivered for sweat generation. The onboard electronics can be wirelessly controlled to monitor the output of the current source. The wireless control can also determine the time intervals for sweat induction and rates of sweat production.

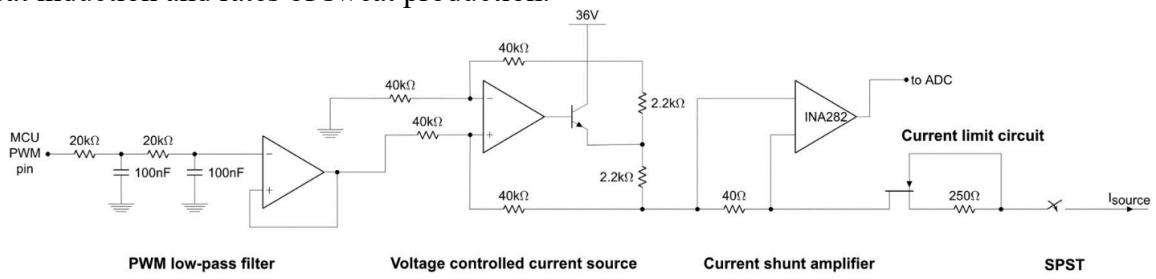

Figure 10: Sweat Generation Circuit for Reverse Iontophoresis [43].

The first phase of this circuit is a PWM low pass filter for a digital to analog signal conversion. The next stage is a voltage controlled current source which regulates the current across the load; this ensure the correct amount of current is being providing for sensing. The current shunt amplifier provides a proportional voltage in response to the current being produced in the previous

stage; this then goes to the ADC. Lastly, the current limiting circuit is needed to make sure too much current is never passed through the skin.

Furthermore, the sweat-inducing electrodes are in contact with the skin via a hydrogel for improved electrical connectivity and the reduction of the risk of electrical discharge [52]. The sweat-inducing electrodes' design also helps to prevent direct skin contact with the glucose detecting electrodes. Finally, the switches are capacitive actuators that use a pull-in voltage to attract a micromachined beam that is fixed from both ends and acts like a spring to control the opening and closing of the sweat chamber. This setup ensures that sweat is collected and evaporated in a controlled manner, making it easier to measure sweat glucose concentration.

Analyte Sensing

Most sweat analytes have low concentrations compared to blood, and, for glucose, the range is 0.02 to 0.6 mM. In blood that value is 2.0 to 30 mM [53]. This range can still be achieved through amperometry sensing; this sensing works by analyzing the change in current between the working electrode and the reference electrode at the electrode given a redox reaction [43].

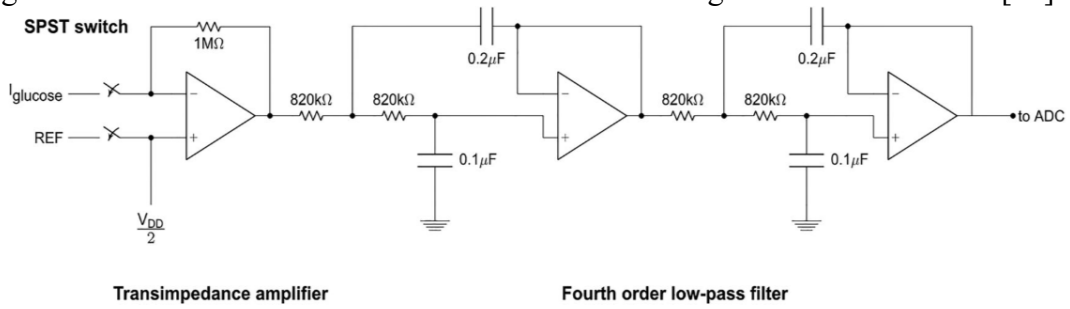

Figure 11: Transimpedance Amplifier for analyte sensing of glucose [43].

