A framework for low intensity low frequency ultrasound neuromodulation sonication parameters identification from micromechanical flexoelectricity modelling

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Abstract

Low intensity, low frequency ultrasound (LILFU) has recently emerged as a promising technique to modulate non-invasively nerve activities at lower cost than other traditional and more-invasive neuromodulation methods. However, there is currently no consensus on the optimum sonication parameters to be used in LILFU applications, and most of the accepted ranges have arisen from trial-and-error approaches. Here we utilise a recently proposed micromechanics model of membrane flexoelectricity, a potential candidate for neuromodulation and simulate action potentials/membrane polarisation triggered by acoustic pulses of different pulse frequencies, pulse magnitudes and duty cycles. Results show that at constant duty cycles, increasing the transmit frequency increases the thresholds of both the pulse magnitude and the elastic energy rate density required to mechanically trigger an action potential, whereas at constant frequencies, increasing the duty cycle reduces both. The influence of transmit frequency is weakened at lower duty cycles. Our simulation results offer some guidance on the selections of sonication pa-

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rameters used in LILFU for neurological disorder treatments in the context of the flexoelectricity hypothesis.

Keywords: Flexoelectricity, Neuromodulation, Low intensity low frequency ultrasound, Sonication parameters, Computational model

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Introduction

In the past decade, low intensity, low frequency ultrasound (LILFU) has emerged as a new technique to alter and modulate nerve activities with high spatial precision and penetration depth (Tyler et al., 2008; Baek et al., 2017; Jerusalem et al., 2019). Compared with traditional neuromodulation approaches, LILFU is non-invasive, low-cost and bi-modal, and possessing the capability to both excite and suppress neuronal activity (Baek et al., 2017). Compelling evidence of LILFU-mediated neuromodulatory effects through, e.g., nerve electroencephalography or behavioural responses have been published in both human and animal studies (Kubanek, 2018; Feng et al., 2019; Blackmore et al., 2019). Paradoxically, the underlying micromechanisms through which LILFU neuromodulation operates are still unclear. Different theories have already been proposed as candidates: e.g., acoustic radiation force, sonoporation and cavitation, flexoelectricity, among others (Sassaroli and Vykhodtseva, 2016; Jerusalem et al., 2019; Blackmore et al., 2019). In addition to this, sonication parameters used in LILFU such as transducer frequency and intensity, duty cycle (DC), pulse repetition frequency (PRF) and sonication duration vary dramatically across literature studies. A consensus on the identification of optimum parameters thus still remains elusive (Fomenko et al., 2018; Lozano and Fomenko, 2019).

Recently, several numerical models of mechano-electrophysiological coupling in neurons have been proposed (Hady and Machta, 2015; Plaksin et al., 2016; Cinelli et al., 2018; Kwong et al., 2019; Chen et al., 2019) with the purpose of helping to understand how mechanical waves may interact or are coupled with the electrophysiological pulses and, for some, how LILFU may

modulate neuronal activities.The study proposed here uses MECAXON, the numerical model based on the direct flexoelectricity hypothesis previously proposed by the authors (Chen et al., 2019), to simulate ultrasonic stimulation of the neuronal axon. In particular, this work investigates how action potentials (AP) can be triggered under different combinations of stimulation parameters, eventually providing some insight on the selection of sonication parameters used in LILFU neuromodulation.

Materials and Methods

The Mechano-Electrophysiological Coupling of Axon program (MECAXON) was recently proposed as a 1D axisymmetric finite element model simulating the flexoelectricity-induced electrical excitation of neuron/axon arising from external mechanical stimuli Chen et al. (2019). In this section, we briefly summarise the model formulation with emphasis on its further development for this study. A detailed description of the model formulation including all mathematical formulae and schematic diagrams can be found in the work of Chen et al. (2019).

In MECAXON, the axon is modelled as a 1D axisymmetric cylindrical tube, where the thin wall represents the membrane with a constant thickness. It is observed that lipid bilayers usually exhibit both elastic and viscous properties, and their mechanical properties may influence the propagation (elastic) or attenuation (viscous) of mechanical signals across the cell membrane (Zubko et al., 2013). Therefore, the axon mechanics is modelled by means of viscoelasticity in a dynamic framework, governed by the balance of linear momentum. A two-branch generalised Maxwell model is adopted

to model the membrane viscoelasticity. Material parameters in the model are calibrated by simultaneously nonlinear-least-square fitting the equivalent storage and loss moduli to the frequency-dependent rheological properties of neurons experimentally measured in Ayala et al. (2016) using Prony series. Mechanical deformations of the axon membrane alter the electrical properties of the membrane through geometrical (i.e., areal) changes, but also redistributes the membrane dipole moments. This results in the development of a self-polarised electrical field altering the membrane potential Petrov (2002), following the direct flexoelectricity theory. This is adopted as the main hypothesis that couples axon mechanics to cell electrophysiology: a local polarisation density vector is defined and linked to the membrane strain gradient field via a fourth-order direct flexoelectric tensor (Gharbi et al., 2011; Yudin and Tagantsev, 2013), in turn used to compute the polarisation current density through the membrane. To update the membrane potential, the axonal electrophysiology is modelled using the cable theory for the internodal regions combined with the classic Hodgkin-Huxley (H-H) model (Hodgkin and Huxley, 1952) for the Nodes of Ranvier.

