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Diabetes Diagnosis and Control

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Diabetes has been a prevalent problem of modern society for quite a while, the remedies to the problems are present but either they are too expensive or stressful to be implemented by all. This project focuses on the technologies behind the old methods and initiatives taken to develop new and improved methods of testing while reducing the cost and margin of error.

Monitoring of glucose had been done conventionally by the means of a blood sample on a test strip, due to the advancements in the technology over the years, more minimally invasive and noninvasive methods have been tried and tested. They provide reliable enough data to monitor glucose level without the need of pricking the finger continuously. In this project, the possibility of a cheaper and more accurate glucometer by using the components easily available on the market is proposed, which will be compared to the ones already available. CGM (Continuous Glucose Monitoring) has been at the forefront of diabetes solutions because it provides flexibility and portability which has never been offered before and monitoring which is done every minute so that even the smallest fluctuations can be known beforehand. With the help of the system already in place for CGMs, a new and revolutionary method known as the closed-loop system is introduced. This method is implemented by integrating an insulin pump and the CGM, making the insulin injection automatic.

Analyzing the results of the proposed system, it is possible to make a cheaper and more accurate glucometer than those already available on the market. However, the future lies in the systems that do not need blood or human intervention such as minimally and noninvasive methods of glucose testing, therefore artificial pancreas is the next step of evolution for the diabetes community.

Keywords	CGM, diabetes, glucose, insulin, artificial pancreas

Table of Contents

List of Abbreviations

ATP   Adenosine Triphosphate

CGM   Continuous Glucose Monitoring

DIY   Do It Yourself

FRET   Förster (or Fluorescence) Resonance Energy Transfer

GBP   Glucose Binding Protein

GLUT   Glucose Transporter

HBGM   Home Blood Glucose Monitoring

H_2O_2 Hydrogen Peroxide

ISO   International Organization for Standardization

MI   Minimally Invasive

NAD   Nicotinamide Adenine Dinucleotide

NADH   Nicotinamide Adenine Dinucleotide Reduced

NI   Non-Invasive

QD   Quantum Dot

SPR   Surface Plasmon Resonance

T2D   Type 2 Diabetes

1   Introduction

In this thesis, the history and problems associated with glucose in the form of diabetes, the steps and measures are taken in the past as well as present to remedy the solution are discussed, and the final goal is to present a new world of possibilities in diagnosis and control of blood glucose by monitoring byways of minimal and noninvasive methods. The thesis will also try to shed some light on the market of glucometers and try to build a better alternative with existing technology to make it cheaper and more accessible.

Human body functions are complicated mesh of organs, hormones, and energy. The everyday activities need energy to be performed which is supplied to the cells in the form of ATP (adenosine triphosphate). The food we eat has carbohydrates, when it is broken down it converts into simple sugar which is further broken down into glucose which can be observed into the blood. Cells use glucose and convert that into ATP which is the energy we consume when we walk, talk, or even digest the food.

The body maintains a suitable level of glucose in the body for constant supply of energy either through converting sugars or burning fat stored. When there is excess glucose in the blood it releases a hormone called insulin which is produced in the pancreas. Insulin keeps the blood glucose in check so that it does not exceed 130 mg/dl if the person has not eaten or drank anything for at least 8 hours [1]. If the blood glucose exceeds this level, the condition is known as hyperglycemic (fasting hyperglycemia). Hyperglycemia is dangerous, it may cause damage to the kidney and eyesight. Slow healing of wounds, skin infections, and nerve damage are also some of the dangers.

When the body is running low on glucose it can cause blurred vision, weakness, dizziness, confusion. This state is called hypoglycemia. This can happen to people with diabetes if they take more insulin than required or they perform vigorous exercise. Consumption of alcohol in excessive amounts can also cause the blood glucose level to plummet.

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2 Glucose

2.1 Definition

The word glucose comes from the Greek word glykys meaning sweet. It is also commonly known as dextrose, which belongs to the group of carbohydrates known as simple sugars. The molecular formula for glucose is $C_6H_{12}O_6$ and the structure can be seen in figure 1.
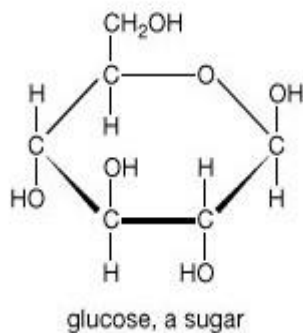

Figure 1. Molecular structure of glucose [1].

Glucose is a monosaccharide available most abundantly. Glucose formation is the main result of photosynthesis from carbon dioxide and water, with the help of sunlight from the Sun. It is formed by plants and most forms of algae during photosynthesis.

2.2 History of Glucose

Raisins were used to isolate the first glucose in 1747 by a chemist named Andreas Marggarf. Later, Johann Tobais Lowitz discovered glucose in grapes in 1792 and recognized the difference when compared to one from sugar cane (sucrose). The term glucose, now prevalent in chemical literature was first used by Jean Baptiste Duman in 1838. [2.]

Since glucose plays a major part in the sustenance of many organisms, understanding of the chemical structure and composition of glucose has played a vital role in the advancement of organic chemistry to a great extent. German chemist Email Fischer who was awarded Nobel Prize in Chemistry in 1902 for his contribution and findings from his

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investigations was primarily responsible for this understanding [2]. The structure of organic material was proven with the synthesis of glucose and the first definitive confirmation of chemical kinetics and the composition of chemical bonds in carbon-bearing molecules theories by Jacobus Henricus Van't Hoff [3].

2.3   Blood Glucose Levels

In a normal adult blood glucose levels (measured in mg/dl) can vary throughout the day and night. It can also change depending upon the physical exercise and food that might have been consumed. A normal fasting blood sugar level is between 70 and 99 mg/dl if no food has been consumed for eight hours and two hours after having a meal the blood sugar is less than 140 mg/dl [4].

A diabetes diagnosis is achieved by measuring two consecutive fasting blood glucose tests that are equal to or greater than 126 mg/dl. It can also be confirmed by taking a random blood glucose test which should have a measurement greater than 200 mg/dl. [4.] Symptoms of diabetes such as fatigue, thirst, excessive urination, or unplanned weight loss can be seen in people with more than the normal blood glucose levels but often people have no symptoms with underlying diabetes.

