CHAPTER 3

The Biotic–Abiotic Interface

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INTRODUCTION

Brain-computer interfaces (BCI), or brain-machine interfaces (BMI), are systems designed to aid humans with central nervous system disabilities, including disabilities in movement, communication, and independent control of one's environment (Donoghue, 2002; Friehs et al., 2004; Lebedev and Nicolelis, 2006; Schwartz et al., 2006). Although these same approaches have the potential to augment normal function, as currently envisioned this new class of biomedical devices is being developed to help those with disabilities. As such, these devices may be useful for patients suffering from a variety of conditions including spinal cord injury, musculodegenerative diseases, stroke, amyotrophic lateral sclerosis, or other neurological or neuromuscular diseases. The intent of these devices and their associated components is to provide or supplement motor or sensory function that has been lost. The theoretical basis for such devices lies in our ability to detect neural signals and translate volitional commands into control signals for external devices including computers, robotics, or other machines. The acquisition of neural signals has traditionally occurred in the cerebral cortex, and the recording of these signals from implanted electrodes has a fairly extensive history.

Although several forms of technology are being developed, this chapter will focus exclusively on our present knowledge of the foreign body response to invasive technologies. Generally speaking, such devices are small by present biomedical-devices standards and are implanted in the cortex, the most superficial aspect of the mammalian brain. As currently designed, they penetrate a few millimeters depending on the target region and species. They contain multiple recording or stimulating sites located on one or more penetrating shafts that consist of conducting ceramics, metals, or polymers and have at least one insulating material (see the figures in Chapter 2 that illustrate some of the hardware under development). At present, such devices are tethered to insulated wires that exit the skull and lead to external amplifiers and other devices that can be substantial in size and are not

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very portable. Due to the nature of their design, the recording devices are frequently referred to as "penetrating electrode arrays."

To date, CNS recording devices have taught us much about the functional organization and neurophysiological underpinnings of the mammalian cortex and other brain regions, and appear, based on evidence to date, to become increasingly utilized in a variety of healthcare applications that will improve the quality of life of those affected with CNS-related disabilities (Lebedev and Nicolelis, 2006; Schwartz et al., 2006). The future economic impact of the technology appears equally significant. Coupled with other emerging technologies, we find ourselves on the doorstep of understanding one of the most elaborate and complex systems ever studied the human brain. What has been shown is that neural signals can be recorded from different brain regions by a number of different technologies in a variety of species for periods of time extending from months to well over a year. With direct relevance to BCI or BMI technology, neural activity can be interpreted and used to control a computer or robot or prosthetic device.

With the feasibility and proof of principle firmly established for various BCI and BMI applications, some of the focus has shifted to understanding how to maintain consistent, long-term operation of the implanted devices. Even though current designs usually perform as intended in short-term studies and applications, the major limitation of our current state of technology is inconsistent performance in chronic or long-term applications, which limits clinical implementation of this promising technology (Polikov et al., 2005; Schwartz et al., 2006).

Although the brain-tissue response to implanted electrode arrays is believed to be a major contributing factor, the precise mechanisms that cause inconsistent recording performance are unknown. Thus, until the mechanisms that underlie loss of function are understood, we are unlikely to develop rational strategies to improve their usefulness.

This chapter first discusses what is perceived to be the problem and establishes a foundation of common terminology. It then provides evidence that invasive electrodes can function over extended time frames as a proof of concept that this new class of biomedical device as currently envisioned can be biocompatible. It then reviews the current state of understanding of what happens following implantation of electrodes into the mammalian brain, trying where possible to identify gaps in our knowledge in an attempt to shed light on what still needs to be done. It concludes with a discussion of various strategies are under development to modulate the biotic–abiotic interface in an attempt to achieve better integration into brain tissue and achieve superior device performance. We caution that most of the technology focused on augmenting device performance, as promising as it may appear, is still under development, and for the most part has not been replicated sufficiently to understand its ultimate impact on advancing the field.

