Biomedicine and Molecular Biosciences

COST Action BM1309 EMF-MED

COST EMF-MED

European network for innovative uses of EMFs in biomedical applications

Working module proposal

Effect of stimulus waveform to nerve excitability

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1. Working module description

Generally speaking, electrostimulation refers to excitable tissue stimulation by using electrical energy, either by using direct contact with current source or by exposure to external electromagnetic fields (EMFs). Regardless possible beneficiary effects (induced by controlled, intentional exposure) or adverse side-effects (induced by uncontrolled, unintentional exposure) the stimulus waveform plays very important role and its influence on overall neurophysiologic response has to be determined, regarding both beneficiary and/or adverse outcomes. However, numerous studies related to stimulus waveform effects mainly deal with a specific neurophysiologic responses which are observed individually (such as selective stimulation, nerve type or brain region selectivity, energy efficiency, adverse electrochemical effects at electrode-tissue junction, etc.) and basically encompass few standard stimulating signal types (monophasic or biphasic rectangular or sinusoidal pulses with eventual variations regarding signal slope in terms of exponential or ramp rise/fall times).

Studies related to this working module (WM) will aim to encompass stimulation equipment optimization (stimulators and current electrodes, especially regarding energy efficient stimulation and adverse effects reduction) as well as resulting excitable tissue responses, by considering several neurophysiologic effects such as:

- spatial/temporal nerve selectivity and specific nerve type selectivity;
- known, but insufficiently investigated phenomena related to nerve excitation, especially:
    - action potential phase locking and rate modulation;
    - subthreshold superexcitability;
    - synaptic interactions (temporal/spatial integration at synapse).
- integration effects related to interplay among numerous mutually connected nerves.

The main intention is to encompass fundamental research related to these effects, both individual and combined.

These studies will be primarily related to optimization of Functional Electrical Stimulation (FES) procedure, since it includes quite demanding tasks related to controlled stimulation such as: long stimulation period, spatially selective nerve stimulation, individual nerve type recruitment, full muscle contraction control, etc. However, it can be assumed that results obtained from these studies will give rise to new insights that could be utilized in even more demanding Central Nervous System-CNS stimulations (related to brain region selectivity and cortical/subcortical mapping, focal magnetic stimulation optimization, pain control during electroconvulsive therapy (ECT), etc.).

The optimization of nerve response should be achieved by finding optimal stimulus waveform that would result in optimized neurophysiologic response (e.g. smooth and well controlled muscle contractions in FES with reduced adverse effects). Optimization by stimulus waveforms is especially attractive since waveform parameters can be software-controlled without necessities for possible invasive techniques. However, application of a specific waveform for possible beneficiary effects, related to mentioned neurophysiologic responses, should not induce adverse side-effects. Thus, this study will also encompass investigation of possible adverse side-effects caused by specific stimulus waveform, such as:

- adverse electrochemical reactions at electrode-tissue junctions;
- fatigue and accommodation of stimulated nerves;
- early axonal degeneration (EAD);
- muscle fatigue;
- uncontrolled stimulation and responses at spatially distant body parts.

By encompassing both positive and negative stimulation effects, the stimulus waveform that would present an optimal tradeoff between beneficiary (therapeutic) and adverse side-effects, could be suggested.

Beside some typical stimulus waveforms used in FES, the WM would include stimulation by long-duration, repetitive, amplitude-modulated signals, which are not sufficiently covered in published scientific studies.

The studies related to this WM will be based on:

- experiments that involve *in vitro*, animal and/or human (*in vivo*) studies, which will be based on recently developed arbitrary-waveform constant-current stimulators (aimed for medical approval);
- complex, realistic human and animal body simulation models (*in silico* studies), based on multiphysics platforms (such is recently introduced *Sim4Life* simulation software);
- possible stochastic (rather than purely deterministic) approach that would encompass statistical variation in neurophysiologic response with respect to probability of action potential generation, spatial/temporal integration effects in nerve bundle and synapse and, finally, statistical variations among individual organisms.

2. State-of-the-art review

Electrostimulation of excitable tissues (nerves and muscles) has been extensively used for therapeutic, diagnostic and experimental purposes [1]. Regarding PNS (Peripheral Nervous System), electrostimulation of peripheral nerves has been widely used for diagnostic purposes (SD curve procedure), pain management (Transcutaneous Nerve Stimulation - TENS [2]) as well as for restoring functions in the upper and lower extremity, bladder and bowel, and respiratory system (FES) [3]. Regarding CNS, both invasive and noninvasive techniques (Transcranial magnetic stimulation - TMS, Transcranial electric stimulation - TES, Functional Magnetic Resonance Imaging - fMRI, Deep Brain Stimulation - DBS, Transcranial Direct-Current Stimulation - tDCS, etc.) have been applied for neurophysiologic monitoring, cortical/subcortical mapping, treatment of CNS disorders, etc. [4, 5, 6]

Depending on purpose, all of these procedures involve wide variety of stimulus waveforms that are applied to achieve desirable neurophysiologic response (muscle contraction control, pain reduction, specific brain region activation, etc.). Neurophysiologic responses with respect to stimulus waveforms, regarding PNS stimulation, were mainly studied for FES purposes. Regarding CNS stimulations, the impact of stimulus waveform has been studied with respect to brain region selectivity [4, 5], focal magnetic stimulation optimization [7], pain control during electroconvulsive therapy (ECT) [8], etc.

