

ECE 480

Proposal

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Low-Cost Electrochemical Sensor System for Proteomics

MSU Advanced Microsystems/Controls Research Group

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Executive Summary

Early detection of tumor cells among healthy human cells is one of many problems in the medical industry that presents challenges both financially and technically. One possible solution to this problem is using the human body's cellular proteins as detectors. The process of testing for the presence and characterization of protein functions in bi-layer lipid membranes can be accomplished using three individual tests. Each of these tests demands its own set of equipment costing upwards of thousands of dollars. Dr. Mason has tasked Design Team 2 with creating a single efficient unit capable of performing all three tests. This unit will cost significantly less than the current equipment used for any

one of the tests. Given the ability to drastically enhance the medical and food safety fields please approve funding for the development of this project immediately.

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Introduction

The design project our group is presented with is called Electrochemical Instrumentation for Functional Proteomics. We are going to use modern analog components, microcontrollers, and computer data acquisition systems to design low cost electrochemical instrumentation. Our system will be capable of performing multiple electrochemical techniques, including chronoamperometry, cyclic voltammetry, and low frequency impedance spectroscopy to determine the presence or state of proteins. This will accommodate a broad range of signal levels to suit a variety of analysis scenarios. Such an instrument would be a great asset to advancing functional proteomics and could lead to improved scientific understanding of biological processes and future generations of drug and treatment options for adverse conditions and diseases. Currently, there exists commercial equipment available from companies like Gamry that can perform the above tests. Their devices can measure the femto amp currents associated with biological processes; but this equipment is quite expensive. Also the current equipment takes significant time to reach an analysis on an electrochemical test. Our design will provide a product that includes all of the above tests in one portable piece of equipment while reducing the cost and meeting the specifications of our customer.

Background Information

Functional proteomics is the systematic perturbation or functional inactivation of proteins within a given physiological environment to address the potential role of the target protein in a cellular process¹. Changes in the impedance of the protein channel correspond to the opening or closing of the channel in the bi-layer lipid membrane. These changes can occur on the femto scale, which requires extremely precise equipment to measure accurately. Some of the benefits of functional proteomics can be seen in the medical field. Knowing the individual functions of proteins in the human body has great implications for human health in the future. Protein targeted medicines, more effective anti-rejection treatments or even better biological implants² are made possible by knowing specific protein functions. Obviously, the characterization of proteins is imperative for creating biological interfaces and electrochemical techniques that will help advance future medical treatments.

Chrono-amperometry

Chrono-amperometry is an electrochemical measuring technique used for the analysis of electrode reactions. A fast rising step in voltage is applied on the working electrode of an electrochemical cell and the current is then measured. The imposed voltage value is then divided by the measured current value resulting in a value of resistance corresponding to the state of the protein.

Chrono-amperometry is very useful in numerous applications. Some examples of its versatility are: finding relationships between common pharmaceuticals³, helping with the study and creation of electrodes⁴, the study of dental bonding polymers⁵, the study of

effects of various brain endorphins⁶, and the creation of body implants.⁷ By no means is this list all inclusive, these examples barely scrape the surface of chronoamperometric potential.

Cyclic Voltammetry

In this test a triangle stimulus is imposed on an electrode and the current is then measured. The current measurements are then plotted vs. voltage values to create a hysteresis curve. This test provides information regarding how fast the state of the protein can fluctuate in relation to the rate of change of the stimulus. The capacitance of the bi-lipid membrane layer can be determined by comparing the current to the change in voltage also known as the scan rate.

Low frequency Electrochemical Impedance Spectroscopy (EIS)

“Impedance spectroscopy can be used to investigate the various physical processes occurring at the electrode such as diffusion, charge transfer and double layer capacitance.⁸” In systems such as cellular bi-lipid layer membranes, the impedance of the protein can be modeled as a resistor in parallel with a capacitor (see figure 1). Using EIS, the frequency response of this model can be found. The amplitude of the returning This information is determined by sweeping the frequency of a sinusoid input and recording the relative amplitude and phase of the output to create a Bode Plot.

