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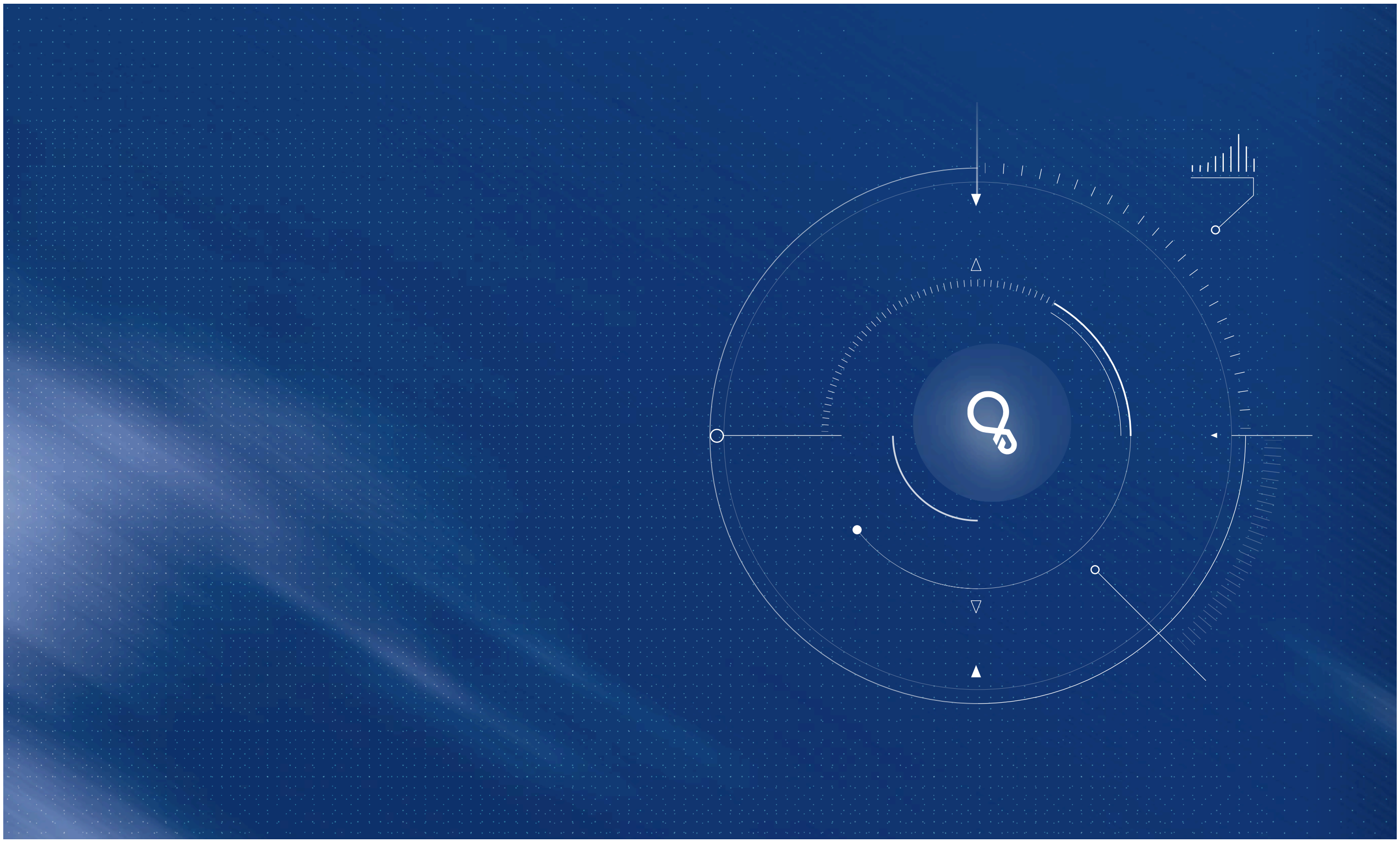

RESEARCH BRIEF

NONINVASIVE VAGUS NERVE STIMULATION

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Executive Summary

The intention of this Insight Brief is to detail the latest academic research and technology innovation related to non-invasive vagus nerve stimulation (nVNS). This research is inclusive of a discussion of the increasing use cases for this technology, benefits relative to invasive solutions, and a broader analysis of bioelectronics in medicine.

