Modulation of Neuronal Activity With Extremely Low-Frequency Magnetic Fields: Insights From Biophysical Modeling

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Abstract—**Time-varying magnetic stimulation of the central nervous system is nowadays a promising therapeutic approach already used to alleviate the symptoms in a variety of neurological disorders. Transcranial Magnetic Stimulation (TMS) is an example of a successful application involving specific patterns of magnetic field (MF) for therapeutic use, which provides clinical improvement in movement disorders or depression. Other neuromodulation strategies consist in proposing several orders of magnitude lower magnetic stimuli that are more flexible in terms of shape and frequency of the signal. However, the refinement of both of these techniques is limited due to the lack of understanding of the underlying mechanisms supporting the interaction between the magnetic stimulus and brain tissue. To provide insights into the modulation of neuronal activity by extremely low-frequency (ELF) MF, we present biophysical modeling results regarding 1) single neuron exposure to an ELF MF, and 2) neuronal network exposure to an ELF MF. These results shed light on the effect of ELF MFs on neuronal activity from the single cell to the network level, and illustrate the importance of a number of factors both in ELF MF characteristics and brain tissue properties in determining the outcome of the exposure. These principles may guide future therapeutic developments.**

Extremely low-frequency magnetic fields, neuronal networks, brain oscillations, spike timing

I. INTRODUCTION

Magnetic stimulation of the central nervous system (CNS) is today a conventional therapeutic option to alleviate the symptoms of a number of neurological disorders. One of the most well-known examples of neuromodulation using magnetic stimulation is the use of extremely low-frequency (ELF) magnetic stimulation such as Transcranial Magnetic Stimulation (TMS) of the dorsolateral prefrontal cortex for drug-refractory depression [1]. TMS is delivered non-invasively (i.e. it does not require any surgery), which is a major advantage over other techniques such as deep brain stimulation (DBS). Pulsed Magnetic Field therapy (PMF) is also a technique of growing interest, since the levels of ELF magnetic field (MF) amplitude are significantly lower than TMS (on the order of 1 mT for PMF vs. 1 T for TMS) [2]. The common point between these neuromodulation techniques is that the mechanisms by which brain function seems at least partially restored are not well understood. Furthermore, these techniques have mostly been developed on empirical basis, and not using a solid rationale-driven methodology.

One hypothesis proposed to explain the benefits of neuromodulation is that the impaired neural rhythms originating the symptoms are re-organized by the stimulus toward physiological rhythms [3]. This is partly supported by experimental results in which DBS blocks the abnormal low-frequency (5 Hz) rhythm taking place in the sub thalamic nucleus (STN) [4]. Interestingly, as early as 1938, Gibbs [5] proposed that neurological disorders originate from *thalamocortical dysrhythmia*, and exaggerated frequency bands of neural activity have been identified in a number of neurological diseases such as beta activity in the motor cortex of patients with Parkinson's disease (PD) [6], delta activity in the prefrontal cortex of patients with Alzheimer's disease [7], or alpha activity in several regions including orbito-frontal and temporo-frontal regions in obsessive-compulsive disorders [8]. Later on, in 1977, Mackey and Glass proposed the concept of

dynamical disease, stating that abnormal dynamics occur when control parameters of the physiological system are out of range [9]. To summarize, the dynamics of neuronal networks is tightly related to their function, and perturbation of control parameters governing the dynamics of the system result in qualitatively different dynamics, and thus impacting the corresponding function. As a consequence, providing neuromodulation strategies aiming to normalize the dynamics of neuronal activity appears an appealing perspective for therapeutic applications.

Brain exposure to ELF MFs has been shown to induce a variety of effects on the central nervous system. These effects include a modulation of pain threshold [10], slower postural oscillations [11], modulation of the electroencephalogram (EEG) in the alpha (8-12 Hz) band [12], or modulation of blood oxygenation level-dependent (BOLD) activity in the sensorimotor cortex during a finger-tapping task [13]. However, it is difficult to integrate these findings into a unified framework, since results are not always reproducible among studies, probably because of the large variability of protocols used [14].

In this paper, we address the question of ELF MF exposure effects on brain tissue from the biophysical modeling point of view. First, we study the response of a single neuron to different spiking patterns during exposure to an ELF MF at different frequencies. Second, we perform an analog study at the neuronal network level and study the potential modulation of synaptic plasticity induced by the exposure. Finally, we discuss how the principles deducted from our results may be used for the development of therapeutic methods using ELF MFs.

