



FUTURE NEURAL THERAPEUTICS

Closed-Loop Control of Neural Activity
Technology Roadmap White Paper
Version 1

Identifying technology challenges and advancements required to promote
development of next generation closed-loop neural control systems

IEEE Brain Initiative
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The mission of the IEEE Brain Initiative is to facilitate cross-disciplinary collaboration and coordination to advance research, standardization, and development of technologies in neuroscience to help transform our understanding of the brain to treat diseases and to improve lives. Learn more about the program and activities at brain.ieee.org.

This white paper is an ongoing effort to assist with mapping future development of next generation bidirectional closed-loop neural devices. As a living document, the information will evolve with input from key stakeholder groups over time. We welcome your feedback on this document and topic area. Please direct all comments and correspondence to: brain-clwp@ieee.org

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Background and Motivation

Over the last two decades, the neuroscience research field has generated a tremendous amount of information on the cellular components of the nervous system. However, the major impediment to research and technology development is the lack of a fundamental understanding of how the brain functions and how neural circuits operate. Early emphasis placed on the study of the brain through monitoring and recording single neural cells has yielded preliminary data, but an operational understanding of how the brain functions as a whole is incomplete. In the United States, the [Brain Research through Advancing Innovative Neurotechnologies \(BRAIN\) Initiative](#)¹ was formed to spur development of new tools and technologies required to deepen understanding of the brain, including efforts in high-throughput imaging approaches for mapping brain tissues. Other countries and regions around the world also have large-scale brain projects and programs to advance the field of neuroscience such as the [Human Brain Project](#)² and the [Brain/MINDS](#)³.

Currently, multiple research efforts are underway to record, to stimulate, and to better understand brain function fueled by interdisciplinary teams, and a promising area of potential growth in neuroscience includes developing new methods to both read and write activity into the nervous system, e.g., through bidirectional closed-loop control of neural systems.⁴ Findings from these explorations may eventually lead to greater understanding of fundamental brain function as well as to a plausible theory of how the nervous system works. As such, the field of neuroscience is at a moment of historical significance: the ability to read and write activity of the nervous system provides a crucial step in decoding and understanding the human brain.

A variety of closed-loop brain-machine interface (BMI) neurotechnologies to treat movement disorders as well as neurological diseases such as epilepsy are in the research and development phase, including closed-loop deep brain stimulation (DBS)⁵. Based on past technology trajectories, development of next generation closed-loop devices that decode and encode neural activity from multiple nervous system sites (e.g., central nervous system, peripheral nervous system, autonomic nervous system [CNS/PNS/ANS]) will take place within the next ten to twenty years. However, challenges to widespread adoption of such devices remain, as well as multiple technological challenges in developing these complex systems. Even so, the potential therapeutic benefits offered by closed-loop neurotechnologies will be essential in successfully addressing neurological disease and nervous system injury in the future as pharmacological therapies continue to exhibit limitations in efficacy.

It is therefore vital that at this moment in time a path be developed that lays out the projected trajectory of growth for closed-loop BMI devices over the next ten to twenty years as well as the necessary dependent technologies and advancements required to ensure success of next generation technology development. Preparing a roadmap at the early stages will contribute to efforts to guide development in an ethical and principled way, with the aim to benefit society as a whole.

1. Introduction

Brain-machine interfaces (BMIs) are generally defined as systems that establish communication between the brain and external devices (e.g., a computer or prosthetic), using recorded signals to control these devices. Closed-loop BMIs extend this cycle further by continuously recording signals from the brain and nervous system, decoding this information, and then encoding information and sending it back to the brain and/or nervous system, usually in the form of localized stimulation. Next generation closed-loop BMIs will continue to build on this technology to further expand information and signal gathering throughout the nervous system, offering more precise target stimulation as required for a personalized therapeutic intervention.

Research and development of closed-loop technologies for control of neural activity has increased steadily over the last decade due in part to the potentialities that both reading and writing into the nervous system may offer for both the advancement of neuroscience as a field as well as for therapeutic interventions. Recently, closed-loop neurotechnologies have shown promise for providing therapeutic and rehabilitative options⁶ for patients, as well as the potential for augmentative capabilities. These efforts range from restoring movement function, providing functional cures for neurological diseases such as epilepsy, and treating memory disorders such as Alzheimer's, to increasing learning speed and ability by selectively amplifying someone's plasticity or potential for plasticity, having the ability to transfer or recall memories using a machine, treating neuropsychiatric disorders with devices rather than drugs, and creating devices that can both sense and stimulate activity in our sensory motor system—changing the way our bodies interface with the world. Research employing closed-loop BMIs for stimulating touch sensation⁷, stroke rehabilitation⁸, motor recovery⁹, and as a therapeutic alternative for treatment of Parkinson's disease¹⁰ serve as examples of future pathways for exploration and translation.

The purpose of this white paper is to encourage an industry-wide dialogue on the challenges and advancements needed to develop next generation closed-loop neurotechnologies.*

1.1. Need for a Roadmap

IEEE occupies a unique position to provide guidance and recommendations in the field of neurotechnology as it continues its rapid growth cycle and maturation.[†] This roadmap process in part provides a model for thoughtful consideration of potential opportunities as well as the ethical¹¹ and social implications of neuroscience research for closed-loop systems and applications. Now is the time to explicate the questions and challenges surrounding the development of closed-loop systems as well as potential uses of such systems in order to

* *Open-loop brain-machine interfaces also have the potential to offer therapeutic solutions as well as add to knowledge of the brain and body systems. However, the purpose of this paper is to concentrate solely on next generation closed-loop BMI devices that both encode and decode signals from the brain and nervous systems.*

† *IEEE recognizes that the future of neurotechnology is more than closed-loop systems and we welcome industry-wide input on focus areas beyond closed-loop systems.*

identify and address problematic areas. Generating guidelines and potential solutions at this stage will benefit the field as a whole. The larger neuroscience community has a social responsibility to think about these possibilities (both good and bad), as new technology will always bring disruption to society.

