Implanted intracortical electrodes as chronic neural interfaces to the central nervous system

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Abstract

Recent developments in neural interfaces show that it is possible to have fine control of a robotic prosthetic by interfacing with the motor cortex of the human brain. Development of long term systems for this purpose is a challenging task with many different possibilities. Intracortical implants have shown the most promise in providing enough signal selectivity and throughput for complex control systems with many degrees of freedom. Intracortical systems generally fall into two categories: MEMS devices and bundle of wire systems. While both show promise, MEMS systems have been greatly popularized due to their reproducibility. In particular, the Michigan probe and Utah microarray are often used as a base for construction of more complex intracortical systems. However, these systems still carry many downsides. Their long-term viability is questionable, with mixed results. The effects of damage from implantation are still inconclusive and immune responses remain a problem for long-term use. While there is some promising research in the use of bioactive molecules and biocompatible materials to prevent immune responses, more controlled study is needed before intracortical systems become widespread.

Keywords: chronic neural interfaces, central nervous system, intracortical electrodes

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1 Introduction

Since the early 20th century, much progress has been made in understanding how the nervous system works. To accomplish this, however, techniques for measuring neural impulses had to be developed. Edgar Adrian first developed methods for measuring the activity of neuron clusters by way of simple metal electrodes [1]. His work was expanded to more complex methods in studying both intracellular and extracellular neuronal signals *in vivo*, leading to many important discoveries, such Hubel and Wiesel's finding of visual receptive fields [2].

Loss of sensory or motor function from amputation, neuro-degenerative diseases, spinal cord injury, or other reasons, can have a devastating effect on a person's quality of life. There is clear segue from measurement techniques of individual neurons to rehabilitative technologies which can both record and stimulate neurons in the the central and peripheral nervous systems. House et al. first began human trials of single-channel cochlear implants in the early 1960's [3, 4] and are often cited as implementing one of the first neuroprosthetics. Since then, numerous other neuroprostheses have been created for restoring or aiding motor function [5], vision [6], and pro-actively treating epileptic seizures [7] or the effects of Parkinson's disease [8]. While all of these are promising and worthwhile, here an emphasis is placed on neural interfaces with the intention of controlling a robotic prosthetic (as in the case of an amputee). These systems require a high level of specificity and a high signal-to-noise ratio[1] to accomplish quick and complex movement with many degrees of freedom, and as such are more precise in specification [10].

There are currently a wide variety of techniques to record and stimulate neurons, from non-invasive techniques, such as external fMRI or EEG readings, to more invasive techniques, like surface cortical electrodes, to cortically penetrative techniques, like intracortical electrodes. All techniques have their benefits for particular tasks, but non-invasive techniques are perhaps more attractive for human trials. However, the level of specificity and the low signal-to-noise ratio of non-invasive techniques (fMRI, EEG) and even minimally invasive techniques (cortical surface electrodes), often are not sufficient for accomplishing more complex real-time tasks [10]. While research continues and these techniques improve and become more promising, as has recently been demonstrated in improved versions of cortical surface electrode arrays [11], minimally invasive systems have not had as much success in real-time fine control of robotic prosthetics. Additionally, single intracortical electrodes do not provide a large enough sample size for determining refined control [12]. Intracortical electrode arrays, however, have had great success in demonstrating realtime movement of a robotic limb by recording signals from the M1 (motor) cortex of the brain in both animal [13] and human trials [5]. As such, further emphasis is placed on intracortical arrays of electrodes as a technique for controlling robotic prosthesis.

2 Background

2.1 Brief History

To understand the functionality of neurons, it is necessary to provide a method for capturing and interpreting their signals. Edgar Adrian became one of the first people to measure electrical discharges in single nerve fibers using a Lippmann electrometer and simple wire electrodes [1], winning the Noble Prize for his work in improving our understanding of the functionality of neu-

[1]Signal-to-noise ratio is defined as the "root-mean-square (RMS) level of the recording after the identified spikes have been removed, or as 2-6 standard deviations from the average signal level" [9]. A signal-to-noise ratio of 2.5-4.0 is considered the minimum useful threshold of a signal and indicated the recording of multiple neurons. Anything greater than 4.0 indicates the recording of a single neuron's activity.

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rons [14]. A number of important discoveries have subsequently been made in understanding the functionality of the brain using single neuron measurement techniques. This includes Hubel and Weisel's discovery of receptive fields [15] using tungsten and steel electrodes to measure individual neurons in a cat's visual cortex.

2.2 Single Cell Measurement Techniques

Single cell measurement techniques, generally fall into two categories: intracellular and extracellular. Intracellular techniques involve measurement of the potentials inside a neuron with the recording electrode, allowing for measurement of resting potentials and post-synaptic potentials[2], as well as action potentials. Conversely, extracellular techniques typically only measure the action potential outside of a neural cell membrane, but do not gain much insight into resting potentials or post-synaptic potentials. The method by which action potentials are created will be discussed later.

2.2.1 Intracellular

While there are several techniques for measuring intracellular potentials including: voltage clamp, current clamp [16], patch-clamp [17], and sharpened penetrative electrodes. These often result in cell death due to rupturing of the cell membrane and, as such, are typically only used to gain insight into neuron functionality rather than functional purposes.

2.2.2 Extracellular

Extracellular systems, however, usually retain cell viability, and are often used for both research and functional purposes when measurement of action potentials is needed. Extracellular single cell measurements typically involve placing an electrode close to the cell membrane to detect the voltage change, typically "50 to 500 microvolts (V) in amplitude, with a frequency content from 100 Hz to about 10 kHz" [18]. This is possible because the depolarization of the inside of a neuron during activation affects the extracellular mileau due to the opening of ion channels in the cell membrane (to be discussed later).

There are two main types of electrodes used commonly for measuring these action potentials: glass and metal. The glass micropipette electrode is attributed to Gerard and Ling [19]. A glass pipette is extruded to a fine tip and filled with an electrolyte "to form a conductive link to the tissue" [18]. A larger electrode is then placed in the electrolyte to connect relevant measurement instruments. Glass micropipettes are typically used for intracellular measurements due to the high resistance of the tip and high capacitance of the pipette wall. This forms what is essentially a low-pass filter, making it ideal for measuring lower potentials (such as resting potentials).

2.3 Electrodes for Neuroprosthesis

It is currently possible to use non-invasive techniques, such as EEG readings, to accomplish relatively simple tasks, such as cursor movement on a screen [20, 21]. However, more complex systems, like control of a prosthetic limb, where actions can consist of many degrees of freedom, are limited by the low signal-to-noise ratio of these measurement techniques. As such, even in existing methods for complex functions in non-invasive systems, such as control of a humanoid robot seen in [22], patients will learn how to select one of a set of given options rather than be given direct

[2] A post-synaptic potential measures the membrane potential of the receiving terminal of a neuron.

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control of the entire system. In the case of controlling the humanoid robot, all functionality of the robot was abstracted to preprogrammed functions and the users simply selected which object they wished the robot to pick up from a set of four images.

To use the intricate signals involved with complex movement for control of a prosthesis, it is necessary to measure more than one neuron's action potential spikes at a time, while retaining a high signal-to-noise ratio and a high level of selectivity for distinguishing neurons [12]. As such, we focus on intracortical microarray techniques which retain such properties, allowing for spatial and temporal analysis of neuron activation [23]. Using intracortical microarrays, several groups have been successful in enabling control of a robotic prosthetic arm for executing complex motions in both animal and human trials [13, 5].

2.4 Neuron Function

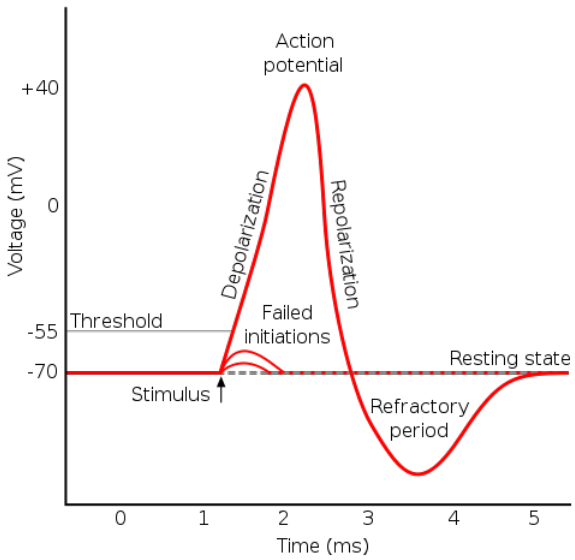

Figure 1: A representation of the action potential of a cell. Image reproduced from Wikipedia: `http://en.wikipedia.org/wiki/Action_potential`.

