NCBI Bookshelf. A service of the National Library of Medicine, National Institutes of Health.

Nicolelis MAL, editor. Methods for Neural Ensemble Recordings. 2nd edition. Boca Raton (FL): CRC Press/Taylor & Francis; 2008.

Chapter 3 Technology for Multielectrode MicroStimulation of Brain Tissue

Timothy Hanson, Nathan Fitzsimmons, and Joseph E. O'Doherty.

HISTORICAL HIGHLIGHTS OF BRAIN STIMULATION

From early arguments between Galvani and Volta in the late 1700s, to later experiments by Helmholtz in the mid-1800s, the scientific examination of the electrical excitability of biological tissues has a rich history (Galvani, 1791; Volta, 1800; Helmholtz, 1842; Hess, 1994), particularly regarding the use of electrical stimulation to induce focused cortical activation, which enabled the discovery of motor maps in different locations of the cortex. This tradition started in the late 19th century when German neuroscientists Fritsch and Hitzig used electrical stimulation in animals to generate crude motor cortex maps, demonstrating contralateral activation of muscles for the first time (Fritsch and Hitzig, 1870). Sir Charles Sherrington, one of the founders of modern neuroscience, later used more focused stimulation to form early maps of ape motor cortex (Brown and Sherrington, 1911). In the 1930s, Wilder Penfield, one of Sherrington's students extended this work to human motor cortex, as he showed the existence of a spatial map of muscles in the body (Penfield and Boldrey, 1937). His rigorous examination demonstrated that the size of a body part's cortical representation is proportional to the fine nature of that body part's movements. Penfield's work helped popularize the technique of electrical stimulation as a useful tool for extending understanding of the brain (Penfield and Rasmussen, 1950).

During the 1960s, Robert Doty performed a series of experiments that explored cortical stimulation of awake, behaving animals in a behavioral context. By stimulating a variety of cortical areas, Doty was able to operantly condition animals, using the microstimulation pulses as the conditioned stimulus, to perform limb flexion movements. This extraordinary body of work provided one of the earliest demonstrations that microstimulation might be used to inject information into the brain (Doty, 1965; Doty, 1969; Doty et al., 1956).

In the early 1990s, Newsome and colleagues at Stanford University demonstrated some of the earliest examples of perceptual biasing using cortical microstimulation. Working with directionally selective neurons in the visual area MT, the researchers used microstimulation to modify neuronal firing rates, thus biasing psychophysical performance on a motion direction discrimination task. This not only exhibited a direct link between physiological properties and perception, but proved the usefulness of microstimulation current pulses as a means to affect perceptual judgments (Salzman et al., 1990; Salzman et al., 1992; Murasugi et al., 1993).

More recently, Ranulfo Romo and his colleagues successfully demonstrated that cortical microstimulation in monkeys could mimic the sensory perception of flutter in these animals. Using macaque monkeys, they examined neurons in area 3b of primary somatosensory cortex that were presumed to be associated with Meissner's corpuscles—neurons with responses that vary with tactile flutter frequency. After inserting microelectrodes near such neurons, a train of current pulses was delivered to the cortical tissue, and effectively substituting for the peripheral tactile stimulation the animal was trained to recognize. The monkeys then performed a frequency comparison task between peripheral and cortical stimulation. Performance on frequency comparisons between artificial (microstimulation) and natural (peripheral vibration) stimuli were indistinguishable from comparisons between two natural stimuli. Not only did this study help identify the specific nature of some of the cortical circuits in area 3b of the primary somatosensory cortex, but it served as a proof of concept for the idea that peripherally provided tactile information could be mimicked through direct cortical stimulation (de Lafuente and Romo, 2005; Romo et al., 2000; Romo et al., 1998).