The amperometry sensing can be accomplished by utilizing a transimpedance amplifier which converts a current into voltage. The first stage is a transimpedance amplifier which works like an inverting amplifier circuit and would increase the gain by increasing the feedback resistor value. The output voltage of the transimpedance is given by $V_{out} = V_{REF} - R_f(I_{glucose})$. The higher the current the higher the magnitude of the voltage with -180 phase shift. The second stage is a fourth order low pass filter comprised of two second order low pass filters which have cut-off frequency given by $\frac{1}{\sqrt{R_1 R_2 C_1 C_2}}$. The low pass filter removes high frequency noise that might arise from amplifying the input signal giving a more coherent measurement reading.

Power and Wireless Transmission

To operate effectively, the device requires power for three different stages - iontophoresis, sensing, and transmission. To perform iontophoresis, the device must have a power source that can generate the necessary electrical current. The sensor measures glucose levels and to collect this data accurately, the sensor must be powered continuously. All this information must be transferred from the sensor to another device, such as a smartphone or computer, using wireless technology such as Bluetooth Low Energy (BLE). BLE is a low-power wireless technology that allows for data transfer with minimal power consumption. To transmit data wirelessly, the device must have a BLE module and a power source that can sustain the transmission for an extended period.

To power the device for all three stages, the power source and BLE module are integrated into a flexible printed circuit board. The use of a flexible printed circuit board allows the device to be more compact and lightweight, making it more comfortable for users to wear. Additionally, the integration of the power source into the circuit board eliminates the need for an external battery or power source, further reducing the size and weight of the device [43].

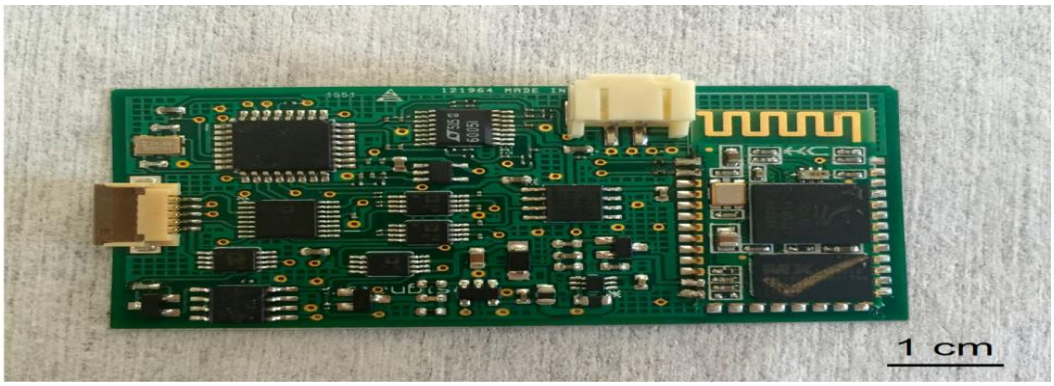

Figure 12: Flexible PCB with BLE chip [43].

The flexible PCB has a microcontroller embedded inside. To induce sweat using iontophoresis, the current is driven through the microcontroller's Digital-to-Analog port. The circuit for iontophoresis converts the low-voltage DC power provided by a small battery into a high-voltage, low-current signal that is used to stimulate the sweat glands. The battery voltage is boosted to a higher voltage using a DC-DC converter circuit. The boosted voltage is then fed into a high-voltage driver circuit, which generates the high-voltage, low-current signal needed for iontophoresis. The high-voltage driver circuit is designed to deliver a precisely controlled electrical current to the skin. The current is typically in the milliampere range, which is well within the safe limits for human skin [43]. The amount of power required for sensing, which involves collecting data from the body using embedded sensors, is low. There are commercial sweat patches available in the market that can run for 2-4 hours without a power source. These patches use sweat as a source of power, and the generated electrical current is used to power the sensors. The fact that these patches can operate without an external power source indicates that the power consumption for sensing is relatively low, from few to few hundred milliwatts.

