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A Programmable Ramp Waveform Generator for PEMF Exposure Studies on Chondrocytes

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Abstract - **Osteoarthritis is a debilitating joint disease where the surface of articular cartilage degrades and is unable to repair itself through natural processes. Controlling the migration of transplanted chondrocytes to the defective cartilage non-invasively could be a novel treatment for osteoarthritis. Our research group has performed an in-vitro investigation into the response of cultured human chondrocytes to pulsed electromagnetic fields (PEMF). Development of a treatment for osteoarthritis patients will require the use of a programmable waveform generator to generate the PEMF. This paper discusses the design and testing of a programmable ramp waveform generator for such purpose. When this ramp waveform generator is connected to the PEMF coil driver circuitry, it will be able to produce linearly ramping magnetic fields ranging in strength from 0.5mT to 4.5 mT. It also has an attainable pulse width ranging from 6ms to 100ms, with a selectable duty cycle from 1% to 99%.**

I. INTRODUCTION

Osteoarthritis is a debilitating joint disease where the surface of articular cartilage degrades and is unable to repair itself through natural processes. As a result, the bones rub against each other resulting in pain, swelling and loss of motion in the joint. Osteoarthritis affects 20 million people in the United States costing over $86.2 billion per year in health care [1]. Although there are treatments available to reduce the symptoms of osteoarthritis, there is no cure [2]

Chondrocytes are the cells that exist within the cartilage matrix that produce type II collagen and proteoglycans to help maintain cartilage structure. When cartilage is mechanically compressed, an electric field is induced across the tissue. These naturally occurring electric fields have been measured to be from 1V/cm to 15V/cm, depending upon physiological conditions [3].

PEMF therapy has been proposed to treat osteoarthritis. Clinical trials have been performed on patients with osteoarthritis using coil systems that induce an electric field in the body. These studies reported an improvement in knee pain, function, flexion and active daily living following treatments with PEMF [4]. However, no scientific explanation is provided for the reported change in symptoms.

Experiments using direct current (DC) electric field strengths ranging from 1V/cm to 15V/cm have demonstrated the migration of cultured chondrocytes, in vitro, towards the cathode of an electric field [3]. Cultured chondrocytes exposed to DC electric fields have also shown an increase in proteoglycan and type II collagen synthesis compared to non-exposed control cells [5].

Studies have also been performed exposing cells to static magnetic fields. Due to the diamagnetic properties of membrane phospholipids, there is a partial reorientation of molecular domains. This results in a deformation of the membrane and the functional impairment of ion channels. Studies using 6mT magnetic fields on a variety of cell types have demonstrated that the cells detached from the surface of the culture dishes. Exposure causes increased level of intracellular [Ca^{++}] and increased cell proliferation [6].

A variety of studies have been performed on cultured human chondrocyte cells using pulsed electromagnetic fields. In these studies, the strength of the magnetic field ranged from 1mT to 2.5mT, the frequency varied from 30Hz to 75Hz and the duty cycle was approximately 10%. These studies demonstrated that exposure to PEMF increases chondrocyte proliferation and proteoglycan synthesis [7],[8],[9].

Experiments from our laboratory have verified that pulsed electromagnetic fields can induce a shape change in cultured human chondrocytes [10]. The observed shape change is indicative of cell detachment. As a result there exists the potential to control cell movement since cells migrate by forming and releasing adhesion structures. Our goal is to treat osteoarthritis using pulsed electromagnetic fields to guide cultured human chondrocytes into the sites of degraded cartilage. With the assistance of PEMF therapy the chondrocytes would be able to regenerate cartilage tissue

This paper is focused on the design and testing of a device to generate a customizable ramp waveform. A ramp magnetic field is desired because it induces a DC electric field. Its waveform characteristics will be limited to those that affect chondrocyte behaviour. The output voltage from this instrument is converted to a current using a coil driver circuit, thereby producing PEMF in the Helmholtz coils. The motivation is to create an inexpensive, compact and programmable waveform generator for application of PEMF in a clinical setting.