II. Materials And Methods

This section describes our model of ELF MF-brain tissue interaction. First, we use Maxwell equations to determine the electric field induced in brain tissue by MF exposure. Second, macroscopic equations are used to describe the perturbation of membrane electric potential by the movements of charges induced by MF exposure in the extra- and intra-cellular medium. Third, we include this perturbation of the membrane potential in a model of neuronal membrane dynamics. Overall, we link ELF MF exposure, induced electric field, displacement of charges by the induced electric field, and perturbation of membrane potential dynamics.

When a time-varying MF is applied to the brain, then a time-varying induced electric field (EF) is induced according to Faradays' law:

$$E(t) = \frac{r}{2}\frac{dB(t)}{dt} \quad (1)$$

where r is the radius of exposure. This induced electric field induces charges movement in brain tissue, depending on their sign (since the electric force exerted by the EF on charges is $\mathbf{F(t)}=q\mathbf{E(t)}$, where q is the charge). Since the resistivity of the membrane is significantly higher than the extracellular medium, the current flow (since, by definition, a movement of charges forms a current) occurs mostly in the extracellular medium [15]. In brain tissue, ions are present both in extra- and intra-cellular medium, with different concentrations. This differential of ionic concentrations between the extra- and intra-cellular medium originates the *membrane potential* V(t) of the cell. The cell membrane potential can be described by a single equation that was derived by Goldman, Hodgkin and Katz: the GHK equation [16,17]. This equation describes the relationship between the ionic concentrations inside and outside the membrane:

$$V_m = \frac{R_g T}{F}\ln\left(\frac{P_{Na+}[Na^+]_{extra} + P_{K+}[K^+]_{extra} + P_{Cl-}[Cl^-]_{intra}}{P_{Na+}[Na^+]_{intra} + P_{K+}[K^+]_{intra} + P_{Cl-}[Cl^-]_{extra}}\right) \quad (2)$$

where R_g is the ideal gas constant, T the temperature, F Faraday's constant, intra/extra denotes the ionic concentration [ion] in the intra/extracellular medium, and P_{ion} the ionic permeability for the ion.

A simple relationship between a static EF of amplitude E_0 and the field-induced membrane

depolarization ΔV was derived by Schwan in 1957 [18]:

$$\Delta V = 1.5 R E_0 \cos\theta \qquad (3)$$

where R is the cell radius (typically, on the order of 10 μm) and θ the angle between the axis of the EF and the cell (equal to 1 in the following, i.e., to simplify we assume that either the cell is affected by ELF MF exposure, or not at all). This relationship was derived assuming spherical cell geometry, however, cells are not perfectly spherical, and rather have a complex geometry (with a large number of dendrites, the axonal hillock…). As a consequence, charges displaced by the MF-induced EF may accumulate in parts of the membrane, and the field-induced membrane depolarization can be greater. In order to take into account cell geometry and their polarisability when exposed to an EF, the polarization length λ has to be used instead [19]. Values of polarization length can be determined from recordings of neuron membrane potential for different EF values [19]. The Schwan equation describes the field-induced polarization for a steady EF, and is the solution to the following differential equation describing the charge of the membrane during MF exposure:

$$\Delta V' + \frac{1}{\tau}\Delta V = \frac{\lambda}{\tau} E_0 \qquad (4)$$

where τ is the Maxwell-Wagner time constant, indicating at which "speed" charges accumulate on the cell membrane [20]. In the case of a time-varying MF, a time-varying EF is induced, that replaces E_0 in (3). For a sinusoidal MF of pulsation ω and amplitude B_0, the solution to (3) becomes:

$$\Delta v(t) = \pi R f B_0 \lambda \cos\theta \frac{\cos(\omega t) + \omega\tau \sin(\omega t)}{1 + \omega^2 \tau^2} \qquad (5)$$

Using (4), one can compute the field-induced membrane depolarization at any time for a sinusoidal MF.

