A System for Electrical Retinal Stimulation for Human Trials

by

Shawn Kevin Kelly

Submitted to the Department of Electrical Engineering and
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in partial fulfillment of the requirements for the degree of

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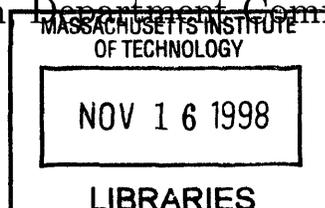
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Abstract

The goal of the Retinal Implant Project is to restore useful vision to patients with degenerative diseases of the retina. Electrical stimulation of the retina via a microelectrode array is achieved using a battery powered stimulation system. This thesis describes the design of this system, including features that ensure the subject's safety from electrical shock. The stimulation system delivers charge balanced current pulses to the 100 electrodes in the array. The system has been tested in the laboratory setting as well as in rabbit experiments and one human retinal stimulation trial. It functions as specified, and is very robust.

Thesis Supervisor: John L. Wyatt, Jr.
Title: Professor

Acknowledgments

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Chapter 1

Introduction

The Retinal Implant Project is a collaborative research effort between the Massachusetts Institute of Technology and the Massachusetts Eye and Ear Infirmary, dedicated to the development of an epiretinal prosthesis. The primary goal of the Retinal Implant Project is to restore useful vision to victims of age-related Macular Degeneration and congenital *Retinitis Pigmentosa*. These diseases result in the death of the photoreceptor cells, the rods and cones, causing eventual blindness. Experiments done in rabbits have shown that electrical stimulation of the overlying retinal ganglion cells causes evoked potential responses in the visual cortex.[6, 3] The next step toward a retinal prosthesis, in parallel with biocompatibility studies, is testing for human perceptual responses to electrical retinal stimulation. This thesis describes the hardware designed and constructed for the first human trial of the Retinal Implant Project.

1.1   The Stimulator System

A current source stimulator system is described in this thesis. It is a battery powered box, measuring one foot square and six inches high, weighing roughly twenty pounds. An array of 100 manually operated switches controls which electrodes are on, or stimulating, and which are off.

1.1.1 Theory of Operation

Charge-balanced rectangular waveforms are used for stimulation. These waveforms consist of two pulses, opposite in polarity but equal in area. Ten such biphasic pulses are generated in rapid sequence and sent to a current source, which drives a column of ten electrodes serially through a demultiplexer. Ten such current source and demultiplexer units cover all ten columns and 100 electrodes. The waveforms are shown in Figure 2-2. The amplitude of the waveforms is controllable by the user, as is the period between the beginnings of sets of ten stimulus pulses. The number of ten-pulse sets delivered during one stimulation is also controllable. The period range allows stimulation at frequencies between 0.5 Hz and nearly 200 Hz. A typical stimulation might be 30 Hz and consist of 30 sets of stimulus pulses, lasting for one second.

1.1.2 Specifications

The main specifications for this system are reliability during the human experiment, an intuitive user interface, and most importantly, complete safety for the subject. The concrete system specifications are as follows:

1. The current pulses must be charge balanced, one pulse being one quarter the amplitude and four times the duration of the other.

2. The narrow pulse should be $100\mu s$.

3. The maximum amplitude of the narrow pulse should be $100\mu A$.

4. The entire system must be battery powered, with no connections to line power or earth ground.

5. The system must allow no DC currents to the subject.

1.1.3 Block Description

A digital circuit generates pulses with the correct timing. It is very flexible, and has inputs to control period, number of ten-pulse sets, and the sequence of pulses. An analog circuit then scales these pulses to the appropriate ratio, inverts one, and adds them. Ten current sources then convert the voltage signals to currents. The currents pass through demultiplexers, which switch between the ten electrodes in a column. Each electrode has its own switch, which can be used to determine whether an electrode is on or off, and can be used to test the electrode arrays. These switches are connected to a seven foot long wire bundle attached to a printed circuit board. The electrode array attaches to this board, and has metal traces running down to the electrodes, at the end of the array which will be inserted into the eye.

1.2 Human Safety Issues

Throughout this thesis, the human safety issues incorporated into the design are highlighted. In every case, potential harm to the patient is prevented by several safety features, all of which would have to fail to allow harm to come to the patient, and any one of which is very unlikely to fail. This design has been approved by human studies committees both at MIT and at the Massachusetts Eye and Ear Infirmary, and is very safe for human experimentation.

1.3 Description of Previous System

A system has been in place for some time to deliver stimulus currents to rabbit retina via a 25 electrode array. The timing is controlled by a computer, which also acquires and averages data. A commercial pulse generator drives a pair of commercial current sources. This system has been used for investigating electrically evoked potential thresholds in rabbits. For the rabbit experiments described in Chapter 6, the battery powered stimulation system was interfaced with the computer to allow recording of the cortical waveforms seen in Figure 6-1.

1.4 Thesis Outline

Chapter 2 describes the digital timing unit responsible for control and timing of the stimulus pulses.

Chapter 3 describes the analog waveform shaping circuitry, current sources, and demultiplexers.

Chapter 4 serves as a users' manual for the interface, explaining the switching grid and control inputs.

Chapter 5 discusses the electrode arrays, including connecting schemes and electrochemical issues.

Chapter 6 recounts the retinal stimulation experiments, both in rabbit and in human subjects.

Chapter 7 concludes the thesis and introduces future changes to the current system as well as plans to integrate the stimulation hardware with a computer controlled system.

Chapter 2

Digital Control System

The timing and waveform control for the stimulation system is provided by a digital circuit. This circuit forms the core controller of the stimulation system, and is very flexible and easy to interface, as required by the experimental circumstances.

2.1   Motivation for Discrete Digital Circuit

The digital control circuit was built from discrete digital chips for ease in debugging and speed in production. A programmable logic circuit was considered, but the system needed to be operational in too short a time to allow learning a new hardware description language.

2.2   Description of Digital Circuit

2.2.1   Overview

The circuit implements a finite state machine in discrete digital components using counters and JK flip flops. A number of control and data inputs and outputs interface this basic setup to configure various timing parameters of the generated waveform. The stimulus waveform consists of two time related pulses created by the digital circuit. The timing of a single pulse, the grouping of ten pulses into one stimulation,

and the timing and number of stimulations are all controlled by various subsections of the circuit (Figure 2-1). CMOS logic was used for all digital chips to reduce power dissipation.
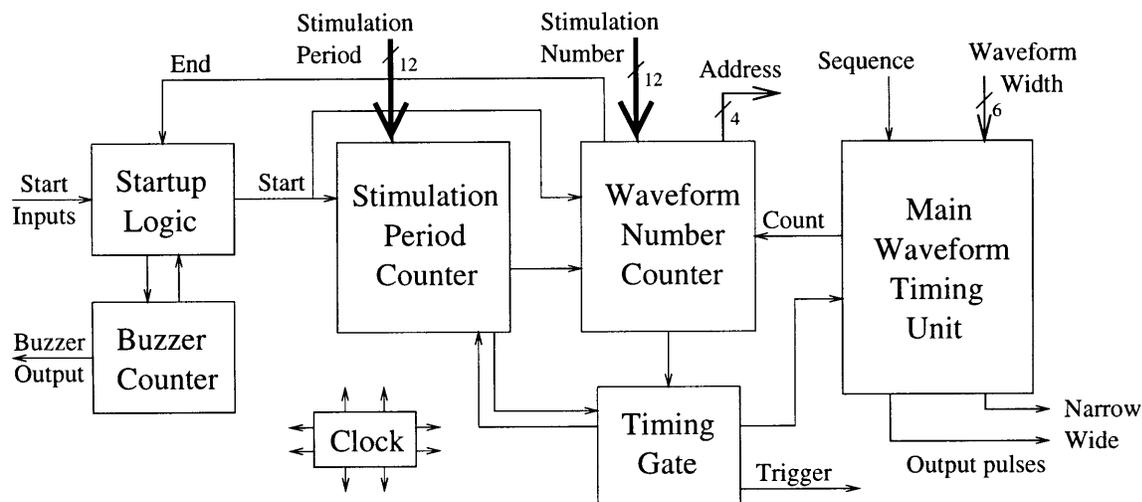
Figure 2-1: Block Diagram of Digital Circuit

The digital controller circuit is broken into three main and several lesser functional blocks. The Main Timing Unit generates the basic stimulus waveform pulse. The Waveform Number Counter, with the assistance of the Timing Gate, forms groups of ten pulses and outputs a sequences of addresses, and together with the Waveform Period Counter, repeats the groups of ten pulses at specified intervals a specified number of times. The startup block initializes the system for one of three different modes, one of which uses the buzzer counter to sound an external buzzer. Together these blocks form the stimulator control unit.