II. MATERIALS AND METHODS

The generation of the PEMF signal requires three main modules: a programmable waveform generator, a coil driver circuitry and a pair of Helmholtz coils. A block diagram of this setup is shown in figure 1. This paper is focused on the design of the programmable waveform generator.

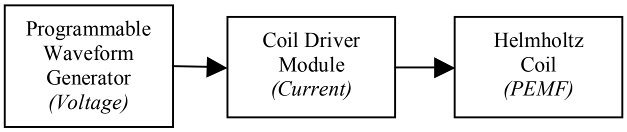

Figure 1: Block Diagram of PEMF Generation System

Helmholtz Coils

The portability is the major consideration during the design of the Helmholtz coils. Two sizes of the coils have been explored. The small coil has a radius of 4.25cm with 120 turns; the large coil has a radius of 6.5cm with 230 turns. The dimension of the coil wire is 22AWG. As shown in figure 2, the chondrocyte culture dish is placed at the midpoint of the Helmholtz coil.

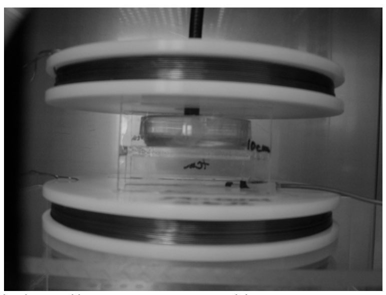

Figure 2: Helmholtz coil arrangement used in PEMF exposure experiments

Coil Driver Module

The major component of the coil driver circuit is a current operational amplifier which converts the voltage supplied by the programmable waveform generator into a current according to the equation.

$$I_{out} = 2.5 * V_{out} \qquad (1)$$

The output current produced by the coil driver circuit, is delivered into the Helmholtz coils to produce the electromagnetic field. According to the Biot-Savart law, the magnetic field produced at the center of a Helmholtz coil is:

$$B = \frac{\mu I N}{R} \qquad (2)$$

Programmable Waveform Generator

The programmable waveform generator consists of three main modules: microcontroller, USB interface, and integration circuit. A block diagram of the system is shown in figure 3.

The programmable waveform generator when connected to the coil driver module can produce a PEMF signal with configurable magnetic field intensity, pulse width and duty cycle. The instrument is designed to produce a voltage ramp signal which can generate a magnetic field intensity ranging from 0.5mT to 4.5mT, a pulse width ranging from 6ms to 100ms, with a selectable duty cycle from 1% to 99%.

A. Microcontroller

The microcontroller chosen to control the programmable waveform generator was the Atmel ATMEGA 168. This microcontroller can function from a power supply of 5V. It features both SPI and serial communication ports for interaction with external hardware. This microcontroller contains 512 Bytes EEPROM and 16 Kbytes flash program memory that can be configured using the C-programming language. The 16-bit onboard timer regulates the shape of the resulting waveform. With these features, the microcontroller is capable of regulating all aspects of the programmable waveform generator.

The flexibility of the design allows the user to specify the coil size to be used, as well as the magnetic field strength, pulse width and duty cycle of the PEMF signal. This PEMF configuration is stored in the EEPROM memory. When using the small coil, the allowed magnetic field strength is from 0.5mT to 3.5mT. When using the large coil, the allowed magnetic field strength is from 2.0mT to 4.5mT. The magnetic field strength is selectable in 0.5mT increments. The pulse width of the PEMF signal can be specified by inputting an integer value between 6ms and 100ms. Similarly the duty cycle is specified by inputting an integer value between 1% and 99%.