To model the response of cortical neurons during MF exposure, we used the Izhikevich model [21]. This model consists in a set of two coupled non-linear equations describing the dynamics of the membrane potential and of a recovery variable accounting for ionic channels dynamics. Despite its simplicity, this model is able to reproduce accurately realistic spiking patterns observed *in vitro* and *in vivo*. Let *v* be the membrane potential and *u* the recovery variable, the Izhikevich model is [21]:

$$\frac{dv(t)}{dt} = 0.04v(t)^2 + 5v(t) + 140 - u(t) + I(t) \qquad (6)$$
$$\frac{du(t)}{dt} = a[bv(t) - u(t)]$$

with the following reset condition: if v>30 mV, then *v*=c and *u*=*u*+d, where (a, b, c, d) are non-physical parameters, and I is the sum of synaptic currents and external inputs (e.g., *via* an external stimulation electrode). To include the field-induced membrane depolarization in the Izhikevich model, we considered that ΔV acts as an additive perturbation to the membrane potential *v*. Thus, the equations of the Izhikevich model describing the dynamics of a neuron during MF exposure are:

$$\begin{aligned} \frac{dv(t)}{dt} &= 0.04[v(t) + \Delta V(t)]^2 + 5[v(t) + \Delta V(t)] + 140 - u(t) + I(t) - \frac{d\Delta V(t)}{dt} \\ \frac{du(t)}{dt} &= a[b(v(t) + \Delta V(t)) - u(t)] \end{aligned} \qquad (7)$$

Overall, MF exposure induces a non-linear perturbation in the membrane potential in non-linear membrane equations. In the following, simulations are performed using a fourth-order Runge-Kutta method with a time step of 0.1 ms.

Finally, when simulating a neural network, we introduced additive Gaussian white noise in the membrane potential equation (variable *v* in (7)). We introduced this noise to simulate to some extent the stochastic fluctuations of the membrane potential caused by background synaptic noise or the finite number of ionic channels among the cell membrane.

III. Single Neuron Exposure To a Time-Varying Magnetic Field

A. *Frequency dependence of MF exposure effects*

We studied the response of a single cortical neuron model exposed to an external ELF MF. More specifically, we studied the shift in spike timing (SST), i.e., the perturbation in each spike time (positive is spike timing is delayed, negative is spike timing is advanced). As mentioned earlier, we used the Izhikevich model to simulate a single cortical neuron during 10 seconds of simulated time. The simulated neuron was in Regular Spiking (RS) mode, using the parameters (a=0.02, b=0.2, c=-65, d=8). A constant bias current of amplitude I_0=5 pA was injected into the neuron membrane to induce regular spiking at a frequency of 10.5 Hz. First, we simulated neuron activity without MF exposure (ΔV=0 mV in (6)). Second, we simulated neuron activity during ELF MF exposure of frequency *f* (sinusoidal, range: from 1 to 100 Hz, every 1 Hz) and amplitude B_0=50 mT. The polarization length was λ=0.5 mm and the radius of exposure R=10 cm. Depending on ELF MF frequency, we computed the maximum SST value σ_{max} that was induced by ELF MF exposure. Fig. 1 presents the time course of the membrane potential for *f*=60 Hz.

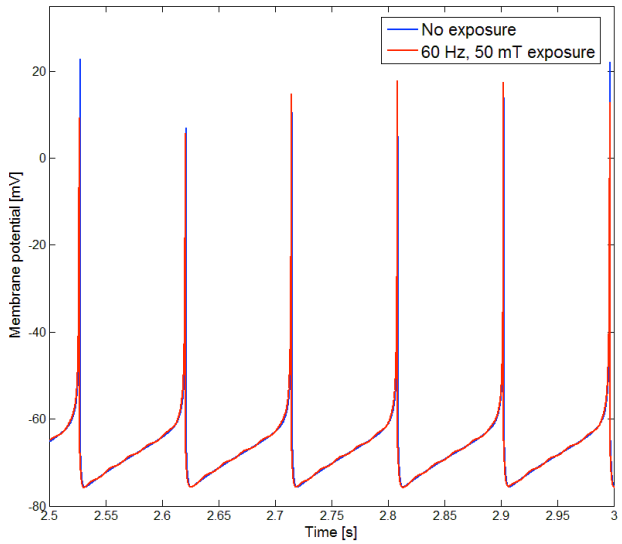

Figure 1: Membrane potential of a regular spiking cortical neuron during exposure to an ELF MF of frequency 60 Hz and amplitude 50 mT.

