Ultrasonic neuromodulation by intramembrane cavitation in multi-compartmental neuron models

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Objective

To develop a computational model of ultrasonic neuromodulation by intramembrane cavitation in morphologically realistic multi-compartmental models.

Introduction

Transcranial focused ultrasound (tFUS) has gained attention as a technique to modulate neuronal activity reversibly, non-invasively and with high spatial accuracy. However, the **underlying mechanism** of ultrasonic neuromodulation (UNMOD) is not well understood. Although several possible mechanisms have been proposed (e.g. acoustic radiation pressure, mechanosensitive ion channels, extracellular cavitation...), only the bilayer sonophore (BLS) model of intramembrane cavitation has been able to provide a comprehensive mathematical framework, predicting how ultrasound can induce action potentials [1, 2].

However, numerical modeling studies with the BLS-model have been restricted to **single-compartment point-neurons** [1, 2, 3] and a **two-compartment nanoscale model** of the BLS and its surrounding proteins [4], leaving important questions with respect to UNMOD in the BLS-framework unanswered.

In this study, a computational model is constructed to study ultrasonic neuromodulation by intramembrane cavitation in **morphologically realistic** (multi-compartmental) neurons.

Methods and results

1. Ultrasound-neuron coupling: bilayer sonophore model (Krasovitski)
   → Rayleigh-Plesset and air diffusion equations solved in MATLAB:

$$\frac{\mathrm{d}^2Z}{\mathrm{d}t^2}+\frac{3}{2R(Z)}\left(\frac{\mathrm{d}Z}{\mathrm{d}t}\right)^2=\frac{1}{\rho_\mathrm{l}|R(Z)|}\Big[P_\mathrm{in}+P_\mathrm{M}+P_\mathrm{ec}-P_0+P_\mathrm{A}\sin(\omega t) - P_\mathrm{S}(Z)-\frac{4}{|R(Z)|}\frac{\mathrm{d}Z}{\mathrm{d}t}\left(\frac{3\delta_0\mu_\mathrm{s}}{|R(Z)|}+\mu_\mathrm{l}\right)\Big].$$

2. Neuron models: modified blue brain project cortical cells (Aberra et al.), multi-compartmental subthalamic nucleus model (Gillies-Willshaw) and peripheral nerve SENN-model in pyNEURON (hoc, NMODL).

→ Interface between MATLAB and pyNEURON to pass information on the US-induced capacitance oscillations, membrane charge and states.

The spatially extended UNMOD model allows to answer interesting questions in the BLS-framework, that can be tested experimentally:

1. Location of the excitation node
2. Sensitivity to spatially distributed parameters
3. Importance of the phase and intensity distribution in the pressure field

Furthermore, the implementation allows the **coupling of neuronal and ultrasonic propagation** (FDTD) simulations, benefiting future neural engineering studies concentrating on the design of the ultrasonic transducer or transducer array.

Conclusion

The extension of the BLS-model to morphologically realistic neurons is an important step to improve understanding of the mechanism of UNMOD and enables the combined simulation of the acoustic field and neuronal response.

References

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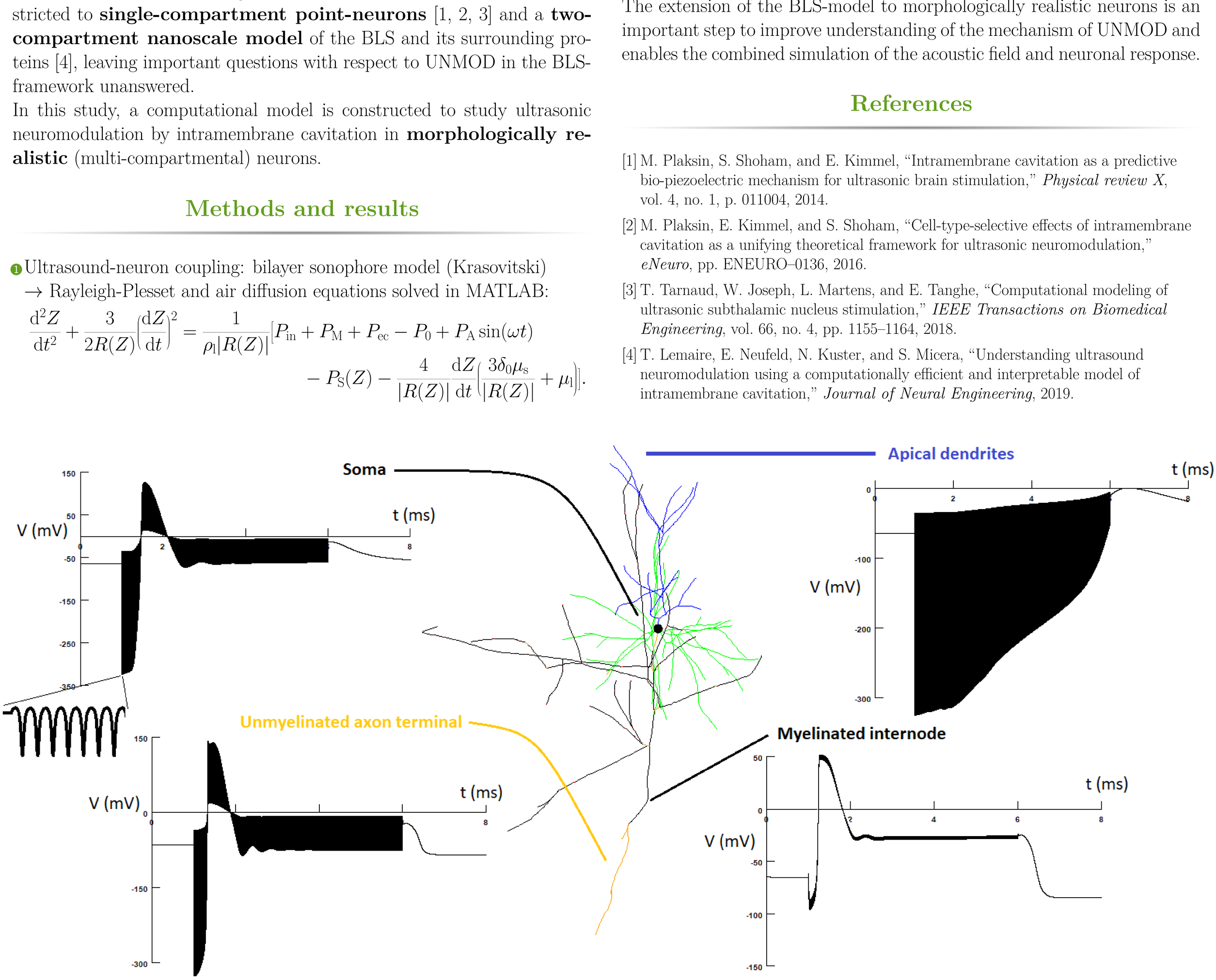

Figure 1: Ultrasonic neuromodulation in a morphologically realistic L2/3 pyramidal cortical cell (blue brain project: Markram et al. (2015), Aberra et al. (2018)).