Through collaboration with other stakeholders throughout the neuroscience community, IEEE can facilitate a technology roadmap that would define expectations of future closed-loop neurotechnology along with appropriate uses of that technology. Doing so will allow participants to realize critical benefits in areas such as:

- addressing needed changes to the regulatory arena and criteria for neurotechnology to assist with evaluation and approval of devices,
- facilitating professional and ethical frameworks and guidelines for development and responsible use of closed-loop technologies,
- identifying the necessary associated technologies needed to realize next generation closed-loop technology capabilities (e.g., improved sensors),
- optimizing investment strategies for research and development (R&D),
- leveraging R&D costs through resulting collaborations and partnerships, and
- providing valuable input on the formation of standards.

1.2 Roadmap Process

To this end, the community realized that there was both a need and an opportunity to orchestrate a shared vision for future closed-loop neurotechnology.

The roadmap process begins with awareness and identification of the challenges, recognition of what factors are holding back the field, as well as gathering information on the new technologies that can be realized. A balance between vision and awareness that feeds into potential impact is required when determining successful technology solutions for the coming decade (e.g., solving Alzheimer's is clearly an opportunity to have high impact). The broader community needs to think outside the box to identify promising solutions to therapeutic challenges, and the development of a technology roadmap is intended to serve as an aid for identifying scalable opportunities for the future.

With the support of The Kavli Foundation, the IEEE Brain Initiative coordinated a think tank with shared stakeholders that took place in September 2018 with the goal of identifying future neurotherapies, including sensory, cognitive, and/or motor augmentation enabled by disruptive neurotechnology as well as innovative experimental paradigms that harness the brain-body axis. Researchers from diverse fields including neurotechnology, systems and computational neuroscience, clinical practice, and neuroethics discussed potential pathways for growth of closed-loop control of neural systems in areas of mental health, bioelectronic medicine, and augmentation. In addition, an emphasis on neuroethics helped to identify and address key challenges beyond engineering and implementation.

Input from this September 2018 think tank was used in part to shape this white paper. The aim is to build partnerships and collaborations among all stakeholders to continue an industry-wide dialogue to move beyond this white paper to a technology roadmap effort. This process begins with the development of an outline/template for a technology roadmap with key technology domains identified. These technology domains will help formulate roadmap working groups diving deeper and further exploring key drivers and challenges. The roadmap development will require the support of many individuals leading and engaged in roadmap working groups and discussions. IEEE Brain will work closely with the IEEE Roadmap User Group (IRUG) and the Steering Committee of the IEEE Roadmap Strategy and Governance (IRSG) Ad Hoc Committee to develop a plan and timeline for the roadmap effort.

1.3 White Paper Structure

This white paper presents the case for a roadmap effort for emerging closed-loop neurotechnologies. It is structured as follows:

- Section 2 covers the scope and timeline.
- Section 3 describes various stakeholders.
- Section 4 focuses on the state of the technology and presents potential use cases.
- Section 5 discusses design drivers.
- Section 6 highlights key challenges.
- Section 7 addresses potential technology solutions.
- Section 8 offers concluding statements.

2. Scope and Timeline

The goal of this white paper is to stimulate an industry-wide dialogue on the challenges inherent in advancing to next generation closed-loop control neurotechnologies and systems. These discussions will help establish key stakeholders in order to create a broad picture of the roadmap required, develop a working plan to establish the roadmap, and then release a first edition of the table of contents for a comprehensive interactive IEEE roadmap for development of closed-loop neurotechnologies.

Short-term plans (Fall 2019 through 2020) are to engage with the wider community (interviews, workshops, etc.) for input and perspectives and to develop a consortium of stakeholders interested in championing this roadmap effort as part of roadmap working groups. Mid-term plans are to track development of related technologies as well as relevant neuroscience and closed-loop technology breakthroughs that could impact the ecosystem in the next 10-20 years, and long-term goals are to update the working document every 12-24 months.

The mission of the roadmap working groups will be to identify short, mid-term, and long-term research, development, and innovation in the closed-loop control for neurotherapies

ecosystem. This will enable the development of a comprehensive roadmap to guide the diverse community of stakeholders in the coming years.

This IEEE Brain Technology Roadmap effort focuses on identifying technical and research needs for the future development of closed-loop technologies that access the brain and body's nervous systems. The translation of the roadmap findings is left to individual research institutions and industry entities.

3. Technology Stakeholders

There are several groups of stakeholders that will participate in or will be affected by emerging closed-loop technologies designed for control of neural activity. These include those from the healthcare ecosystem (clinicians, neurologists, patients); neuroscience and biomedical researchers; academic institutions and science foundations; neuroethicists; the device and software industry (biomedical engineers, systems engineers, component manufacturers, developers); pharmaceutical companies; government entities and funding agencies such as the National Institutes of Health (NIH), National Science Foundation (NSF), Defense Advanced Research Projects Agency (DARPA), Office of Naval Research (ONR), Army Research Office (ARO), and Veteran Affairs Office of Research and Development (ORD); national labs including Sandia National Laboratory and Lawrence Livermore (LLNL); as well as standards and regulatory bodies such as the IEEE Standards Association (IEEE SA) and Food and Drug Administration (FDA).

Consumer applications (e.g., for entertainment/gaming), and thus, new stakeholders are continually emerging as neurotechnologies find new uses. Identifying emerging stakeholders is one aspect of this roadmap effort and every attempt will be made for this roadmap to be representative of all perspectives.

3.1 Value Chain

Different stakeholders define the added value for each group, which may differ according to needs and desires.

- **Researchers/Developers**—The desire to balance neuroscientific knowledge (e.g., how the brain functions) with a potential solution for a clinical need (e.g., epilepsy) is often a driving force for research and development. Viability of translating a device or system to market is an inhibitor; profitability and competition with pharmaceutical solutions increase the need for value add of the proposed closed-loop system.
- **Academic Institutions and Science Foundations**—Investment in scientific understanding is often value-add for non-profit science institutions and academic research centers. Moving beyond lab research to translation is a driver for many institutions, but paths to funding and translation remain hurdles.

