

# A Digital Twin Model of Ultrasound-Induced Activation in Human Cortical Interneurons

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**Abstract**—This study presents an integrated computational model combining a biophysically detailed simulation of ventrolateral prefrontal cortex (VLPFC) interneurons with an ultrasound wave propagation solver modeled in k-Wave using finite-difference solutions. This hybrid model enables exploration of how low-intensity ultrasound perturbs neuronal membranes to modulate ion channel dynamics and trigger action potentials. This methodology couples an ultrasound simulation with a biophysical neuron model using confocal microscopy-derived morphologies and specialized calcium channels to simulate membrane vibration, targets human ventrolateral prefrontal cortex (VLPFC) interneurons despite limited source data, and develops a machine learning model to predict action potential generation from ultrasound-induced membrane interactions. Due to the scarcity of direct human VLPFC biophysical data, anatomical and electrophysiological data were fused from various sources, resulting in a biophysically plausible model of ultrasound-induced activation in VLPFC interneurons. This framework enables exploration of parameter-dependent stimulation effects to guide the development of ultrasonic neuromodulation devices aimed at enhancing cognitive control.

**Keywords**—*Ultrasound neuromodulation, Mechanosensitive ion channels, VLPFC interneurons, Action potential prediction*

## I. INTRODUCTION

Low-intensity focused ultrasound (LIFU) is an emerging neuromodulation technique offering deep, noninvasive brain stimulation with millimeter precision. Low-intensity focused ultrasound can activate ion channels from membrane oscillations, offering a favourable alternative to electrical or pharmacological methods that involve greater risk and invasiveness. While this method has broad potential for various forms of brain stimulation, our study specifically focuses on its application for cognitive enhancement.

However, predicting how specific ultrasound parameters affect neuronal firing remains difficult. Existing computational models often rely on over-simplified morphologies, rodent neuron data, or lack a unified model that combines neuronal activity with ultrasound simulation. Many models do not estimate pressure fields or membrane displacement which makes it difficult to link ultrasound stimulation to spiking behavior, specifically in human VLPFC interneurons involved in attention and working memory [14].

This study introduces an advanced computational model that supports building a digital twin that couples k-Wave ultrasound simulation with a detailed NEURON model of a VLPFC interneuron reconstructed from confocal microscopy. The model estimates ultrasound pressure fields intensity and converts them into voltage inputs to amplify the membrane response and drive action potential generation. Mechanosensitive and voltage-gated channels are incorporated to simulate the pressure-induced voltage shifts and spike initiation. Additionally, a machine learning classifier is currently under development to identify the most effective ultrasound parameters for eliciting action potentials. This model supports testing of realistic stimulation effects and helps guide the development of precise and safe neuromodulation approaches.

## II. CONCEPTUAL BACKGROUND

Focused ultrasound (FUS) enables noninvasive, spatially precise neuromodulation by delivering mechanical pressure waves that interact directly with neuronal membranes. These waves deform the lipid bilayer, triggering ion channel gating and changes in membrane excitability. Key mechanisms fall into two broad categories: direct mechanical effects on ion channels and biophysical changes in membrane capacitance and state.

One primary pathway is force-from-lipid activation, where ultrasound-induced tension stretches the bilayer and directly opens mechanosensitive channels like TRAAK and Piezo1. This process does not require neurotransmitters, synapses, or receptor proteins, instead, the channels respond purely to mechanical deformation of the membrane. Their activation has been observed even in cell-free systems, confirming that bilayer mechanics alone are sufficient for gating. The response is faster than other gating mechanisms ( $\sim 0.2$  ms), reversible, and depends on the intensity of the applied ultrasound [1, 2, 5].