Here, in order to model the mechanical stimuli as acoustic waves, the axon boundary is displaced following a prescribed periodic function resembling the pulsed ultrasound to achieve a propagating vibration in the radial and longitudinal direction. Accordingly, the ultrasound is modelled as a pulsed wave of 3 ms duration and 1 ms fixed pulse repetition period, i.e., three full repetitions per simulation with 1 kHz PRF. Doing so, we simplify our investigation by solely focusing on examining the effects of the other three major parameters which conjointly specify an acoustic wave, i.e., transmit

frequency, DC and pulse magnitude. The threshold of the mechanical wave for AP excitation is then identified at various combinations of transmit frequency (50–850 kHz) and DC (10%–100%). Here, we define the threshold for neuromodulation (TN) as the threshold for ultrasound conditions at which a H-H driven membrane depolarisation is triggered through flexoelectricity, taken here when the depolarisation reaches −42 mV (Kole and Stuart, 2008). We also calculate the pulse averaged elastic energy rate density (PAPEERD) of the axon during one pulse period T to quantify the mechanical effect of acoustic wave by conjugating the elastic stress and strain tensors:

$$\text{PAPEERD} = \frac{1}{T}\int_0^T \boldsymbol{\sigma}_e\,(t) : \dot{\boldsymbol{\epsilon}}_e\,(t)\;\mathrm{d}t \tag{1}$$

where $\boldsymbol{\sigma}_e$ and $\boldsymbol{\epsilon}_e$ are the elastic stress and strain tensors, respectively Chen et al. (2019). PAPEERD has the unit of W/cm^2, which is same as the most common unit used for ultrasound intensity. Physically, PAPEERD is related to the spatial peak pulse average intensity ($\mathrm{I_{SPPA}}$) of ultrasound that is locally transformed into axon vibration. In each simulation, the transmit frequency and DC are fixed at different combinations, while the pulse magnitude is gradually varied to identify the TN and the PAPEERD. The transmit frequency is varied from 50 kHz to 850 kHz with an increment of 200 kHz, whereas DC is varied from 10% to 90% with an increment of 20%.

Results

Figure 1 shows the temporal evolutions of membrane potential at the Node of Ranvier at the axon end subjected to four different conditions of acoustic stimuli. In the figure, three unsuccessful cases of AP induction in

which the TN is not achieved are compared to one successful case where H-H driven membrane depolarisation occurs. In these three unsuccessful cases, the values of membrane potential did not reach the threshold (-42 mV) for triggering an AP during the full simulation of 3ms. Therefore, only perturbations of the membrane potential could been observed. In the successful case, the membrane potential depolarises and peaks after 1.2 ms, and repolarises afterwards, i.e., the typical features of an AP.

Figure 2 shows the thresholds of the axial strain magnitudes above which an AP can be induced by acoustic stimulation at different combinations of pulse DCs and frequencies. It can be seen that at a constant fixed transmit frequency, a larger magnitude is needed to excite the membrane enough if the pulse DC is reduced. On the other hand, increasing the transmit frequency generally requires a larger pulse magnitude for an AP initiation.

Figure 3 shows the PAPEERD at TN above which an AP is acoustically triggered for different DCs and frequencies. Increasing the DC reduces the PAPEERD threshold, and this trend is more notable at lower frequencies. At constant DC, when the transmit frequency is increased, the PAPEERD threshold is also elevated. However, at lower DCs, the influence of transmit frequency on the PAPEERD at TN is weaker.

Discussion

Our simulation results demonstrate a clear trend of the combination of the sonication parameters that can successfully induce an AP, i.e., higher frequencies and lower DCs require higher pulse magnitudes and PAPEERDs, whereas lower frequencies and higher DCs are accompanied by lower pulse

magnitudes and PAPEERDs. These trends generally agree with the simulation results predicted from other pioneering numerical models (Plaksin et al., 2016; Lemaire et al., 2019) which explicitly simulate local APs resulting from acoustically induced intramembrane cavitation, despite the fact that the underlying modulation mechanisms between our model (MECAXON) and theirs (NICE and SONIC) are different (direct flexoelectricity in MECAXON model vs. intramembrane cavitation excitation in NICE and SONIC models). This further highlights the need to acquire a deeper understanding of the underlying natural principles behind LILFU neuromodulation. However, it should be noted that a success in inducing an AP cannot directly imply a good response rate. In fact, experimental findings suggest that high response rates usually occurs at intermediate levels of DC (50% – 75%), and are affected by other sonication parameters such as PRF and total stimulation duration (Kubanek et al., 2018; Yoon et al., 2019; Wang et al., 2020). Additionally, there is still no consensus on whether higher or lower intensity and pressure amplitude can result in a better modulation effect. More work is clearly needed to find an optimised combination of sonication parameters to achieve the best modulation outcome.