By all indications, a full understanding of what needs to be done to consistently interface various hardware with the variety of potential neural targets is still far off. A major obstacle at present is in understanding the science responsible for loss of function. This understanding is unlikely to occur in the near term without enhanced

and targeted funding to increase the number of investigators working in the field. The scientific breadth and depth needs to advance sufficiently, as has occurred with cochlear implants, so that the challenge shifts from lack of scientific knowledge to engineering.

BCI ABIOTIC-BIOTIC INTERFACE WORLD OVERVIEW

It is generally held by the scientific and engineering communities that maintaining a stable, long-term interface between an implanted recording electrode and adjacent neural circuitry is one of the major challenges that limit the widespread clinical implementation of BCI/BMI-based therapies.

The majority of science in North America is focused on describing the events that accompany the implantation of multielectrode recording arrays into brain tissue over time, with a particular emphasis on describing the temporal and spatial nature of the events that take place at the biotic–abiotic interface and assessing their potential to affect device function. Although the broad brush strokes are in place, significant detail is lacking, thus limiting the development of rational strategies to enhance consistency of long-term performance.

In Europe, China and Japan, there appears to be little direct work in the BCI/BMI-related domain that is focused specifically on understanding the biological underpinnings of invasive sensor biocompatibility. Here the emphasis of the research has been directed more toward the development of noninvasive technology and to adding intelligence to the robotic or external components of such devices. It was apparent from our visits in Europe and Asia that numerous groups are planning or developing implantable neural interfaces or are developing technology that has the potential to significantly improve the performance of invasive sensors for BCI and BMI applications. Clearly, the emphasis on such technology is increasing. The future potential capability of this community to improve or displace existing technology is significant.

A number of laboratories, mostly in North America, have explicitly acknowledged focused efforts at developing strategies to manipulate the tissue response in an effort to improve the long-term function of BCI/BMI and related invasive technologies. While some results appear promising, it is still too early to know which, if any, of these will ultimately improve the consistency of long-term recording performance of penetrating electrodes. Alternatively, perhaps practitioners need to radically change the approach as it is currently envisioned.

After an analysis of the peer-reviewed literature, two workshops, and visits abroad, we conclude that major gaps still remain in our understanding of the science behind the loss of function that occurs over time with the use of penetrating recording electrode arrays. It appears that this is unlikely to change significantly at the present levels of funding. Investments in science and technology are increasing abroad. We suggest that targeted funding also be provided in the United States to

increase our knowledge of the underlying science of CNS implant biocompatibility in order to maintain a leadership position in this sector, with corresponding general benefits to U.S. healthcare and the economy.

The Major Challenge: Consistent, Long-Term, Functional Integration

The key to the long-term operation of penetrating recording electrodes is in consistently and reproducibly maintaining connectivity with the system of interest. It is impossible to implant anything as large as a penetrating electrode into brain tissue without causing some damage at the site of implantation. Therefore, the goal is to achieve a response that allows the device to function as intended without causing unacceptable harm to the patient. The term used to describe this condition is biocompatible; notice that the definition is conditional. For a BCI or BMI device to be biocompatible, by definition it must be functional; that is, it must be capable of recording the activity of neurons, and the information sensed must serve some intended function. The definition does not require zero response, and it does not necessarily require that every electrode site record activity that is maintained over its lifetime. To be biocompatible, the tissue response to the implanted electrode, or risk, must be offset by the benefit of the device; that is, it has to remain functional. Ambiguity is often derived from the conditional nature of the definition. As the definition implies, at one point in time a device can be biocompatible, and a little later it may not be. Notice also that by definition, materials cannot be considered biocompatible unless they serve some measurable function. The ambiguity of terms makes a critical reading of the literature somewhat confusing, especially for students and members of constituencies outside the field who do not understand the nuance of the term. The ideal goal is full or seamless integration with nervous system tissue, or the achievement of a functional symbiosis between the biotic and abiotic interface that maintains device function over the lifetime of the patient. At present, we are far from the ideal.