Before looking at various intracortical electrodes, it is important to return to, and define, how such electrodes work on a general level and which signals they measure. While previous reviews [24, 25] describe the in-depth processes involved in charge transfer and measurement or stimulation by electrodes, it is important to note here briefly the mechanism of action. Neurons retain a constant voltage difference across the plasma membrane known as a membrane potential [26]. This membrane potential is upheld by various ion channels and pumps (using sodium and potassium) that continuously balance the voltage difference between the inside and the outside of the cell. Synapses cause the cell to depolarize (or hyperpolarize) on stimulation. Once this depolarization reaches a threshold, an action potential is triggered. During an action potential, the membrane rapidly increases and then suddenly drops back down in a spike-like waveform (see Figure 1). This sudden action potential then triggers synapses in the next connected neuron. This waveform is typically fairly consistent within a cell throughout activation potentials. The sudden change in potential also results in a measurable extracellular current due to the interaction of the ion channels and pumps with the extracellular mileau. When placed sufficiently close to a neuron, an electrode can noticeably record these changes. The low-pass filter (capacitive) properties of the extracellular

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environment result an attenuation of this signal, and noise from surrounding cells will result in a low signal-to-noise ratio in the electrode if the electrode is not placed close enough to the cell.

3 Review of Current Intracortical Electrode Systems

The control mechanism for use of a robotic prosthetic via an interface with the central nervous system can be divided into four main parts: the recording mechanism (intracortical electrode arrays), the recording electronics, extraction algorithms (for determining movement intention), and robotic actuators [27]. Here focus is placed on the recording mechanism. Electronics and algorithms vary greatly between projects and depend on the site of implantation and the probe or electrode array used. As such, they are not discussed. Robotic actuators are also highly varied in prosthetics and are beyond the the scope of this review. However, a number of systems have previously been discussed [28, 29, 30, 31, 32].

Generally, intracortical electrodes fall into two categories: MEMS devices and bundles of wires. Bundles of wires involve forming individual electrode wires into structures for intracortical study and also include neurotrophic methods. MEMS devices include two main devices: the Michigan probe and the Utah array which are often used as a base for creating new intracortical systems.

3.1 Wire electrodes as bundles or arrays

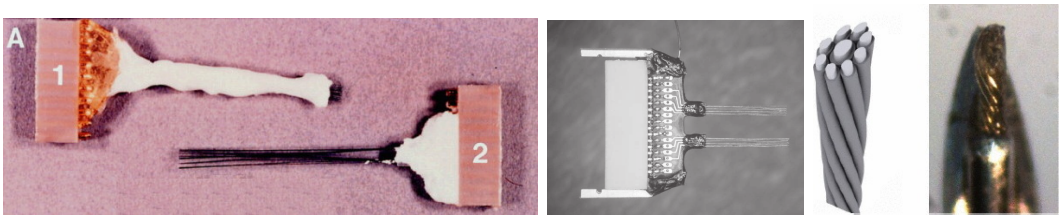

Figure 2: Examples of microwire arrays and bundles. Left, microwire arrays (1) were used for cortical and thalamic implants and bundles (2) used for brain stem implants. Image reproduced from [33]. Middle, examples of two 4x4 electrode arrays sharing a 32-channel connector. Image reproduced from [34]. Right, an example of a bundle of "eight Ni-Chrome wires spun around one Pt/Irwire in a braiding type manual process" used for deep brain recording [35].

Some of the earliest examples of recording of multiple neurons simultaneously in a long-term implantation have been using bundles or arrays of microwire electrodes [36]. These methods continue to be used by some groups, such as at Duke University [34] for many applications, but most commonly bundles of wires are used for deep brain recordings (as seen in Figure 2) [35, 37]. In these systems, individual microwire electrodes are placed into the brain and then connected externally through some sort of channel connection mechanism or bundled together and encapsulated by plastic or other material before being placed in the brain (as seen in Figure 2).

The microwires can be fabricated through electrolytical sharpening [38] or mechanical beveling such that the diameter of the wire is in the 20 - 50 μm range and the wire is brought to a fine tip (less than 1 μm) [18, 34]. The wire is then subsequently insulated, except for the tip, to prevent signal noise from other neurons touching the rest of the electrode. An alternative to this, is to use a pre-insulated wire and to cut the tip of the wire in a blunt or angled fashion resulting in exposure of the metal. In this case, an angled cut results in easier insertion and less damage to surrounding neurons during implantation. However, this reduces the electrode's ability to record from single neurons because of greater exposure to the metal by neighboring cells [34]. The metal wires can

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be made of any conductive metal, but typical metals seen are tungsten, stainless steel, platinum, iridium, or gold.

Metal electrodes, and most of the subsequently described methods here, detect changes in neuron's membrane potential by forming an interface with the aqueous extracellular surroundings. In this way, changes in the extracellular current, as previously described, can be relayed and interpreted as spikes during an action potential.

Fabrication methods vary greatly for connecting the wires together. In arrays, often used with shorter lengths of wires and applications close to the surface of the brain, mechanisms generally fall into two categories: discretely wired and layered approaches [34]. In either case, wires are typically spaced 200 μm to 1000 μm apart. In the discretely wired approach, straight wires are typically bound together through a glue and then deposited onto a silicon substrate (or printed circuit board) to be wired to other amplification, filtering, or channel-switching circuitry. In the layered approach, printed circuit boards (PCBs) are used to adapt the spacing of the electrode array to a given connector. The differences between these two methods can be seen in Figure 3. The choice of technique highly depends on the circuitry used for signal processing at the base and the channel connector of choice.

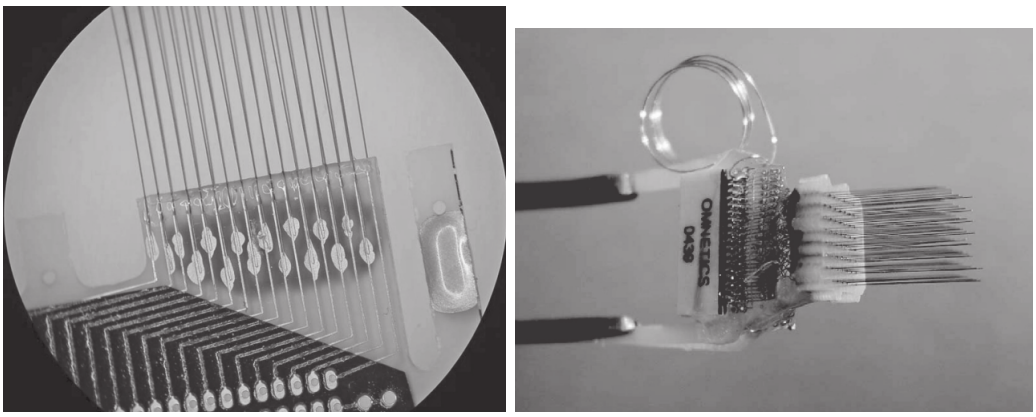

Figure 3: Images of the layered methodology for making electrode arrays (left) and the discrete method (right). In the discrete method the wires are straight and placed on a silicon substrate, and wired subsequently to the channel connector. In the layered method a PCB is used to create an interface adapting the array to the desired circuitry. Images reproduced from [34].

Electrode bundles are typically used in deep brain recording as they are usually tightly packed, adding stability and stiffness for insertion deep into the brain (so they don't bend or break and so there is damage on implant). A bundle can be seen in Figure 2. The wires are manually spun together in a braid and then insulated further with a guide tube (for further stability), which can be removed on insertion [35].

Overall, electrode wire arrays are often well suited for making customizable interfaces that are specifically designed for a certain part of the brain, or for a certain purpose. However, these same characteristics also make them more difficult to reproduce and the large size of the arrays could result in more tissue damage during insertion [18]. However, for deep brain stimulation, it may be necessary to use a technique such as bundling microwires to provide stability (so the wires do not bend on insertion) for the length of wire needed, which may not be possible with other subsequently described techniques.