2.4   Transportation of Glucose in Blood

Glucose is utilized successfully by a substantial number of different cell types under normal conditions. However, its content in the blood must be maintained very precisely. Glucose has a significant role in metabolism and maintaining the equilibrium in a cell. Glucose is supplied continuously to all the cells in the body in the form of ATP to provide energy. Unbalanced levels of glucose are the reason for diabetes in a person, even though the reasons for this disorder can be different. Glucose enters the cell through the membrane by absorption. Micronutrient molybdenum cannot travel through the cell membrane by diffusing because the high molecular pathway cannot pass through the

infinity matrix of the double lipid phosphorus layer. An efficient system of transportation is needed to transfer glucose molecules in and out of the cell for its uses. In certain cases, such as epithelial cells of the small intestine, glucose is absorbed into the cell also known as active transport against the concentration gradient formed by the Na+/K channel system. Passive transportation of glucose occurs to all cells in the body by diffusion which is effective for red blood cells because the concentration of glucose in the blood is stable and higher than the cellular concentration. The transporter protein involved is known as glucose transporter (GLUT). [5.] The two methods of diffusion are illustrated in figure 2.

Figure 2: Active diffusion (on the right) and facilitated diffusion with the help of GLUT (on the left). The molecules can move from regions of higher to lower concentration, relying on the specificity of the protein carrier GLUT to pass through the membrane. This process is called passive transport or facilitated diffusion and does not require energy. The molecules can move from regions of lower to a higher concentration. This process is called active transport and requires a form of chemical energy. [5.]

3. Blood Glucose Testing

Many types of glucose tests can be used to estimate the level of glucose in the blood at a certain instance, or over a prolonging interval of time, to acquire average levels or to see the time it takes the body to normalize the elevated or depleted glucose levels. Consuming food causes the blood glucose to rise, in a healthy individual these levels swiftly return to the usual via increased blood insulin which facilitates the increase in cellular glucose uptake.

Glucose tests can reveal the underlying condition related to blood glucose levels, such as hyperglycemia or hypoglycemia. Persistent cases of these conditions can damage organs in the long term without the appearance of any symptoms. Unnaturally high or low levels with continual slow return or/and failure to return to normal blood glucose levels mean the person could be diagnosed positive for a medical condition such as type 2 diabetes due to insulin resistance or cellular insensitivity. Therefore, glucose tests are regularly used to diagnose these conditions.

3.1 Glucose Testing by Invasive Methods

Laboratory tests are performed to detect any underlying disorder. Once a person is diagnosed with diabetes or any condition related to unnatural blood sugar levels, further tests are then performed mostly at home. Home testing is often used in the blood glucose monitoring for sicknesses that have already been confirmed with the medical condition and thus can be regulated with medication, meal timing, and exercises.

A glucose meter is the most common type of device used to check blood glucose at home. It uses a strip of glucose paper dipped into a substance and measured to the chart. A tiny drop of blood is obtained by piercing the skin with a sterile lancet and collected by a capillary tube by the natural process of surface tension. The strip is connected to the meter with a circuit which then calculates the blood glucose level and displays in units of mg/dl or mmol/dl.

Since the discovery of diabetes, the main goal of the management of any type of diabetes has been attaining a prolonged period of near-normal levels of glucose with an assist from HBGM numerous times a day. This benefits in the reduction of manifestation of long-term complications from hyperglycemia along with the drop-in short term, fatal complications of hypoglycemia.

3.1.1 Determination of Blood Glucose by Enzyme Methods

Glucose absorption disorder is diagnosed with a blood glucose test, which is performed by enzyme and chemical methods. However, these days enzymes are preferred over chemical methods because of better accuracy, effectiveness, and duration for the result. The main three enzymes commonly used to calculate blood glucose are glucose oxidase, hexokinase, and glucose dehydrogenase [6].

Glucose oxidase is an enzyme obtained from the growth of Aspergillus Niger. This enzyme catalyzes the oxidation of Beta D- glucose existent in the plasma to D glucono -1, 5- lactone with the creation of hydrogen peroxide (H_2O_2), the lactone is then gradually hydrolyzed to D-gluconic acid. The hydrogen peroxide created is then fragmented down to oxygen (O_2) and water (H_2O) by peroxidase enzyme. The oxidation of oxygen with an oxygen acceptor, for example ortho toluidine produces a colored compound, the amount of which can be measured colorimetrically. [7.] Alternatively, hydrogen peroxide can be electrochemically oxidized at the anode of the electrochemical probe which produces a signal that is proportional to the glucose concentration in the used sample as shown in figure 3.
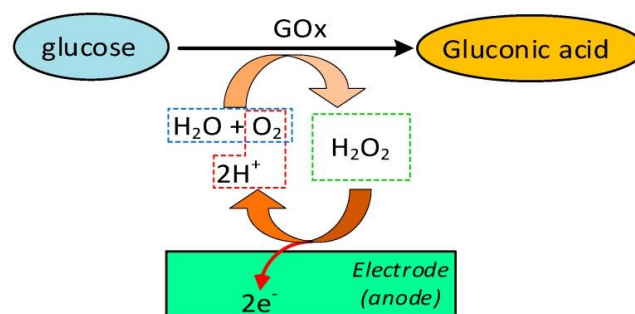
Figure 3: Enzymatic-amperometric method of glucose concentration measurement in-vitro [8].