- **Device Industry**—Research, development, and manufacture of closed-loop neurotechnology devices is considered a potential high-growth area, but current high costs and regulatory constraints limit investment (including venture capital). Closed-loop therapeutic devices will need to become simpler and easier for clinicians to implement and patients to use in order to compete with pharmaceutical solutions. Direct-to-consumer devices will need to navigate efficacy and reproducibility hurdles for translation as well as acknowledge ethical challenges.
- **Component Manufacturers**—Development of smaller, flexible, low-power electrodes and sensors that are viable long-term is key to next generation devices. Multiple efforts in this area are underway (e.g., microwire and microthread electrodes, small carbon fiber electrodes, soft electrodes, optical sensors, tissue-engineered nerve scaffolds). Solutions to encapsulation and other biological incompatibilities will need to be overcome. Inhibitors include lack of standardization of materials and testing procedures (e.g., ageing) as well as miniaturization.
- **Computational Software Developers**—Artificial intelligence (AI) and machine learning will continue to be invaluable components of next generation closed-loop devices. Development of advanced, adaptable algorithms and new ways to interpret and manage large data captures are needed to enable solutions that encompass the body's nervous systems.
- **Healthcare Providers / Clinicians**—Ease of use and proven success as a therapeutic solution for difficult to treat conditions (e.g., movement disorders as well as neurological diseases) or medication non-responsive conditions will be essential for adoption. Ultimately, less invasive or non-invasive approaches may be required to supplant pharmaceutical use; invasive devices will need to further ensure precision efficacy to provide value add.
- **Healthcare Insurance Providers**—Cost of device must be less than pharmaceutical interventions over successful long-term use.
- **Users / Patients**—Focus should be on user-centered design early in the process—users typically want flexibility and some control as well as to understand the device and its mechanisms. Concerns about privacy and safety (e.g., anonymity, hackability) as well as protocols for defining/labeling found markers for social behaviors will need to be addressed. Sensitivity and specificity will be essential if the markers predict maladaptive/criminal tendencies. Device lifespan and longevity (e.g., smart and changeable over time to supply upgrades to users) is of key importance to research subjects as well as end users, and also ties to questions around clinical trial entry, trial cessation, and trial interruption. Researchers and manufacturers need to plan for long-term care of devices and have protocols and standards in place for trial and therapeutic use.
- **Pharmaceutical Companies**—Closed-loop neurotechnology devices are in many instances direct competition for pharmaceuticals. However, in cases where drugs have reached therapeutic limitations or for neurological or movement disorders that do not benefit from drug therapy, pharmaceutical companies may view closed-loop devices as an investment for co-therapy.

- **Government Entities and Funding Agencies**—Government entities provide the majority of research funding but are often result-focused, which limits ability to take risks in development. Much of government funding currently comes through defense agency channels, and this investment is predicated on developing closed-loop neurological systems and tools that increase defense advantage, accelerate learning and productivity, restore function and promote enhancement, and have the potential to work in partnership with artificial intelligence (AI). Potential tension between desires for augmentative applications vs. therapeutic solutions may require further emphasis on neuroethics.
- **Regulatory Bodies**—Regulatory bodies have historically been ill-equipped in their ability to evaluate closed-loop therapeutic devices, however recently some progress has been made (e.g., reclassifying BMI devices used for paralysis treatment and adapting approval requirements for non-clinical testing¹²). Further education and industry efforts may be needed to adjust requirements for clinical trials and approval for the range of closed-loop neurotechnologies.
- **Standards**—Currently, there is not a ‘gold standard’ requirement for materials and validation. Standardization protocols for components as well as closed-loop devices could offer a value add to the field as a whole. Ethical standards for development, testing, and implementation of devices are also required.

3.2 Applications of Value Add for Stakeholders

Next generation closed-loop neurotechnologies hold promise as therapeutic devices as well as fulfilling potential consumer applications. As of yet, not all stakeholder areas are determined. However, general traits required for stakeholders to recognize that a next generation closed-loop system is a value add in a particular therapeutic or consumer area would likely include at minimum:

- Increased efficiency and efficacy (dynamic stimulation based on feedback will better achieve desired outcomes/performance),
- Safety at all points and steps as well as cybersecurity of data,
- Device design grounded in real physiology,
- Neural targets would need to become more specific and precise,
- Individuality/customization available for each patient or user, and
- Autonomy/reduced cognitive load for clinician and for user.

3.3 Stakeholder Interactions

The roadmap effort will include a series of meetings over the course of several years with the aim to bring representatives and stakeholders together to assess relevant research and evaluate current technology and industry trends, projecting and mapping that information into future scenarios for emerging next generation closed-loop BMI technology. In addition, it is anticipated that representatives from stakeholder groups will be active members in the roadmap working groups.

4. Closed-Loop Brain-Machine Interface Technology Development

4.1 Technology Landscape

Development of brain-machine interfaces (BMIs) gained momentum in the early 2000s. Generally, BMI devices are designed to use signals from the brain to control other devices including prosthetics (efferent devices) or enable external signals to access the brain through neural stimulation (afferent devices).

Examples of efferent BMIs include motor BMIs where signals from the brain control a prosthetic arm. The most ubiquitous example of an afferent BMI is deep brain stimulation, where electrical current is injected into neural tissue to modulate pathological neural activity. These two types of BMI may be open-loop or closed-loop. Open-loop designs lack feedback in control of the external device, while closed-loop systems provide feedback within the system. Simple closed-loop control systems, for example, include an efferent BMI where neural signals control a prosthetic arm and the user is provided feedback (e.g., through vision or hearing) to close the control loop. Afferent BMIs can also operate in closed-loop, for instance by using movement monitoring to detect a tremor and modify levels of deep brain stimulation. (See Figure 1.)