Proof of Principle

For many BCI and BMI applications, a sufficient number of recording sites in an implanted array must be located exceedingly close to actively depolarizing neuronal cell bodies. Moreover, these neuronal cell bodies must remain viable independently and maintain their integrated activity and connectivity with the rest of the central nervous system. Practitioners in the field will tell you that recording sites need to be placed within a few hundred micrometers to as little as 50 μm away from the neuronal cell bodies in order to sense single-unit activity, and slightly farther away

to record local-field potentials. The literature also supports this view (Buzsaki and Kandel, 1998; Henze et al., 2000; Rall, 1962; Mountcastle, 1957). One of the major challenges is to determine how to achieve a higher level of consistency than is possible with the current state of the art.

Despite this seemingly difficult specification hurdle, the technology of recording devices has progressively advanced from the benchtop into the clinic (Hochberg et al., 2006; Schwartz et al., 2006). The earliest identifiable publications that describe the idea behind the approach may be credited to Schmidt (Schmidt, 1980; Schmidt et al., 1976). Since then, a variety of investigators have illustrated the potential of using recording devices to facilitate motor function. The earliest study demonstrating the use of a brain-computer interface in humans used a neurotrophic cone electrode implanted into the cortex of three patients who reportedly gained the ability to move a cursor on the computer screen through volitional commands recorded by indwelling electrodes (Kennedy et al., 2000). Since then, a multishank, silicon-microelectrode array was implanted into several paralyzed patients who demonstrated a substantial gain of function for volitionally moving a computer cursor (Hochberg et al., 2006).

Despite the successful experimental work in humans, the bulk of the proof of principle for BCIs and BMIs has been derived from studies in nonhuman primates (Musallam et al., 2004; Santhanam et al., 2006; Serruya et al., 2002; Taylor et al., 2002; Wessberg et al., 2000), as well as the contribution from numerous groups that have developed hardware or have used the hardware to advance our knowledge of neuroscience (Table 3.1).

As it stands, a number of groups have reported the ability to record signals for periods ranging from months to several years. Collectively, the publication record shows that the implementation of such technology for BCI and BMI applications is clearly possible. Furthermore, it can be achieved using a variety of designs, including glass microelectrodes, ceramic-based sensors, microwires insulated with a variety of materials, and doped silicon. These designs may be constructed as planar arrays or as multipoint tip electrodes, indicating that economic opportunity

Table 3.1 Longevity of Recording Performance in the CNS

Year	First Author	Species Implanted	Electrode Type	Functional Period of Signal Recording (day)
1976	Schmidt	Monkey	Parylene-coated iridium wires	223
				138
1977	Loeb	Monkey	Parylene-coated iridium wires	136
1984	Legendy	Cat	Parylene-coated platinum-iridium wires	9–25
1988	Schmidt	Monkey	Parylene-coated iridium wires	1,144
1989	Kennedy	Rat	Neurotrophic cone electrode (glass)	201[a]
1992	Kennedy	Monkey	Neurotrophic cone electrode (glass)	~450
1993	Carter	Cat	Michigan electrode (silicon)	~30
1994	Hetke	Guinea Pig	Michigan electrode (silicon)	~330

(Continued)

Table 3.1 (Cont.)

1998	Rousche	Cat	Utah intracortical electrode array (UEA; silicon)	~390[a]
1999	Williams	Guinea Pig	Polyimide-insulated tungsten wires	283[a]
				81
				101
				151
				35
				55
				51
				54
1999	Liu	Cat	Iridium wires	242
2000	Kennedy	Human	Neurotrophic cone electrode (glass)	426[a]
2003	Cui	Guinea Pig	Polypyrrole-coated Michigan electrodes (silicon)	14
2003	Kipke	Rat	Michigan electrode (silicon; 4-shank)	382
2003	Nicolelis	Monkey	Teflon-coated stainless steel microwires	~540
2004	Moxon	Rat	Ceramic-based microelectrodes	~91
2004	Kennedy	Human (40 years old)	Neurotrophic cone electrode (glass)	>636
2004	Vetter	Rat	Michigan electrode (silicon)	127
2005	Johnson	Rat	Michigan electrode (silicon)	>131 (when voltage biasing occurred)
2005	Rennaker	Rat	Tungsten microwires	21 (manual insertion)
				42 (mechanical insertion)
2005	Suner	Monkey	Bionic (Cyberkinetics; silicon multishank array)	569[a]
				870 (no data provided)
				425 (no data provided)
				92 (no data provided)
				1,264 (no data provided)
2006	McCreery	Cat	Parylene-coated iridium wires	220
				343
				320
				302
				293
2006	Ludwig	Rat	Michigan electrode (silicon)	42[a]
2006	Hochberg	Human (25 years old)	Bionic (Cyberkinetics; silicon multishank array)	~300[a]
2006	Hochberg	Human (55 years old)	Bionic (Cyberkinetics; silicon multishank array)	~330
2006	Liu	Cat	Iridium microwires	1,061

