

NOVEL MATERIALS FOR BRAIN COMPUTER INTERFACES: PERSPECTIVES AND ASPECTS OF COMBINATION OF A MAGNETOELECTRIC STIMULATOR AND A GRAPHENE MICROTRANSISTOR ARRAY RECORDING SYSTEM

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ABSTRACT: In this paper, we explore the innovative combination of magneto-electric nanoparticles (MENPs) and graphene solution-gated field-effect transistors (gSGFETs) to advance brain-computer interfaces (BCIs). ME materials, known for their wireless and minimally invasive brain stimulation capabilities, are combined with gSGFETs, known for their high-resolution neural recording. Our research explores the potential benefits of this hybrid approach, including reduced artifacts, enhanced spatial resolution, and improved detection of subthreshold phenomena and DC potentials. A hardware and software setup is proposed and possible data analysis methods that will assist in the further development of the system are reviewed. This combined technology offers a promising direction for advanced BCIs and represents a significant advance in neural engineering.

INTRODUCTION

In the rapidly evolving field of neural engineering, significant advances have been made to improve brain-computer interfaces (BCIs) through innovative materials and technologies. One notable development is magneto-electric (ME) materials, which are known for their unique ability to convert magnetic fields into electric fields and vice versa through mechanical coupling between magnetostrictive and piezoelectric components [1]. The application of ME materials in brain stimulation is a promising option for low magnetic field stimulation in the range of a few mT. They can be fabricated in various sizes, from milliliters to nanometers, thus facilitating minimally invasive procedures. At the nanoscale, MENPs can even be administered intravenously, providing a wireless, less invasive approach to stimulating deep brain regions [2-6]. While previous *in vitro* and *in vivo* research on MENPs for brain stimulation has shown promising results for their modulatory effects on brain activity, these studies have primarily used calcium imaging to measure neuronal activation [3-5]. This technique has the advantage of simultaneously visualizing the activity of

large populations of neurons while not requiring the use of implants, thus reducing invasiveness. Another key advantage, particularly relevant in magnetic field stimulation, is the absence of interference from induced voltages in the measurements. Calcium imaging, however, has significant limitations. It detects changes in calcium ion concentrations within neurons, which indicate neuronal activity. When neurons fire, these calcium ions flow into the cells and are detected by fluorescent calcium indicators. However, the kinetics of these indicators and related physiological processes limit the temporal resolution of the method. In addition, calcium imaging cannot detect subthreshold changes in activity [7].

Therefore, this method is not suitable for a complete study of stimulation-related phenomena that require good temporal resolution, such as evoked potentials or entrainment at a specific stimulation frequency.

Electrophysiological methods, on the other hand, can directly record electrical potentials with high temporal resolution, making them well suited for use with neural stimulation techniques. However, they offer limited spatial resolution, and induced voltages become a significant issue when stimulation involves magnetic fields [8].

To address these challenges and fully exploit the capabilities of MENPs stimulation, we propose the combination with a graphene microtransistor array recording system. The graphene-based active sensors, specifically graphene solution-gated field-effect transistors (gSGFETs) are notable for their flexibility, biocompatibility, high carrier mobility, chemical stability, and mechanical conformability [9]. Recent advancements in gSGFETs have demonstrated their effectiveness for broadband recordings and their potential for spatially resolved mapping, making them ideal for exploring various neural activities, including infra-slow oscillations [10-12].

The combination of these two systems promises to provide the high spatial resolution and minimal interference typical of imaging methods, along with the high temporal resolution and subthreshold phenomenon

detection capabilities of full-band electrophysiology methods. We also propose a detailed hardware and software setup and suggest the exploration of specific data analysis methods that will further the development of the system. By combining the wireless, minimally invasive stimulation capabilities of ME materials with the high-resolution recording capabilities of gSGFETs, this research aims to create a more comprehensive and effective approach to studying and modulating brain activity, making a significant contribution to neurological research and potential treatments for neurological disorders.

