Magnetophophene perception and associated neurophysiological responses of the human central nervous system exposed to 50 and 60 Hz magnetic fields of up to 50 mT

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SUMMARY

In the Extremely Low Frequency range (ELF), international guidelines on magnetic field (MF) exposure are based on acute 'well-established effects' on the human central nervous system, characterized by the best estimate of retinal magnetophosphene perception threshold. Magnetophosphenes are described as 'flickering-lights' perceived in a dark environment when exposed to a sufficiently strong time-varying MF. Although magnetophosphenes are the most robust exposure-related established effect, the perception threshold at power frequencies (50 and 60 Hz) remains uncertain, since it is based on extrapolated estimates from non-replicated experimental data acquired at lower frequencies. This project is therefore aiming to supplement the results from the literature regarding exposure in the milliTesla range at power frequencies with reliable MF exposure thresholds systematically inducing effects in humans and with plausible mechanisms of action. The main specific objective here is to experimentally test the magnetophosphene detection threshold in humans exposed to MF flux densities between 0 and 50 milliTesla at 50 and 60 Hz. The electrical activity of the brain (electroencephalographic - EEG) and the physiological tremor responses are also investigated. This project is in its early stages, and only preliminary data confirming that the magnetophosphene perception threshold is actually below 50 milliTesla at 50 and 60 Hz, and that human EEG and physiological tremor can be recorded during the exposure periods, are presented here. When completed, this project will provide accurate MF flux density exposure thresholds measured in humans at 50 and 60 Hz systematically inducing magnetophosphene perception and associated changes in EEG, as well as potential physiological tremor and associated EEG changes.

KEYWORDS

Magnetophosphenes, Threshold, Power-line frequency magnetic field, 50 milliTesla, Human exposure, Neurophysiological responses

INTRODUCTION

Many studies suggest neuromodulatory effects (i.e. modifications of electrical, metabolic, or chemical processes taking place in the central nervous system as a consequence of an exogenous stimulus) due to electric fields induced by time-varying magnetic fields (MF) exposure in the Extremely Low Frequency range (ELF, < 300 Hz, see [1-3] for review). For instance, electroencephalography (EEG) is the central nervous system biomarker that has probably been studied the most in the context of ELFMF research. Although the literature results are very heterogeneous (partially because of the wide variety of protocols used), the most consistently reported effect on EEG is an increase of the resting occipital alpha rhythm (8-12 Hz) as a consequence of exposure [4, 5]. It is interesting to note here that these reported effects are persistent (i.e., outlast the duration of exposure), since in most cases the EEG cannot be recorded during the ELFMF exposure conditions due to MF-induced signal artefacts. Other studies have focused on human motor or cognitive behaviour and possible exposure effects on physiological baselines and performances. In terms of motor control, results show that an ELFMF exposure can, under certain circumstances, reduce the normal antero-posterior standing balance [6, 7] or modulate physiological tremor amplitude [7-9] in healthy volunteers. Vestibular-related postural responses and vertigo have also been reported as a consequence of moving the head in the strong static magnetic field of a Magnetic Resonance Imaging (MRI) scanner [10, 11]. In terms of cognition, disruptions in attention and working memory were reported with exposures as low as 0.6 milliTesla (mT) at 50 Hz [12], and our group has also observed changes in short-term memory processes with a one hour, 3 mT exposure at 60 Hz [13]. More specifically, this last result suggests a cancellation, with ELFMF exposure, of the performance improvement classically associated with the repetition of a task. It is interesting to notice that this same interference in performance improvement has also been reported in a reaction time task when given before and after a 1 hour exposure to a 1.26 mT MF at 45 Hz [14]. A movement-induced time-varying MF exposure tested in an MRI environment has been reported to impact neurocognitive performance as well [15]. Post-exposure persistent effects have also been observed using functional Magnetic Resonance Imaging (fMRI) in a standard finger tapping task: specific brain regions displayed higher levels of activation after one hour of exposure to a 60 Hz, 1.8 and a 3 mT MF (2 different experiments) as compared to after a sham condition [16]. One of the putative mechanisms potentially supporting these observations could involve an increase in cortical excitability due to synaptic plasticity processes (i.e., dynamic changes in synaptic efficiency). Capone et al. have tested this hypothesis and have shown that a pulsed MF (peak value 1.8 mT) delivered during 45 minutes can indeed have a persistent effect by increasing cortical excitability [17]. Interestingly, MRI imaging procedures given in a 1.5 and 7T scanner have also been shown to impact cortical excitability in healthy volunteers [11].

