2 Literature Review on Neural Signal Recording and Headstages

2.1 Introduction

As mentioned in the previous chapter, one of the most important functionalities of neural headstages is recording the neural signals in the brain and since this recording is carried out via electrical circuits, the electrical characteristics of neural signals prove crucial in the design and test of the circuitry that amplifies and conditions the acquired signals. This chapter is devoted to understanding the neural signals *as electrical signals*. Of course, neural signals can be studied from different points of view. However, we are interested in certain of their characteristics, which allow us to design and build neural headstages.

In the first two sections of this chapter, neural signals and their electrical properties are introduced and in the third section we will briefly introduce the technique of optogenetics that is a new method for optical neural stimulation. Finally, in the last section, we will present a literature review on the state of art headstages.

One of the most important aspects of neural headstages (especially the ones that operate wirelessly) is their signal processing capabilities. Without digital signal processing, wireless neural headstages will have to transmit all digitized samples of the acquired signals to a base station, which means higher energy consumption in the headstage, higher bandwidth requirements and the need for high speed radio transceivers [27]. The mentioned characteristics are not desirable for wireless neural headstage as the limits of the energy source and the transmission rate of the RF (radio frequency) system are design bottlenecks.

Since digital signal processing capabilities (soft capabilities of headstage) can be treated separately from the actual hardware and physical features of headstages, we have dedicated a whole chapter of the thesis to neural signal processing.

2.2 Physiological Aspects of Action Potentials

Neurons are cells that constitute the nervous system. Using the nervous system, humans, among many other species, are capable of acting as intelligent entities i.e., they are able to interact with the world and think and decide. The human brain consists of approximately 10^{11} neurons and these neurons are supported by the glial cells [2]. The glial cells support the neurons in different ways including but not limited to: 1) nutrition of neurons, 2) deactivation of some neurotransmitters, 3) integration with the blood-brain barrier, 4) facilitating the action potential transmission and 5) removing cellular debris during neuronal death [2]. The complex functionality of a brain is based on neurons capability of sending and receiving messages. These messages have an electrical nature and are created in an electrochemical process that takes place in close proximity *and*

inside the neurons [2]. As a result of this mechanism, the neurons are capable of sending messages in a wave-like manner to each other. These waves of messages will eventually result into some action commanded by the brain [2]. The resulting command might be received in the brain itself or by the peripheral nervous system, which connects different components of the body to the central nervous system [2].

In the next sections of this chapter, we will describe the physiological origins and also the mathematical characteristics of action potentials. These mathematical characteristics are interesting from an electrical engineering point of view when designing headstages.

2.3 Electrochemical Process of Creating Action Potentials

As mentioned before, neurons are able to send electrical messages to each other and these electrical messages are called *action potentials*. It should be noted that neurons are similar to other cells (in terms of internal components), but they are also able to send electrical messages [2]. Also, it should be noted that there are different types of neurons; some of them act as connections between other neurons and some are able to interact with other types of cells like muscle cells. There is also one type of neuron that is able to be stimulated by different non-neural stimuli. The headstage system introduced in this work focuses mostly on the neurons that are found in the brain and transfer messages between other neurons.

A neuron as a cell has, among others, a *cell body* (also called the soma), a number of *dendrites* and an *axon*. Dendrites and axons are extensions of the cell, which receive and transmit electrical signals, respectively. Most neurons have only one axon but they can have many dendrites. Axons are the transmission medium of the action potential and tend to be long, depending on the type of the neuron. Figure 2 (derived from [28]) shows a drawing of a neuron where it can be seen that the axon is a long extension of the cell. The many dendrites of the same cell can also be seen.

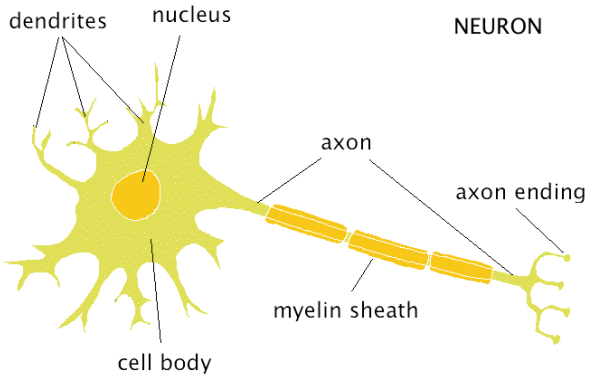

Figure 2. Sketch of a neuron (derived from [28]).

