

Brain Interfacing with Materials: Recording and Stimulation

Electrodes

TASK GROUP DESCRIPTION

Background

A new view in systems neuroscience is that variability of spikes is centrally coordinated and that this brain-generated ensemble pattern in cortical structures is itself a potential source of cognition. Large-scale recordings from neuronal ensembles are needed for testing this theoretical framework. Most thought-controlled brain-machine interface (BMI) devices are also based on such invasive techniques. Ideally, feedback signals from BMI devices should also be utilized to directly alter firing patterns of central neurons.

Action potentials produce large transmembrane potentials in the vicinity of their somata that can be measured by placing a conductor in close proximity to a neuron. A cylinder with a radius 150 μm contains up to 1000 neurons in the cortex. The use of two or more recording sites allows for the triangulation of the position of the neurons because the amplitude of the recorded spike is a function of the distance between the neuron and the electrode.

Initial Challenges to Consider

Currently, there is a large gap between the number of routinely recorded and theoretically recordable neurons. An ideal electrode has a very small volume, so that

tissue injury is minimized, and has a large number of recording sites for monitoring many neurons simultaneously. Micro-electro-mechanical system based devices can reduce the technical limitations inherent in wire electrodes, because with the same amount of tissue displacement the number of monitoring sites can be substantially increased. Furthermore, multiple sites can be arranged over a longer distance, thus allowing for the simultaneous recording of neuronal activity in the various cortical layers.

Progress in large-scale recording of neuronal activity depends on the development of three critical components:

1. Neuron-electrode interface for long-term recording and stimulation;
2. Spike sorting/identification of parallel spike trains; and
3. Extraction of the “neuronal code.”

In addition to increasing the numbers of recording sites, on-chip amplification, filtering, and time-division multiplexing will dramatically decrease the number of wires between the brain and electronic equipment by directly feeding the multiplexed digital signal into a computer processor. Programmed microstimulation through the recording sites and potentially real-time signal processing will not only facilitate basic research but is also a prerequisite for efficient, fully implantable neural prosthetic devices.

Initial References

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TASK GROUP SUMMARY—GROUP 1

(Due to the popularity of this topic, two groups explored this topic. Please be sure to review the second write-up that immediately follows this one.)

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Summary

The use of penetrating electrode arrays provides unprecedented access to individual or small groups of neurons in forming a basic foundation for neuroprosthetic applications. In his introduction group leader, Ravi Bellamkonda, addressed the importance of prosthetics and the use of electrode arrays at the interface between the brain and external electronics. Essentially, the promise of neuroprosthetics is the improvement of quality of life in persons with sensory or motor deficits caused by disease or injury to the nervous system.

Applications utilized by electrode arrays include, but are not limited to, recording signals from neurons and stimulation of neuronal activity. An invasive electrode array provides the interface between the brain and the prosthetic, and successful implantation and integration may result in full restoration of neurological function. An example of cochlear implants was provided, which currently employ an electrode array to transmit impulses from a stimulator to various regions of the auditory nerve. Also, individuals who experience profound levels of blindness may be able to restore some functional

vision by way of a cortical-based visual neuroprosthesis, a research interest of group member Richard Normann.

Recordings can sometimes be made over significant periods of time, but in many instances the quality of those recordings deteriorates over a six-month time frame.

Working group members identified the following as a major challenge for brain interfacing with materials: creation of penetrating electrode arrays that can reliably record or stimulate neuronal activity for longer than one year without jeopardizing the biocompatibility of the implant.

Mechanisms of Electrode Failure

Understanding the importance of electrode arrays in neuroprosthetic applications first requires recognition of the mechanisms of electrode failure. Group members agreed that failure is not limited to the physical construction of the electrode itself, but may also be the result of other factors, such as implantation, scarring, or micromotion.

The implantation of an electrode array runs the risk of cell and/or tissue damage, either vascular or neuronal. Group member Kendall Lee discussed deep brain stimulation for Parkinson's disease, as an example. There is a 2 percent to 3 percent chance of brain hemorrhage in the implantation process, as it involves advancing the electrode through the brain to the target site where nerve signals generate tremors or other symptoms associated with the disease. Although considered safe and effective, he said that improvements in targeting may further lower the risk.