Theory of Operation   The stimulus waveform consists of two pulses, one of which is four times the amplitude of the other, yet lasts one quarter of the time, giving equal areas. Since the stimulus is a current, this corresponds to equal charge deposited onto and withdrawn from the retina. The digital controller creates two 5 Volt pulses with the appropriate timing (Figure 2-2), and leaves scaling to the analog circuit in Section 3.1. These pulse pairs are then repeated in rapid sequence ten times, corresponding to the ten electrodes in each column, as described in section 1.1.1. The time between the beginning of these sets of ten pulses is set to a defined value, which sets the stimulus frequency for a given electrode. This process repeats for a

specified number of stimuli, then ceases. The contribution of each of the blocks in Figure 2-1 to this operation is described in the sections below.
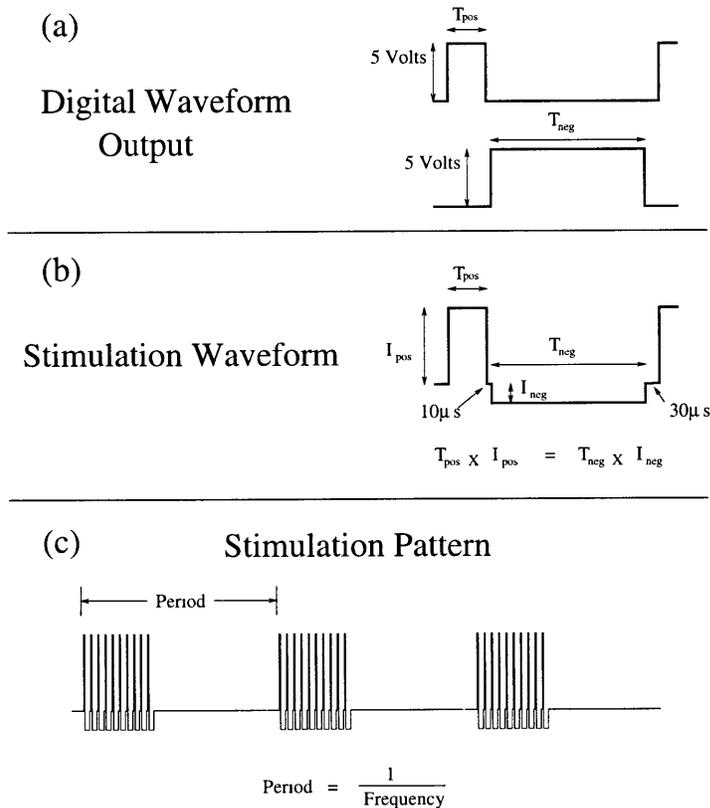
Figure 2-2: Stimulation Waveforms

(a) shows a typical waveform output of the digital circuit. The pulses have the correct timing, but are on two separate wires and have the same polarity and voltage, V_{dd}. The final stimulus waveform is shown in (b). This waveform is the output of the analog circuitry described in Chapter 3, and is a single signal with charge-balanced pulses. The only surviving feature from (a) is the timing. The whole stimulation pattern is shown in (c). Ten rapid pulses are generated, each driving one of ten electrodes in a given column. The period between the first pulse of each set determines the frequency of stimulation.

2.2.2 Clock

To avoid designing an oscillator from a quartz crystal, an off-the-shelf crystal oscillator was used. However, the clock speed of the digital circuit was a factor of ten less than the slowest readily available crystal oscillators. A simple but elegant circuit, shown in Figure 2-3, is used to divide the 1 MHz crystal oscillator by ten to 100 KHz.

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0 0 1

P   A B C D   /CL

>   74HC163   RCO

T $Q_A Q_B Q_C Q_D$ /LD

1 MHz
Crystal
Oscillator

100 KHz
Clock
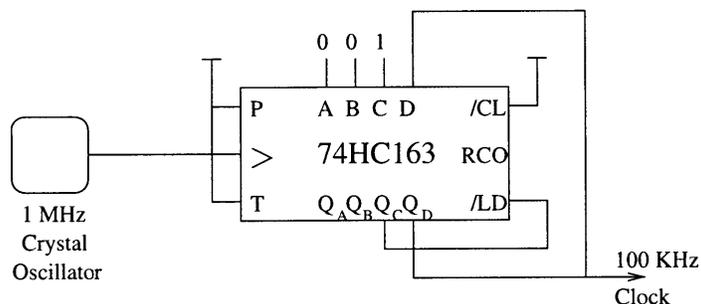
Figure 2-3: System Clock

This circuit divides the crystal oscillator by ten, producing the system clock. It loads a new value, either hexidecimal 4 or C, when the Q_C bit is zero. The count sequence, in hexidecimal, is as follows: 4,5,6,7,8,C,D,E,F,0,4,5. . .

2.2.3   Main Timing Unit

This unit serves as the core FSM controller for the system. It's four states are, from top to bottom in Figure 2-4, are the period before/between pulses (lasting $30\mu s$ between pulses), the narrow pulse (typically $100\mu s$), the pause period within a pulse (lasting for $10\mu s$), and the wide pulse (always four times the narrow pulse, typically $400\mu s$). These four states make up the timing parameters of the waveform in Figure 2-2 (b). The JK flip flops hold the state, and the AND gates enable the counters based on state. A sequence input to the circuit toggles the narrow and wide pulses between the second and fourth states, allowing the large, narrow pulse and small, wide pulse to toggle in sequence. Typically, the large, narrow pulse is first. The DIP switches in Figure 2-2 allow the timing to be configurable, but are typically set such that the narrow pulse is $100\mu s$.

When a given counter or series of counters finishes, its Ripple Carry Out (RCO) triggers a JK flip flop to set or reset, changing the state and enabling a different counter. The transition between the first and second states is gated by the Timing Gate subcircuit, which halts the Main Timing Unit after ten pulses have been generated. The Timing Gate waits until the appropriate period has passed before allowing stimulation to resume (Section 2.2.6).

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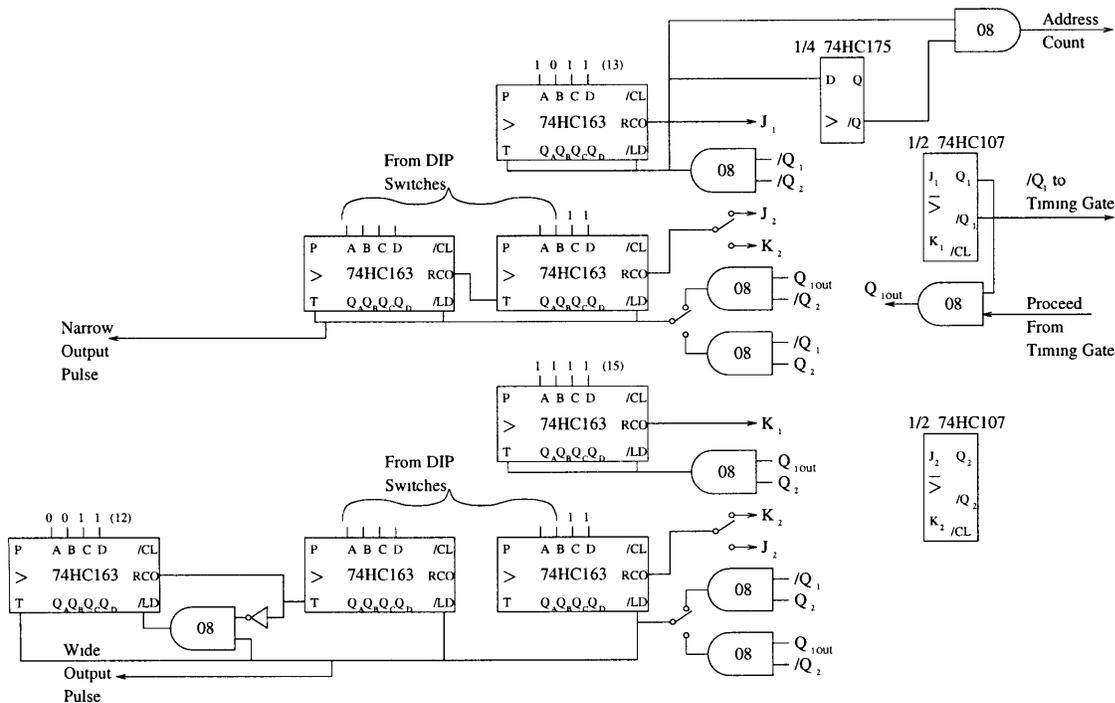
Figure 2-4: Main Timing Unit
This circuit serves as the core FSM for the system, generating the two output pulses that will become the stimulation waveform.

The first state counter generates a single pulse telling the Address Counter to change to the next address. The change in address occurs $10\mu s$ into the $30\mu s$ delay between stimulus waveforms to allow plenty of settling time between stimuli and demultiplexer switching. The Address Counter forms part of the Waveform Number Counter, discussed in Section 2.2.5.

