Pulsed magnetic field exposure induces lasting changes in neural network dynamics

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How extremely low frequency (ELF) electromagnetic fields (such as power line exposure) impacts brain activity is today an intense area of research. One challenge is to unveil transduction mechanisms allowing ELF to interact with brain tissue. Thus, we present a cortical network model receiving internal and external stimuli. Using frequency analysis, we study how these stimuli durably modulate network dynamics depending on exposure duration, stimuli properties and transduction mechanisms. Our results indicate that these stimuli induce different responses in the frequency domain. Ultimately, such models might be useful in evaluating power line exposure thresholds, and in developing innovative brain stimulation methods.

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1. Introduction

There have been a multitude of studies seeking to explain the interaction between weak (< 200 μT) extremely low frequency magnetic fields (ELF MFs) and biologic response [1–3]. Many have demonstrated that ELF MFs can influence opioid-like behavior in animals [4–6] and humans [7]. However, despite the considerable biological evidence, the quest for a transduction mechanism has yielded no conclusive results.

Previous studies suggest that exposure to ELF MFs can influence human brain electrical activity as measured by electroencephalography (EEG), particularly within the alpha-band (8–13 Hz) [8–13]. We previously demonstrated perturbation of human behavior and EEG by a complex pulsed electromagnetic field (PEMF) [15], and that such perturbations are both acute (observed during exposure) [16,17] and residual (after exposure termination) [18]. In the current absence of an accepted mechanism for physical transduction, it may be useful to characterize – and perhaps predict – some of the aforementioned perturbations, which can be performed using biophysical modeling. To achieve this goal, we developed a model of neuronal activity, including neurotransmission and taking into account the interaction with external stimulus. This mesoscopic cortical network model (CNM) possesses many features observed experimentally such as sensitivity to frequencies near 60 Hz [19,20] and neuromodulation due to PEMF [21–23]. With this model as an investigation tool to predict the response of a small neural network exposed to an ELF MF, our aim was to simulate spontaneous network dynamics, driven by a thalamo-cortical input, and then simulate exposure of this cortical network to specific ELF MFs to compare how network activity is affected by the exposure, e.g., potential entrainment to the stimulus or modulation of specific frequency components of membrane potential time course. Such computational models constitute one possible avenue to investigate the plausibility of candidate mechanisms for transduction.

The CNM considered in this paper is based on modeling a population of interconnected cortical neurons. Indeed, since the cortex constitutes the most superficial part of the brain, cortical neurons receive the highest level of exposure. In this model, each neuron is modeled using a simplification [24] of the Hodgkin–Huxley equations [25]. The baseline state of this model, or resting state, is simulated by stimulating randomly chosen individual
neurons to mimic background thalamic influence, as performed in [26]. To study the response of the model to a variety of stimuli, we included in the model the interaction with two types of stimuli: (1) a series of pure sinusoids, and (2) the PEMF. The effects of these stimuli on network dynamics were evaluated by analyzing the average membrane potential of simulated neurons, which may be used to provide a rough estimate of an electroencephalographic measurement (frequency components present in the signal).

2. Methods

2.1. Cortical network model

The well-known Hodgkin–Huxley equations [25] have been long-used as biophysically accurate representations of nerve transmembrane potential at rest and during depolarization. Unfortunately, the Hodgkin–Huxley model is computationally prohibitive, motivating efforts to find simplified yet accurate approximations. The approximation due to Izhikevich [24] is a simple spiking model that meets these criteria. The simple spiking model is a two-dimensional system of ordinary differential equations:

$$\frac{dv(t)}{dt} = 0.04v(t)^2 + 5v(t) + 140 - u(t) + I(t)$$

$$\frac{du(t)}{dt} = a(bv(t) - u(t))$$

where $d/dt$ is the time derivative operator and $t$ is time in milliseconds (ms). The variables $v(t)$ and $u(t)$ represent, respectively, the transmembrane potential in millivolts (mV) of the neuron, and membrane recovery (also expressed in mV) involving activation of the potassium ion current, inactivation of the sodium ion current, and negative feedback to $v(t)$. In Eq. (1), the series of terms $0.04v(t)^2 + 5v(t) + 140$ was derived by fitting the spike initiation dynamics of a cortical neuron [24]. The resting transmembrane potential is between $-70$ and $-60$ mV, depending on the parameter $b$. The threshold for spike initiation lies between $-55$ and $-40$ mV, where the precise value depends on the history of the transmembrane potential prior to the spike. The parameter $a$ relates to the time scale of $u(t)$, and $b$ describes the sensitivity of $u$ to the subthreshold fluctuations of $v$. The variable $l(t)$ makes possible the introduction of currents into the model. These can be currents induced by random thalamic input or spiking input from other neurons in a neuronal network, but also currents induced by external electromagnetic stimuli. After a spike (depolarization) occurs and its apex of $+30$ mV is reached, the membrane voltage and recovery variable are reset according to

If $v(t) \geq 30$ mV then:

$$v(t) \leftarrow -c$$

$$u(t) \leftarrow u(t) + d$$

where $c$ relates to the after-spike reset value of $v(t)$ caused by the fast high-threshold potassium ion conductances; and $d$ describes after-spike reset of $u(t)$ caused by slow high-threshold sodium and potassium ion conductances. Depending on the values of the parameters $a$, $b$, $c$, and $d$, the model can approximate many known types of cortical neurons [24]. The dynamics of the model are shown schematically in Fig. 1. Despite its advantages and its computational efficiency, the Izhikevich model has also some drawbacks. First, the parameters $(a, b, c, d)$ used in the model are not physical, and therefore cannot be related to physiological parameters of the neuron membrane [24]. Second, this model does include a single variable to describe the dynamics of voltage-gated ionic channels; therefore it is not possible to gain insight into the effect of complex stimuli on identified ionic channels as it can be done with the Hodgkin–Huxley model (that includes leak, potassium, and sodium channels).

