Nanotechnology in BMIs

Abstract

Extensive communication directly with the human brain provides the ability to aid neurological disorders that have never before been understood or presented with feasible treatment. This paper shows some nanotechnology techniques that could help make BMIs possible so that new medical solutions can be provided. Existing work with a closed-loop feedback system that can read and write to the brain via electrodes has been proven capable of controlling computer operations by reading neural activity. The opposite is also possible such that artificial brain stimulation can be used to aid or rehabilitate neural deficiencies. These electrode channels provide readings of neural signals to a receiver for near immediate analysis, and then instructions can be sent back in a similar fashion to stimulate specific neurons before the brain realizes it happened. This research is being extended by monitoring more specific neural signals made possible by new nanotechnologies that can allow for efficient and safe implantation of orders of magnitude more information channels that last for a longer period of time.

Introduction

Approximately 1 billion people in the world are affected by some variation of neurological disorder. While traditional neurosurgery provides an option for some patients, it is far too invasive, inaccessible, and expensive. Additionally, there is a high risk involved due to medical errors with a wide variation in capabilities from individual surgeons. Many people don't even have the chance to take the risk as there is an endless list of brain diseases that do not have any sort of effective treatment yet. Aside from this, BMIs can also provide a vast increase in accessibility for handicapped or frail patients.

The brain remains the most physically untouched part of the body which accompanies a lack of understanding of how it works. BMIs can potentially eliminate all of these downfalls with implantable brain-machine interfaces that can interact with neural signals via electrodes. Every action that humans perform along with anything we might experience from the outside world is described by information that interacts through the brain in the form of neural signals. These neural signals occur when an action potential is triggered due to any sort of stimulus from our internal or external environment. Each neuron forming the 100 billion neuron network produces an electric field when triggered. Localized electric fields can be measured from microelectrode threads precisely placed extremely close to the neurons. Variation in strength of the electric field provides quantitative data in the form of spikes. The rate statistics and precise timing of spikes provides the data that needs to be analyzed. Once analyzed, the reverse can be done in order to send signals to specific parts of the brain to provide corrected or additional information that is required.

While the medical field is an important first step for BMI technology, this can be put to use for the enhancement of healthy individuals as well.

These devices all work with microelectrodes that require significant upgrades to improve safe, long term integration with the human brain. These upgrades require innovative engineering and modifications at the nano scale to reduce the biological mismatch that currently causes so many problems.

Past research, scientific basis & working principles

This research is being built upon the demonstrated ability to control computers with the brain, as well as the ability to control the body with sensory input by artificially providing the necessary stimuli. The brain has been studied extensively by a noninvasive approach in the way that humans act/react to the environment around them. However, studying the brain from the outside quickly hit its limitations. This information is too general to pinpoint exactly what is happening on the inside, which is why it is necessary to go into the brain.

Cochlear implant

The first cochlear implant was invented to stimulate hearing nerves with only a single channel. In a patient with hearing loss, this device produces electrical currents to relay audio information past the inner ear to directly stimulate the cochlear nerve. This invention is the first direct interface to the central nervous system that restores sensory function [1]. Adopted widely in clinical usage, this laid major groundwork for working with the brain from the inside.

One of the many important influences taken from this work include the necessity of biocompatible materials. Important things to consider were how the device would affect nearby tissue and ear internals under electrical stimulation. It was observed that there was a possibility to cause permanent damage to the auditory nerve under high intensity stimulus rates. Carefully designed studies minimizing complications were an essential part of developing these implants.

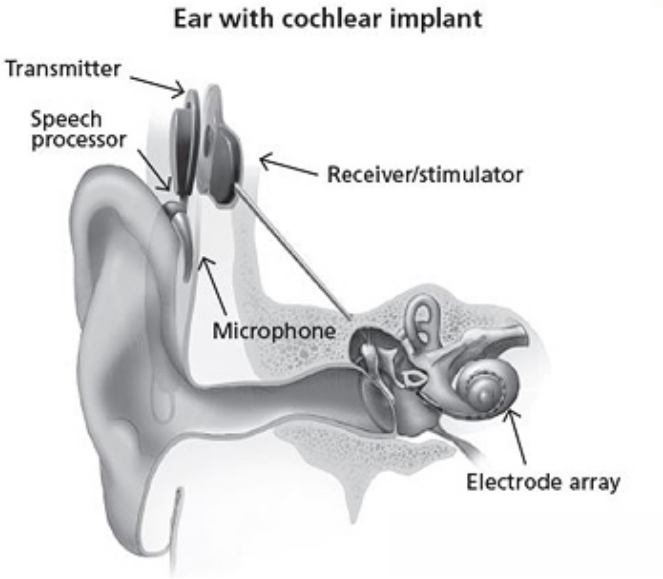


Figure 1. Cochlear implant diagram

The Utah Array

The Utah Array was a significant breakthrough in the demonstration of electrically recording and stimulating groups of neuron spikes. Becoming a standard in the neuroscience community and with decades of work applied to it, applications include communicating with the motor cortex, sensory cortex and spinal cord [2]. This now FDA-approved device has a brain-machine interface setup with 256 electrodes which allows control of prosthetic devices in real time. The problem is that this array cannot stay inserted for a long period of time and with constant reinsertion, tissue scarring and neural damage occur. This still shows high potential for what can be done with increasing the number of electrodes.