Put together, these effects suggest that an ELFMF stimulus in the mT range could be capable of having a persistent effect (in the order of minutes) on neurophysiological processes and behaviours, which could be interpreted as the consequence of synaptic plasticity modulations. ELFMF exposure induces an electric field as described by Maxwell-Faraday’s law, resulting in an additive cell membrane potential perturbation [18, 19] dependant on neuronal morphology and electric field orientation [20]. For ELFMF exposure in the low mT range, this membrane perturbation is insufficient to trigger action potentials, but might play a role in synaptic communication [21-23]. Synaptic processes can indeed be affected by a presynaptic membrane depolarization of 1 mV, while a depolarization as little as 60 μV seems to be capable of affecting the synapses in the retina [24-26], and to give rise to the perception of phosphenes. Magnetophosphenes are described as flickering visual perceptions and are the most well-established and consistent biological effect of ELFMF on human neurophysiology [22, 23, 27]. Following the work from Lövsund et al. [28], Silny reported human perception of magnetophosphenes induced by an intermittent 1 hour ELFMF between 10 and 20 mT (frequency range = 5-60 Hz) [29]. In the same study, an effect of exposure was reported on visual evoked potentials (VEP) lasting past the end of the exposure period, suggesting a persistent effect and thus a possible impact on synaptic plasticity.

Both ICNIRP and IEEE recommendations/guidelines aim to protect individuals against adverse health effects [21, 22] of electromagnetic fields (EMF) exposure. The threshold for magnetophoshene perception is estimated to be the lowest at 20 Hz (between 5 and 10 mT - 50 to 100 V/m of induced E-field – 10 to 14 mA/m^2 of induced current density) and then to increase with frequency [21, 22, 28-31]. Although magnetophosphenes are the most robustly exposure-related established effect, the perception threshold at power frequencies (50 and 60 Hz) remains uncertain, since it is based on estimates extrapolated from non-replicated experimental data acquired at lower frequencies.

Our current project aims to: 1) establish the magnetophosphene perception threshold at 50 and 60 Hz in healthy volunteers; 2) simultaneously study the electroencephalographic (EEG) response in corresponding brain regions, 3) study the impact of the same stimulus on physiological tremor, which is another highly sensitive neurophysiological indicator.

MATERIAL AND METHODS

Two exposure systems have been designed and developed for this project: a local head exposure system and a global head exposure system. Both systems are controlled using a LabView™ program driving a MTS™ Magnetic Resonance Imaging gradient amplifier capable of delivering up to 200 A (rms) at ± 345 V (MTS Automation 433 Caredean Dr. Horsham PA). First, the local exposure system consists of a 176 turn coil (16 layers of 11 turns each – 6 cm inner diameter and 22 cm outer diameter) made of hollow square copper wire cooled by circulating water (Figure 1, right). This coil allows MF exposures between 0 and 100 Hz up to 50 mT at 3 cm from the coil side without any perceptible noise or vibration produced. Second, the global exposure system consists of a set of two 50 cm diameter 22-turn coils separated by 25 cm, positioned parallel to the ground at the head level, centered with the eyes, which allows homogeneous exposure at 50 and 60 Hz of up to 50 mT (± 5% across the human brain and eyes – Figure 1, left). The MTS constant-current amplifier drives the required current trough a transformer and a set of capacitors, pushing up to 650 A (rms) in the coils at full power. The global exposure system is developed in collaboration with the Research Institute of Hydro-Québec (Dr. Duc Nguyen – IREQ). Volunteers will wear earplugs to prevent them from earing the small "buzz" produced by the coils during exposure. The distributions of the MF produced by both coil systems, calculated using the 'Biot and Savart Law', are presented in Figure 1. Calculations have been confirmed by measurements made using a single axis MF Hall transducer (± 200 mT range with 0.1 % accuracy- Senis™ 0YA05F-C.2T2K5J probe, GMW Associates, San Carlos, USA).