MAGNETOELECTRIC MATERIALS FOR NEURAL STIMULATION

The ability of ME materials to convert magnetic fields into electric fields with significant high performance has led to increasing research on the application of ME materials in neural stimulation. ME materials consist of a magnetostrictive component that deforms under a magnetic field and a piezoelectric component that converts this deformation into voltage. These components can be configured in several forms: two bonded linear thin films are common at the submillimeter scale, while a magnetostrictive core with a piezoelectric shell is typical for MENPs. Depending on their size, ME materials can be either implanted or injected—submillimeter devices are usually implanted, whereas nanoscale devices like MENPs are injected. Injection can be performed stereotactically in the targeted brain region or even intravenously, depending on the MENPs' nanodiameter, which influences their ability to cross the blood-brain barrier. In this work, we focus on MENPs (Figure 1) due to their minimal invasiveness, which is significant for biomedical applications. However, the proposed hardware and software system can also be integrated with submillimeter ME devices, which offer a comparatively lower level of invasiveness than other solutions.

Stimulation using low-intensity magnetic fields and MENPs in deep brain regions could provide a wireless and less invasive alternative to traditional deep brain stimulation (DBS) [2]. Furthermore, MENPs could enhance precision and depth in targeting neural activity compared to techniques like transcranial magnetic stimulation (TMS), transcranial alternating current stimulation (tACS), and transcranial direct current stimulation (tDCS) [2-6]

Significant experiments with ME materials have shown their ability to modulate brain activity, using nanoparticles for targeted stimulation in *in vitro* studies and demonstrating neuromodulation feasibility *in vivo*. These studies suggest ME materials could offer new treatments for neurological disorders [3-5]. However, they often rely on indirect methods like calcium imaging to assess neural responses, highlighting a gap in direct neural activity measurement through electrophysiology.

This gap suggests a need for integrating ME materials with advanced systems like graphene electrode arrays for a deeper, more accurate understanding of neural dynamics and stimulation effects.

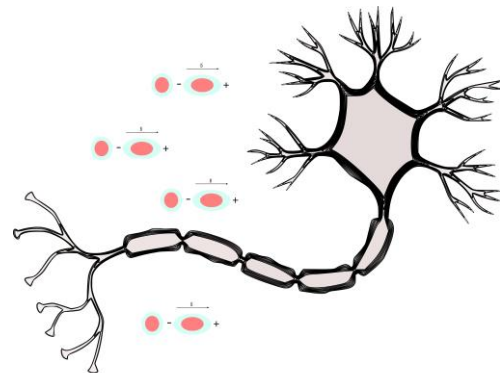


Figure 1: Magneto-electric nanoparticles deform when a magnetic field is applied, creating electrical dipoles that can potentially modulate neuronal activity.

SOLUTION-GATED GRAPHENE FIELD-EFFECT TRANSISTORS FOR NEURAL RECORDINGS

Electrolyte-gated transistors have emerged as a promising technology in the field of active sensors. The unique properties of graphene, such as its high electrical conductivity, flexibility, and biocompatibility, make gSGFETs especially suitable for interfacing with biological systems. GSGFETs offer several advantages over traditional neural recording systems. Their high carrier mobility allows for rapid response to neural signals, enhancing the temporal resolution of recordings. Additionally, the thin and flexible nature of graphene enables gSGFETs to conform to neural tissues, reducing mechanical mismatches and improving signal fidelity. Compared to conventional metal-oxide-semiconductor field-effect transistors (MOSFETs), gSGFETs exhibit lower noise levels, which is crucial for detecting subtle neural activities. [9-10].

Several studies have demonstrated the efficacy of gSGFETs in neural recording applications. For instance, a landmark study [9] illustrated how gSGFETs could be used to record electrophysiological signals from cardiac cells with higher clarity than traditional methods. Another study [11] successfully employed gSGFETs in recording complex neural networks, showcasing their potential in understanding neural dynamics and disorders. Furthermore, experiments have shown that gSGFETs are capable of operating in harsh biochemical environments, maintaining their stability and functionality over extended periods, a crucial factor for long-term neural monitoring [12]. gSGFETs have been successful in capturing a wide range of frequencies, including those below 0.1Hz, known as infra-slow oscillations, with performance similar to glass micropipettes. They also provide the capability for detailed spatial imaging. [10].

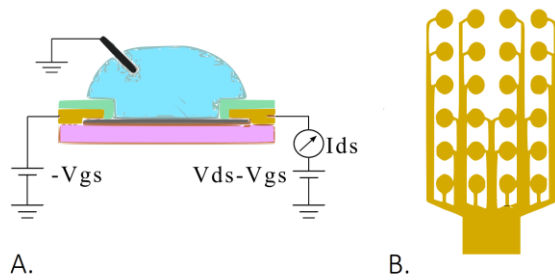


Figure 2: gSGFET visualization with applied gate-source and drain-source polarizations. Drain-source current I_{ds} is measured at drain B. Multielectrode array structure visualization with positions for multiple gSGFETs.