Various BLE chips are available in the market now. The popular and advanced choices include, but are not limited to – BlueNRG2 by STMicroelectronics, nRF52840 by Nordic Semiconductors, and CC2541 by Texas Instruments. The communication range of commercially available CGMs is 15-20 feet, and the size of the data that needs to be transmitted is 2 bytes. Therefore, the crucial factor that determines the chip is the cost. BlueNRG2 by STMicroelectronics is the cheapest option, which will cost only roughly $2 for mass production. The average power consumption for transmission once every 6 minutes is 91microwatts [54].

$$Average\ power\ = (Power\ consumption\ for\ 1\ transmission\{J\})\ /\ 360seconds$$

Assuming every sensing consumes an average power of 100milliwatts, iontophoresis consumes 3.6milliwatts, and transmission consumes 91microwatts, the total power consumption of the sensor for one sensing and transmission will be 0.103691watts.

$$Total\ power\ =\ Power(iontophoresis)\ +\ Power(sensing)\ +\ Power(transmission)$$

Using a commercially available 3V Lithium battery with a capacity of 235mAh, the device will last for approximately 90 days or 3 months [55].

$$Battery\ consumption\ =\ Battery\ life\ (mAh)\ /\ Power\ Consumption\ (milliwatts)$$

MEMS Fabrication

The glucose sweat sensor is fabricated in several stages that are critical to the device's performance and reliability. The diagram in figure 13 depicts a schematic of the fabrication process. The process begins with the deposition of a thin sacrificial layer of aluminum onto a silicon wafer using an electron-beam physical vapor deposition (E-beam PVD) technique. After that, a polyimide layer is spin-coated and cured on a hot plate. To create the interconnects

that connect the various electrodes to the controlling circuit, titanium is deposited with PVD on polyimide. The interconnects are then spin-coated with another layer of polyimide to protect them from corrosion, electrically isolate them, and prevent oxidation-induced surface passivation [56]. Following that, tungsten layers are deposited to form the working electrode and counter electrode using the electroplating technique. Similarly, the reference electrode is created by depositing silver using the same procedure. followed by silver chloridization, resulting in silver/silver chloride [57].

By depositing titanium using PVD in an oxygen/argon environment causing oxidation, a layer of titania is formed over the sensor electrodes [58]. The sweat-inducing electrodes and the switches are then made through the use of PVD to deposit a thick layer of titanium. After using photolithography to pattern the electrodes, metal anisotropic reactive ion etching with oxidation (MARIO) is used to etch Titanium until the Titania layer is reached. The MARIO technique involves using reactive ions to etch the metal, followed by the generation of an oxidizing plasma to stop lateral etching. This cycle is repeated until the desired depth is reached [58]. Hydrofluoric acid is eventually used to etch the titania layer [59], revealing the glucose-detecting electrodes and releasing the suspended switch beam.

Electroplating is used to coat the tungsten in the working electrode with platinum [51], enhancing both the sensor's sensitivity and its ability to perform redox reactions [60]. To guarantee sufficient electrical contact, avoid surface passivation, and minimize skin irritation, the sweat-producing electrodes are then covered with a layer of hydrogel [61]. The glucose sweat sensor's performance and reliability are significantly reliant on these intricate multi-step manufacturing processes.

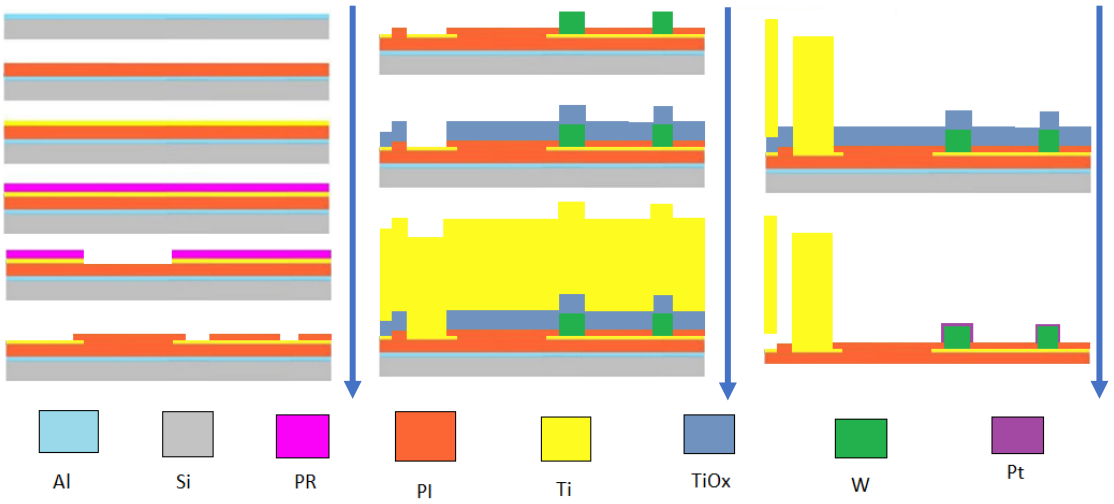

Figure 13: Sensor fabrication process.