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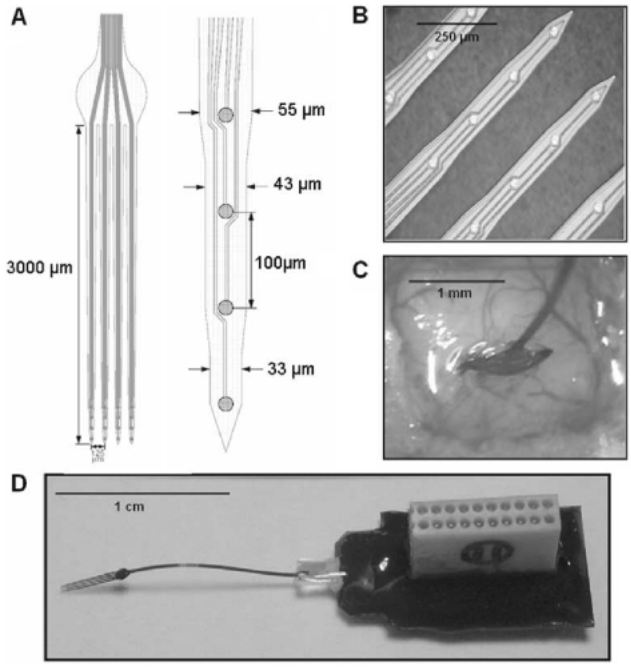

Figure 4: (A) A schematic of a 16-channel, 4-shank Michigan electrode. (B) 20 μm diameter recording sites, 4 per shank on a picture of the Michigan probe. (C) Implanted probe in the auditory cortex, covered by a thin ALGEL layer. (D) A complete probe assembly. Shanks are connected to a 1-cm long 5-μm-thick ribbon cable which is then connected to further instrumentation. Images reproduced from [39].

3.2 Michigan Probe

The Michigan probe [40, 18] seen in Figure 4, named after the University of Michigan where it was created, is a bit more versatile than some of the other electrode systems described here. It is highly reproducible in its geometric and electrical properties, small with greater site packing density, can be be made in batches, and is compatible with ribbon cables for connection to other electronics. However, it remains highly customizable [39]. In fact, the Michigan probe has been modified previously with microchannels in the shanks[3] for controlled drug delivery through the blood brain barrier [41].

While, the Michigan-probe has spurred numerous similar devices to be made, all with slight variations. Generally, Michigan probes take the form of several shanks made of a silicon substrate that have lithographically patterned arrays of electrodes and conductors on them, running back to leads that a ribbon connection can be bonded to. Dimensions of Michigan-like devices vary greatly, between 1.5 mm and 5 cm long and as narrow as 5 μm wide [42].

The device is typically fabricated in several steps [39]. First, seen in Figure 5A, a silicon wafer is doped through the selective diffusion of boron[4] This defines a conductive substrate, and later the size and shape of the device as will be described. Three layers of silicon dioxide, silicon nitride, and silicon dioxide again, respectively, are deposited onto the boron substrate, acting as insulators from its conductivity and forming the lower dielectric layers. This process is done using low-

[3]The protruding spike of the probe which contains the electrodes, see Figure 4

[4]To accomplish this selective diffusion, the silicon wafer is thermally oxidized, preventing boron from diffusing. As parts of the oxidation are removed, the boron is free to diffuse, resulting in this formation. Once boron is diffused to a desired thickness, typically 15 μm [18], the oxidation mask is removed completely.

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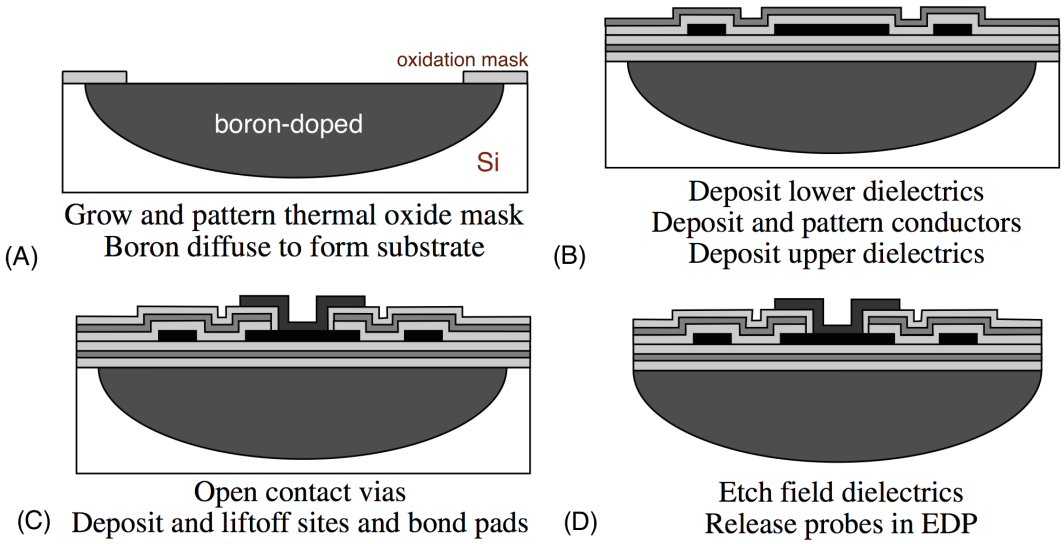

Figure 5: Figures depicting the various steps of fabricating a Michigan probe. Images reproduced from [18].

pressure chemical vapor deposition (LPCVD)[5]. Subsequently, a conductive interconnect material (typically phosphorous-doped polysilicon [18]) is deposited and patterned using photolithography onto the lower dielectrics. These interconnects lead the electrodes back to bond pads which a ribbon connector can be bonded to to connect other circuitry. The deposited interconnects are then insulated by another tri-layer of silicon dioxide, silicon nitride, and silicon dioxide. These steps can be seen in Figure 5B. To form the electrodes, wet (HF) and dry etching (reactive ion etching) are used to open up electrode and bond pad (ribbon pad connection) sites for metalization. The sites are then metalized using a lift off procedure.[6] Iridium is typically used for the electrodes (due to their ability to be electrochemically activated to act as a stimulation site [44, 45] and carry a lower impedance[7]) and gold is typically used for the bond pads. See Figure 5C. Lastly, the unneeded insulation tri-layers are removed using reactive ion etching, the wafer is thinned in an acid mixture, and then the non-boron-doped silicon is etched away using ethylenediamine-pyrocatechol. This can be seen in Figure 5D.

It is important to note that this fabrication process is highly customizable, as aforementioned. For example, it is possible to add circuitry onto the probe [47], microchannels for drug delivery [41], among other constructs. The shape and size of the probe can be customized by the boron doping step for different uses as well. For example, to reduce risk of more injury during insertion, the tip of the shanks can be made sharp by adjusting the boron diffusion so that it is extremely shallow at the tip and then tapers at an angle less than 10 degrees [48, 18].

[5]Briefly, in LPCVD, two gases react over a wafer to deposit oxide. The wafer is exposed to volatile substances, decomposing the substrate and producing the deposited layer [43].

[6]Typically, with lift off processes, a photoresist is patterned onto the device. Then the device is coated with the desired material. The resist is then dissolved, removing the material from those sites, but leaving it everywhere else. Here, sputtering deposition is used to deposit the metal.

[7]Ross et al. state that "reduction in impedance reduces the required magnitude of the voltage stimulus, which in turn has the advantage of reducing the stimulus artifact" [46]. Essentially, a lower impedance lowers the noise in the system. A lower impedance can be obtained by a greater surface area at the cost of sensitivity and selectivity of the electrode. However, iridium carries a low impedance and as such allows the reduction of the surface area to retain sensitivity and selectivity.