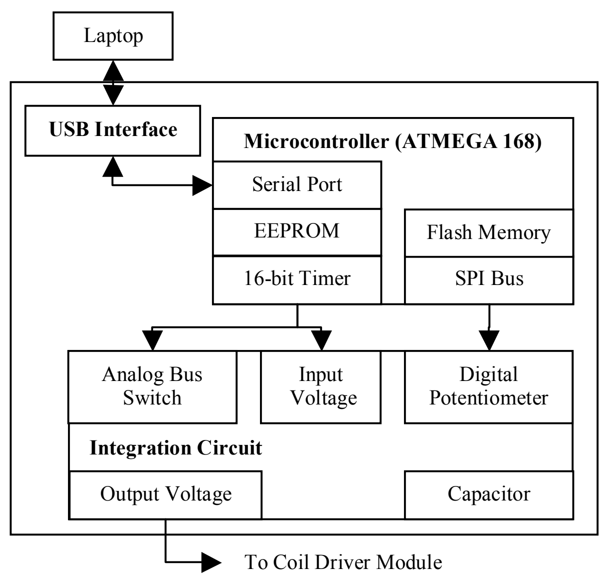

Figure 3: Block Diagram of Programmable Waveform Generator

B. USB Interface

A USB interface was chosen because it is a common interface with computers, readily available in laptop use. This interface uses a chip (FT232EM) to convert the laptop USB port information to serial port information for communication with the microcontroller. Using C-programming, an easy to understand menu system was established. This interface allows the user to program the desired PEMF characteristics into the ramp waveform generator, using appropriate input from the laptop keyboard. An example of this user interface is shown in figure 4 with the current configuration settings for the PEMF waveform generator.

Settings:
Magnetic Field = 2.0 mT
Pulse Width = 50 ms
Duty Cycle = 50%
Coil Size = Small (radius = 4.25cm)

Do you want to change your settings? (y/n)

Figure 4: User Terminal Interface

C. Integration Circuit

The integration circuit consists of four main components: a digital potentiometer, an analog bus switch, a capacitor and an input voltage. The relationship for the integrator circuit is given as:

$$V_{out}(t) = \int_0^t \frac{-(V_{in} - V_{ref})}{RC} + V_{out}(0) \qquad (3)$$

The output voltage, V_{out}, from the integrator circuit serves as the input to the coil driver circuit for the generation of the electromagnetic fields.

Since the programmable waveform generator is powered from a single rail +5V power supply, a biased reference voltage must be introduced to the integration circuit. The microcontroller provides an input voltage, V_{in}, to the integration circuit. V_{in} is zero during integration and is V_{ref} during reset. As a result, the integration circuit creates a positive ramp waveform.

A 100KΩ digital potentiometer (MCP41100) is used to regulate the slope of the output ramp signal. The slope of the output ramp signal is dependant upon the desired pulse width and magnetic field settings. The minimum and maximum pulse width, for a given magnetic field setting, is bounded by the resolution of the digital potentiometer and the maximum resistance respectively.

The choice of capacitor for the integration circuit also affects the slope of the output ramp signal. The use of a 1μF capacitor allowed the circuit to generate pulse widths ranging from 6ms to 100ms when configured for a magnetic field between 0.5mT and 4.5mT. A small capacitor is desired for use in the integrator circuit since it allows for a short discharge time during the reset period.

The integration circuit requires a reset mechanism to initiate the start of another ramp waveform. This design uses an analog bus switch, NC7SZ66 (Fairchild Semiconductor), placed in parallel with the integrating capacitor. When the bus switch is turned off, the integration circuit produces a positive ramp waveform. When the bus switch is turned on, a short circuit is created across the integrating capacitor, causing a discharge to the reference voltage. This configuration allows the resulting ramp waveform to have a sharp reset characteristic.

D. Programming the Microcontroller

The microcontroller is programmed using the C-programming language. This provides the microcontroller with the capability to use the specified parameters of the PEMF signal to configure the other components of the programmable waveform generator.

Using the pulse width and magnetic field obtained from the configuration settings, the microcontroller must configure a setting for the digital potentiometer according to equation 3. The values for capacitance and V_{ref} are stored in the onboard EEPROM memory. The optimal resistance value is matched to the nearest resistance that can be established by the digital potentiometer. Using the SPI bus, the microcontroller can program this value into the resistor.