To create the CNM, the simple spiking model was used to build a network of 1000 neurons, with population and connectivity ratios approximating the mammalian cortex [27]. Eight hundred of these neurons were modeled as excitatory cortical pyramidal neurons exhibiting regular spiking firing patterns, for which the parameters in Eq. (1) were chosen as $[a, b, c, d] = [0.02, 0.2, -65, 8]$. The remaining 200 neurons were modeled with inhibitory characteristics: more specifically cortical interneurons exhibiting fast spiking firing patterns with parameters $[a, b, c, d] = [0.1, 0.2, -65, 2]$ [26]. Each excitatory neuron was connected to 100 neurons randomly selected from the population of all neurons. Each inhibitory neuron was connected randomly to 100 excitatory neurons only. Therefore, each of the 1000 neurons simulated received 100 synaptic afferents, giving a ratio of 1/10. This was used in [26], and is justified by the fact that, in a cortical macrocolumn that contains about 100,000 neurons [28], and each neuron receives on average 10,000 synaptic afferents. By scaling down this cortical macrocolumn by a factor 100, one obtains a network of 1000 neurons with 100 pre-synaptic neurons, which is the size of the network simulated in this paper. Finally, the cortical network model was implemented using Matlab (Mathworks, USA) based on the source code provided by Izhikevich [26] using customized scripts using Matlab's programming language.

2.2. Synaptic plasticity

In order to account for the dynamic regulation of synaptic weights (synaptic plasticity) that has been shown to take place in vivo, and since the modulation of this physiological process might represent a mechanism for MF detection by neural networks, we included synaptic plasticity in our model. In this paper, spike-timing dependent plasticity (STDP) was chosen to describe the modulation of synaptic weights regulated by the timing of spikes. In brief, if a spike arrives from an excitatory pre-synaptic neuron (possibly making the post-synaptic neuron fire), then the synaptic weight is potentiated (strengthened). In contrast, if the spike arrives immediately after the post-synaptic neuron fired, the synaptic weight is depressed (weakened). Even if other types of synaptic plasticity could have been used, we focused on STDP since it is a form of plasticity that has been found to be present in a wide range of brain regions such as the visual cortex, the
The equations governing the additive change 1 and 20 ms, which approximate delays typical of cortico-cortical weights values and to keep synaptic weights in a biologically to 10 mV (as in 8 mV during simulations. The synaptic weights were normalized while the weight of excitatory synapses typically between 4 and weights were set at 6 and 8 mV as in [26], respectively. As in [26, 30], the weight of inhibitory synapses was kept constant; while the weight of excitatory synapses typically between 4 and 8 mV during simulations. The synaptic weights were normalized to 10 mV (as in [26]) in order to simulate a saturation of synaptic weights values and to keep synaptic weights in a biologically plausible range.

Finally, synaptic connections have conduction delays between 1 and 20 ms, which approximate delays typical of cortico-cortical connections [32]. We emphasize that taking into account time delays is crucial when the dynamics of neural networks is studied. Indeed, time delays are known to induce interesting phenomena in dynamical systems such as neuron networks, including induction of oscillatory behavior via a Hopf bifurcation, oscillator death, loss of stability of oscillations [33], constraining the temporal modes of the network, or affect the level of synchronization [34]. Since the EEG originates from synchronized neuronal activity, and since time delays play an important role in the dynamical properties of neural networks such as synchronization, the introduction of time delays is relevant to the main objective of our modeling work: improve our understanding and prediction of EEG data during and after magnetic fields exposure. In our model, we consider that time delays assigned to each connection model finite conduction times along axons. Consequently, these time delays can be seen as the consequence of network topology, chosen as random in our model.

2.3. Pseudo-EEG generation

In experimental measurements, the voltage signals recorded by scalp EEG originate from summation and averaging of activity due to post-synaptic currents from neurons oriented radially relative to the scalp. However, our computerized model does not include spatial information regarding neuron orientation or connectivity. Instead, in our model, we sum voltages (variable $v$) in Eqs. (1) and (2)) from all sub- and super-threshold (firing) neurons. We have computed a variable representative of global membrane depolarization in the network, i.e., the mean membrane potential (MMP) $\mu$, expressed as the mean of the potential over all the neurons of the network:

$$\mu(t) = \frac{1}{N} \sum_{i=1}^{N} v_i(t)$$

Since the signal that is measured in EEG is generated mainly by pyramidal excitatory neurons in the cortex, this mean membrane potential can be viewed as an approximation of a simulated EEG since the network simulated includes 80% of excitatory neurons. Consequently, in the following, we present comparisons between the computed MMP and experimental data (EEG) obtained in humans during pulsed magnetic field exposure [18]. This is interpreted as an instantaneous computer-simulated approximation of an EEG signal (Fig. 2), which should be considered with caution since the spatial scale of EEG is on the order of a centimeter, whereas the scale of our simulated network is on the order of a millimeter. Thus, in reality, the computed average of membrane potentials rather reflects a local field potential (LFP). However, we assume that temporal frequency components (which are the focus of our study) remain comparable at these different spatial scales.

