Design of Back-end Electronics for Biological Sensing Applications
Final Report
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by
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ABSTRACT

Recent advances in technology have allowed living tissue to be extracted from animals and analyzed in vitro via electronic methods. The focus of this paper is the processing of the signals generated by cyclic voltammetry and amperometry. Both of these processes create small signals on the order of 1nA. These signals must be amplified, converted to a digital signal, and communicated to a computer so that they can be appropriately analyzed. In addition, we wish this design to be scalable, so that multiple channels can be monitored simultaneously.

The processing of the signal must be achieved in multiple stages. The first stage must convert the small current output of the sensor to a voltage signal that the ADC can detect. To do this, a transimpedance amplifier was used in a single stage design to generate a signal between 0 and 4.8V. A Cypress evaluation board was then used to perform the Analog to Digital conversion and communicate the data via USB to the host computer. The evaluation board PSoC was programmed using an incremental ADC with 8 bit precision able to generate approximately $6.5 \times 10^3$ samples per second. While this is not sufficient for the general use of the sensor, it does allow most tests to be run reasonably. The data is then transferred to the host computer over the evaluation board’s full speed USB connection using isochronous data transfer.

By modeling the sensor output using a simple integrator circuit, we successfully tested each stage of our design. We successfully wrote a binary file using the bytes generated by the ADC at a rate sufficient to record all of the data from the ADC.
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Chapter I. Introduction

The Biological Sensing field has been growing rapidly in the past several years. Recent advances in technology have allowed living tissue to be extracted from animals and analyzed in vitro. To assist in examining the tissue, Dr. Chen et al. developed an integrated circuit to perform several of the standard procedures used to analyze the chemistry occurring in the tissue. Each of these procedures produces a small output signal, on the order of 1 nA, as its output. Because the signal is so small, a fair amount of post processing must be done to get useful results.

The two most common procedures, and the procedures this implementation focuses on, are cyclic voltammetry and amperometry. Cyclic voltammetry is a process in which a voltage is applied to the tissue and the swept linearly up to a maximum voltage and back down to the initial voltage. This produces a voltometric curve which varies with a number of factors that define an oxidation-reduction reaction. Both the margin that separates the peak currents and the voltages that the peak currents occur give information about the reaction.

![Cyclic Voltammetry Example Input/Output](image)

Figure 1. Cyclic Voltammetry Example Input/Output

Amperometry is a passive measurement that can detect information about the exocytosis of neurotransmitters and other elements. During exocytosis, the cell forms a
vesicle that contains the neurotransmitter. When this vesicle is released from (or docks to) the cell, a current spike is created that can be detected by the amperometric equipment. By measuring the magnitude of these spikes, and the frequency at which they occur, interesting information can be determined about the function of the tissue being observed.[1]

The first stage of the post processing is an amplification stage, to boost the signal to a point where it can be detected by an Analog to Digital Converter (ADC). This requires an amplifier with a large gain, high sensitivity, and low input noise. The amplifier must also detect a current signal and create a voltage output. The signal frequency from the sensor device is fairly low, only up to approximately 1MHz, so it plays a negligible role in determining the requirements for the amplifier; however, it plays a much larger role in the conversion stage of processing.

The second stage of processing is converting the analog signal from the amplifier to a digital signal that can be stored and analyzed by a computer. In this section the frequency of the signal is the most significant driving force for the design. The ADC must be able to produce a value quickly enough so that the signal can be sampled at its Nyquist frequency. For the maximum frequency of the input signal, this would require $2 \times 10^6$ Samples per second. In addition, the converted values must have sufficient precision to provide useful information about the reactions occurring in the tissue. This threshold for this appears to be eight bit precision.

Finally, the converted bytes must be transferred to a computer where they can be stored and analyzed at a later time. Due to the limitations on memory connected to the ADC, this transfer must occur at least as fast as the ADC is producing information. While
this is not generally a significant limitation, it does prevent some communication protocols from being used, and increases the complexity of others.

Chapter II briefly describes some of the work that has already been done in field of biological sensing. Chapter III describes the amplification techniques that were used and the strategy for analog to digital conversion. Chapter IV describes the communication to the host computer. Chapter V presents our results and possible future improvements to the design.
Chapter II. Existing Work in Biological Sensing

Biological sensing has developed in two separate directions. The first occurs in the sensor itself. Early methods required that the sensors be inserted directly into the animal. While useful, this approach lacked the precision required to determine the chemical activity in specific areas. This approach was also particularly susceptible to noise generated by nearby tissues or other uncontrollable factors. Recently, technology has progressed to the point where tissue samples can be evaluated in vitro, so that the environment can be controlled more fully. This eliminates many of the precision and noise concerns that were present in the in vivo methods. The next step, being pursued by several labs is the development of a VLSI design that can be used for incorporating the sensor.\textsuperscript{[2][3]} A layout of the biosensor for which this research was conducted can be seen in figure 2.
In addition to the improving sensor technologies, there are a number of efforts to enable processing the data from the sensors to be done in a more streamlined fashion. There are several papers addressing filtering techniques that allow easier recognition of parameters that are useful in analyzing the signal. There have also been a number of efforts to develop software to handle large blocks of data generated by various sensing techniques. The main developments have been centered around the analysis of the current spikes of an amperometric output, and the deciphering of large collections of hundreds of thousands of readings in an offline environment. [4]
Chapter III. Amplification and Conversion

Figure 3 illustrates a block diagram of the overall design of the finalized system. The blocks contained in the red bordered areas are the main focus of this design research.