Recently, Graziano and colleagues used cortical microstimulation to augment our understanding of the organization of motor and premotor cortices by repeating classical mapping studies with a minor, yet ultimately important alteration. Rather than using the short durations (~50 ms) from previous stimulation studies, the researchers used longer durations (~500 ms), more in line with the actual duration of a typical monkey reach motion. These researchers observed that longer stimulations produced complex motions and postures, as opposed to the simple twitching elicited

by short stimulations. The movements observed varied from stimulated area to area, and often the response coordinated disparate areas of the body, i.e., arms and mouth. In each of these stimulated movements, the initial position of the related body parts had no effect on the position moved to when stimulated, that is to say that stimulation was associated with a specific position rather than direction. Their results show that these motor areas do not have a sort of homunculus-type mapping, but rather have elements of a body-centered spatial map (Graziano et al., 2002).

Also in 2002, John Chapin and his fellow researchers at the State University of New York (SUNY–Downstate) successfully trained rats to navigate through a complex, three-dimensional terrain, following control cues delivered by cortical microstimulation. Microelectrodes were implanted in somatosensory cortical whisker representation areas to deliver left or right directional cues, and electrodes implanted in the medial forebrain bundle were used to deliver rewarding stimuli. Furthermore, the rewarding stimuli had the effect of urging the animal on, acting as a functional "forward" cue. In this way, the researchers were able to guide the rats' movements to overcome a myriad of obstacles that would not typically be explored by rats. By using cortical microstimulation for a sequence of cues and rewards, Chapin and his colleagues have hinted at the potential bandwidth of microstimulation-based information delivery (Talwar et al., 2002).

In fact, findings such as these helped lay the groundwork for feedback in the field of neural prosthetics. Future neuroprosthetics will not only need to decode and process the neural code, but also provide the somatosensory and proprioceptive inputs back into the system that our biological limbs naturally produce. The potential here for neural prosthetics is strong, offering an interesting hope for a streamlined decoding solution.

Although much progress has been made towards an understanding of how microstimulation interacts with the brain and how it can be used for functional purposes, there is still much more to be learned. Importantly, we must probe the limits of this technique, determining just what kinds of signals it can be used to deliver. For example, to deliver the breadth of information that we typically receive from one of our own limbs, stimulation bandwidth will have to be expanded significantly. Experiments designed to elucidate some of these issues have been undertaken in the Nicolelis Lab at Duke University (Fitzsimmons et al., 2007). Owl monkeys in a two-choice task have shown long-term performance stability in a variety of stimulation discriminations, including amplitude, temporal, and spatiotemporal characteristics (Figure 3.1).

PRINCIPLES OF CORTICAL MICROSTIMULATION

The means by which neurons can be stimulated is heavily reliant on the same component of the cell that allows action potentials to propagate along the length of an axon: the cell membrane. In typical physiological conditions, voltage-gated sodium channels in the membrane initiate the action potential and sustain it as it propagates by allowing an influx of positive ions when triggered by an incoming pulse in voltage. During extracellular electrical stimulation, current pulses are delivered via electrodes placed near the tissue of interest. The injected current can depolarize (or hyperpolarize) the membrane, opening (or closing) voltage-gated ion channels, thus rendering the cell more (or less) excitable.

When electrodes are used for stimulation in the cortex, typically the number of neurons excited is large, as affecting a single neuron is often not enough for a behavioral response. Ideally, we would like to know the precise nature of what cells are activated by a given stimulus, however, there are a number of spatial effects, which prevent a complete understanding of stimulus effects. First and foremost, the brain is neither an isotropic nor a homogenous medium. The resistance of the brain to the spread of current depends on several factors including temperature and the material properties of the tissue in that region (gray matter, white matter, CSF, etc.). Furthermore, the local characteristics of the tissue being stimulated also have significant effects. For instance, axon diameter, whether or not the axon is myelinated, axon orientation with respect to the electrodes, and whether the soma or axon is closest to the site of stimulation all affect the excitability of a given neuron. However, with increasing stimulation strength, many of these effects are averaged out, and the area of stimulation approximates a sphere in most cortical regions.