Several mathematical models of brain circuits have been proposed in the literature to realistically simulate the human EEG, mostly using neural mass models [35–37]. In our approach, we focused on a network of spiking neurons including spike-timing dependent plasticity (STDP) to evaluate how the perturbation of spike timing by a complex stimulus (in this case, ELF MF exposure) could affect network dynamics. Let us note that neural mass models could be used to simulate realistically the EEG, but would not allow to study the effects of ELF MF exposure on time-coding or STDP. The use of the Bienenstock, Cooper, and Munro (BCM) rule [38] could, however, represent a possibility to investigate the effects of ELF MF exposure on rate-coding and synaptic plasticity (not STDP since this plasticity rule is dependent on spike timing) in neural mass models.
In Eqs. (1) and (2), the derivative operator was discretized to 1 ms. Thus, analysis of the MMP signal was performed in the Fourier domain with a maximum frequency of $(2\Delta t)^{-1}=500$ Hz. Simulations were conducted on a 4-processor SunFire X2200M2 with 16 GB of RAM. Izhikevich [24] demonstrated previously that the neuron model described by Eqs. (1)–(3) reproduces the diverse behavior of biological neurons, including spiking, bursting, continuous spiking with frequency adaptation, and subthreshold oscillations. Despite this richness, the model allows efficient computer simulations, allowing the simulation of 1000 interconnected neurons over 2 h of simulation time with 1 ms resolution. Simulations were conducted on a multi-core computer, allowing parallelized calculation of the simple frequency response, since each simple stimulus frequency can be simulated independently. Each 1 s of simulation time took 2.5 s real time on a single 2.2 GHz processor.

2.4. Brain model stimulation

To mimic background thalamic influence in the CNM resting state, for each millisecond of simulation time, one neuron is selected randomly and 20 mV (depolarization) are added to its transmembrane potential via the variable $l(t)$ in Eq. (1) [26]. The CNM may also receive synaptic inputs via the variable $l(t)$ in Eq. (1), assuming a capacitive coupling mechanism [39] between synaptic inputs and neurons. External stimuli (simple and complex) are also introduced in the model using the variable $l(t)$ via two different mechanisms (capacitive and inductive coupling): simple stimulation by a pure tone sinusoid (assuming capacitive coupling, meaning that the current received by each cell membrane has the same shape as the stimulus); complex stimulation by the PEMF waveform (assuming capacitive coupling), and complex stimulation by the time derivative of the PEMF waveform (denoted PEMF’) (assuming inductive coupling, meaning that the current received by each cell membrane is proportional to the derivative of the magnetic pulse). More precisely, in the case of the inductive coupling, we assume that the neuron membrane is depolarized by the electric field induced by the ELF MF; whereas in the capacitive coupling, we assume that neuron membrane depolarization has the same waveform than the ELF MF. Let us note that, in our simple model, there was no explicit relationship between magnetic field strength and current intensity. Instead, we have directly used as an input a signal of fixed amplitude determined arbitrarily, and future work should include such a functional relationship. Random background thalamic influence is present even during external stimulation. Prior to exposure to the external stimuli, the CNM was simulated first for 2400 s without stimulation to record “baseline” output.

The baseline activity of the network (or spontaneous activity) was generated by including a random, additive membrane depolarization of 20 mV to a different neuron each ms. Consequently, this random thalamic input is responsible for transient low-frequency bursting taking place at the beginning of the simulation that rapidly disappears towards high-frequency spiking activity. We performed simulations (not shown) in which the level of thalamic input was changed from 18 to 22 mV to confirm that this transition from low-frequency spiking to high-frequency spiking remained qualitatively similar, which was verified. Similarly, setting the initial inhibitory synaptic weights between $-4$ and $-6$ mV resulted in qualitatively similar dynamics (not shown); whereas for excitatory synaptic weights, initial values between 6 and 8 mV also resulted in qualitatively similar dynamics (let us not that, below a value of 6 mV for the excitatory synaptic weights, neuronal firing is sparse and hardly synchronized around any specific frequency band). Therefore, the baseline activity of the model is robust to reasonable parameter variations, either in the depolarizing thalamic input or in excitatory and inhibitory synaptic weights. One possible reason for this stability is that systems with distributed delays are more stable than with discrete delays [33]. Also, in order to be confident in the robustness of the baseline state of the model, we also ran simulation in which neuron parameters were not identical, but instead in which we introduced a variability (in the vein of [24]) of $\pm 10\%$. Again, the qualitative behavior of the network’s spontaneous state with STDP (switching from low-frequency to high-frequency spiking) was robust to these parameter variations.