Another mechanism is capacitive coupling, as modeled by the Neuronal Bilayer Sonophore (NBLS) and Neuronal Intramembrane Cavitation Excitation (NICE) frameworks. Ultrasound creates transient nanocavities which are short-lived bubbles that form in the cell membrane under ultrasound that deforms the bilayer, changing its capacitance ( $C_m$ ). This generates displacement currents ( $dC_m/dt \times V_m$ ) that shift the membrane potential and can lead to action potentials, especially at specific pulse durations and frequencies [4,9].

Ultrasound also induces mechanosensitive calcium entry via stretch-activated channels like TRPC1, TRPP1/2, and Piezo1.

- TRPC1 (Transient Receptor Potential Canonical 1) is a non-selective cation channel that opens in response to mechanical stretch, allowing  $\text{Ca}^{2+}$  and  $\text{Na}^{+}$  to enter.
- TRPP1/2 (Polycystin-1/2 complex) are mechanosensitive channels involved in pressure sensing, especially in kidney and neuronal tissues.
- Piezo1 is a highly sensitive stretch-gated  $\text{Ca}^{2+}$  channel activated by direct membrane tension.

These allow  $\text{Ca}^{2+}$  influx, which can depolarize the membrane and activate calcium-amplifying channels (TRPM4/T-type), reinforcing excitability [5].

Thermodynamic state shifts add another layer of control to how membranes respond to ultrasound. When a membrane is near its phase transition temperature, it becomes much more sensitive to pressure changes. This is because its physical properties, like how easily it compresses or absorbs heat, are at their peak. That makes it easier for ultrasound to change the membrane's state and trigger ion channels to open [6].

In addition, Acoustic Radiation Force (ARF) transfers momentum from the ultrasound wave to the cell membrane, creating a steady, non-oscillating pressure. This sustained force stretches the lipid bilayer, increasing membrane tension and causing subtle deformation. These mechanical changes make it easier for mechanosensitive ion channels to open. ARF is especially important under low-intensity, non-thermal conditions ( $<0.7$  MPa), where heating effects are minimal. Both experiments and biophysical models identify ARF as a key driver of ultrasound-induced neuromodulation [9, 3].

Together, these mechanisms converge on a unifying principle: ultrasound exerts mechanical forces that vibrate and deform the neuronal membrane, altering its biophysical state in ways that open ion channels and initiate action potentials. The DTUSN model implements this principle through a pressure-to-voltage ( $P \rightarrow V$ ) conversion framework that maps ultrasound-induced pressure changes to local membrane voltage shifts. By incorporating compartment-specific gating of mechanosensitive and voltage-sensitive channels, the model captures how pressure-driven membrane perturbations, whether via tension, capacitance changes, or ion influx, can directly lead to neuronal firing. However, Acoustic Radiation Force (ARF) and temperature-dependent effects are not yet fully incorporated into the current model. This foundation enables simulation of parameter-specific neuromodulation effects and supports the development of physically grounded, targeted stimulation strategies without relying on thermal or secondary signaling pathways.

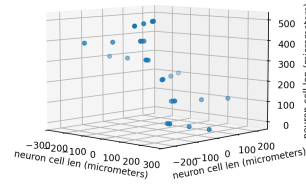
### III. MODEL ARCHITECTURE AND CONTRIBUTIONS

Existing ultrasound-neuron models fall short in three key areas. First, they rely on oversimplified geometry, often using cable or spherical abstractions that ignore realistic dendritic branching and the spatial distribution of ion channels [4, 10, 11]. Second, their channel modeling is limited, with most either

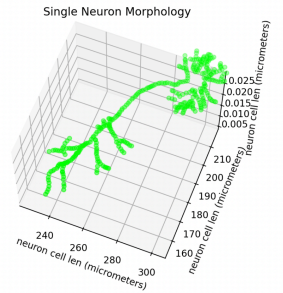
omitting mechanosensitive ion channels entirely or treating ultrasound pressure as a passive input, without linking it to active gating mechanisms [16,17]. Third, these models lack integration: no existing framework combines confocal-derived morphology, ultrasound field modeling, and includes a predictive machine learning component, though currently under development, to assess the likelihood of action potential generation [12].