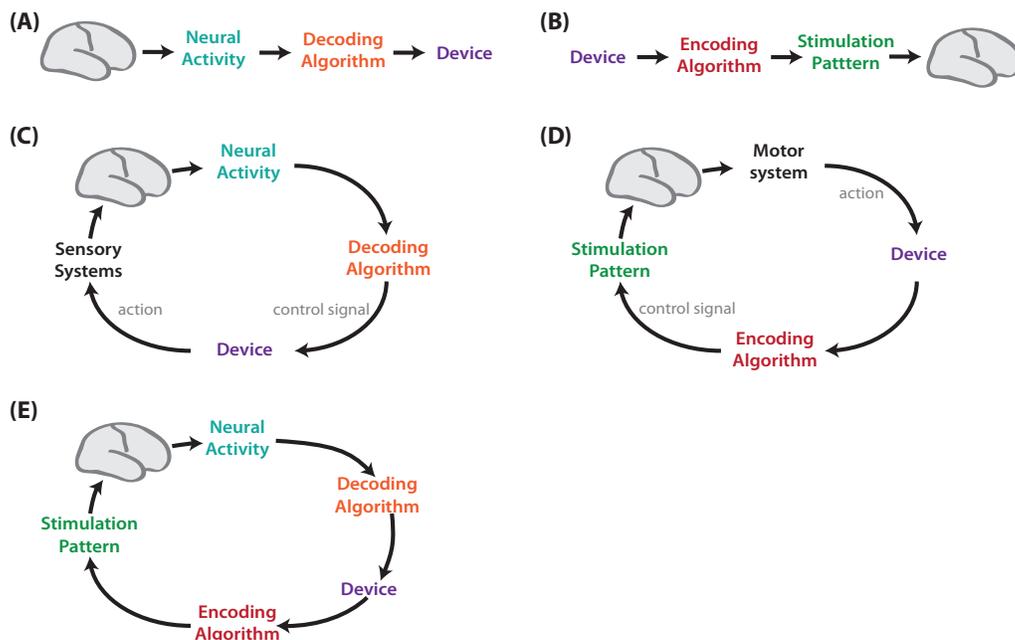


Figure 1: Sensorimotor BMI systems demonstrating (A) open-loop efferent BMI, (B) open-loop afferent BMI, (C) closed-loop efferent BMI, (D) closed-loop afferent BMI, and (E) bidirectional afferent closed-loop BMI.

A more recent research path consists of continuously recording signals from the brain and then sending a mathematical transformation of them back into the brain or nervous system via an external device, typically using electrical stimulation as the neuromodulation approach, i.e.,

bidirectional BMIs. The key to this process is sensing of endogenous neural activity and using this in a control loop to precisely stimulate and/or regulate the same or another neural activity. Applications for this technology potentially include neural prosthetics and neural rehabilitation for movement disorders as well as functional cures for neural abnormalities such as those associated with epilepsy.

One example of a recent closed-loop bidirectional technology is the implanted responsive neurostimulator device—RNS System—from [NeuroPace](#) used for treating epilepsy. The RNS system is a responsive (closed-loop) focal cortical stimulator approved by the FDA for therapeutic use for medically intractable partial onset seizures in adults.¹³ The closed-loop neurostimulator device continually senses brain activity through electrocorticography (ECoG) electrodes placed on the surface of the brain; when the device detects specific ECoG patterns, it delivers brief stimulation pulses in response and the stimulation in turn mediates the seizure-related activity that the device is monitoring.

Other closed-loop BMI technology includes gathering data from multiple brain areas, using other neural signals (e.g., local field potentials), and using other modalities to record and/or modulate neural signals. An example would be using optogenetics for neural control, as in the [CANDO](#) (Controlling Abnormal Network Dynamics using Optogenetics) project currently in development for patients with focal epilepsy.¹⁴ Here, the device provides precisely timed stimulation by continuously monitoring brain waves with implanted electrodes and modifying the waves through implanted light sources in order to modulate abnormal activity and prevent seizure development.

Next generation closed-loop BMI technology will build on current technology in order to further focus on gathering sensor feedback from other areas of the nervous system, decoding these signals through advanced algorithms, and then stimulating as needed to affect a therapeutic or augmentative intervention, becoming more autonomous and adaptive to the requirements of the therapy as well as responsive to feedback obtained from the individual user over time.

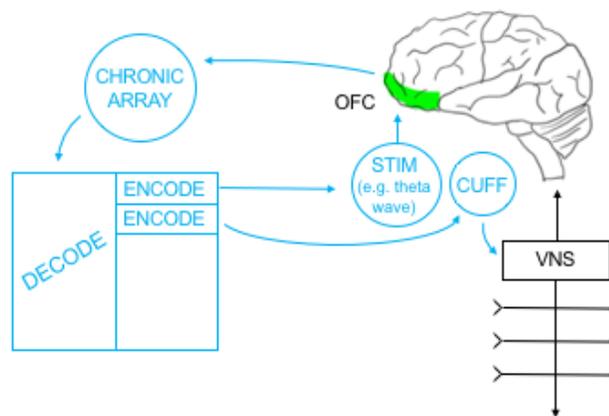


Figure 2a: Current phase of closed-loop system technology, with read (decode) and write (encode) capabilities.

The development of a generalized bidirectional closed-loop system with multiple inputs and outputs that can operate as autonomously as possible would be a long-term goal. Milestone technology developments over the next 10 to 15 years should include the following:

- Current Phase: System gathers data over time; very limited continuous sensing, including in areas of gathering feedback on how the target is responding to the actuation applied and having the ability to tune that effect. Figure 2a provides a general example of closed-loop BMI technology with limited sensing and vagus nerve stimulation (VNS).
- Phase 1: Evolution of better sensor capabilities for understanding downstream effects of stimulation will assist in creating more accurate models of how information travels downstream.
- Phase 2: More detailed data will promote access to improved model-based control schemes that will be able to act and better inform algorithm development and training as well as optimize input/output.
- Phase 3: Closed-loop systems will be more self-adaptive and autonomous and will require safe adjustments to parameters. The controller will be connected to an actuator that delivers an intervention through multiple pathways to a precise target, which has a downstream effect on a number of systems. Development of such a system requires a better understanding of dynamics, environmental parameters and effect, as well as how the body and target interact. Figure 2b builds on current capabilities to show the potential evolution of next generation closed-loop systems that gather sensor data from multiple points over longer time scales, including non-neural signals.