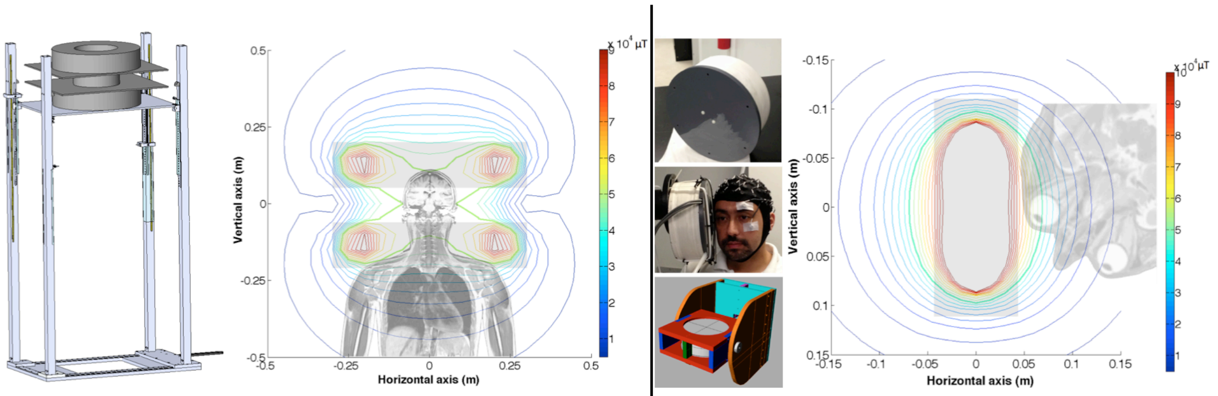

Figure 1: **Left section** - A graphic sketch of the global exposure system. The left graph represents a scaled coronal view of a human anatomical image superimposed to the field distribution, as calculated using the 'Biot and Savart Law', produced by our global head exposure system (represented by the 2 horizontal transparent grey rectangles). The head of the subject is exposed to a homogeneous 50 mT MF (5 mT contour lines). **Right section** - Our local exposure coil. A scaled representation of a transversal slice of human head is superimposed with the field distribution, calculated using the 'Biot and Savart Law', is presented in the right graph. The vertical transparent grey rectangle represents the coil dimensions. The exposed eyeball is non-homogeneously exposed to 50 mT at 50 and 60 Hz.

Two separate experimental protocols detail these objectives; both are approved by the Western University ethics board (HSREB #18882 and #103066). The first protocol tests 2 groups of volunteers (n = 25 at 60 Hz, n = 5 at 50 Hz), each tested in 2 local exposure conditions (eyeball and occipital cortex using the small coil) and 1 entire head exposure condition, each scanning 11 magnetic flux density conditions (0 to 50 mT, 5 mT increments). Each flux density condition is repeated 5 times (random order) and separated with 5 seconds without exposure. Tested volunteers report magnetophosphene perception by button-press, while their occipital EEG activity is continuously recorded (MRI-compatible EEG system, caps, and cables allowing recordings of EEG and ECG during 50 mT exposure - Neuroscan-Compumedics Inc, Melbourne, Australia). Magnetophosphene perception is expected to be associated with an EEG alpha spectral power decrease (8-12 Hz).

The second protocol involves a local motor cortex exposure, and primarily aims to establish a magnetic flux density threshold at 60 Hz showing a systematic modulation in human brain, muscle and/or physiological tremor activity. This pilot study consists in testing the physiological tremor recorded at the tip of the dominant index finger (Microlaser sensor LM10, series ARN11, Matsushita Electronic Work, Ltd., Osaka, Japan – 5 µm resolution), the associated electromyographic (EMG - extensor carpi radialis) and EEG activity (sensorimotor cortex region), under the 0-50 mT flux density scanning protocol described above. We anticipate an increase of physiological tremor amplitude and associated electrophysiological signals at the flux density corresponding to the magnetophosphene perception threshold.

PRELIMINARY RESULTS

Although the experiments have not started yet, we have started testing volunteers acquiring pilot data to test our protocols. All the volunteers we have pilot tested so far (n=9) have reported visual perceptions qualified as being magnetophosphenes, both at 50 and 60 Hz, for flux densities reaching 50 mT. Tremor and EEG data have been acquired in both phantoms and humans before, during and after the exposure conditions to test for MF artefacts in the data (button-press has also been tested). Analyses confirm that all the data, including EEG data (which are the most prone to distortion due to electromagnetic noise/interference), are artefact-free in the frequency ranges of interest, even during MF exposure conditions. Various Fourier and wavelet based filtering procedures have been tested and are very effective in removing the 50 and 60 Hz contaminations. Regarding the magnetophosphenes protocol, post-processed preliminary data show the absence of exposure-induced artefacts in the EEG data while recorded during exposure, both in a phantom and in a volunteer (presented in Figure 2). The data also show a decrease in alpha EEG activity in the 50 mT exposure condition at 60 Hz. Physiological tremor time series recorded before, during and after the MF exposure conditions of up to 50 mT are also artefact-free and can be used for both individual and group analyses (see Figure 3 for an example).