To address these limitations, I developed the Digital Twin for Ultrasound Stimulation of Neurons (DTUSN), a simulation framework that systematically integrates biophysical realism with ultrasound modeling and data-driven prediction. The simulation couples a multicompartmental NEURON model of a human cortical interneuron with two-dimensional ultrasound field data computed using the k-Wave Python toolbox [7]. The NEURON model includes Hodgkin-Huxley dynamics across dendritic and somatic compartments, while ultrasound propagation is modeled in a homogeneous tissue medium.

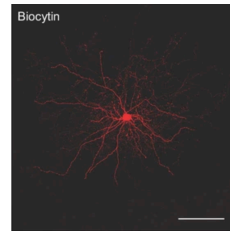
This proposed methodology uses confocal microscopy to reconstruct detailed morphologies of human ventrolateral prefrontal cortex (VLPFC) interneurons [10], as shown in Figure 1. These reconstructions are integrated into NEURON [11], where ultrasound pressure fields simulated in k-Wave are mapped to each segment. Initial segment coordinates are aligned to a 3D imaging reference before mapping pressure values based on segment position. This anatomical resolution supports accurate pressure assignment and improves prediction of spatially heterogeneous responses to stimulation.



**Figure 1a.** Initial neuron segment positions before confocal alignment.



**Figure 1b.** Final neuron morphology extracted from confocal microscopy and rendered in 3D.



**Figure 1c.** Confocal microscopy image used for morphological reconstruction [15]

To link the acoustic and biophysical domains, a pressure-to-voltage conversion equation was incorporated to reflect both mechanosensitive and capacitive ion channel dynamics:

$$V = \alpha \times P \quad (1)$$

where  $V$  is the induced voltage perturbation (in mV),  $P$  is local pressure amplitude (in Pa), and  $\alpha$  is an empirically tuned scaling factor currently set as 0.01. A linear pressure-to-voltage approximation is used, as it best fits mechanosensitive ion channels in the low-pressure regime. Yoo et al. [2] report voltage changes in the  $\mu\text{V}$ -mV range for  $<1$  MPa, with conversion factors of 0.001-0.01 mV/Pa depending on cell properties. This allows real-time simulation of ultrasound-induced biophysical responses, which are modeled in NEURON and used to train machine learning models predicting action potential generation.

Core membrane dynamics are governed by Hodgkin-Huxley equations eq.2 [13], where total ionic current is modeled as

$$I_{\text{ion}} = \sum I_x = g_x(V - E_x) \quad (2)$$

with  $g_x$  as maximal conductance,  $E_x$  as reversal potential, and  $V$  as membrane voltage. Specifically, sodium and potassium channel currents are calculated using

$$I_{\text{Na}} = g_{\text{Na}} \cdot m^3 h (V - E_{\text{Na}}) \quad (3)$$

$$I_{\text{K}} = g_{\text{K}} \cdot n^4 (V - E_{\text{K}}) \quad (4)$$

where gating variables follow time-dependent differential equations linked to voltage activation states [13].

To simulate ultrasound-driven mechanical effects, a membrane vibration function was introduced, modeling displacement as a sinusoidal function of frequency, amplitude, and duration. These ultrasound parameters modulate the gating of stretch-sensitive  $\text{K}^+$  (e.g., TRAAK) and  $\text{Ca}^{2+}$  (e.g., PIEZO1) channels by scaling their conductances in proportion to vibration amplitude. This mechanism is implemented using the general ion current formulation (Eq. 2), with specific equations for sodium and potassium currents shown in Eqs. 3-4. Both voltage-gated and stretch-sensitive channels are distributed across neuronal compartments, and mechanosensitive channel activation is modeled as a function of local acoustic pressure and frequency. This approach reflects experimental findings linking membrane tension to calcium influx and neuronal excitation [2], enabling physiologically grounded simulations of ultrasound neuromodulatory effects.