Hexokinase method, also generally known as a photometric method, includes consecutive chemical reactions. The first stage of reaction starts with the glucose reacting with the enzyme hexokinase, with the help of adenosine triphosphate (ATP) and ions of magnesium to create glucose-6-phosphate (G6P) along with nicotinamide diphosphate (ADP). In the later stage, nicotinamide adenine dinucleotide (NAD) and G6P oxidize with G6P dehydrogenase which is then reduced to 6-phosphogluconate and nicotinamide-adenine-dinucleotide-reduced (NADH). The glucose in the used sample and the amount of NADH produced are proportional and the resulting compound can absorb light of 340 nm wavelength which can be used to determine glucose levels using standard methods of spectrometry since the glucose content is proportional to NADH. [8.] The reaction is shown in figure 4.
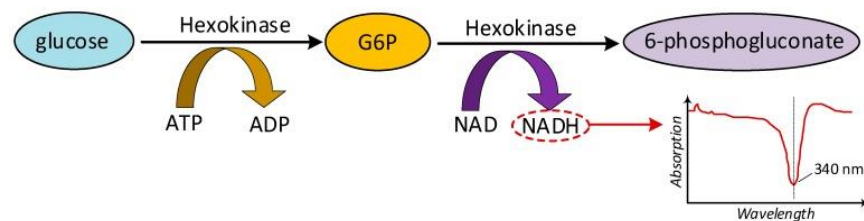

Figure 4: Hexokinase method for measurement of glucose concentration in-vitro [8].

Glucose dehydrogenase (GDH) method is used on handheld glucose meters due to the simplicity and ease to obtain results corresponding to the amount of glucose in the sample. It consists of only a single-phase reaction which is fundamentally analogous to the electrochemical technique described previously in figure 3. The only major difference is that the reaction and detection occur on the test strip used to collect blood by pricking skin which is connected to the meter via electrodes to detect the change in current. The reaction is best described from equation (1),

$$\beta - D - Glucose + NAD^+ \xrightarrow{GDH} D - Glucono - \Delta - lacton + NADH + H^+$$
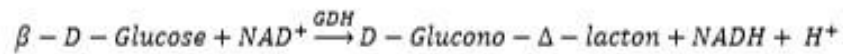
..........(1)

In equation (1), NADH is created because of the reaction, which absorbs 320 nm wavelength of light so it can also be detected by photometry. GDH from the strain of Bacillus cereus is used to get better accuracy and consistent results. The addition of Mutarotase in the reaction causes the conversion of α-Glucose to β-Glucose for further accuracy. [6.]

3.2 Minimally Invasive and Non-Invasive Technologies for Detecting Blood Glucose

Glucose monitoring without the discomfort of pricking the finger, alleviating the pain and risks associated with standard methods have been a major driving force in the research for minimal and non-invasive technologies. These can be classified into two main parts: minimally invasive (MI) and non-invasive (NI). MI technologies need some way of extracting bodily fluids such as tears and interstitial fluid to measure the glucose content in the body with the help of well-developed enzymatic reactions. NI technologies exclusively rely on optical, thermal, or electric methods without accessing any bodily fluids.

3.2.1 Surface Plasmon Resonance (SPR)

SPR is a phenomenon that happens when a polarized light meets a metal layer at the interface of a medium with different refractive indices. SPR techniques use Kretschmann configuration to excite and detect collective oscillations of free electrons also known as surface plasmons. In this configuration the light is focused onto a metal film through a glass prism and the reflection that occurs is then subsequently detected and analyzed as shown in figure 5. This technique is commonly known as spectral interrogation mode. SPR also works by exciting surface plasmon polaritons (SPPs) by an electromagnetic field radiated onto a thin film of extremely conductive and inactive metal. The outcome

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is an exponentially decaying electric field that is extremely sensitive to the change in the refractive index of the surrounding medium. Thus, the changes in the glucose levels of the skin can be confirmed by a change in refractive index in the interface, along with the shift in the resonance frequency which is also called the SPR shift. This results in the reflective intensity curve with loss of intensity compared to a different variation of glucose. [9.]
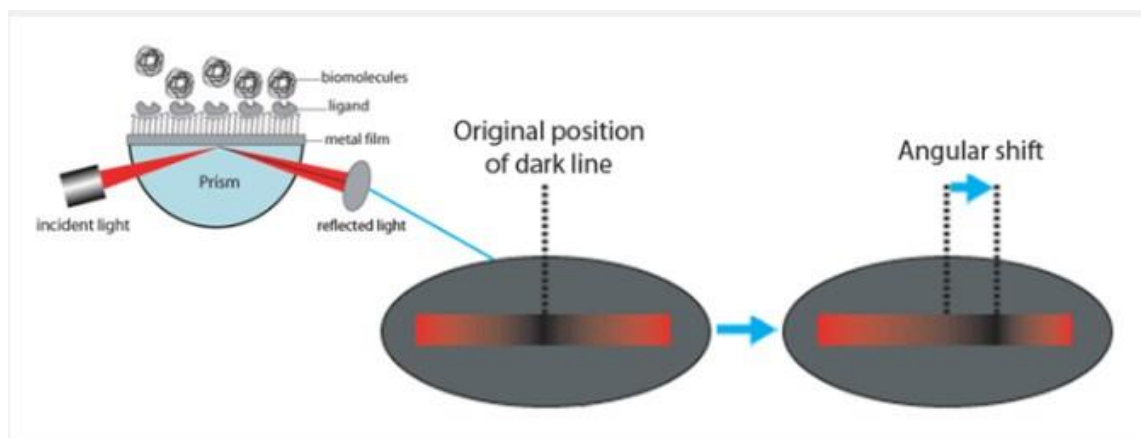
Figure 5: The excitation of surface plasmons results in a dark line in the reflected beam, and the angular position of the dark line shifts as a molecule binding event takes place [9].

3.2.2 Fluorescence Monitoring

The fluorescence approach is different from other types of optical methods because it requires a sample to be in close contact with the sensor to work. Therefore, it cannot be marketed as a non-invasive method of monitoring. This technology is based on the principle that light is emitted at a certain wavelength after it absorbs the radiation from another source or surrounding, which causes the wavelength to shift, the phenomenon known as Stoke's shift. The technology relies on the use of highly specific molecules