Since the digital resistor only has 256 taps, the implemented resistance will likely be different than that obtained by the above equation. This error is accounted for by calculating a new pulse width value corresponding to the implemented resistor setting.

The microcontroller has an onboard 16-bit timer that features a fast pulse width modulation compare output mode. This allows for the configuration of both the pulse width and duty cycle of the PEMF waveform with the use of two registers. The first register corresponds to the time period, t_{on}, when the integration circuit is activated; it is implemented as the adjusted pulse width from the digital potentiometer calculation. The second register corresponds to the period, t_{max}, of an entire waveform. It is the value t_{on} multiplied by the duty cycle. During the time period from t_{on} to t_{max} the integration circuit is reset. The 16-bit timer utilizes these two registers to set flags, within the microcontroller. The microcontroller polls these flags to regulate the activity of two I/O pins controlling the integration circuit. One of these pins provides the voltage, V_{in}, to the integration circuit, and the other pin controls the activation of the analog bus switch for the integrator reset.

Using the properly configured integration circuit, the waveform generator creates the ramp voltage signal indefinitely until the device is turned off. If power to the device is reset, the program initiates by asking the user to confirm its PEMF configuration settings.

III. TESTING & RESULTS

The programmable waveform generator was tested in two steps. First, the functionality of the timer circuitry was verified. Second, the functionality of the integration circuitry was verified.

Testing of the timer circuitry was executed by using an oscilloscope to measure the voltages on the two microprocessor pins controlled by the 16-bit timer module. A resulting waveform of these two voltages is shown in figure 5. The top waveform shows the voltage that controls the analog bus switch and the bottom waveform shows the input voltage, $V_{in,}$ to the integration circuit. This waveform was captured for a pulse width of 10ms and a duty cycle of 25%. Various settings of pulse width and duty cycle were configured into the device during the testing procedure. A subset of these tested values is recorded in table 1. Table 1 also specifies the recalculated pulse width due to the resolution of the digital potentiometer. Testing proved that the measured values matched the expected values for the pulse width and duty cycle of the timer circuitry.

Case	Pulse Width (ms)	Duty Cycle (%)	Recalculated Pulse Width (ms)	Measured Pulse Width (ms)
1	20.0	50	19.8	19.7
2	10.0	25	9.7	9.7
3	10.0	99	9.7	9.7

Table 1: Timer Circuit Functionality Tests

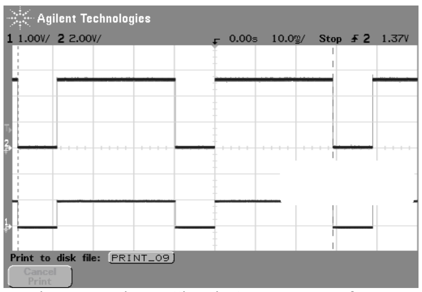

Figure 5: Timer Circuit Output Waveforms

The functionality of the integration circuitry was verified using an oscilloscope to measure the output voltage from the programmable waveform generator.

Several trials were used to test the ramping capability of the device. Initially, a 1μF capacitor, V_{ref} = 2.5V, pulse width of 20ms and duty cycle of 25% were used as parameters for the integration circuit. The desired magnetic field setting was varied for each trial, hence causing a different output voltage. A comparison of the expected and measured voltages from these tests is summarized in table 2.

Case	Expected Output Voltage (mV)	Obtained Output Voltage (mV)	Error (%)
1	207	210	1.45
2	542	543	0.18
3	813	812	0.12

Table 2: Integration Circuit Functionality Tests

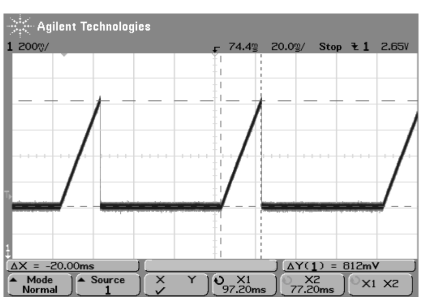

Figure 6: Output Voltage Ramp Waveform

Additional tests were performed with the capacitor changed to 2.2μF. Compared to using a 1μF capacitor, the linear profile of the ramp degraded. The maximum error of the waveform generator increased from approximately 2% to 13%. Figure 6 shows the high linearity of the ramp waveform obtained when using a capacitance of 1μF.