The formation of scar tissue around an electrode array unquestionably contributes to the failure of the electrode in its ability to accurately collect and transmit neuronal

signals. Scarring is a result of the body's natural wound repair process, occurring as a result of implantation, and the physiology of scar tissue may make for diminished electrode functionality. Identifying whether a correlation exists between scarring and failure, and whether a scar is electrically insulating may bridge a gap in understanding electrode failure. Micromotion, or the movement of the electrode away from its targeted active site, may be a contributing factor to scarring as well.

With respect to physical properties of electrode arrays, materials may induce biofouling of electrical contacts between the electrode array and the neuron with which it is interacting, meaning that a contamination linked to protein deposition from brain interstitial tissue or even microbial activity may occur. A high-charge injection may also cause the device to fail.

Parameters

In the construction of short- and long-term solutions to the aforementioned predicaments, group members established engineering and process parameters, as they were necessary in defining the capabilities and limitations of a system. The materials used to construct the electrode arrays may potentially be influenced by the electrode geometry, the ratio of stress it can withstand within the targeted tissue, or tools used for implantation.

What Constitutes "Smartness"?

Before addressing short- and long-term solutions to the task at hand, group members paused to define what exactly a smart prosthetic would be. In order for a

material interface to the brain to be considered smart, it would need to be adaptive and sensitive to its dynamic environment. It may include properties of self-healing and/or self-repair, and have feedback or feed-forward controls. Suggestions from group members included designing an electrode to move autonomously or to be able to dynamically sense the local environment and release drugs to mitigate damage.

The group recognized the cost associated with smartness: Smartness requires complexity, and the potential cost of making the device too smart would be an increased chance of failure. Until there is a clear understanding of the mechanism of neurite extension and growth, in conjunction with knowledge of neuron function, a smart neuroprosthetic will remain a concept of the future.

Potential Short-Term Approaches

Group members decided on the second day of collaboration that a working timeline over 10 years would be considered in identifying a potential solution short-term. A short-term approach would be able to utilize present knowledge and/or present research data in the construction of new and improved neuroprosthetic systems.

An active exploration of scarring and its contribution to electrode failure, either by immunohistological techniques, state-of-the-art in vivo molecular imaging, or impedance spectroscopy, would provide a more detailed understanding of the mechanisms with which they fail. The group also identified the need for quantitative assessment of micromotion and a correlation with neural recording stability.

The group members speculated on potential solutions to fixing mechanisms of electrode failure. These included the development of electrodes with smaller cross-

sectional areas, like implantable quantum dots with nanowire connections. There was also recognition that there may be considerable benefits in usage of other materials beyond silicon and microwires. Advances in biomaterial research could result in electrode materials that match the compliance of brain tissue.

The smaller size of the electrode inherently reduces implantation risks, but achieving electrical interfaces become an issue. Group member Pedram Mohseni suggested wireless interfacing, as the technology is highly prevalent in today's society. The development of a wireless communication system to power the electrode, as well as allowing it to receive and transmit signals, would naturally be the next step. Also, proper packaging of the electrode for implantation, perhaps by hermetic sealing, is vital to the success of the implanted electrode array.

Potential Long-Term Approaches

The group maintained a "blue sky" mentality as they considered long-term solutions. Identifying whether or not fundamental differences existed between tissue responses to recording and stimulating electrodes posed the challenge of whether there needed to be completely different strategies for designing electrodes or electrode arrays for recording and stimulation.

While there was a consensus in the necessity to make smaller high-density electrodes, group members decided it was just as important to consider biology in the actual architecture and design. This means utilizing present working knowledge of specific system functions and physiologies in the creation, which may become known as application-specific electrode arrays.

As far as implantation is concerned, it may be feasible to consider the development of methods to make tissues surrounding the implant site more permissive to the implant. Also, using nanomaterials in the construction of the electrode may significantly reduce resistance and enhance the biocompatibility of electrode surfaces.

Once the electrode is implanted, a source of power is necessary for function, and then a network can be built throughout the body to power electrodes and interact with arrays.

The group also considered the option of developing an alternative, nonelectrical means of interfacing with the peripheral or central nervous systems. Harnessing light or using molecular photovoltaic structures may provide other avenues for stimulation, while neurotransmitters as well as field potentials may be an alternative for sensing.