called fluorophores that emit the fluorescence light which comes in contact with the analyte. The characteristics of these molecules are proportional to the concentration of the sample under testing. Fluorescence monitoring is promising in the sense that it can be highly specialized to glucose because the sensing apparatus must be in contact with the sample which can mitigate the issues associated with low selectivity, interference, analyte depletion, and irreversibility. Additionally, receptors of the fluorescence emission can be of varying nature from enzymes, carbon nanotubes, boronic acid derivatives, glucose binding proteins (GBPs), and quantum dots (QDs), making a way to have several measuring techniques and a broad spectrum of light from ultraviolet to near-infrared. Fluorescence resonant energy transfer (FRET) is based on an existing principle of energy transfer between two light-sensitive molecules, fluorophore, and receptor which works by binding a glucose molecule to an acceptor molecule. [10.] This binding disturbs the link between acceptor and donor leading to a reduced sharing of electrons and increased fluorescence. A further detailed explanation can be seen in figure 6,
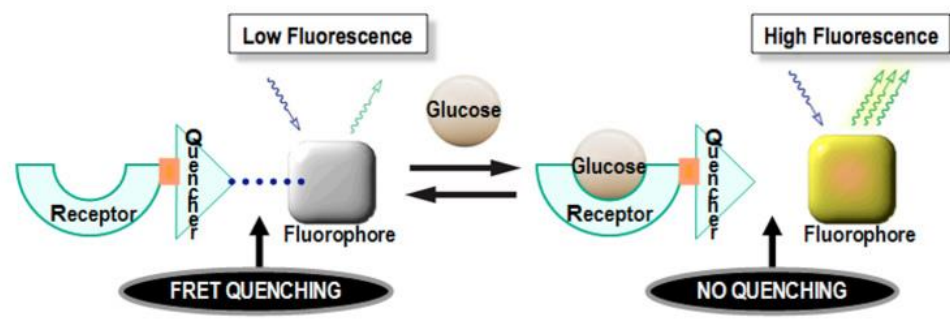

Figure 6: The receptor and quencher interactions cause the fluorophore molecule to exhibit low fluorescence (left half), known as FRET quenching. When a glucose molecule reversibly binds to the receptor part of the receptor molecule (right half), then the FRET becomes disrupted because of decreased electron sharing between the two interacting groups. In the absence of FRET, quenching of the fluorophore ceases and the fluorophore becomes highly fluorescent. [10.]

3.2.3 Electromagnetic Sensing

This technology is based on the current or voltage induction between two inductors which is proportional to the magnetic coupling. Since the coupling of two inductors is directly affected by the media between them (concentration and type of analyte), the ration between the input and output voltages or current is directly proportional to the concentration of glucose in the analyte. The frequency used in the experiment also plays a vital role to produce enough coupling between the inductors, although the ambient and analyte temperature also has some effect on the test. Therefore, frequencies ranging from 2.4 MHz to 2.9 MHz, part of the full spectrum of electromagnetic radiation as seen in figure 7 are typically used for a suitable coupling and detection of glucose.
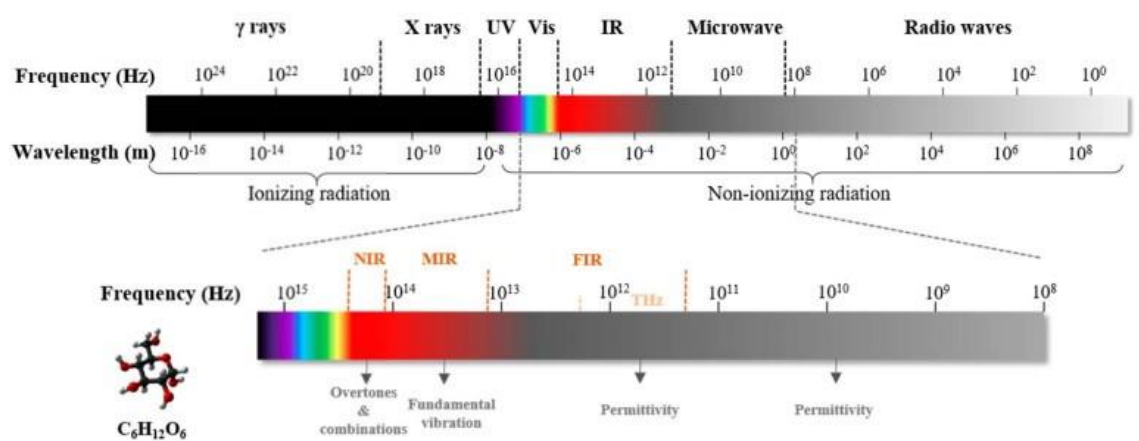

Figure 7: Full spectrum of electromagnetic radiation dividing it into ionizing and non-ionizing radiation, we can see that the frequency range of 2.4 MHz to 2.9 MHz falls under the radio waves which is a tiny part of the whole spectrum. While ionization radiation is useful in a different situation, non-ionizing radiation is used in glucose monitoring so that the devices are safe when used for extensive periods. [11.]

3.2.4 Bioimpedance Spectroscopy

The human body is inherently composed of resistors and capacitors in the form of tissues, fluids, fats, muscles, and bones. When an electric signal flows through the body at a certain frequency the penetration depth is limited, the resistance offered by that part of the body determines the conductivity and permittivity of that substance. Since, different molecules have different conductivity, transmitting the frequency from an antenna ranging from 5 GHz to 12 GHz while the receiver continuously monitors the signal attenuation, the blood glucose level can be determined by analyzing the received signals for glucose specific attenuation as illustrated in figure 8. Thus, the ease and simplicity of this technique make it potentially affordable and easy to employ in most practical scenarios, if the limitations of temperature variations and sweat are mitigated.
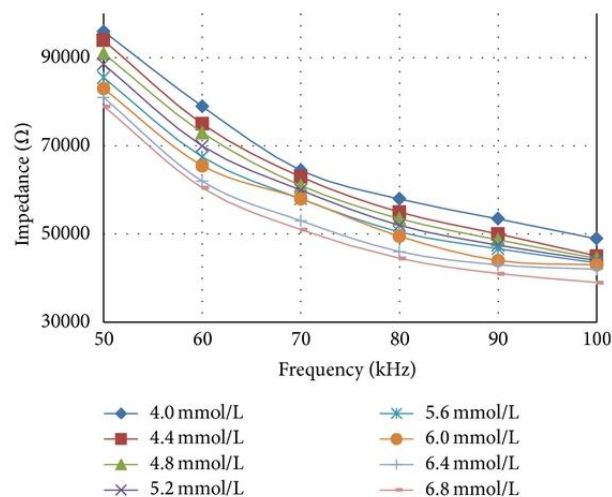

Figure 8: The relation of impedance and frequency and blood glucose level in a range from 50 kHz to 100 kHz. The impedance decreases when the blood glucose level rises. [12.]