ADVANTAGES OF THE COMBINATION OF THE TECHNOLOGIES

The use of gSGFETs to record the outcomes of magnetic stimulation with MENPs offers several benefits, demonstrating a promising match between these two technologies and marking a significant advancement in neurotechnology.

A. Reduced Induced Artifacts from Magnetic Fields and Less Interactions

A significant advantage of using MENPs for stimulation is their reliance on low-intensity magnetic fields [18], which opens up possibilities for employing various waveform types beyond those used in traditional transcranial magnetic stimulation (TMS). In TMS, short pulses of high intensity, up to 1.5 T, typically saturate recording systems, which are only able to record when stimulation is not occurring. This causes manageable problems in recordings since the duration of the pulse is only in the range of microseconds. In contrast in the case of MENPs, using lower magnetic fields of some mT allows for the exploration of alternative waveforms, such as sinusoidal signals. However, even at these reduced intensities, saturation issues in recording systems can occur, necessitating measures to mitigate these artifacts.

Graphene material exhibits low magnetic susceptibility, making gSGFETs an effective solution for recording in environments with magnetic interference. The stability of graphene's electrical properties in magnetic fields, as demonstrated by Harrysson Rodrigues et al. [19], further underscores the suitability of gSGFETs for such uses. Additionally, a study by Zhao et al. [20] showed that graphene fiber electrodes used for deep brain stimulation in conjunction with fMRI effectively mapped activation patterns without being disrupted by the MRI scanner's magnetic field. This confirms that graphene electrodes can function reliably in magnetic environments, making them ideal for simultaneous stimulation and recording applications.

Therefore, combining MENPs and gSGFETs has several beneficial effects, such as reducing artifacts in

electrophysiological recordings and enabling the examination of more waveforms and frequencies of stimulation. Additionally, the minimal magnetic force interaction between the MENPs and gSGFETs prevents the alteration of MENP distribution that could occur with metallic electrodes.

B. Enhanced Spatial Resolution

High resolution in neural recording and stimulation is essential to precisely target and record from specific neuronal populations or individual neurons. This level of precision is critical for unraveling the complex mechanisms of neural communication, synaptic dynamics, and network functionality. The integration of MENPs with gSGFETs, could greatly enhance this capability, allowing researchers to probe neural circuits with the necessary spatial fidelity. MENPs offer targeted brain stimulation with high spatial precision [18], while graphene electrodes provide the flexibility and high-resolution recording critical for capturing neural activity [13-16]. Furthermore, the inherent non-uniformity of the magnetic field in magnetic stimulation applications, coupled with the potentially non-uniform distribution of the applied nanoparticles, underscores the need for high spatial resolution in recordings. This is critical for accurate interpretation of neural responses to magnetic stimulation and for precise delivery of therapeutic interventions. Together, MENPs and gSGFETs promise to advance our understanding of brain function by facilitating precise modulation and detailed observation of neuronal activity.

C. Recording DC potentials and Infra-slow oscillations

The incorporation of graphene electrodes, known for their sensitivity in recording direct current (DC) potentials and Infra-slow oscillations [13-16], in conjunction with a stimulation device is critical. Recent literature suggests that such neural activity may occur during or after transcranial direct current stimulation (tDCS) [16]. Given the shared principles between magnetic and electrical stimulation, it is plausible to expect similar results in experiments involving stimulation with magnetoelectric nanoparticle systems (MENPS).

Exploring the relationship between subthreshold stimulation and potential changes in direct current (DC) potentials or infra-slow neural activity presents an intriguing research opportunity. Stimulation with magnetoelectric (ME) materials often involves magnetic fields in the range of tens of milliteslas for brain stimulation [2-6]. This intensity is generally considered to be below the threshold required to produce noticeable effects. Therefore, a study investigating whether such subthreshold stimulation levels can lead to changes in DC potentials or infra-slow activity could significantly enhance our understanding of neural responses to ME materials.

This investigation is feasible, especially in experiments with MENPS. Typically, only magnetic field is used as a negative control in these studies. Using a plain magnetic field as a baseline allows for a clearer distinction between the unique effects of magnetoelectric materials and the inherent activity of the brain. This methodological approach may provide valuable insights into the subtleties of brain responses to subthreshold magnetic stimulation.