Generally, stimulus waveforms can be monophasic and biphasic. Although it is well-known that monophasic stimuli will result in more effective nerve stimulation when compared to equivalent biphasic stimuli (considering single axon and ideal electrode-tissue connection), the biphasic waveforms are usually used for FES since they provide:

- greater spatial and threshold separation selectivity regarding electrode to nerve distance and stimulus amplitude to maximum recruitment level relation [9];
- wider fiber diameter selectivity, regarding reversal recruitment phenomena related to artificial nerve stimulation [10];
- avoidance of electrochemical products buildup at tissue-electrode junction that may interact with surrounding tissues [11], [12].

Regarding waveform shape, it is also well-known that rectangular pulses will result in the lowest possible stimulus (current) threshold levels. However, it has been shown [13] that signals with very short rise times could cause negative tissue-electrode junction properties in means of high transient impedance, low energy efficiency and adverse electrochemical reactions. The pulses with finite slope (Gauss pulses, ramp and trapezoidal signals) were reported to be more energy efficient but could also cause nerve accommodation. It is also known that asymmetrical, but charge-balanced biphasic pulses, with exponentially decreasing anodic phases (as well as signals with long-duration/low-amplitude [14] or decreasing staircase [15] or trapezoidal [16] anodic phases) can create efficient anode block with lesser charge injection which can be used to achieve stimulation selectivity. Regarding other waveform parameters, stimuli with shorter phase duration will result in higher stimulus threshold level [1], but will also provide greater spatial selectivity. Other stimulation waveforms, based on different subthreshold prepulses, are given in [17].

The impact of higher frequency (kHz region), repetitive signals (including possible amplitude modulation) are not well studied from the FES point of view. Generally, high frequency stimuli can result in more natural and more pleasant feeling during TENS or FES stimulations [2], although fundamental explanation for such behavior is not documented. High frequency sinusoidal signals can affect the number of generated action potentials, depending on current amplitude (action potential phase locking) but can also inhibit action potential propagation initiated elsewhere on the axon [1]. The impact of amplitude modulated signals was thoroughly studied in [18], from the human exposure to EMFs point of view, where it was found that amplitude modulated signals with favorable envelope characteristics can result in the same or even lower stimulus threshold level, when compared to a pure sinusoidal signal with the same amplitude.

Other reported excitation phenomena, such as subthreshold superexcitation [19] and synapse interactions are not well studied (not even at a fundamental scale) [1], and effect of stimulus waveform on these phenomena should be considered, especially since these phenomena could be used for improved stimulation/response control.

3. Gaps, challenges and objectives to be achieved

The neurophysiologic responses, which arise as a consequence of external stimulation, have been analyzed for a limited number of stimulation waveforms that mainly involved single monophasic or biphasic (mainly charge-balanced) pulses. The experimental *in vivo* studies (including both animal and human subjects) have determined the impact of some basic stimulus waveforms on few neurophysiologic effects regarding stimulus threshold levels, spatial nerve selectivity and nerve type selectivity, as well as some adverse electrochemical effects at tissue-electrode junction. From the stimulation equipment point of view, the energy efficient waveforms (for battery supplied stimulators with specific current electrode geometries) were investigated.

The main drawback of these studies is that observed effects were mainly considered as individual phenomena. However, even if a specific stimulus waveform was proved to be an optimal choice for a specific neurophysiologic effect, it could cause non-optimal, unwanted or even adverse (neuro)physiologic effects at other body parts (for example, monophasic pulses will provide lower stimulation threshold levels when compared to biphasic stimuli but will also provide inferior nerve selectivity and more pronounced adverse electrochemical reaction; by applying long-duration, high-frequency stimuli one can achieve better control over temporal action potential integration but these signals will be energy inefficient and can result in more pronounced nerve fatigue, etc.). Therefore, it would be convenient to determine the optimal stimulus waveform (as well as optimal waveform parameter values) that would result in a required neurophysiologic effect (e.g. optimal control of muscle contraction during FES). However, the optimal waveform selection should be suggested by considering all relevant neurophysiologic effects that arise during stimulation (combined) and by decreasing unwanted side-effects at minimum, simultaneously.

The special attention should be given to repetitive, high-frequency, amplitude-modulated stimuli, which are not well covered in scientific literature, but could provide enhanced nerve excitation control. Although not explained at fundamental level, it has been reported that repetitive, amplitude modulated stimuli (with different modulation schemes) will induce more natural feeling during FES and TENS among different human subjects.