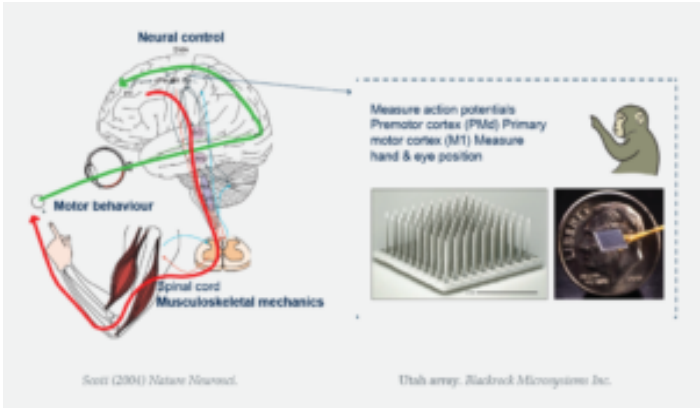


Figure 2. Utah array diagram

Deep Brain Stimulation

Deep brain stimulation involves sending electrical signals to targeted areas of the brain via a neurostimulator. This artificial feedback has demonstrated ability to regulate neural signals that have trouble communicating in Parkinson's patients [3]. The viability proved by DBS has had an impact in extending the treatment with other neurological problems including depression and obesity.

Closed-loop BMI

A functional closed-loop feedback BMI system using a neural recording array was demonstrated in primates almost two decades ago [4]. In these studies, monkeys could interact with the 3D neuroprosthetic devices directly from their brain, as well as adjust their behavior based on the response of the device. This feedback demonstrates the major components of a closed-loop feedback system. More recently, similar

studies with more available neural data, predicted and observed trends with continuous tests aligned increasingly closer with one another [5]. Many components of arm movement (position in 3D space, speed of movement, grip strength) were observed to correlate with very diverse neural data. This demonstrated that the BMI had improved correlation between neural activity and primate behavior, and enforces the importance of the number of neurons being read.

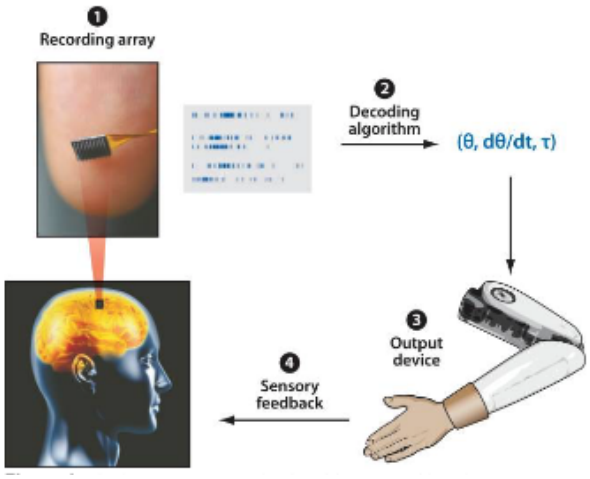


Figure 3. The four components of a closed-loop, neural interface system. [4]

Neuralink

Neuralink is a neurotechnology company that is currently one of the all-in-one frontrunners of brain machine interface technology. This team has developed a small implantable chip that can be placed inside the brain with the capability to amplify signals from 3'072 attached individual electrodes in order to transmit the data to a receiver outside the skull for processing [6]. This data can then be analyzed and electrical signals can be sent back in real time if necessary. Neuralink has developed a robot that can efficiently and safely implant these electrodes through a small hole in the skull at a rate of 192 per minute. The brain moves with breathing and heart rate, and the robot is able to track and make adjustments accordingly.

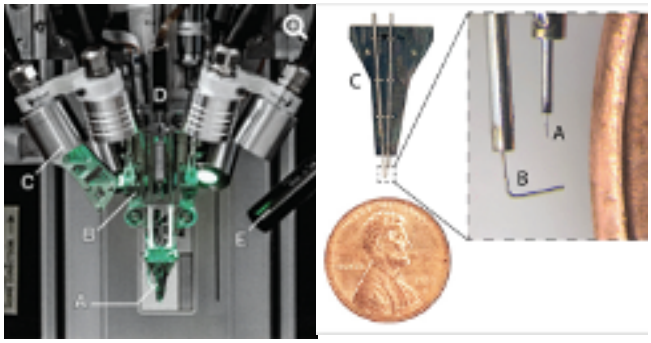


Figure 4. Neuralink Robot

Human trials are set to begin this year, but they still have a long way to go before the electrodes are able to last for a long enough period of time. Polymer coatings on the electrodes extend their life but they still deteriorate much too fast to be considered acceptable for a long term implant. Another problem is the electrodes (~5 um) are too large, and cause glial scarring that impede neurotransmitter performance. At the same time they are too small, and can easily break and be rendered useless, much like the ones that form scarring around them. This mutually conflicting problem can potentially be solved by nanotechnology approaches.