2.2.4 Timing Gate

The Timing Gate, shown in Figure 2-5, ensures that the Main Timing Unit proceeds with another series of ten pulses only when the Stimulation Period Counter (Section 2.2.6) determines that the appropriate period has elapsed. This circuit also sends the signal that starts the Waveform Period Counter for the next cycle. The Trigger pulse, used to trigger the oscilloscope monitoring the circuit, is also generated by the Timing Gate.

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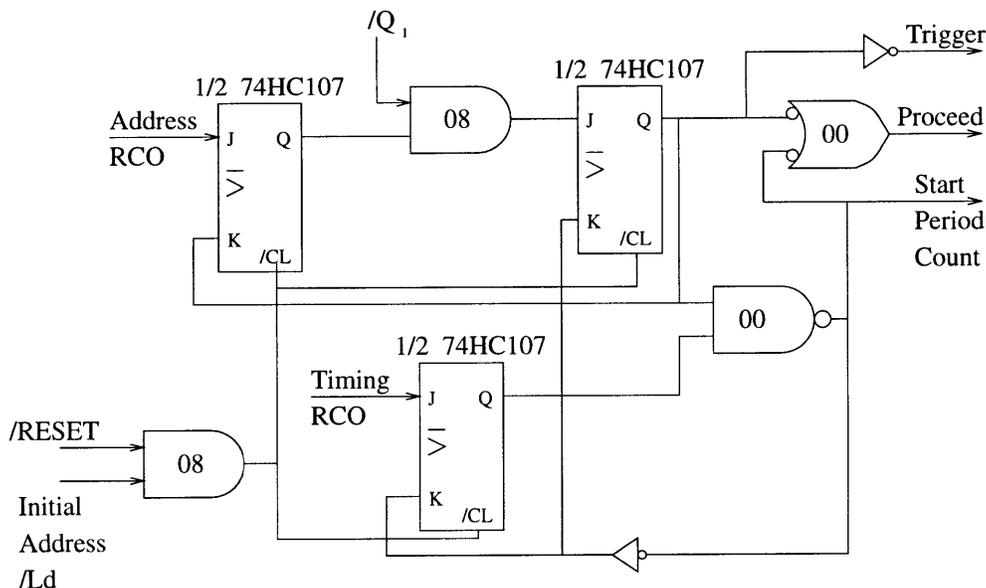
Figure 2-5: Timing Gate

This circuit gates the Main Timing Unit (Section 2.2.3), allowing it to proceed with another series of ten pulses only when the Timing RCO signal arrives from the Waveform Period Counter of Section 2.2.6.

2.2.5   Waveform Number Counter

This section begins with the address counter, which controls the demultiplexer. The counter takes its enable trigger from the Main Timing Unit (Section 2.2.3). The address counter's RCO, in turn, triggers the number counters to count. When the number counters carry over, the Startup circuit in Section 2.2.7 shuts down the system.

Note that the address counter, after sequencing through the ten addresses, clears itself to zero, a non-existent address. This means that during the period without stimulations, which is typically the majority of the time, all ten electrodes are open-circuited with respect to the current source. If the address counter simply loaded in the first value at the end of a stimulation set, the first electrode would be connected to the output of the current source, which, during this time, should be driving zero current. Due to non-zero offsets in op amps, however, the current source output during the pause is non-zero. While this current is very small, the pause between

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stimulations is typically long compared to the length of a ten-pulse stimulation (typically 5.4ms), so it was thought best to leave all electrodes unconnected from the current source during this time.
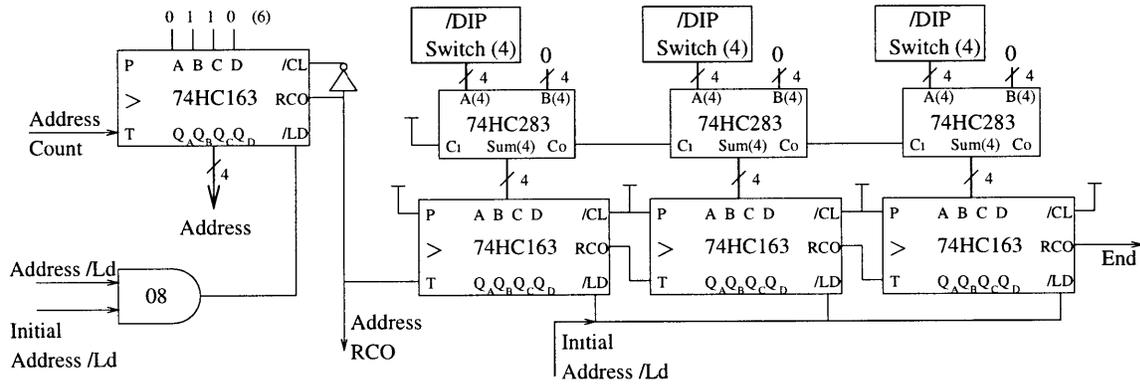
Figure 2-6: Waveform Number Counter
The Waveform Number Counter ensures that the system stimulates the correct number of ten-pulse groupings. The 74HC283 adders convert the inverted DIP switch data to the appropriate 74HC163 inputs by adding one. The DIP switch inputs are designed to be intuitive binary, i.e. 011 generates three stimuli, and the '163 inputs are the two's complement negative of that.

The Waveform Number Counter is used to obtain exact stimulation times for a given period. It was decided that this method is easier to implement than directly controlling the stimulation time. Direct control would require a large counter to determine when to stop stimulating, incurring fencepost problems and stimulation time inaccuracies at the end of a stimulation.

2.2.6 Waveform Period Counter

Implementation of the desired stimulation frequency occurs in this subcircuit. The delay between the beginning of one ten-pulse stimulation and the beginning of the next, in increments of 0.5ms, is entered in the DIP switches. The RCO of the period counter informs the Timing Gate of Section 2.2.4 that the period has elapsed, and the inverted RCO reloads the address counter to the value of the first electrode for the beginning of the next stimulation. The RCO also resets the JK flip flop, shutting down the Period Counter.

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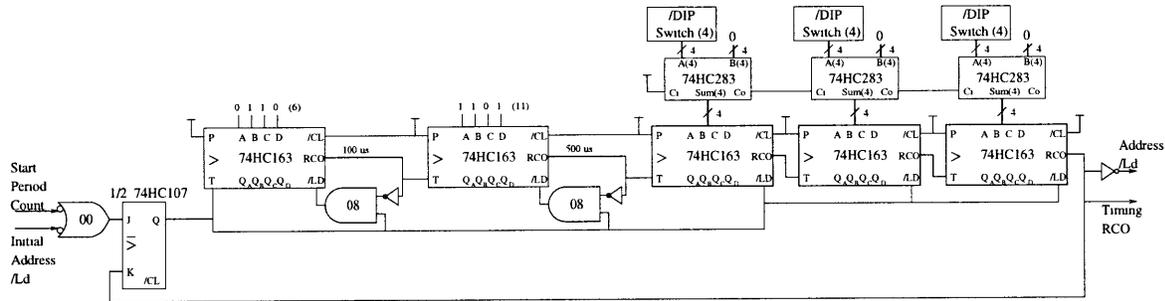
Figure 2-7: Waveform Period Counter

A large counter for setting the stimulation period. As in the Waveform Number Counter in Figure 2-6, the '283s calculate the two's complement negative of the binary input. The first two counters set the clocking increment for the counter to $500\mu s$.

2.2.7 Startup Circuitry

The design of digital circuitry to operate in the steady state does not produce a complete control system. The startup case invariably presents challenges. This stimulation system, for example, has three different start mechanisms. The first simply turns stimulation on indefinitely at the given frequency (period), with no regard to the waveform number input. This mode is used primarily for debugging. The second start mechanism uses a push button to start a stimulation of the desired number of waveform sets at the desired frequency, starting immediately after the button is pressed. The third, used during the human experiment, uses another push button and generates a buzz sound for one second, waits one second, and then stimulates at the appropriate frequency for the appropriate number. This buzz sound makes the subject aware that a stimulus might be coming.

This startup circuitry sets initial conditions on some counters and flip flops, enables the bulk of the counters and state flip flops, and drives an external LED, indicating that the system is stimulating. The two push-button start subcircuits receive the END signal from the Waveform Number Counter to shut down the stimulation. The Buzzer Counter, enabled by the buzzer push button, is described in Section 2.2.8.