Additionally, calcium channels were inserted into the dendritic compartments to simulate ultrasound-induced calcium influx. A custom .mod file defines the channel's reversal potential and maximum conductance, allowing voltage-dependent  $\text{Ca}^{2+}$  dynamics to be triggered when pressure-induced depolarization occurs. These channels enhance the model's ability to simulate localized excitation and support realistic action potential generation.

After the simulation runs using the equations above, action potential detection is performed using:

$$\text{AP}_{\text{detected}} = \begin{cases} 1, & \text{if } \exists t \text{ such that } V(t) > -55 \text{ mV} \\ 0, & \text{otherwise} \end{cases} \quad (5)$$

This indicates whether a spike occurred by checking if membrane voltage crossed -55 mV threshold at any timepoint.

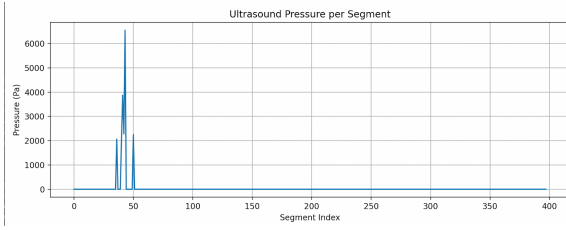
In addition, a convolutional neural network (CNN) is being developed to predict whether an action potential will occur with frequency as the only variable, while amplitude and duration are fixed throughout all simulations. The model is trained on labeled outputs from the biophysical simulation, learning the relationship between frequency input and spiking behavior. Once trained, it will enable rapid prediction of neuronal responses without rerunning full simulations, allowing efficient exploration of the stimulation parameter space.

To the best of current knowledge, this appears to be among the first end-to-end models that unifies realistic neuronal structure, physics-based ultrasound simulation, and data-driven prediction to enable mechanism-based ultrasonic neuromodulation of human cortical interneurons.

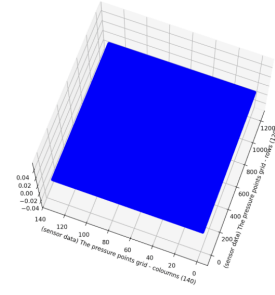
#### IV. EXPERIMENTAL SETUP

The experimental framework was designed to evaluate the model's ability to predict neuronal activation, and this methodology systematically varies frequency, amplitude and variation. The goal is to generate a comprehensive map linking these input parameters to action potential outcomes using the biophysical model. This setup also enables the generation of labeled data to train a machine learning model, allowing for rapid prediction and validation of the simulation's accuracy.

To combine the ultrasound and neuron model, the confocal derived morphology in the neuron model was aligned with the spatial coordinates of the k-Wave pressure field. As shown in Figure 2b, Ultrasound pressure was simulated on a  $140 \times 120$  Cartesian grid using arc-arranged transducers, producing time-resolved pressure data at each grid point. Each NEURON segment's spatial location was mapped to its nearest point on the k-Wave grid using coordinate scaling and translation. This allowed segment-specific pressure values to be assigned and converted into local voltage shifts to drive realistic biophysical responses, as shown in Figure 2a.



**Figure 2a.** Pressure field output from k-Wave simulation across 2D sensor grid (140×120).



**Figure 2b.** Ultrasound pressure amplitudes mapped to neuron segments based on morphology.

A parameter study was then performed across ultrasound frequency (0.79–0.82 MHz), amplitude (1.0  $\mu\text{m}$ ), and duration (150 ms). The experiment applied the variations of input frequencies, duration and amplitudes to the model to generate output action potentials from each induced pressure point. The resulting dataset of input-output pairs will be used to train the machine learning model.

