Computational Modeling of Ultrasonic Subthalamic Nucleus Stimulation

Thomas Tarnaud, Wout Joseph, Luc Martens, Emmeric Tanghe

Abstract—Objective: To explore the potential of ultrasonic modulation of plateau-potential generating subthalamic nucleus neurons (STN), by modeling their interaction with continuous and pulsed ultrasonic waves. **Methods:** A computational model for ultrasonic stimulation of the STN is created by combining the Otsuka-model with the bilayer sonophore model. The neuronal response to continuous and pulsed ultrasonic waves is computed in parallel for a range of frequencies, duty cycles, pulse repetition frequencies, and intensities. **Results:** Ultrasonic intensity in continuous-wave stimulation determines the firing pattern of the STN. Three observed spiking modes in order of increasing intensity are low frequency spiking, high frequency spiking with significant spike-frequency and spike-amplitude adaptation, and a silenced mode. Continuous-wave stimulation has little capability to manipulate the saturated spiking rate in the high frequency spiking mode. In contrast, STN firing rates induced by pulsed ultrasound insonication will saturate to the pulse repetition frequency with short latencies, for sufficiently large intensity and repetition frequency. **Conclusion:** Computational results show that the activity of plateau-potential generating subthalamic nucleus neurons can be modulated by selection of the stimulus parameters. Low intensities result in repetitive firing, while higher intensities silence the STN. Pulsed ultrasonic stimulation results in a shorter saturation latency and is able to modulate spiking rates. **Significance:** Stimulation or suppression of the STN is important in the treatment of Parkinson's disease, e.g., in deep brain stimulation. This explorative study on ultrasonic modulation of the STN, could be a step in the direction of minimally invasive alternatives to conventional deep brain stimulation.

Index Terms—Acoustical neurostimulation, Computational modeling, Otsuka-model, Subthalamic nucleus (STN), ultrasonic neuromodulation

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T. Tarnaud, W. Joseph, L. Martens, and E. Tanghe are with the Department of Information Technology (INTEC-WAVES/IMEC), Ghent University/IMEC, Technologypark 15, 9052 Zwijnaarde, Belgium. E-mail: thomas.tarnaud@ugent.be

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I. INTRODUCTION

SUBTHALAMIC nucleus deep brain stimulation (STN-DBS) is a surgical treatment that is mainly used to treat symptoms (rigidity, bradykinesia, tremor, and levodopa-induced dyskinesias) in patients with advanced Parkinson's disease [1]. However, although DBS has proven to be effective in appropriately selected patients, the surgery is associated with significant risks, such as haemorrhage and infection [2], [3]. As a consequence, several authors have explored the possibility of non-invasive alternatives to conventional deep brain stimulation. Two examples are temporal-interference and wireless magnetothermal deep brain stimulation [4]–[6].

Another option is the use of ultrasound (US) to reversibly modulate neuronal activity. As multiple-element phased-arrays of ultrasound transducers have been used for non-invasive thalamotomy or tumour ablation with millimeter precision [7]–[10], the possibility of using similar array designs for ultrasonic modulation of deep brain structures has been considered before [4], [11], [12]. Although the initial idea of using ultrasound to modulate neuronal activity is almost nine decades old [13], [14], the field has recently gained significant attention [11], [12], [15]–[23]. In conclusion, transcranial focused ultrasound seems to be promising as alternative for conventional deep brain stimulation, because of its theoretical ability to modulate deep brain nuclei non-invasively, selectively and with high-precision and without the need to genetically alter the target neurons (cfr. wireless magnetothermal DBS and optogenetics).

However, the therapeutical potential of ultrasonic subthalamic nucleus stimulation is still elusive, as no experimental or computational studies have been performed on this topic. The goal of this paper is to provide for the first time an explorative and computational study on ultrasonic stimulation of subthalamic nucleus neurons.

Although the nature of this study is completely computational and experimental validation will be necessary, we believe that at this stage a theoretical investigation on the potential of ultrasonic STN-stimulation is worthwhile, because:

- Interpretation of US-STN stimulation might not be straightforward without computational modeling, due to the ability of subthalamic nucleus neurons to generate plateau-potentials in a voltage-dependent manner [24]–[27]. Furthermore, the mechanism of ultrasonic neuromodulation is likely to be indirect, mediated by membrane charge accumulation driven by the hyperpolarized state of the neuronal membrane [28]–[30]. As a consequence, the relation between the stimulation param-

eters (frequency, intensity, duty cycle, pulse-repetition frequency...) and the observed neuronal behaviour, is less intuitive for ultrasonic stimulation than for electrical stimulation. Here, computational modeling might help to obtain a clear understanding of how these stimulation parameters interact with the intrinsic dynamics of plateau-potential generating STN-neurons. In this regard, comparison of the presented computational results with future experimental studies might improve understanding on the underlying mechanism of ultrasonic neuromodulation.

- We constructed a computational model of ultrasonic subthalamic nucleus stimulation, from the Otsuka-model of plateau-potential generating STN-neurons [26] and the bilayer sonophore model of ultrasound-membrane coupling [29] (BLS-model). Although no experimental data on ultrasonic STN stimulation exists, several experimental studies correspond well with both the Otsuka-model and the BLS-model.
- The presented results can be used as a basis for future computational work in which the impact of ultrasound on the basal ganglia system is investigated, paving the way for in vivo validation. Furthermore, this study might inspire future translational bioengineering efforts, focusing on the design of the transducer arrays required for non-invasive ultrasonic deep brain stimulation.