Problems / improvements

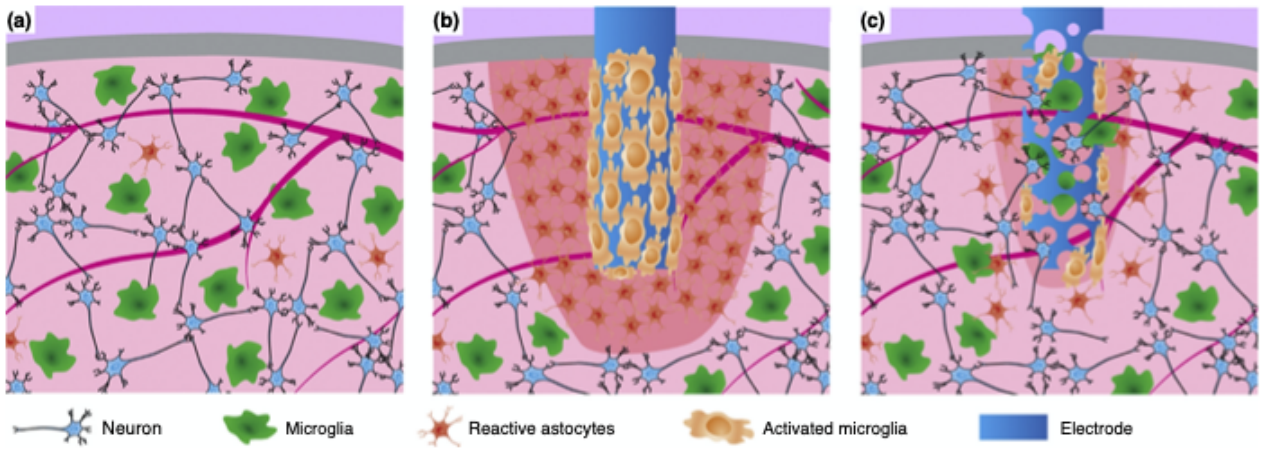
A large obstacle with brain machine interfaces is the biocompatibility of nanomaterial technology used. Since the procedure for an implantation of a BMI can be quite intrusive, the biocompatibility between the nanotechnology and the intimate brain tissue is crucial to extend the longevity of the interface and to reduce

permanent scarring of the tissue. With electrode tissue reactivity and long-term stability, a BMI would enhance understanding of diseases and complications of the brain in the medical field. Many complications can arise if there is not enough biocompatibility, even starting from inserting the devices by breaching the blood-brain barrier, along with any tears or strains of the tissue due to its displacement.
Figure 5. Electrode tissue reactivity

The higher the compatibility, the more reliable the interface is in providing a link to the neuron communications with the brain. While protecting the brain from foreign objects is the first logical item to consider, the technology must also be protected from the “moisture barrier to prevent fluid ingress and prolong functional lifetime” [6].

BMIs in the past as well as currently have a standard of using various types of microelectrodes to sense cell activity as this has proven most reliable for interaction with neurons. Typical instability of interfacing the brain with electrodes comes from cellular/vascular damage, inflammation, tissue response, neuronal degradation, and scar formation rendering the electrodes useless [7].
In Figure 5, (a) shows a healthy section of tissue, and in (b) with a stiff noncompliant electrode a reactive site is visible. Inflammation is visible where a high amount of reactive astrocytes and activated microglia gather around the impacted area. (c) shows a soft, porous electrode that provides a higher level of tissue integration and causes less impact to the surrounding cells.

Nanotechnology strategies are being worked on more to reduce negative long term interactions with neural tissue. One major approach is to use a carbon nanotube substrate coupled with micro-technology that can provide useful neural stimulation. In the most important first few weeks to months, there are many factors that impact the survivability of an electrode and the damage it creates. Shape, size, density and how the devices are tethered together all play significant roles. The initial insertion of electrodes must be delicate and precise as local cells can be damaged which also causes nearby
neurons to be pushed away from electrodes. Electrodes need to be in extremely close proximity to neurons to be able to interact and so this needs to be carefully considered. This initial gap is only amplified over time by the mechanical mismatch. Ideal matching stiffness can possibly be solved by using soft conductive material, or ultra thin and flexible high modulus electrodes. Alternatively to the strategy of compliance, 3D macroporous nanoelectronic implants have been suggested to be able to achieve high biological integration.



Comparison of microelectrode technologies.

	Type	Properties			
		Substrate Materials	**Electrode Site Materials**	**Recording duration**	**Dimension**
Wires	Single microwire	Glass or polyimide insulated microwires	Pt/Ir Pt/Ir	62%/1 week 25%/151 weeks	Single wire
	Microwire array	S-isonel (or Teflon)-coated tungsten (or stainless steel)	Tungsten, Ir, Pt/Ir alloy	up to 18 months	3D array with diameters ranging from 20 to 50 μm
	Single NW FET	Quartz/Silicon	Si3N4, Germanium	Seconds In vitro	3D array with diameters ranging from 30 to 200 nm
	Vertical NW array	Silicon-on-insulator	Metal-coated	N/A	3D array 150 nm
Silicon MEMS arrays	Michigan electrode	Silicon w/Silicon dioxide/nitride	Ir Pt	92%/12 weeks 92%/18 weeks	Planar, 2D and 3D array Site area: ca. 1250 μm^2
	Utah array	Silicon coating materials: Parylene-C	Au and Pt	45%/12 weeks 18%/52 weeks	3D array, Site area: ca. 760 μm^2
	Other Si micro-electrode array	Silicon on insulator (SOI) wafer	Cr, Pt	N/A	N/A
Polymer MEMS arrays		Polyimide	Pt	N/A	Site area: ca. 900 μm^2
	Flexible array	Polyimide–platinum–polyimid	N./A	8 weeks	Planar array
	Flexible array	Silk-supported PI array	Cr/Au	4 weeks	Planar array
	Flexible array	Silk array	Cr/Au	4 weeks	Planar array

Table 1. Previous techniques with their average lifespan in the brain.