The axon of one neuron is connected to the dendrites of one or many other target cells (either neurons or other types of target tissues like muscle) [29]. So, these target cells can receive the action potentials transmitted by the first neuron. Between the axon of one neuron and the dendrites of another neuron, there is a small gap called the *synapse* where neurotransmitters travel from the axons to the dendrites and transfer the message carried by the action potential. Figure 3 (derived from [30]) shows the connection of one axon to the dendrites of another neuron.

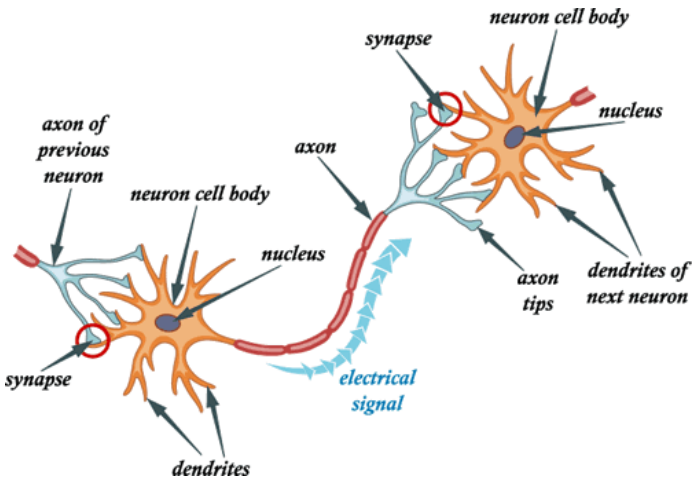

Figure 3. Connection of one neuron to another (derived from [30]).

2.4 Creation of Action Potentials

A neuron can be either at rest or can be in the process of creating an action potential. When a neuron is at rest there is a negative potential difference between the inside of its cell body and the outside of the cell where the outside of the cell has a more positive voltage. This voltage difference is due to the concentration (and also type) of ions that are present inside and outside the neuron body. The resting potential (voltage difference between inside and outside of a neuron at rest) is around -70 to -80 mV [2].

When a neuron is stimulated by an action potential, it opens its ion channels for the positive sodium ions to rush in the cell body. These ions increase the inner potential of the neuron from almost -70 mV to almost +20 mV [2]. After some time, the sodium ion channel closes and another type of ion channel opens that lets the positive potassium ion leave the neuron body; as a result, the inner potential decreases until it reaches the resting potential. This process in which the inner potential of the neuron depolarizes results in the creation of an action potential. With similar mechanisms, this sudden change in the inner potential travels through the axons and reaches another neuron where another action potential might or might not be created depending on many factors [2]. Figure 4 (derived from [31]) shows the neuron inner potential during creation of an action potential.

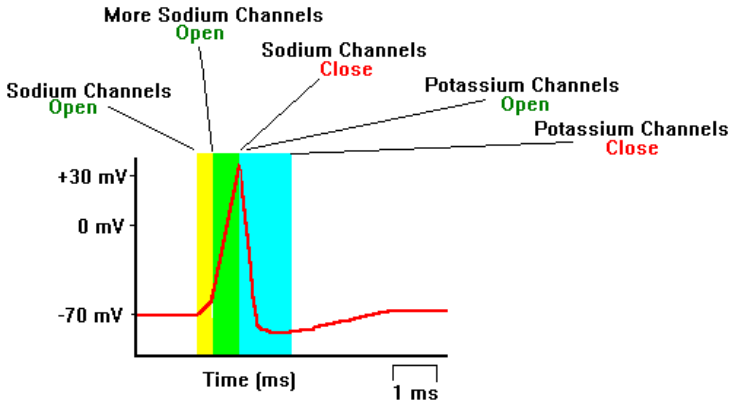

Figure 4. Inner potential of a neuron during creation of an action potential (derived from [31]).

2.5 Action Potentials and their Mathematical Characteristics

When sampled, action potentials are discrete-time signals so many mathematical properties can be attributed to them. In this section, we will introduce different mathematical characteristics of the neural signals.

2.5.1 Time-Domain Characteristics of Action Potentials

Temporal characteristics of neural signals are of significant importance as they will directly affect the design process of the brain-machine-interfaces. Although many different (statistical) time-domain characteristics can be defined for discrete-time signals, only the following temporal characteristics are mostly used for processing neural spike-trains [32] [33] [34] [27]:

1) Temporal duration (minimum, maximum and average) of individual action potentials
2) Number of action potential per second (rate)
3) Average duration of inactivity between two action potentials

2.5.1.1 Temporal Duration

In general, temporal duration of action potentials, although very close, is different for each species [29]. Different research papers have also reported average and minimum/maximum durations of action potentials for specific species based on many recordings [35].

