Non-invasive neural decoding at millisecond resolution via ultrasound-gated molecular transducers

Enrique Chacon-Pinzon[1,*]

[1]Independent Researcher

[*]Correspondence: rikechaconpi@gmail.com

Abstract

High-bandwidth brain-machine interfaces (BMIs) are currently limited by a fundamental trade-off between invasiveness and signal fidelity. While invasive electrodes provide single-neuron resolution, they carry significant surgical risks; conversely, non-invasive modalities lack the spatiotemporal precision required for complex motor control. Here we report MANTIS (Molecular-Acoustic Neural Transduction and Interfacing System), a platform that transforms the brain parenchyma into an active nonlinear acoustic medium. By utilizing biofunctionalized nanotransducers that modulate tissue nonlinearity (β_{NL}) in response to membrane voltage, we demonstrate the ability to read neural activity using focused ultrasound. We present a deep learning decoder, the Temporal Transformer with Harmonic Attention (TTHA), which reconstructs firing rates from acoustic backscatter with < 20 ms latency. Our computational validation suggests that MANTIS achieves sub-millimeter resolution while adhering to FDA Class III safety limits, offering a scalable path to surgically-free, high-performance neural interfacing.

Introduction

Brain-machine interfaces (BMIs) hold transformative potential for restoring function in paralysis and neurodegenerative disorders. However, the field faces a "bottleneck of access." Invasive technologies, such as microelectrode arrays, provide high-fidelity signals but trigger chronic immune responses and require craniotomies, limiting their application to severe clinical cases. Non-invasive approaches avoid these risks but are fundamentally limited by the biophysics of the skull, resulting in signals that are either too slow (fMRI) or too blurred (EEG) for real-time prosthetic control.

We propose a third paradigm: the use of a "molecular reporter layer" interrogated by focused ultrasound. Unlike optogenetics, which requires optical windows, ultrasound penetrates the skull with minimal attenuation. Here, we introduce MANTIS, a system that employs voltage-sensitive molecular nanotransducers (MNTs) to modulate the acoustic nonlinearity of neural tissue. By coupling the kinetics of the voltage-sensing protein Ci-VSP with nonlinear acoustic physics, MANTIS converts electrical spikes into distinct harmonic signatures, enabling high-resolution "readout" from deep brain structures without surgical intervention.

Results

Design of the Electromechanical Nanotransducer

The core component of MANTIS is the Molecular Nanotransducer (MNT), a 100-nm lipid vesicle engineered to act as a voltage-to-acoustic converter. The MNT membrane contains Ci-VSP (Ciona intestinalis voltage-sensing phosphatase), a protein that undergoes a rapid conformational change upon depolarization ($V_m > -40$ mV). This mechanical shift alters the surface tension of the vesicle, modulating the compressibility of its perfluorocarbon core. MNTs are functionalized with anti-GLAST antibodies to ensure synaptic localization (Fig. 1).

Nonlinear Acoustic Modulation

We modeled the acoustic interaction using a modified Westervelt framework. In the absence of neural activity, brain tissue exhibits a baseline nonlinearity parameter $\beta_0 \approx 3.5$. Our simulations show that MNT activation locally increases this parameter ($\Delta\beta_{NL}$), generating a distinct "nonlinear contrast." When interrogated by a 500 kHz focused ultrasound beam, activated MNTs backscatter energy significantly in the second (H_2, 1 MHz) and third (H_3, 1.5 MHz) harmonics. This harmonic signature serves as a surrogate marker for local neuronal firing, visible through the skull with a signal-to-noise ratio (SNR) of ≈ 20 dB (Fig. 2).

Deep Decoding via Harmonic Attention

Extracting these minute harmonic signals from linear skull reflections requires advanced signal processing. We developed the Temporal Transformer with Harmonic Attention (TTHA). Unlike standard denoising filters, TTHA employs a "Physical Saliency Bias," weighing time-points based on the ratio of harmonic to fundamental energy. In simulated trials using k-Wave, TTHA successfully reconstructed neural spike trains with a temporal correlation of $R > 0.85$ and a latency of 18 ms (Fig. 3).

Safety and Biocompatibility Profile

Clinical translation requires strict adherence to safety standards. We conducted a Failure Mode and Effects Analysis (FMEA) compliant with FDA Class III guidelines. The system operates with a Mechanical Index (MI) < 1.9 to prevent inertial cavitation and a Thermal Index (TI) < 0.7 to avoid heating. Furthermore, the MNTs are designed with biodegradable DPPC lipids to ensure clearance via the glymphatic system within 48 hours.

Discussion

MANTIS represents a convergence of molecular engineering, nonlinear acoustics, and artificial intelligence. By shifting the complexity from the surgical domain to the molecular and computational domains, we circumvent the primary barriers of current neurotechnology. While challenges remain regardi ng skull variability, our results establish a theoretical minimum viability for non-invasive, high-bandwidth neural reading. Future work will focus on *in vivo* validation in rodent models.

Methods

The MANTIS framework integrates molecular kinetics with nonlinear acoustic propagation to enable neural decoding. The coupling between membrane potential fluctuations, protein conformational states, and harmonic generation is summarized in the multi-physics transduction pathway (**Fig. 4**).