This research also provides an analysis of investment and funding trends in this space to answer the question of what entities/technologies are gaining the most funding traction and profiles the key investors in this area.

Analyst Opinion

The transition to nVNS represents a compelling paradigm shift in neuromodulation, promising reduced patient risk, enhanced accessibility, and broadening clinical applications. As outlined in this Brief, traditional VNS, though beneficial, is often limited by high costs, surgical complications, and patient adherence challenges. Noninvasive alternatives like trans-auricular and cervical transcutaneous methods have effectively removed these barriers, suggesting that nVNS could revolutionize treatment across a spectrum of neurological and inflammatory conditions. This shift positions nVNS as a potential first-line intervention in neuromodulation, especially for conditions where invasive methods were previously the only viable option.

The patent landscape highlights a dynamic innovation environment around nVNS, with patents exploring diverse techniques and use cases, such as alternating channel stimulation to prevent tolerance or using wearable devices tailored for acute cardiovascular intervention. This diversity in innovation suggests that the field is not only growing rapidly but is also responding to specific clinical demands through increasingly specialized devices. This adaptability could strengthen nVNS's utility across both medical and wellness markets, distinguishing it from other neuromodulation approaches that lack the scalability and user-centered design seen in nVNS development.

Investment trends further underline the growing confidence in nVNS technology, with venture capital and public health organizations actively funding research and development in this area. This momentum highlights the perceived long-term value of nVNS, with venture funding particularly backing startups that focus on expanding the device market into everyday healthcare settings. This could ultimately shift nVNS devices into a more integrated role within healthcare systems, allowing healthcare providers to prescribe these devices in a way that complements traditional treatments, potentially opening up new revenue models and expanding patient access to neuromodulation therapy.

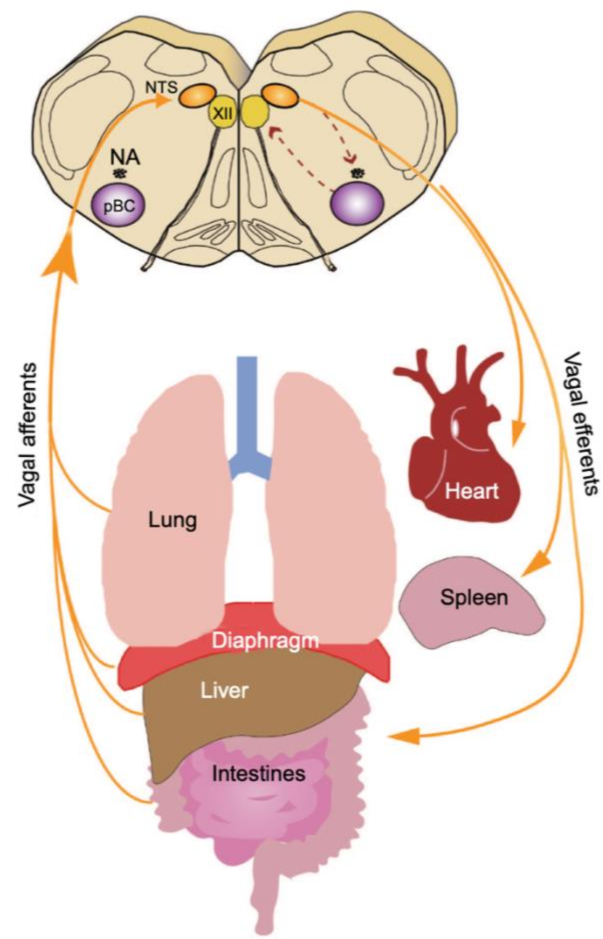
Moreover, the expansion of nVNS into consumer wellness markets underscores its flexibility, offering users accessible options for managing stress, sleep, and other non-clinical applications. This dual market—targeting both medical and consumer audiences—places nVNS at a unique intersection, aligning with the broader trend of healthcare democratization. As nVNS technology continues to evolve, its applications could redefine both patient and consumer expectations, positioning it as a foundational tool in both neuromodulation and personal wellness ecosystems.