[a]Denotes electrode was still functioning at time of publication

exists. Moreover, the record supports the notion that it is indeed possible to have a long-lasting biocompatible recording electrode implanted in the mammalian cortex.

It is clear from discussions with practitioners that this kind of performance is not achieved routinely and represents a smaller subset of the total cases. We believe that it is safe to say that this type of performance is not the norm even though this point is hard to make from a review of the archival literature. Animals implanted with nonfunctioning electrodes are typically not used for experiments, and hence a rich source of failure analysis is not readily available. Nonetheless, anecdotal information informally deliberated at conferences among participating scientists acknowledges the challenge. Indeed, one can find discussions in the peer-reviewed literature that draw attention to performance problems with chronic recording electrode arrays where typically the number of functional recording sites and the quality of signals observed diminish over time (Burns et al., 1974; Liu et al., 1999; Ludwig et al., 2006; Nicolelis et al., 2003; Rousche and Normann, 1998; Schmidt et al., 1976; Williams et al., 1999).

The State of the Science

The available evidence emerging in numerous fields indicates that the biological processes that accompany the implantation of such devices into brain tissue involve the integration of different cellular and molecular events. Indeed, a mechanistic understanding of the type that allows manipulation of the biocompatibility of implanted electrode arrays is still beyond our grasp.

Studies from numerous groups performed on a variety of devices in a number of species have begun to sort out the details, and the broad dynamics of the process have been uncovered (Biran et al., 2005; Polikov et al., 2005). Collectively, the research has revealed certain patterns of response regardless of the size or the type of device or of the materials employed. Many investigators believe that the cellular response to the implanted electrode contributes significantly to inconsistent performance, and this belief may be traced back to several pioneering studies. These seminal studies showed that the number of electrode sites capable of recording well-defined single units decreased with time following implantation (Burns et al., 1974; Schmidt et al., 1976). The investigators postulated that the foreign body response, particularly astrocyte encapsulation that forms around the implanted electrode, may be responsible for the performance problems. Despite a lack of direct experimental evidence to support the hypothesis, many practitioners believe that astrocytic encapsulation is one of the major contributing factors to decreasing device performance. On the other hand, it is possible that a portion of inconsistent recording performance may have nothing to do with the tissue response and may be a normal attribute of an exceedingly plastic network-based physiology.

Studies conducted over the last half century evaluated the cortical brain tissue response to indwelling electrodes, both passive and active. The earliest studies showed that the foreign body response to indwelling electrodes involved reactive encapsulation of astrocytes and fibroblasts as well as activation of leucocytes, macrophages, and microglia, which was accompanied by neuronal degeneration (Bickford et al., 1957; Collias and Manuelidis, 1957). Collectively, these early studies established that the biotic–abiotic interface was well defined and composed of astrocytes surrounding the implantation tract. The implantation tract was well established by one month and remained stable through six months, the longest time frame studied. Macrophages, which are generally not observed in the normal cortical parenchyma, were observed at all time points at the brain tissue device interface. Similar observations have been reported with the latest generation of implants (Biran et al., 2005).