Simple and complex stimuli injected in the cell membranes have amplitudes (several pA) several orders of magnitude higher than the current amplitude generated by weak time-varying magnetic fields. Indeed, we assume that putative amplification mechanisms, suggested by experimental evidence [40] exist but are not explicitly included in the model. One possible amplification mechanism is stochastic resonance (i.e., the presence of noise in a non-linear system may improve signal-to-noise ratio [41]) that may amplify the effects of an input by a factor up to 1000 for a neural network. The potential amplifying role of stochastic resonance has been emphasized in a study by Jung et al. [42] who illustrated how cooperation processes between network elements, such as in a biological system, resulted in an amplification factor of the input signal.

In our modeling approach, we considered that the magnetic field to which cortical neurons are exposed has a constant value for the whole network. By doing so, we neglect the heterogeneity of the magnetic field as well as the interplay between cortical geometry and field orientation. Furthermore, in a realistic model where the geometry of the skull and cortical surface would need to be taken into account, it would be necessary to consider the boundary conditions of magnetic field transmission at the interfaces. However, we did not include boundary conditions in our study for two reasons: first, since our model represents a very small portion of cortical tissue (less than 1 mm²), the heterogeneity of the magnetic field is not critical and one can safely assume that the magnetic field value is constant on this surface; and second, the EEG originates mainly from pyramidal neurons that are oriented radially (normally) to the scalp. It is well-known from the application of Gauss’s law at an interface that the normal component of the magnetic field flux remains unaffected at an interface. However, the normal component of the magnetic field amplitude may be affected, depending on the magnetic permeability of the considered medium. Interestingly, the magnetic permeability of brain tissue is approximately the same than vacuum [43], thus the normal component of magnetic field amplitude will remain almost unaffected through the different boundaries from outside the body to the cortex. Moreover, since this normal component of magnetic field amplitude is the one that will affect pyramidal neurons because of their radial orientation, the effect of boundary conditions can be safely neglected in a first step. Finally, as mentioned above, exposure of the brain to ELF MFs induces electric fields in brain tissue according to Maxwell–Faraday’s law. In the model presented in this paper, we study the interaction of a network of spiking neurons directly with magnetic fields (capacitive coupling) or with electric fields that result from exposure to external magnetic fields (inductive coupling). An interesting future perspective would be to investigate the possible interaction of electric fields generated by neurons on the activity of neighboring neurons (epiphaptic interactions) that represents a possible amplification mechanism of small electric fields [44].

2.4.1. Exposure to simple stimuli

50 of 1000 total neurons were selected randomly and exposed to pure tone sinusoid stimuli for 500 s (simulation time). The peak
amplitude of the current induced by the sinusoidal magnetic stimulus, and received by the cell, was chosen to be ±10 pA. The MMP signal was recorded throughout exposure to characterize both transient and steady states. Sinusoids from 2 to 200 Hz were applied individually in 1 Hz increments, thus characterizing the response of CNM in that frequency band, as shown schematically in Fig. 2. Analysis of our results (Fig. 3) identified two regions where the CNM demonstrated unusually complex or altered behavior: 2–20, and 50–60 Hz. Simulations were repeated in these two bands with a 0.1 Hz stimulus frequency spacing to further characterize behavior.

2.4.2. Exposure to complex stimuli

50 neurons were randomly selected and exposed to the PEMF stimulus for 2400 s. This duration was selected since our pilot computer simulations (not shown) demonstrated that the CNM took a longer time to reach a steady-state response for the PEMF stimulus than for a pure tone sinusoid. Furthermore, this simulation time approximates the PEMF exposures used in our previous human studies (15 min [18], 30 min [45], and twice-daily exposure of 40 min [46]). Subsequently, the stimulation was terminated, and the CNM was run for another 2400 s to record post-exposure output. The peak amplitude of the current induced by the PEMF was chosen to be ±10 pA. The MMP signal was recorded throughout the 7200 s simulation in order to characterize transient and steady states. In addition to these experiments, in which we assumed a capacitive coupling mechanism between external stimuli and the CNM, we also stimulated the CNM with the time derivative of PEMF (PEMF') according to the same method as the PEMF stimulation but assuming an inductive coupling mechanism in this case. The PEMF and PEMF’ stimuli in the time and frequency domains are shown in Fig. 6, and represent input current to cell membranes. Note that the peak amplitude of PEMF’ ranges between +10 and −20 pA.

3. Results

3.1. Baseline

During the resting state, the CNM was stimulated only randomly to mimic background thalamic influence. In this case, the CNM transiently exhibited rhythms in the 2–4 Hz frequency band. These rhythms disappeared gradually with the continued evolution of synaptic connections (effect of plasticity), and were replaced by rhythms mostly present in the 30–100 Hz (gamma) frequency band but also in the alpha band, as previously reported [26]. This phenomenon occurs because the STDP rule induces a re-organization of synaptic weights in the neuronal network, thus profoundly affecting the CNM dynamics. It is worth noting that alpha and gamma frequency bands are prominent frequencies in human EEG recordings [47].