D. Minimal invasiveness, broadband recordings and biocompatibility

MENPs enable miniature, wireless neural stimulation devices combined with the flexibility of graphene electrodes could lead to minimally invasive neural interfaces. The wide frequency response range of graphene complements the ability of ME materials to operate over various frequencies, allowing versatile neural modulation and recording. Finally, gSGFETs and MENPs are both known for their biocompatibility, making them well-suited for use in neural interfaces, with minimal risk of biological rejection or adverse reactions.

In conclusion combining magnetoelectric stimulators with graphene electrode recording systems unlocks several benefits. This innovative approach holds great promise for future developments in neural technology, including advanced brain-computer interfaces and sophisticated neurological research tools.

A PROPOSED SETUP FOR ELECTROPHYSIOLOGY EXPERIMENTS

A. HARDWARE DESCRIPTION

The proposed setup consists of a ME stimulator and a gSGFET multichannel recording system. The ME stimulator is similar with the one presented in [21], it is designed for *in vitro* and *in vivo* experiments, features a two-channel power capability using a Class-D audio amplifier, each channel delivering up to 100W. This design enables the operation of two experimental setups simultaneously. The stimulator can generate magnetic fields up to 20 mT RMS, adjustable based on selected protocols and frequencies. A microcontroller collects temperature, current and other important measurements. A capacitance board allows the capacitance to be adjusted to meet specific frequency requirements. The system includes a specially designed circular coil, ensuring effective magnetic field generation across various experimental conditions, including those in electrophysiology chambers.

The recording system is an innovative 64/128-channel amplification system for neural signal processing, incorporating graphene-based transistors and has been tested in several experiments [16-17], [22]. The system includes key components such as gSGFETs, a breakout board, a preprocessing device, an amplifier, and a

software interface.

A critical element, the preprocessing device, is responsible for converting and preamplifying analog signals and setting bias voltages for the gSGFETs. Its architecture includes a mainboard, several analog modules, a digital board, and an accumulator board. The mainboard's primary role is to process signals from electrodes through analog modules, converting them from current to voltage, and segregating them into DC and AC components, as detailed in the circuitry described by C. Hébert et al [8]. This design allows versatility in using different electrode arrays and includes functionalities for electrode characterization.

Each analog module on the mainboard can process eight channels, with the capability to adjust to various electrode configurations. Furthermore, these modules are equipped with bypass switches to facilitate electrode characterization. The digital board features a Bluetooth module-microcontroller for wireless adjustments of voltage settings and managing bypass switches.

Post-preprocessing, the signal gets divided into 64 AC and 64 DC channels. The amplification stage employs the g.RAPHENE device, an advanced version of the g.Hiamp with 128 input channels, 64 for AC and 64 for DC amplification. The g.Hiamp [23], a high-performance biosignal amplifier developed by g.tec medical engineering, is noted for its excellent signal resolution and sensitivity. Its application in ultra-high-density electroencephalography has been pivotal, as indicated by recent data from g.Hiamp recordings.

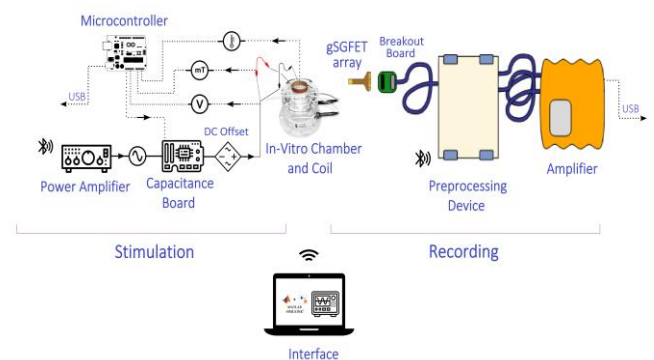


Figure 3 Hardware diagram of the proposed system

B. SOFTWARE DESCRIPTION

A common software interface controls the two systems developed in MATLAB/Simulink.

The user interface of the ME stimulator communicates seamlessly with the amplifier via Bluetooth, facilitating easy control even through mobile apps. The software supports various waveform options, enhancing the adaptability of the system to diverse research requirements. Its ability to simulate the magnetic/electric field effects and estimate coil temperature rise based on

selected protocols is crucial for evaluating stimulation parameters and ensuring safety.