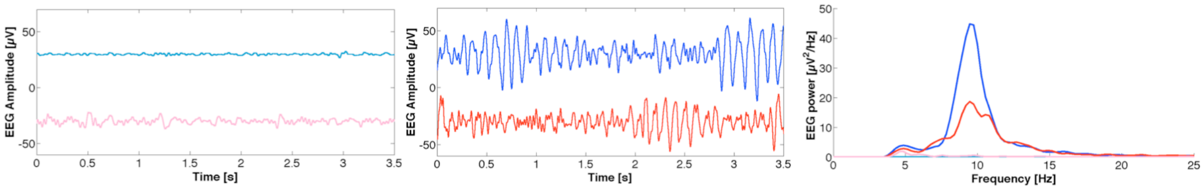

Figure 2: Band-pass filtered (4 – 45 Hz) EEG (O2 electrode) recorded in an organic phantom (watermelon - left) and a subject (middle) with the 50 mT, 60 Hz exposure OFF (blue lines) and ON (red lines). Averaged power spectra (5 repetitions/condition) show decreased EEG alpha activity (8-12 Hz) in the exposed subject. Phantom data and power spectra show artefact-free EEG in the alpha band.

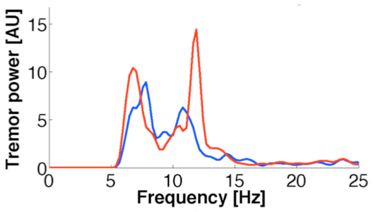

Figure 3: Averaged tremor power spectra (5 repetitions/condition) in the 50 mT, 60 Hz exposure OFF (blue) and ON (red) conditions. Increased power can be visualized near 12 Hz. Simultaneous EEG and EMG data have also been collected but are not presented here.

CONCLUSION

We have demonstrated the feasibility of our protocols and have initiated preliminary data collection in order to test the human central nervous system responses to 50 and 60 Hz MF exposures of up to 50 mT. To date, all the subjects who went through the protocol were able to describe MF exposure-induced magnetophosphene perceptions when exposed at eyeball-level, in a dark environment, to flux densities approaching 50 mT. The perception is mostly described as a vibration of the visual flux (in various locations of the visual field) starting and stopping at the onset and the offset of the MF exposure. More specifically, we have demonstrated so far that we can produce local and global head MF exposures of up to 50 mT in the 0-100 Hz frequency rang, that artefact-free EEG data are available without and with MF exposure, that artefact-free tremor data are available without and with MF exposure, that we can systematically induce magnetophosphene perception at 50 and 60 Hz at 50 mT (20 Hz also tested), and will we therefore be able to detect individual and group threshold values. The protocol tested in 1 preliminary subject suggests a decrease in EEG alpha activity measured in the occipital cortex, which would be, if confirmed when the project will be completed, coherent with our hypotheses.

We are therefore confident that this project will lead to the establishment of reliable well-characterized acute effects as a consequence of ELFMF exposure. This should provide new experimental evidences supporting a plausible underlying interaction mechanism, which we propose to related to modulations of synaptic plasticity processes, with the support of theoretical modeling [19, 32]. Indeed, mathematical models mimicking neuronal activity at various spatial and temporal scales offer an opportunity to approach the mechanisms of action from a complementary perspective. Computational neuroscience models describe neuronal electrical activity (e.g., generation and propagation of action potentials) using validated equations simulating synaptic communication [33]. With our already initiated mathematical modeling work to explore the interaction between ELFMFs and brain activity [19, 34, 35], we show that lasting changes may be induced in neuronal activity by specific stimuli [35], and that ELFMF exposure can theoretically impact single neurons' activity predominantly in two frequency bands: 60-70 Hz and 100-120 Hz, confirming earlier findings [18]. These are converging evidence of the theoretical capability of an ELFMF in the mT range (10 mT and higher) to sufficiently depolarize neuronal membranes to impact their spike timing, which is critical since a well-characterized form of synaptic plasticity, termed 'spike-timing dependent plasticity' (STDP), is a function of the timing between pre-/post-synaptic spikes [36]. The plausible chain of events here would suggest that induced electric fields from ELFMF could cause a membrane depolarization capable of changing spike timing and thus synaptic plasticity. If this hypothesis can be further confirmed, it would not only identify a plausible biological chain of events describing the interaction between ELFMF and the human central nervous system, thereby bringing a precious contribution available to international regulators; but it would also pave the way for novel non-invasive medical and/or performance-related translational applications.