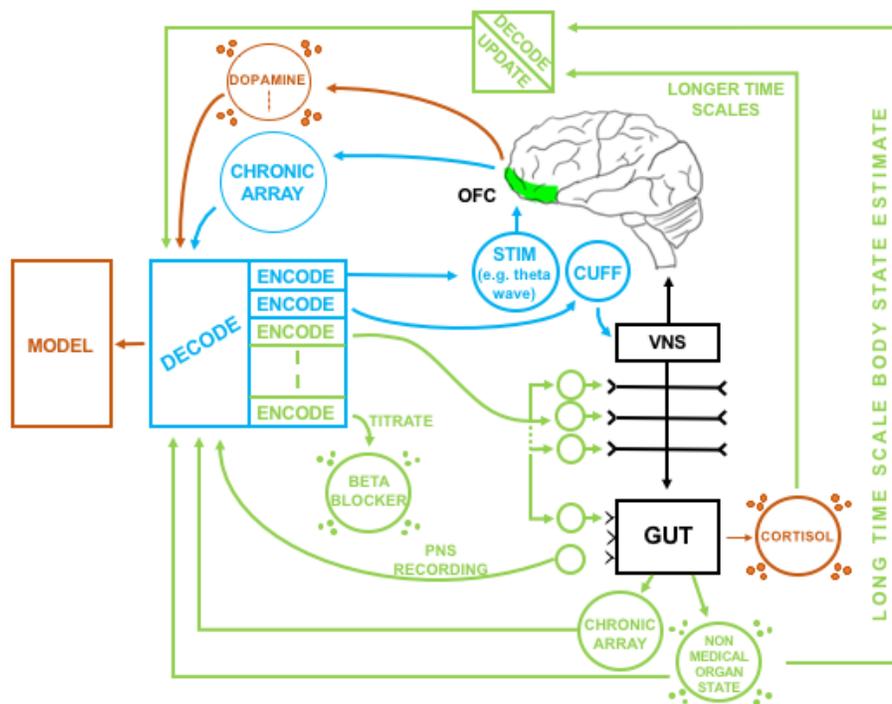


Figure 2b: System design for 10-year horizon. Current neurotransmitter recording technology is in blue; green designates potential horizon goal; red refers to beyond the horizon (non-neural signals).

Accessing the peripheral and/or autonomic nervous systems (PNS/ANS) of the patient has the potential to make a given therapy more effective, which would be a significant value add for patients, clinicians, and the biomedical device industry. The gut, for example, contains dense neural layers. There is also the possibility of targeting with sensors that detect chemicals such as cortisol, which may grant access to what is missed by shorter timescale loops and provide feedback that would allow for modification as needed. Potentially, rich data can be obtained from the constellation of signals within the autonomic system; addressing incumbent challenges in encoding and decoding would enable a next generation closed-loop device that incorporates data from the PNS/ANS to provide therapeutic and augmentative solutions beyond what is currently available.

4.2 Next Generation Closed-Loop Neural Technology Applications

Next generation closed-loop neurotechnologies will offer therapeutic and rehabilitative options as well as augmentative capabilities. Potential applications include restoring movement function, providing functional cures for neurological diseases such as epilepsy, treating memory disorders such as Alzheimer's, increasing learning speed and ability, treating neuropsychiatric disorders, and devices that can both sense and stimulate activity in our sensory motor system, changing the way our bodies interface with the world for both therapeutic and entertainment uses.

Any development of closed-loop system technologies for therapeutic and/or augmentative applications should both serve to fill a need and deliver a high-impact solution (e.g., closed-loop technologies that enhance memory function might also serve as a therapeutic treatment for diseases such as Alzheimer's). As emerging technologies, the key will be to coordinate value add for the stakeholder (clinician, patient, government agency) while minimizing potential harm (Figure 3). Targeted solutions for control of medication-resistant epilepsy and seizure currently in development and use, such as the NeuroPace RNS System, fulfill these requirements.

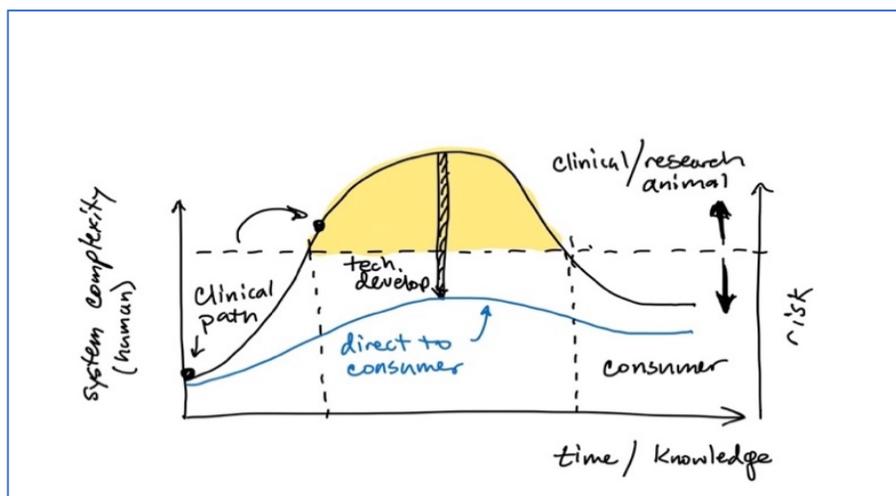


Figure 3: Clinical path vs. direct to consumer for technology development in relation to complexity and risk over time.

In the future, closed-loop neurotechnology devices have the potential to provide viable solutions in areas where pharmaceutical treatments have variable and often, low positive, results. These solutions could expand personalized medicine by sensing electrical signals throughout the body, taking measurements of molecular physiology, and intervening with electrical stimulation delivered through the peripheral nervous system (PNS).

For example, development of a closed-loop system for general psychiatric therapy encompassing the orbitofrontal cortex (OFC) and the brain-body axis has the potential to provide therapeutic benefits for complexes such as addiction, anxiety, obsessive compulsive disorder (OCD), schizophrenia, eating disorders, and depression. This type of intervention is highly generalizable and could be adapted to promote or suppress a wide range of behaviors. This means that the treatment is highly personalized and symptom-driven as opposed to being generic for all subjects with a given diagnosis, offering significant value as a more personalized treatment approach.