Typically, stimulation is accomplished using microelectrodes of various materials including stainless steel, platinum,

platinum-iridium, and tungsten. Electrodes can be coated with a variety of compounds, which serves not only to insulate, but also to increase biological compatibility. It is important, especially in the case of chronic electrode implantation, that the brain's injury and immune responses to the electrodes are minimized. A strong injury response can lead to encapsulation, and furthermore to a loss in the electrodes effectiveness for both measurement and stimulation.

Ideally, the interface between the uninsulated metal tips of these microelectrodes and the tissue of the brain they are placed in approximates a Helmholtz double-layer capacitor, drawing excess charge in the electrolytic medium to the surface of a layer of water along the electrode. Typically, stimulation electrodes are used in pairs, producing changes in extracellular voltage as current on the order of 10–100 μA is passed between them through the brain. There are two primary types of stimulators in-use for cortical microstimulation: constant-current stimulators and constant-voltage stimulators. Given that stimulation occurs at each neuron as a reaction to changes in extracellular voltage, it might seem that constant-voltage stimulators should be better suited, however, the aforementioned capacitive relationship of the electrode–tissue interaction means that extracellular voltage is actually a function of the electrode current. If a constant-voltage stimulator is used, the fluctuations in resistance due to local variations in brain composition can have large effects on the actual current, which passes through the electrodes, making the true nature of the stimulation hard to predict.

The stimulus waveform used in stimulation is also an important consideration. For extracellular stimulation, a quick (10 s to 100 s of μs) rectangular cathodic (negative) current pulse is considered most effective at eliciting neuronal action potentials because it quickly depolarizes cells to threshold before any significant channel inactivation can occur, thus minimizing the necessary charge injection. However, monophasic-stimulation pulses, when repeated, can result in charge buildup at the electrode or tissue interface, leading to electrode corrosion, tissue damage, and eventually lesions. As a result, most stimulators operate in a charge-balanced biphasic stimulation mode, where a square cathodic pulse is followed by an equal-sized anodic pulse. Although the second pulse can actually impair the ability of the stimulation to cause excitation, the prevention of damage to the electrode and surrounding tissue is a necessary step for most sorts of stimulation.

While charged-balanced biphasic current pulses offer an effective, damage-minimizing means for electrical stimulation, there is certainly room for improvement. For instance, there is some evidence that slightly imbalanced pulses actually minimize damage over the long term. Given that chronic, long-term usage of electrodes for microstimulation will be needed to provide feedback for such devices as neural prosthetics, new ways to minimize damage or increase stimulation efficiency are important avenues of future stimulation research.

DESIGN CONSIDERATIONS

As mentioned above, stimulators are primarily regulated in terms of either current or voltage, and limited in terms of the complementary voltage or current. Much like for recording, the range of stimulator regulation and the parameters of its limits are dictated by the size and impedance of the electrodes to be used, the size and nature of the area to be stimulated, the desired complexity of the stimulation, and power or channel requirements. Each of these is determined by the intended application of electrical stimulation. There are many, including: functional electrical stimulation (FES) for control of muscles in paralyzed patients; stimulation of the spinal cord for similar muscle control, deep-brain stimulation (DBS) for treatment of the symptoms of Parkinson's disease, such as akinesia and tremor; abatement of chronic pain; and sensory prosthetics such as cochlear implants. Applications that use large electrodes, like DBS and FES, employ higher current levels, (1–40 mA), whereas cortical electrodes, typically smaller, therefore have higher impedances and need lower currents.