Nanotechnology Methods/Approaches/Solutions

Applying nanomaterials for neural prostheses has developed a large interest in the possibilities that can be applied to create a long lasting interface. Some of these possibilities include nano materials that were originally developed for purposes other than BMIs. Important requirements of current state of the art electrodes include a large signal to noise ratio and the ability to communicate with maximum individual neurons. Materials such as carbon nanotubes, various nanowires, and conducting polymer nanowires have been interfaced with the nervous system [8]. These nanomaterials provide effective neural recording and stimulation as they make better use per unit surface area.

Nanowire field effect transistors (FETs) have improved sensitivity over more standard silicon FETs. They also have a significantly smaller diameter (50nm) allowing a higher density of electrodes to be placed closer together.

Incorporating bioactive molecules with some nanomaterials has shown improvement in biocompatibility. More recently rather than bioactive molecules, integrating hydrogels with these materials provide soft and conductive coatings that further reduce the biological mismatch.

List of composite materials for neural interfaces.

Type of composite material	Examples	Impedance at 1 kHz (kΩ)	Charge storage capacity (mC cm^{-2})	Applications
IPNs of HG	Poly(vinyl alcohol)/poly(acrylic acid) (PVA/PAA)	3.3	48	Improving the electrode-tissue interface
HG/CP	Alginate/PEDOT,[38] alginate/Ppy,[387] PVA-heparin methacrylate (Hep-MA)/PEDOT,[39] chitosan/Ppy[464]	2.5,[38] 7[387]	223.8,[38] 560,[387] 68.4[39]	Acute neural recording[387]
HG/CNT	PEGDA/SWCNT,[386] agarose/ CNT[398]	N/A	N/A	Chronically implantable neural electrode, long-term neural recording device[398]
CP/CNT	PEDOT/MWCNT[404,405], Ppy/ SWCNT[280], Ppy/MWCNT[283,406]	26[405], 2.06[280], 0.0147[406]	14[405], 244.4[406],1244[280]	Neural recording,[405] improving microelectrode stability[404]
CNT/Non-conducting polymer	MWCNT/PVA[249], SWCNT/ laminin[467]	0.277[249]	170[249]	Reducing immune response of the neural electrode[467]
Graphene/CP	Graphene oxide /Ppy[280], graphene Oxide/PEDOT[389]	26[280], 2.5[389]	278[280]	Biosensing, neural interfacing[389]
Graphene/HG	Graphene/poly(N,N-dimethylacrylamide) (PDMAA)	1.3	N/A	Neural tissues

Table 2. Hybrid nanomaterials used and their purposes.

One of the most significant polymeric materials used are hydrogels (HG in Table 2). These are hydrophilic polymeric networks that are cross linked which can be tailored to match biological tissue from their water content/mechanical properties.

A certain stability is required between the tissue and the electrodes that sense or transmit charges for neural interfacing. This stability can be obtained through the use of carbon nanotube composites that provide a structural stability to prevent fracturing of the neural interface, along with a chemical stability to ensure biocompatibility and the delivery of charges. These carbon nanotubes are constructed as multilayered electrodes assembled layer-by-layer to provide the most successful results for neural interfacing. The stability of the interface is due to the multilayered design applied since it provides a strength while preserving the flexibility required. The layer-by-layer assembly is a technique of fabricating thin films by alternating between layers of oppositely charged materials. The advantages that this assembly provides are the control over the thickness of uniform coatings, and the ability to carry both ionic and electronic currents. Overall, the stability that the carbon nanotube composites provide creates a solution that could lead to a new brand of electrodes used neural interfacing. [9]

In 2012, a team developed a carbon-nanofiber neural chip with lithographically defined arrays of vertically aligned carbon nanofiber electrodes and demonstrated its capability of both stimulating and monitoring electrophysiological signals from brain tissues in vitro [12]. These chips also monitor dynamic information of neuroplasticity and have potential to be very biocompatible even inside cells.

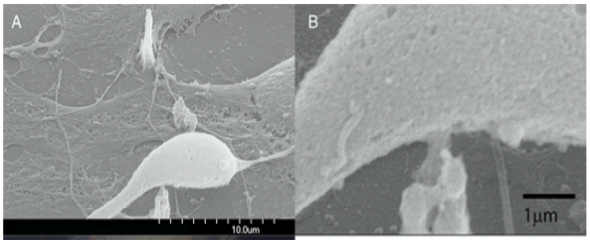


Figure 6. Neuron sitting on electrode

This figure shows a neuron sitting over a carbon nanofiber electrode. The electrode can penetrate the cell via endocytosis. This process could allow detection of intracellular signals and delivery of molecules into the cell. Once inside the cell, detection of individual neuron action potentials. These electrodes can be extremely densely packed due to their small nature and 3D structure. Higher quality neural information and control is achieved with this approach. The nano-scale tip can effectively pin and enter single cells. This nano-neuron interface technique can potentially also carry ligands for proteins, allowing for recording of chemical signals on top of electrophysiological.