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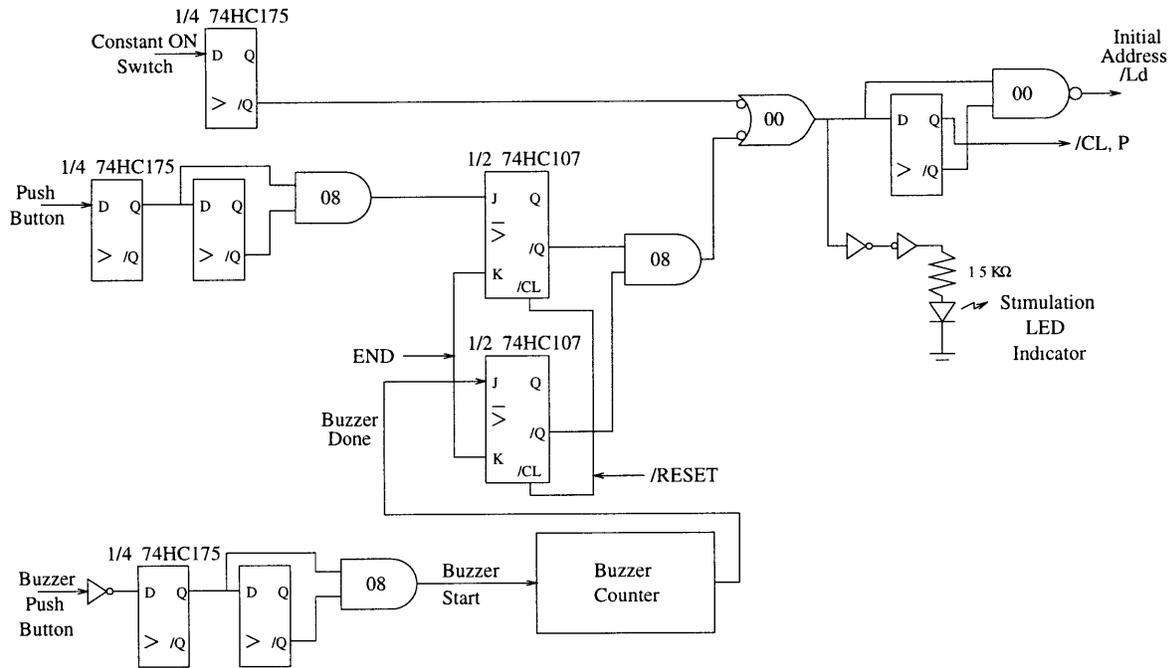
Figure 2-8: Startup Circuitry

This circuitry controls the startup of the stimulation control circuitry. A negative logic pulse is generated to set initial conditions of the address counter and the Waveform Number Counter, and to start the Waveform Period Counter and clear the Timing Gate flip flops. The more important output of this circuit is the $\overline{CL}$, P output, which enables and unclears nearly all counters and flip flops in the system.

2.2.8 Stimulation Buzzer Counter

This unit drives a buzzer circuit, described in Section 3.7, for exactly one second, then waits for one more second before passing the Buzzer Done signal to the Startup block, which will start (or not start, depending on the experiment) the stimulation.

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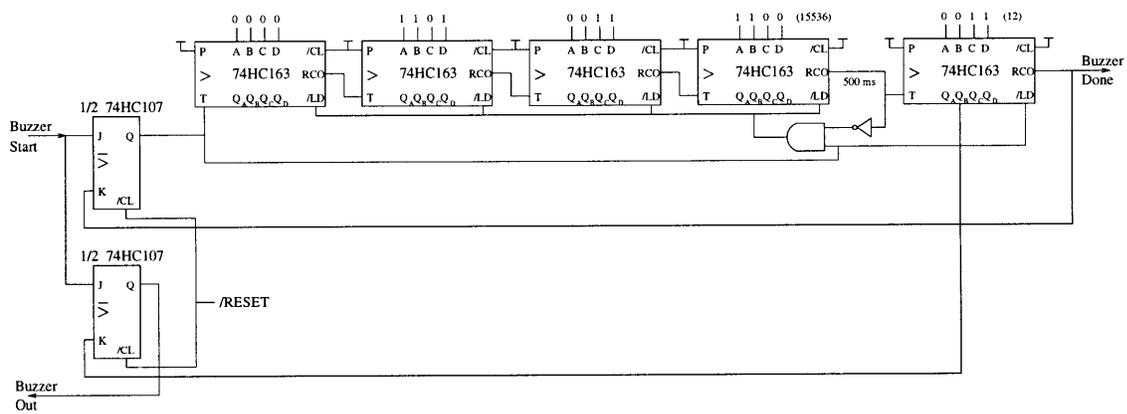
Figure 2-9: Buzzer Counter

This simple circuit serves primarily as a delay. The first four counters generate a slow clock with period $500ms$, while the last counter divides further by four, using Q_B to shut off Buzzer Out halfway through the delay.

Chapter 3

Analog Circuitry

Output pulses from the digital circuitry are shaped into the desired waveform, scaled, converted to a current drive, and distributed by the analog circuitry (Figure 3-1). All operational amplifiers used in the analog circuitry are LMC6582.
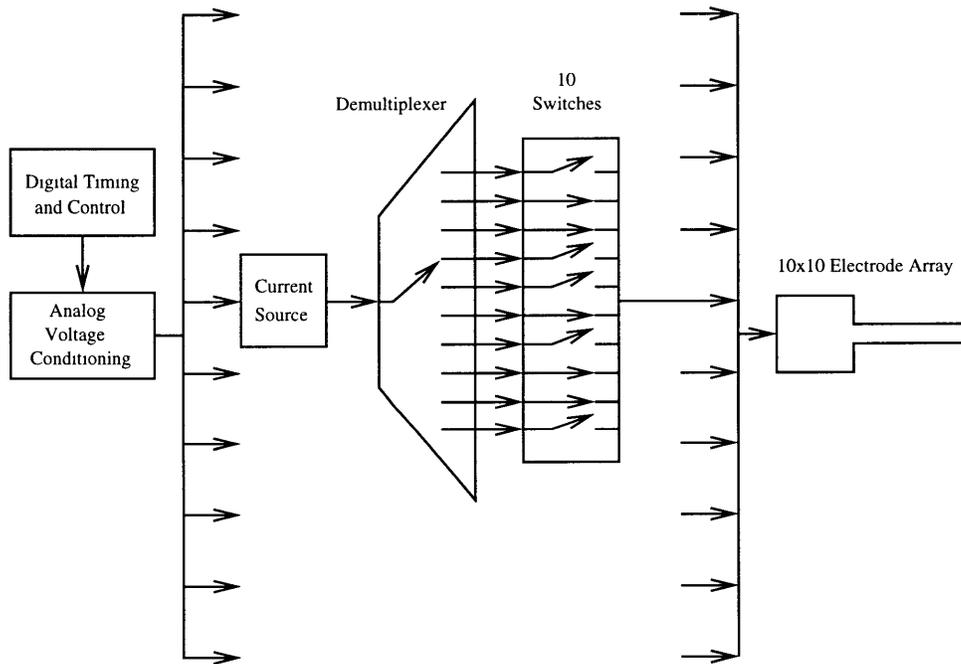
Figure 3-1: System Block Diagram
This block diagram shows the entire system, focusing on the role of the analog circuit to shape and distribute the stimulus current pulse. The current source, demultiplexer, and column of ten switches are each repeated ten times.

3.1 Voltage Conditioning and Control

The two pulses generated by the digital circuitry need to be scaled and added together after one has been inverted. This action is performed by the circuit in Figure 3-2. The pulses are first scaled for equal area, the narrow one to $4V$ and the wide one to $1V$. Depending on the desired polarity, one of the pulses is inverted by a unity gain inverting amplifier, then the two pulses are averaged by a pair of resistors. A potentiometer controls the amplitude of the pulses, and a non-inverting amplifier normalizes the voltage. An additional stage allows a slightly different voltage level to be delivered to the current sources driving odd-column electrodes, and this ratio is controlled by another potentiometer.
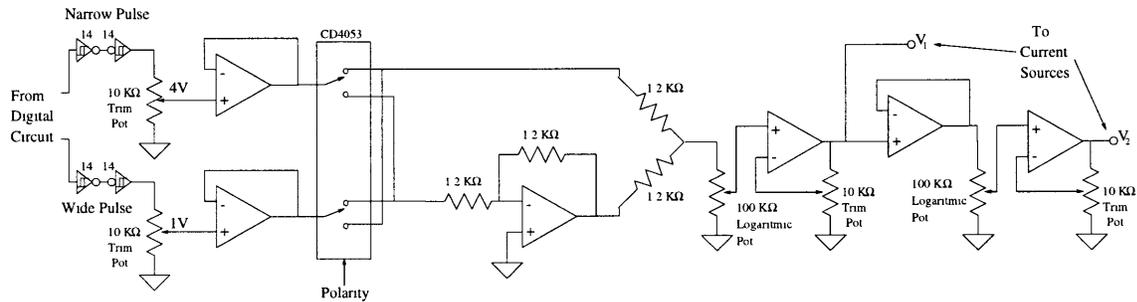
Figure 3-2: Waveform Voltage Conditioner

This circuit takes the narrow and wide pulses generated by the digital logic and forms them into the waveform of Figure 2-2 (b). The CD4053 is an electronic DPDT switch which changes the polarity of the waveform by changing which pulse is inverted. Output V_1 drives the current sources for even columns, and V_2 drives the current sources for the odd columns. The first non-inverting amplifier gives gain of 2.5 to normalize the maximum voltage to $5V$, while the second non-inverting amplifier gives gain of 4, to allow the odd-column current to be greater or less than the even column current.