3.3 Utah Electrode Array

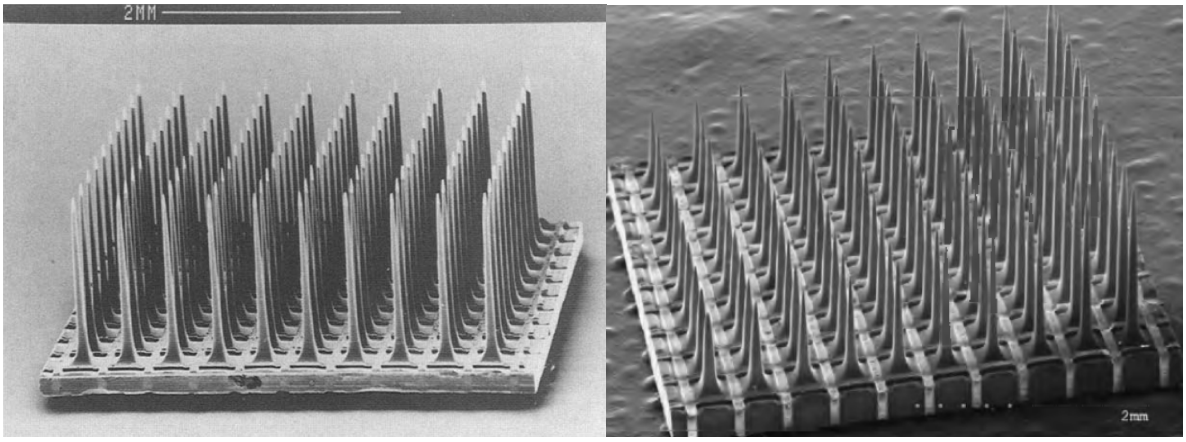

Figure 6: (Left) A scanning electron micrograph image of the Utah Electrode Array. Image reproduced from [49]. (Right) A scanning electron micrograph image of the Utah Slanted Electrode Array. Image reproduced from [50]

The Utah Electrode Array (UEA) [51, 52] has been used as a base for a number of modified systems and is extremely popular due to its reproducibility and high electrode density. A UAE is typically an array of 10 x 10 electrodes machined from a monocrystalline block of silicon. Each electrode (or shank) is about 1.5 - 2.0 mm long with about 250 μm to 400 μm between them. In the Utah Slanted Electrode Array, the shank sizes are varied from 0.5 mm to 2.0 mm long, but the slanted array was developed for use in peripheral nerves to compensate for the tubular nature of the nerve [50]. Both the slanted array and the typical Utah array can be seen in Figure 6.

To fabricate the device, a diamond dicing saw is used to cut out grooves for the electrodes. Then a powered frit sealing glass is mixed with methanol and used to fill the grooves until the mixture covers the entire surface a few 100 μm above the silicon. The mixture is then degassed in a vacuum and fired to melt the glass.

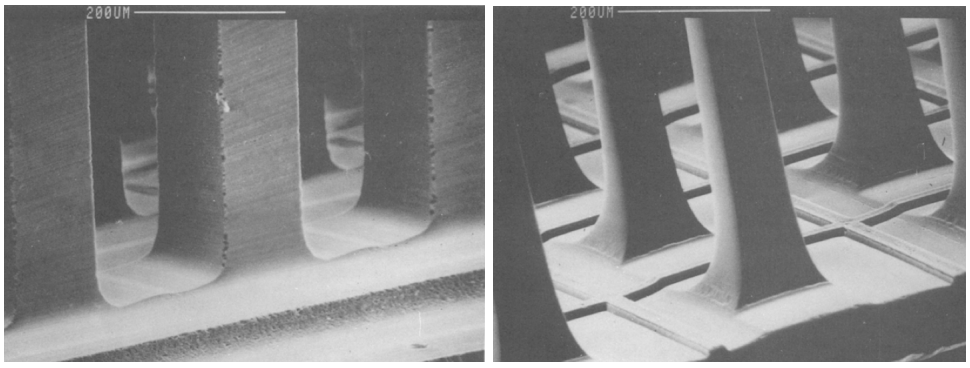

Figure 7: Scanning electron micrograph images of the individual electrodes on the UEA before (left) and after (right) etching via acid baths. Post-etching, the columns are noticeably smaller and more smooth. Glass grooves can be seen separating the columns in a grid. Images reproduced from [52]

Photolithography is used to place square aluminum contact pads on each silicon island, behind each individual silicon shank. Square columns are subsequently sawed out using a diamond dicing saw, and the columns are placed in two acid baths to reduce the size of the columns and sharpen the

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tips of the electrodes, respectively (see Figure 7). Finally, the tips are coated with platinum and the entire array except for the tips is encased in polyimide to prevent current passing through the rest of the shanks. It is important to note that more recent works have modified this technique, with better performance, by using iridium instead of platinum for the tips and parylene instead of polyimide for encapsulation [53]. This work has further been improved to use a two layer encapsulations of parylene and Al_2O_3 to increase the lifespan of the device and improve biocompatibility [54].

Utah microarrays retain a relatively high signal-to-noise ratio of 6:1 on average [23], making them well-suited for precision tasks. In fact, both the animal and human trials previously mentioned [13, 5] which successfully translated recorded signals from the M1 cortex to real-time precise movements of a robotic arm, used a Utah microarray for recording of the signals.

Additionally, the fabrication methods are highly reproducible and the geometry well-defined. As such, it has become commercially manufactured and is commonly used for clinical trials. Additionally, recent work in progress has begun to make the manufacturing process more efficient and allow for the chip size to be reduced. One study uses Su-8 to insulate the needles and deep reactive ion etching to replace the dicing saw [55]. Using photolithography an etching techniques to replace manual parts of the manufacturing process could potentially make the process much more parallelizable and efficient.

3.4 Others

While this is a subset of the highly varied space of intracortical electrode systems, the major systems which are commonly used as a base for further work have been described. In particular, the Utah array is often used in the field for control of robotic prosthetics as aforementioned.

There are several other classes of system which are noteworthy to mention: floating arrays [56] and neurotrophic systems [57, 58]. Floating arrays can be comprised of any of the aforementioned systems, but rather than strictly attaching the system to the skull, a lose wire is attached to the array and the bulk of the electronics attached to the inside of the skull. Since the brain is free moving, this ensures that further damage to the array or the brain is not undertaken with stiff structures that bolt the microarray directly to skull. While this is not a subset of systems, but rather a technique for implantation and electronics, it is important and often used in conjunction with all of the aforementioned systems.

Neurotrophic systems typically consist of a glass cone (or funnel) with electrodes on its inside and openings on the tip, as well as the bottom. It is filled with a neurotrophic material, spurring neuron growth through the cone. This results in high quality and reliable signals with the drawback that signals from fewer neurons overall are acquired. With regard to control of a robotic prosthesis, the issues with scalability of neruotrophic systems do not make them ideal until more improvements are made in this regard. However, current systems do show promise due to proven long-term implantation (greater than 3 years) and the high quality of signals [59, 60]. With more scalable solutions, it may be possible to use neurotrophic systems with better results than conventional systems previously described.

One recent noteworthy direction, is the increasing use of carbon nanotubes (CNTs) for measuring neuron activity and steps toward intracortical arrays of CNTs to replace current techniques. CNTs are cylindrical tubes of pure carbon molecules [61] with many interesting properties and potential uses. They are biocompatible, mechanically strong, flexible, have a high conductance, and are electrochemically and biologically stable [62]. Because of these properties, they are ideal candidates for use in intracortical recording. Already, carbon nanotube coatings have been used to increase biocompatibility of electrode microarrays and were found to improve quality of recordings by lowering impedance and increasing charge transfer [63, 64]. Further work has continued in

using carbon nanotubes for intracellular recording [65] with promising results. Additionally, proposed methods for creating microarrays of carbon nanotubes for intracortical recording had been proposed [66], and recently successfully implemented with promising *in vitro* results [67].

3.5 Implantation

Due to the larger sizes of microwire systems and the shanks of Michigan-based systems, procedures for implantation typically involve either insertion by hand [68] or by use of a mechanical device for precision (which positions the device and ensures a straight line of insertion) [34].

However, due to the density of Utah microarray based devices, it was determined that manual insertion under constant slow pressure resulted in elastic compression of the tissue underneath the device such that significant damage was incurred and the array did not fully penetrate the tissue throughout [69]. As a result, it was determined that high speeds of around 8.3 m/s were needed to safely insert a Utah array to a depth of 1.5 mm into the cortex. A pneumatic impact insertion system was made for this purpose [69, 70].

3.6 Issues and Possible Solutions

While early versions of these devices may not have been suitable for long-term implantation due to lack of thoroughly tested encapsulation or surgical procedures. Recent versions of the discussed systems have been shown to be viable for extended periods of time. In fact, one of the patients in the previously mentioned human trials of the Utah microarray for controlling a robotic prosthetic had the microarray implanted five years prior [5] and continued to be able to control the robotic arm with many degrees of freedom. However, there are still issues which need to be considered in evaluating the possibility of long term implantation of intracortical devices.

