Non-Invasive, Continuous, Wearable Blood Glucose Monitor
1. BACKGROUND

30.3 million Americans have diabetes

1.25 million have type I diabetes.

7th leading cause of death in the United States in 2015
Diabetes: Type I vs. Type II

T1D:
- Autoimmune disease causing death of insulin-producing beta cells
- Requires insulin therapy

T2D:
- Insulin resistance—body can make insulin, but not enough
- Management with medications and may use insulin
- Long-term complications such as heart, nerve and kidney disease

Left unmonitored/untreated, both types risk additional severe long-term consequences, including blindness, ketoacidosis, stroke, and limb amputation!
Current Solutions

- Implantable monitoring devices
- Some non-invasive devices exist, but have issues: awkwardness, limited accuracy

Common Monitoring Approaches

- Invasive monitoring techniques
- Requiring patients to collect their blood by pricking their fingers
- Single-use test strips
Invasive Continuous Monitoring

Advantages:
- Avoid insulin overdose and hypoglycemia
- Valuable for monitoring overnight without requiring user interaction

Disadvantages:
- Potential surgical procedures
- Implantation of device in patient
- Biocompatibility requirements

Non-invasive Monitors (Non-continuous)

Advantages:
- Avoid surgical procedures
- Less risk of potential negative long-term effects from device implantation

Disadvantages:
- Not continuous monitoring
- Requires multiple glucose level checks daily
- Potentially less accurate
Current Sensors:
- Optical sensors in Apple watch measure heart rate using green LED and infrared
- ECG measurement by closing an electrical circuit
- Apple watch haptics: MEMs actuators (either linear resonant actuator or piezoelectric actuator)
- Microphones
- Pressure sensors
- Accelerometers
Desired Sensor Requirements

- As minimally invasive as possible
- Continuously monitoring
- Transmits data to smart device for data integration and analysis
- Potentially combine device with smart watch
- Alerts user to out of range values
- Ability to monitor trends
2. Semi-invasive glucose sensor

Proposed Solution

Two components: implanted piece (ear or wrist/arm) and external receiver in smart watch

- Implanted component senses interstitial glucose, generates signal to transmit information to smart device to be integrated, analyzed and recorded

- External receiver: after recording, smart device determines whether action needs to be taken (i.e. insulin delivery or glucose consumption) and alerts user

- Bluetooth or wifi communication

- Calibrate sensor with regular glucometer
**Chemical Glucose Sensor structure**

Molecular-recognition element (GOD enzyme) + signal transducer (electrode)

Examples: cellulose acetate, poly(vinylpyridine)

Layers of the Glucose Sensor

- Semi Permeable Membrane
  - Selective to glucose and oxygen
- Enzyme
  - The membrane surrounds a glucose oxidase enzyme
- Electrode

Limits diffusion of unwanted analytes

(Pt electrode = Pt electrode)
Glucose sensor principles

GOD catalyzes the oxidation of β-D-glucose to produce gluconic acid

Oxygen is reduced to generate hydrogen peroxide (H2O2)

H2O2 in contact with electrode is converted to hydrogen, oxygen, and two electrons

*Indirect glucose detection*

Measurable current

Reaction Scheme:
Electrode output: **current**

Second component of device = transducer:
- **Amperometry** with Ag/AgCl reference electrode
- Calibration curve compares current to glucose concentration

**Limitation:** $\text{H}_2\text{O}_2$ high positive overpotential → ascorbic acid and acetaminophen may interfere with detection
- **Solution:** ensure membrane component is not permeable to these species via size or charge-based selectivity
Fabrication

- Proposed improvement to current sensors: **3D bioprint** a structure that traps layers of **glucose oxidase** by exploiting degradable polymers, similar to design of Polypills
- **Semipermeable membrane**: solvent casting & particulate leaching, electropolymerization
- **Platinum microelectrode**: wet etching technique
Glucose oxidase (GOD) has a very high specificity for glucose.

The requirements for industrial production of GOD are minimal and the various components are low-cost.

Direct interaction between sensor and interstitial fluid enables relatively fast, robust measurements.

Current sensors last a maximum of 14 days → proposed solution would extend this.

Must be placed under skin (not completely non-invasive).

GOD is used up with reaction.
3. **Noninvasive glucose sensor**

Near-Infrared (NIR) Spectroscopy

The NIR spectrum operates at a wavelength ranging from 750–2500 nm.

The molecular formula for glucose molecule is C6H12O6, which consists of C-H, O-H and C=O bonds.

The presence of these bonds causes the absorption of NIR light in blood.

Glucose showed one of the weakest absorption rates.
Calibration and Usage Procedure

The calibration process was performed 24 hours before the actual testing of the system.

Run the tests: Invasive and non-invasive

The test results are displayed in as little as 4 seconds.
The total cost of the components of the new device is relatively inexpensive, less than $300, compared to the cost of the current commercially available system.
PCB Fabrication

Step 1: Form design & Output it on the film

Step 2: Print the Inner layers & Remove the Unwanted Copper

Step 3: Layer Alignment & Optical Inspection

Step 4: Layer-up and Bond & Drill & Plating and Copper Deposition

Step 5: Outer Layer Imaging & Plating

Step 6: Final Etching & Solder Mask Application & Surface Finish
Comparing invasive and NIR Measurements

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<th>Person 1 value mg/dl</th>
<th>Person 2 value mg/dl</th>
<th>Person 3 value mg/dl</th>
<th>Person 4 value mg/dl</th>
<th>Person 5 value mg/dl</th>
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The results have been compared on determining and benchmarking the glucose levels of five volunteers. This type of glucose meter allows accurate, convenient testing and requires a tiny sample size of only 0.5 microliter.
Advantages & Disadvantages

- Low manufacturing and maintenance cost
- **Non-invasive** continuous monitoring
- Shows a very promising future for the implementation of NIR technology in biomedical field especially in optical spectroscopy for real-time and continuous non-invasive glucose monitoring
- Patient variation: skin roughness which can cause light scattering, different body fluids concentration, etc., which could have an impact on the system performance
- Accuracy and robustness of device
ISO 10993 Testing

Surface components (long-term, skin contact):
- cytotoxicity, sensitization, irritation

Implanted components (long-term, blood contact):
- add tests for system toxicity, genotoxicity, implantation, hemocompatibility, chronic toxicity, and carcinogenicity

Is it a medical device?
Yes!

It fits the ISO definition of a medical device because it is a device intended for monitoring of a disease

Foreign Body Response and Biofouling
- Host protein adsorption to device
- Neutrophil infiltration $\rightarrow$ inflammation
- Fibrous encapsulation by foreign body giant cells, which can interfere with device function (biofouling)
- Concern for implanted component $\rightarrow$ use non-fouling coating such as PEG?
Device testing:

- Generate “Glucose Precision Profile” by testing sensor output compared to known glucose input to ensure accuracy over a wide range of glucose levels
- For optical sensor: clinical testing would need to include patients with a variety of skin colors, textures, and thicknesses to determine whether certain patient groups may not be able to use this device

- Combine non-invasive glucose monitoring with insulin delivery for closed loop system (“Artificial Pancreas”)
- Optical system could be configured to measure other things by configuring with their absorption spectra


Thank You!
Questions?