The earliest reports to describe the cellular nature of the interface indicated a reduction in synapses adjacent to the gliotic sheath surrounding implanted electrodes, whereas normal synaptic density was found just outside of this region (Collias and Manuelidis, 1957; Schultz and Willey, 1976). Astrocytes were observed to span a region 50–100 μm away from the edge of the electrode, and meningeal cells were observed in the gliotic sheath that may have migrated from the overlying meninges. These early studies, which used insulated metal wires as electrode arrays, showed that foreign-body, giant cells were always present adjacent to the implanted electrode.

Other researchers built upon this work by examining the brain tissue response to a variety of materials using approaches that attempted to preserve the interface (Babb and Kupfer, 1984; Dymond et al., 1970; Robinson and Johnson, 1961; Schultz and Willey, 1976; Stensaas and Stensaas, 1976, 1978). These studies taught us that the tissue response surrounding the implant could be quite variable, which may have reflected differences in the dorsal ventral architecture of the cortical columns, differences in the physical and chemical attributes of the implants, and differences in implantation techniques. At the end of the day, we learned that a wide variety of materials in such devices appeared safe whereas others were not.

Although descriptive studies refined our understanding of the range of usable materials, other pioneering work began to examine the usefulness of semiconductor technology for fabricating high-count, neural interfaces (see Chapter 2 for details). This led to a series of targeted funding initiatives by the National Institute of Neurological Disorders and Stroke (NINDS) of the National Institutes of Health (NIH) that culminated in the formation of the Neural Prosthesis Program. For over 30 years, NINDS has supported grants and contracts in numerous areas within the neural prosthesis field, including functional neuromuscular stimulation, deep-brain stimulation, multielectrode cuffs for nerve interfaces, cortical microelectrode arrays, biocompatibility of neural interfaces, implantable neural stimulators, and brain/computer interfaces. One of the noteworthy results of this funding was recognizing the importance of the biological understanding driving innovation in the field and

a shift from emphasizing the materials component of the biomaterials to a shared emphasis on the biology and the materials aspects of the technology.

Increased funding opportunities and awareness of the challenges pulled researchers from other areas into the field and increased the collective knowledge of the brain-tissue response to implanted electrodes. At its initiation, the Neural Prosthesis Program was funded primarily through contracts; however, the program now makes use of both grant and contract mechanisms to enable progress in the field. The transition from contracts has been facilitated by the increasingly widespread recognition of the importance of data-driven research. Program funding, along with the organization of workshops, conferences, and symposia, has been an effective driving force to attract researchers from allied fields. As a result, major changes have occurred in the way designers and fabricators envision neural interfaces.

One of the first papers to describe the tissue response to the newer generation of microelectrodes described gliosis and neuronal loss in the recording zone surrounding implanted electrodes (Edell et al., 1992). This study was one of the first to report increased gliosis near the tips of the implanted electrodes, which has encouraged others to model the biomechanics of implant design and generate hypotheses regarding the relationship between tethering forces and gliosis (Lee et al., 2005a; Subbaroyan et al., 2005); however, these models have not been completely validated experimentally.

The discovery of cell-specific antigens led to the increasing use of immunofluorescent histology to describe the spatial arrangement of specific cell types involved in the response. What we have learned to date is that the response to the newest generation of implanted microelectrode arrays resembles what has been reported in the past for simple insulated wires and other biomaterials. The major observation is the presence of encapsulating hypertrophic astrocytes that appear regardless of device type or design or whether the device is free-floating or tethered (Biran et al., 2005; Hoogerwerf and Wise, 1994; Schmidt et al., 1993; Szarowski et al., 2003; Turner et al., 1999). These observations motivated hypotheses that astrogliotic encapsulation contributes to the failure of such devices to maintain connectivity with adjacent neurons. The reasoning is that the reaction increases the distance between the recording site and nearby neurons. In addition, astrocytes can form a syncytium owing to their expression of junctional complexes (Lee et al., 2005b; Nagy and Rash, 2000). Although this has not been experimentally shown as a mechanism of function loss, it may affect electrode impedance. The thought is that astrocytes increase extracellular tortuosity in the surrounding tissue, which increases the path length for diffusion of solutes enhancing impedance at electrode sites or moves viable neurons out of the recording zone through hypertrophy and the overexpression of matrix (Polikov et al., 2005; Sykova, 2005).