In 2013 macroporous nanoelectronic scaffolds were developed to achieve intracellular recordings and merging of electrical and biological systems in three dimensions. The goal of this product was to reduce invasivity and toxicity to cells. The free standing devices can be utilized for synthetic tissue constructs and thus be able to monitor cellular activity throughout 3D networks [13]. This process uses FET devices where the nanowire or nanotube channel serves as the voltage sensor. The structure, morphology and physiological properties can be controlled making them attractive for hierarchical device design.

The main problem with this device is the FETs linear geometry which disrupts more cells upon insertion. Using kinked nanowires where the voltage channel is close to the tip of the kink provides an efficient solution.

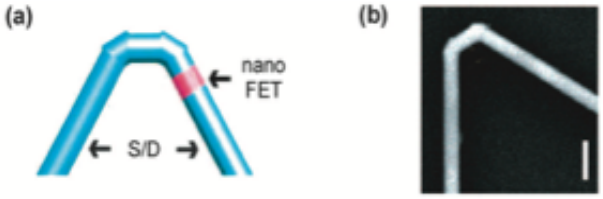


Figure 7. Kinked nanowires

The arms of the kink are a heavily doped source/drain of the FET. These arms help ensure that the tip can enter the cell while preventing disruption of the cell from the electrode. Connecting these nanoscale arms with microscale metal interconnects allow insertion of the tip into the 3D space.

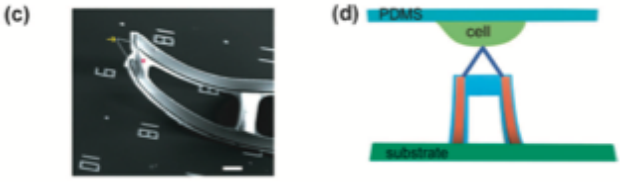


Figure 8. Metal interconnects guiding kinked nanowire.

This allows for high sensitivity in recording as the active part of the nanowire is at the tip of the region and coupled to the interior of the cell. Successful cell membrane penetration required the addition of phospholipid layers that had a similar structure to the target cell.

A variety of bioprobes are able to be created from this technique.

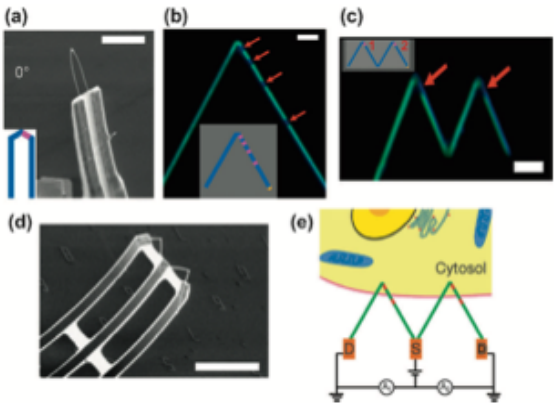


Figure 9. Kinked nanowire bioprobes

The first (a) has two parallel arms forming a U shape. (b) is a 60 degree kink that has multiple FETs in series along the arms which allow the possibility to record from multiple sites with a single probe.
(c) and (d) are double kink nanowires which offer high density and simultaneous recording of extra and intracellular signals.
(e) illustrates how this W shape construction can do this as well as create multiplexed recording of the signals.

Merging nanoelectronic networks with living tissues in 3D can be achieved with the following process.

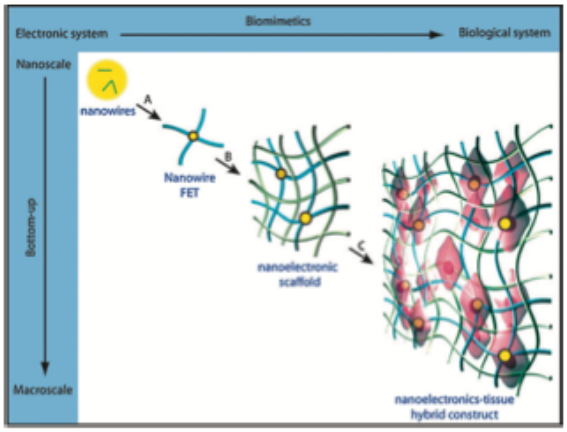


Figure 10. 3D nanowire integration

First the nanoelectronic network must be fabricated in 2D with substrate support (A), then it is combined with tissue scaffold materials (B). Finally cell seeding yields 3D nanoelectronic tissue hybrids.

Electronic dura mater is an approach where a neural interface is made with the properties of dura mater. Mimicking the tissue surrounding the CNS provides high functionality within tissues.
This dura matter can sustain millions of stretch cycles, electrical pulses and chemical injections [14]. This approach demonstrated the ability to deliver electrochemical spinal neuromodulation that restored movement after a spinal cord injury.