The impact of ELF MF frequency (from 1 to 100 Hz, increments of 1 Hz) on the maximal SST for a regular spiking neuron is presented in Fig. 2.

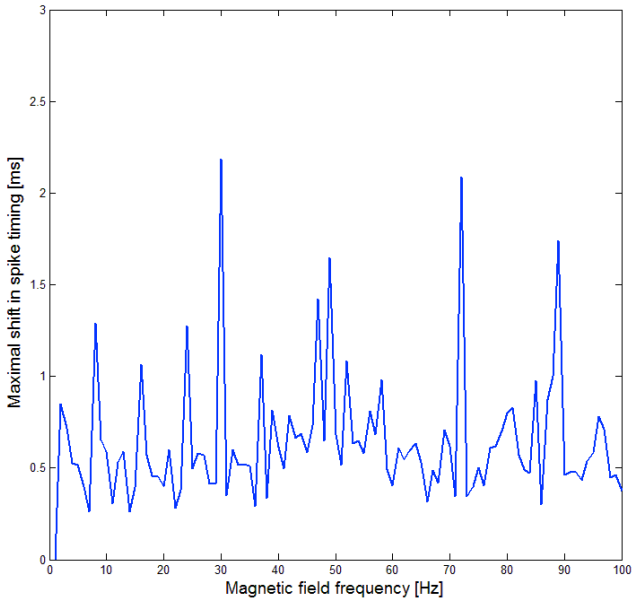

Figure 2: Role of the ELF MF frequency on the perturbation of spike timing as measured by the maximal SST.

From the results presented in Fig. 2, one can see that the perturbation of spike timing induced by MF exposure is maximized at several harmonics (though two are missing) of the intrinsic spiking frequency of the neuron (here, approximately 10.5 Hz). This indicates that the response of brain tissue to ELF MF could occur in narrow frequency bands. This could be tested by identifying well-known rhythms that can be measured with EEG (such as the alpha -8 to 12 Hz- rhythm), and recording EEG during MF exposure to a similar frequency and its harmonics. It would be of interest to test experimentally if the "missing harmonics" also exist in EEG response to ELF MF at harmonic frequencies.

B. *Role of spiking pattern on neural response to MF exposure*

To investigate if the impact of ELF MF exposure on SST is modulated by the neuron spiking pattern, we performed the same simulation on a bursting neuron, i.e., that triggers several spikes at a time. Since these neurons have different properties in terms of ionic channels, and thus different membrane dynamics (since voltage-gated ionic

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channels have kinetics that regulate membrane dynamics), and since the response of a single cell to ELF MF exposure appears typical of the response of nonlinear systems, it is likely that a different pattern than the one observed in Fig. 2 will be observed. To simulate bursting dynamics, we used the parameters for the chattering mode of the Izhikevich model ([21], a=0.02,b=0.2,c=-50,d=2). A constant current of amplitude I=5pA was injected in the neuron membrane in order to force a regular bursting at approximately 10 Hz. Note that 10 Hz was the frequency of the burst, but that the frequency of spikes within each burst is significantly higher (up to 500 Hz). In Fig. 3, we present the time course of a bursting neuron during exposure to an ELF MF of frequency 60 Hz and amplitude 50 mT.

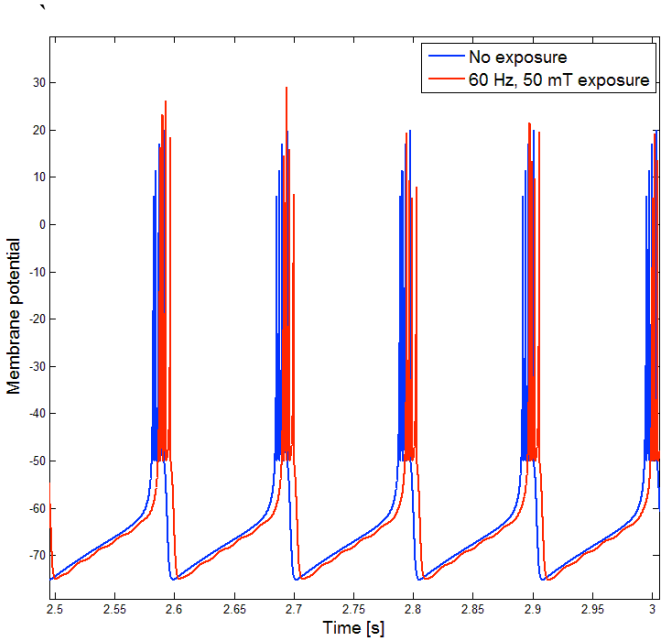

Figure 3: Membrane potential of a bursting neuron during exposure to an ELF MF of frequency 60 Hz and amplitude 50 mT.