3.6.1 Risk of Injury During Implantation

An obvious risk with itracortically implanted devices is the possibility of injury during implantation. As previously mentioned, several steps in each of the described systems have been taken to reduce the risk of injury (angled cutting of microwires, sharpening of tips in Michigan arrays, and pneumatic implantation of Utah arrays). However, depending on the skill of the surgeon, among other factors, there may still be a resultant injury. Few in depth studies have been done about every type of system and surgical method, but from the available literature [71, 72, 73] it is clear that there is always tissue damage incurred during insertion of devices due to the invasive nature of the technique. Bjornsson et al. [73] demonstrate a direct correlation between the amount of damage and the speed of insertion, again indicating that faster insertion results in less damage. While seemingly no studies have yet been done on the effects of this damage on the typical function of the affected area of the brain, the resiliency of the brain suggests that alternative neural pathways can be used to compensate for minimal damage. A study using the Utah Slanted Electrode Array in the sciatic nerves of anesthetized rats [74] suggested that crush injury from implantation did not have a significant impact on the rats' use of the affected nerve and muscles. However, the authors state that implantation caused a marked decrease in action potential amplitudes of both impacted nerve and muscle tissue of "38%, 36%, and 13% in nerve, medial gastrocnemius, and tibialis anterior compound action potential amplitudes, respectively". These results are likely applicable to the directly affected portion of the brain. While more study is needed to determine the extent of damage which insertion causes in the brain, current literature seems to suggest that it is acceptable for chronic use.

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3.6.2 Signal Stability

Studies [75] have shown that day to day fluctuations occur within the consistency of a signal waveform and patterns, as well as signal viability. Harris et al. suggest that this is largely due to either human operator error or wrongful attribution of spikes to certain neurons [76]. In their study, they measure cell spiking through both a tetrode (four electrode) array and glass pipette methods. They see up to 30% error between the two. However, they show that introduced automatic spike-sorting algorithms reduced error by up to 8%. It seems as though the fluctuations in signal stability seen in various studies, have inconclusive results due to the possible error rates of microarray attributions. Additionally, the measure for signal stability involves comparing similarity of waveforms for a neuron action potential [75]. It is possible that this measure is not reflective of signal stability, but rather the plasticity of the brain in that signal pathways grow and change over time. Since the signal waveforms are thought to be highly dependent on the geometric morphology of the cell and the extracellular mileau [25] it is possible that changes in interconnections or the extracellular mileau could be the cause of these inconsistencies.

3.6.3 Long Term Viability

Examination of both Utah and Michigan microarrays showed similar results in that only about 60% of implanted microarrays remained viable[8] after 6 months of implantation [77, 68]. Nicolelis et al. performed a study of *in vivo* implantation of low-density microwire arrays and found that viability ranged from 3 months to greater than 18 months [78]. This data is supported by another study using microwires [79]. Other studies of the Utah microarray with a parylene encapsulation (as opposed to the traditional polyimide encapsulation) suggested viability after more than 12 months of in vitro submersion in a phosphate buffer saline at room temperature [80, 81]. Suner et al. performed an extensive study on Utah electrode microarrays in monkeys yielding viabilities ranging from a minimum of 3 months to greater than 1.5 years [75]. All this data suggests the possibility for long term use, but a high level of variability *in vivo*, where some electrodes cease to be viable early on, yet others remain viable for years (as in the previously described patient in [5]). The main cause of the loss of viability of the signals from these microarrays has been associated often with the immune response to the implant. Polikov et al. provide an in-depth explanation of the mechanics of such foreign body responses [82].

This immune response has been linked to the long-term signal degradation of implants. Some studies suggest that the signal loss is attributed to glial scarring (seen in Figure 8) [83, 48, 84], yet others suggest that the prolonged immune response results in loss of neurons in a so called "kill zone" [85, 48]. While it is still an open question as to what the actual cause is, both of these theories seem promising, yet both are caused by the immune response of the body. As such, it is important to address the immune response, for long term viability of intracortical implants to become reliable.

Several attempts have been made to address the immune response which appears to be the cause of signal loss over time: use of biocompatible encapsulation materials, use of flexible materials for electrodes, and coating or delivery of bioactive molecules.

As previously mentioned, some promising work has been done in encapsulating Utah microarrays with alternative, more biocompatible, materials [54], further work has been done in constructing arrays out of entirely biocompatible polymers or coating existing arrays with such polymers [87, 88].

[8]Note, viability here is defined as a signal-to-noise ratio within accepted standards, as aformentioned of at least 4. While this varies from paper to paper, this generally seems to a be a valid indicator of viability of the electrode signal.

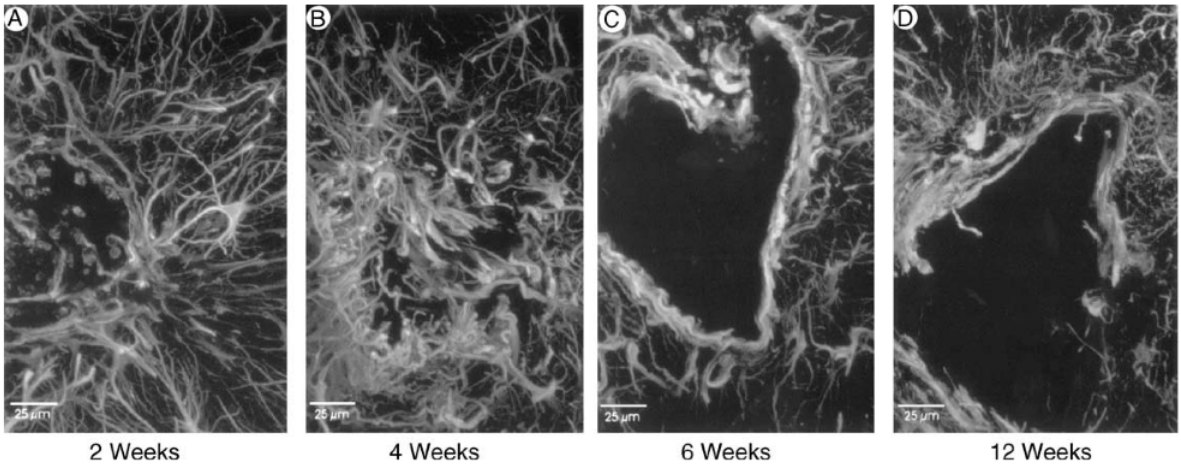

Figure 8: The progressive formation of a glial scar. Between 6-12 weeks no change occurs, suggesting completion of a glial scar by 6 weeks. Image reproduced from [86]

Additionally, carbon nanotube coatings have been shown to improve recording capabilities [63]. While there seems to be no concrete evidence from controlled studies suggesting that the immune response is caused by the materials used, the improvements from the use of biocompatible polymers suggests that there is some slight correlation and may be worth pursuing in combination with other mechanisms.

Another theory for the continued immune response at the site of implantation is due to the difference in flexibility of the electrode shanks and the brain. The brain's elastic modulus is about 5 kPa, while the elastic moduli of silicon (as in the Michigan probe shanks and the Utah electrode array shanks) is 166 GPa [9]. It is possible that movement of the brain and the difference in elasticity could result in more damage or strain that furthers an immune response. However, Winslow et al. suggest that there is little difference in glial scarring or immune response if more elastic materials are used [89].

Further, Szarowski et al. suggest that there is in fact little difference made to the immune response by changing the material and mechanical properties of the devices (though they didn't take into account biocompatible coatings) [90]. Thus, it is important to look to other ways of dealing with immune responses.

Some of the most promising systems relate to the coating or drug delivery of bioactive molecules on intracortical electrode devices. As previously mentioned, Michigan-like structures can be customized to contain drug delivery channels or wells through photolithography. These can now be used to deliver bioactive molecules to the site of implantation. Alternatively, bioactive molecules can simply be coated onto the shanks of all aforementioned systems through simple covalent bonding techniques. Various bioactive molecules have been used with different goals in mind. Some groups have attempted to use motifs and peptides found in the extracellular matrix (collagen, fibronectin, RGD, YIGSR, etc.) to encourage growth of neurons around the electrodes and even adhesion to the electrodes [91, 92]. While these methods show increased neuron attachment and growth around the electrodes [91], studies have shown that glial scarring remains an issue [93].