3.2 Current Sources

As seen in Figure 3-1, the voltage waveforms drive ten current sources in parallel. The current sources must be capable of both positive and negative current, and having all current sources return to the same ground node simplifies analysis. The Howland

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current source was chosen for its simplicity (Figure 3-3). This one op amp circuit gives excellent performance in theory, but not in practice. High output impedance and stability depend on perfect resistor matching, and offset rejection is poor. However, this current source functioned well enough when properly tuned for stability and low offset current that it was used in the system. More complex current sources with lower offset current and higher output impedance are being designed for the revised system (Section 7.1).
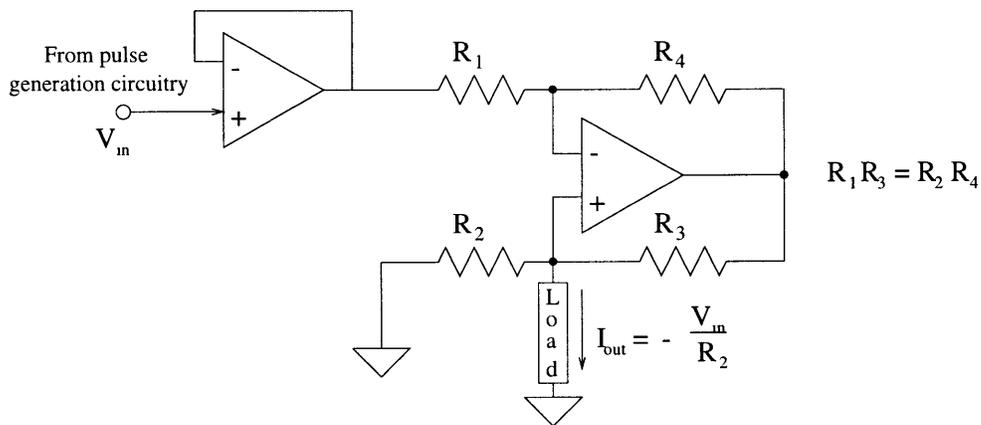
Figure 3-3: Howland Current Source
The Howland current source works by balancing positive and negative feedback. R_1 and R_2 were $47K\Omega$, and R_3 and R_4 were $2.5K\Omega$. So a 5 Volt input should be able to drive just over $100\mu A$ through the load.

3.3 Differential Measurement Amplifier

To measure the actual current out of the current sources, the voltage drop across a known resistor in series with the load was measured. A resistor large enough to give measurable voltages decreases the overhead voltage, or compliance voltage, of the current source. So a $5.1K\Omega$ resistor was used, and a differential amplifier was built to give a measurable voltage.

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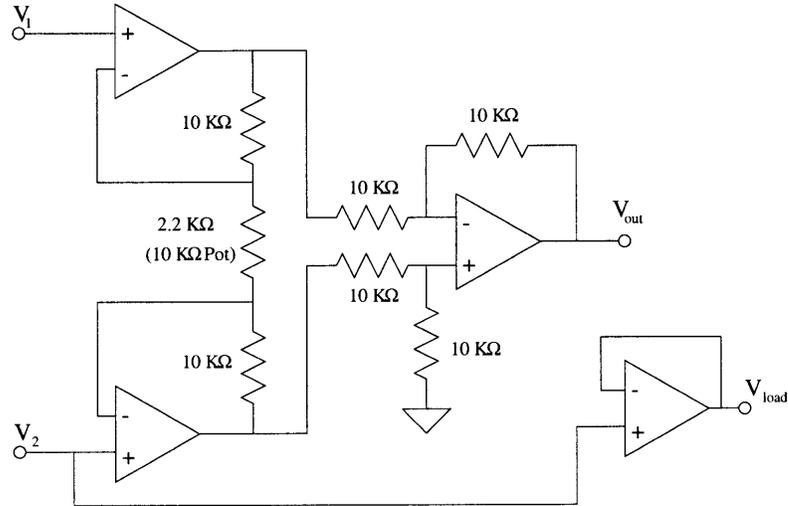
Figure 3-4: Differential Amplifier and Follower

This differential amplifier gives gain of ten, since $V_{out} = (V_1 - V_2)(1 - \frac{2*10K\Omega}{2.2K\Omega})$. It has a CMRR of $\frac{2*10K\Omega + 2.2K\Omega}{2.2K\Omega} = 10$. Since it represents the drop across a resistor, V_{out} can be read as a current of $20\frac{\mu A}{V}$. The extra follower gives buffered access to the voltage at the current source output.

3.4 Demultiplexers

The ADG406 is a 16:1 analog multiplexer with 80Ω on resistance. It is used here as a demultiplexer, distributing current from each source to ten electrodes in series. The addresses, provided by the digital circuit, pass through limiting resistors to prevent large DC current from reaching the electrodes in the case of multiplexer and blocking capacitor (see Section 3.6) failure.

3.5 Manual Switching Hardware

While the column switches (Figure 3-5), which shut off an entire column of electrodes and shunt the current through a $50K\Omega$ resistor, are fairly simple, the individual electrode switches are much more complicated than shown in Figure 3-5. They were designed to be used for electrode testing, and therefore have more than two positions. Double pole triple throw (DP3T) switches were implemented from three position quadruple pole double throw switches. These switches turned out to be quite useful

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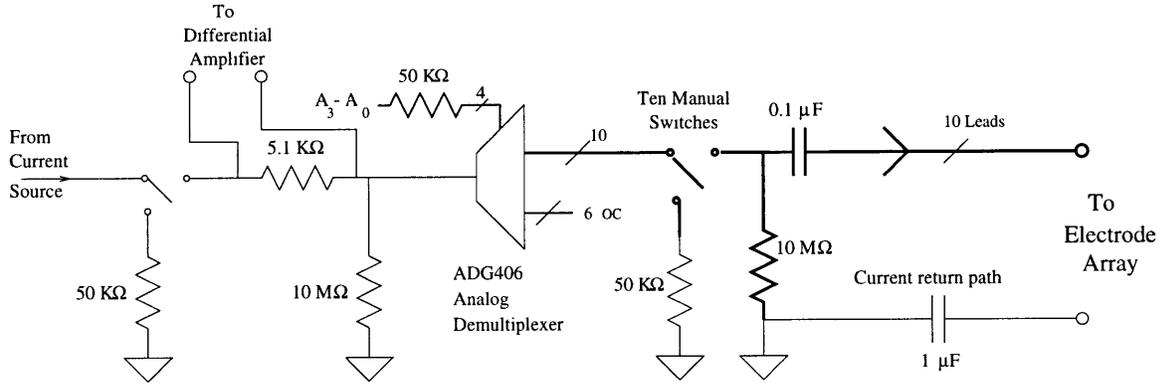
Figure 3-5: Analog Circuitry Downstream of Current Sources
The column switch at the left diverts current away from an entire column. The terminals of the $5.1K\Omega$ resistor go to the differential amplifier of Section 3.3. The $10M\Omega$ resistors serve as leakage resistors. The $50K\Omega$ on the addresses of the demultiplexer serve as limiting resistors in the case of component failure. The switches, described further in Section 3.5, turn on or off single electrodes, while the $0.1\mu F$ and $1\mu F$ capacitors block DC currents to the electrode array.

for bipolar stimulation across the array, driving through some electrodes and returning through others.

3.6 Blocking Capacitors

Capacitors were added in series with the patient to block any DC current. Capacitors were included both in the return path and at the output of the demultiplexer, reducing the probability of a DC path, even if one capacitor fails, which is unlikely. Polypropylene capacitors were chosen for their low leakage current. Capacitors of $0.1\mu F$ were used to allow a DC source to pass as little charge as possible, while giving relatively small back voltage when the maximum stimulus charged is used. The maximum stimulus charge is $100\mu A * 100\mu s = 10nC$, giving a back voltage of $V = \frac{Q}{C} = 100mV$. Since the return path receives current from ten electrodes in parallel, its blocking capacitor must be ten times as large to keep the same back voltage, so a $1\mu F$ capacitor was used.