The transmit frequency of focused low frequency ultrasound for neuromodulation typically lies in the sub-MHz range (Kubanek, 2018; Wang et al., 2019). In this study, we limit the ultrasound transmit frequency in all simulations to be within 50 – 850 kHz. In finite element simulations, modelling dynamic response of materials under high frequency vibrations requires very small time steps. This results in an enormous increase in the computational cost and limits the total duration for which the dynamic event can be simu-

lated. This situation is further exacerbated if the geometry of the modelling object is complex, or if the material itself is heterogeneous, both of which potentially requiring finer space discretisation. For this reason, we limit the duration of our simulations to be 3 ms, i.e., three full pulse repetitions. A simulation of 50 kHz transmit frequency runs for roughly 20 hours on a single core processor on a 64GB RAM, Intel Core i7-7700 desktop, and run for roughly more than two hours on a 2-node, 32-core cluster, including the time to transfer simulation data back to local desktop from the server. Comparatively, a simulation of 850 kHz transmit frequency will need more than two days to finish on the same cluster. A typical LILFU sonication duration usually lasts for hundreds of milliseconds, with up to 1,000 tone bursts (Wang et al., 2019). There are indications that it is in fact the longer temporal effect of the acoustic wave that has the neuromodulatory effect and in this case, a longer simulation that can depict a full neural response will be more appropriate. For achieving this, high performance computing with more advanced hardware or the utilisation of graphics processing unit computing is clearly indispensable. Adoption of another faster numerical methods to solve the mathematical equations, such as the k-space pseudospectral method, could also be one alternative option to speed up a simulation of a full LILFU neuromodulation duration.

Currently, the mechanisms at play during LILFU neuromodulation are still unclear, and a few hypotheses have been proposed as promising candidates to explain this mechanism (Sassaroli and Vykhodtseva, 2016; Jerusalem et al., 2019; Blackmore et al., 2019). The direct flexoelectricity theory, being one of them, suggested that ultrasound may affect neuron electrophys-

iological activities through the process of redistributing and reorientating membrane dipole molecules, inducing a self-polarised electrical field altering membrane potential. This hypothesis is adopted as the main bridging mechanism linking axon electrophysiology to its mechanics. Note, however, in the model, this hypothesis could be substituted by other proposed mechano-electrophysiological coupling hypotheses, such as membrane sonoporation and cavitation, as well as interference with membrane thermodynamic waves. When additional experimental data become available, one can then compare the results from different hypotheses, and select the most appropriate one to be used within the future framework.

In classical ultrasound neuromodulation studies, intensity is a quantity associated with the ultrasound transducer, normally measured and calibrated together with the transducer using a hydrophone in a water tank (Civale et al., 2018). The intensity of an ultrasound beam usually attenuates exponentially with the propagation distance due to both absorption and scattering (Feng et al., 2019). Ultrasound attenuates fast when penetrating the skull as much more scattering and absorption occurs in bone than in soft tissue. As a result, when reaching the targeted neurons, the actual intensity of the ultrasound beam might be much lower than the one specified by the transducer. In this study, we use the PAPEERD to quantify the strength of the acoustic stimulus.This parameter could potentially be directly related to the I_{SPPA} of ultrasound by an empirical power law (Naor et al., 2016), depending on both the viscous property of the brain tissue and the distance that the ultrasound has travelled. Therefore, values of PAPEERD evaluated in our study should be used as a reference with caution when compared with typical values of

ultrasound intensities used in literature experiments.