II. METHODS

The dynamics of the neuronal membrane as a bilipid layer in the presence of an ultrasonic source is modeled by the bilayer sonophore (BLS) model [28]. In this model, a modified Rayleigh-Plesset equation is used to calculate the maximal displacement Z of the membrane with respect to its resting position:

$$\frac{d^2 Z}{dt^2} + \frac{3}{2R(Z)} \left(\frac{dZ}{dt} \right)^2 = \frac{1}{\rho_l |R(Z)|} [P_{in} + P_M + P_{ec} - P_0 + P_A \sin(\omega t) - P_S(Z) - \frac{4}{|R(Z)|} \frac{dZ}{dt} \left(\frac{3\delta_0 \mu_s}{|R(Z)|} + \mu_l \right)]. \quad (1)$$

Here, $R(Z) = (a^2 + Z^2)/(2Z)$ is the radius of curvature of a leaflet of the symmetrical bilipid layer, $\rho_l = 1028 \frac{\text{kg}}{\text{m}^3}$ is the density of the surrounding liquid ($a = 32 \text{ nm}$ is the radius of the considered circular membrane patch), and $\omega = 2\pi f$ is the angular frequency of the US-wave. The pressure terms P_{in} , P_M , P_{ec} , P_0 , P_A , and $P_S(Z)$ represent the internal gas pressure, molecular pressure, electrostatic pressure, static pressure, amplitude of the applied ultrasonic source, and the pressure due to the tension in the leaflets, respectively. The last term in (1) represents the effect of viscosity, with δ_0 the thickness of a leaflet, μ_s the dynamic viscosity of the leaflet and μ_l is the dynamic viscosity of the cerebrospinal fluid (CSF).

In the neuronal intramembrane cavitation excitation (NICE) model, the dynamics of the bilipid layer (eq. (1)) is coupled with a Hodgkin-Huxley type equation, by adding a displacement current $V \frac{dC_m}{dt}$ [29], [30]. Here, C_m is a function of the displacement Z :

$$C_m(Z) = \frac{C_{m0} \Delta}{a^2} \left(Z + \frac{a^2 - Z^2 - Z\Delta}{2Z} \ln \left(\frac{2Z + \Delta}{\Delta} \right) \right). \quad (2)$$

$C_{m0} = 1 \mu\text{F}/\text{cm}^2$ is the membrane capacitance of the bilipid layer at rest ($P_A = 0 \text{ Pa}$) and $\Delta = 1.29 \text{ nm}$ is the separation between the leaflets if the bilipid layer is at equilibrium (calculated for $V = -58 \text{ mV}$). Equations for the mentioned pressure terms, as well as model constants of the BLS-model, are adopted from [28]–[30] and are summarized in Appendix A.

In this study, ultrasonic neuromodulation of the plateau-potential generating subthalamic nucleus neuron is modeled by adding the capacitive displacement current $I_D = V \frac{dC_m}{dt}$ to the Otsuka-model [26], [29], [31]:

$$C_m \frac{dV}{dt} + V \frac{dC_m}{dt} = -I_{Na} - I_K - I_A - I_T - I_L - I_{CaK} - I_l. \quad (3)$$

Here, C_m is the membrane capacitance and V is the membrane potential. The model includes a sodium current (I_{Na}), a delayed-rectifier K^+ current (I_K), an A-type K^+ current (I_A), a low threshold Ca^{2+} current (I_T), a high-threshold Ca^{2+} current (I_L), a Ca^{2+} dependent K^+ current (I_{CaK}) and a leak current (I_l). Equations for the membrane currents and gate parameters and the associated constants are adopted from Otsuka et al. and summarized in Appendix A [26].

The calcium dynamics were modeled as in Otsuka [26] and Hahn and McIntyre [32]:

$$\frac{dC_{a_i}}{dt} = -\alpha(I_T + I_L) - K_{Ca}C_{a_i}, \quad (4)$$

where C_{a_i} is the calcium concentration available near the calcium-dependent membrane gates. The intracellular calcium concentration is increased by calcium currents (I_T and I_L) and decreased by calcium pumps ($K_{Ca} = 2 \text{ ms}^{-1}$). Finally, $\alpha = 1/(2Fd_{\text{eff}})$, with F the Faraday constant and d_{eff} an effective depth, accounting for buffering mechanisms and geometry considerations¹. In this study, d_{eff} is calculated so that the equilibrium calcium concentration is 5 nM at $V = -58 \text{ mV}$ and $T = 33 \text{ }^\circ\text{C}$.

Spike rate, latency and saturation intensity

Incidence of a neuronal spike is determined by the zero-crossing with positive slope of the membrane charge $Q = C_m V$. The spiking time t_i^{AP} corresponds with the i th spike after ultrasonic stimulus onset. The interspike interval (ISI) is the time interval between two subsequent spikes: $\text{ISI}_i = t_{i+1}^{\text{AP}} - t_i^{\text{AP}}$. An instantaneous spiking rate SR_i is then defined as the reciprocal of the interspike interval (i.e., $\text{SR}_i = \text{ISI}_i^{-1}$). In spiking rate plots, SR_i is plotted against the spiking times t_i^{AP} .