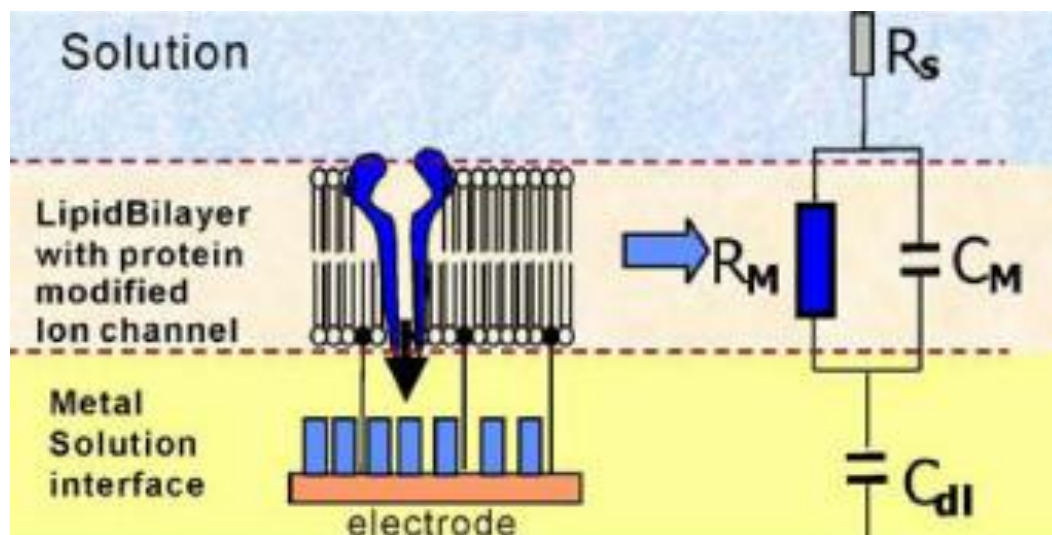


Figure 1: Equivalent Impedance Model of Cellular Bi-lipid Layer Membrane

Objectives and Design Specifications

The goal of this project is to create a low cost alternative to commercially available equipment for functional proteomics.

There are several objectives this project must complete. These objectives include the generation of various frequencies, voltage signals and the measuring of very small currents ranging from femtoamps to milliamps. Next the data will be analyzed on a local microprocessor and then displayed to the user. In order to perform the above tasks we will need to take the following into consideration:

Cost – The target cost for our final product is under \$100 dollars at mass production. We will do this by building the device with discrete components that are readily available.

Size – Ideally the device would be handheld for field use, however initial designs will be tethered to a computer. The target size will be 1 inch by 3 inches by 4 inches.

Accuracy – Precision current measurement is a must for this project. In order to achieve a high degree of accuracy we must maintain a clean environment and use high precision components. This will greatly help reduce the noise that could otherwise limit our ability to accurately measure the currents associated with our tests.

Power Consumption – In order to meet our final goal of being handheld, we need to keep the project low power so it can operate for extended periods of time using only batteries. We will be using two AA batteries that will nominally supply three volts.

Simple Design (manufacturing purposes) – The intention of this design is to become a manufactured product that is highly repeatable.

Ease of Use (user standpoint) – The finished product will be easy to use and understand. The user interface will have logical controls that could be used without a manual. The system will easily connect with the test solution and perform calculations as specified automatically. The output display will be easy to read and understand.

Satisfaction of Sponsor – Ability to meet sponsors ranked priorities.

Specifications from sponsor ranked by priority:

<i>(1 highest)</i>	<i>Feature</i>
1	AC readout (1mHz – 1kHz, 10pts/decade)
1	DC readout (constant potential and triangle wave modes)
1	DC programmable rate and amplitude
1	Mode select
1	Wide current readout range
2	Programmable Vref

- 2 AC programmable amplitude
- 3 Automatic current readout ranging
- 3 Bluetooth connection to a PC (not critical but neat addition)
- 3 DC readout (saw tooth and normal pulse modes)

		DC bias Voltage (volt)	Max voltage	Min voltage	Scale rate(volt/second)	Resolution
DC	triangular/ saw tooth/ constant /voltage pulse wave	1.5-3.5V with 8b resolution, nominal value half of vdd	1V above the DC bias	1V below the DC bias	10m-1v/s	10bits
AC	Sinusoid/ cosinusoid		amplitude		Frequency:	SDFR>70dB
			5mV		1mHz-1KHz, 10 pts/decade	

Table 1: The specifications of the signal generator @5V supply voltage

parameter		Max (volt)	Min (volt)
working electrode current (ampere)	Small range	100n	10f
	Large range	1m	100n