Research Methodology

In our research, we utilized the Cypris platform, third-party datasets, and broader internet searches to identify relevant data. Throughout this process, we refined our approach by adapting our keywords to synonyms and related terms to ensure comprehensive data collection within this sector. For our foundational query, we used Cypris' semantic searching functionality with the following search term: '[noninvasive vagus nerve stimulation](#)'.

Introduction to VNS[1]

The vagus nerve, originating from the medulla oblongata, is a critical part of the autonomic nervous system that connects the brain to various organs, including the heart, lungs, and digestive tract. This nerve plays an essential role in maintaining autonomic functions, such as heart rate, gastrointestinal motility, and immune responses. Recent studies have shown that stimulating the vagus nerve can have therapeutic effects due to its involvement in the cholinergic anti-inflammatory pathway, a neural circuit that helps modulate inflammation.



Disorders associated with vagus nerve dysfunction are diverse, as this nerve impacts several bodily systems. For instance, **epilepsy and depression are two conditions where VNS has gained FDA approval**. Additionally, the nerve's influence over inflammatory processes has sparked interest in using VNS for autoimmune and chronic inflammatory diseases like rheumatoid arthritis, sepsis, and diabetes. VNS is also being explored for pain management in conditions like fibromyalgia and migraines, as well as for potential benefits in cardiovascular disease, obesity, and lung injury management.

The history of VNS dates back to the 1880s, but it became clinically significant in the 1980s when it was first tested for epilepsy. VNS for epilepsy management was FDA-approved in 1997, marking the start of its recognized therapeutic role. Since then, over 100,000 devices have been implanted worldwide, and its scope has widened to include treatment-resistant depression in 2005. Emerging research and clinical trials continue to explore the potential applications of VNS across various conditions, revealing its broader promise as a tool for neuromodulation and anti-inflammatory intervention.

[1] For a comprehensive review of VNS, see *Johnson and Wilson, 2018*

Transition to Noninvasive Approaches

Traditionally, VNS has been delivered through invasive means, requiring surgical implantation of a device. Recent advancements have led to noninvasive VNS (nVNS) methods, which stimulate the vagus nerve without the need for surgery. This transition offers several benefits over invasive approaches. Invasive VNS involves surgically implanting a pulse generator in the chest with leads attached to the left cervical vagus nerve. This method has been approved for refractory epilepsy and treatment-resistant depression. While effective, invasive VNS poses risks such as surgical complications, infections, and nerve damage. Additionally, the high cost and the requirement for surgical facilities limit its accessibility.

The limitations of invasive VNS have spurred interest in developing noninvasive techniques. Noninvasive VNS typically uses transcutaneous electrical stimulation applied to areas where the vagus nerve is superficial, such as the auricular branch in the ear or the cervical branch in the neck. Devices deliver mild electrical pulses through the skin to modulate vagal activity without surgical intervention.

Benefits of Noninvasive Vagus Nerve Stimulation

- **Reduced Risk and Increased Safety**: Noninvasive methods eliminate surgical risks, including infections and anesthesia-related complications. Studies have shown that nVNS is generally well-tolerated, with side effects being mild and transient, such as skin irritation or tingling sensations.
- **Cost-Effectiveness**: Without the need for surgery and implanted hardware, nVNS significantly reduces costs. This makes the therapy more accessible to a broader patient population and can ease the financial burden on healthcare systems.
- **Convenience and Accessibility**: nVNS devices are portable and user-friendly, allowing patients to administer therapy at home or in various settings. This convenience can improve adherence to treatment protocols and enhance quality of life.
- **Expanded Therapeutic Applications**: Research indicates that nVNS may be effective in treating conditions beyond epilepsy and depression, such as migraines, cluster headaches, and inflammatory disorders. This broadened scope increases its clinical utility.
- **Reversibility**: Since nVNS does not involve permanent implantation, therapy can be easily adjusted or discontinued without additional surgical procedures, offering flexibility in treatment management.

The shift from invasive to noninvasive VNS represents a significant advancement in neuromodulation therapies. Noninvasive techniques provide a safer, more cost-effective, and accessible alternative to surgical methods, with the added benefit of broader therapeutic potential. Ongoing research continues to explore and expand the applications of nVNS in clinical practice.