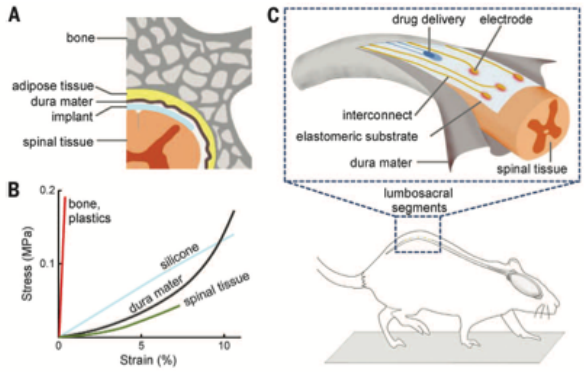


Figure 11. Dura mater in the spinal cord

This figure illustrates how the electronic dura mater implant is utilized to deliver chemical and electrical signals to the CNS.

Using nanoparticle coating is an effective way to increase electrode functionality. Carbon based nanoparticles significantly enhance the recording capabilities of electrodes. This is achieved by lowering the impedance of the electrode probes.

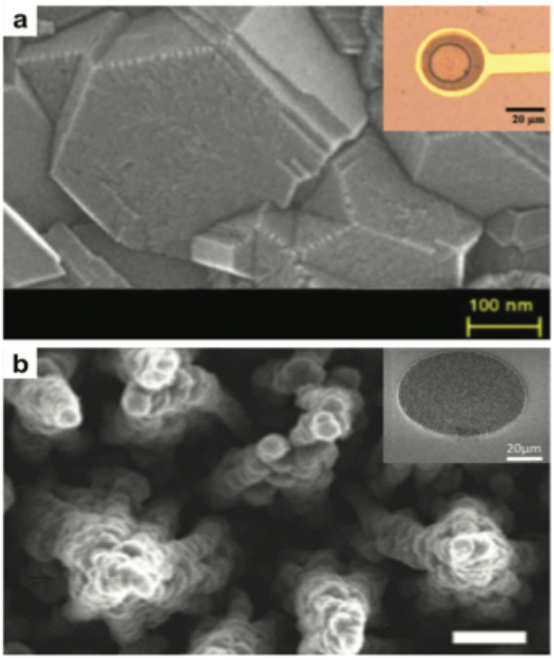


Figure 12. Electrodes fabricated with boron doped diamond.

This figure shows an electrode with a boron doped microstructure (a) and the diamond electrode before an insulation layer is added (b). These techniques improve stability and biocompatibility of the electrodes [15].

The use of nano-bioelectronics applied to living biological systems was determined to be more capable of electrophysiological recording and stimulating than prior technologies. This recording of the brain is paramount to conducting revolutionary neuroscience research, and though the use of non-invasive technologies have been helpful in this area, the neural network and its functionality are harder to explore with these techniques such as MRI and PET scans. Through the use of nano-bioelectronic devices, the spatiotemporal resolution of the data is seen to be much higher than previous technologies.

Two methods of electrophysiological recording are extracellular recording or intracellular recording. Traditional extracellular recording is when a microelectrode is placed close to the outer membrane of a cell and detects any change in extracellular potential. Nanowire transistors or graphene transistors were proposed to be used to provide extracellular recordings, since the traditional method had an impedance limitation, reduced electrical coupling, and needed signal detection improvements.

While extracellular recording provides long-term capabilities, the quality and strength of the recordings were low and correspondence between the cells and the electrodes weren't one-to-one. Intracellular recording solves these problems, but can also cause irreversible damage to the cells it contacts therefore sacrificing any long term connections. The two forms of intracellular recording uses 3D nanowire transistors and MEA-based (multielectrode array) nanopillars. [19]

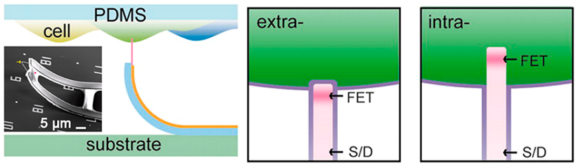


Figure 13. Cellular recording from a cardiomyocyte monolayer on a PDMS support (left) and extracellular (middle) and intracellular (right). [19]

The relationship between the neurons and the electrodes in a neural interface is important, and requires careful consideration to ensure the formation of scar tissue is minimal due to the close physical coupling of the two. While scar tissue in itself is undesired, it also prevents the neural interface from working due to the

detachment of the neurons to the electrodes. The current solution in preventing this scar tissue formation is the use of pharmaceuticals but this interferes with the coupling of neurons and electrodes in the neural interface. To prevent the formation of scar tissue and also ensure reliable coupling, the use of nanoporous gold (np-Au) as a neural interface coating was introduced, due to the nanostructure of np-Au having a high ratio of neuron-astrocyte surface coverage. The compatibility of microfabrication and the ability to deliver required drugs, along with the biocompatibility in np-Au coating also helps in preventing scar tissue. Both chemical and topographical cues serve the purpose of controlling the tissue connected with the neural interface. A critical thing to note is that the benefits provided by the np-Au coating comes from the use of topographical cues and not through the use of surface chemistry. These topographical cues reduce the astrocyte surface coverage due to the tunable length scale of np-Au, therefore suppressing the formation of scar tissue and in turn increasing neural-electrode coupling in a nontoxic manner. [10]