The maximal values of the SST induced by ELF MF exposure for frequencies from 1 to 100 Hz (increments of 1 Hz) and an amplitude of 50 mT are presented in Fig. 4.

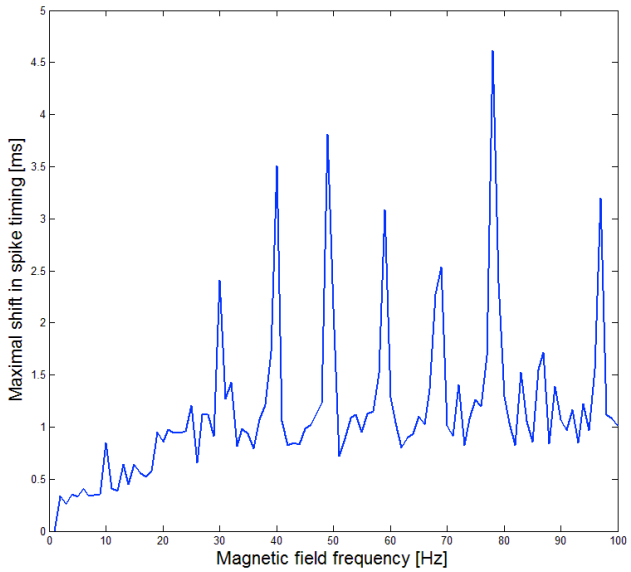

Figure 4: Influence of the spiking pattern on the perturbation of spike timing induced by ELF MF exposure as measured by the maximal SST.

From the results presented in Fig. 4, the maximal SST induced by the same level of ELF MF exposure appears higher for a bursting neuron (up to 4.5 ms, vs. up to 2.2 ms for a regular spiking neuron, cf. Fig. 2). Also, the SST is not maximized at the bursting frequency (10 Hz), but rather at higher frequencies (e.g., 50, 60, 70 and 80 Hz, harmonic frequencies). This may due to the different frequencies of bursting dynamics, that is an interplay of slow (10 Hz) and fast (up to 500 Hz) dynamics. Consequently, from the results obtained using our spiking neuron model, bursting neurons appear more prone to perturbations of spike timing induced by ELF exposure. This suggests that it would be possible to affect brain areas featuring mostly bursting neurons with relatively weak ELF MF exposure.

Hence, at the single cell level, our results bring the following conclusions: first, the perturbation of spike timing is dependent on both ELF MF frequency and neuronal intrinsic spiking frequency. Second, the spiking pattern (in our case, regular spiking or bursting) is crucial in determining the amplitude of the SST. In the following, we move to the level of the neuronal network, in order to understand how the perturbation of activity of single cells may impact network activity at a larger scale, which may be detectable using different brain imaging techniques (e.g., EEG, functional magnetic resonance imaging -fMRI-).

IV. Neural Network Exposure To a Time-Varying Magnetic Field

We simulated the activity of a network of 1000 synaptically interconnected cortical neurons. In this network, 80% of neurons were excitatory and 20% were inhibitory. Each individual neuron was modeled according to the Izhikevich model [21], and field-induced membrane depolarization was introduced into this single cell model as explained in the Materials and Methods section. Each neuron received 100 synaptic afferences from other neurons, these connections being assigned randomly. Every millisecond, a random neuron received an input causing a membrane depolarization of 20 mV to simulate background thalamic inputs [21]. The network was simulated using the Python-based simulator BRIAN [22].