Innovation Snapshot

Patents

Title: Ear rim vagus nerve magnetic stimulation device
Publication Number: CN108066890A
Publication Date: May 24, 2018
Assignee: Renmin Hospital of Wuhan University
Summary: This patent describes a non-invasive ear-based vagal nerve stimulation device designed to treat cardiovascular conditions such as arrhythmias and myocardial infarction by stimulating the ear's vagus nerve via electromagnetic waves. Unlike existing invasive autonomic interventions, this device is worn on the ear, resembling an earbud or patch, with embedded electromagnetic wave generators positioned in contact with the skin near the ear's vagus nerve. The device is powered by an energy source and can be controlled through a mobile app, allowing the user to adjust stimulation parameters like intensity and frequency. Key features include its ability to offer tailored, real-time stimulation for managing acute cardiovascular episodes, reducing infarct size, and potentially inhibiting arrhythmias through a non-invasive, user-friendly interface. The device's unique selling point is its integration of electromagnetic wave technology in a compact, wearable format, which broadens accessibility and minimizes the risks associated with more invasive approaches.
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Title: Non-invasive vagus nerve stimulation devices and methods to treat or avert atrial fibrillation
Publication Number: US10213601B2
Publication Date: February 25, 2019
Assignee: electroCore, Inc
Summary: This patent details a non-invasive device designed to deliver controlled electrical impulses to the vagus nerve through the skin to treat or prevent episodes of atrial fibrillation (AF). The device monitors patients with or at risk of AF and uses external energy sources to create a precisely controlled electric field that reaches the vagus nerve without requiring invasive procedures. Unique features include the ability to customize pulse bursts (3-100 Hz) and durations (50-1000 microseconds) to stimulate the vagus nerve selectively, which helps in managing AF by either converting the heart rhythm back to normal or by averting imminent AF episodes. This non-invasive approach offers a targeted alternative to invasive methods, presenting reduced risks, increased ease of use, and adaptable stimulation parameters that are tailored to each patient's cardiac activity.
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Title: Method and multichannel device for non-invasive stimulation of vagus nerve
Publication Number: US120240238582A1
Publication Date: July 17, 2024
Assignee: Heby, LLC
Summary: This patent describes a noninvasive multichannel device for Vagus nerve stimulation (VNS) aimed at treating various conditions like anxiety, depression, and pain without the limitations of tolerance development seen in conventional methods. The device utilizes a novel approach with alternating stimulation of both the right and left branches of the auricular and cervical Vagus nerve through electrodes placed on the ears and neck, modulating at specific frequencies with bipolar waveforms. Unique to this invention is its prevention of acquired tolerance and tachyphylaxis by alternating channels and using randomized modulating frequencies. This design allows for

sustained therapeutic effects without increasing current amplitude, potentially enhancing long-term efficacy and stability in VNS treatments.
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Title: Non-invasive vagus nerve stimulation
Publication Number: US12021220644A1
Publication Date: July 21, 2021
Assignee: electroCore Inc
Summary: This patent describes a noninvasive, self-administered device and method for treating medical conditions such as migraines by modulating the vagus nerve via transcutaneous electrical impulses. The device is designed for application on the neck or auricular area, providing controlled pulses to the vagus nerve to alleviate symptoms without requiring a healthcare provider. Unique to this invention is its self-guided usage capability, allowing patients to manage their symptoms at home or work immediately when needed. This innovation addresses practical issues such as ensuring correct placement and dosage control, supported by a mobile interface for remote configuration and data exchange, thus offering a convenient, lower-cost alternative to clinical visits and traditional invasive nerve-stimulation methods.

Products

Noninvasive vagus nerve stimulation (nVNS) products are generally marketed in two categories: medical-grade devices and consumer-oriented wellness devices. **Medical-grade nVNS products** are FDA-cleared or approved for specific clinical applications like migraine, cluster headaches, and epilepsy, and are often prescribed by healthcare providers. These devices are highly regulated, typically require a prescription, and undergo rigorous clinical trials to ensure efficacy and safety for particular conditions. Medical nVNS devices generally provide targeted, controlled stimulation settings to achieve therapeutic effects, with the goal of modulating neurological or inflammatory responses as part of a broader treatment plan.

gammaCore

- First and only FDA cleared non-invasive device to treat and prevent multiple types of headache pain via the vagus nerve
- Handheld device that is placed and held on the neck on the cervical portion of the vagus nerve

Vagustim

- Medical grade trans-auricular nVNS device marketed towards both consumers and health professionals.
- The device is worn bilaterally on the ears and stimulates both the tragus and concha. Stimulation is controlled by a mobile app that controls the stimulator hardware. The app can collect data for customized therapy.