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BIBLIOGRAPHY

[1] C.M. Cook, D.M. Saucier, A.W. Thomas, et al., "Exposure to ELF magnetic and ELF-modulated radiofrequency fields: The time course of physiological and cognitive effects

observed in recent studies (2001-2005)". (Bioelectromagnetics number 27(8), May 24 2006, pages 613-627).

[2] C.M. Cook, A.W. Thomas and F.S. Prato, "Human electrophysiological and cognitive effects of exposure to ELF magnetic and ELF modulated RF and microwave fields: a review of recent studies". (Bioelectromagnetics number 23(2), Feb 2002, pages 144-157).

[3] V. Di Lazzaro, F. Capone, F. Apollonio, et al., "A consensus panel review of central nervous system effects of the exposure to low-intensity extremely low-frequency magnetic fields". (Brain Stimul number 6(4), Jul 2013, pages 469-476).

[4] S. Ghione, C.D. Seppia, L. Mezzasalma, et al., "Effects of 50 Hz electromagnetic fields on electroencephalographic alpha activity, dental pain threshold and cardiovascular parameters in humans". (Neurosci Lett number 382(1-2), Jul 1-8 2005, pages 112-117).

[5] C.M. Cook, A.W. Thomas and F.S. Prato, "Resting EEG is affected by exposure to a pulsed ELF magnetic field". (Bioelectromagnetics number 25(3), Apr 2004, pages 196-203).

[6] A.W. Thomas, D.J. Drost and F.S. Prato, "Human subjects exposed to a specific pulsed (200 microT) magnetic field: effects on normal standing balance". (Neurosci Lett number 297(2), Jan 12 2001, pages 121-124).

[7] A. Legros, M. Corbacio, A. Beuter, et al., "Neurophysiological and behavioral effects of a 60 Hz, 1,800 muT magnetic field in humans". (Eur J Appl Physiol number 112(5), May 2012, pages 1751-1762).

[8] A. Legros, P. Gaillot and A. Beuter, "Transient effect of low-intensity magnetic field on human motor control". (Med Eng Phys number 28(8), Oct 2006, pages 827-836).

[9] A. Legros and A. Beuter, "Effect of a low intensity magnetic field on human motor behavior". (Bioelectromagnetics number 26(8), Dec 2005, pages 657-669).

[10] P.M. Glover, I. Cavin, W. Qian, et al., "Magnetic-field-induced vertigo: a theoretical and experimental investigation". (Bioelectromagnetics number 28(5), Jul 2007, pages 349-361).

[11] L.E. van Nierop, P. Slottje, H. Kingma, et al., "MRI-related static magnetic stray fields and postural body sway: A double-blind randomized crossover study". (Magn Reson Med number 70(1), Jul 2013, pages 232-240).

[12] A.W. Preece, K.A. Wesnes and G.R. Iwi, "The effect of a 50 Hz magnetic field on cognitive function in humans". (Int J Radiat Biol number 74(4), Oct 1998, pages 463-470).

[13] M. Corbacio, S. Brown, S. Dubois, et al., "Human cognitive performance in a 3 mT power-line frequency magnetic field". (Bioelectromagnetics number 32(8), Dec 2011, pages 620-633).

[14] E. Lyskov, J. Juutilainen, V. Jousmaki, et al., "Influence of short-term exposure of magnetic field on the bioelectrical processes of the brain and performance". (Int J Psychophysiol number 14(3), May 1993, pages 227-231).

[15] L.E. van Nierop, P. Slottje, M.J. van Zandvoort, et al., "Effects of magnetic stray fields from a 7 tesla MRI scanner on neurocognition: a double-blind randomised crossover study". (Occup Environ Med number 69(10), Oct 2012, pages 759-766).

[16] A. Legros, J. Miller, J. Modolo, et al., "Multi-modalities investigation of 60 Hz magnetic field effects on the human central nervous system". (Electra number 2562011, pages 4-18).