3.2.5 Thermal Emission Spectroscopy (TES)

This method is based on the discovery that the human body naturally radiates mid-infrared emissions, especially from the tympanic membrane. During this process, part of that radiation is absorbed by glucose and other molecules in the body in the range of 9.4 µm wavelength. The analysis of the intensity and characteristics of this radiation form glucose molecules provides extremely useful insight into the concentration and presence in the body. Limitations of TES are the disturbances caused by the intensity of infrared radiation because of the thickness of the analyte. Although the laboratory results are promising, it has not been accepted under the clinical accuracy standards.

4. Economic Aspect of Diabetes and Glucose Monitoring

Diabetes was considered the disease of the rich nations but with the globalization and availability of high carbohydrate foods at a fraction of what it used to cost, mid to low income counties are following the trend. 79% of adults with diabetes are now living in low- and middle-income countries but this is not even the full picture. One in two people with diabetes are undiagnosed. People can use self-assessment forms as in appendix 1 to assess the risk of type 2 diabetes at home even before visiting a doctor. The aging population is facing most of the risks with everyone in five people above the age of 65 with diagnosed diabetes. According to the WHO, there are currently around 450 million cases of diabetes in the entire world, this number is expected to reach 700 million by 2045. [13.] Around 1.6 million deaths are directly the cause of diabetes each year and both deaths and prevalence of diabetes have been steadily increasing each year significantly. In Finland alone, there are about 50000 people with type 1 diabetes and about 350000 people with type 2 diabetes [18].

In 2015 the absolute cost of diabetes on the economy was 1.32 trillion dollars which are expected to increase to 2.12 trillion dollars by 2030. Health expenditure in 2019 by the direct cause of diabetes was 760 billion dollars. In Finland, the treatment costs increased by 83% from 1998 to 2007. The cost of care of diabetes was 1.350 million euros compared to 1998 which was 738 million euros as illustrated from figure 9. [18.] Treatment costs for a diabetic person has slightly diminished over recent years due to the intensified diagnostics which prevents any long-term complications such as heart, brain, and kidney that can result in expensive treatment and procedures.

Total costs for the treatment of diabetes 1998–2007
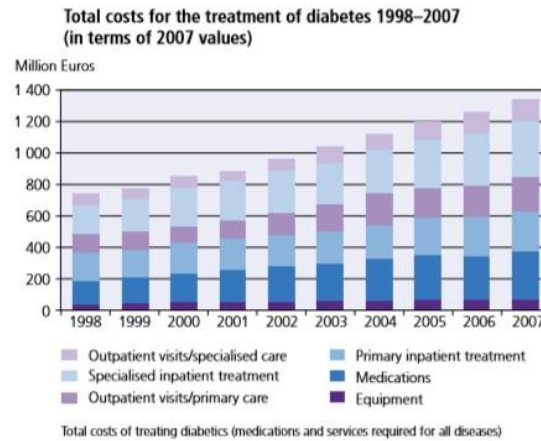(in terms of 2007 values)

Million Euros

Figure 9: Costs related to diabetes from the year 1998 to 2007 and their gradual increase [18].

Expenditure at this rate means a market with billions of dollars of potential revenue for the medical companies. The global blood glucose monitoring devices market size was valued at USD 10.4 billion in 2018 which is expected to increase by 7.1% by 2026. These billion markets are propelled by the increasing cases of diabetes each year coupled with the aging population more prone to diabetes-related risks. Blood glucose monitoring devices are economically profitable and vital for essential diagnostics and treatment. Early detection of diabetes can help in the prevention of other health conditions such as retinopathy, neuropathy, and cardiovascular diseases. There are several types of monitoring devices available varying in price, size, length of testing time, and ease of operation. By the product, the market has segmented into self-monitoring and continuous monitoring devices. Self-monitoring blood glucose devices are the largest share of the market because of the ease of use and low price. This segment of the market is forecasted to increase by 6.4% over the next 10 years. The leading segment in continuous glucose monitoring was held by transmitter and receiver which is projected to rise by 7.5%.

5. Future of Blood Glucose Monitoring

There are plenty of glucose monitoring devices in the market strictly regulated by the authorities to enforce safety and reliability when functioning, but they do not provide the full service and ease that everyone is searching for in the diabetes community. The next step in the ladder of glucose monitoring is a closed-loop system. This system uses a

continuous glucose monitor (CGM) to measure blood glucose levels throughout the day. When the blood glucose levels rise from the desired range, it sends a signal to an insulin pump to automatically administer a fixed amount of insulin. When the blood sugar level begins to level off, the monitor detects the change, the insulin pump is shut off automatically. The name closed-loop system comes from the feature of not having to interfere manually as everything from monitoring to injecting insulin is all controlled by the system to be automatic.

In a recent study, involving a six-month trial of using a closed-loop system, the system was able to control the blood sugar level to their desired target 61% to 71% of the time compared to the individuals with self-administering glucose monitoring devices which remained around 59%. Also, the participants in the closed-loop system spent less time outside of the 180 mg/dl and lower than 70 mg/dl which can be extremely beneficial. [14.] While the closed-loop system is far from perfect, these findings from a controlled group of the study shows the potential for the future while eliminating human error and time spent manually tracking diabetes. Further study is needed to prove that the closed-loop system is viable for mass deployment, but people are already referring to the system as an artificial pancreas.

6. Designing of Cheap and Portable Glucose Meter with High Precision.

There are several options to choose from when someone is looking to buy a glucose meter, but none of them are cheap from a developing world perspective. The price ranges from tens of dollars to hundreds, this kind of money is not easily disposable to poor families who cannot afford health insurance. Moreover, if the accuracy can be improved from commercially available glucometers whose precision lies somewhere between 85 and 90 percent, that's always a plus. Since, the main purpose of the design is to keep the costs as low as possible without compromising the accuracy of the results, microcontroller ATMEGA8A AVR will be used with the software part from AVR studio using C programming.