![Figure 3. Block Diagram of Finalized System](image)

Due to the small signal created by the biological sensor, a very high sensitivity amplifier must be used. To achieve this we used the Texas Instruments OPA381, as can be seen in figure 4. This is a transimpedance amplifier which provides sufficient sensitivity and low enough input noise for our application. It is also a very affordable piece of equipment, at only $3.60 per unit. When put in a simple, single stage amplifier circuit, this part amplifies the ~1nA signal we receive to a range between 0 and 4.8 volts. This is the maximum range that the PSoC ADC can accept, and optimizes the range of values we can output from the ADC.
The analog to digital conversion is done using the ADCINC module on the Cypress CY3714 evaluation board. This board uses the CY8C24894 PSoC chip as its core, and also provides numerous IO peripherals. This board constitutes the largest part of our budget at $198 per board. However, this cost allows the design to be implemented in a scalable manner. Each board can handle one channel of output from the sensor array, and the boards can be linked together using the bus system provided by Cypress, or another method using the board IO. This allows a single board to be connected by USB to the computer controlling the data from each sensor channel.

The ADC is connecting to the input signal using a unity gain PGA on one of the PSoC’s analog blocks. This is requires as the ADC cannot be connected directly to the analog MUX included in the PSoC. However, it also provides additional flexibility for the system, since the gain can be adjusted on the PGA to offset variations in the external amplifier. This ADC provides us with $6.25 \times 10^3$ samples per second at 8 bit precision. This is significantly lower than the required sampling rate for the maximum frequency
output by the sensors. It does, however, cover a large enough range to be useful for many applications. Increasing the speed of the analog to digital conversion is the primary goal of future work on this project, though it may be difficult to achieve without using additional hardware. Figure 5 shows the interface used to program the PSoC device and the internal connections including input, PGA, ADC, and USB interfacing.

Figure 5. PSoC Programming Interface with Connections
Chapter IV. Communication

In order to make the design as scaleable and as flexible as possible, the communication with the computer was designed to operate as fast as possible, despite the bottleneck at the ADC. We evaluated several possibilities using the USB interface in the evaluation board including the Cypress Human Interface Device (HID) driver, standard byte-wise USB communication, bulk USB, and Isochronous USB. We determined the HID driver operated too slowly for us to use effectively, and included many features we did not need. Both standard USB and bulk USB operate more slowly than Isochronous USB as well, and we do not require the additional direction of communication they provide. For this reason we configured the USB endpoint on the evaluation board as an isochronous endpoint, and modified the code to use the isochronous capabilities.

In addition to configuring the board for USB communications, we also had to develop an application to run on the computer side of the communication. Cypress provided a simple example, which we modified to suit our purposes. The application simply reads the data coming from the isochronous endpoint and writes it to a file, still in binary format. This file can then be read by another program which can do any analysis that is deemed useful. Our USB communication is capable of operating at 1 MB / sec, which was more than enough bandwidth for the current implementation.
Chapter V. Conclusions and Future Work

Our design for the back-end electronics for processing signals generated by cyclic voltammetry and amperometry laid a solid groundwork to continue developing the necessary components. We have designed an amplifier circuit, an ADC component, and a USB communication mechanism that are usable to collect useful data. There are a number of issues that still need to be resolved however, and will be addressed by future work.

1. The first, and most critical issue is the rate at which samples are collected by the ADC. It may be necessary in the future to use an external ADC and simply feed the data through the evaluation boards to be communicated to the computer.

2. In addition, it may be worthwhile to use the evaluation board to control the voltammetric input into the actual biosensor to produce a single integrated control and data acquisition system.

3. Finally, future work will need to demonstrate the scalability of the design by using it as a building block to monitor each channel of the arrays of the biological sensors, achieving the ultimate goal of this project.

In conclusion to the design documented, our objectives were met with adequate results allowing the further development of the integrated biosensor system.
References


Bibliography


### Appendix A – Abbreviations

1. PSoC  -  Portable System on Chip  
2. ADC  -  Analog to Digital Converter  
3. USB  -  Universal Serial Bus  
4. IO  -  Input/Output  
5. MUX  -  Multiplexer  
6. PGA  -  Programmable Gate Array  
7. HID  -  Human Interface Device
Appendix B – Cost Considerations and Timetable

Monetary Costs:

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<thead>
<tr>
<th>Item</th>
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<tr>
<td>TI OPA381 Transimpedence Amplifier</td>
<td>$3.60</td>
<td>4</td>
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<tr>
<td>Cypress PSoC USB Evaluation Board</td>
<td>$99</td>
<td>2</td>
</tr>
<tr>
<td>Cypress C-Compiler</td>
<td>Free (Donated)</td>
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<tr>
<td><strong>Total</strong></td>
<td><strong>$212.40</strong></td>
<td></td>
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Timetable:

Over the course of the 14 weeks of work on this project, approximately 60 hours of total work were allotted by each individual member.

Total work hours of group : ~120

Average hours per week : ~8.5
Acknowledgements:
1. **Tom Chen, Ph. D.** – For defining the problem, acting as project manager / advisor, paper editor, and inspiration.

2. **Cypress Semiconductor** – for donating their C compiler.

3. **CSU Honors Program** – for providing funding.

4. **Anita** – for helping design, test and verify the amplifier circuit