Unfortunately, using a V_{ref} = 2.5V, for the integration circuit yields the incorrect pulse width requirements for the device. The optimal circuit conditions utilize a capacitance of 1μF for the best linear ramp response, and a V_{ref} = 0.5V to center the operation of the programmable waveform generator in the pulse width range of 6ms to 100ms.

IV. CONCLUSION

A programmable ramp waveform generator was designed and tested. The device can produce linearly ramping magnetic fields ranging in strength from 0.5mT to 4.5mT, with a pulse width ranging from 6ms to 100ms and a duty cycle from 1% to 99%. Using a USB connection with a computer, the user can interact with the waveform generator to configure the desired PEMF settings. The availability of a low cost, portable user programmable ramp-waveform generator is important to the advancement of these studies investigating the effects of PEMF on chondrocyte cells.

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REFERENCES

[1] Press Release. Arthritis Foundation – The facts about arthritis, 2005.
[2] Press Release. Arthritis Society - Osteoarthritis – Quick Fact Sheet, 2005.
[3] P. G. H. Chao, R. Roy, R. Mauck, W. Liu, W. B. Valhmu, C. T. Hung, "Chondrocyte Translocation Response to Direct Current Electric Fields," *Journal of Biomechanical Engineering*, vol. 122, pp. 261-67, 2000.
[4] D. H. Trock, A. J. Bollet, R. Markoll, "The Effect of PEMF in the Treatment of OA of the Knee and Cervical Spine. Report of Randomized, Double Blind, Placebo Controlled Trials," *Journal of Rheumatology*, vol. 21, pp. 1903-11, 1994.
[5] W. Wang, Z. Wang, G. Zhang, C. C. Clark, C. T. Brighton, "Up-regulation of Chondrocyte Matrix Genes and Products by Electric Fields," *Clinical Orthopaedics & Related Research*, vol. 427S, pp. 163-73, 2004.
[6] A. Chionna, B. Tenuzzo, E. Panzarini, M.B. Dwikat, L. Abbro, L Dini, "Time Dependent Modifications of Hep G2 Cells During Exposure to Static Magnetic Fields", *Bioelectromagnetics*, vol. 26, pp. 275-286, 2005.
[7] F. Pezzetti, M. De Mattei, A. Caruso, R. Cadossi, P. Zucchini, F. Carinci, G. C. Traina, V. Sollazzo, "Effects of Pulsed Electromagnetic Fields on Human Chondrocytes: An In Vitro Study," *Calcified Tissue International*, vol. 65, pp. 396-401, 1999.
[8] A. Fioravanti, F. Nerucci, G. Collodel, R. Markoll, R. Marcolongo, "Biochemical and morphological study of human articular chondrocytes cultivated in the presence of pulsed signal therapy", *Ann Rheum Dis*, vol. 61, pp. 1032-1033, 2002.
[9] M.D. Mattei, A. Pellati, M. Pasello, A. Ongaro, S. Setti, L Massari, D. Gemmati, A. Caruso, "Effects of physical stimulation with electromagnetic field and insulin growth factor-I treatment on proteoglycan synthesis of bovine articular cartilage", *Osteoarthritis and Cartilage,* vol. 12, pp. 793-800, 2004.
[10] Jahns M, Lou E, Durdle N, Bagnall K, Raso V, D. Cinats, J. Cinats, N. Jomha, Kwok D: The Effect of Pulsed Electromagnetic Fields on Chondrocytes, *Proceeding of 6th Alberta Biomedical Engineering Conference*, p.36, 2005.