3.2. Response to a simple stimulus

For each sinusoid frequency, the CNM reached a steady-state asymptotically following approximately 100 s of exposure time. To ensure measurements at steady-state, an additional 400 s of exposure time was simulated, and the last 1 s of simulation time of MMP was then recorded (in 1000 sample points), and frequency-transformed. These response spectra were tabulated for each sinusoid frequency and arranged into an image, presented as Fig. 3.

Frequency-domain analysis of the MMP signal showed that exposure to frequencies between 2 and 20 Hz elicited a complex response with a discrete frequency spectrum, visually discernable to 200 Hz. For all exposure frequencies, the CNM passed the exposure fundamental frequency. In addition, Fig. 3 shows the presence of a first harmonic (up to 100 Hz) and even a second harmonic (up to 60 Hz)—all visually discernable at the 1 Hz stimulus sampling resolution. Analysis of the CNM modulation transfer function (MTF) indicates that the CNM has a tendency to pass low frequencies, but has a notable response peak around 55–60 Hz (Fig. 4). Based on these two simple stimulus frequency

![Fig. 3. Response of the cortical network model (CNM) to simple stimuli. Stimulus sinusoid frequency is indicated on the y-axis with 1 Hz frequency spacing resolution. For each stimulus frequency, the corresponding output is shown after 500 s of stimulus exposure. Output response frequencies – interpreted as the mean membrane potential (MMP) – are indicated on the x-axis after Fourier transform. Output frequency is shown only between 0 and 200 Hz to enhance detail. Dark color indicates greater amplitude in response. The band along the matrix main diagonal (τ) is the modulation transfer function (MTF) which describes how the CNM amplifies or attenuates the stimulation frequency. The darkened color of the MTF indicates presence of the stimulus frequency in the MMP signal. (This is shown in greater detail in Fig. 4.) Harmonics (Ψ) are also visible. Simple stimuli below approximately 20 Hz elicited a wide-band response. The cortical network model also demonstrated sensitivity to simple stimuli of approximately 55–60 Hz. These two frequency bands were analyzed in more detail (see Fig. 5).](image)

![Fig. 4. Modulation transfer function of the brain model in response to simple stimuli. Stimulus sinusoid frequency is indicated on the x-axis with 1 Hz frequency spacing resolution, and response amplitude is indicated on the y-axis. The brain model demonstrated sensitivity to simple stimuli below approximately 5 Hz, and between approximately 55 and 60 Hz.](image)
bands of interest (approximately 2–20 and 50–70 Hz), further simulations were conducted to examine finer structures in the CNM response, sampled at 0.1 Hz stimulus frequency increments (Fig. 5). Below 4 Hz, the CNM does not entrain to stimuli, responding only in accordance with background thalamic random stimulation. Above 4 Hz, the model responds with successive layers of harmonics above the fundamental stimulus frequency. The model demonstrated sensitivity between 52 and 60 Hz, with asymmetric dispersion of frequency response above fundamental stimulus. (See label δ in Fig. 5B.) Thalamic background influence

**Fig. 5.** Response of the cortical network model (CNM) to simple stimuli. Stimulus sinusoid frequency is indicated on the y-axis with 0.1 Hz frequency spacing resolution, and frequency response is indicated on the x-axis: (A) Below 4 Hz (label α), there is no effect of entrainment of the CNM by stimuli, and the CNM is only responding in accordance with background thalamic influence. Above 4 Hz, the model responds with successive layers of harmonics above the fundamental stimulus frequency (fundamental is labeled β); (B) The CNM demonstrated sensitivity between 52 and 60 Hz (label χ), with asymmetric dispersion (label δ) of frequency response above stimulus fundamental (label δ). Thalamic background influence (label ε) is unperturbed up to 60 Hz. Above 60 Hz, the frequency of background increases by approximately 10 Hz (label Φ).

**Fig. 6.** Two complex stimuli were used in our simulations: the PEMF (A) and its time derivative PEMF’ (B). The corresponding frequency spectra are shown in C and D.
is unperturbed for external stimuli below approximately 60 Hz. For external stimuli above 60 Hz, the frequency of thalamic background influence increases by approximately 10 Hz. (See labels e and φ in Fig. 5B.)

3.3. Response to a complex stimulus

Exposure to PEMF (capacitive coupling) and PEMF' (inductive coupling) had immediate effects on the MMP signal. Time domain analysis revealed that the MMP entrained asymptotically to some features of the PEMF signal, as shown in Fig. 7. Fig. 8 shows this evolution in the frequency domain, where frequency content evolves most during the initial 500 s of exposure, with low frequencies entraining first. The CNM also demonstrated residual effects following exposure termination. For PEMF, immediately following exposure termination, the CNM demonstrated broadband suppression of the MMP signal, with an evolving gradual recovery after exposure termination (see Figs. 8 and 9). In contrast, the effects of PEMF' were found to be more subtle, and not apparent in Fig. 8. However, a more detailed perspective is provided in Fig. 9, which demonstrates increased amplitude in the 30−50 Hz frequency band that persisted throughout the exposure duration. Following PEMF' exposure termination, the frequency content returned gradually (but not instantly) to its pre-exposure state. One interesting observation is that, contrary to PEMF exposure, the PEMF' does not affect the whole spectrum of neuronal activity. Instead, only frequencies below or equal to 60 Hz are affected.