Table 2: The range of the current through the working electrode

FAST Diagram

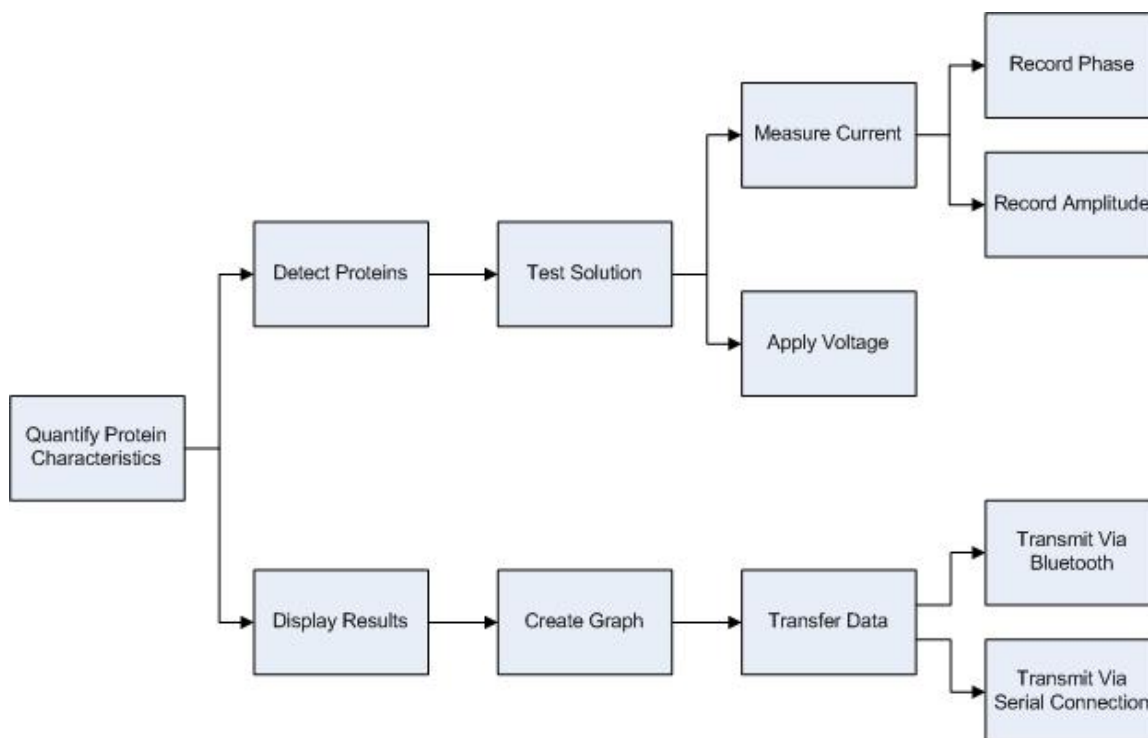


Figure 2: FAST Diagram

Conceptual Design Descriptions

There are two approaches we are considering to accomplish this project. The first design will be independent of a computer. The device will be stand alone with the capability for taking measurements, analyzing them locally, and providing the results on a display. The second design will require computer interaction. It will have the capability to take measurements independent of a computer, but the data will then be transmitted back to a computer where it will be analyzed and reviewed.

Design 1

This design is the stand-alone solution for solving this project. The process that this design will follow will start with the user. The user will select which test they want to perform (chronoamperometry, cyclic voltammetry, or low frequency impedance spectroscopy.) Once selected, the user will be able to select the appropriate parameters: frequency, peak voltages, DC offset, and scan rate. Once selected, the signal generator will produce the appropriate signal to be sent to the potentiostat. The function of the potentiostat is to maintain the working electrode at a constant potential to the reference electrode. Next, the signal will be applied across the electrodes where a current is induced through the protein. This current

will travel back through the potentiostat where the signal will be amplified and converted to a voltage. This is then sent into an analog to digital converter to be analyzed and stored by the local microprocessor. Finally the results will be presented to the user via the onboard display. This solution provides limited ability for post processing of data.

Design 2

Design two encompasses all of the same testing circuitry as is design one. The difference lies in how the data is analyzed and displayed. Once the data is ready for analysis it is sent to a computer. On the computer the data is analyzed and displayed using LabVIEW giving the user more flexibility for signal processing and storage.