HARDWARE IMPLEMENTATION

In this section we focus on intracortical microstimulation (ICMS) applications, where electrode impedances range from 0.5–2 MΩ and effective stimulation currents are between 40–180 μA. The high impedance of the electrodes necessitates relatively high voltages, typically 50–100 V in many systems, though care must be taken not to exceed the often-low breakdown voltage of the thin insulation on microwires. In ICMS, current is usually delivered in 100 μs

cathodic-first charge balanced biphasic pulses at a frequency of one to several hundred hertz. The required current, voltage, and speed are not difficult to achieve with modern electronic systems, and many commercial off-the-shelf product can satisfy the conditions. However, the other requirements of a laboratory or clinical system—such as size (as in subcutaneous FES), power (as in DBS, where the stimulator is powered by an implanted battery), complexity of stimulation train, and number of electrodes—enforce more rigorous requirements on stimulation technology. For experimental ICMS, the latter two requirements are pivotal, a design that satisfies these and allows dense-multichannel stimulation is outlined below.

We have investigated two methods of sequencing control in microstimulation: one that is based on a program running on a desktop computer, and a second that uses an embedded microprocessor. In the former, a general-purpose program controls the isolation hardware through one or more National Instruments data acquisition (DAQ) cards (see Figure 3.2). The program updates the DAQ buffers every 100 μs; within this interval, the program can specify stimulation activity based on pulse, time, or channel frequency, which in turn are generated autonomously or as a consequence of recorded neural activity or behavioral events. Four or eight stimulus isolation units are assembled on a circuit board, providing independent and isolated monopolar or bipolar stimulation per electrode.

An alternate form of control is provided by embedded microprocessors, which can autonomously produce the pulsed stimulation train, often used in experiments (see Figure 3.3). This stimulation pattern is described by five parameters: (1) the pulse width, (2) the primary period, which determines the frequency of the stimulation pulse, (3) the duration of the pulse, (4) the secondary period, which determines the period between pulses, and (5) the total length of the train. The parameters are held in the memory of the microprocessor and are set via serial control. Each microprocessor can control up to eight channels simultaneously with a resolution of 100 μs, and is mounted on the PCB with the isolation units. The stimulus train is initiated either with a byte through the serial port or a transistor-transistor logic (TTL) pulse applied to hardware interrupt pins on the microprocessor.

There are four elements to each channel of the stimulus isolation units: the power supply, current regulator, voltage regulator, and optical switches (see Figure 3.4). The stimulus isolation unit uses a 1 W miniature DC-DC converter to provide isolated power per channel. Although it is not strictly necessary to have an isolated supply on every channel with monopolar stimulation (due to the common ground), this allows greater freedom in using bipolar stimulation. A high-voltage linear regulator controls the voltage across the optical switches and is adjusted via an serial-addressable digital potentiometer. In turn, a metal oxide semiconductor field effect transistor (MOSFET) regulates the current. Current is controlled through a MOSFET biased in a feedback loop with an operational amplifier (op-amp). The op-amp adjusts the gate voltage to keep the MOSFET in the saturation regime and the voltage across a current sensing resistor, Rfb, equal to a reference set by a digital potentiometer. This simple feedback system has been found to work very well in practice, though the feedback resistor must be tailored to the range of intended-current output; a smaller resistor would allow the isolation unit to be used with larger, lower impedance FES or DBS electrodes. Current is switched to the electrodes via four optical complementary metal-oxide semiconductor relays arranged in an H-bridge configuration. Control from the switches is via two lines from either the microprocessor or DAQ card. The other two control lines (serial clock and data) for the digital potentiometers are shared between the four isolators per board (the three address bits per potentiometer allow eight addresses). It has been found that the digital potentiometers are fast enough to change current or voltage regulation within a biphasic pulse when the isolator is controlled through the DAQ card, permitting charge balancing via a brief, high-current negative pulse followed by a longer, slower positive recovery. The built-in microcontroller cannot do this, nor can it vary the time between positive-negative phases. Instead, the time between negative and positive pulses is determined by the turn on or turn off asymmetry in the opto-CMOS relays. To prevent charge imbalance due to this effect, a small ceramic capacitor should be put in series with the electrode.

Presently, we have only tested the ICMS system using the embedded microprocessor, though a prototype of the DAQ-controlled digital isolation units has recently been completed. The system has proven to be compact, reliable, and expandable to as many channels as required.