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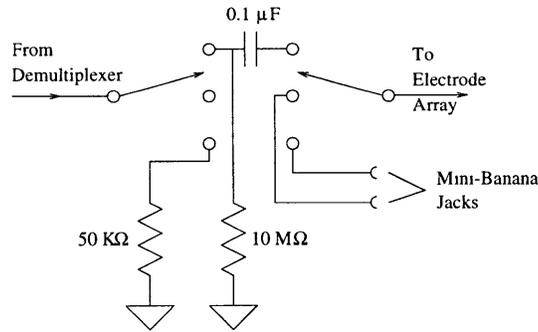
Figure 3-6: Double Pole Triple Throw Electrode Switch

This switch controls whether a single electrode is on, and is also used for testing the array for short circuits, and in distant bipolar stimulations. In standard use, the topmost position is on, with current passing through a blocking capacitor (Section 3.6), and the bottommost position is off, shunting the current through a resistor.

3.7 Buzzer Circuit

The buzzer circuit is a fairly simple relaxation oscillator with variable frequency and volume. For the human trial, the patient was allowed to manually set the frequency and volume to his preferred levels, since he had degenerative hearing loss which affected frequency range. The buzzer circuit drove a small set of battery powered amplified speakers.
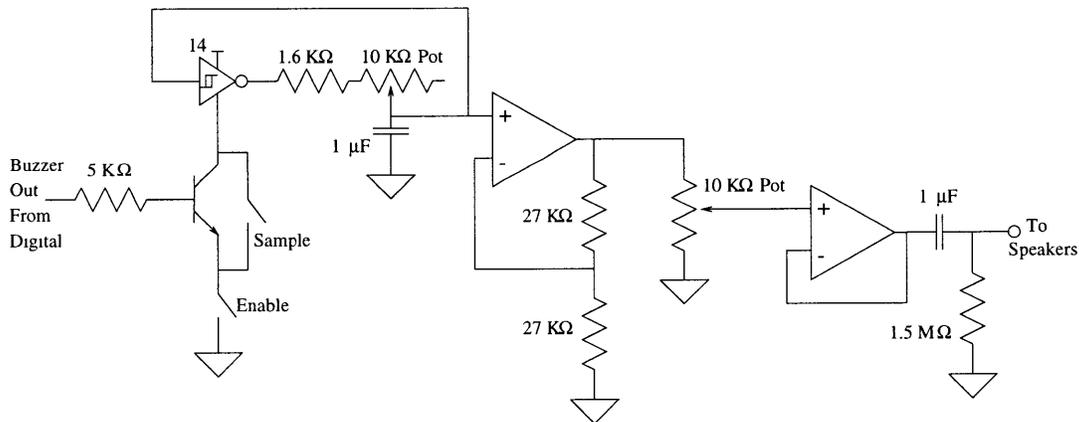
Figure 3-7: Buzzer Circuit

This circuit uses a Schmitt trigger inverter ring oscillator with a variable RC delay to produce oscillation.

3.8 Voltage Regulators

The entire circuit is powered by twelve D-cell batteries to avoid any contact with line power. Linear voltage regulators are used to provide stable supply voltages for the digital and analog circuitry from the ± 9 Volts of the batteries. An LM79L05 regulator provides -5 Volts for the analog circuit, and two LM78L05 regulators provide +5 Volts separately for the analog and digital circuits.

Chapter 4

User Interface

This chapter serves as the users' manual for the stimulation system. It describes setting up and using the system for electrode tests and retinal stimulation.

4.1 Connections

4.1.1 Electrode Array

The electrode array, described in Chapter 5, connects to a printed circuit board (PCB), which then connects via a 102-wire harness to the stimulation system. Mounting the polyimide array on the PCB is a challenging endeavor. The PCB must be clamped to the stage of a low-power microscope. 20x total magnification was typically used, though 10x would be ideal. The large, PCB-contact end of the array is not touched directly, but moved by electrostatic attraction to a piece of cellophane plastic, which is manipulated by hand. The very end of the array, reading THIS SIDE UP, should stick out a few mm from under the cellophane. The array is moved while viewed under the microscope until the contact pads of the array align with the raised gold contacts of the PCB. The array is then held in place with the cellophane plastic while two small slivers of scotch tape are used to hold the edge down to the PCB. The cellophane is then removed, and another one or two pieces of tape are added to hold down the other corners of the contact end of the array. When the array is aligned

with the PCB contacts, completely flat and free of wrinkles, and taped in place, the steel top plate is screwed down to the bottom plate, clamping the array in place.

The wire harness of the PCB terminates in two 50-pin connectors and one 9-pin connector. The 50-pin connectors are color-coded red and white, corresponding to the colors of the 50-jack connectors on the stimulator box. The 9-pin connector carries only the two return wires, and should be handled with care.

4.1.2 Grounds

The two return wires of the 9-jack connector are wired to the two black miniature banana plugs nearest the connector. These are the connections to the electrode array's return plane, and, for normal bipolar stimulation, must be connected to the circuit ground through the $1\mu F$ blocking capacitor. This is done with the black Y-connected miniature banana plug jumper, which should plug into the two return plugs and the capacitively coupled ground. The circuit ground plug is provided for oscilloscope reference.

Distant Bipolar To drive current through some electrodes and return through others, set the drive electrode switches to the up position, as usual, but set the return electrode switches to the center position. All unused electrodes should be set to the down position. Ensure that the array return plugs are open circuited, and jumper the plug labeled "Center" to the capacitively coupled ground.

Monopolar Ensuring that the array return plugs are open circuited, connect to the subject via a body lead. An EKG lead on the arm is used for human subjects; an ear lead is used for rabbits. This body return should be connected to the capacitively coupled ground.

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4.1.3 Buzzer

The buzzer DIN plug to the stimulator system plugs into the front right side of the box. The speaker audio plug connects to the buzzer audio jack.

4.1.4 Oscilloscope

The battery powered oscilloscope has custom-made connectors for the stimulation box, incorporating safety BNC connectors and shrouded banana plugs. For normal current and voltage measurement, the A and B inputs to the oscilloscope connect to the red and white current and voltage jacks on the box top. The ground references for these leads connect to the circuit ground in the same area of the box top. The external trigger input connects to the trigger jack on the upper center of the box front. This trigger input may need to be shielded in some environments, though this has not yet been necessary.

4.2 Front Panel Controls

4.2.1 Startup

The red Power switch is located at the lower left corner of the front panel. The white switch next to it is a digital reset switch, which resets in the down position. It should be switched up after the power is turned on, and can be reset at any time if the digital system ends up in an erroneous state.

The red switch in the lower right corner with the large red switch guard is the constant stimulation switch. When it is on, the system will stimulate forever at the prescribed frequency with no regard for the waveform number input. This is very useful for debugging and array testing, but should never be used in live experiments, hence the switch guard. The switch guard automatically shuts off the constant stimulation switch when it is closed.

For finite stimulations without the buzzer, a black push button and green enable switch are located above the constant stimulation switch in the lower right corner of the box front. Flipping the green switch up will enable the button, and pushing the button once will start the stimulation. The red LED in the upper right of the box front indicates that the system is stimulating.

For stimulations with the buzzer, the plug for the buzzer box is located just above the constant stimulation switch, and its three-way enable switch is located just above the plug. Moving the enable switch from left to center enables the buzzer alone, but will not stimulate. The far right position will enable both buzzer and stimulation.

Buzzer Control The separate buzzer box has its own red power switch and its own green push button enable switch. Stimulations with the buzzer sound are initiated by the push button on this box. The buzzer box must be plugged into the stimulation system box in order to create the buzz sound. To bypass this feature and sample the buzz sound without the stimulation box, move the white sample switch to the up position while the buzzer box is powered and enabled. While the volume and frequency dials on the buzzer box are self-explanatory, one other switch is not. The black switch to the right of the others controls whether the buzzer drives both speakers, or whether the buzzer drives one and the audio amplifier drives the other. The audio amplifier, whose design was postponed until after the first human trial, amplifies the voltage seen at an electrode and filters noise and hum in an attempt to hear nerves firing on the retina.

4.2.2   Current Control

There are two dials, located on the upper left of the box front, which control the current.

Current Amplitude The leftmost dial controls the current amplitude of the narrow pulse in the even columns. The amplitude of the wide pulse is automatically

one quarter of this value. The values on the label are approximate, and exact values should be measured with the oscilloscope.

Ratio Because of the difference in return size of the odd and even columns of the electrode array (Chapter 5), the ratio dial allows the currents in the odd columns with the smaller returns to be set to a ratio times the current in the even columns with larger returns. It is thought that even and odd columns may have different thresholds.