When it comes to designing signal processing systems and algorithms, the temporal duration plays an important role since a system which is not flexible enough (in the time domain) might partially or completely lose information carried by the action potentials. Different research papers have tried to find minimum and optimum requirements for neural signal processing and also to find reasonable assumptions about the incoming action potentials trains [36]. Specifically, some papers have tried to regenerate action potential trains in a realistic way [32] [37] [38]; using these artificial but realistic spike trains, researchers can develop new

signal processing algorithms. The following table summarizes the action potential duration found in different literature.

Table 1. Action potential duration in the literature.

Publication	Average Duration (milliseconds)
[33]	2.5
[34]	2.6-3.6
[27]	1.025
[39]	2
[35]	1.46

It can be seen that the average duration of an action potential is almost 2 milliseconds and the maximum and minimum are 3.6 and 1 milliseconds.

2.5.1.2 Number of Action Potentials per Second

As the temporal duration of action potentials affects the short-term memory requirements (i.e., small buffers that only hold the data of one spike) of neural signal processing systems, the number of action potentials per second manifests its effect in the long-term memory requirements or transmission speed of such systems.

Unlike the temporal duration, the frequency (number of spikes per second) can vary considerably according to the conditions and stimulations of a neuron [35]. In fact, the frequency of occurrence of action potentials is a key factor in designing the architecture of neural signal processing systems that are low on computation and/or energy resources, especially when such systems have multiple input channels. The following table summarizes the average action potential firing rate found in different publications.

Table 2. Average Firing Rate of Action Potentials.

Publication	Average Firing Rate (Hz)
[32]	20
[33]	20
[34]	75
[40]	20-160
[39]	100
[41]	10-100

2.5.1.3 Inactive Time between Action Potentials

The third parameter that poses certain difficulties in designing low-power neural signal processing systems is the time interval in which there will be definitely no action potentials fired from a neuron. This time interval affects the data buffers in the first stages of signal processing and can be problematic in system in which the data transfer in the memory is not fast or there is not much memory. In extracellular neural recording

scenarios, there is the possibility that multiple neurons be close to the recording electrode so multiple action potentials might be captured by the electrode at the same time. In this case, it is required to separate the overlapped action potentials and some research papers are dedicated to this subject [42] [43].

The following table summarizes the average ISI (inter-spike interval) of neurons in the literature.

Table 3. Inactivity Interval of Neurons.

Publication	Average ISI (milliseconds)
[32]	2
[33]	2

2.5.2 Amplitude and Noise Characteristics of Action Potentials

Amplitude and the signal-to-noise ratio of the captured action potentials is another determining factor in designing the amplifier in the animal headstage. As mentioned before, there are different ways of obtaining neural signals from neurons [4]. However, one of the methods that is widely used and allows the researchers to carry out long experiments on the animal is extracellular recording [4]. In this method, the electrodes are placed in close proximity of the neurons(s) but not inside the neuron. Since the neuron stays intact, it does not die and the experiment can last longer compared to the intracellular recording where the electrodes are placed inside the neurons.

In extracellular recording scenarios, the amplitude of the captured action potentials is reported to be between 50 microvolts to a few millivolts. The following table summarizes the reported amplitude of action potentials in extracellular recordings.

Table 4. Action Potential Amplitude in the Literature.

Publication	Average Action Potential Amplitude (microvolts)
[44]	< 500
[27]	< 200
[45]	50-150
[3]	50-200
[4]	50-500

2.5.2.1 Sources of Noise in Neural Signals

Different sources of noise affect the quality of recorded action potentials [32]. However, unlike other signal acquisition scenarios occurring in other domains of electrical engineering, these noise sources are not all white and/or Gaussian.

In general it can be said that four different sources of noise affect the quality of a captured action potential [32]:

1) Background noise: activity of neurons that are very far from the electrode. This neural activity (action potentials) shows itself as a low-amplitude thick cloud of noise in neural recordings.
2) Activity of nearby neurons: this kind of noise is actually action potentials from relatively far neurons with amplitudes so small that it is not possible to determine the source neuron creating the action potential. The difference between this type of noise and the previous one is that, this type of noise is mostly recognizable action potentials interfering with the neural recording processing while the first type of noise is not distinguishable from random noise.
3) Thermal noise and inherent noises of electronics and the electrodes involved in the system
4) Power-line noise: 50 Hz or 60 Hz power line noise.

