Computational Study of Temporal Interference Modulation in CA1 Neurons

Temporal Interference (TI) is a non-invasive neuromodulation technique that uses two slightly detuned high-frequency electric fields (e.g., 2000 Hz) whose interference produces a low-frequency envelope within the physiological firing range of neurons, allowing the neurons to be entrained by performing an envelope extraction of the signal, as illustrated in Fig 1. While early work demonstrated that neurons can follow this envelope, enabling selective stimulation of deep structures such as the hippocampus [1], subsequent analyses suggest that TI cannot be explained by passive membrane filtering alone, given that carrier frequencies exceed the membrane time constant (τ_m). Instead, effective TI stimulation likely depends on nonlinear, ion channel-mediated rectification mechanisms that enable neurons to extract the beat frequency from high-frequency inputs [2].

Within this framework, a key unresolved question is which neuronal subtypes are biophysically equipped to perform envelope extraction. Here, we investigate the responses of biophysically detailed neuron models from the Blue Brain Project [3,4], including parvalbumin-positive (PV^+) basket cells and CA1 pyramidal neurons, to kHz electric field stimulation. We examine how intrinsic ion channel properties, including their characteristic timescales and densities, shape frequency-dependent responses and drive the nonlinear mechanisms required for envelope extraction. Furthermore, we explore how the dynamical operating regime (proximity to a bifurcation point) and the class of neural excitability (Class 1 vs. Class 2) modulate the neuron's sensitivity to interference patterns and influence its capacity for high-frequency signal processing.

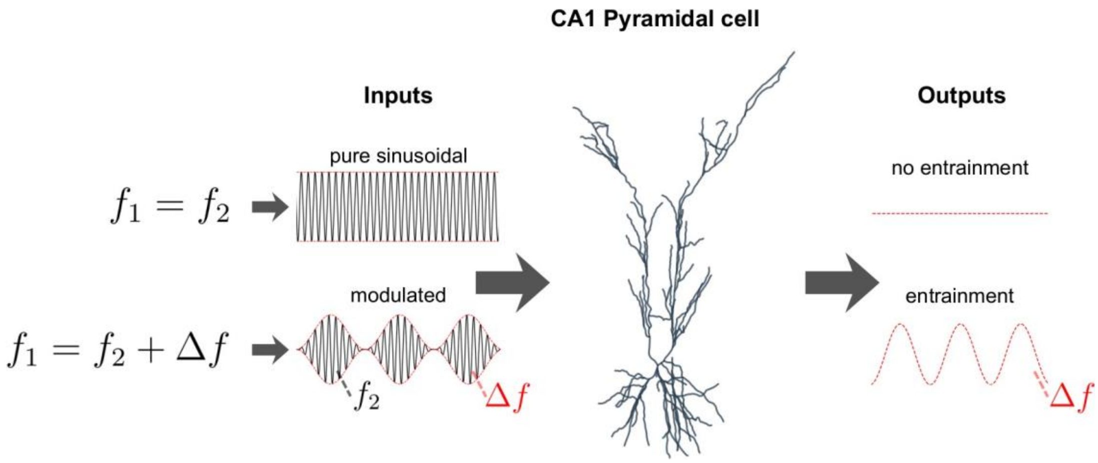

Figure 1: **Neural response to Temporal Interference (TI) stimulation.** While a high-frequency pure sinusoidal input (top) exceeds the membrane time constant and fails to drive the cell, an amplitude-modulated input (bottom) enables the CA1 pyramidal neuron to perform nonlinear envelope extraction. This process results in neural entrainment at the low-frequency beat (Δf), effectively bypassing passive membrane filtering.

[1] Grossman, N. *et al*, Noninvasive Deep Brain Stimulation via Temporally Interfering Electric Fields. Cell 2017, PMID: 28575667

[2] Mirzakhalili, E. *et al,* Biophysics of Temporal Interference Stimulation. Cell Syst. 2020. PMID: 33157010

[3] Bologna, L. L. *et al* Online interoperable resources for building hippocampal neuron models via the Hippocampus Hub. *Frontiers in Neuroinformatics* 2023. PMID: 38025966

[4] Blue Brain Project, "Hippocampus Hub," [Online]. Available: https://www.hippocampushub.eu. [Accessed: April 13, 2026].