Spiking rates of the subthalamic nucleus, insonicated with a pulsed wave with sufficiently high pulse repetition frequency ($\text{PRF} \geq 100 \text{ Hz}$) and ultrasonic intensity ($I_{\text{US}} > I_{\text{sat}}$), will saturate to the pulse repetition frequency (i.e., $\exists i_{\text{sat}}, \forall j \geq i_{\text{sat}} : |\text{SR}_j - \text{PRF}| \leq \alpha_c \text{PRF}$). Here I_{sat} is the saturation

¹Note that although d_{eff} is not mentioned in Otsuka et al., it has to be included in the definition of α for dimensional consistency

Fig. 1 (a)-(b) Spike firing rate as function of time after onset of stimulation (pulse start PS = 1 s, pulse duration PD = 1 s, $f = 0.69$ MHz). (a) Ultrasonic continuous-wave stimulation of Otsuka-STN model. (b) Electrical stimulation of Otsuka-STN model. (c-f) Membrane charge versus time for the ultrasonic stimulation configurations indicated with arrows in (a).

intensity and α_c is a convergence factor. The latency is then defined as the corresponding spiking time $t_{i_{sat}}^{AP}$. For continuous-wave stimulation, the saturated spiking rate is defined as the inverse of the interspike interval at the end of the ultrasonic stimulus.

In this study, all ultrasonic intensities are reported in their spatial-peak pulse-averaged (sppa) form and are related with the applied ultrasonic pressure P_A by:

$$I_{sppa} = \frac{P_A^2}{2\rho_l c}. \quad (5)$$

Here, c represents the speed of sound.

III. RESULTS

A. Model verification²

In this study, a model for ultrasonic stimulation of the subthalamic nucleus was constructed, by coupling a Hodgkin-Huxley type model (Otsuka-model of the STN, [26]) with the bilayer sonophore model [28] of ultrasound-membrane interaction. Although this is the first modeling study of ultrasonic STN-stimulation, partial verification of our implementation of the BLS-STN model was still possible, by closely comparing results with literature [29]–[31]. More specifically, we verified the implementation of the Otsuka-model without ultrasonic stimulation ($P_A = 0$ Pa) by reproducing the observed features of the STN-model (spontaneous firing, steady state I-V

curves, plateau-potential generation, dependency of firing rate on injected current, and rebound spiking) [31]. In order to verify our implementation of the bilayer sonophore model, we reproduced the results obtained by Plaksin et al. [29], [30], for ultrasonic stimulation of cortical (RS, FS, and LTS) neurons (NICE-model).

The model equations are solved in a similar fashion to Plaksin et al. [29], [30]. Eq. (1) and eq. (3) are solved by separate ode113-Matlab functions. The ode113-solver is a variable step variable order method, which uses Adams-Bashforth-Moulton predictor-corrector pairs of variable order between 1 and 13 [33], [34]. The membrane charge in eq. (1) is updated every $T_{up} = 25 \mu s$ (we observed that a shorter update time T_{up} was required for simulations with the Otsuka-STN model, as compared to simulations with cortical RS, FS and LTS neurons [29], [30]). A maximal step size of $dt = 0.025/f$, as well as appropriate absolute and relative tolerances are imposed on the ode113-solvers. To ensure that the results are independent of the implementation details, control simulations were performed with a smaller maximal timestep ($dt = 0.0125/f$), smaller update time ($T_{up} = 12.5 \mu s$), smaller absolute and relative tolerances (factor 10) and higher resolution for the look-up tables of the rate constants (refinement factor 10). The mentioned discretization parameters were determined by refinement until relative errors, obtained by comparison of the default and control simulations for continuous-wave stimulation, are lower than 10%.

In Fig. 1 the spiking modes of the subthalamic nucleus, due to continuous-wave ultrasonic stimulation are summarized and

²A distinction between verification and validation is made in this study. Verification refers to the correctness of the implementation and numerical convergence. Validation refers to the correspondence with experimental results.

Fig. 2 Upper and lower threshold intensity I_{tr}^u and I_{tr}^l versus ultrasonic driving frequency. Low ultrasonic intensities ($I < I_{tr}^l$) result in repetitive firing, while high intensities ($I > I_{tr}^u$) will generate silenced plateaus. The intermediate regime ($I_{tr}^l < I < I_{tr}^u$) corresponds with STN-neurons, that will fire some spikes at stimulation onset, before transitioning to a stable plateau. Threshold are determined with $PD = 1$ s.

a comparison is made between ultrasonically and electrically induced firing rate curves. The ultrasonic firing rate curves in Fig. 1(a) are used to determine numerical convergence, by calculation of the relative error on the maximal and saturated firing rate (f_{max} and f_{sat}) and the peak firing rate time τ_p . Because a change in neuronal spiking rhythm can be observed when increasing the ultrasonic intensity from 110 W/m^2 to 115 W/m^2 (Fig. 1(a)), relative errors are calculated separately for low intensities (10 W/m^2 to 100 W/m^2 , sampling step of 10 W/m^2) and intermediate intensities (from 120 W/m^2 to the lower intensity threshold I_{tr}^l , see section III-B, sampling step of 1 W/m^2)³. Comparison between the default and control simulations indicates that relative errors are always lower than 10%. In particular, maximal errors are 7.72%, 6.94%, 9.9844% (low intensities) and 0.59%, 1.47%, 3.14% (intermediate intensities) for the saturated firing rate, maximal firing rate, and peak firing rate time, respectively. The relative error on the low intensity threshold I_{tr}^l (see section III-B) is lower than 1%.

B. Continuous-wave stimulation: excitation by low-intensity, silencing by high-intensity ultrasound

A first prediction obtained from the BLS-STN model is that stimulation of a plateau-potential generating STN-neuron with a continuous-wave of low-intensity ultrasound leads to a sequence of action potentials, while higher intensities will silence the STN-neuron by generation of a plateau-potential.