3.4. Comparison with EEG data in humans

To evaluate the relevance of our modeling approach and the validity of our results, we compared results for our cortical neural network exposed to the PEMF to experimental data (EEG) acquired in healthy human subjects exposed to the PEMF [18]. To do so, we used the following methodology: from the power spectra shown in Fig. 9, we extracted the following frequency bands of EEG: delta (1−4 Hz), theta (4−7 Hz), alpha (8−13 Hz), beta (13−30 Hz), and gamma (30−100 Hz) in the pre- and post-exposure cases. Then, we computed the difference in spectral

![Fig. 7. Evolution of the cortical network model in response to complex stimulus: (A) Illustrates neuron spiking (black dots) for each neuron (y-axis) as a function of time (x-axis) for 1000 ms of simulation time. For diagrammatic illustration, the neurons are sorted such that excitatory neurons are shown at the bottom, and inhibitory neurons are shown at the top. (B) Illustrates the PEMF used as the complex stimulation, on the same time scale. C, D, and E illustrate the effect of gradual entrainment resulting from continuous exposure to the complex stimulation after 10, 500, and 1200 s of exposure, respectively. For diagrammatic illustration, the stimulated neurons are shown grouped together (identified by the arrow in C).](image-url)
Fig. 8. Evolution of the cortical network model (CNM) activity spectrum in response to PEMF and PEMF’ stimuli. The image shows simulation time on the y-axis, and response – interpreted as the mean membrane potential (MMP) – is indicated on the x-axis after Fourier transform. The CNM evolved in the absence of any external stimulation for the initial 2400 s: (A) Following PEMF stimulus presentation, the response of the CNM evolved in frequency content, stabilizing at approximately 500 s. This was visualized in the time domain as entrainment (Fig. 7). Following cessation of the complex stimulus, the CNM entered a transient period of broad spectrum suppression of the MMP, gradually returning to a pre-exposure frequency profile. See Fig. 9 for additional details (i.e., cross-sections through Fig. 8). (B) Response of the CNM to PEMF’ stimulation was more subtle, and not observable in this presentation. The CNM response to PEMF’ is better visualized in Fig. 9.

Fig. 9. Impact of complex stimulus exposure on frequency characteristics of the cortical network model (CNM) output (MMP), using two different transduction mechanisms: capacitive (PEMF) and inductive (PEMF’): (A) During resting state (Pre-exposure), the model exhibited delta (2–4 Hz), and gamma (30–100 Hz) rhythms. Upon presentation of the PEMF stimulus (at 2400 s), the output was amplified immediately, but did not change shape appreciably. Over time, the output was further amplified and changed shape considerably by 4700 s (2300 s after exposure initiation). (B) The model demonstrated residual effects following termination of the PEMF: a transient broad-spectrum suppression was visible immediately after exposure termination (4800 s); however by 7100 s the output had returned to its pre-exposure shape. C and D correspond to A and B, but for the PEMF’ stimulus. Its effects were not as pronounced as PEMF stimulation. Instead of affecting a large frequency band (from ~0 to 150 Hz), the PEMF’ affects neuronal activity in narrow frequency bands (from ~20 to 40 Hz and from 50 to 60 Hz).
power pre- and post-exposure for each of these frequency bands, providing an estimate of the rate of variation in spectral power for each frequency band. This information is shown in Table 1.

From the results shown in Table 1, one can see that the PEMF complex stimulus induces a drastic decrease in almost all of the EEG frequency bands (except for the delta band) just after the cessation of exposure compared to pre-exposure network activity, with up to a 75% decrease of power in gamma activity. A comparison with the experimental results of EEG recordings in healthy humans exposed to PEMF [18] indicates that our model results do not fit with experimental data. Indeed, such important decreases in spectral power for almost all frequency bands of the EEG have not been observed experimentally [18]. In contrast, our model results just after dPEMF stimulus are more moderate, with a variable direction (increase or decrease) of dPEMF exposure on the spectral power in the frequency bands of EEG activity. While the delta and theta bands appear barely affected by dPEMF exposure, the alpha and gamma bands are moderately decreased (approximately −5% for each) and the beta band is increased of almost 8%. These more modest effects of dPEMF exposure on our MMP signal generated by the model are more likely to be compatible with EEG recordings in humans exposed to the PEMF. However, a comparison with the results of Cook et al. [18] indicates discrepancies with model predictions: indeed, Cook et al. found that alpha activity was significantly increased in regions of the occipital cortex, and with a tendency (p=0.052) to be also increased in regions of the parietal cortex; whereas, in our model, alpha activity is decreased. In [18], the total occipital alpha activity was increased by 25% following PEMF exposure, whereas the modulation of alpha activity induced in our model is a decrease of approximately 41% using the PEMF and 5% using the dPEMF. Finally, the gamma band was shown to be not significantly impacted in [18], and but our model predicts a very modest decrease (less than 5%) in gamma spectral power following PEMF exposure. Consequently, our model results regarding the effect of PEMF on the gamma band of the EEG fits reasonably well with EEG recordings in humans.