What All of This Means for Smart Prosthetics

The short- and long-term possibilities for the advancement of neuroprosthetics ultimately bring into context where the future of smart prosthetics may be. Continuing from the earlier discussion about what constitutes “smart,” group members brainstormed examples of smart interfaces including encapsulating materials that react to emerging scar formation, the aut positioning of individual electrodes for optimizing signal acquisition, and microfluidics for injecting materials to make the tissue more permissive.

Interdisciplinary research in smart prosthetics will essentially evolve better devices and systems for improvement in the quality of life. As an example, utilizing biology to interact with biology to create the bio-based/hybrid interface may be the smart prosthetic of tomorrow. Instead of having solid electrode arrays as we do now, it may be

possible to create self-inserting bioelectrodes that grow into the tissue with minimal issues in biocompatibility. For instance, this may be done by sowing a feeder layer of genetically modified neurons onto the surface of the cortex, from which dendrites and axons grow into brain tissue. Synaptic connections are made and can thus “tap” brain signals. Electrical activity within this feeder layer could then be recorded. It may also be possible to create optically based interfaces by utilizing the work of group member Elias Greenbaum, who works in extracting Photosystem I of green plants and inserting them into excitable cells. He said that Photosystem I is a robust system and works quickly by capturing photon energy to do reduction-oxidation reactions.

As with all biological, chemical and engineering processes, it comes down to feasibility and practicality of the proposed solutions. How would neurite in-growth and targeting be controlled? How would reliable and functional synapses be formed and how would we promote that action? How would access be provided for the tissue-engineered interface? Would they be electrical or optical? And could the concept of creating the functional smart prosthetic lie in biomimetic interfacing? With all of these questions in mind and after almost eight hours of collaboration, group members were excited to be on the brink of developing the next successful smart prosthetic.

TASK GROUP SUMMARY—GROUP 2

(Due to the popularity of this topic, two groups explored this topic.

Please be sure to review the first write-up which immediately precedes this one.)

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Summary

Using technology to restore lost functions of hearing, vision, movement, scientists are working to make reality out of what was once considered within the realm of miracles.

One of the first success stories in this field of bionics, or neural prosthetics, is the cochlear implant. For those with severe hearing impairment it brings the ability to hear sound again. The technology is based on the simple idea that by stimulating the auditory nerve with electrical signals from a microphone, a person can understand those signals and hear again. Thousands of people around the world have been surgically implanted with this technology and are capable of hearing again, proof of the remarkable concept that electronics can communicate directly with human nerves. Now researchers are attempting to move from the auditory system to more complex systems, such as vision, and thereby developing new technology that could restore a greater variety of abilities.

The scientists in this arena generally don't talk about the miraculous nature of their research. Rather, they discuss the very concrete problems of actually making the devices work. One question at the very center of this endeavor is what happens when hard and rigid devices physically touch the soft, ever changing and adapting human tissue. How can the device be affected, and how does the tissue react? Despite much

research, there is still much debate surrounding these questions, especially when the tissue in question is brain tissue.

A diverse group of 12 researchers, engineers and funders convened as part of the Fourth Annual National Academies Keck *Futures Initiative* in Irvine California to discuss this problem, central to the future of many critical technologies. The group was charged with discussing how the brain interacts with materials. It soon became clear that the central and unavoidable first problem was why electrodes implanted in the brain often stop performing their function after a period of time.

Solving this problem of limited robustness of the interface between electronics and the nervous system could greatly advance the science of bionics. Finding ways to make the electrode work longer in the brain would help advance technologies like the retinal implant (bionic vision), cochlear implant (already available bionic hearing). Longer lasting brain electrodes could also improve the electrical brain stimulation systems, like those used to relieve the tremors of Parkinson's disease, as well as electrodes that pick up the brain's signals and help paralyzed patients control electronic devices just by thinking.

Researchers working on brain implantation in animals have been frustrated by the problem of why electrodes don't work consistently for sustained periods of time. Researchers have observed that over time, some implanted electrodes stop receiving signals from the surrounding neurons. "The problem is that we don't know why it doesn't work" said Karen Moxon, associate professor of biomedical engineering at Drexel University. However, she and others doubted that it was a failure of the electrode itself.

Her laboratory had taken an electrode that failed in one animal, cleaned it, and implanted it again in a new animal. “The electrode would work fine,” she said.