Soterix Medical

- Manufactures nVNS products for clinical research, including nVNS systems that can be used in an MRI machine

Consumer-oriented nVNS devices, on the other hand, are marketed for general wellness and often do not require a prescription. These products are less regulated, as they are marketed as wellness or lifestyle tools rather than medical devices, and thus generally lack the rigorous clinical validation seen in medical nVNS devices. Although these consumer products use similar principles of vagus nerve stimulation, they usually offer less precise control over stimulation parameters, focusing instead on user-friendly interfaces and broader wellness claims suitable for at-home use.

Nurosym

- Marketed towards those with Vagus Nerve Impairment and claims to promote relaxation, mood, sleep, healthy digestion, increased HRV, as well as to alleviate symptoms of stress, burnout, and adrenal fatigue
- Over the ear clip that users attach to their tragus

Truvaga Plus

- Marketed towards addressing stress, sleep, calmness, and mental clarity
- Handheld device that users place against their neck

VeRelief

- Marketed as a stress relief biohacking tool
- Handheld device that users place just under the ear

Pulsetto

- Marketed as a tool for stress relief and improved sleep and calmness
- Work as a device that wraps around the neck to apply bilaterial stimulation to the cervical portions of the vagus nerve

Apollo

- Marketed towards a variety of uses, including increased calmness, sounder sleep, relaxation, reduced stress, and as an energy and focus boost- depending on the stimulation protocol selected
- Users are instructed to wear the device around the wrist or ankle, and it has a detachable clip that can be used to attach the device to the sternum

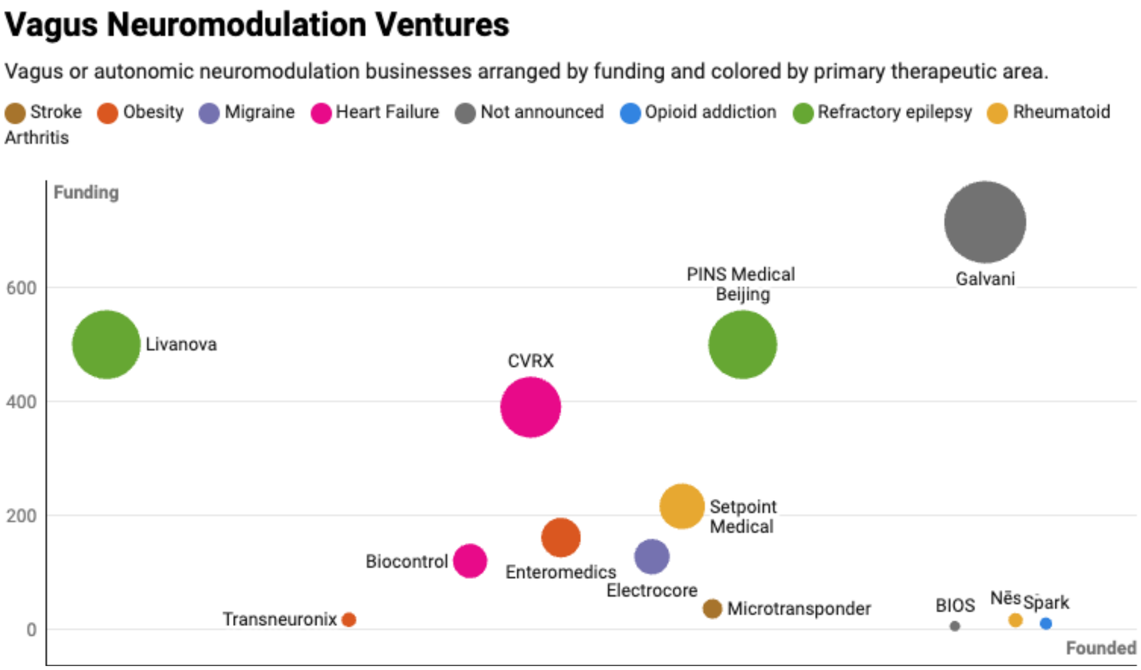
Investment Trends

nVNS has emerged as a significant area of interest in medical research and therapeutics due to its potential to treat a variety of conditions without the risks associated with surgical procedures. The funding landscape reflects this growing interest, with several notable trends:

