Supplementary Information: Mathematical Derivations of the MANTIS Framework

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S1. Derivation of the Nonlinear Acoustic Coupling

The propagation of high-intensity focused ultrasound in biological tissue is governed by the Westervelt equation, which accounts for diffraction, absorption, and nonlinearity. In standard tissue, the equation is given by:

$$\nabla^2 p - \frac{1}{c_0^2}\frac{\partial^2 p}{\partial t^2} + \frac{\delta}{c_0^4}\frac{\partial^3 p}{\partial t^3} = -\frac{\beta}{\rho_0 c_0^4}\frac{\partial^2 p^2}{\partial t^2} \tag{S1}$$

Where p is acoustic pressure, c_0 is the speed of sound, δ is acoustic diffusivity, and β is the coefficient of nonlinearity.

In the MANTIS framework, we introduce a spatially variant and time-dependent nonlinearity parameter $\beta_{eff}(x,t)$ modulated by the local concentration of activated nanotransducers (c_S). We define the effective nonlinearity as a linear superposition:

$$\beta_{eff}(x,t) = \beta_{tissue} + \eta \cdot [MNT]_{total} \cdot \Phi(V_m(x,t)) \tag{S2}$$

Here, η is the molar nonlinearity coefficient of the perfluorocarbon core in the MNTs. Substituting (S2) into the Westervelt source term (RHS of Eq. S1), and assuming the perturbation is small, we derive the source term for the second harmonic component (p_2):

$$S_{H_2} \approx -\frac{\beta_{tissue}}{\rho_0 c_0^4}\frac{\partial^2 p_1^2}{\partial t^2} - \frac{\eta\Phi(V_m)}{\rho_0 c_0^4}\frac{\partial^2 p_1^2}{\partial t^2} \tag{S3}$$

The second term in Eq. S3 represents the *neural signal of interest.* Since $\Phi(V_m)$ varies with the neural spiking frequency (low frequency relative to ultrasound), it acts as an amplitude modulator on the carrier harmonic $2f_0$.

S2. Kinetics of the Ci-VSP Voltage Sensor

The function $\Phi(V_m)$ is governed by the conformational thermodynamics of the Ci-VSP protein. We model the transitions between the "Resting" (low compressibility) and "Active" (high compressibility) states using a Boltzmann distribution coupled with first-order kinetics.

The steady-state activation m_∞ is:

$$m_\infty(V) = \frac{1}{1 + \exp\left(\frac{V_{1/2} - V}{k}\right)} \tag{S4}$$

Where $V_{1/2} \approx -20$ mV is the half-activation potential and k is the slope factor.

The temporal evolution of the fraction of open sensors $m(t)$ is:

$$\frac{dm}{dt} = \alpha(V)(1-m) - \beta_{rate}(V)m \tag{S5}$$

Where the rate constants α and β_{rate} are defined to fit the experimentally observed time constant $\tau \approx 2 - 5$ ms:

$$\tau(V) = \frac{1}{\alpha(V) + \beta_{rate}(V)} \tag{S6}$$

This derivation confirms that the MANTIS system acts as a low-pass filter with a cutoff frequency of approximately 200 Hz, sufficient to capture Local Field Potentials (LFPs) and spike rates, but filtering out ultra-fast channel noise.