Patient-Controlled Current A small box, separated from the stimulator box by a seven foot cable, was constructed to allow the human subject to control the current level themselves. The box contained a potentiometer dial which could be switched in to replace the current amplitude dial on the box. The subject could then control the current, setting it to the perception threshold and then resetting it to a comfortable level. The wires for this box plug into the red and white miniature banana jacks on the front panel between the ratio potentiometer and the polarity switch. The ground wire plugs into the black ground jack below the current dials. When the red switch is moved to the up position, the patient's current dial is used; when down, the stimulator box current dial is used.

4.2.3 Wave Shape Control

Two inputs control the shape of the waveform. A black polarity switch, located in the upper center of the box front, determines which pulse is inverted by the circuit in Figure 3-2. It has been found in rabbits that driving the large narrow pulse to a negative current works best. The black sequence switch to the right of the polarity switch controls which pulse comes first. Typically the large narrow pulse comes first.

4.2.4 Stimulation Parameters

An experimental stimulation will include sets of ten rapid stimulations, one to each electrode of a column, repeated at a certain frequency, i.e. occurring once during a

preset period. This stimulation repeats for a preset number of times. These numbers are input in binary via DIP switches on the center of the front panel.

Waveform Period   The period, the top set of DIP switches, is a twelve bit input in units of $0.5ms$. The maximum period, then, is $2.0475s$. The minimum useful period is the total time for the ten rapid waveforms to complete, which is $5.4ms$.

Number of Waveforms   The number of waveforms is set by the bottom set of DIP switches. It is also a twelve bit binary number, and has a maximum value of 4095 stimulations.

4.3   Top Controls

4.3.1   Electrode Switches

The most striking feature on the top of the stimulator box is the array of 100 switches, with odd columns white and even columns green. The exact function of these switches is described in Section 3.5. The columns are numbered from one to ten from left to right, and the rows are numbered from one to ten from front to back. For stimulation, the switches should be positioned pointing toward the back of the box. When off, they should point toward the front of the box.

Column Switches   In front of each column of electrode switches is a red switch which will shut off the entire column when pointed down toward the front of the box.

Testing for Short Circuits   Short circuits in the electrode array are located by manipulating the switches while monitoring with the digital ohmmeter function of the batter powered oscilloscope.

1. The first test is to ensure that the two ground leads from the array are intact. Place the ohmmeter probes in the two black return jacks nearest the 9-pin return connector. A resistance of approximately $2K\Omega$ should be measured. If

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an open circuit is found, then at least one of the redundant returns is broken, and the array is not suitable for surgical trials.

2. The next step is to check for shorts to ground. Set all switches to the middle position, and monitor the resistance between the "Center" miniature banana jack and the two return jacks. If a short is found (typically $1K\Omega$ to $10K\Omega$), move the ohmmeter probe from the center to the down jack, and start flipping the electrode switches to the down position. If a short is found, flip that switch back to the center position and continue searching.

3. To check for short circuits among the electrodes themselves, set all switches to the center position, monitor the resistance across the center and down jacks, and flip switches down one at a time. A short found in this manner (Typically $1K\Omega$ to $12K\Omega$) is a short between the most recently flipped switch and all unflipped switches. Since short circuits typically occur between adjacent electrodes within a column, it should be relatively easy to isolate pairs (triplets, etc.) of shorts.

Testing for Open Circuits Open circuits are located by constant stimulation through an electrode array immersed in saline, with all electrode switches in the up position. For a moderate current of $20\mu A$, a total peak-to-peak back voltage of approximately 2 Volts is expected across each electrode. A voltage of over 9 Volts is indicative of a broken wire or a switch in the center position. A voltage of 3 to 7 Volts is an open circuit in the array. Care must be taken to distinguish true open circuits from air bubbles. The array may be gently brushed with forceps or squirted with a stream of saline to remove bubbles.

4.3.2 Rotary Measurement Switch

To facilitate examination of the ten different columns, a rotary switch is located in the front center of the box top. Its position determines which column is monitored from the red current and white voltage jacks to the right of the rotary switch.

4.3.3 Rotary Audio Amplifier Switch

An audio amplifier, to be built at a later time, will amplify and filter signals from electrodes into an audible sound of retinal ganglion cell action potentials. The rotary switch in the back right of the box top switches the output to its black miniature banana jack between the four corner electrodes. This feature may be used to determine which electrode is nearest the retina, giving feedback on the tilt of the electrode array.

Chapter 5

Electrode Arrays

Our electrode arrays were fabricated by Doug Shire, PhD, at the Cornell Nanofabrication Facility. The PCB connector was designed and built by Terry Herndon at the MIT Lincoln Laboratory with the assistance of Jim Howard.

5.1 Polyimide 10 x 10 Electrode Array

The retinal tissue is very thin and delicate, and is easily cut and detached. The electrode array, then, must be very thin and flexible so that it does not damage the retina. Electrodes can be microfabricated on polyimide to be thin enough and flexible enough to suit the needs of the project. The final electrode array design involves iridium on gold on chrome. The entire array is encapsulated in polyimide, with holes etched for the electrodes and returns (Figure 5-1). The returns are annuli surrounding the electrodes. Even column electrodes have a larger return annulus than odd column electrodes, to investigate which size yields lower thresholds. To aid in surgical maneuvering of the array, a gold weight with stiff posts was attached to the top side of the array.

Each electrode measures $40\mu m$ in diameter, and they are spaced $200\mu m$ center to center. The array of 100 electrodes, then, is slightly over $2mm$ x $2mm$. The contact pads on the other end are square, $750\mu m$ on a side, and spaced over $1.6mm$ center to

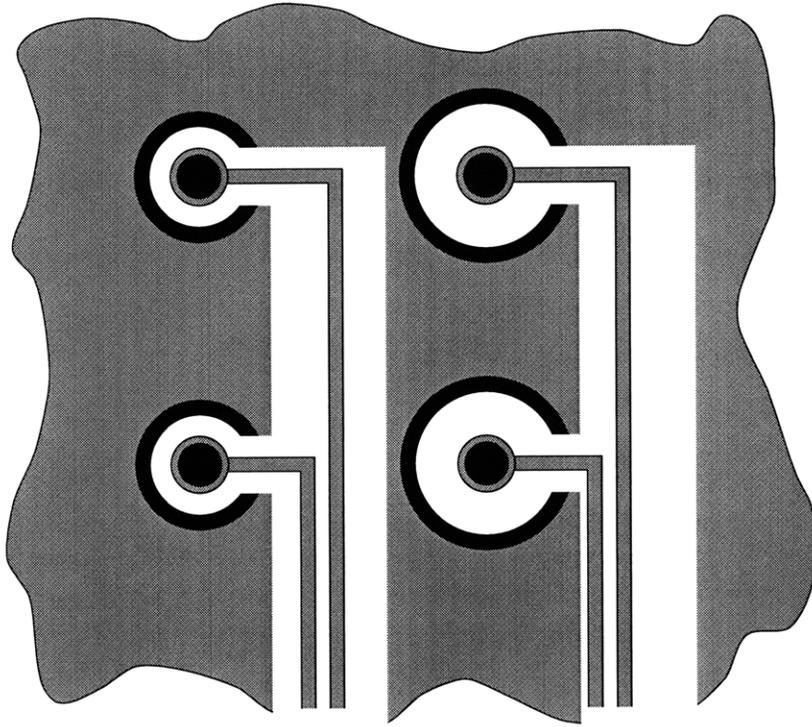center, giving plenty of room for error in contacting the PCB.

Figure 5-1: Section of Electrode Array
The darkest areas are metal exposed by etching away the polyimide. The gray areas are metal covered by polyimide, and the white areas have no metal. On the left are two representative electrodes from an odd column; on the right, from an even column.

5.1.1 Electrical Model

The interface between metal and tissue allows some charge flow at low frequencies via the redox reactions, but will also allow significant temporary charge buildup at higher frequencies, and can thus be modeled as a parallel RC circuit. There is also significant series resistance in the metal wires of the electrode array (Figure 5-2). For oxidized iridium, the series resistance is roughly $20K\Omega$, the capacitance is roughly $14nF$, and the parallel resistance is large enough that the RC time constant is on the order of, or slightly larger than, $400\mu s$, giving $R_{parallel}$ of between $25K\Omega$ and $50K\Omega$.
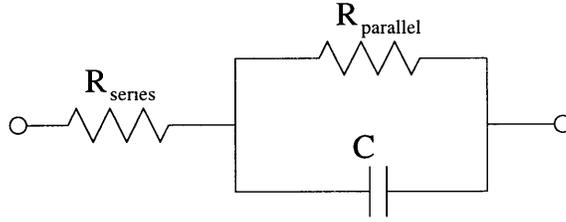
Figure 5-2: Electrical Model of Electrode

5.1.2 Metal Issues

A number of issues arise when electrical current is passed through a metal-tissue interface. Metals conduct current via free electrons, while electrolytes within tissue conduct via ions. The interface between the two is a redox reaction, often resulting in destructive oxidation of the metal and toxic oxides deposited in the tissue. Electrochemical studies have resulted in suggested safe charge density limits for various metals[1]. While platinum is commonly used, oxidized iridium is capable of far greater charge densities.[2, 4] Platinum arrays were used for some of the rabbit experiments, but iridium arrays were fabricated to replace them, and oxidized using a standard procedure described by Weiland[5]. Cyclic voltammetry was used to ensure that they were oxidized to the suggested limit of $30 \frac{mC}{cm^2}$.