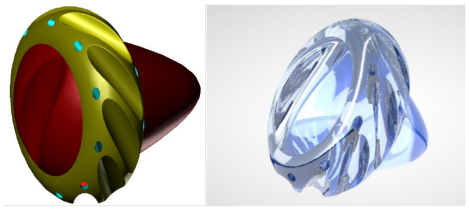
In this scenario, we cannot neglect that also nanotechnology based supramolecular hydrogels have the viscoelastic and dynamic character of neural tissue, but typically lack the high conductivity and resilience required for interfaces with electrically active tissues and subject to mechanical stress [10]. Hydrogel integration with nanomaterials such as carbon nanotubes (CNTs) or graphene could impart the needed properties. Interestingly, in our laboratories, we tested ultra-soft nanoporous 3D networks of unfunctionalized CNTs, generated by chemical vapor deposition (CVD), that appear to possess ideal morphology and compliance for the biointegration with remarkable neuronal fiber re- growth in CNS explants, and negligible inflammatory response when implanted [16]. An elongated morphol- ogy appeared to be a key feature for efficient communi- cation with neurons toward their integration into hybrid systems.

Along the same line, graphene contributed to the engi- neering of flexible electronics for implants in both ex vivo and in vivo contexts, proving superior performance, in terms of sensitivity and resolution, over conventional materials [17]. Graphene, electrospun into nanofibers, was implanted and even found to attract migrating neu- roblasts from their brain niche [18].

One strategy to approach is the use of neural nanorobotics to implement the human brain/cloud interface. This solution is currently under extensive research but has been labelled to be an important discovery that could lead to the next age of invention. Once in place, the neural nanorobots would assist in diagnosing and curing diseases and within the brain with the use of a supercomputer based in the cloud. It is said that the use of neural nanorobots will provide the capabilities to cure most, if not all, brain disorders. The neural nanorobots would provide the transfer of data wirelessly through the use of nanorobotic fiber optics and allow monitoring, recording, and manipulation of information in real-time.

Currently, there are three different forms of the neural nanorobots that would help in the navigation of the human brain, and those are endoneurobots, gliabots, and synaptobots. Both the endoneurobots and synaptobots enter the body via bloodstream, cross the blood-brain barrier, enter the brain parenchyma, navigate within the neuropil, enter the neuron soma, and position

themselves at either the axon initial segment or the synapse. The gliabots enter the bloodstream but immediately position themselves within glial cells. Nanosensors are used by all of the neural nanobots to monitor and process action potential information. The endoneurobots would monitor most action potentials and also receive information from synaptobots to forward them to the supercomputer. The synaptobots could help with forms of autism, in which synapses are not formed as they should, by monitoring and interacting with information processed by the synapses. Gliabots monitor glial cells and could be used as supportive infrastructure. [11]



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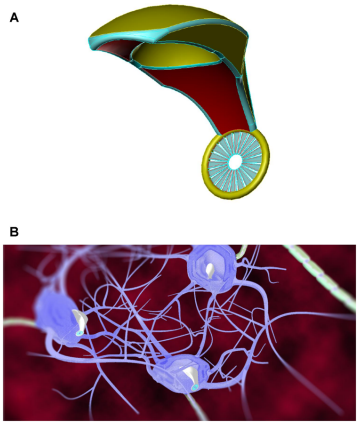

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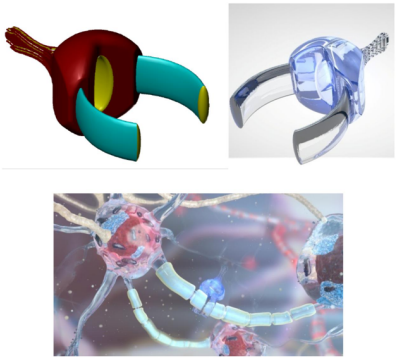

(c)

Figure 14. Neural Nanorobotics
(a) Artistic representation of endoneurobot (left) with diamondoid depiction (right), (b) Artistic representations of gliabots (top) and their placement in glial cells (bottom), (c) Artistic representations of synaptobot (left) with diamondoid depiction (right) and calibrating at an axon (below). [11]

Conclusion

Currently the most significant benefit of this technology is how it will serve critical needs of medical patients by further understanding the brain. Creating a one size fits all BMI provides a long-term economical solution to neurological issues that you can live with and use at home. For this to be achieved, the constructs of BMIs must use novel nanotechnology solutions to increase the survival of electrodes while protecting brain tissue for long duration insertions. Without an invasive conscious surgery, limitations in the brain can be improved by selectively stimulating a large number of neurons across diverse brain areas. When nerve stimulation is understood better, it could be possible to rehabilitate and restore control of damaged body parts. Some diseases will be presented with cures for the first time.

Depression for example, is a commonly misunderstood neurological disorder that is often treated with wrong or ineffective solutions. By interacting with the brain, exact neurological deficiencies may be pinpointed and dealt with. The benefits possible also include the increased speed and control of computer systems whether directly medical assistive or otherwise.

The demonstrated capability of an implantable BMI system will improve the lives of those suffering from neurological issues, as well as preventing them from originally occurring.

Proper connectivity in the brain is arguably the most important part of what makes and keeps us human. A standardized and scalable approach will provide accessibility to an incredibly diverse number of medical patients. BMIs promise not only a platform for numerous medical solutions, but also for providing increased accessibility to others.

References

[1] Implants, C., Clark, G. and York, S. Cochlear Implants - Fundamentals and Applications | Graeme Clark | Springer. [online] Springer.com, (2019).