Material selection was also critical in the sensor fabrication procedure. Polyimide was chosen as a substrate material because of its desirable qualities such as flexibility, electrical insulation, and thermal stability [62]. Furthermore, Polyimide can be easily deposited by spin coating, adding to the convenience of the fabrication process [62]. Aside from the substrate, the electrode material is also important for sensor performance. Titanium was chosen for its strong adhesion to Polyimide [64], [65], low cost, and ease of deposition to construct the interconnects, sweat-inducing electrodes, and switches. Titanium is a transition metal with excellent mechanical and electrical properties, including high strength, low density, and good corrosion resistance [12]. Overall, the selection of materials in the sensor fabrication process plays a significant role in determining the sensor's performance and stability. The combination of Polyimide as a substrate, Titanium for interconnects, sweat inducing electrodes, and switches, and Platinum-coated tungsten

for the working electrodes results in a sensor with desirable mechanical, electrical, and electrochemical properties.

Final Device Design and Testing

The sensor is constructed on a 13um thick Polyimide film to guarantee flexibility, while the height of the titanium structures is 15um to maintain flexibility and prevent direct skin contact with the measurement electrodes. The dimensions of the sweat chamber are 2cm by 2cm, roughly the size of an American quarter, with electrode cylinders measuring 3um in height, as seen in the close-up image in figure 14, to ensure a large surface area for measurement. The sensor is intended to be integrated with a flexible battery which will be on top of the Polyimide film and will power the control circuit responsible for controlling the reverse iontophoresis, opening and closing of vents, glucose concentration measurement, and data storage and transmission. The control circuit is located on top of the flexible battery, and the entire device is packaged in a breathable fabric with adhesive to ensure proper adherence to the skin. This innovative design allows for seamless glucose monitoring in real-time, and the flexible nature of the device enables it to conform to the contours of the skin, providing enhanced comfort to the wearer.

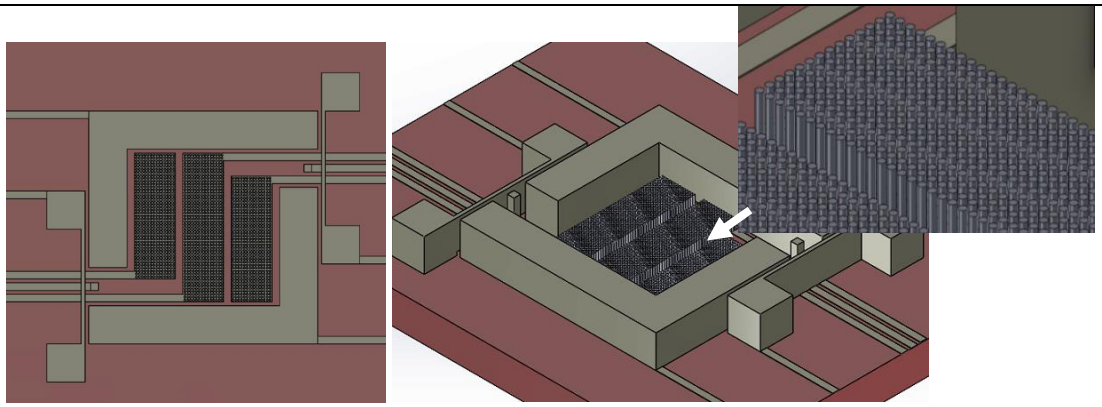

Figure 14: Glucose sensor design. (Left) Top view. (Right) Isometric view.