Design methodology, implementation techniques, unexpected downtimes, performance, results, and overall evaluation of specifications of the meter will be discussed in the fol-

lowing sections. The proposed glucometer should provide many features like low manufacturing costs, high precision, increased sensitivity, portability, and lower margin of error. At the end of the design, the costs and benefits analysis will be conducted to check if the product designed is worth the effort.

6.1 Design Methodology

The design of an effective meter should encompass a wide variety of functions in the system to check for the sample of blood, calculate and compute the concentration of glucose in the blood sample and display that information to the end-user in a user-friendly way. It should also be able to store the results for future analysis if necessary. The relation between various parts of the device can be seen in figure 10,
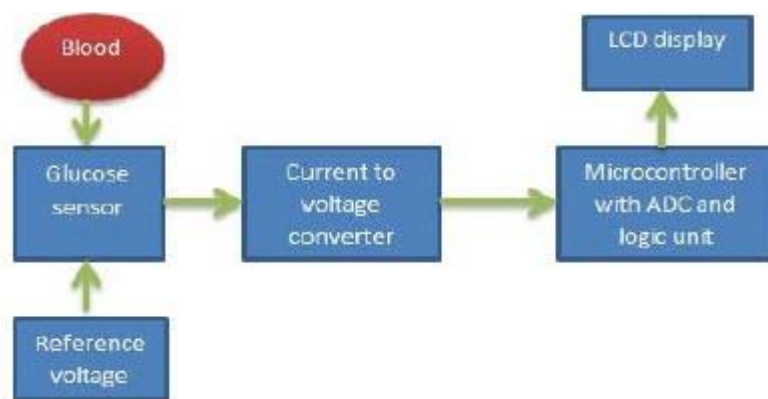
Figure 10: Block Diagram of the proposed glucose meter [15].

As seen in Figure 10, the blood sample taken will be measured for glucose concentration by using electrochemical test strips which are to be discussed.

6.2 Electrochemical Blood Glucose Test Strips (EBGTS)

EBGTS is kind of a transducer, the first contact place with blood. EBGTS is a small disposable cell that produces a small electrical current injunction with a test meter which is directly proportional to the concentration of glucose in the blood. The current values are tiny, typically in μA. The test strip is composed of three electrodes, such as the working electrode (WE), reference electrode (RE), and counter electrode (CE). The strip produces current when a potential is applied in the RE and WE electrodes ranging from -400 mV to 8 V. This is the optimal voltage at which is the strip produces maximum current. [15.]

Current at the strip is produced by selective oxidation of blood glucose, which occurs due to the help of two reagents which are already pre-coated in the strip at the manufacturing. One of the agents is an enzyme that reacts with the molecule of glucose to remove two available electrons. The action of the mediator which is another reagent is to produce a potential at the terminals so the free electrons from the glucose can be transported to the working electrodes. These mediators are made such that they are easily stabilized and highly soluble. Many of the commercially available test strips follow the fundamental process discussed above. For this design, a freestyle test strip will be used, which uses glucose oxidase as an enzyme. The reaction is the same as in Figure 3 of the determination of blood glucose by enzyme methods which has already been explained in detail earlier in the thesis.

6.3 Relationship between Voltage, Current, and the Concentration of Glucose.

The current in the EBGTS stabilizes after a couple of seconds. The current produced is different from test strips from different companies. For this device, freestyle strips are used for sensing blood glucose concentration. The voltage and current values concerning the concentration of glucose in the blood after 5 seconds of contact with the strip are obtained from Abbott enterprise and are presented in table 1. [15.]

Table 1: Relationship between Current and Voltage concerning the Glucose Concentration

Glucose (mg/dl)	Voltage (V)	Current (μA)
46	0.7	7
130	1.7	17
198	2.4	24
297	3.4	34
393	4.2	42

Since, the output voltage value depends on the circuit that converts the current into voltage. A transcendental equation can be fitted to values in the table to get the final relation between the glucose concentration and the output voltage after it is inverted through the amplifier.

6.4 Proposed Circuit Details and Designs

When the reaction of the enzyme and glucose takes place, a current is produced at the working electrode (WE) proportional to the concentration of glucose. This current needs to be expressed as a voltage by using a current to voltage converter. Mathematically,

$$V1 = - (\text{input current* feedback resistance (RF1)}) ....(2)$$

Since, the microcontroller cannot operate with a negative voltage, it needs to be inverted by a unity gain inverting amplifier.

$$A_V = - \text{feedback resistance (RF1) / Input resistance (R1)} ....(3)$$

The connections between components in the system such as sensor, crystal, and battery can be seen in figure 11. Similarly, the step by step working of the system can be better explained by the flow chart in figure 12.
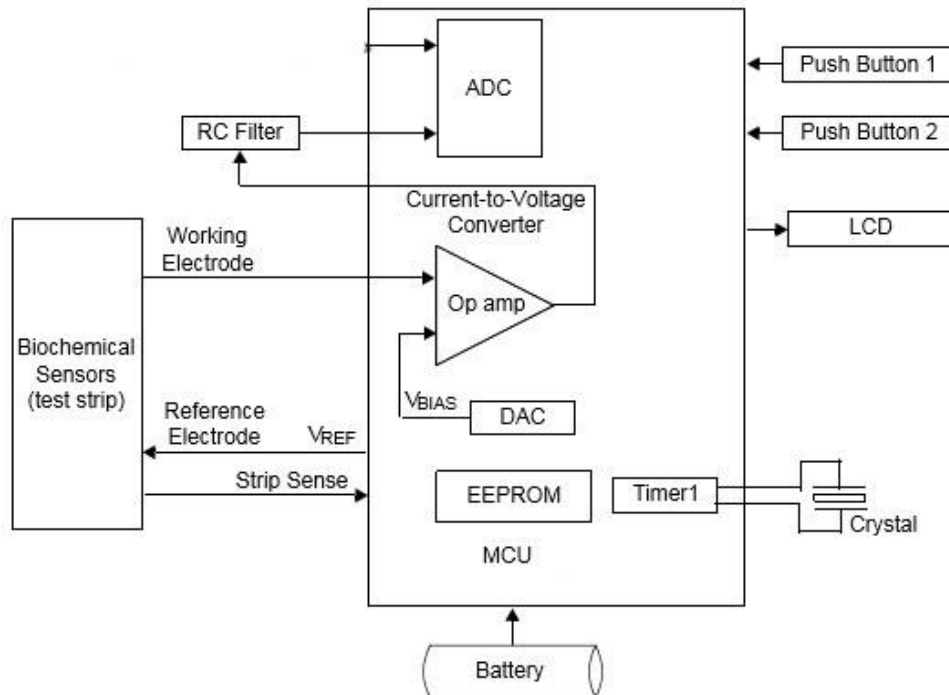
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Figure 11: Block diagram of the proposed circuit showing the inner components of MCU and their connection with the peripherals. The test trip, LCD, and battery are peripherals to gather information and display that processed data in the form of letters and numbers in the LCD.