5.2 Printed Circuit Board Connector

The printed circuit board (PCB) connector has an array of raised gold contacts on which the contact pad end of the electrode array is placed. Two $\frac{3}{4}$ inch by 2 inch steel plates clamp the array. A bundle of 102 wires extend from the back of the PCB, running seven feet and terminating in the plugs described in Section 4.1.

Chapter 6

Retinal Experiments

6.1 Rabbit Retinal Stimulation

On three occasions, electrode arrays were surgically placed on the retina of anesthetized rabbits for acute retinal stimulation experiments using the stimulator system. Cortical recordings of electrically evoked potentials were made from electrodes in the visual cortex. All four possible waveform shapes (varying polarity and sequence) were used, and it was found that having the large narrow pulse occurring first, and in the negative direction, yields the largest cortical responses (Figure 6-1).

The primary goals of the rabbit experiments with this system were to test the robustness of the system under surgical conditions and to try to achieve cortical responses to stimulation, both of which were achieved.

6.2 Human Trials

The entire reason for designing and building this stimulation system was for use in acute human retinal stimulation trials. The first of these trials has been performed, and more are expected to occur in the near future.

6.2.1 First Human Trial

The first human trial occurred on April 27, 1998 at the Massachusetts Eye and Ear Infirmary. The subject was a *Retinitis Pigmentosa* patient. The array was surgically inserted into the patient's right eye and placed very near the retina. The protocol involved stimulating with various patterns and asking the subject to describe what, if anything, he saw. At times the buzz sound was not followed by stimulation, thus providing an experimental control case. Stimulations were attempted at varying current levels up to the maximum output current of the system. The patient reported occasionally seeing brief flashes of light at moderate currents, but did not report more affirmatively at higher current levels. It was thought that a different area of retina might yield better results, but at that time surgical difficulties prevented moving the array. The experiment yielded some valuable insights into what parameters of the stimulation system may need to be changed for future experiments, namely the maximum current levels and the flexibility to set the duration of a single pulse.

6.2.2 Future Prospects

Some crucial changes to the stimulation system will be made before the next human experiment, and the computer controlled system will likely be used for later experiments (Section 7.1). One human trial is expected to occur during the summer of 1998, with several others to follow.
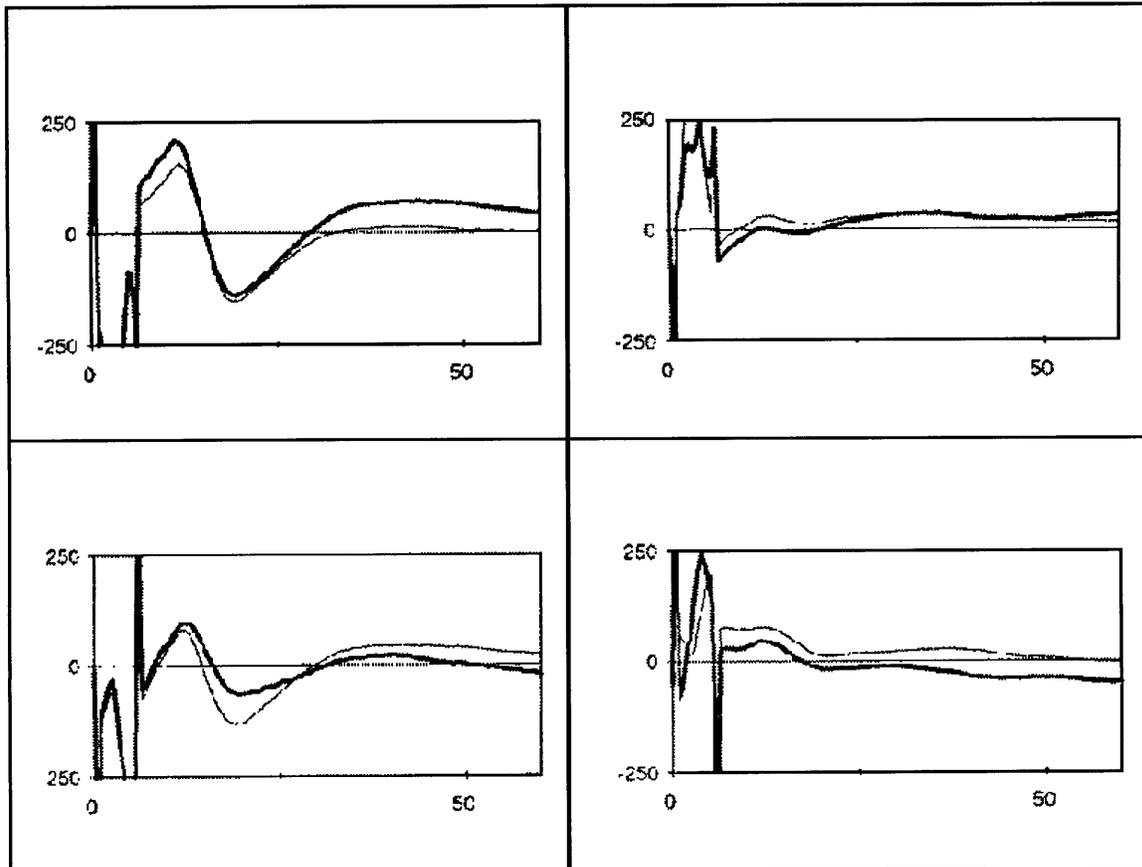
Figure 6-1: Rabbit Cortical Waveforms

These cortical waveforms are from rabbit retinal stimulations performed on February 17, 1998. Two stimulations were performed with each waveform shape. In the upper left, the large narrow pulse is negative, and occurs first. In the lower left, the large narrow pulse is negative and second. In the upper right, the large narrow pulse is positive and first; in the lower right, positive and second. The vertical axis units are μV; the horizontal axis units are ms. The first 5 or 6 ms of each waveform is stimulus artifact, and the cortical response occurs between about 8 and 25 ms.

Chapter 7

Conclusion and Future Work

The system designed and built during the course of this thesis functioned according to specifications, providing robust current source stimulation during rabbit and human experiments. The user interface is intuitive; the digital electronics, robust and flexible. The current sources functioned according to specification, and were sufficient to produce electrically evoked potentials in rabbit retina.

7.1 Changes to the Present System

The primary change to the present implementation will be current sources with higher output impedances and capable of delivering higher currents, supported with higher voltage sources. The new current sources will likely contain separate negative and positive sources, based on the source shown in Figure 7-1. If this current source drives a current mirror, the result is a source that returns to the circuit ground, allowing positive and negative sources to be connected in parallel.

7.2 Computer Controlled System

Brad Lichtenstein has been working to design and implement a computer system to take over the control of the current sources, allowing more timing and waveform flexibility, as well as a more intuitive graphical user interface. Timing information
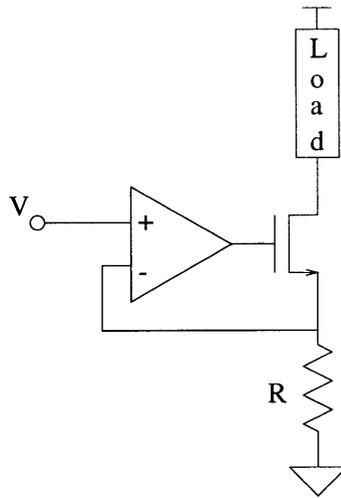
Figure 7-1: Basis for New Current Source Design

In this current source, $I_{Load} = \frac{V}{R}$, but the load is connected to the upper supply rail instead of ground.

and analog levels are output via an I/O board in the computer, and in the near future, current sources and the necessary digital control logic to interface the computer system will be designed and built.

7.3   IC Design

The more distant future holds the challenge of reducing all the function of the 12 x 12 x 6 inch, 20 pound stimulation box into one integrated circuit chip for long-term implantation on the retina. All power must come from outside the eye, and the visual information will likely come from a CCD camera. Several options have been considered, including transmitting all of the power and data via a laser through the lens to an array of photodiodes and transmitting via magnetic coupling, the latter seeming more promising. But that is the topic for a PhD thesis.

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