Ranking of Conceptual Designs

Engineering criteria	Importance	Possible solutions	
		Stand alone	LabVIEW
Size	5	3	9
Handheld Functions	5	9	3
Low Cost	4	3	9
Ease of Use	3	9	9
Appearance	2	9	3
Low Power Consumption	5	1	9
Reliable	5	9	9
Mobile	4	9	9
Post-processing upgrades	2	1	9
Data Storage	1	3	9
TOTAL		208	282

Table 3: Solution Selection Matrix

The proposed solutions were ranked by comparing their individual attributes in the above solution selection matrix. First, the additions of a larger display on the stand alone version created many deterrents. The screen will result in a larger product, increased cost, greater power consumption, less storage and limited processing capabilities. For this reason conceptual design 2, the LabVIEW interface, was selected. The LabVIEW interface will provide less immediate feedback at the time of testing and not be as aesthetically pleasing with the removal of the screen. However, the immediate feedback provided by the screen can potentially be supplemented by creating a Bluetooth to handheld device (cellular phone or PDA) graphical display application. This alternative can be implemented with a module that will require less power than an onboard screen. The external device will supply its own power and is already owned by the user so the only cost is the application development.

Proposed design solutions

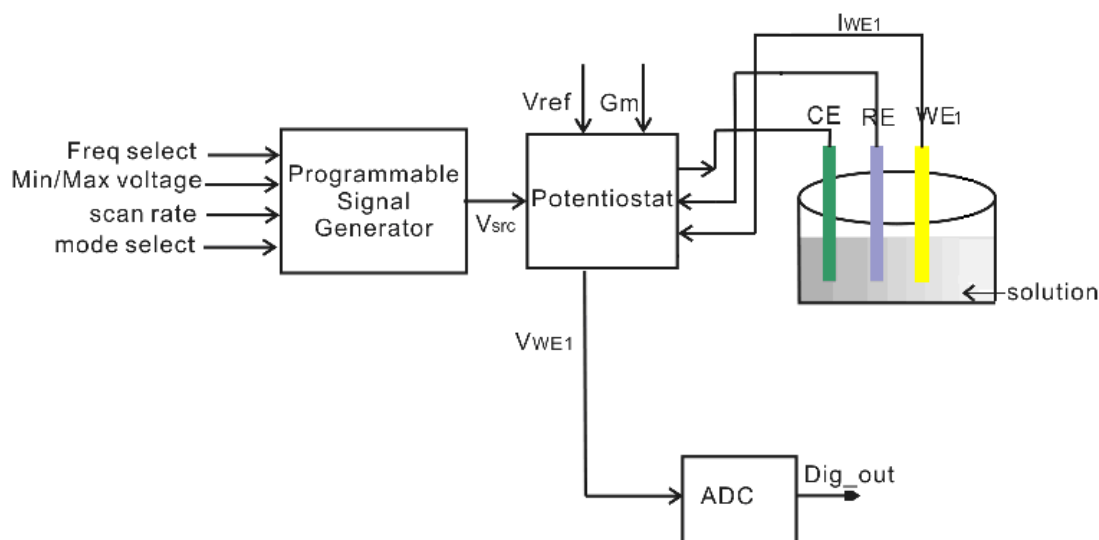


Figure 3: The block diagram of the electrochemical analysis system

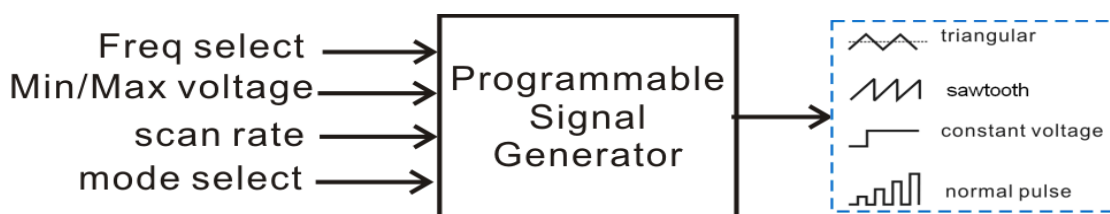


Figure 4: The function schematic of the programmable signal generator.