REFERENCES

1. Brown TG, Sherrington CS. Observations on the localisation in the motor cortex of the baboon (“Papio anubis”) J Physiol. 1911;43(2):209–218. [PMC free article: PMC1512688] [PubMed: 16993092]
2. De Lafuente V, Romo R. Neuronal correlated of subjective sensory experience. Nat Neurosci. 2005;8(12):1698–1703. [PubMed: 16286929]
3. Doty RW. Conditioned reflexes elicited by electrical stimulation of the brain in macaques. J Neurophysiol. 1965;28:623–640. [PubMed: 14347624]
4. Doty RW. Electrical stimulation of the brain in behavioral context. Annu Rev Psychol. 1969;20:289–320. [PubMed: 4888623]
5. Doty RW, Larsen RM, Ruthledge LT Jr. Conditioned reflexes established to electrical stimulation of cat cerebral cortex. J Neurophysiol. 1956;19:401–415. [PubMed: 13367871]
6. Fitzsimmons NA, Drake W, Hanson TL, Lebedev MA, Nicolelis MAL. Primate reaching cued by multichannel spatiotemporal cortical microstimulation. J Neurosci. 2007;27(21):5593–5602. [PubMed: 17522304]
7. Fritsch G, Hitzig E. Über die elektrische Erregbarkeit des Grosshirns. Arch Anat Physiol Med Wiss. 1870:300–332. [PubMed: 19269348]
8. Galvani L. De viribus electricitatis in motu musculari. Commentarius De Bononiesi Scientarium et Ertium Instituto atque. Acad Commentarii. 1791;7:363–418.
9. Graziano MS, Taylor CS, Moore T. Complex movements evoked by micro-stimulation of precentral cortex. Neuron. 2002;34:841–851. [PubMed: 12062029]
10. Helmholtz HLF. De fabrica systematis nervosi evertebratorum. Berlin: 1842. D.Phil. thesis.
11. Hess CW. [Developments in neurophysiology in the 19th century] German. Schweiz Rundsch Med Prax. 1994;83(16):483–490. [PubMed: 8191189]
12. Murasugi CM, Salzman CD, Newsome WT. Microstimulation in visual area MT: Effects of varying pulse amplitude and frequency. J Neurosci. 1993;13:1719–1729. [PubMed: 8463847]
13. Penfield W, Boldrey E. Somatic motor and sensory representation in the cerebral cortex of man as studied by electrical stimulation. Brain. 1937;60:389–443.
14. Penfield W, Rasmussen T. The cerebral cortex of man: A clinical study of localisation of function. New York: Macmillan; 1950.
15. Romo R, Hernández A, Zainos A, Salinas E. Somatosensory discrimination based on cortical microstimulation. Nature. 1998;392(6674):387–390. [PubMed: 9537321]
16. Romo R, Hernández A, Zainos A, Brody CD, Lemus L. Sensing without touching: psychophysical performance based on cortical microstimulation. Neuron. 2000;26(1):273–278. [PubMed: 10798410]
17. Salzman CD, Britten KH, Newsome WT. Cortical microstimulation influences perceptual judgements of motion direction. Nature. 1990;346:174–177. [PubMed: 2366872]
18. Salzman CD, Murasugi CM, Britten KH, Newsome WT. Microstimulation in visual area MT: Effects on direction discrimination performance. J Neurosci. 1992;12:2331–2355. [PubMed: 1607944]
19. Talwar SK, Xu S, Hawley ES, Weiss SA, Moxon KA, Chapin JK. Rat navigation guided by remote control. Nature. 2002;417:37–38. [PubMed: 11986657]
20. Volta A. On the electricity excited by the mere contact of conducting substances of different kinds. Philos Trans R Soc (Lond) 1800;90:403–431. (in French)