For the part of the graphene device the interface supports intricate tasks like electrode characterization and recording execution. It includes features for configuring Bluetooth communication, setting amplifier parameters, and specifying voltage sweeps. The system provides real-time visualizations of both AC and DC signal components, allowing for detailed analysis of neural activities

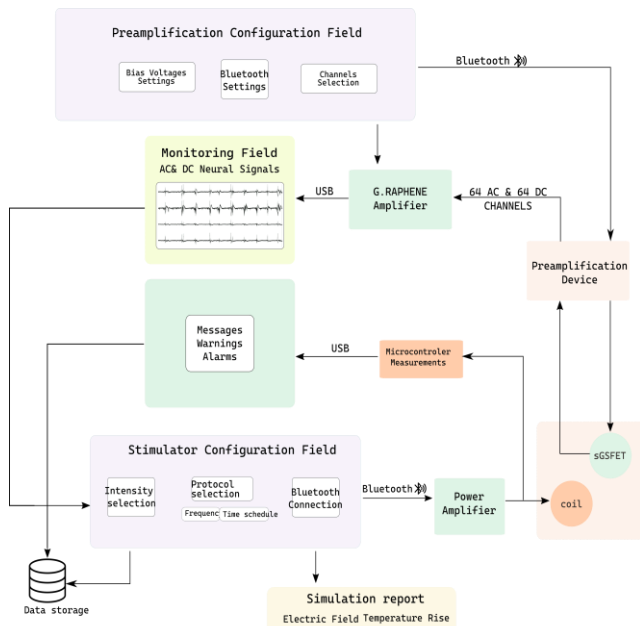


Figure 4 Software diagram of the proposed system.

In summary, the combined magnetolectric stimulator and graphene electrode recording systems present a sophisticated, highly adaptable, and user-friendly platform. This integrated approach enhances the capability for precise neural stimulation and recording, opening new avenues for advanced neuroscience research and potential therapeutic applications.

DATA ANALYSIS METHODS

In the direction of further development and evolution of a system integrating gSGFETs with MENP-based magnetic stimulation, especially in local field potential (LFP) recordings, a thorough research approach could focus on some data analysis methods.

Time-frequency analysis is a technique in which LFP signals are decomposed into their component frequencies over time using methods such as wavelet transforms or short-time Fourier transforms. It's useful for identifying changes in power over different frequency bands, including Infra-slow oscillations. Research such as that of Unakafova and Gail [24] provides a practical guide for neuroscientists in selecting open-source toolboxes for spike and LFP data analysis, including those with time-frequency analysis functionality. Spike-field coherence

analysis examines the relationship between neuronal spiking activity (UP states) and LFPs. It can show how changes in UP and DOWN states correlate with fluctuations in slower frequency bands, including DC shifts. Henningson and Illes [25] proposed a model to study subthreshold fluctuations.

Phase-amplitude coupling (PAC) analysis examines the interaction between the phase of lower frequency oscillations, such as infraslow or theta bands, and the amplitude of higher frequency activity. This approach is particularly relevant for studying the interplay between Infra-slow oscillations and fast neuronal dynamics. An important application of PAC analysis is demonstrated in the study by Hiroaki Hashimoto et al [26], who found that PAC between infra-slow and high-frequency activity can effectively discriminate between preictal and interictal states in epilepsy, underscoring its potential as a useful biomarker. Cross-frequency coupling (CFC) examines the relationship between different frequency ranges in neural signals [27]. It can be used to study how infraslow oscillations influence, or are influenced by, other frequency bands in LFP data. Finally, machine learning approaches [28], such as neural networks or support vector machines, can be trained to classify and predict patterns in LFP data, taking into account both fast neural fluctuations and slower DC shifts. infra-slow activity or DC potentials following stimulation.

DISCUSSION

The current work explores the combination of neural stimulation with MENPs and recording with gSGFETs as a novel technique for future brain-computer interfaces. Significant benefits such as reduced artifacts, enhanced spatial resolution, and detection of subthreshold phenomena are highlighted. The proposed hardware and software setup is designed to accommodate a range of experimental conditions with ease of use, while comprehensive data analysis methods, including time-frequency analysis and machine learning approaches, enable detailed interpretation of the intricate neural signals recorded.

Overall, this integrated approach represents a significant step forward in neural engineering, promising advances in neurological research and potential therapeutic applications.

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