One of the most important aspects of the first and second sources of noise is that they share the same frequency content as the signals (action potentials) of interest. The reason is simply that these noise sources are also neurons similar to the neurons from which we would like to capture signals [32].

2.5.3 Frequency-Domain Characteristics of Action Potentials

So far we have discussed the different characteristics of action potentials in the time domain. However, the spectral content of action potentials also plays an important role in the design and quality of a headstage system.

In extracellular capturing scenarios, typically two spectrally separate signals are captured: 1) the low frequency local field potentials (LFPs) and 2) the action potentials [46] [4]. The LFPs usually occupy a bandwidth from a few Hz to almost 300 Hz [4] [32] [33], while the action potentials occupy a larger bandwidth starting from 300 Hz to almost 3000 Hz or more [4] [32] [33]. The following table summarizes the reported action potential bandwidth in the literature.

Table 5. Spectral Content of Action Potentials.

Publication	Lower Limit (Hz)	Upper Limit (Hz)
[32]	300	3000
[33]	300	6000
[34]	300	N/A
[47]	300	3000
[48]	250	5000
[49]	300	10000
[35]	300	3000

Another point worth mentioning is that the amplitude of the LFPs is much larger than that of the action potentials [4]. As a result, care must be taken when designing analog or mixed-signal systems that process the LFPs and the action potentials because the LFPs might saturate the signal processing block. As an example, an amplifier with a gain of 5000 V/V would amplify the action potentials to less than 2 volts. However, the LFPs having amplitudes in the millivolt range would saturate the amplifier when the power rail is not large enough.

In this project, we focus on capturing and processing only the action potentials. So the LFPs are filtered out in the early stages of the signal chain.

2.6 Optogenetics

Optogenetics is a neural activity control method in which light controls the activity (or lack) of genetically light-sensitized neurons [50] [22] [23] [17] [51]. In this method, different techniques in genetics, electronics and optics are combined to provide neuroscientists with a neural stimulation tool with high temporal and spatial resolution. As mentioned in the introduction, the field of optogenetics has made great contributions to the understanding of the neural circuits in the brain and also to the treatment of different diseases [50] [19] [20] [21].

In optogenetics, light-sensitized proteins (for example ChR2, ChR1, VChR1, SFOs and NpHR) are used to make neurons respond to light quickly. For example, ChR2 causes the neuron to depolarize (activate) in response to blue light and NphR causes the neuron to silence in response to yellow light [51] [50] [52]. The light source can be high-power LEDs or lasers tuned to specific wavelengths [16] [17] [18].

Optogenetic tools provide the researcher with stimulation temporal accuracies in the order of milliseconds. Researchers also need to track the effects of the stimulation by some means. One way of carrying out such readings is to monitor the neural activity using microelectrodes connected to signal-recording electronics.

In this project, an animal headstage that is capable of delivering light to light-sensitized neurons has been designed. This headstage is also capable of electrically recording the neural activity resulting from the stimulation. Optogenetic experiments can be carried out on small animal test subjects using this headstage as it has a small footprint and low weight. This headstage has two LED-based optical stimulation channels and has also two electrophysiological reading channels.

2.7 State of the Art Wireless Neural Headstages and Brain Interfacing Systems

In this section, an overview of currently available wireless animal neural research systems is presented. We focus, in particular, on the part of these systems that interfaces the brain and that are wireless. Both commercial and research headstages are presented. In general, we can divide the brain-interfacing systems into two groups: 1) systems that are based on an ASIC (application-specific integrated circuit), and 2) systems that are based on discrete electronic components.

2.7.1 Neural Interfacing Systems Based on ASICs

These systems are specifically designed to be extremely low-power, compact and efficient. A high number of neural recording/stimulation channels are also of great importance. Although this type of neural interfacing systems is not the focus of this work, a short overview of available systems is presented in Table 6.

Table 6. Comparison of ASIC-Based Brain Interfacing Systems.

Work	No. of Recording Channels	Ch. Sampling Rate (KSamples/sec.)	Bits/Sample (Stim. or Rec.)	Power Consumption (mW)
[27]	128	40	9	6
[49]	256	20	5	5.4
[44]	12	40	10	12
[41]	100	15	10	13.5
[3]	16	30	8	2.21
[53]	64	62	8	14.4
[46]	96	31	10	6.4

As can be seen in Table 6, the power consumption of ASIC-based systems is low relative to the discrete system (presented in the next section) and the number of recording/stimulation channels is relatively higher. Although ASIC-based systems can have a much superior performance compared to the discrete systems, their fabrication costs are also much higher. Furthermore, there is a clear trade-off between the system configurability, cost, complexity and time-to-market.