Figure 12 shows the step by step process of the working of a glucometer. The circuit starts with the initialization of all the components, and the test strip is inserted into the glucometer, the circuit has a waiting command to wait for the blood and test strip. Once the sensor and analyte are present, it waits until the user turns the switch. After the switch is pressed, the EGBTS produces the current, which is converted into an analog voltage. The ADC already present in the MCU converts the analog voltage into a digital signal so that the program can perform the calculation of the glucose concentration. The result is then displayed in the LCD in the form of mg/dl and stored in the MCU for future purposes.
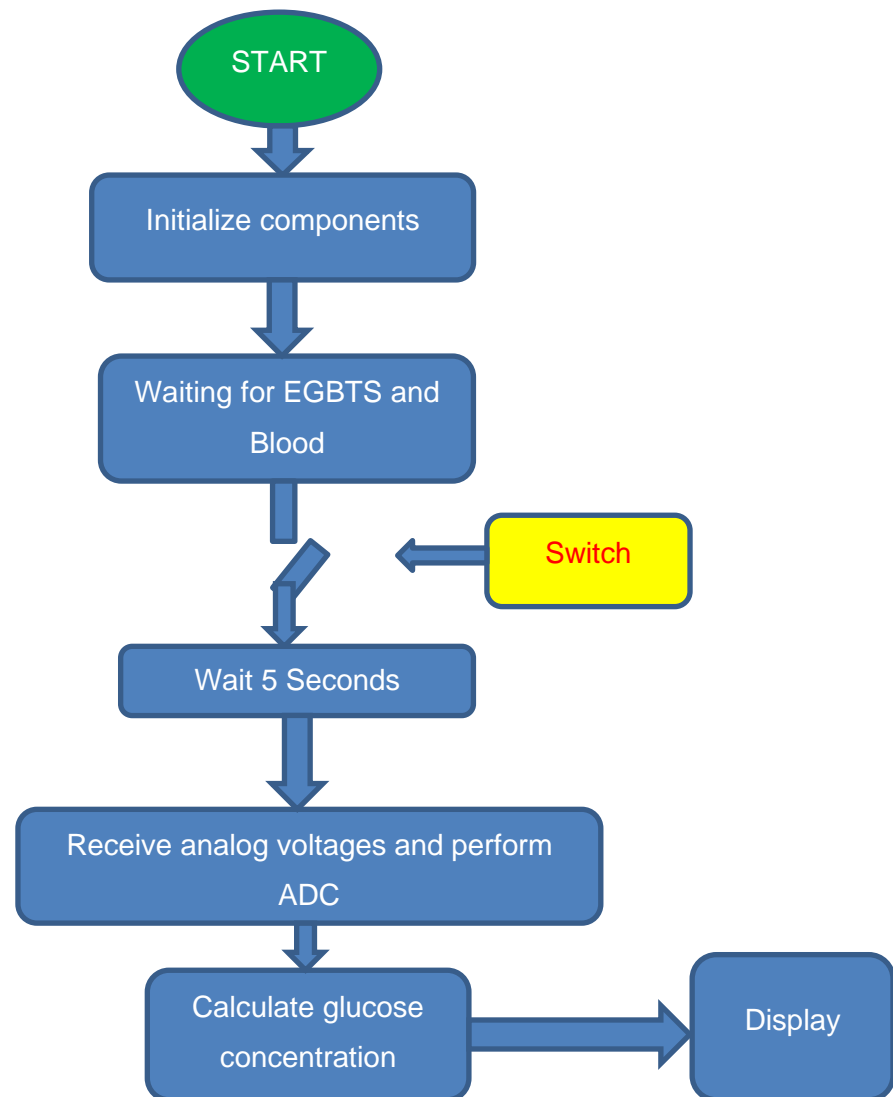
```
          ┌─────────────┐
          │    START    │
          └─────────────┘
                 │
                 ▼
      ┌────────────────────┐
      │ Initialize components │
      └────────────────────┘
                 │
                 ▼
      ┌────────────────────┐
      │ Waiting for EGBTS and │
      │        Blood        │
      └────────────────────┘
                 │                    ┌──────────┐
                 ◇ ◄──────────────────│  Switch  │
                 │                    └──────────┘
                 ▼
      ┌────────────────────┐
      │   Wait 5 Seconds   │
      └────────────────────┘
                 │
                 ▼
      ┌──────────────────────────────┐
      │ Receive analog voltages and perform │
      │              ADC              │
      └──────────────────────────────┘
                 │
                 ▼
      ┌──────────────────┐          ┌──────────┐
      │ Calculate glucose │ ───────► │ Display  │
      │   concentration   │          └──────────┘
      └──────────────────┘
```

Figure 12: Flow chart for the proposed system of the glucometer.