VI. Results

The development of a wearable, flexible glucose sensor was successfully developed and tested. The reverse iontophoresis system is functional with different voltage frequencies, allowing dynamic control over sweat generation. The transimpedance based analyte sensing effectively sensing a change in current that can be used over time to develop an accurate understanding of a user's sweat glucose concentration. This design also demonstrates a noninvasive means to monitor glucose that is comfortable and easily controlled by the user. The precise ability to develop the device with small margins of errors allows for the device to be expanded in future projects and translated into devices that can be used in consumer markets.

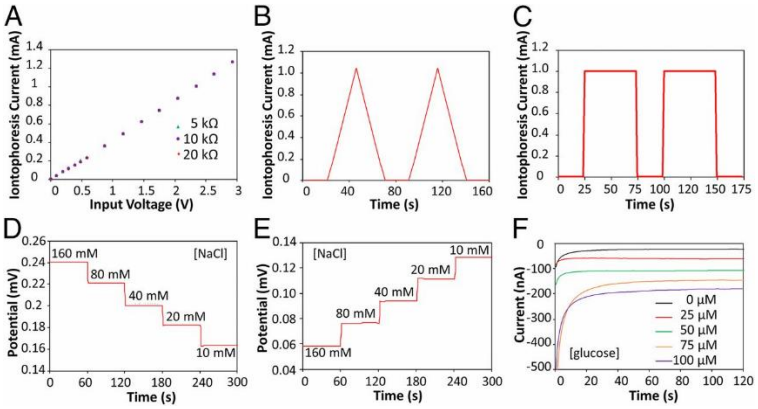

Figure 15: Results graph showing: (a-c) different current generations when given different input voltage signals. (d-e) shows example of analyte sensing for Na and Cl ions in sweat. (f) shows current generated at different concentrations of glucose [43].

VII. Broader Impact

The device has potential for further improvement by incorporating additional sensing capabilities. For instance, integrating a heart rate or temperature sensor would enable passive monitoring of physiological signals. This would allow the device to detect an increase in heart rate or body temperature, which would indicate the onset of sweating, without the need for iontophoresis. By reducing power consumption, this could increase the longevity of the device.

Furthermore, the device could be enhanced with sensors capable of detecting a broader range of anolytes beyond glucose. Expanding the range of anolytes detectable by the device would make it a more versatile and reliable all-in-one smart medical wearable device.

This type of wearable sweat sensor would allow for not only major advances in quality of life for diabetics, but allow for easy integration into a bionic pancreas sensing. The ability to easily monitor glucose with added sensors that relate to physical exercise gives valuable information to a bionic pancreas system that is trying to predict glycemic events. The more data it has on physical exertion over time will allow for it to better predict patterns. These patterns can relate to spikes due to substances, such as increased heart rate due to caffeine, or to daily movement patterns, workouts and commuting. These pattern recognitions would unlock the ability to treat diabetes on an individual level and bring diabetes management a step closer to fully autonomous treatment.

Energy harvesting and supercapacitors can be considered as a future development area for power generation. Integrating various sources of energy harvesting with a supercapacitor that can charge quickly, also having high energy density will lead to the development of self-powered wearable sensors [34].

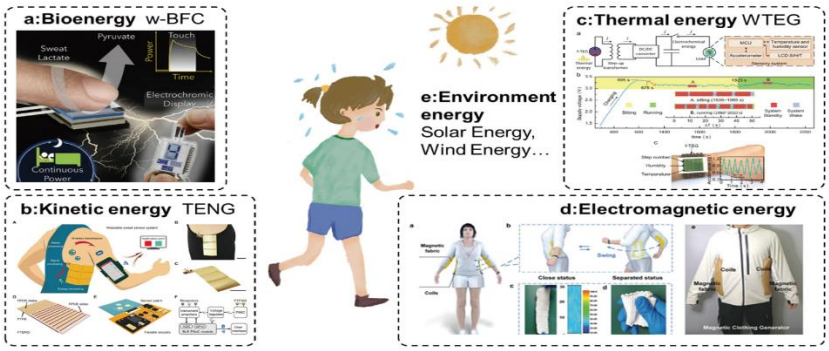

Figure 16: Energy Harvesting Ideas to power wearable sensors

Triboelectric nanogenerators are gaining popularity in the field of energy harvesting now. Integrating a triboelectric nanogenerator and supercapacitor to the already existing power source of the sensor can increase the life span by 2-3 weeks [50].