Few studies have had success when addressing glial scarring and response through bioactive molecule coatings. One study showed that dextran coating of DLC[9]-poly-lysine surfaces significantly reduced adhesion of glial cells *in vitro* [94]. While this study is promising, *in vivo* conditions

[9]Diamond Like Carbon

may prove to have different results or affect neuron growth adversely as well. Another study shows mixed results using laminin as a coating [95]. The initial glial response was increased, but the long-term results showed reduced glial scarring.

Targeted drug delivery of immunosuppressants is another possible avenue in reducing glial scarring and the overall immune response. Two promising works used Dexamethasone[10] during implantation resulting in decreased glial scarring and improvements to implant performance [83, 96]. While the drug delivery of Dexamethasone was only during implantation, it is possible to combine this technique with constant drug delivery systems suggested by Rousche et al [97]. In their system, they etch drug delivery wells into a Michigan-like probe to deliver dextran. This could be modified to release other immunosuppressants (like Dexamethasone) at intervals to alleviate the chronic immune response and, potentially, glial scarring.

While many systems, using widely different techniques, show promise, no one combination has been found to completely or significantly reduce the immune response to negligible levels. As such further study and work is needed.

4 Conclusion

Currently, intracortical electrode arrays have shown the most promise in successful real-time control of a robotic prosthesis with many degrees of freedom. However, there are several downsides to intracortical systems which must be addressed before widespread clinical use. First, long term viability is questionable. While in some cases, implants seem to last for years, in others they become unusable after just a few months [5, 75, 77, 68]. Because of the widely varied results within studies, more thorough investigation is needed, with more tightly monitored controls, to determine long term viability and possible reasons for variation.

One mainly cited reason for loss of signal, however, is immune response, which appears throughout many studies. For chronic implantation, it is necessary to overcome the immune response of the brain to prevent glial scarring or chronic inflammation of the implantation area. While many systems have been proposed to address these issues, no one solution has proven to sufficiently alleviate the problem in *in vivo* studies. Again, variability between studies and tested systems leads to inconclusive results and further controlled research is needed. Some promising emerging alternatives, such as CNTs, suggest the possibility of addressing immune responses and providing increased performance. However, these also need further study, and have yet to be proven *in vivo*.

In choosing which type of intracortical system to use, it is important to keep in mind its intended purpose and to design it as such. While microwire arrays and bundles allow for more customization, they are typically larger and have less electrode density, acquiring fewer signals. Michigan arrays are also highly customizable and allow for photolithographic incorporation of sub-structures like drug delivery systems and on board circuitry. Michigan arrays also allow for 3D readings of neurons at different levels. Utah arrays are commonly used due to their simplicity and high electrode density and seem to have the most promise in robotic prosthetics due to current availability and ease of fabrication. However, any and all of these systems must be modified to address the aforementioned issues to truly be viable in truly long-term (greater than 5 years) of implantation.

While non-invasive techniques currently do not have the same amount of precision and control as intracortical systems, new improvements in surface cortical electrodes [11] and the use of signal-processing, machine learning, and ensemble systems [98, 99, 100] may bridge the gap between intracortical techniques and less invasive techniques. The ease of human trials and the less-damaging nature of non-invasive techniques make them far more attractive, but the their complexity make it

[10] A steroid with anti-inflammatory and immunosuppressant effects.

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unlikely that they can be of comparable quality (in precision of movement and speed of feedback) to current intracortical systems for years to come.

Either way, both intracortical and non-invasive techniques still have much investigation and experimentation to be completed before commercially viable long-term solutions are popularized for control of robotic prosthetics.

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References

[1] Adrian, E. D. & Bronk, D. W. The discharge of impulses in motor nerve fibres Part II. the frequency of discharge in reflex and voluntary contractions. *The Journal of physiology* **67**, i3–151 (1929).

[2] Hubel, D. H. & Wiesel, T. N. Receptive fields, binocular interaction and functional architecture in the cat's visual cortex. *The Journal of physiology* **160**, 106 (1962).

[3] Eshraghi, A. A. *et al.* The cochlear implant: historical aspects and future prospects. *The Anatomical Record* **295**, 1967–1980 (2012).

[4] House, W. F. & Urban, J. Long term results of electrode implantation and electronic stimulation of the cochlea in man. *The Annals of otology, rhinology, and laryngology* **82**, 504 (1973).

[5] Hochberg, L. R. *et al.* Reach and grasp by people with tetraplegia using a neurally controlled robotic arm. *Nature* **485**, 372–375 (2012).

[6] Normann, R. A., Maynard, E. M., Rousche, P. J. & Warren, D. J. A neural interface for a cortical vision prosthesis. *Vision research* **39**, 2577–2587 (1999).

[7] Sterman, M. B. & Egner, T. Foundation and practice of neurofeedback for the treatment of epilepsy. *Applied psychophysiology and biofeedback* **31**, 21–35 (2006).

[8] Deep-Brain Stimulation for Parkinson's Disease Study Group. Deep-brain stimulation of the subthalamic nucleus or the pars interna of the globus pallidus in Parkinson's disease. *The New England journal of medicine* **345**, 956 (2001).

[9] Wolpaw, J. & Wolpaw, E. W. *Brain-computer interfaces: principles and practice* (Oxford University Press, 2011).

[10] Humphrey, D. R. & Hochberg, L. R. Intracortical recording of brain activity for control of limb prostheses. In *Proceedings of the RESNA Annual Conference*, vol. 15, 650–658 (1995).

[11] Viventi, J. *et al.* Flexible, foldable, actively multiplexed, high-density electrode array for mapping brain activity in vivo. *Nature neuroscience* **14**, 1599–1605 (2011).

[12] Lebedev, M. A. & Nicolelis, M. A. Brain–machine interfaces: past, present and future. *Trends in Neurosciences* **29**, 536–546 (2006).

[13] Velliste, M., Perel, S., Spalding, M. C., Whitford, A. S. & Schwartz, A. B. Cortical control of a prosthetic arm for self-feeding. *Nature* **453**, 1098–1101 (2008).

[14] Adrian, E. *The Basis of Sensation: The Action of the Sense Organs* (Christophers, 1934).

[15] Hubel, D. H. Single unit activity in striate cortex of unrestrained cats. *The Journal of physiology* **147**, 226–238 (1959).

[16] Hodgkin, A. L., Huxley, A. & Katz, B. Measurement of current-voltage relations in the membrane of the giant axon of Loligo. *The Journal of physiology* **116**, 424 (1952).

[17] Hamill, O., Marty, A., Neher, E., Sakmann, B. & Sigworth, F. Improved patch-clamp techniques for high-resolution current recording from cells and cell-free membrane patches. *Pflügers Archiv* **391**, 85–100 (1981).

[18] Hetke, J. & Anderson, D. *Silicon microelectrodes for extracellular recording* (CRC Press, 2002).

[19] Ling, G. & Gerard, R. The normal membrane potential of frog sartorius fibers. *Journal of cellular and comparative physiology* **34**, 383–396 (1949).

[20] Fabiani, G. E., McFarland, D. J., Wolpaw, J. R. & Pfurtscheller, G. Conversion of EEG activity into cursor movement by a brain-computer interface (BCI). *Neural Systems and Rehabilitation Engineering, IEEE Transactions on* **12**, 331–338 (2004).

[21] Wolpaw, J. R., McFarland, D. J., Neat, G. W. & Forneris, C. A. An EEG-based brain-computer interface for cursor control. *Electroencephalography and clinical neurophysiology* **78**, 252–259 (1991).

[22] Bell, C. J., Shenoy, P., Chalodhorn, R. & Rao, R. P. Control of a humanoid robot by a noninvasive brain–computer interface in humans. *Journal of neural engineering* **5**, 214 (2008).

[23] Maynard, E. M., Nordhausen, C. T. & Normann, R. A. The Utah Intracortical Electrode Array: a recording structure for potential brain-computer interfaces. *Electroencephalography and clinical neurophysiology* **102**, 228–239 (1997).

[24] Merrill, D. R., Bikson, M. & Jefferys, J. G. Electrical stimulation of excitable tissue: design of efficacious and safe protocols. *Journal of neuroscience methods* **141**, 171–198 (2005).

[25] Cogan, S. F. Neural stimulation and recording electrodes. *Annu. Rev. Biomed. Eng.* **10**, 275–309 (2008).

[26] Lodish, H. *Molecular cell biology* (Macmillan, 2008).

[27] Schwartz, A. B. Cortical neural prosthetics. *Annu. Rev. Neurosci.* **27**, 487–507 (2004).