Physical Model of Transduction

The effective nonlinearity parameter β_{NL} is modeled as a function of the local concentration of activated MNTs:

$$\beta_{\mathrm{NL}}(V_m) = \beta_0 + \eta \cdot \Phi(V_m) \tag{1}$$

where β_0 is the tissue baseline, η is the molar nonlinearity contribution, and $\Phi(V_m)$ is the fraction of transducers in the active state.

Ci-VSP Sensor Kinetics

The temporal dynamics are governed by the kinetics of the Ci-VSP sensor:

$$\tau(V)\frac{dm}{dt} = m_\infty(V) - m \tag{2}$$

where m is the open probability and $\tau(V)$ is the voltage-dependent time constant ($\approx 2 - 5$ ms).

Simulation Environment

Acoustic simulations were performed using the k-Wave MATLAB toolbox[5]. The computational grid was defined with a spatial resolution of 100 μm and a temporal step of 10 ns (CFL = 0.3).

Transformer Architecture

The TTHA decoder utilizes a modified attention mechanism:

$$\text{Attention}(Q, K, V) = \text{softmax}\left(\frac{QK^T}{\sqrt{d_k}} + \lambda \cdot \mathcal{G}\left(\frac{H_2}{H_1}\right)\right)V \tag{3}$$

where $\mathcal{G}$ is a gating function prioritizing harmonic content.

Data Availability

The synthetic datasets generated during the current study using the k-Wave simulation environment are available from the corresponding author upon reasonable request.

Code Availability

The custom code for the TTHA decoder and the scripts for processing harmonic backscatter will be made available upon publication at a dedicated repository. The acoustic simulations were conducted using the k-Wave toolbox, which is open-source and can be accessed at its primary academic distribution site (k-wave.org) or via its peer-reviewed documentation [Ref 5].

Competing Interests

The author declares the following competing interests: A patent application covering the molecular-to-acoustic transduction mechanism and the TTHA decoding architecture is currently in preparation. The author reserves all intellectual property rights related to the MANTIS framework.

Author Contributions

E.C.P. conceived the MANTIS framework, developed the physical-mathematical model, designed the TTHA algorithm, conducted the simulations, and wrote the manuscript.

Figure Legends

Figure 1 | The MANTIS framework for non-invasive neural interfacing. **a**, Schematic representation of the molecular-to-acoustic transduction pathway. Neuronal depolarization triggers conformational changes in membrane-bound voltage-sensitive nanotransducers (MNTs). **b**, Detail of a biofunctionalized MNT (100 nm) showing the Ci-VSP sensor integration and the perfluorocarbon core. **c**, Targeting strategy utilizing anti-GLAST antibodies for synaptic localization within the brain parenchyma. **d**, System-level architecture showing the transcranial ultrasound phased array interface and real-time decoding pipeline.

Figure 2 | Nonlinear acoustic reporting and harmonic generation. **a**, Computational phantom setup for transcranial focused ultrasound (tFUS) at 500 kHz. **b**, Spectral analysis of the backscattered signal. The activation of MNTs (red) induces a significant rise in second (H_2) and third (H_3) harmonics compared to the baseline tissue response (gray). **c**, Pressure field distribution showing the focal spot and the nonlinear distortion induced by local MNT concentration. **d**, Signal-to-noise ratio (SNR) as a function of depth through the human skull model.

Figure 3 | Real-time neural decoding via TTHA. **a**, Architecture of the Temporal Transformer with Harmonic Attention (TTHA), highlighting the physical saliency gating mechanism. **b**, Comparison between ground-truth simulated neural spike trains (top) and the TTHA reconstructed signal (bottom) at a temporal correlation of $R > 0.85$. **c**, Decoder performance (Bit-rate vs. Latency) across variable skull thicknesses (3–7 mm), demonstrating robustness to transcranial attenuation.

Figure 4 | Mathematical coupling and multi-physics validation. **a**, Temporal coupling between V_m input and the state probability $m(t)$ of the Ci-VSP sensor, governed by Eq. 2. **b**, Correlation between MNT activation and the shift in the effective nonlinearity parameter β_{NL} (Eq. 1). **c**, Sensitivity analysis of the Westervelt-derived harmonic source term (S_{H2}) across various insonification pressures.

References

[1] Musk, E. et al. An integrated brain-machine interface platform with thousands of channels. *J. Med. Internet Res.* **21**, e16194 (2019).

[2] Tyler, W. J. Noninvasive neuromodulation with ultrasound? A continuum mechanics hypothesis. *Neuroscientist* **17**, 25-36 (2011).

[3] Murata, Y. et al. Phosphoinositide phosphatase activity coupled to an intrinsic voltage sensor. *Nature* **435**, 1239-1243 (2005).

[4] Vaswani, A. et al. Attention is all you need. *Adv. Neural Inf. Process. Syst.* 5998–6008 (2017).

[5] Treeby, B. E. & Cox, B. T. k-Wave: MATLAB toolbox for the simulation and reconstruction of photoacoustic wave fields. *J. Biomed. Opt.* **15**, 021314 (2010).