If the electrode isn't broken and the brain isn't broken – that leaves the area of space where the two touch. The problem appears to hinge exactly on “the mysterious 100 μm of space” surrounding the electrode, as Bruce Wheeler, professor and interim head of the bioengineering department at the University of Illinois, put it. The group floated a number of ideas of what might be happening in that area. David Martin, professor at the materials science and engineering department of the University of Michigan provided several images of his work that showed the area around the electrode in an experimental animal stained for neurons and for cells that typically respond to injury to the brain (e.g., astrocytes and microglia). In one image the neurons cleared away from the area surrounding the electrode, and in another image, astrocytes crowded in close. While it was unclear whether the scarring caused by the brain's reaction caused the failure, there was agreement that this space between the neurons and the electrode would somehow need to be bridged.

Another issue was what Martin called, “the fork in the Jell-O problem.” The microscopic wiggling of a hard metallic device against the mushy brain tissue could either change the position of the electrode, or cause continual inflammation in the area.

Soon the real brainstorming of this lively group began. The “what about a thing that does this” and “what if we do that” ideas started flying across the room. Every new suggestion was returned with another even more fantastic sounding solution: “What if we coated the electrode with chemicals that would suppress the inflammation that might be causing the inflammation and scarring?” “What if we made an electrode that would

deliver those chemicals to the area as they were needed?” “You can’t deliver a drug forever, plus there’s the question of toxicity.” “What if we could make electrodes grow wires deeper into the brain, past the area of interface?”

But even as the ideas got more creative, it was clear that these scientists weren’t simply daydreaming, but that these were actual technologies and techniques that were currently in development in their labs. Some of them already exist, while others were on their way to being created.

What if we could make an electrode that had the ability to scrape away the scars as they formed: “an in situ cleaning tool” said Gareth Hughes, senior biomedical engineer at Zyvex Corporation. To this seemingly wild suggestion Themis Kyriakides, assistant professor of biomedical engineering and pathology at Yale University, replied with a straight face, “We’re working on it.”

To address the problem of the neurons that were retreating away from the electrode, two approaches were suggested. There was the “Hansel and Gretel approach,” as Martin put it, which was to attract the neurons to the electrodes by candy coating them with chemicals that neurons could not resist drawing towards. The other method was to bring the technology out to the neurons themselves. Tiny nanowires were sent out from the electrode, past the problematic 100 μ m, to make connections with neurons that could still provide a signal.

An alternative version of the nanowire approach was proposed by Chet de Groat, professor of pharmacology at the University of Pittsburgh. Perhaps the surface of the electrode could be engineered in such a way to improve the electrical and mechanical interactions with the tissue, either by using stem cells or genetically engineered cells.

“We could make these cells sniffers,” said de Groat, using tissue engineering to create biological wires that would seek out and communicate with the surrounding neurons.

In order to address the fork in the Jell-O problem, Martin suggested a number of changes that could be made to the electrodes that would make them less like a fork and more like another piece of Jell-O. In addition to electrodes that were “fuzzy” and had a greater surface area with which to interact with the surrounding neurons, he proposed creating a polymer or gel that approached the softness of the brain, but was still able to transmit electric current or to act as a scaffold for very thin electrodes.

But all of the potential attempts at bypassing the problem to make a better connection between the brain and the electrode boiled down to the fundamental issue articulated by Moxon, “We still don’t know what it means to stick something in the brain.” However, there was still disagreement as to whether the basic research should be completed before development went forward, or whether the two lines of research could progress in parallel.

At first those who primarily studied biological systems felt that understanding how brain tissue reacts should be addressed before one could think about designing a better electrode. To learn more about the problem itself, Kyriakides boldly stated, “I don’t think the answer is going to come from the materials side,” to the great frustration of group members like Martin, whose research focused on ways to engineer materials to make better electrodes.

After considerable discussion, it became clear that the future would require work on both fronts, and that work on one front could help inform work on the other. For example, the electrode itself could be used to study the effects of its own presence on the

cells around it. Fashioning an electrode that could detect the chemical and cellular changes in its vicinity could inform biologists and provide a fascinating challenge for engineers.

Eventually, and beautifully reflecting the spirit of collaboration and the ultimate goal the conference itself, both sides began to see the usefulness of the others' approaches. "This is the first time I've sat in a room with people who talk like this," said Kyriakides. Many other group members echoed the sentiment. "This has turned into a much more productive session than I had hoped for," said Martin. By the end of the sessions the group members were discussing future collaborations. And the major hurdles in this field will require just this kind of team work.