Private Sector and Venture Capital Investment:

- **Startup Funding:** Venture capital firms are investing in startups that specialize in nVNS technology, attracted by the promising market growth and innovative approaches.

- **Industry Partnerships:** Established medical device companies are partnering with smaller firms or research institutions to co-develop nVNS technologies, pooling resources for mutual benefit.



[Going Long on the Vagus Nerve: Startups Re-discover the Autonomic Neuromodulation Goldmine]

Of these entities, electroCore in particular has pursued funding from venture capital. In 2017, they [completed $70 million in Series B funding]. Financing was led by Core Ventures II, who also participated in the Company's Series A round. This Series B financing also included significant participation from Merck's Global Health Innovation Fund (a venture capital arm of Merck & Co. Inc), who also participated in the Series A round.

- This investment proved fruitful, as electroCore's gammaCore nVNS device [recently received] Breakthrough Device Designation for the treatment of PTSD

Government Grants and Public Funding:

- **Increased Research Funding:** Government agencies are allocating more funds to nVNS research. For example, the National Institutes of Health (NIH) has supported studies exploring nVNS for conditions like migraines, depression, and inflammatory diseases.
- **Public Health Initiatives:** Public health organizations recognize the potential cost savings and improved patient outcomes associated with noninvasive therapies, leading to supportive funding policies.

Active NIH Funding Opportunities Snapshot[2]

Title	Notice Number	Issuing Organization	Participating Organization(s)	Release Date	Expiration Date
Combined Neuromodulation and Behavioral Treatment Algorithm Development for Stimulant Use Disorder (StUD) Enriched for Vulnerable Phenotype (U01 Clinical Trial Required)	RFA-DA-25-057	NIDA	N/A	June 27, 2024	November 28, 2024
BRAIN Initiative: New Technologies and Novel Approaches for Recording and Modulation in the Nervous System (R01 Clinical Trial Not Allowed)	RFA-NS-25-018	NINDS	NCCIH, NIMH, NEI, NIA, NIAAA, NIBIB, NICHD, NIDA, NIDCD	September 24, 2024	January 21, 2026
Mechanistic Research on Neuromodulation for Substance Use Disorders Treatment (R01 Basic Experimental Studies with Humans Required)	RFA-DA-24-032	NIDA	N/A	September 29, 2023	August 15, 2026
Mechanistic Research on Neuromodulation for Substance Use Disorders Treatment (R61/R33 Basic Experimental Studies with Humans Required)	RFA-DA-24-034	NIDA	N/A	October 5, 2023	August 15, 2026
Neuromodulation/Neurostimulation Device Development for Mental Health Applications (R01 Clinical Trial Not Allowed)	PAR-22-039	NIMH	N/A	October 12, 2021	January 8, 2025
Neuromodulation/Neurostimulation Device Development for Mental Health Applications (R21 Clinical Trial Not Allowed)	PAR-22-038	NIMH	N/A	October 12, 2021	January 8, 2025

The Future of Bioelectronics in Medicine

nVNS is far from the only exciting area in bioelectronics. The future of bioelectronics in medicine is set to revolutionize healthcare by seamlessly integrating advanced technologies such as sophisticated neural interfaces, flexible and biodegradable electronics, and intelligent closed-loop systems powered by artificial intelligence. Innovations like energy harvesting devices and wireless power transfer will enable implantable devices to operate more efficiently. Developments in nanorobotics promise targeted drug delivery at the cellular level, and the expansion of bioelectronic medicine will broaden treatment options for a range of diseases. Personalized and wearable bioelectronics will facilitate continuous health monitoring, and integration with genomics and biomarker detection will usher in an era of highly individualized therapies. Together, these advancements herald a new era of precise, efficient, and minimally invasive medical care.