³In this study, only neuromodulation by low-intensity focused ultrasound (LIFU) is considered. For convenience, we use the relative terms low, intermediate and high intensity to refer to the intensities, corresponding with the observed spiking modes.

Fig. 3 Membrane channel dynamics of Otsuka-STN model, stimulated by low intensity ultrasound ($I = 115$ W/m^2). The traces represent the membrane charge Q , the intracellular calcium concentration Ca_i and the gate parameters (I_{Na} (m , h), I_K (n), I_T (p , q), I_{KCa} (r), I_A (a , b), I_L (c , d_1 , d_2)).

This is illustrated in Fig. 1(a) ($f = 0.69$ MHz sonication of BLS-STN model). Low ultrasonic intensities ($I_{US} \leq 110$ W/m^2) modulate the behaviour of the subthalamic nucleus by inducing repetitive spiking at low rates (≤ 45 Hz) and with small spike-frequency adaptation. Furthermore, the amplitude of the spikes induced by low ultrasonic intensities is approximately constant during sonication (Fig. 1(c-d)). Increasing the ultrasonic intensity (115 $W/m^2 \leq I_{US} \leq 126$ W/m^2) leads to high-frequency spiking with significant spike-frequency and amplitude adaptation during the pulse duration (Fig. 1(a) and Fig. 1(e)). For instance, for $I_{US} = 115$ W/m^2 , the subthalamic nucleus will reach spiking rates of about 120 Hz (saturated spiking-frequency), after a spike-frequency adaptation period of about 850 ms. For intensities high enough to induce high-frequency spiking with significant spike-frequency adaptation, increasing the ultrasonic intensity will not affect the saturated spiking rate (between 124 Hz and 128 Hz, Fig. 1), but will shorten the timespan necessary to obtain a stabilized spiking rate (peak firing rate times decrease to 500 ms, when increasing the ultrasonic intensity I_{US} to the lower intensity threshold $I_{tr}^l = 126.5$ W/m^2).

Plateau-generating subthalamic nucleus neurons will be silenced at a stable plateau potential, if sonicated with a 0.69 MHz continuous ultrasonic wave with intensity larger than $I_{tr}^l = 126.5$ W/m^2 (Fig. 1(a) and Fig. 1(f)). This stable plateau potential is preceded by a “transient regime” of repetitive spiking. With increasing ultrasonic intensity, the

Fig. 4 Membrane channel dynamics of Otsuka-STN model, stimulated by low intensity ultrasound ($I = 115 \text{ W/m}^2$). The traces represent the active (I_{Na} , I_K , I_T , I_L , I_{KCa} , and I_A) and passive (I_l) membrane currents, as well as total current flowing through the active membrane I_{tot} .

duration of this transient regime decreases. Eventually, for ultrasonic intensities larger than $I_{tr}^u = 135 \text{ W/m}^2$, the stable plateau potential induced by the ultrasonic wave will be preceded by a single action potential.

The results obtained for ultrasonic sonication of the Otsuka-model are compared with electrical stimulation results in Fig. 1(b) (constant current injected in subthalamic nucleus model neurons). Spike-frequency adaptation is of course also present for electrical stimulation, but is much more modest than in ultrasonic stimulation. Furthermore, initial spiking frequency is higher in electrically stimulated than in ultrasonically stimulated neurons. Finally, no transition from repetitive spiking to a stable plateau for higher current injections is observed.

The impact of the frequency of the continuous ultrasonic wave on the transition from high-frequency spiking to a stable plateau-potential, is illustrated in Fig. 2 (lower and upper ultrasonic intensity thresholds I_{tr}^l and I_{tr}^u as function of frequency). Due to the inertia of the cerebrospinal fluid surrounding the oscillating intraleaflet cavity, higher frequencies will have higher threshold intensities. Fig. 2 defines a threshold-frequency curve, delineating different neuronal spiking modes, useful for experimental validation of the BLS-STN model.

C. High-threshold calcium current mediates spike-frequency adaptation. Steady plateaus are maintained by calcium currents.

The membrane channel dynamics responsible for the spike-frequency adapting high-frequency firing in STN-neurons is shown in Fig. 3. The corresponding membrane currents are shown in Fig. 4. Here, the Otsuka-model is simulated for insonication with $I_{US} = 115 \text{ W/m}^2$ ($f = 0.69 \text{ MHz}$).

Most of the time-dependence after stimulus onset is due to the slowly decaying and depolarization activated c -parameter

Fig. 5 Membrane channel dynamics of Otsuka-STN model, stimulated by high intensity ultrasound ($I = 1000 \text{ W/m}^2$). The traces represent the membrane charge Q , the intracellular calcium concentration Ca_i and the gate parameters (I_{Na} (m , h), I_K (n), I_T (p , q), I_{KCa} (r), I_A (a , b), I_L (c , d_1 , d_2)).

of the high-threshold calcium current I_L . Blocking the I_L -current in the Otsuka-model ($g_L = 0 \text{ S/m}^2$), indeed shows disruption of the spike-frequency and spike-amplitude adaptation, which is replaced by steady and low frequency firing at rates of about 23 Hz (results not shown).

The results on the membrane dynamics of repetitively firing STN-neurons (Fig. 3 and Fig. 4) should be compared with the membrane parameters and currents, obtained for silenced STN-neurons (insonication with $I = 1000 \text{ W/m}^2$ ($f = 0.69 \text{ MHz}$)) in Fig. 5 and Fig. 6, respectively.