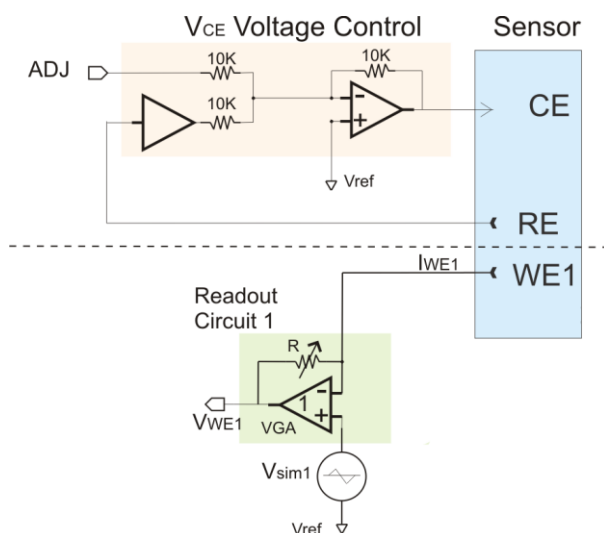


Figure 5: The Architecture of the CMOS bipotentiostat with connected counter electrode (CE), reference electrode (RE), and working electrodes (WE).

Proposed Design Components

- **Case**
 - Dimensions: 1” by 3” by 4”
 - Made from a prototyping box
- **Power**
 - Two AA batteries
 - Boost Converters
 - Voltage Regulators
- **User Interface**
 - Three position switch for specific test selection
 - Direction pad
 - Enter key
 - Back key
 - Two line LCD Screen
 - Power Button On/Off.
- **Processor**
 - 16-bit PIC
 - Onboard RAM
 - Onboard ADC
 - Onboard DSP module
 - Onboard UART port.
- **Signal Generator**
 - Monolithic function generator IC controlled by the PIC
 - Digital Potentiometers will be used with capacitors to control frequency and amplitude.
- **Potentiostat**
 - Low noise op-amps
 - High precision resistors.
- **Probes**
 - Provided by sponsor.
- **Output Display**
 - LabVIEW
 - Bode Plot
 - Nyquist Plots
 - Hysteresis Curve

Build/Test Plan

Each bullet above represents an individual system in the design. During Construction, each system will be built and tested individually before it is integrated into the complete design. Once fully assembled the whole product will be tested systematically to test for all possible user selections and external problems.

Evaluation Plan

Real life test of an electrolyte solution using our design will provide data that can be compared to data obtained by existing methods. PSPICE will be provided for early simulation of the design.