6.5 Microcontroller Unit

The brain of the system Atmega8A is used as a microcontroller unit. It is a low cost, low power CMOS 8-bit microcontroller based on the AVR enriched RISC architecture. Atmega8A is capable of throughputs close to 1 MIPS per MHz by executing powerful instructions in a single clock cycle. Although tiny by size, it is significantly fast since the clock speed can run at 16 MHz. Special microcontroller features include an internal calibrated oscillator and 6 channels analog to digital converter. The microcontroller has a 512 Byte of EEPROM and 8 KB of in-system self-programmable flash program memory

which can be used to both store the results and operate the device. Power consumption at 3.6 mA when active and 1 mA when idle, the microcontroller can be powered for a longer duration of time without the need of replacing power source every so often. In the operating voltage range of 2.7 V - 5.5 V, Atmega8A can be powered with the smallest batteries making it excellent for projects that need a small footprint. The schematic diagram of components and connections can be seen in figure 13. The layout of the components can be demonstrated from appendix 2.
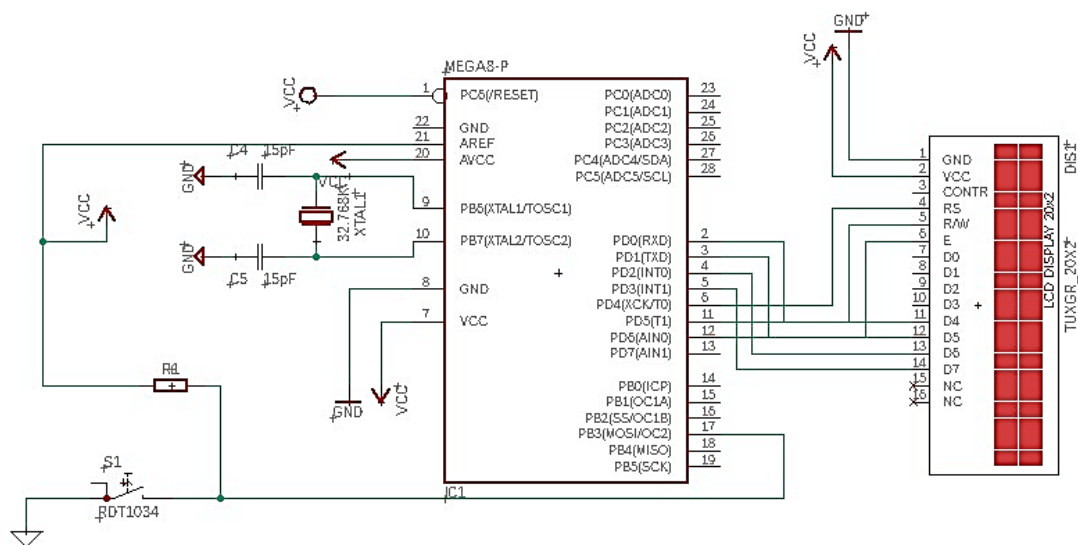
Figure 13: Schematic diagram showing the connections between microcontroller and the LCD. When the microcontroller receives an analog voltage signal as an input in pin 27, it is converted to a digital signal by an ADC built inside the microcontroller. Atmega8A has an internal ADC of 10 bits therefore the digital signal has a resolution of 1024 levels. 0 V to 5 V is the input, the resulting ADC value is then used to calculate the concentration of glucose in the blood and the result is displayed on the LCD.

6.6 Cost Analysis

The cost of building the proposed glucometer compared to the ones available in the market is significantly cheaper. The parts to be used in the project are selected such that the cost remains low without affecting the quality of the product. The list of parts used along with prices can be seen in Table 3. The overall price comparison of the device compared to the ones easily accessible in the market can be seen in Table 2.

Table 2: Price list of proposed device vs commercially available glucometers.

Glucometer name	Price (EUR), approx.
Bayer	43
CONTEC	18
ELERA	27
Roche	12
McKesson	13
Proposed meter	7

Table 3: Total cost of building the glucometer, parts with prices.

Components	Price (EUR)
Atmega8A	1.5
Resistors	0.6
Wires and headers	0.5
LCD	1.8
Op-amp	0.8
Switch	1
Total	6.2

The data depicted above in both tables can confirm that it is possible to make a cheaper version of a glucometer which has a better precision of accuracy. Even though there were some unnamed brands close to the price of the proposed glucometer, but they lack many features. The prices were taken at the time of the research.

7. Conclusion

The project was about studying diabetes and problems associated with the diagnosis and treatment. Understanding the technology and methods behind the existing solutions and finding new ways for the improvement of the overall diabetic community. Also, a new alternative to the present system of diagnosis was studied along with a new prototype of glucometer for cheaper and more accurate results were researched. By using the most cost-effective parts on the market and taking measurements in a non-traditional nonlinear way, a more accurate and cheaper alternative was possible.

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In this study, it was found that some forms of non-invasive and minimally invasive methods are as equal or better than the existing traditional methods of diagnosis of diabetes. Continuous glucose monitoring and closed-loop systems are the future of diagnosis of diabetes and keeping it in control. Due to the technical problems and time constraints, the proposed cheaper alternative was not brought to life even though it was deemed possible. However, there are still many areas where the innovation is needed, such as the recalibration, lack of standardization of the software, and test strips, which is still causing an impact in the mass adoption of the technology very difficult. The data shows an upward trend in the increase of diabetic people in the world, which can cause the health system to be overwhelmed if the diagnosis and prevention cannot be carried out before the long-term complications of the disease is set. The people with undiagnosed diabetes were still in the thousands, this problem needs to be managed by making the testing and information about diabetes easily available at an affordable price. This is especially true in the developing countries as the technology has not necessarily been in mass adoption and there is still misinformation or skepticism regarding the technology used. Even when the cost of owning and testing glucose might not be a problem, market availability plays a key role. Because of the lack of competition in those markets, there is a monopoly of certain companies which can raise the prices to their benefit, so the affordability decreases significantly. The production of insulin and regulation has seen hurdles in some countries especially, the united states, where the price has jumped from tens to hundreds in the span of a couple of years. This problem of price gouging is also the reason many people need to opt for risky and unproven methods of controlling glucose which can cause a surge in the death toll. Even though some nonprofits are working towards a cheaper alternative of the product of these mega-giant companies, it also needs to be addressed by the government and taken appropriate steps to combat the issue.

The advancement in the CGM and the close loop systems can play a vital role in alleviating the world problem diabetes has become at the present. Non-invasive methods of testing and artificial pancreas will increase many people to embrace the technology as it does not need constant attention from the patients. Someday in the future we can reach a certain point where diabetes will not kill millions of people each year. Instead, it will be non-threatening as the flu or cold. Akin to the diseases of the past like measles and polio, we can move past the diabetes epidemic without stressing about it

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Appendices

Appendix 1. Risk assessment form for type 2 diabetes.

Appendix 2. The layout of the components connected.