Spike-timing dependent plasticity (STDP, [23]) was included to simulate the dynamic modulation depending on the timing between pre- and post-synaptic spikes. Parameters of the STDP rule were τ_+=20 ms and τ_-=20 ms for the time constants and A_+=0.1, A_-=0.12 for the amplitude of synaptic weight change. Time delays induced by finite conduction speeds of action potentials along axons were assigned randomly between 1 and 20 ms. ELF MF exposure was taken into account as explained in the Materials and Methods section. A proportion of 25% of neurons were affected by ELF MF exposure, to simulate the fact that only neurons with a favorable orientation with respect to the field will be impacted by the exposure. Also, we introduced Gaussian white noise of amplitude was 3 pA for each cell. We focused on the case of an ELF MF of frequency f=60Hz (power-line frequency in North America) and amplitude B_0=50 mT. Indeed, preliminary simulation results indicate that exposure to a 60 Hz, 1.8 mT MF has no significant effect on any of the frequency bands of neural activity [24]. Consequently, we used a more important value that is accessible experimentally (even using small coils) to evaluate its potential effects on collective oscillations.

To evaluate the effect of the 50 mT, 60 Hz exposure on activity of our cortical network model, we simulated 10 minutes of network activity in two conditions: sham (the network was not exposed to the ELF MF) or exposed (25% of neurons were exposed to the ELF MF). For each condition, 40 independent runs of the model were conducted. We computed the power spectrum of neural activity during the last 5 seconds of exposure for each run, and the power in the four main frequency bands was extracted: delta (1-4 Hz), theta (4-8 Hz), alpha (8-12 Hz) and beta (13-30 Hz). Finally, we performed a one way ANOVA for independent variables using SPSS® to determine if the post-exposure power in any frequency band of neural activity had been affected by ELF MF exposure. The threshold for statistical significance was set at its usual value of 0.05. The mean power spectra of neuronal activity for each condition (averaging the 40 "sham" and 40 "exposed" runs) after 10 minutes of exposure are presented in Fig. 5.

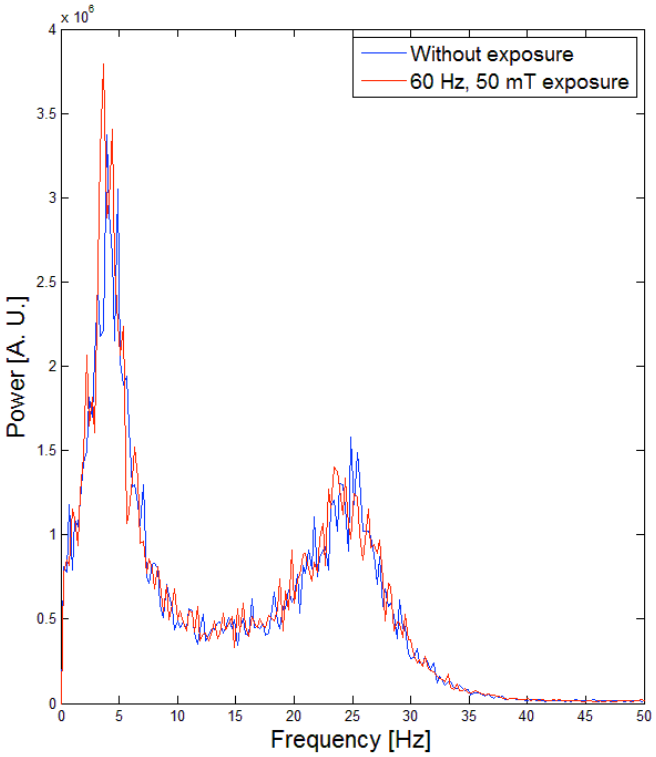

Figure 5: comparison of the average power spectrum of neuronal activity for the "sham" and the "exposed" conditions.

Results from the ANOVA showed that a 10 minutes exposure to a 50 mT, 60 Hz ELF MF does not induce significant changes either in the delta (F=0.047, p=0.83), theta (F=0.953, p=0.33), and beta (F 0.236, p=0.63) bands. Though non

significant, the power in the alpha band had a tendency to be higher in the exposed condition as compared to the sham condition ($F=2.26$; $p=0.13$). This results is encouraging and needs to be further investigated, especially since it has been demonstrated that the stimulus intensity explored here is sufficient to actually modulate the activity of specific neuronal networks in vivo (e.g. Atwell 2003). Additional simulations are therefore needed to better understand the relationship between the stimulus and the network, and to establish a threshold at which a neuronal network consistently respond to an ELF stimulus.