4.3 Applications by Industry

Table 1: Potential Industry Applications for Closed-Loop Neurotechnologies

Medical	Clinician and direct-to-consumer therapeutic devices to diagnose and treat disease.
Wellness	Consumer devices used for improving general wellness, including mood, memory, cognition, and low-level pain.
Education	Cognitive and learning enhancement devices for use in the classroom and training.
Workplace	Devices that monitor and enhance efficiency and promote skills learning.
Military/National Security	Devices that support military engagement and enhance physical and mental ability.
Sports	Devices that enhance and improve physical performance and monitor physical well-being.
Entertainment	Virtual and augmented reality devices assisted by brain control, silent speech, etc.

5. Design Drivers and Trends

Traditional drivers for closed-loop systems for neural control have been therapeutic applications, including but not limited to attempts to correct and/or restore function in cases of movement disorders and spinal cord injuries (neural prosthetics, neural rehabilitation), and interventions and potential cures for neurological diseases such as epilepsy and Parkinson's disease. Other applications are potentially augmentative, and include investigating solutions for memory and learning enhancement (these also hold therapeutic value), military/defense applications, as well as consumer applications in wellness (basic therapeutics such as mood enhancement) and entertainment (e.g., gaming and virtual reality).

In addition, the opportunity to gain further knowledge about the brain and how it functions has been and will continue to be a key driver for innovation and transformation of the field. Non-profit science institutions and initiatives along with funding agencies such as DARPA have placed emphasis on decoding of the brain, and next generation closed-loop devices offer a unique opportunity to learn from recorded signals and stimulation of the brain. DARPA brain interface projects¹⁵ including Next-Generation Nonsurgical Neurotechnology (N3), Neural Engineering System Design (NESD), Restoring Active Memory (RAM) and RAM Replay, Systems-Based Neurotechnology for Emerging Therapies (SUBNETS), Targeted Neuroplasticity Training (TNT), and Hand Proprioception and Touch Interfaces (HAPTIX) aim to support neurotechnology development and translation.[‡] Earlier this year, six teams were chosen as part of the N3 project to develop high-resolution bidirectional BMIs¹⁶ using diffuse optical tomography, magnetic fields, nanoparticles, and ultrasound among other techniques.

A prevailing trend for design of closed-loop devices is toward becoming less invasive to minimally- or non-invasive as stakeholders and industry continue to make these demands (i.e., DARPA requirements and clinician preference). However, it is of particular importance that devices show proven efficacy for treating disease with minimum side effects, which in part requires becoming more precise with dosage as well as target areas for stimulation (e.g., precision electronic medicine¹⁷) regardless of level of invasiveness. Building on neurostimulation treatments already approved by the FDA such as transcranial magnetic stimulation (TMS) and electroconvulsive therapy, research is underway that would combine closed-loop electroencephalography (EEG) with TMS, for example, in order to promote precision target dosage. One of the inhibitors to adoption of currently available therapeutic neurological device systems, such as deep brain stimulation (DBS) systems, is the variability of

[‡] N3 aims to develop high-resolution technology that will read and write to multiple brain locations without implantation; NESD is intended to fund efforts to improve signal resolution and bandwidth between implantable neural interfaces and devices; RAM aims to support development of a fully-implantable neural device that will aid in formation and restoration of memory; RAM Replay supports efforts to develop novel computational methods to identify brain those brain components vital for memory and recall; SUBNETS is intended to create closed-loop implantable therapeutic and diagnostic devices for treating neuropsychological illness; TNT aims to pursue platform technology that would advance cognitive skills training through activation of peripheral nerves and support neural connections; the goal of HAPTIX is to create wireless, modular neural micro-interfaces that work with external modules in order to deliver sensations to amputees.

side effects as well as difficulty in reproducing results across patients. Next generation closed-loop devices designed to record signals in real time and respond therapeutically as needed will push the reliability and success of these therapies further.

Ultimately, in order to be competitive with pharmaceuticals as therapeutic interventions, surgery and implants will need to be kept to a minimum. Having a safe, easy to implement device solution that is as simple as a needle is essential, otherwise pharmaceuticals will be preferred. Improved and miniaturized electrodes and components consisting of soft, flexible, biocompatible materials that are more stable over the long-term will open avenues to new experimental techniques. The current trade-off between invasiveness and spatiotemporal resolution (i.e., non-invasive electrodes such as EEG provide less signal information compared with electrocorticography (ECoG), intracortical, or deep brain recording electrodes) will guide the push for alternative surgical approaches for implantable devices such as injecting ECoG arrays through small holes in the skull.

Sensors that further expand to encompass signals from the peripheral and autonomic nervous systems will be crucial to next generation devices. Using these signals to optimize the control signals in real time will maximize effectiveness and aid precision. Non-invasive devices that incorporate peripheral nerve stimulation, such as vagal, occipital, or trigeminal nerve stimulation (TNS), including the device developed by NeuroSigma for treatment of pediatric ADHD and approved by the FDA in early 2019¹⁸, will provide additional knowledge on the effects of stimulation on these neural systems.

Demand for coordination of closed-loop devices with artificial intelligence (AI) and machine learning to assist with algorithm development and training, data management, and feedback will also determine future design and implementation. Increases in cloud computing capabilities will assist with managing the data, although establishing protocols for security and privacy will be of critical importance. Establishment of neural data repositories, such as [Neurodata Without Borders](#)¹⁹, will assist in moving the field toward standardization and reproducibility in testing and clinical trials, aiding in regulatory approvals and translation of next generation devices.

6. Design Challenges

Significant challenges exist in moving from current closed-loop systems to designing and building a future system²⁰ that further taps into the body's nervous systems in areas of technology (e.g., access, sensing, distributed PNS stimulation); system integration (e.g., multiple distributed PNS contact points, the need for robust wearable computing); decoding (e.g., multiple embedded loops operating at different time scales, difficulty in establishing ground truth); and regulatory approval and clinical trials. Other approaches, such as the need to access and/or sequence genomic information to improve system design and feedback would present additional challenges.

Multiple design challenges are also inherent in migrating from devices that are rather large to devices that are vanishingly small and/or minimally- or non-invasive as well as moving from animal models to human models. Other barriers include identifying where to stimulate and how to do so in order to deliver crucial therapies. In addition to understanding neural circuits, this requires identification of the expected responses from the neural stimulation. Models of this process are necessary to build control systems effectively.