The membrane gate parameters will reach steady values, some time after the plateau potential has been reached. The action potential that precedes the plateau potential is generated by a short ultrasound-induced hyperpolarization. This hyperpolarization is a consequence of the oscillating membrane capacitance (membrane potential not shown). Note that this short ultrasound-driven hyperpolarization before the action potential preceding the plateau-potential is strong enough to deactivate the membrane gates b and q at stimulus onset. This results in a short peaktime of the A-type K-current I_A and the T-type (low threshold) Ca-current I_T (Fig. 6). In contrast, smaller ultrasonic intensities I_{US} (but still high enough to induce a plateau: $I_{US} > I_{tr}^l$) are not able to deactivate these gate-parameters, resulting in smaller I_T and I_A values.

The calcium currents I_L and I_T prevent the membrane from repolarizing during the long plateau by injecting charge (i.e., depolarizing currents), while I_A , I_{KCa} , I_l and $I_{Na} + I_K$ are ex-

Fig. 6 Membrane channel dynamics of Otsuka-STN model, stimulated by high intensity ultrasound ($I = 1000 \text{ W/m}^2$). The traces represent the active (I_{Na} , I_K , I_T , I_L , I_{KCa} , and I_A) and passive (I_l) membrane currents, as well as total current flowing through the active membrane I_{tot} .

tracting charge from the membrane (i.e., repolarizing currents). However, closer observation of the injected charge indicates that in the first 20 ms after stimulus onset, the contribution of $I_{Na} + I_K$ to the total current is actually depolarizing, due to the mostly hyperpolarizing oscillations of the membrane potential in phase with the ultrasonic wave, while the contribution of $I_L + I_T + I_A + I_{KCa}$ is still repolarizing. Nevertheless, the relatively slow n -gate parameter will then saturate (about 20 ms after stimulus onset) and the $I_{Na} + I_K$ -contribution becomes repolarizing. At the same time $I_L + I_T + I_A + I_{KCa}$ will start to inject positive charge. As we noted earlier, the relative contributions of I_T and I_L to the long plateau depends on the ultrasonic intensity of the incident wave. I_L becomes relatively more important for lower ultrasonic intensities, when the inactivation constant q of the low-threshold calcium current I_T is not deinactivated anymore by the short ultrasound-induced hyperpolarization at stimulus onset.

D. Pulse repetition frequency determines STN saturating firing rate. Latencies are reduced at high duty cycles and intensities.

At sufficiently high intensities ($I_{US} > I_{sat}$) and pulse repetition frequencies ($PRF > PRF_{min} > 90 \text{ Hz}$), pulsed ultrasonic waves are able to entrain subthalamic nucleus spiking patterns. Here, we define the saturation intensity I_{sat} as the minimal ultrasonic intensity for which the firing rate will saturate at the pulse repetition frequency. This is illustrated in Fig. 7(a),(c) for ultrasonic stimulation with $PRF = 100 \text{ Hz}$, duty cycle $DC = 10\%$, and intensity $I_{US} = 270 \text{ W/m}^2$. After a latency of 300 ms the spiking rate will saturate, i.e., $PRF(1 - \alpha_c) \leq SR \leq PRF(1 + \alpha_c)$, as indicated by the dotted and dashed lines in Fig. 7(a). In Fig. 7(c) the corresponding charge spikes are shown. For pulse repetition frequencies lower than $PRF_{min} (< 100 \text{ Hz})$, multiple spikes

Fig. 7 Firing rate saturates to the PRF of the pulsed ultrasonic wave. (a) Spiking rate for pulsed ultrasonic stimulation ($DC = 10\%$, $PRF = 100 \text{ Hz}$, $I_{US} = 270 \text{ W/m}^2$). Horizontal dashed lines indicate the $PRF(1 \pm \alpha_c)$ values. The determination of the latency is indicated by the vertical dotted line. (b) Latency until spike saturation as function of ultrasonic intensity. Duty cycle is indicated by the arrows. (c) Membrane charge plot corresponding with the ultrasound parameters used in (a). (d) Saturation intensity versus duty cycle. **Legend** ((b),(d), PRF): (—) 100 Hz, (---) 130 Hz, (.....) 160 Hz. **Method**: convergence factor is $\alpha_c = 1\%$, latencies are smoothed with gaussian kernel (width $\sigma_w = 25 \text{ W/m}^2$)

will occur during the interpulse interval and the spiking rate will not saturate reliably to the pulse repetition frequency.

Fig. 7(b) illustrates how the latency decreases with ultrasonic intensity. At the highest considered ultrasonic intensity ($I_{US} = 500 \text{ W/m}^2$), the latency is close to the interpulse interval (PRF^{-1}). Furthermore, latencies are inversely proportional with the duty cycle, if the pulse repetition frequency is held constant. Finally, in Fig. 7(d) it is shown that the saturation intensity I_{sat} is inversely proportional with the duty cycle as well.