The discrepancies observed between EEG data recorded in healthy humans exposed to PEMF [18] can be explained by several factors. First, our model simulates a small number of neurons (1000), compared to the tens of millions of neurons needed to generate a measurable EEG signal. It is likely that increasing significantly the size of the network simulated would have an impact on the results reported. Second, whereas the cortex is not homogeneous in terms of geometry, connectivity and neurophysiological properties of local neurons; our model simulates generic cortical neurons that do not aim to model the behavior of a given brain area. Therefore, our model might not capture the specific properties of connectivity or sub-cortical afferents that could underlie the specific response in the occipital response as observed in [18]. This suggests that in future modeling works it might be useful to incorporate the specific properties of given brain areas in order to perform meaningful comparisons with EEG recordings obtained in humans exposed to PEMF. Finally, our model may lack of existing interaction mechanisms between PEMF and brain tissue that underlie the modulated EEG in humans after PEMF exposure.

4. Discussion

We have found that the CNM exhibits specific behaviors in response to certain stimuli such as sinusoidal stimulation between 2 and 15 Hz and stimulation by a complex waveform. These responses imply a certain degree of entrainment to the stimulation—which in turn implies mass recruitment of neurons and a certain degree of synchronous firing. For simple stimuli presented at low (2–15 Hz) frequencies, the CNM had a discrete wide-band frequency response. The observable responses in the frequency domain suggest the presence of strongly interconnected small groups of neurons having similar conduction delays and capable of firing time-locked spikes—a phenomenon known as polysynchrony [28]. These sequentially firing groups emerge and self-organize gradually in response to certain frequencies as a result of the plasticity characteristics incorporated into the network. Furthermore, as was demonstrated for PEMF, the CNM can retain some characteristics of its stimulated state following exposure termination. This suggests that the PEMF or the PEMF' may durably modify synaptic weights, which are crucial in the generation of neuronal rhythms. It is important to note that the MMP signal represents a summation of v(t) across all neurons and not just firing neurons. For this reason, sub-threshold stimuli are also observable directly within the frequency response. For example, the simple stimulus, which was presented to a small subset of neurons, is observable directly in the frequency domain. It is observed as the diagonal elements of the frequency response. For this reason, sub-threshold stimuli are also observable directly within the frequency response.

In this study, we varied the amplitude of the PEMF signal from 0.5 to 10 mV to evaluate the amplitude at which neural network stimulation would be observed. As previously mentioned, this amplitude is higher than the current induced by exposure to MFs such as the PEMF, but we assumed that amplification mechanisms are at work as experimental and theoretical evidences suggest. We previously investigated the effect of the amplitude of the PEMF needed to obtain network response [48]. In this study, we varied the amplitude of the PEMF signal from 0.5 to 10 mV to evaluate the amplitude at which neural network dynamics is significantly affected. This threshold was found to be approximately 5 mV. A future direction of research could be to study detailed mechanisms underlying possible amplification of the input signal, resulting in a stimulus amplitude at the cell level compatible with this threshold value. Indeed, the effect of ELF MF exposure was modeled as an additive current to the neuron membrane, which is a significant simplification. In order to provide a comprehensive view of the effects of ELF MF exposure on the dynamics on a neural network, it will be necessary to increase the detail of the interaction between ELF MF and neuron membranes, for instance by computing the non-linear membrane depolarization resulting from the electric field induced by ELF MF exposure (for an example, see [49]). Such improvements should lead to an improved fit between model and experimental results.

Table 1

Spectral power for each of the usual EEG frequency bands pre- and post-exposure (duration 2400 s) in the case where target neurons receive the PEMF and derivative of PEMF waveforms.

<table>
<thead>
<tr>
<th>Frequency Band</th>
<th>Pre-exp</th>
<th>Post-PEMF exp.</th>
<th>Variation (%)</th>
<th>Pre-exp</th>
<th>Post-dPEMF exp.</th>
<th>Variation (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>δ (1–4 Hz)</td>
<td>6.7971 x 10^7</td>
<td>5.974 x 10^7</td>
<td>−12.6</td>
<td>6.9732 x 10^7</td>
<td>1.856 x 10^7</td>
<td>−74.6</td>
</tr>
<tr>
<td>θ (4–7 Hz)</td>
<td>4.0399 x 10^7</td>
<td>3.9399 x 10^7</td>
<td>0.27</td>
<td>4.0391 x 10^7</td>
<td>6.0903 x 10^7</td>
<td>10.0</td>
</tr>
<tr>
<td>α (8–13 Hz)</td>
<td>1.3852 x 10^7</td>
<td>1.3852 x 10^7</td>
<td>0.0</td>
<td>1.3017 x 10^7</td>
<td>1.3017 x 10^7</td>
<td>0.0</td>
</tr>
<tr>
<td>β (13–30 Hz)</td>
<td>5.2248 x 10^6</td>
<td>5.2248 x 10^6</td>
<td>0.0</td>
<td>5.9789 x 10^6</td>
<td>5.9789 x 10^6</td>
<td>0.0</td>
</tr>
<tr>
<td>γ (30–100 Hz)</td>
<td>7.561 x 10^6</td>
<td>7.561 x 10^6</td>
<td>0.0</td>
<td>4.9949 x 10^6</td>
<td>4.9949 x 10^6</td>
<td>0.0</td>
</tr>
</tbody>
</table>
Let us note that, in this paper, we quantified the effect of MF exposure by computing the mean membrane potential of neurons in the simulated network, and extracting frequency bands corresponding to the usual classification of EEG frequency analysis. The spectral power in these frequency bands was computed just before and just after MF exposure. One possibility to improve this analysis and to provide a better understanding on the relationship between MF exposure time and the modulation of neuronal dynamics would be to proceed to time–frequency analysis, allowing to quantify the effect of MF exposure over time, such as finding the time needed to reach a new steady state. Indeed, the duration of exposure to an external stimulus such as a magnetic field is a critical factor to consider if its effects are studied. Indeed, if we assume that MF exposure induces changes in spike timing, and therefore, in synaptic weights, than the longer the exposure will be, the more important the change in synaptic weights will be. Since synaptic weights represent coupling variables between neurons’ activity, the distribution of synaptic weights represent a control parameter of network dynamics that can affect qualitatively its dynamics (changes in synchronization, frequency of collective oscillations) [34].