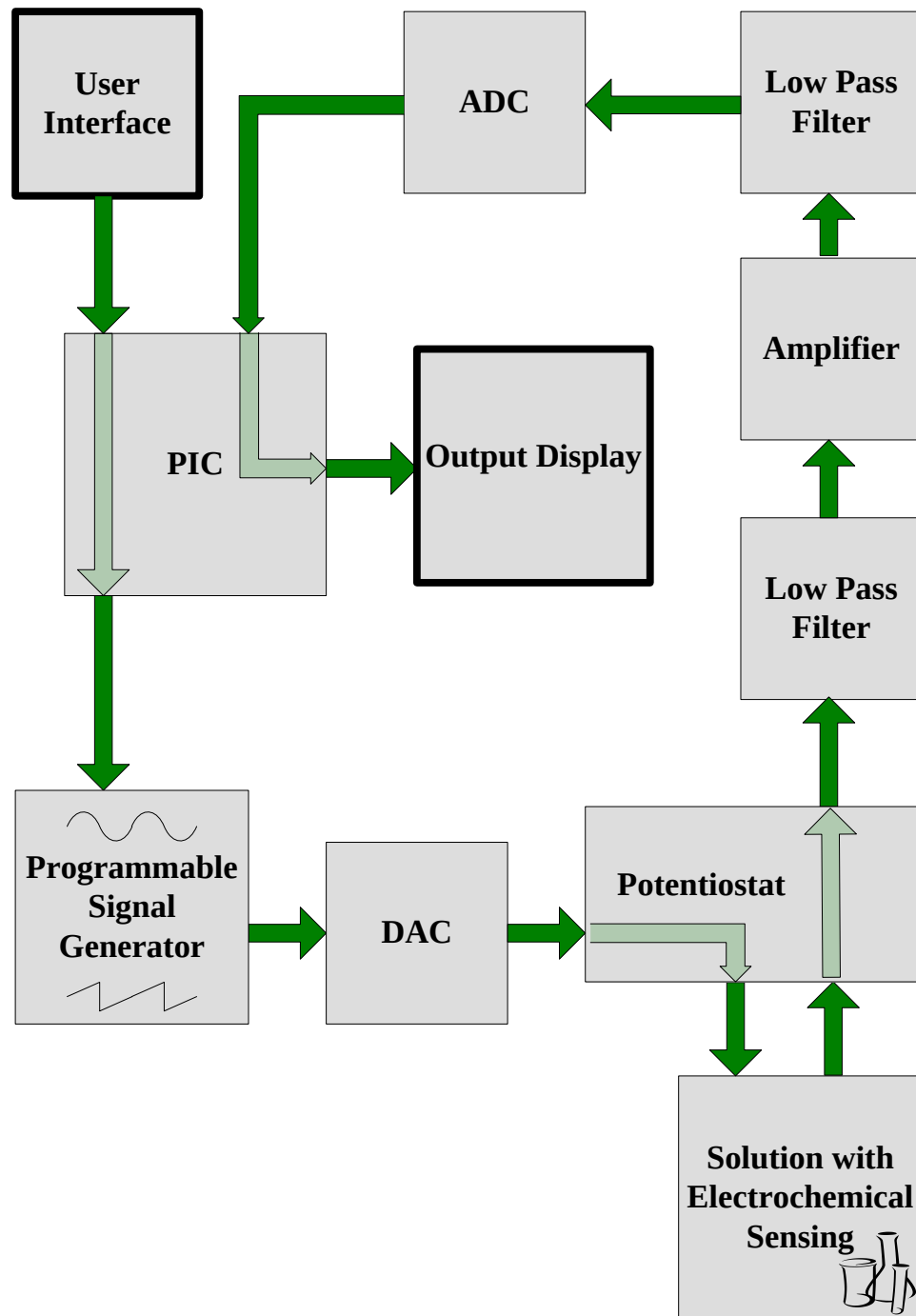


Figure 6: Design 2 Block Diagram

Risk Analysis

Some of the design concerns surrounding the construction of the aforementioned system are as follows.

Accuracy: When it comes to measuring currents in the femto amp range, most lab equipment will have significant errors in the readings. These errors could be introduced from the tolerance of the components. For measurements in the femto amp range, even the smallest interferences will distort the signal or the measurement. High frequency light from the sun or lights in the lab can induce a current of equal or larger magnitude than the current we are measuring, which will completely invalidate the results.

Noise: With extremely low currents and frequencies, noise becomes a big issue. Every component in our design will add some degree of noise which could corrupt the data and yield inaccurate results.

Clean Environment: When assembling the system, care must be taken to not add fingerprints or dirt to the circuit. Doing so can result in significant errors in measurements and possibly ruin the functionality of the circuit altogether. This primarily becomes an issue when dealing with currents in the pico to femto amp range.

Mobility: Moving the device will cause vibrations which can produce undesired piezo electric noise. To avoid this, the device should be shock resistant to prevent skewing the results.

Supplying Power: There will be multiple chips in our design, each with their own power requirements, which makes supplying the correct power efficiently to each component mandatory. Supplying too much power could burn up a chip and not supplying enough power will result in the chip not working.

Battery Life: Due to long test durations, the battery may be drained at a fast rate. Our selection in battery must be able to store large amounts of charge in a cell. For example, when taking a measurement at 1 millihertz, the time it takes to complete one period is 1000 seconds. During this time, the system will be running at full power, acquiring data, which will be strenuous on the battery.

Financial Issues: Our goal for this project is to stay under \$100 when mass produced, however the budget for initial prototype and design is \$500. This is a great reduction in cost when compared to commercially available equipment that already exists. These devices which are capable of measuring currents in the femto amp range cost upwards of two thousand dollars.

Project Management Plan

Each team member is responsible for a technical role and a non-technical role. The technical roles are shared responsibilities among the team. Each person will be assigned to a technical role which they will be responsible for. Their responsibilities include design, development and resource management.

Luke LaPointe – Web Design

Software Programming

Nick Timpf – Manager

Analog Circuitry

Mark VanCamp – Document Prep.

PCB Design

Brent Woodman – Presentation Prep.

Analog Circuitry

Steve Zuraski – Lab Coordinator

Lab VIEW Programming

Each team member will be involved in the systematic testing of their respective technical areas. All members will be involved in the final testing of the design.

Budget

Equipment	Quantity	Price
Signal Generator	1	\$20.00
High Precision Resistors and Capacitors	Multiple	~\$5.00
PIC	1	\$10.00
DC-DC Converters	2	\$5.00
Op Amps	5	\$15.00
Electrodes	2	Donated
LED Display	1	\$10.00
User Interface Buttons	5	\$15.00
Case	1	\$10.00
AA Batteries/Mount	2	\$10.00
	TOTAL	\$100.00

Many of the parts will be free of charge courtesy of the ECE Shop.

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