IV. DISCUSSION

In this study, a computational model of the plateau-potential generating subthalamic nucleus neuron (Otsuka-model, [26]) is combined with the bilayer sonophore model for ultrasound-membrane interaction (BLS-model) [29]. The ultrasound-neuron interaction is described with the neuronal intramembrane cavitation excitation (NICE) model [28]–[30]. In the NICE-model, oscillating intraleaflet cavitations are assumed to be the main mechanism of ultrasonically induced neuron excitation. Other potential explanations of the mechanism of ultrasonic neurostimulation include flexoelectricity (Petrov-model) [35], tension-dependent voltage-gated channels [36], and the Heimburg-Jackson soliton model [37]. In this paper, several distinctive qualitative and quantitative consequences of the application of the NICE-model to the subthalamic nucleus are presented. E.g., continuous-wave insonication results in different intensity-dependent firing modes (low frequency

repetitive spiking with negligible adaptation, high frequency spiking with significant frequency and amplitude adaptation, silenced plateaus) and pulsed excitation with sufficient repetition frequency and intensity will entrain subthalamic nucleus neurons with small latencies. Consequentially, comparison of these computational results with future experimental studies on subthalamic nucleus insonication, would help to elucidate the mechanism of ultrasonic neuromodulation.

Some limitations with respect to the Otsuka-model should be taken into account. First, the Otsuka-STN model is not physiologically complete, as currents have been omitted that have no clear relationship with the capability of subthalamic nucleus neurons to generate voltage-dependent plateau-potentials [31], [38]–[41]. These include a persistent TTX-sensitive sodium current I_{NaP} , a hyperpolarization-activated inward current I_h and high-threshold Ca^{2+} -currents. Second, the Otsuka-model is a single compartment model and as a result neglects the spatial extent of the STN-neurons.

An alternative single compartment subthalamic nucleus model is the Rubin-Terman model [42]–[44]. However, in contrast with the Rubin-Terman model, the Otsuka-model is developed to reproduce the capability of subthalamic nucleus neurons to generate voltage-dependent plateau-potentials. Furthermore, the shape of the action potential, the dependency of the duration of the rebound response on the shape of the current pulse and the decrease in the spiking rate during a rebound burst, is simulated more reliably with the Otsuka-model [31].

A multi-compartment model of the subthalamic nucleus exists as well (Gillies-Willshaw model) [45]. However, we opted for the Otsuka-model, because of the high computational demands of the BLS-STN model (short time steps are required due to the small ultrasonic periods) and because the relatively large set of parameters in the Gillies-Willshaw model might complicate the analysis. Furthermore, as future work we aim to investigate the capabilities of ultrasonic stimulation, with a computational model of the basal ganglia network. The Otsuka-model is interesting in this context, because it has been used in computational studies on the impact of electrical deep brain stimulation on the basal ganglia network [32], [46], [47].

Another important consideration is the impact of neuronal diversity within the STN on the response to insonication and its implications for the tentative therapeutic effects of US-STN stimulation. First, variety in the electrophysiological and dynamical parameters of the plateau-potential generating STN neuron is likely to influence quantitative modeling results, e.g. lower and upper intensity thresholds (I_{tr}^l and I_{tr}^u , respectively). Consequentially, our results suggest that during continuous-wave insonication, different plateau-potential generating STN-neurons will exhibit different spiking rhythms (low frequency spiking, high frequency spiking or a silenced plateau). Furthermore, computational results indicate a narrow intensity range corresponding with the high frequency spiking mode ($115 \text{ W/m}^2 \leq I_{US} \leq 126 \text{ W/m}^2$). This fact will further contribute to the diverse response to continuous-wave insonication, as practical considerations (phase aberration, variable attenuation...) will limit the possibility of achieving this level of precisely controlled ultrasound in vivo at the subthalamic

nucleus. This diversity in the neuronal response would be therapeutically interesting, as a similar heterogeneous response, consisting of spiking and silenced neurons, is likely to play an important role in the mechanism of conventional electrical deep brain stimulation as well [48], [49]. Furthermore, assuming that qualitative results are robust to this neuronal diversity, our results indicate that a homogeneous high-frequency spiking response in the STN will be induced by pulsed ultrasonic stimulation. Second, more profound sources of STN-diversity are GABAergic interneurons [50] and neurons incapable of generating plateau-potentials [25], [38]. Because these sources will interact with the response to ultrasound of the plateau-potential generating STN neurons, we believe that this topic is best addressed as future work within the context of a computational model, coupling ultrasound with the basal ganglia network.

Finally, the reported computational simulations of STN insonication predict that relatively low intensity levels are required to elicit high frequency spiking or silenced plateau-potentials, compared to previous modeling studies for cortical insonication [29], [30] and experimental studies [23]. We attribute these significantly lower required ultrasonic intensities to the different membrane channel dynamics of the STN. E.g., STN-neurons are spontaneously active and are able to generate voltage-dependent plateau-potentials. The former STN-property (spontaneous firing) corresponds with the low required intensities to induce high-frequency spiking, while the latter property (plateau-potentials) is associated with the induction of a silenced plateau at higher, but still relatively low, intensities. This prediction that lower intensities are required in order to modulate STN-activity, compared to cortical stimulation, contributes to the theoretical feasibility of safe low-intensity ultrasonic deep brain modulation without activating overlying cortical areas.

V. CONCLUSION

In this study, a computational model for ultrasonic STN-stimulation is constructed, by combining the Otsuka-STN model with the bilayer sonophore model for ultrasound-membrane interaction. The model implementation was verified by a careful comparison of simulation results with literature for two restricted cases of the STN-BLS model: electrical stimulation of the STN and ultrasonic stimulation of cortical neurons (STN is substituted by RS, FS or LTS neurons). Furthermore, a convergence analysis was performed on the discretisation parameters (maximal timestep, tolerances, update time, table resolutions, ...) to ensure that the model results are not significantly dependent on the implementation.

