Microsensors, Implantable Devices and Rodent Surgeries for Biomedical Applications

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Greetings everyone, and welcome to the course on micro sensors, implantable devices, and rodent surgeries for biomedical applications. My name is Sreenivas Bhaskara, the Teaching Assistant for this course. In today's lecture, we will explore the types of electronic systems developed for brain stimulation in rodent models.

Let's begin by understanding why brain stimulation is necessary. Parkinson's disease, a neurological disorder, manifests with various symptoms such as tremors, slowness of movement, and loss of balance. Initially, medication is used to manage these symptoms. However, if medication proves ineffective, a procedure called deep brain stimulation (DBS) can be considered.

DBS is an established clinical therapy for advanced Parkinson's disease. It involves implanting electrodes into a specific brain region, typically the subthalamic nucleus (STN). These electrodes deliver electrical signals to the targeted area, which can help alleviate tremors and other Parkinson's symptoms.

While DBS has shown significant benefits, it's important to acknowledge potential side effects. Therefore, neurosurgeons are constantly seeking alternative brain regions for stimulation to further improve patient outcomes. Current research explores areas like the pedunculopontine nucleus (PPN) and the globus pallidus internus (GPI) as potential alternatives to the STN.

Now, let's delve into the electrical aspects of brain stimulation. The stimulation involves delivering a train of electrical pulses. Each pulse typically consists of an anodal phase followed by a cathodal phase. The duration of one complete pulse, including both phases, is known as the pulse width. Following each pulse, there is a period of rest or relaxation time before the next pulse is delivered. This pattern of pulses and relaxation times continues throughout the stimulation process.

In the next part of the lecture, we will explore the specific parameters and characteristics of these electrical pulses and their impact on brain stimulation.

In a pulse train, there will be a certain number of pulses, let's say 12 for this example. Remember, one pulse consists of both an anodal phase and a cathodal phase. Each phase has a specific amplitude, or current magnitude, and a duration known as the "on time." Between the anodal and cathodal phases, there's a brief "interface delay," typically around 100 microseconds. The on time for each phase is usually around 200 microseconds. After each pulse, there's a "relaxation time" before the next pulse begins.

The specific values for current magnitude and pulse duration can vary depending on the application. The number of pulses in a train, typically around 12 in our applications, also depends on the specific needs. Once a pulse train is complete, there's a longer "inter-pulse interval" or "relaxation time" before the next train begins. This interval is usually around 1 or 2 seconds.

So, a typical electrical signal for brain stimulation consists of multiple pulse trains, each with a specific number of pulses, followed by relaxation periods. The parameters of these signals, like amplitude, pulse duration, and number of pulses, are carefully chosen based on the desired outcome of the stimulation.

Now that we understand the objective of generating these signals, let's consider the challenges involved, especially when working with animal models. Before new therapies can be tested in humans, they must first be validated in animals, often laboratory rats. These rats are much smaller than humans, typically weighing between 300 and 500 grams.

One approach to brain stimulation in rats could involve using a larger electronic system connected by wires. However, this wired setup can significantly hinder the rat's natural movement and behavior, potentially affecting the accuracy and reliability of the experimental results. Additionally, the wires themselves could cause discomfort or injury to the animal.

Therefore, there's a clear need for miniaturized and wireless electronic systems that can be implanted in these small animals without impeding their movement or causing harm. These systems must be capable of generating the precise electrical signals required for brain stimulation while being small and lightweight enough to be comfortably carried by the rat.

In the following sections, we will explore the various technological advancements and design considerations that enable the development of such miniaturized and wireless brain stimulation systems for rodent models. We will also discuss the potential impact of these systems on future research and therapeutic applications in neuroscience.

So, the ideal system for brain stimulation in rodents would be wireless, eliminating any hindrance to the animal's movement caused by dangling wires. Additionally, maintaining charge neutrality is crucial. We'll discuss this in more detail shortly, but in essence, it means using biphasic pulses to ensure no net charge is introduced into the brain.

Another vital consideration is the weight of the implant. Ideally, it should be less than 10% of the rat's total body weight, preventing any undue burden on the animal that could affect the experiment's outcome.

Now, let's elaborate on charge neutrality. As mentioned earlier, brain stimulation involves delivering electrical signals, which essentially means pumping charge into the brain. It's critical that after each pulse, the total charge in the brain returns to zero. If excess charge accumulates due to various electrochemical reactions, it can alter the brain's environment, potentially leading to pH changes and even brain damage. Hence, the use of biphasic pulses, where an anodic phase is followed by a cathodal phase of equal magnitude, is essential for maintaining charge neutrality.