[2] "Utah Array |", Blackrockmicro.com, [Online]. Available: https://www.blackrockmicro.com/electrode-types/utah-array/, (2019).

[3] Gardner, John. “A history of deep brain stimulation: Technological innovation and the role of clinical assessment tools.” Social Studies of Science vol. 43, no. 5, (2013).

[4] Hatsopoulos, Nicholas G, and John P Donoghue. “The science of neural interface systems.” Annual review of neuroscience vol. 32, (2009).

[5] J. M. Carmena, M. A. Lebedev, R. E. Crist, J. E. Odoherty, D. M. Santucci, D. F. Dimitrov, P. G. Patil, C. S. Henriquez, and M. A. L. Nicolelis, “Learning to Control a Brain–Machine Interface for Reaching and Grasping by Primates,” PLoS Biology, vol. 1, no. 2, (2003).

[6] E. Musk, “An integrated brain-machine interface platform with thousands of channels,” [Online]. Available: https://www.biorxiv.org, (2019).

[7] D. Scaini and L. Ballerini, "Nanomaterials at the neural interface.", www.sciencedirect.com, 2018. [Online]. Available: https://www.sciencedirect.com/science/article/abs/pii/S0959438817302337?via%3Dihub

[8] P. Fattahi, G. Yang, G. Kim, M. R. Abidian, “A review of organic and inorganic biomaterials for neural interfaces.” Advanced materials, vol. 26,no. 12, pp. 1846-85, (2014).

[9] E. Jan, J. L. Hendricks, V. Husaini, S. M. Richardson-Burns, A. Sereno, D. C. Martin, N. A. Kotov, “Layered Carbon Nanotube-Polyelectrolyte Electrodes Outperform Traditional Neural Interface Materials.“, Nano Letters, vol. 9, no. 12, pp. 4012-4018 (2009).

[10] C. A. R. Chapman, H. Chen, M. Stamou, J. Biener, M. M. Biener, P. J. Lein, E. Seker, “Nanoporous Gold as a Neural Interface Coating: Effects of Topography, Surface Chemistry, and Feature Size.”, ACS Applied Materials & Interfaces, vol. 7, no. 13, pp. 7093-7100, (2015).

[11] Martins Nuno R. B., Angelica Amara, Chakravarthy Krishnan, Svidinenko Yuriy, Boehm Frank J., Opris Ioan, Lebedev Mikhail A., Swan Melanie, Garan Steven A., Rosenfeld Jeffrey V., Hogg Tad, Freitas Robert A., “Human Brain/Cloud Interface.“ Frontiers in Neuroscience, vol. 13, no. 112, pp. 112, (2019). https://www.frontiersin.org/articles/10.3389/fnins.2019.00112/full?fbclid=IwAR2RD4aI9kGdar2MOhdiocZCB1hP7UwHalpcRbAkwcFigrDh3QJYmMcNjAU

[12] Z. Yu, T E. McKnight, M. N. Ericson, A. V. Melechko, M. L.Simpson, B. Morrison III, “Vertically aligned carbon nanofiber as nano-neuron interface for monitoring neural function”, www.sciencedirect.com, 2012. [Online]. Available: https://www.sciencedirect.com/science/article/abs/pii/S1549963412000871

[13] X. Duan and C. Lieber, "Nanoelectronics Meets Biology: From New Nanoscale Devices for Live-Cell Recording to 3D Innervated Tissues", Chemistry - An Asian Journal, vol. 8, no. 10, pp. 2304-2314, 2013. Available: 10.1002/asia.201300630.

[14] I. Minev and P. Musienko, "Electronic dura mater for long-term multimodal neural interfaces", Science, vol. 347, no. 6218, 2020. Available: https://science.sciencemag.org/content/347/6218/159.abstract.

[15] A. Young, N. Cornwell and M. Daniele, "Neuro-Nano Interfaces: Utilizing Nano-Coatings and Nanoparticles to Enable Next-Generation Electrophysiological Recording, Neural Stimulation, and Biochemical Modulation", Advanced Functional Materials, vol. 28, no. 12, p. 1700239, 2017. Available: 10.1002/adfm.20170023

[16] H. Jang, Y. Park, X. Chen, T. Das, M. Kim and J. Ahn, "Graphene-Based Flexible and Stretchable Electronics", Advanced Materials, vol. 28, no. 22, pp. 4184-4202, 2016. Available: 10.1002/adma.201504245

[17] H. Jang, Y. Park, X. Chen, T. Das, M. Kim and J. Ahn, "Graphene-Based Flexible and Stretchable Electronics", Advanced Materials, vol. 28, no. 22, pp. 4184-4202, 2016. Available: 10.1002/adma.201504245

[18] A. Young, N. Cornwell and M. Daniele, "Neuro-Nano Interfaces: Utilizing Nano-Coatings and Nanoparticles to Enable Next-Generation Electrophysiological Recording, Neural Stimulation, and Biochemical Modulation", Advanced Functional Materials, vol. 28, no. 12, p. 1700239, 2017. Available: 10.1002/adfm.201700239

[19] A. Zhang, C. M. Lieber, “Nano-bioelectronics”, *Chemical Reviews*, vol. 116, no. 1, pp. 215–257, (2015).

Figures