This research indicates that ultrasonic neuromodulation might be promising in the context of non-invasive STN-DBS. While pulsed or intermediate intensity continuous-wave stimulation results in high-frequency firing of the STN-model, high intensity continuous-wave insonication is able to silence the STN at an elevated plateau. The former is similar to electrical deep brain stimulation, while the latter might have similar functionality as subthalamotomy. The intensity thresholds for continuous-wave stimulation that delineate the transition from

high frequency firing to a silenced plateau are increasing with ultrasonic driving frequency. The predicted ultrasonic intensity thresholds are relatively low, implying that low-intensity non-invasive ultrasonic deep brain stimulation without excitation of the overlying cortical areas is feasible. Furthermore, pulsed ultrasonic stimulation is able to modulate spiking rates with small latencies (close to PRF^{-1} for $I_{\text{US}} = 500 \text{ W/m}^2$, latency inversely proportional to DC and I_{US}).

The theoretical capability of ultrasound to differentially silence or excite subthalamic nucleus neurons non-invasively and with millimeter precision, makes acoustic neuromodulation interesting as a tool to study basal ganglia function and the mechanism of deep brain stimulation in the treatment of movement disorders. The authors intend to use this study as a basis for future research, by incorporating the BLS-STN model in a computational network model of the cortex-basal ganglia-thalamus system. The goal is to examine the capability of ultrasound to modulate pathological beta-oscillations and hypersynchrony in the Parkinsonian basal ganglia.

VI. CONFLICT OF INTERESTS

The authors declare that there is no conflict of interest regarding the publication of this paper.

APPENDIX

SUMMARY OF MODEL EQUATIONS

This appendix complements the method section, by including all model equations and parameter values that are necessary to reproduce the results obtained in this paper. A summary of the general parameter values is given in Table I.

TABLE I Summary of General Model Parameters

Abbr.	Value	Description
T	33 °C	Temperature
R_g	8.314 J/(K · mol)	Universal gas constant
F	96485 C/mol	Faraday constant
ϵ_0	$8.85 \cdot 10^{-12} \text{ F/m}$	Absolute vacuumpermittivity
ϵ_r	1	Relative vacuumpermittivity
c	1515 m/s	Speed of sound in CSF
ρ_l	1028 kg/m ³	Density of CSF
k_a	$1.63 \cdot 10^5 \text{ Pa} \cdot \text{m}^3/\text{mol}$	Henry constant (air in CSF)
D_a	$3 \cdot 10^{-9} \text{ m}^2/\text{s}$	Diffusion coefficient (air in CSF)
k_s	0.24 N/m	Areal modulus
δ_0	2 nm	Thickness leaflet
μ_s	0.035 Pa · s	Dynamic viscosity of leaflets
μ_l	$0.7 \cdot 10^{-3} \text{ Pa} \cdot \text{s}$	Dynamic viscosity of the CSF

A. Subthalamic nucleus model

The subthalamic nucleus model is adopted from Otsuka et al. [26], [31]. The membrane currents are modeled by:

$$I_{\text{Na}} = g_{\text{Na}} m^3 h (V - V_{\text{Na}}), \quad (6)$$

$$I_{\text{K}} = g_{\text{K}} n^4 (V - V_{\text{K}}), \quad (7)$$

$$I_{\text{A}} = g_{\text{A}} a^2 b (V - V_{\text{K}}), \quad (8)$$

$$I_{\text{T}} = g_{\text{T}} p^2 q (V - V_{\text{Ca}}), \quad (9)$$

$$I_{\text{L}} = g_{\text{L}} c^2 d_1 d_2 (V - V_{\text{Ca}}), \quad (10)$$

TABLE II Summary of Membrane Current Model Parameters

Membrane current	g [mS/cm ²]	V_r [mV]
I_{Na}	49	60
I_{K}	57	-90
I_{A}	5	-90
I_{T}	5	$\frac{R_g T}{2F} \ln \frac{C_{a0}}{C_{a1}}$
I_{L}	15	$\frac{R_g T}{2F} \ln \frac{C_{a0}}{C_{a1}}$
I_{CaK}	1	-90
I_l	0.35	-60

The calcium reversal potential is calculated by the Nernst-equation ($C_{a0} = 2 \text{ mM}$)

$$I_{\text{CaK}} = g_{\text{CaK}} r^2 (V - V_{\text{K}}), \quad (11)$$

$$I_l = g_l (V - V_l). \quad (12)$$

The membrane conductance and reversal potential for the different membrane currents are summarized in Table II.

The dynamics of the gate parameters is given by:

$$\frac{dX}{dt} = \frac{X_{\infty} - X}{\tau_X}. \quad (13)$$

X_{∞} is a function of V_m , if X represents m, h, n, p, q, a, b, c or d_1 :

$$X_{\infty} = \frac{1}{1 + \exp \left[\frac{V_m - \theta_X}{k_X} \right]}. \quad (14)$$

Conversely, X_{∞} is a function of C_{a1} if X represents d_2 or r . In this case, the membrane potential V_m in eq. (14) is replaced by the intracellular calcium concentration C_{a1} .

Similarly, general expressions are used for the time constant τ_X . If X represents m or a :

$$\tau_X = \tau_0 + \frac{\tau_1}{1 + \exp \left(\frac{-[V_m - \theta_{\tau}]}{\sigma_{\tau}} \right)}. \quad (15)$$

And for $X = h, n, p, q, b, c, d_1$:

$$\tau_X = \tau_0 + \frac{\tau_1}{\exp \left(\frac{-[V_m - \theta_{\tau 1}]}{\sigma_{\tau 1}} \right) + \exp \left(\frac{-[V_m - \theta_{\tau 2}]}{\sigma_{\tau 2}} \right)}. \quad (16)$$

Finally, for calcium dynamics we used the time constants: $\tau_r = 2 \text{ ms}$ and $\tau_{d_2} = 130 \text{ ms}$. The model constants for the membrane gate dynamics are summarized in Table III.