Furthermore, consider the concept of current mirroring. In deep brain stimulation, multiple electrodes are often used to target a larger brain region. Current mirroring allows you to supply the same signal to all these electrodes simultaneously. It works by having a stable current source connected to a current mirroring network. This network then generates multiple copies of the source current, ensuring all electrodes receive identical signals. Of course, designing an effective current mirroring network requires careful consideration, but when done correctly, it enables precise and consistent multi-electrode stimulation.

Finally, remember that in exploratory research, the ideal stimulation parameters, like pulse duration and current amplitude, might not be known beforehand. Researchers often need to experiment with different settings to determine the most effective stimulation protocol for a particular study. This flexibility in parameter adjustment is another important design consideration for brain stimulation systems.

Let's say, for instance, we initially set the current amplitude at 100 microamperes. During experimentation, we might find that this value isn't sufficient and needs to be adjusted to 150, 200, or even 300 microamperes. The ability to program the electronic system while it's implanted in the subject is crucial. Imagine the inconvenience and potential distress caused to the animal if we had to repeatedly remove and re-implant the device every time we needed to change a parameter.

Another critical factor is the size of the system. Laboratory rats typically have a body width of 6 to 8 centimeters and a length of 15 to 25 centimeters. The electronic system must fit comfortably within these dimensions to ensure it remains mechanically secure and doesn't interfere with the rat's natural movements.

Power consumption is also a key consideration, particularly for wireless applications that rely on batteries. The system's power consumption directly impacts the battery life and, consequently, the duration of experiments that can be conducted without interruption.

Now, let's take a look at a system developed in our lab for biomedical applications in rodents. It consists of several components:

- **Neural Implant:** This is designed for cortical surface stimulation and has an L-shape with multiple electrodes, typically 5 or 6. Each electrode has a corresponding contact pad.
- **Electrode Interface Board (EIB):** This board houses the implant and provides an interface for controlling the currents delivered to the electrodes. We typically have one EIB for each hemisphere (left and right).

- **FPC Connectors:** Flexible printed circuit (FPC) connectors are used to connect the implant to the EIB and to provide access for controlling the currents.
- **Electronic System:** This is the main unit responsible for generating the stimulation signals and controlling the EIB. It can be wireless or wired, depending on the specific application.

The neurosurgeon performs the implantation procedure, carefully placing the neural implant on the brain's surface. The EIBs are then connected to the implant, and the electronic system is attached, completing the setup.

This is just a brief overview of the system. In the subsequent sections, we'll delve deeper into each component, exploring their design, functionality, and the technological advancements that have made such miniaturized and sophisticated systems possible. We will also discuss the challenges and considerations involved in developing implantable devices for biomedical research and the potential impact of these systems on future therapies for neurological disorders.

So, you can access each individual electrode on the neural implant through the Electrode Interface Board (EIB). The electronic system houses various integrated circuits (ICs) like regulators, microcontrollers, and Bluetooth Low Energy communication modules. We'll discuss the architecture of wireless electronic systems later in the course. However, it's important to understand that the wireless system alone isn't sufficient; it needs the EIB.

You might wonder why we can't directly interface the implant with the wireless system, eliminating the need for the EIB. Well, imagine the weight of the entire system, including the electronics, resting on the rat's head. We aim to keep the weight of the head-mounted components to around 10-20 grams. Attaching the entire electronic system directly would make it too heavy and cumbersome for the rat. Therefore, we use the EIB as a bridge between the implant and the electronics, which are typically housed in a backpack worn by the rat.

The EIB offers another advantage: flexibility. If you wish to use a different electronic system in the future, you only need to ensure it has an FPC connector compatible with the EIB. This modularity allows for easy upgrades or modifications without needing to replace the entire setup.

Now, let's explore one of the fundamental concepts used in brain stimulation: current mirroring. If you need to generate multiple identical currents simultaneously, you can extend a basic current mirror network. By shorting the gate and source terminals of multiple MOSFETs and replicating the same network structure, you can create multiple current outputs.

To understand how current mirroring works, let's consider a simple circuit with a resistor and an NMOS transistor. The transistor's drain is connected to ground, and its gate is connected to a 5-volt supply through a 1-kilohm resistor. This configuration creates a current flow through the transistor.