## V. RESULTS

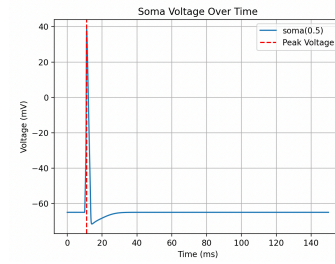
The model successfully simulated membrane responses across a range of ultrasound input parameters. A frequency study was conducted from 0.79-0.82MHz, with amplitude and duration fixed at 1.0  $\mu\text{m}$  and 150 ms, respectively. Action potentials were detected when the soma voltage crossed a -55 mV threshold at any time point during stimulation shown in Figure 3. The binary outcome (yes/no spike) was recorded for each parameter set to support downstream machine learning training.

Across all tested frequencies, consistent action potential generation was observed. Although the original aim was to test a broader range down to 0.3 MHz, numerical instability in the k-Wave solver at lower frequencies limited the study. The 0.8 MHz band was selected for its computational stability and prior use in experimental studies, providing a reliable baseline for evaluating the model's predictive capacity.

I.

**TABLE 1**

| Frequency (MHz) | Amplitude ( $\mu\text{m}$ ) | Duration (ms) | Peak Soma Voltage (mV) | Time action potential occurred (ms) | Action Potential Occurrence (yes/no) |
|-----------------|-----------------------------|---------------|------------------------|-------------------------------------|--------------------------------------|
| 0.79            | 1.0                         | 150           | -36.066                | 11.150                              | Yes                                  |
| 0.80            | 1.0                         | 150           | -35.786                | 11.150                              | Yes                                  |
| 0.81            | 1.0                         | 150           | -35.098                | 11.150                              | Yes                                  |
| 0.82            | 1.0                         | 150           | -35.095                | 11.150                              | Yes                                  |



**Figure 3.** Ultrasound-Induced Soma Voltage Response Showing Action Potential at 11.15 ms

Figure 3 shows a clear action potential at 11.15 ms, with the soma voltage peaking at -35.786 mV. This confirms that the ultrasound input triggered sufficient depolarization to cross the -55 mV threshold. The sharp spike matches expected neural firing behavior, validating that the model accurately captures the biophysics of ultrasound-induced activation. Consistent spike timing and voltage across frequencies, as shown in Table 1, supports the reliability of the simulation for machine learning prediction.

These results confirm the model's ability to identify which ultrasound parameters do or do not trigger action potentials based on mechanosensitive and voltage-gated ion channel dynamics. This simulation dataset now serves as the input for training a convolutional neural network (CNN) to rapidly predict action potential outcomes as a function of ultrasound frequency.

VI.

## CONCLUSION AND FUTURE WORK

We present a biologically grounded digital twin model that simulates how low-intensity ultrasound modulates membrane dynamics and drives spiking in human ventrolateral prefrontal cortex (VLPFC) interneurons. Our framework integrates k-Wave acoustic simulation, confocal-derived morphologies, and biophysical ion channel modeling to link ultrasound parameters with neuronal responses.

By converting segment-level pressure gradients into voltage changes, the model connects acoustic input to changes

in ion conductance and spike probability. While current implementation uses a simplified linear pressure-to-voltage mapping and omits full NBLS or NICE models, it establishes proof-of-concept for ultrasound-driven modulation of neuronal excitability.

A machine learning layer is under development to predict spiking outcomes and accelerate parameter exploration. Limitations include idealized channel kinetics, limited experimental calibration, and the single-neuron focus.

Future work will expand the model to include network-level dynamics across multiple neurons, incorporate additional input parameters such as neuron type or ion channel densities, and refine the pressure-to-voltage mapping using more advanced biophysical processes. Resonance-based amplification mechanisms will also be explored. The machine learning classifier is currently under development and will be enhanced to support efficient, data-driven parameter tuning. Together, these extensions will advance the platform toward a mechanism-informed, scalable framework for noninvasive neuromodulation tailored to cognitive and brain-computer interface applications.

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