In the next section, we present an overview of research and commercial headstages (neural interfacing systems) that are based on discrete components.

2.7.2 Neural Interfacing Systems Based on Discrete Components

Compared to ASIC-based neural systems, headstages that are based on discrete components tend to occupy a bigger volume and to be less power-efficient. However, the configurability of these systems (in terms of upgrading the functionality) and their much lower cost make these devices much more common and desirable in the industry as well as in practical neuron-research labs.

The higher configurability of discrete headstages comes from the fact that they usually incorporate some sort of available processor (or other types of configurable devices like FPGAs) which is easy to program. Also, the manufacturing time and complexity of these headstages is lower since only discrete components need to be bought and soldered on some sort of carrier, usually a PCB in a biocompatible package. From this point on

and for brevity, the term headstage means an animal headstage based on COTS (commercial off-the-shelf) components.

In our research to identify (COTS-based) headstages we encountered some headstages that supported only one channel of data acquisition and they would transmit the acquired data using continuous FM (frequency modulation) modulation [54] [55]. However, there were other publications that would time-multiplex multiple channels of analog neural signals into one broadband channel and would then FM-modulate that channel [56]. One problem with FM modulation is that the quality of the signal that is finally received by the *base station* depends on the quality of the FM transmitter, the analog time-multiplexer (if any), antennas and all other parameters that affect analog modulation quality [54] [55] [56].

On the other hand, there are many wireless headstages that use digital modulations to transmit the acquired data back to the base station. For example, [57] and [58] use Bluetooth technology to transmit the data back to the base station and have 1 and 16 data acquisition channels, respectively. There are also headstages that use raw-data transmitters (no protocol stacks) to transmit data [17].

Recently, there has been a tendency to build light-weight and compact optical stimulation tools for optogenetics. In [59], researchers have developed a 4-by-4 array of LEDs fused with electrodes for optogenetics stimulation and neural recording. In [60], a wireless headstage with an array of optrodes and micro-LEDs has been presented. In [61], authors have designed an implantable optogenetic interface with 4 optical stimulators while in [62], a 64-channel optrode array with light-delivery system has been deign for optogenetic stimulation. Finally, in [17], the design of a wirelessly powered optogenetic headstage with a high-power LED and two recording channels has been discussed. There are also some optogenetic headstages without recording capabilities where the optical power delivered to neurons is supplied by a wireless power-delivery link [63].

Table 7 presents a comparison between currently available COTS-based headstages. In this table, some optogenetic stimulators are also shown that are not complete headstage systems but can be connected to wireless transmitters.

Different types of optogenetic and non-optogenetic headstages were presented in this review. One of the common features of all (except for [17]) optogenetic stimulators in Table 7 is their lack of high-power optical stimulation. In [63], however, high-power stimulation is possible but there is no means for neural signal recording.

Besides the research headstages that were mentioned in this section, there are also commercial headstages available for optogenetic and non-optogenetic experiments [64] [65] [66]. However, at the time of this writing, these commercial solutions did not have an equivalent for the headstage design that is presented in this work.

Table 7. Comparison of COTS-based Optogenetic and Non-optogenetic Headstages.

Work	No. of Recording Channels	No. of Stimulation Channels	Sampling Rate per Recording Channel (Samples/Sec.)	Bits/Sample (Stimulation or Recording)	Stimulation Power Consumption	Total Power Consumption
[54]	1	N/A	N/A	N/A	No Stimulation	≈3.8 mW[1]
[67]	1	1	11,7	N/A		40-120 mW
[68]	1	1	10,000	N/A		N/A
[57]	1	1	12,000	12		≈220 mW[2]
[58]	16	N/A	25,000	10		N/A
[56]	15	N/A	20,000	12		30.8 mW
[69]	32	N/A	30,000	12		142 mW
[17]	2	1 (opt. fiber)	20,000	8	20 – 380 mW	115-475 mW
[59]	16	16 (surface LED)	N/A	N/A	Minimum 3.4 mW per LED	21 mW (LEDs)
[60]	32	32 (surface LED)	N/A	N/A	Average irradiance of 1.4 mW/mm^2 per optrode tip	N/A
[61]	N/A	4 (surface LED)	N/A	N/A	No Stimulation	N/A
[62]	64	N/A	32,000	14		N/A
[63]	16	N/A	N/A	N/A		up to 2 W

[1] This value has not been mentioned in the paper but has been deduced using calculation made by author of this thesis.
[2] This value has not been mentioned in the paper but has been deduced using calculation made by author of this thesis.