Figures

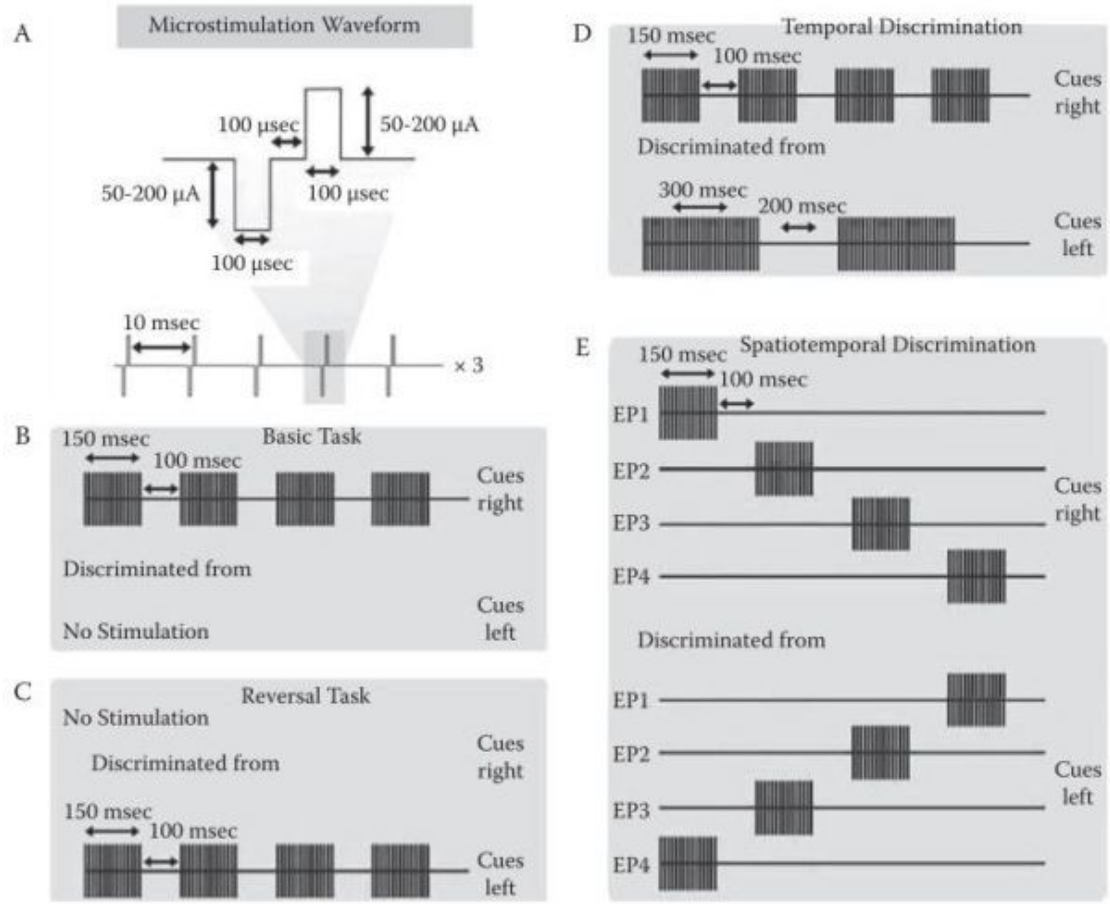

FIGURE 3.1

Temporal patterns of microstimulation. (A) In all sessions, stimulation pulses were delivered biphasically, with a cathodic phase preceding an anodic phase of equal amplitude. Pulse width, pulse delay, and frequency were kept constant at 0.1 ms, 0.1 ms, and 100 Hz, respectively. For all tasks except the one in which psychometric curves were measured, current amplitudes were held constant at 0.1 and 0.15 mA, for monkeys 1 and 2, respectively. To construct the psychometric curves, we varied the stimulation currents between 0.05 and 0.2 mA. Pulse bouts of 150 ms with 100 ms delays were used in the basic (B), reversal (C), and spatiotemporal (E) tasks, whereas a second stimulation waveform consisting of 300 ms pulse bouts with 200 ms delays was also used in the temporal-discrimination task (D). By keeping the low-level stimulation parameters constant between the two cues in the temporal and spatiotemporal tasks, the absolute charge injection was kept constant. In panel E, electrode pairs (EP1 through EP4) designate the sequential stimulus and ground electrode pairs along the linear electrode array. (Fitzsimmons, N.A., Drake, W., Hanson, T.L., Lebedev M.A., and Nicolelis, M.A.L. (2007). Primate reaching cued by multichannel spatiotemporal cortical microstimulation. *J Neurosci* 27(21) 5593–5602.)