Closing the loop also means having to deal with potentially unanticipated events. Using AI to help develop predictive models as well as rigorous and standardized testing procedures will be vital in anticipating and preparing for possible reactions. Working with regulatory agencies to expand possibilities for clinical trials and approval of devices will be necessary for successful market translation of devices.

6.1 General Design Requirements

Next generation closed-loop neural devices need to:

- Function at a minutely or non-invasive level.
- Offer improved sensing capabilities at multiple and varied locations (encompass multi-modal/multidimensional/multi-state estimation).
- Be compatible with physiology as well as have the ability to adapt to the body's changing physiology (feedback-controlled).
- Provide secure and private data collection and storage.
- Demonstrate proven safety and comfort in order to promote widespread adoption.

6.2 Technology Challenges

6.2.1 Scale

There are significant design challenges when moving from animal models to humans as well as biocompatibility when moving from large, invasive devices to small, minimally- or non-invasive devices. Smaller sizes must still be robust enough for implementation (e.g., implanted by surgeon; viable for long-term use).

6.2.2 Materials

Flexible, stable materials are needed that will remain viable over longer terms. Biocompatibility and non-toxicity are required to avoid encapsulation. New fabrication processes and methods are critical for production and availability. Ageing standards and access to ageing facilities needs to be improved in order to standardize materials for long-term devices.

6.2.3 Electrodes and Sensors

Current electrode designs are limited in scale, number, and longevity. Standardization and miniaturization, as well as biocompatibility, are key challenges. Chronic hormone / neurotransmitter sensors do not exist and chronic organ state sensors are limited (e.g., pressure).

6.2.4 Recording

Improvements in processing speed and sensitivity to noise are needed. Multiple electrodes capture each signal differently; local field potential recordings are more stable but more difficult to interpret.

6.2.5 Computation

Machine learning and adaptive algorithms are needed for continuous adaptation using a range of multiscale models (electrical, chemical, behavior) such as adaptive inverse control, reinforcement learning, and hierarchical optimal control. How data should be bound and evaluated will need to be determined; current data safety monitoring boards may not have the expertise to evaluate this type of data in order to comply with FDA rules.

6.2.6 Robustness

Closed-loop BMI devices need to be designed for long-term (ideally lifetime) use and be resistant to failure. Devices should be equipped with a minimal operational mode, i.e., a fail-safe mode, if an unknown state arrives.

6.2.7 Power

Next generation devices require reliable methods of power delivery to active electronic microchips, sufficient computational power to handle large amounts of data (exact data quantities unknown), and wireless power transfer without heating. New ways to generate power (e.g., combining modalities, harvesting energy from internal organs/muscles) will be necessary.

6.2.8 Multiscale Signal Processing, Modeling, and Control

Neurophysiology knowledge (e.g., prioritization of the variables to be measured and best controlled) will need to be employed to specify engineering constraints in model validation, and toward measurements, modeling, and manipulation of physiological variables. Addressing the spatiotemporal structure of spike trains and local field potentials requires development of advanced algorithms that are more robust and extract specific information from the data, e.g., multiscale modeling methodologies in functional spaces, and new generative models that learn how to explain the input data.

6.2.9 Communications

System design of secure, stable, and reliable wireless communication outside of controlled environments is a key challenge, along with managing the role of cloud computing and data storage. Integration of information from external sensors (environment) needs to be better understood. Other challenges include design and development in areas of:

- Wireless transcutaneous and/or transcranial bidirectional data flow
 - Customized network communication protocols for high speed read/write
 - Network hardware and protocols to enable adaptive targeting of key neural circuits
 - Power and safety limits
 - Cybersecurity
- Real-Time Neural/Biosignal/Encoding
 - Wearable, mobile computational hardware (programmable embedded system)
 - Neurocomputational decoding/encoding models in real time

6.2.10 Safety and Reliability

Few devices have target verification that would provide information that the device is doing what it's supposed to do, i.e. having the ability to know that the system is responding in ways it is meant to is key. Other challenges include ensuring minimal tissue damage, simpler surgical implantation techniques, and reliability for long-term 24/7 chronic use (device robustness, hermetic packaging, etc.). Devices must be designed with the option for user override and expert/surrogate override and parameters need to be clearly defined. Responsible use and meaningful assent guidelines should be in place.

6.2.11 Data Security and Privacy

Guidelines for data management, e.g., who owns the data and how ownership is controlled, should be standardized. Authentication should be required to access, add, and generate the data. Challenges also remain in facilitating data storage and security, as well as with managing data spread, patient privacy, and general cybersecurity.

6.2.12 Regulatory

Current regulatory approval processes need to further adapt without impacting safety. Clinical trial design and testing procedures also need to adapt in order to test dynamic/adaptive systems where it is impossible to test all the states, and better animal models are required. Standardization of trial variables and materials are needed to address issues of reproducibility. Guidelines on augmentation/consumer protection should be in place prior to device translation.

6.2.13 Ethical

Ethical concerns are inherent to questions of controlling access, sharing data, selling data, and bias-free models as well as the boundaries of use for both invasive and non-invasive technologies. Clinical ethics and patient care ethics can serve as starting guidelines but need to be expanded to incorporate the complexity of closed-loop devices. Industry standards should also provide guidelines on the means for opting in and out of studies. Just and ethical use

standards for closed-loop BMI technology need to be drafted, particularly for commercial and direct-to-consumer devices.

6.2.14 Translation

Challenges remain for prototype development procedures, justifying cost of therapeutic devices (computing vs. surgical) as well as securing investment capital. Standardization of materials and device testing could assist in lowering time and cost factors.

6.3 Additional System Challenges

6.3.1 Readout: Sensing, Biomarkers, and Feedback

For a closed-loop system that is designed to gather feedback from the brain and peripheral nervous system, sensors will be needed that can access chemical targets (molecules, neurotransmitters, hormones). Feedback should also include body physiology (blood pressure, pupil dilation, temperature, pH, EKG, cells, immune response) as well as environmental factors. There is also the possibility of factors outside the system that are not tracked that unknowingly feed back into the system and affect response. In addition, how best to design a sensor that adapts to body state (e.g., sleep) is still unknown.