Even though this hypothesis seems reasonable and may account for some of the loss of function, it is important to note that such responses happen irrespective of whether an electrode is functional or not. To the best of our knowledge, no study has established that astrocytic encapsulation is incompatible with device function or is the primary cause for the inconsistent device performance that challenges the

clinical implementation of such technology. At least one study attempted to understand the impact of surrounding silicon planar electrode arrays with cells involved in the foreign-body response and found that such cells indeed increase impedance at 10 kHz but not to a level that would be expected to impede recording *in vivo* (Merrill and Tresco, 2005). In addition, no study has shown that astrocytic encapsulation changes with a time constant, which might explain the inconsistency in performance that occurs beyond the initial month-long period over which it becomes established. Clearly other mechanisms are also at play.

Another prominent observation is persistent macrophage activation at the surface of the device and in the tissue immediately surrounding the implant (Biran et al., 2005; Schmidt et al., 1993; Szarowski et al., 2003). These observations occur irrespective of the indwelling time or type of recording array and suggest that such devices are a persistent source of inflammatory stimuli. As mentioned earlier, macrophages at the biotic–abiotic interface are not seen in the newer generation of devices. Instead, macrophages have been observed to accompany the foreign body response to the earliest implanted stimulating and recording electrodes. It is a general observation seen with all types of currently implanted devices.

Since macrophages can be a source of neurotoxic cytokines, are known to be toxic to oligodendrocytes, and inhibit progenitor division, they may impede healing or replenishment of damaged cells resulting from low-grade persistent inflammation and may contribute to inconsistent device performance over time (Hendriks et al., 2005). These last areas have been unexplored with respect to their potential to contribute to electrophysiological disturbances of recording electrodes.

In addition to the persistence of inflammatory cells, studies have observed significant reductions in nerve fiber density and neuronal cell bodies in the tissue immediately surrounding implanted electrodes (Biran et al., 2005; Edell et al., 1992). Persistent up-regulation of inflammatory cells and neurodegeneration does not accompany stab wound injuries in brain tissue. Therefore, loss of neurons is not caused by the initial mechanical trauma of electrode implantation but is associated with the foreign body response, possibly due to secondary cell loss associated with neuroinflammatory events. This has been observed near more natural foreign bodies occurring in MS, HIV infection, and Alzheimer's disease. Removal of key neurons has the potential to inactivate specific circuitry within the cortical column leading to electrophysiological deficits. Obviously, loss of neurons in the recording zone may also contribute to loss of function of such devices. However, to the best of our knowledge there are no studies that have examined whether neuron viability in the recording zone declines with indwelling time. Moreover, no studies have examined the relationship between neuronal loss and recording inconsistency over time. In addition, we currently have no knowledge of which of the many types of neurons in the cortical column may be affected by the foreign-body response. Clearly, much work remains to be done.

In summary, it appears that a number of factors may contribute to inconsistent performance of invasive recording electrodes. Although glial encapsulation clearly can be a problem, the cellular and molecular aspects of neuroinflammation may

also be important contributing factors. The science emerging in the areas of neuroinflammation may be particularly important in understanding electrical instability in chronic recording devices. For the most part, this newer body of work has reinforced the foundation of knowledge established by earlier studies using light and electron microscopy. Unfortunately, it has not yet provided the specific insights needed to drive improvements in device function.

STRATEGIES UNDER DEVELOPMENT TO IMPROVE ELECTRODE PERFORMANCE

A number of labs, mostly in North America, have explicitly acknowledged focused efforts to develop strategies to improve the long-term function of BCI/BMI and related invasive technologies. The strategies can be grouped into a number of different categories including pharmacological approaches, micro/nanoscale surface science, new materials, novel hardware design, insertion technology and adjustable depth electrodes and wireless technology. We briefly describe some of these developments below.