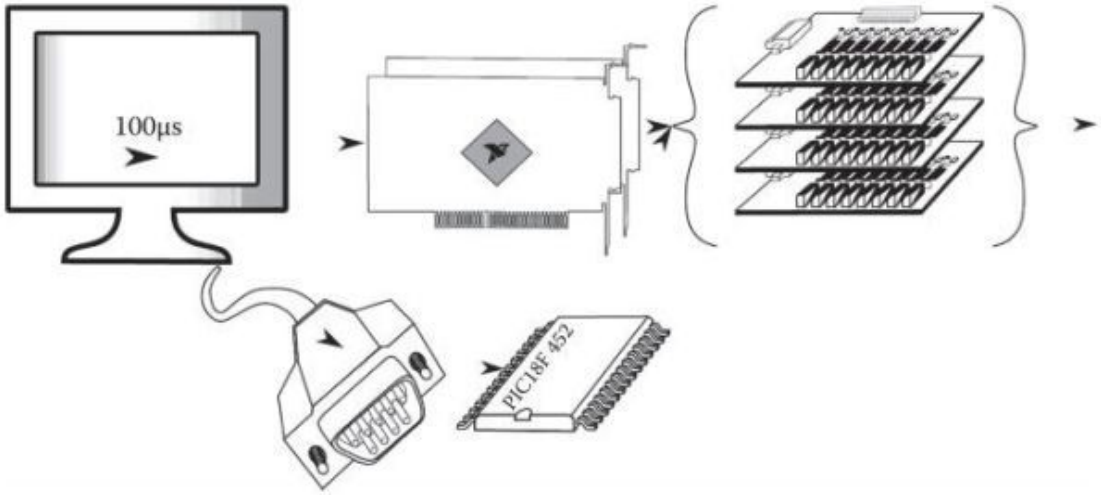

FIGURE 3.2

Schematic of the microstimulator apparatus.

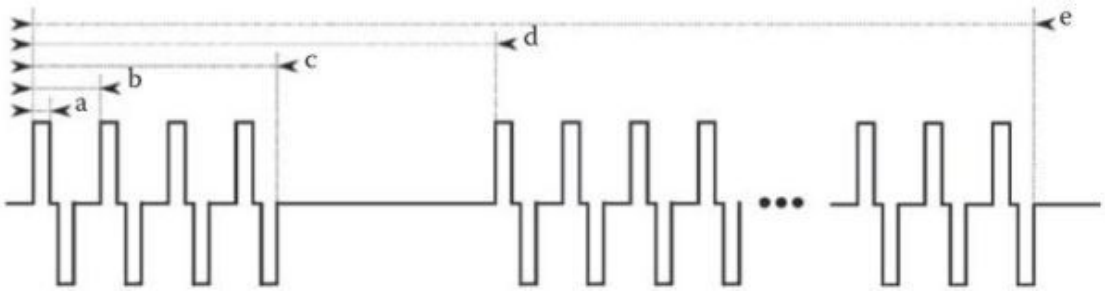

FIGURE 3.3

Pulsed stimulation train features. (1) pulse width, (2) primary period, (3) pulse duration, (4) secondary period, (5) total duration of stimulation.