According to literature studies, ultrasound has been proven to be bimodal, with capabilities of both enhancing and suppressing nerve activities. However, it is still unclear under what circumstances ultrasounds can enhance or suppress a nerve signal. Surprisingly, mixed stimulatory and inhibitory results can be often seen within the same study (Yoo et al., 2011; Yoon et al., 2019). Experimental results show that the outcome depends on multiple factors, including sonication duration, latency time between the pulse and APs, neuron connectivity, and primarily, ultrasound parameters (Blackmore et al., 2019). For instance, it is observed that ultrasounds with lower intensities tend to enhance neuron activity, whereas ultrasounds with higher intensities tend to have an inhibitory effect (Feng et al., 2019). In addition, pulses with lower DCs are more prone to have an inhibitory effect, and a stimulatory effect when the DC is increased (Yoo et al., 2011; Kim et al., 2015; Plaksin et al., 2016). Our study utilises MECAXON to simulate APs triggered by acoustic pulses. As implied from the model itself Chen et al. (2019), enhancement or suppression depends on the directionality of the mechanical pulse: a mechanical pulse travelling in the same direction as the AP will enhance the AP, whereas a mechanical pulse travelling in opposite direction will suppress it. The divergence between experimental observations in the literature and our model predictions was previously attributed to the fundamental assumptions of the model. The H-H theory is adopted to model the ionic mechanisms underlying APs. As a result, AP enhancement is due to voltage-controlled channel opening whereas suppression is linked to cell refractory periods. A more comprehensive understanding of the working

mechanism of LILFU is thus needed so that our model can be improved to better capture experimental observations.

Experimental observations show that myelinated and unmyelinated neurites differ from each other, not only by the presence of myelin layers, but also by the densities and even the types of of ion channels expressed on the neuronal membrane. For example, myelinated axons feature a highly structured distribution of voltage-gated sodium ion channels, with a characteristic accumulation at the Nodes of Ranvier (Neishabouri and Faisal, 2014; Freeman et al., 2015; Stadelmann et al., 2019). Different types of potassium ion channels are also found to possess distinct density distributions along the axon (Waxman and Ritchie, 1985; Röper and Schwarz, 1989; Black et al., 1990). In addition, it has been discovered that the mechanosensitive TREK-1 and TRAAK channels are prone to be localised to the Nodes of Ranvier (Brohawn et al., 2019; Kanda et al., 2019). Bearing in mind that the underlying mechanism of ultrasound neuromodulation is still unclear, this difference in membrane electrophysiological dynamics between neurites with and without myelination may imply significant variations in the way these two types of neurites are modulated by acoustic stimuli. Therefore, it is reasonable to infer that the TN may also be different between different types of neurites. In fact, evidence of the difference of threshold potentials for neuron excitation between myelinated and unmyelinated fibres have already been documented in the literature (Grill et al., 2002; Moffitt et al., 2004). This difference of TN between these fibres could not be predicted by the MECAXON model used in our study. This is mainly due to the mathematical formulation of the model, as unmyelinated regions are assumed to have the same mechani-

cal properties as the myelinated segments (the assumption being made was that the membrane could "vibrate" independently from the myelin layers), and, in order to initiate an AP, the boundary elements of a myelinated axon at which the mechanical stimulus is applied are set to be Nodes of Ranvier. A successful induction is recorded when a mechanically induced flexoelectric current perturbs the local membrane potential and raises the membrane depolarisation above $-42\,\mathrm{mV}$. As such, this formulation cannot distinguish between myelinated and unmyelinated axon, although the electrical pulse propagation patterns will be distinct between these two types of neurites. Another limitation of this research is the lack of a sensitivity study on the influence of model dimensions on the TN. According to experimental findings, fibre radii in the white matter of human brains range from 0.08–4.5 μm (Liewald et al., 2014). The radius of the axon being modelled in the study is set to be 2.5 μm, which is within this range. A systematic investigation of the influence of model dimensions on the mechanical excitation thresholds under different combinations of these sonication parameters is undeniably worth being conducted in the future.

Conclusions

There is currently no consensus on the optimum values of sonication parameters to be used in low intensity LILFU. To this end, we leveraged a recently proposed numerical model, MECAXON, to simulate flexoelectricity driven AP/membrane polarisation triggered by acoustic pulses for multiple combinations of transmit frequency and DCs. Simulation results show that at constant DCs, increasing the transmit frequency increases the thresholds

of both pulse magnitude and elastic energy rate density needed to mechanically trigger an AP, whereas at constant frequencies, increasing the DC has opposite effect. At lower DCs, the influence of transmit frequency is weakened. These simulation results may offer some guidance on the selections of sonication parameters used in LILFU, and may help to gain further insights into the mechanism of ultrasound neuromodulation.

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Figure Captions

Figure 1: Four cases of membrane potential evolution at the Node of Ranvier at the axon end subjected to different combinations of sonication parameters. Red solid curve: successful; Other curves: unsuccessful. TF: Transmit Frequency, AS: Axial Strain, DC: Duty Cycle.

Figure 2: Thresholds of the axial strain magnitudes for an acoustically-triggered action potential at different pulse duty cycles and frequencies; full line: exponential fit.

Figure 3: Thresholds of the pulse averaged elastic energy rate density for an acoustically-triggered action potential at different pulse duty cycles and frequencies; full line: exponential fit.