[28] Bogue, R. Exoskeletons and robotic prosthetics: a review of recent developments. *Industrial Robot: An International Journal* **36**, 421–427 (2009).

[29] Dellon, B. & Matsuoka, Y. Prosthetics, exoskeletons, and rehabilitation [grand challenges of robotics]. *Robotics & Automation Magazine, IEEE* **14**, 30–34 (2007).

[30] Belter, J. T. & Dollar, A. M. Performance characteristics of anthropomorphic prosthetic hands. In *Rehabilitation Robotics (ICORR), 2011 IEEE International Conference on*, vol. 29, 1–7 (IEEE, 2011).

[31] Versluys, R. *et al.* Prosthetic feet: State-of-the-art review and the importance of mimicking human ankle-foot biomechanics. *Disability & Rehabilitation: Assistive Technology* **4**, 65–75 (2009).

[32] Biddiss, E. & Chau, T. Dielectric elastomers as actuators for upper limb prosthetics: Challenges and opportunities. *Medical engineering & physics* **30**, 403–418 (2008).

PeerJ PrePrints | https://dx.doi.org/10.7287/peerj.preprints.1255v1 | CC-BY 4.0 Open Access | rec: 21 Jul 2015, publ: 21 Jul 2015

[33] Nicolelis, M. A., Ghazanfar, A. A., Faggin, B. M., Votaw, S. & Oliveira, L. M. Reconstructing the engram: simultaneous, multisite, many single neuron recordings. *Neuron* **18**, 529–537 (1997).

[34] Nicolelis, M. A. *Methods for neural ensemble recordings* (CRC press, 2007).

[35] Gritsun, T. *et al.* A simple microelectrode bundle for deep brain recordings. In *3rd International IEEE/EMBS Conference on Neural Engineering (CNE'07)*, 114–117 (2007).

[36] Strumwasser, F. Long-term recording from single neurons in brain of unrestrained mammals. *Science* (1958).

[37] Tseng, W.-T., Yen, C.-T. & Tsai, M.-L. A bundled microwire array for long-term chronic single-unit recording in deep brain regions of behaving rats. *Journal of neuroscience methods* **201**, 368–376 (2011).

[38] Kaltenbach, J. A. & Gerstein, G. L. A rapid method for production of sharp tips on preinsulated microwires. *Journal of neuroscience methods* **16**, 283–288 (1986).

[39] Vetter, R. J., Williams, J. C., Hetke, J. F., Nunamaker, E. A. & Kipke, D. R. Chronic neural recording using silicon-substrate microelectrode arrays implanted in cerebral cortex. *IEEE Transactions on Biomedical Engineering* **51**, 896–904 (2004).

[40] Drake, K. L., Wise, K., Farraye, J., Anderson, D. & BeMent, S. Performance of planar multisite microprobes in recording extracellular single-unit intracortical activity. *IEEE Transactions on Biomedical Engineering* **35**, 719–732 (1988).

[41] Rathnasingham, R., Kipke, D. R., Bledsoe, S. C. & McLaren, J. D. Characterization of implantable microfabricated fluid delivery devices. *IEEE Transactions on Biomedical Engineering* **51**, 138–145 (2004).

[42] Hetke, J. F., Lund, J. L., Najafi, K., Wise, K. D. & Anderson, D. J. Silicon ribbon cables for chronically implantable microelectrode arrays. *IEEE Transactions on Biomedical Engineering* **41**, 314–321 (1994).

[43] Hersee, S. & Duchemin, J. Low-pressure chemical vapor deposition. *Annual Review of Materials Science* **12**, 65–80 (1982).

[44] Weiland, J. D. & Anderson, D. J. Chronic neural stimulation with thin-film, iridium oxide electrodes. *IEEE Transactions on Biomedical Engineering* **47**, 911–918 (2000).

[45] Robblee, L., Lefko, J. & Brummer, S. Activated Ir: An electrode suitable for reversible charge injection in saline solution. *Journal of the Electrochemical Society* **130**, 731–733 (1983).

[46] Ross, J., O'Connor, S., Blum, R., Brown, E. & DeWeerth, S. Multielectrode impedance tuning: reducing noise and improving stimulation efficacy. In *Engineering in Medicine and Biology Society (IEMBS'04). 26th Annual International Conference of the IEEE*, vol. 2, 4115–4117 (2004).

[47] Csicsvari, J. *et al.* Massively parallel recording of unit and local field potentials with silicon-based electrodes. *Journal of neurophysiology* **90**, 1314–1323 (2003).

[48] Edell, D. J., Toi, V., McNeil, V. M. & Clark, L. Factors influencing the biocompatibility of insertable silicon microshafts in cerebral cortex. *IEEE Transactions on Biomedical Engineering* **39**, 635–643 (1992).

[49] Nordhausen, C. T., Maynard, E. M. & Normann, R. A. Single unit recording capabilities of a 100 microelectrode array. *Brain research* **726**, 129–140 (1996).

[50] Branner, A., Stein, R. B., Fernandez, E., Aoyagi, Y. & Normann, R. A. Long-term stimulation and recording with a penetrating microelectrode array in cat sciatic nerve. *IEEE Transactions on Biomedical Engineering* **51**, 146–157 (2004).

[51] Campbell, P. K., Jones, K. E., Huber, R. J., Horch, K. W. & Normann, R. A. A silicon-based, three-dimensional neural interface: manufacturing processes for an intracortical electrode array. *IEEE Transactions on Biomedical Engineering* **38**, 758–768 (1991).

[52] Jones, K. E., Campbell, P. K. & Normann, R. A. A glass/silicon composite intracortical electrode array. *Annals of biomedical engineering* **20**, 423–437 (1992).

[53] Bhandari, R., Negi, S. & Solzbacher, F. Wafer-scale fabrication of penetrating neural microelectrode arrays. *Biomedical microdevices* **12**, 797–807 (2010).

[54] Xie, X. *et al.* Long-term reliability of Al2O3 and Parylene C bilayer encapsulated Utah electrode array based neural interfaces for chronic implantation. *Journal of neural engineering* **11**, 026016–026016 (2014).

[55] Pemba, D., Wong, W. M. & Tang, W. C. SU-8/silicon hybrid three dimensional intraneural electrode array. In *6th International IEEE/EMBS Conference on Neural Engineering (NER)*, 295–298 (2013).

[56] Musallam, S., Bak, M. J., Troyk, P. R. & Andersen, R. A. A floating metal microelectrode array for chronic implantation. *Journal of Neuroscience Methods* **160**, 122–127 (2007).

[57] Kennedy, P. R. The cone electrode: a long-term electrode that records from neurites grown onto its recording surface. *Journal of neuroscience methods* **29**, 181–193 (1989).

[58] Kennedy, P. R., Mirra, S. S. & Bakay, R. A. The cone electrode: ultrastructural studies following long-term recording in rat and monkey cortex. *Neuroscience letters* **142**, 89–94 (1992).

[59] Brumberg, J. S., Nieto-Castanon, A., Kennedy, P. R. & Guenther, F. H. Brain–computer interfaces for speech communication. *Speech communication* **52**, 367–379 (2010).

[60] Bartels, J. *et al.* Neurotrophic electrode: method of assembly and implantation into human motor speech cortex. *Journal of neuroscience methods* **174**, 168–176 (2008).

[61] Iijima, S. & Ichihashi, T. Single-shell carbon nanotubes of 1-nm diameter (1993).

[62] Voge, C. M. & Stegemann, J. P. Carbon nanotubes in neural interfacing applications. *Journal of neural engineering* **8**, 011001 (2011).

[63] Keefer, E. W., Botterman, B. R., Romero, M. I., Rossi, A. F. & Gross, G. W. Carbon nanotube coating improves neuronal recordings. *Nature nanotechnology* **3**, 434–439 (2008).

PeerJ PrePrints | https://dx.doi.org/10.7287/peerj.preprints.1255v1 | CC-BY 4.0 Open Access | rec: 21 Jul 2015, publ: 21 Jul 2015

[64] Lu, Y. *et al.* Electrodeposited polypyrrole/carbon nanotubes composite films electrodes for neural interfaces. *Biomaterials* **31**, 5169–5181 (2010).

[65] Yoon, I. *et al.* Intracellular neural recording with pure carbon nanotube probes. *PloS one* **8**, e65715 (2013).