One intriguing observation is that recruitment is enhanced at frequencies similar to those used by the power industry (Figs. 4 and 5). The relevance of this observation is unclear, but warrants further investigation using a refined interaction between the external electromagnetic stimulus and the cortical network. Thus, the presented model should be extended to take into account more rigorously the effect of the electromagnetic stimulus on neuronal membranes (such as membrane polarization, see [49]) or possible fibers activation since axons have a lower threshold for spike initiation [50]. Another issue is that, in this model, the amplitude of currents flowing through cell membranes is several orders of magnitude higher than those induced by the magnetic stimuli applied. This is justified by experimental evidence that neurons are sensitive to currents notably lower than those needed to trigger action potentials, by yet unknown amplification mechanisms.

We demonstrated previously nociceptive and “calming” effects in animals [5,22] and there are corresponding anecdotal reports in humans, during and following exposure to a complex stimulus [46,51,52]. Our CNM demonstrates long-term suppression of gamma rhythms (visualized even at 2400 s post-exposure), with evidence of gradual recovery. Since this phenomenon has not been observed experimentally during previous human studies of PEMF exposure coupled to EEG recordings, we suggest that, based on our modeling results, capacitive coupling is an unlikely mechanism for electromagnetic stimulus transduction. Instead, the inductive transduction mechanism is supported, but may be more difficult to detect in practice since its effects are more subtle, as can be seen in Fig. 9. Furthermore, if the model is robust enough, exposure to the PEMF with inductive coupling (and thus, cell membranes receive a current resembling that of PEMF) should not induce noticeable changes in EEG above 60 Hz. Such a possibility remains to be tested experimentally.

Regarding the observed transient behaviors, future work could determine if transients vary during repeated presentations of PEMF, which could suggest “adaptation” to the signal. Within the limitations of our CNM, these findings provide the beginning of an explanation for our experimental observations of PEMF exposure. Additional EEG experiments and model improvements are required to corroborate our findings; however, our CNM may be useful to narrow search parameters when planning experiments.

The design of our complex stimulus (PEMF) was based on the shape of neuron spikes and inter-spike refractory periods, which vary according to neuron type, as well as considerations for behavior of individual neurons and interconnected groups. The complex stimulus seeks to recruit and entrain specific neuron types according to a desired final effect. However, its design may not be optimal in terms of maximizing specific nerve recruitment while minimizing collateral nerve recruitment (recruitment specificity), or maximizing efficacy across a clinical population. The CNM may be a tool for objective iterative refinement of complex stimuli, or design of new magnetic field pulses for specific effects, provided a quantitative criterion can be established for identifying desirable effects. As an extension of the present work, the variable $l(t)$ in Eq. (1) could be formulated as $l(t) = x_{CAP}(t) + \beta_{IND}(t)$, where $x$ and $\beta$ are capacitive and inductive current coupling constants, respectively, and $I_{CAP}(t)$ and $I_{IND}(t)$ are capacitive and inductive contributions, respectively. It may be possible to investigate the CNM response for different combinations of current coupling constants and compare the CNM output (MMP) with experimental EEG data following PEMF exposure. If a good match is found, this may help elucidate (a) coupling mechanism(s) as well as help with the theoretical design of stimuli to modulate neuronal activity.

5. Conclusion

We have investigated the utility of a computerized cortical network model for bioelectromagnetics applications. Simple and complex stimuli elicited rich responses from the cortical network model, including gradual entrainment to the presentation of a pure tone, and long-term residuals after presentation of a complex signal due to synaptic plasticity—which may be interpreted as the digital equivalent of “memory” or “learning”. Our results highlight that taking into account synaptic plasticity in computational models of brain activity is critical to obtain a comprehensive view of long-term exposure to low-frequency electromagnetic fields. Computational models of brain activity continue to evolve in accuracy and complexity, and we envision them as valuable tools in planning experiments, helping explain the response of the brain to electromagnetic stimulation, and ultimately designing therapies. Another potential application is the evaluation of exposure thresholds above which biological effects might be detected experimentally, such as magnetophosphenes.

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