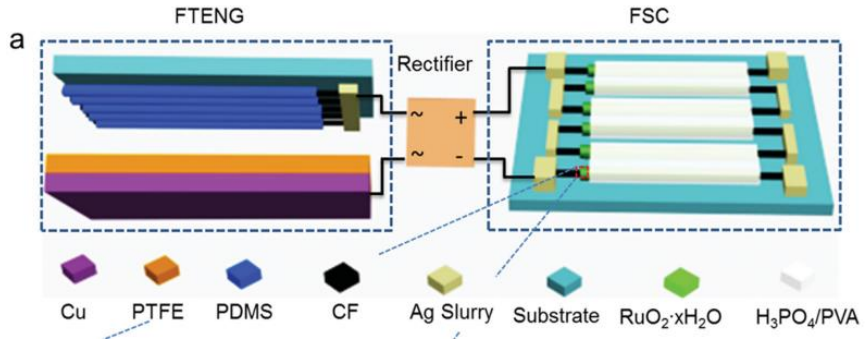

Figure 17: Triboelectric nanogenerator for energy harvesting and Supercapacitor for storage.

This device is complete and once ensured that the design is unique, a patent could be filed protecting the intellectual property. As other sensors are integrated, it would become more competitive for many different health applications outside of just diabetes, including general health monitoring. This area is of particular to many companies such as Apple and Fitbit. Given it is just a singular device and not a platform or devices, making a company off of one device is unlikely, but the probability of it being purchased in its entirety or in a royalty deal by another company is high since it brings flexibility, non-invasiveness, and cheap means of sensing analytes. For this device to be considered for a company, many different models would need to be made to answer more specified applications such as: does it work for people who spend above average times in drastic conditions (hot, cold, submerged in water, in areas with grainy particulates in the air). If a platform is developed and software applications are made for all major platforms, it would be highly competitive with other current industries. Mass production of MEMS devices is easy and cost effective. Most medical device companies need funding in the range of 25 million dollars in order to support the initial development and FDA clearance [65]. The 25 million dollars would ideally cover the first five years of operational needs since the company would not see an immediate profit. Before a commercialization and industry options are considered, FDA clearance would need to be obtained. The cost for most FDA 510(k) premarket notifications is in the range of 25 thousand dollars [66], [67]. The device would have to go through three stages of clinical trials, one of which would need to be human clinical trials. In order to be used in clinical trials a, investigational device exemption has to be filed to show it is safe and effective at data collection [68], [69]. Using a system such as UVA's Padova in silico model could expedite the trial process and reduce trial cost. Assuming the clinical trials are successful, the product would then go under FDA review. After getting approval, there would be a post market safety monitoring to ensure users will not be harmed and the device works as intended [70].

Table 2: Expanded Project Timeline

Milestone	Time (in months)	Comments
Patent for initial design	6-12	Patentability search and filing patent application
Improving functionality	3-6	Developing new sensors to measure other biomarkers and integrating into the existing design
Patent for final design	3-6	Updating the patent application

FDA Clearance	6-12	Waiting for the device to be cleared for the market by FDA
FDA 501(k) Premarket Notifications	6-12	Working with the FDA on the device
Clinical Trials	8-12	Safety and effectiveness
Final Improvements	3-6	Improvising based on results and feedbacks

VIII. Bio Sketches

Sreenath Krishnan Potty completed his bachelors in Electronics and Communications Engineering from Amrita Vishwa Vidyapeetham, one of India's top universities. His academic excellence was recognized when his undergraduate dissertation project was nominated for government funding, which was a testament to his exceptional research skills and expertise. His dissertation project focused on developing a shoe-sole embedded nanogenerator that converts mechanical energy from walking into power using a combination of piezoelectric and triboelectric materials. His outstanding work on piezoelectricity, piezoelectric materials, and the results obtained were presented at the Third International Conference on Materials Science and Manufacturing Technology (ICMSMT 2021), showcasing his deep knowledge in this field.