The current equation for an NMOS transistor is given by:

$I = \mu n\ Cox\ W/L\ (Vgs - Vth)\ (Vds - Vds^2/2)\ (1 + \lambda Vds)$

where:

- μn is the electron mobility
- Cox is the gate oxide capacitance per unit area
- W/L is the transistor's width-to-length ratio
- Vgs is the gate-to-source voltage
- Vth is the threshold voltage
- Vds is the drain-to-source voltage
- λ is the channel-length modulation parameter

We also know that the transistor operates in saturation mode when Vds is greater than or equal to Vgs - Vth.

Let's analyze our circuit to see if the transistor is in saturation. Assuming a threshold voltage (Vth) of 0.7 volts. In this configuration, Vgs (gate-to-source voltage) is the same as the voltage between the drain and source (Vds) because the drain and gate are shorted, and the source is at the same terminal. So, Vds equals Vgs.

Now, let's revisit the saturation condition: Vds must be greater than or equal to Vgs - Vt (threshold voltage). If Vds is equal to Vgs, then the left side of the inequality becomes 0. Let's assume Vt is 0.7 volts. So, the inequality becomes:

0 >= -0.7 volts

This condition is true, which confirms that transistor M1 is indeed in saturation. If this condition wasn't met, the transistor would be operating in the linear region.

Now that we know M1 is in saturation, let's simplify the current equation.

In saturation, the current equation becomes:

$I = \mu n\ Cox\ W/L\ (Vgs - Vt)^2 / 2$

This shows that the current (I) is directly proportional to (Vgs - Vt)^2 and is independent of Vds. However, it's important to note that this is an approximation. In reality, there's a phenomenon called channel-length modulation, which introduces a slight dependence on Vds. But for our understanding, we'll assume I is proportional to (Vgs - Vt)^2.

If we can ensure that (Vgs - Vt) is the same for two transistors and that both transistors are in saturation, then the currents flowing through them (I1 and I2) will be equal.

Let's illustrate this with a configuration involving two transistors (M1 and M2). Their gates are shorted, and their sources are shorted, ensuring Vgs1 equals Vgs2. We already know M1 is in saturation due to its connection.

Now, let's add a resistor and a 5-volt supply to the circuit. If we can design the rest of the network to ensure M2 also operates in saturation, then the currents flowing through both transistors will depend solely on their respective Vgs values. Since Vgs1 and Vgs2 are equal, the currents I1 and I2 will also be equal.

This is the basic principle behind a current mirror architecture. While we've used MOSFETs here, bipolar junction transistors (BJTs) can also be used. However, MOSFETs are generally preferred due to their zero gate current, unlike BJTs which have a small base current.

In essence, a current mirror replicates a reference current in multiple branches. If the reference current is 200 microamperes, the same current will flow through each branch of the mirror, provided all transistors are in saturation and have the same (Vgs - Vt) value.

We'll leverage this current mirroring concept in the design of our brain stimulation system to ensure consistent and precise current delivery to multiple electrodes.

In the previous examples, we explored the concept of current mirroring using NMOS transistors. However, in certain applications, like the one we're discussing, PMOS transistors might be preferred. The choice between NMOS and PMOS often depends on specific design requirements and constraints. In this case, we've opted for PMOS to minimize the number of transistors needed in the circuit.

So, let's assume a current of 200 microamperes flows through M2. Due to the current mirroring principle, the same 200 microamperes will also flow through M1, provided M1 is in saturation (we already know M2 is in saturation).

Now, let's shift our focus to the ultimate goal: generating a biphasic pulse. We want to create a waveform where the current flows in one direction and then reverses, creating a positive and a negative phase.

To achieve this, we'll use Single Pole Double Throw (SPDT) switches. Think of them as 2-to-1 multiplexers. They have one input and two outputs, and a select line controls which output the input is connected to.

By strategically controlling the switch positions, we can direct the current flow in either direction between two electrodes, E1 and E2. In one configuration, the current flows from the supply voltage (VDD) through the switches and transistors to ground, passing from E1 to E2. In another configuration, we change the switch positions, reversing the current flow from E2 to E1.

The currents themselves are generated using IDAC blocks, which are essentially digital-to-analog converters that produce precise and controllable currents. Since the transistors in the current mirror are in saturation and connected in series, the same current flows through both of them.

So, if we program the microcontroller to generate a 200 microampere sink current at the IDAC, the same 200 microampere current will flow from VDD through the transistor and into the IDAC. By carefully switching the SPDT switches, we can alternate the current flow direction between E1 and E2, resulting in the desired biphasic pulse.

In the next lecture, we will dive deeper into the specific switch configurations and timing sequences required to generate these biphasic pulses. We'll also discuss the role of the microcontroller in controlling the switches and the IDAC, ultimately enabling precise and programmable brain stimulation.