[17] F. Capone, M. Dileone, P. Profice, et al., "Does exposure to extremely low frequency magnetic fields produce functional changes in human brain?". (J Neural Transm number 116(3), Mar 2009, pages 257-265).

[18] M. Gianni, M. Liberti, F. Apollonio, et al., "Modeling electromagnetic fields detectability in a HH-like neuronal system: stochastic resonance and window behavior". (Biol Cybern number 94(2), Feb 2006, pages 118-127).

[19] J. Modolo, A.W. Thomas and A. Legros, "Neural mass modeling of power-line magnetic fields effects on brain activity". (Front Comput Neurosci number 72013, pages 34).

[20] T. Radman, R.L. Ramos, J.C. Brumberg, et al., "Role of cortical cell type and morphology in subthreshold and suprathreshold uniform electric field stimulation in vitro". (Brain Stimul number 2(4), Oct 2009, pages 215-228, 228 e211-213).

[21] ICNIRP, "Guidelines for limiting exposure to time-varying electric and magnetic fields (1 Hz to 100 kHz)". (Health Phys number 99(6), Dec 2010, pages 818-836).

[22] IEEE, "C95.6 - IEEE Standard for safety levels with respect to human exposure to electromagnetic fields, 0-3 kHz". (IEEE: New York number 2002).

[23] WHO, "Extremely Low Frequency Fields Environmental Health Criteria Monograph No.238", (W. Press, WHO: Geneva, 2007).

[24] R.W. Knighton, "An electrically evoked slow potential of the frog's retina. II. Identification with PII component of electroretinogram". (J Neurophysiol number 38(1), Jan 1975, pages 198-209).

[25] R.W. Knighton, "An electrically evoked slow potential of the frog's retina. I. Properties of response". (J Neurophysiol number 38(1), Jan 1975, pages 185-197).

[26] J.P. Reilly, "Neuroelectric mechanisms applied to low frequency electric and magnetic field exposure guidelines--part I: sinusoidal waveforms". (Health Phys number 83(3), Sep 2002, pages 341-355).

[27] ICNIRP, "Guidelines for limiting exposure to time-varying electric, magnetic, and electromagnetic fields (up to 300 GHz). International Commission on Non-Ionizing Radiation Protection". (Health Phys number 74(4), Apr 1998, pages 494-522).

[28] P. Lovsund, P.A. Oberg, S.E. Nilsson, et al., "Magnetophosphenes: a quantitative analysis of thresholds". (Med Biol Eng Comput number 18(3), May 1980, pages 326-334).

[29] J. Silny. The Influence of the Time-Varying Magnetic Field in the Human Organism. in Biological Effects of Static and Extremely Low Frequency Magnetic Fields. (Neuherberg: MMV Meizin Verlag München, 1986).

[30] A. Hirata, Y. Takano, O. Fujiwara, et al., "An electric field induced in the retina and brain at threshold magnetic flux density causing magnetophosphenes". (Phys Med Biol number 56(13), Jul 7 2011, pages 4091-4101).

[31] R.D. Saunders and J.G. Jefferys, "A neurobiological basis for ELF guidelines". (Health Phys number 92(6), Jun 2007, pages 596-603).

[32] J. Modolo, A.W. Thomas and A. Legros, "Possible mechanisms of synaptic plasticity modulation by extremely low-frequency magnetic fields". (Electromagn Biol Med number 32(2), Jun 2013, pages 137-144).

[33] A. Destexhe, Z.F. Mainen and T.J. Sejnowski, "Synthesis of models for excitable membranes, synaptic transmission and neuromodulation using a common kinetic formalism". (J Comput Neurosci number 1(3), Aug 1994, pages 195-230).

[34] J. Modolo, A.W. Thomas, R.Z. Stodilka, et al. Modulation of Neuronal Activity With Extremely Low-Frequency Magnetic Fields: Insights From Biophysical Modeling. (IEEE 5th international conference on bio-inspired computing, Liverpool, 2010).

[35] R.Z. Stodilka, J. Modolo, F.S. Prato, et al., "Pulsed magnetic field exposure induces lasting changes in neural network dynamics.". (Neurocomputing number 74(12-13), 2011, pages 2164-2175).

[36] W. Gerstner, R. Kempter, J.L. van Hemmen, et al., "A neuronal learning rule for sub-millisecond temporal coding". (Nature number 383(6595), Sep 5 1996, pages 76-81).