He was also an active participant in technical events, workshops, and competitions, and has organized multiple such events as part of university's technical fests, showcasing his excellent leadership and organizational skills. After completing his bachelor's degree, Sreenath secured an internship position at Smart IOPS where he focused on the development of a 'Smart Storage Cluster Management Software' backend. For six months, he worked in a Linux environment and gained valuable experience in coding. Subsequently, he received an offer to pursue a master's degree in electrical engineering at Virginia Tech. Currently, Sreenath is pursuing his master's degree in electrical engineering from Virginia Tech, where he is focusing on circuits and devices. He is passionate about the semiconductor industry and is looking forward to work with industry giants like Intel, TSMC, and Samsung.

Alex Parrott grew up in Lawrenceville, VA, and started his high school's first STEM course. Upon graduating high school, he went to VCU to pursue a Bachelor's degree in electrical engineering. A year later, he transferred to Virginia Tech where he graduated with a Bachelor of Electrical Engineering in micro/nano systems with a secondary focus and minor in Biomedical Engineering. He is currently a technical writing lead and digital media intern for The(Sugar)Science under Dr. Monica Westley.

He is also conducting research at Virginia Tech for his Masters of Science in Electrical Engineering, in the Nanoelectronics and Biosystems Lab under Dr. Xiaoting Jia. His research areas of interest are: biosensing, Type 1 Diabetes, closed looped biomonitoring and drug delivery, wearable bioelectronics, and polymer-based fibers. His current research is multifunctional, flexible fibers for in vivo biosensing and sweat based analyte sensing. Aside from research and courses, Alex has worked hard to expand his knowledge in Type 1 Diabetes and other areas of electrical engineering through internships and training. He has obtained certification for Stage 1 Biomedical Research in the CITI Program and with IACUC, which is needed for any human and animal trial research. These certifications were obtained in conjunction with the following courses: Commercialization of Biomedical Research, Medical Physiology, and Biomedical Imaging. Through other courses he has participated in many projects: Medication Compliance Verification, SiC Power Module for EV Traction Invertor, Smart Home Power Line Monitoring, and a study done on the next phase of Juvenile Stent Catheters.

In the summer of 2021, he was accepted in the dkNET Summer of Data Internship Program, funded by NIDDK. This program funded his research and taught him FAIR data management tools. In the summer of 2022, he was accepted into the USPRISM program, funded by the NSF and ran by Dr. Mehrizi-Sani. The USPRISM program was a summer research opportunity allowing him to travel to Glasgow, Scotland to assist in research, in Dr. Catherine Jones' lab, focused on studying the electrical properties of Carbon Fiber Reinforced Polymers (CFRP). Simultaneously, he worked in Dr. Rafael Pena-Alzola's lab to developed a force sensing circuit that is used to monitor the anisotropic properties of CFRP. His background in cross discipline and international research has given him insight and knowledge into many important elements of engineering and project management.

Abdulelah Ali graduated from Virginia Tech in December 2021 with a Bachelor of Science degree in Electrical Engineering with a specialization in Micro/nano systems. During his undergraduate studies, he took several notable courses that included circuit design and image processing. In the circuit design course, he demonstrated his skills by designing and building multipurpose circuits and amplifiers. In the image processing course, he gained valuable knowledge of image processing techniques, which he applied in his research projects.

His exceptional academic performance and dedication to his research were recognized when his senior design team presentation was awarded the best presentation in EE EXPO. Currently, he is pursuing a Master of Science degree in Electrical Engineering at Virginia Tech. He is actively involved in the BIOMEMS lab under the supervision of Dr. Masoud Agah, where he is conducting research on cancer cell separation using DEP.

During the summer, he gained hands-on experience in the field of MEMS fabrication while working at Rose-Hulman Institute of Technology in Terre Haute, IN 47803. He was introduced to clean room operations and became proficient in operating devices such as ALD, PVD E-beam, and sputtering, as well as x-ray diffraction. In addition, he learned and practiced many MEMS fabrication techniques, including the concept of photolithography, deposition, and etching. With his experience in both research and fabrication techniques, he hopes to contribute to the development of innovative technologies in the future.

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