[66] Wang, K., Fishman, H. A., Dai, H. & Harris, J. S. Neural stimulation with a carbon nanotube microelectrode array. *Nano letters* **6**, 2043–2048 (2006).

[67] David-Pur, M., Bareket-Keren, L., Beit-Yaakov, G., Raz-Prag, D. & Hanein, Y. All-carbon-nanotube flexible multi-electrode array for neuronal recording and stimulation. *Biomedical microdevices* **16**, 43–53 (2014).

[68] Kipke, D. R., Vetter, R. J., Williams, J. C. & Hetke, J. F. Silicon-substrate intracortical microelectrode arrays for long-term recording of neuronal spike activity in cerebral cortex. *Neural Systems and Rehabilitation Engineering, IEEE Transactions on* **11**, 151–155 (2003).

[69] Rousche, P. J. & Normann, R. A. A method for pneumatically inserting an array of penetrating electrodes into cortical tissue. *Annals of biomedical engineering* **20**, 413–422 (1992).

[70] Balling, K., Robertson, G., Stander, L. & Normann, R. Device and method for manipulating and inserting electrode arrays into neural tissues (2012). URL `http://www.google.com/patents/US8226661`. US Patent 8,226,661.

[71] Schmidt, S., Horch, K. & Normann, R. Biocompatibility of silicon-based electrode arrays implanted in feline cortical tissue. *Journal of biomedical materials research* **27**, 1393–1399 (1993).

[72] Johnson, M. D., Kao, O. E. & Kipke, D. R. Spatiotemporal pH dynamics following insertion of neural microelectrode arrays. *Journal of neuroscience methods* **160**, 276–287 (2007).

[73] Bjornsson, C. *et al.* Effects of insertion conditions on tissue strain and vascular damage during neuroprosthetic device insertion. *Journal of neural engineering* **3**, 196 (2006).

[74] Mathews, K. S., Wark, H. A. & Normann, R. A. Assessment of rat sciatic nerve function following acute implantation of high density Utah Slanted Electrode Array (25 electrodes/mm2) based on neural recordings and evoked muscle activity. *Muscle & nerve* (2014).

[75] Suner, S., Fellows, M. R., Vargas-Irwin, C., Nakata, G. K. & Donoghue, J. P. Reliability of signals from a chronically implanted, silicon-based electrode array in non-human primate primary motor cortex. *Neural Systems and Rehabilitation Engineering, IEEE Transactions on* **13**, 524–541 (2005).

[76] Harris, K. D., Henze, D. A., Csicsvari, J., Hirase, H. & Buzsáki, G. Accuracy of tetrode spike separation as determined by simultaneous intracellular and extracellular measurements. *Journal of neurophysiology* **84**, 401–414 (2000).

[77] Rousche, P. J. & Normann, R. A. Chronic recording capability of the Utah Intracortical Electrode Array in cat sensory cortex. *Journal of neuroscience methods* **82**, 1–15 (1998).

[78] Nicolelis, M. A. *et al.* Chronic, multisite, multielectrode recordings in macaque monkeys. *Proceedings of the National Academy of Sciences* **100**, 11041–11046 (2003).

PeerJ PrePrints | https://dx.doi.org/10.7287/peerj.preprints.1255v1 | CC-BY 4.0 Open Access | rec: 21 Jul 2015, publ: 21 Jul 2015

[79] Williams, J. C., Rennaker, R. L. & Kipke, D. R. Long-term neural recording characteristics of wire microelectrode arrays implanted in cerebral cortex. *Brain Research Protocols* **4**, 303–313 (1999).

[80] Sharma, A. *et al.* Long term in vitro functional stability and recording longevity of fully integrated wireless neural interfaces based on the Utah Slant Electrode Array. *Journal of neural engineering* **8**, 045004 (2011).

[81] Sharma, A. *et al.* Evaluation of the packaging and encapsulation reliability in fully integrated, fully wireless 100 channel Utah Slant Electrode Array (USEA): Implications for long term functionality. *Sensors and Actuators A: Physical* **188**, 167–172 (2012).

[82] Polikov, V. S., Tresco, P. A. & Reichert, W. M. Response of brain tissue to chronically implanted neural electrodes. *Journal of neuroscience methods* **148**, 1–18 (2005).

[83] Shain, W. *et al.* Controlling cellular reactive responses around neural prosthetic devices using peripheral and local intervention strategies. *Neural Systems and Rehabilitation Engineering, IEEE Transactions on* **11**, 186–188 (2003).

[84] Griffith, R. W. & Humphrey, D. R. Long-term gliosis around chronically implanted platinum electrodes in the Rhesus macaque motor cortex. *Neuroscience letters* **406**, 81–86 (2006).

[85] Biran, R., Martin, D. C. & Tresco, P. A. Neuronal cell loss accompanies the brain tissue response to chronically implanted silicon microelectrode arrays. *Experimental neurology* **195**, 115–126 (2005).

[86] Turner, J. *et al.* Cerebral astrocyte response to micromachined silicon implants. *Experimental neurology* **156**, 33–49 (1999).

[87] Abidian, M. R., Ludwig, K. A., Marzullo, T. C., Martin, D. C. & Kipke, D. R. Interfacing conducting polymer nanotubes with the central nervous system: Chronic neural recording using poly (3, 4-ethylenedioxythiophene) nanotubes. *Advanced Materials* **21**, 3764–3770 (2009).

[88] Ludwig, K. A., Uram, J. D., Yang, J., Martin, D. C. & Kipke, D. R. Chronic neural recordings using silicon microelectrode arrays electrochemically deposited with a poly (3, 4-ethylenedioxythiophene)(PEDOT) film. *Journal of neural engineering* **3**, 59 (2006).

[89] Winslow, B. D., Christensen, M. B., Yang, W.-K., Solzbacher, F. & Tresco, P. A. A comparison of the tissue response to chronically implanted Parylene-C-coated and uncoated planar silicon microelectrode arrays in rat cortex. *Biomaterials* **31**, 9163–9172 (2010).

[90] Szarowski, D. *et al.* Brain responses to micro-machined silicon devices. *Brain research* **983**, 23–35 (2003).

[91] Ignatius, M. *et al.* Bioactive surface coatings for nanoscale instruments: effects on cns neurons. *Journal of biomedical materials research* **40**, 264–274 (1998).

[92] Kam, L., Shain, W., Turner, J. & Bizios, R. Selective adhesion of astrocytes to surfaces modified with immobilized peptides. *Biomaterials* **23**, 511–515 (2002).

[93] Cui, X., Wiler, J., Dzaman, M., Altschuler, R. A. & Martin, D. C. In vivo studies of polypyrrole/peptide coated neural probes. *Biomaterials* **24**, 777–787 (2003).

PeerJ PrePrints | https://dx.doi.org/10.7287/peerj.preprints.1255v1 | CC-BY 4.0 Open Access | rec: 21 Jul 2015, publ: 21 Jul 2015

[94] Singh, A. *et al.* Glial cell and fibroblast cytotoxicity study on plasma-deposited diamond-like carbon coatings. *Biomaterials* **24**, 5083–5089 (2003).

[95] He, W., McConnell, G. C. & Bellamkonda, R. V. Nanoscale laminin coating modulates cortical scarring response around implanted silicon microelectrode arrays. *Journal of neural engineering* **3**, 316 (2006).

[96] Maynard, E. M., Fernandez, E. & Normann, R. A. A technique to prevent dural adhesions to chronically implanted microelectrode arrays. *Journal of neuroscience methods* **97**, 93–101 (2000).

[97] Rousche, P. J. *et al.* Flexible polyimide-based intracortical electrode arrays with bioactive capability. *IEEE Transactions on Biomedical Engineering* **48**, 361–371 (2001).

[98] Tombini, M. *et al.* Combined analysis of cortical (EEG) and nerve stump signals improves robotic hand control. *Neurorehabilitation and neural repair* **26**, 275–281 (2012).

[99] McMullen, D. *et al.* Demonstration of a semi-autonomous hybrid brain-machine interface using human intracranial EEG, eye tracking, and computer vision to control a robotic upper limb prosthetic (2013).

[100] Lavely, E., Meltzner, G. & Thompson, R. Integrating human and computer vision with EEG toward the control of a prosthetic arm. In *Proceedings of the 7th annual ACM/IEEE International Conference on Human-Robot Interaction*, 179–180 (ACM, 2012).

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