V. Discussion

Our results highlight that neuronal activity is theoretically impacted by ELF MF exposure. First, let us mention that this does not imply that these effects are negative for the biological system. Indeed, it is important to note that a biological effect is not necessarily an adverse effect. Moreover, a biological effect may occur without functional consequences. Nevertheless, these results support the neuromodulation capabilities of ELF stimuli of lower intensity than TMS. This is of strong interest in the perspective of developing alternative strategies to normalize brain rhythms associated with specific neurodegenerative diseases. Furthermore, if our results were confirmed by experimental investigations, this would support the interaction mechanisms we are proposing through our theoretical approach. This in itself would be a major contribution to the scientific literature regarding the effects of ELF on human brain.

Using our biophysical model, we have identified a number of principles that may be used to ends of therapy design. At the cellular level, the exposure effect in terms of perturbation of spike timing depending on the neuron's oscillation frequency and the ELF MF frequency, with maximized membrane response at several MF frequencies that are harmonics of the neuron's oscillation frequency. Indeed, depending on the phase of the oscillation, the neuron membrane may be minimally affected, or can be affected such that spike timing in either advanced or delayed. Also, the spiking pattern appears critical to determine the perturbation's amplitude of spike timing. Thus, brain areas including mostly bursting neurons may be more prone to modulations of their activity induced by ELF MF exposure.

We also presented the first model of its kind investigating the effect of an ELF MF exposure of several minutes inducing realistic levels of electric field and of membrane depolarization on brain tissue, taking into account synaptic plasticity. Our results suggest that an ELF MF of sufficient intensity might be able to impact synaptic plasticity *via* STDP, and that an oscillation frequency range (alpha oscillations) can be modulated by ELF MF exposure. The result that ELF MF exposure might result in modulated brain rhythms is of interest for the development of innovative therapeutic brain stimulation methods, since, as discussed in Section I, numerous neurological disorders are characterized by modified frequencies of neural activity.

Finally, our model could be improved in several ways to model ELF MF interaction with brain tissue in a more physiologically plausible way. First, one may examine the effect of ELF MF exposure depending on the size of the neuronal network. Indeed, in the present paper, we simulated a network of 1000 cortical neurons, but it would be needed to check if our conclusions still hold with larger networks, or using more refined models of neuronal activity such as the Hodgkin-Huxley model. Second, it would be useful to investigate the influence of the ratio of neurons stimulated by the ELF MF on the perturbation of network activity as measured by its power spectrum. Here, we tested a ratio of 25% of the total number of neurons, and we anticipate that, if each neuron was impacted by ELF MF activity, this would have less effect on network activity. Indeed, if either the pre-synaptic or the post-synaptic neuron is affected (and thus the time period between the spikes of pre- and post-synaptic neurons), synaptic weight changes as described by STDP will be different. Conversely, if both are exposed, then the time period separating pre- and post-synaptic spikes will be exactly the same, and the corresponding weight will remain unchanged. Also, one could study how ELF MF exposure modulates the level of synchronization among neurons in the network.

VI. Conclusion

Exposure of brain tissue to ELF MF does, according to our biophysical modeling, induce perturbations of neuronal activity. Indeed, at the single neuron level, the field-induced membrane depolarization is able to advance or delay the timing of spikes, depending the relative phase between the neuron's oscillation phase and the stimulus phase, which depends on neuron's oscillation frequency and stimulus frequency.

Also, we present a plausible mechanism of interaction between ELF MF exposure and brain tissue that might explain in part experimental results. We propose that, following the perturbation of spike timing by ELF MF, synaptic weights time course via spike-timing dependent plasticity is modified, and that these modified synaptic weights determining emergent rhythms in the network result in modulated network rhythms. Consequently, our results suggest that ELF MF exposure might be able to impact brain oscillations (in our example, alpha oscillations). Further work is needed to evaluate which brain oscillations frequency may be selectively modulated (attenuated or augmented, depending on the disease for instance) depending on ELF MF characteristics (e.g., amplitude, frequency).

Finally, our results support that specific ELF MF stimuli could be implemented for therapeutic applications, with the aim of "correcting" pathological brain rhythms characterizing a number of neurological diseases. Convergence of experimental studies investigating human brain activity in response to a variety of ELF MF stimuli on the one hand, and refined biophysical models of ELF MF-brain tissue interaction on the other hand, will significantly advance the development of such therapeutic strategies based on time-varying magnetic stimulation.

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