The mechanical mismatch between electrodes and surrounding brain tissue has been hypothesized as one of the major factors that determine biocompatibility of indwelling recording electrodes (Lee et al., 2005; Subbaroyan et al., 2005). Several groups have used finite element models to show that current designs are associated with increased strain fields at the biotic–abiotic interface. They propose that the strain fields will exacerbate the brain-tissue response given the movements that likely occur with normal respiration and changes in blood pressure during the cardiac cycle (Lee et al., 2005; Subbaroyan et al., 2005). Indeed, a recent paper has shown that the general tissue response to tethered microelectrode arrays is significantly greater with respect to glial encapsulation, macrophage activation, and loss of adjacent neurons when compared to the same electrode implanted as a free-floating implant. The paper suggests that wireless floating designs may be associated with less tissue reactivity (Biran et al., 2007).

Along these lines, it has been argued that making electrodes out of softer polymeric materials may also reduce the associated brain tissue response (Rousche et al., 2001; Subbaroyan et al., 2006; Yuen and Agnew, 1995). Likewise, a recent report from the Kipke group of the University of Michigan introduced a novel open architecture electrode design that places the recording sites on a thin supporting member. This design removes the function from the most reactive main shaft of the electrode similar to the tip electrode designs of microwire arrays and the Utah electrode array (Seymour and Kipke, 2006). A preliminary report suggests that this design reduces cellular encapsulation and is associated with less neuron loss; however, to the best of our knowledge, a fully functional recording electrode of this design has not been demonstrated.

To create a softer interface, the Bellamkonda group of Georgia Tech has examined the use of layer-by-layer electrostatic deposition of polyelectrolytes and laminin (He and Bellamkonda, 2005). They reported that such coatings reduce astrogliosis after four weeks of implantation compared to uncoated controls (He et al., 2006). Also, the Martin group of the University of Michigan has been developing alginate coatings for electrodes with sustained-release capabilities delivering anti-inflammatory agents (Kim and Martin, 2006). Also, the Martin group has been developing high-surface-area, fuzzy, conducting polymers for application at the recording sites, some of which incorporate growth factors (Cui et al., 2001, 2003). Similarly, the Bellamkonda group is developing strategies to immobilize endogenous anti-inflammatory agents like α-melanocyte-stimulating hormone, a neuromodulatory peptide that appears promising as an approach to reducing inflammation around the electrode (Zhong and Bellamkonda, 2005).

The community is concerned with minimizing the trauma associated with device implantation especially with regard to vasculature damage, which is believed to be an important contributor to downstream events. Minimizing trauma may also improve biocompatibility (Bjornsson et al., 2006). Toward this end, investigators are developing novel means of mechanically controlling insertion technology (Rennaker et al., 2005) as well as developing adjustable-depth electrodes that may be moved after implantation to achieve more consistent recording (Kralik et al., 2001; Musallam et al., 2007).

Despite the promise of these strategies, it is still too early to know which, if any, will ultimately improve the consistency of long-term recording performance of penetrating electrodes as most of the developmental work has not been performed on fully functional electrodes. Whereas in some cases the tissue response has been shown to be improved, it is not yet clear whether recording function will be improved in the same way. Therefore, it is still too early to know whether such approaches will meet the challenge posed by the foreign body response. It is possible that the field needs to radically change its approach as it is currently envisioned. This represents a significant opportunity for the next generation of scientists and engineers.

SUMMARY AND CONCLUSIONS

After an analysis of the peer-reviewed literature, two workshops, and visits abroad, we conclude that major gaps still remain in our understanding of the science behind the loss of function that occurs over time with the use of penetrating recording electrode arrays. It appears that this is unlikely to change significantly at the present levels of funding. Therefore, we suggest that targeted funding be provided in the United States to increase our knowledge of the underlying science of CNS implant biocompatibility in order to maintain a leadership position in this sector,

as well as to accelerate the technological improvements that will be necessary for this technology to contribute to improving U.S. healthcare and economic well-being.

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