6.3.2 Write In: Targets

Determining how best to precisely and successfully write-in (electrical, optical, magnetic) and where (CNS, PNS) to do so to create the most plasticity in the system is a significant challenge.

6.3.3 Encoding/Decoding

Because of the large amount of data generated by these models, questions on how that data should be bound and evaluated remain. Current data safety monitoring boards may not have the expertise to evaluate this type of data in order to comply with FDA rules.

- Collecting sufficient data to train the 'long time-scale' decoder (spanning space/range, training time).
- Developing a principled control policy to update the internal model with 'smart' adaptation for mitigation.
- Creating a real model of this system requires addressing these multiple nested challenges:
 - How to establish an appropriate ground truth,
 - How generalizable will the decoder be—will training at home or in the clinic generalize to the outside world,
 - How will autonomic space be sampled—clinical populations may have a reduced autonomic space (e.g., depressed patients will only have a depressed state), and
 - Challenges in matching sensing data to the neural data (e.g., the dynamics of mood state and neural activity could occupy very different temporal domains).

6.3.4 Controller and Timescales

An ideal controller for a closed-loop system would be flexible, programmable with user and expert input over time, upgradable, and adaptive. This would require robust computational models. Many things collapse under the ideal properties of the controller—timescales on which we act, timescales on which the body responds, as well as timescales of plasticity.

- **Memory:** Little is known about what will happen in certain cases and across long time scales so collection of data from many patients continuously is required to see the changing baseline and then appropriately update the model.
- **Manage unintended consequences:** Currently unable to predict what data may be important for solving new challenges. Unintended consequences may actually be improvements to both the patient and scientific knowledge.

7. Technology Enablers and Solutions

As closed-loop BMI technology is driven forward, the barrier of entry to consumer is lowered, especially as more minutely-invasive and non-invasive devices are developed. The clinical round enables initial opportunity to advance the field but there might not be a financial justification for fulfilling a medical/clinical need without the additional support a consumer product provides. Essentially, all technologies are initially designed to help or fill a need, and consumer or military defense demand will likely be driving some applications (e.g., augmentative).

Other enablers include current growth in the variety and design advancements of sensor and electrode capabilities, as well as improved materials. Development of smaller, flexible, low-power electrodes and sensors that are viable long-term is key to next generation devices. Solutions to encapsulation with improved biocompatibility will promote development of new applications and devices.

Incentives put in place for investment in packaging materials for electrodes and implants will help to increase standardization and robustness of components. Fabrication and design of materials must eventually evolve to further integrate with chemical and optical sensors for human subjects versus animal models.

Alternative approaches including optogenetics, ultrasound, and combining modalities of technologies will lead to more precise and less invasive technologies. Advances in wireless communication and cloud computing will help with management of the large data captures from multiple sensors. Development of multi-modal capabilities for generating power with less heating, including using energy from the body, will assist with sensor capability and longevity.

Machine learning and open data sharing will contribute to advancing the creation of adaptable electronics and more standardized solutions. Generalized algorithms that search recorded brain activity for viable signals may lead to new discoveries. Advancements in genomics will further extend knowledge of the intricacies of individual neural plasticity and excitability, aiding in patient trials. Additionally, as knowledge of the brain network increases, including the role of

glial and other biological components, technology designs will become more adaptable to the nervous system environment.

Examples of some current efforts that likely will prove integral to development of next generation devices include the following:

7.1 Advanced Electrodes and Sensors

- Small and flexible sensors and electrode arrays that mimic cellular or subcellular structures^{21,22}
- Small (7.2 microns) carbon fiber microelectrodes offer precise positioning, less bleeding, alignment of fibers for optogenetics
- Microwire electrodes (e.g., NeuroRoots²³) of 25-30 microns that are needle-like, easy to implant, and more stable
- Soft electrodes (e.g., e-Dura²⁴)
- Neural dust—wireless millimeter-sized devices powered by ultrasound²⁵
- Neural mesh—optimizing interface between implant and neural substrates through ultra-flexible 2D scaffolds²⁶
- Double-sided electrodes
- Chemical sensors and probes with increased sensitivity
- Optical sensors and optical fibers
- Semi-synthetic biosensors

7.2 Improved Materials/Biocompatibility

- Hydrogel electronics
- Organic coatings
- Conductive polymers, micrometallization, polymer electrodes coated with bioactive molecules
- Graphene (porous, transparent)
- Polycrystalline diamond

7.3 Computation and Artificial Intelligence

- Combination of machine learning and adaptive algorithms
- Improved training scenarios
- New models for animal to human device transitions
- Open data repositories
- Automated support tools for identifying optimal stimulation

7.4 Communication

- Improved wireless communication between sensors
- Advanced data security and privacy protocols

8. Conclusions

Although still in its infancy, development of closed-loop BMI neurotechnologies is in part driven by the prevalence of neurological and psychiatric disorders, many of which do not respond well to pharmacological treatments or do not have other viable treatment options. The potential to provide proven therapeutic devices that address chronic depression, post-traumatic stress disorder (PTSD), and diseases such as epilepsy and Parkinson's disease will guide technology development in the near future. Closing the loop on such devices will offer more precision and personalization, as therapeutic stimulation becomes better designed to respond more directly to the patient's own neural physiology.

Tangentially, the search for successful avenues to successfully integrate prosthetic devices with the body and/or restore motor function, as well as enhance and restore capabilities such as memory, contributes to the prevalence in research and development of next generation closed-loop BMI neurotechnologies. Although the majority of current efforts lack the robustness and longevity for translation into clinical solutions, continued investment along with advances in material design, standardization of components and testing procedures, advances in machine learning and adaptable algorithms, as well as efforts to combine methods and modalities to create peak effectiveness with closed-loop BMIs will promote device translation and grow market appeal. Addressing other technological challenges identified here will also support viable solutions for therapeutic and consumer applications.

Ultimately, next generation closed-loop devices will reimagine the partnership between the brain and body's nervous systems, with the potential to provide effective precision electronic medicine and drive new consumer applications.

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