[2] More information about active NIH funding opportunities can be found here.

Advanced Neural Interfaces[3]

Advanced neural interfaces aim to create seamless communication between the nervous system and electronic devices. These interfaces can record neural activity with high resolution and stimulate neural circuits precisely. Innovations focus on improving biocompatibility, scalability, and longevity of neural implants.

- **High-Density Electrode Arrays:** Microelectrode arrays with thousands of channels allow detailed mapping and modulation of neural networks.
- **Wireless Brain-Machine Interfaces (BMIs):** Eliminate the need for wired connections, reducing infection risks and improving patient comfort.
- **Biocompatible Materials:** Use of materials like graphene and organic polymers to enhance integration with neural tissue and reduce immune responses.

Flexible and Biodegradable Electronics[4]

Flexible electronics conform to the body's contours, improving contact with tissues and reducing discomfort. Biodegradable electronics dissolve after serving their purpose, eliminating the need for surgical removal and reducing long-term complications.

- **Stretchable Circuits:** Use of materials like silicon nanomembranes and conductive polymers that maintain functionality under mechanical deformation.
- **Transient Electronics:** Devices designed to degrade via hydrolysis or enzymatic reactions within the body safely.

Closed-Loop Systems with Artificial Intelligence[5]

Closed-loop bioelectronic systems monitor physiological parameters and adjust therapeutic outputs in real-time. Integrating AI and machine learning enables these systems to predict patient needs and optimize treatments autonomously.

- **Adaptive Algorithms:** Machine learning models that adjust stimulation parameters based on feedback.
- **Real-Time Data Processing:** On-device computation for immediate response without external processing delays.

Energy Harvesting and Wireless Power Transfer[6]

Energy harvesting devices convert ambient energy sources (e.g., body heat, movement) into electrical power for medical devices. Wireless power transfer enables devices to receive power externally, reducing the need for batteries and invasive procedures.

- **Thermoelectric Generators:** Devices that convert temperature gradients into electricity.
- **Piezoelectric Materials:** Generate electric charge under mechanical stress, such as body movements.
- **Inductive and Ultrasonic Power Transfer:** Non-radiative methods for powering implants wirelessly.

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[3] Won et al., 2018
[4] Li et al., 2020
[5] Liu et al., 2017
[6] Zou et al., 2021

Microbial Bioelectronics[7]

Microbial bioelectronics harness the electrical properties of microorganisms for biomedical applications. This includes using microbes in biofuel cells, biosensors, and interaction with the human microbiome for therapeutic purposes.

- **Microbial Fuel Cells:** Generate electricity from organic compounds via microbial metabolism.
- **Microbe-Based Biosensors:** Detect specific biological markers or environmental toxins.

Nanorobotics and Targeted Drug Delivery[8]

Nanorobotics involves nanoscale devices capable of performing specific tasks, such as targeted drug delivery. These nanorobots can navigate the bloodstream, identify diseased cells, and release therapeutics directly at the site, minimizing systemic side effects.

- **Magnetically Guided Nanorobots:** Controlled using external magnetic fields for precise navigation.
- **Biodegradable Nanocarriers:** Designed to degrade after delivering their payload, reducing toxicity.

Personalized and Wearable Bioelectronics[9]

Wearable bioelectronics enable continuous monitoring of physiological parameters, facilitating personalized healthcare. These devices can detect early signs of disease exacerbation and help manage chronic conditions effectively.

- **Smart Textiles:** Integrating sensors into clothing for unobtrusive monitoring.
- **Non-Invasive Glucose Monitors:** Devices that measure blood sugar levels without needles.

Integration with Genomics and Biomarker Detection[10]

Bioelectronic devices integrated with genomic data and capable of detecting specific biomarkers enhance precision medicine. They facilitate early diagnosis and enable tailored therapies based on an individual's genetic makeup and molecular profile.

- **Electrochemical DNA Sensors:** Detect genetic mutations and variations.
- **Lab-on-a-Chip Devices:** Miniaturized platforms performing complex analyses, including PCR and sequencing.

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[7] *Terrell et al., 2021*
[8] *Halder and Sun, 2019*
[9] *Kim et al., 2018*
[10] *Zhang and Lieber, 2015*