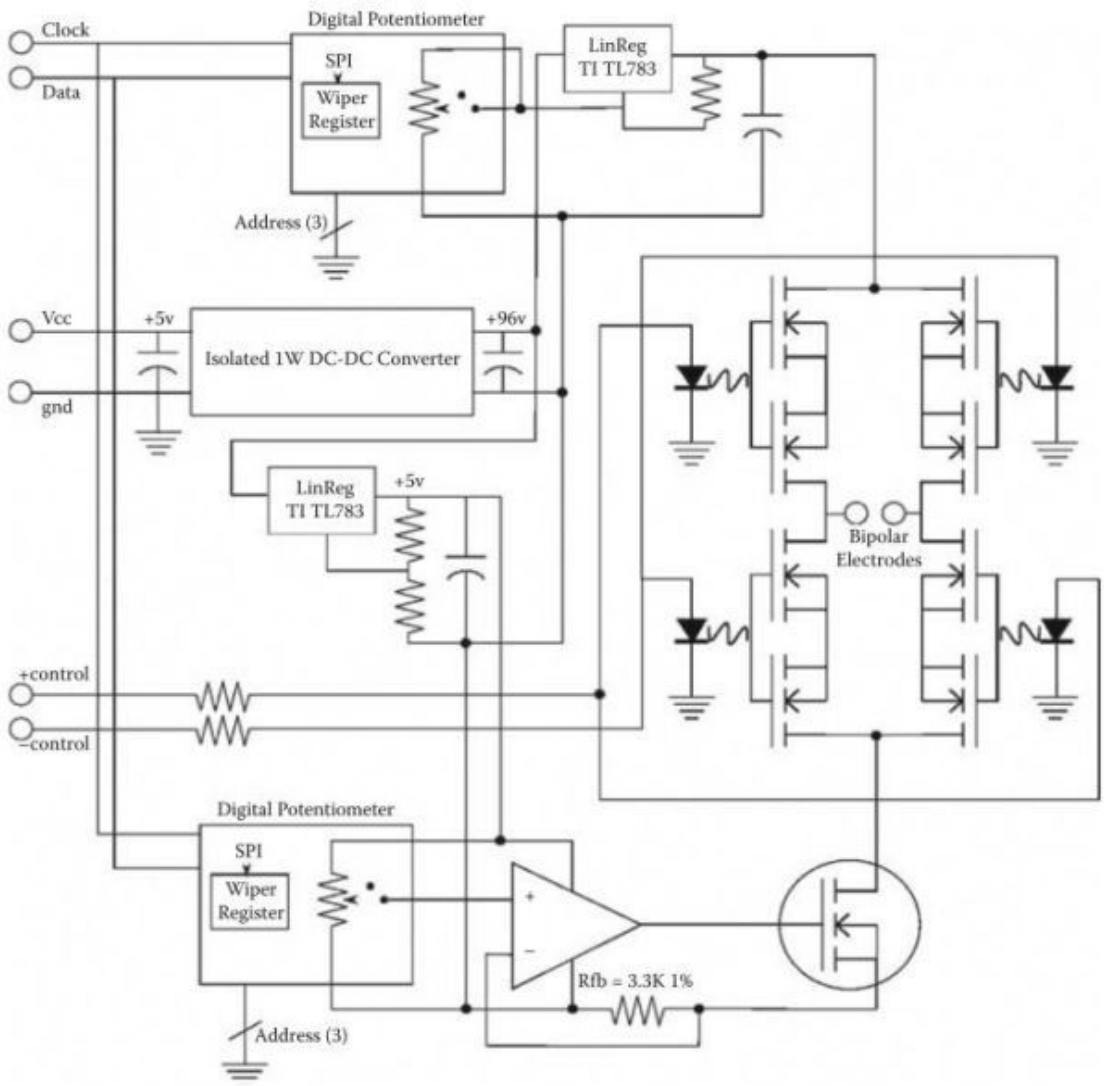

FIGURE 3.4

Engineering schematic of the microstimulator circuitry.

Bookshelf ID: NBK3896 PMID: 21204445