B. Bilayer sonophore model

The bilayer sonophore model equations and parameter values are adopted from [28]–[30]. At $t = 0 \text{ ms}$, the leaflet is at equilibrium (i.e., $Z = 0 \text{ nm}$ and $\frac{dZ}{dt} = 0 \text{ nm/s}$) and a quasi-static approximation can be used to calculate the dynamics of the membrane leaflet:

$$P_{\text{in}}^{\text{QS}} + P_{\text{M}} + P_{\text{A}} \sin(\omega t) + P_{\text{ec}} - P_0 = 0. \quad (17)$$

Here, $P_{\text{in}}^{\text{QS}}$ is a quasi-static approximation of the internal pressure:

$$P_{\text{in}}^{\text{QS}} = P_0 \frac{\pi a^2 \Delta}{V_a(Z)^{\kappa}} \quad (18)$$

The polytropic constant κ is assumed to be unity (small volume of air in the intraleaflet cavity). Eventually, if

$Z \geq Z_{QS}$ for some small value of Z_{QS} , the mechanics of the leaflet and cerebrospinal fluid (CSF) has to be taken into account and the quasi-static equation is replaced by an adaptation of the Rayleigh-Plesset equation.

The internal gas pressure P_{in} in the Rayleigh-Plesset equation is calculated by the universal gas law:

$$P_{in} = \frac{n_a R_g T}{V_a(Z)}. \quad (19)$$

Here, the mole of air n_a inside the intraleaflet cavity, is calculated by a diffusion equation:

$$\frac{dn_a}{dt} = \frac{2S(Z)D_a}{\xi} [C_a - P_{in}/k_a]. \quad (20)$$

$S(Z)$ is the area of a single leaflet, D_a is the diffusion coefficient of air, $\xi = 0.5$ nm is an effective length of the boundary layer for air diffusion, k_a is the Henry-coefficient of dissolved air in CSF, and C_a is the molar air concentration in the CSF. A more general simulation of the diffusion of air in the environment of an oscillating intraleaflet cavity is performed in [28] (Fick's law). However, as noted in [29], the simplification in eq. (20) is justified and is computationally more efficient.

The molecular pressure term P_M is calculated by [29]:

$$P_M = A_r \frac{2\pi}{S(Z)} \int_0^a r dr \left[\left(\frac{\Delta^*}{2z(r) + \Delta} \right)^x - \left(\frac{\Delta^*}{2z(r) + \Delta} \right)^y \right]. \quad (21)$$

Here, $A_r = 10^5$ Pa is the attraction/repulsion pressure coefficient, $x = 5$ and $y = 3.3$ are the repulsion and attraction exponents, respectively, and $\Delta^* = 1.4$ nm is the initial intraleaflet gap if no membrane charge would be present. The local leaflet displacement $z(r)$ is calculated by:

$$z(r) = \text{sign}(R(Z)) \sqrt{R(Z)^2 - r^2} - R(Z) + Z. \quad (22)$$

The electrostatic pressure P_{ec} and the pressure due to the leaflet tension P_S are given by:

$$P_{ec} = -\frac{\pi a^2}{S(Z)} \frac{Q_m^2}{2\epsilon_r \epsilon_0}, \quad (23)$$

$$P_S(Z) = \frac{2k_s Z^3}{a^2(a^2 + Z^2)}. \quad (24)$$

Here, $Q_m = C_m V_m$ is the membrane charge and k_s is the areal modulus of the bilayer membrane. Finally, a static pressure of $P_0 = 10^5$ Pa is used.

In the bilayer sonophore model equations above, the leaflet surface and intraleaflet cavity volume are functions of the displacement Z :

$$S(Z) = \pi(a^2 + Z^2), \quad (25)$$

$$V_a(Z) = \pi a^2 \Delta \left[1 + Z/(3\Delta) \left(\frac{Z^2}{a^2} + 3 \right) \right]. \quad (26)$$

TABLE III Model Parameters for the Gate Dynamics

X	θ_X [mV] ^a	k_X [mV] ^a	τ_0, τ_1 [ms]	θ_τ [mV] ^b	σ_τ [mV] ^b
a	-45	-14.7	1, 1	-40	-0.5
b	-90	7.5	0, 200	-60, -40	-30, -10
c	-30.6	-5	45, 10	-27, -50	-20, 15
d_1	-60	7.5	400, 500	-40, -20	-15, 20
d_2	0.1	0.02	130	-	-
m	-40	-8	0.2, 3	-53	-0.7
h	-45.5	6.4	0, 24.5	-50, -50	-15, 16
n	-41	-14	0, 11	-40, -40	-40, 50
p	-56	-6.7	5, 0.33	-27, -102	-10, 15
q	-85	5.8	0, 400	-50, -50	-15, 16
r	0.17	-0.08	2	-	-

(a) The calcium gate constants θ_{d_2} , θ_r , k_{d_2} , and k_r are expressed in [μ M] instead of [mV]. (b) If two values are tabulated, then they refer to $\theta_{\tau 1}$ and $\theta_{\tau 2}$ or $\sigma_{\tau 1}$ and $\sigma_{\tau 2}$, respectively.

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