Some studies have reported other excitation phenomena that require fundamental explanation at cellular and tissue levels, such as subthreshold superexcitability, action potential phase locking and rate modulation, action potential inhibition by high-frequency signals, as well as very important, but least understood, synapse interactions. All these effects, if well described and completely understood, could also be used for enhanced spatial/temporal control of nerve excitation. Of course, we should not neglect the possibility of finding other, yet unknown neurophysiologic phenomena that arise as a consequence of specific stimulus waveforms.

Another important drawback, regarding experimental studies that involve complex-waveform stimuli, is a lack of true constant-current arbitrary-waveform generators that could operate in a wide frequency and amplitude range. Regular medical stimulators usually generate limited choice of repetitive monophasic or biphasic rectangular pulses (with some variations regarding signal slopes during cathodic or anodic phase) in a limited frequency and amplitude range. Thus, it would be convenient to develop improved constant current medical stimulators, capable of generating true arbitrary-waveform stimuli.

The special effort should be also given to a realistic human and animal simulation model development. Numerous studies have been based on self-developed or widely used nerve fiber models (such are SENN [1] and Neuron [20]), based on standard Hodgkin-Huxley or Frankenhaeuser-Huxley electrodynamics. These oversimplified simulation models usually encompass: single (usually straight) nerve fiber response, homogeneous parameters and oversimplified geometry of tissues that surround nerve fibers, simple electrode geometries with idealistic tissue-electrode junction and limited stimulus waveforms characteristics. Obviously, more realistic simulation models, with realistic tissue geometries and electrical parameters should be applied. These models should take into account all neurophysiologic responses of interests that include:

- electrochemical reactions at electrode-tissue interfaces;
- complex induced electric field distribution for realistic electrode and surrounding tissue geometries and for complex (arbitrary) waveform parameters;
- more realistic nerve tissue properties, especially distribution of fibers in complex nerve bundle geometry,
- nerve-muscle junction and synapse interactions,
- interplay between numerous mutually connected nerve fibers.

4. Proposed research activities

Activities related to this WM would encompass:

1. *Experimental studies on isolated axons, either by using* in vitro *nerve samples or* in vivo *experiments on animals with simple anatomical structure (that possess single nerve fibers, such are leeches and earthworms)*
   The experiments on isolated axons provide controllable excitation of a single axon as well as action potential recordings on the same axon, thus enabling fundamental research at the cellular and tissue level, related to nerve response to complex-waveform stimuli (especially regarding long-duration, repetitive, amplitude-modulated stimuli). Studies performed on isolated axons could be used to find exact (deterministic) relation between specific waveform parameter (phase/pause durations, modulation frequency, modulation index, etc.) and nerve excitability (in means of stimulus threshold level). These experiments could also be used to clarify some insufficiently investigated phenomena at the cellular and tissue level, such as action potential phase locking, action potential inhibition by high-frequency stimuli, as well as subthreshold superexcitability.
2. In vivo *experiments involving animals with more complex anatomy (amphibians, rodents, mammalians) that possess complex nervous system*
   These experiments could be comprehended as an extension of studies explained in the first point and will be used to investigate phenomena related to the impact of stimulus waveform to nerve response at the cellular, tissue and system level (in means of

spatial/temporal nerve selectivity at a nerve bundle, specific nerve type selectivity, action potential rate modulation, interplay among numerous mutually connected nerves, synapse integration, etc). These studies can be also used to determine all possible adverse side-effects arising from neuro-stimulation. Due to complex nerve and synapse interactions, the implementation of stochastic methods will be required to quantify the influence of a specific waveform parameter on a specific (or possibly combined) neurophysiologic response. (Due to its complexity, the application of stochastic methods could be proposed for a separate research activity of even separate WM). Developed stochastic models could be used to predict optimal stimulus waveform (with preferred waveform parameters, such are modulation scheme, duty cycle, pause and phase durations, etc.) for relevant neurophysiologic responses that could be used for FES and CNS stimulation procedures.

3. In vivo *experiments on humans*
   After all neurophysiologic effects have been analyzed and determined (separately and combined) by *in vitro* and *in vivo* animal studies, and after all possible adverse side-effect have been recognized, the experimental studies will be applied to human subjects.
4. *Development of arbitrary-waveform stimulators*
   All previously mentioned studies should be based on constant current stimulator capable of generating arbitrary-waveform, long-duration, high-frequency stimuli, in a wide dynamic range. Moreover, the generator should meet all safety medical requirements before it could be applied to human subjects. The development of such stimulator could be quite challenging and could be a good base for possible innovations.
5. *Combined neurophysiologic response analysis from* in silico *studies*
   To compare experimental results with simulation results, realistic simulation models (both animal and human) based on multiphysics software packages should be developed. This software should be able to calculate precise field distribution in realistic body geometries and, consequently, determine related nerve response. The realistic simulation models should include reliable tissue parameter values, reliable distribution of fibers in complex nerve bundle geometry, realistic interplay between numerous mutually connected nerve fibers, etc. The development of these realistic models could be also quite challenging and could be proposed for separate WM.

5. Final outcomes

- Deeper understanding of interactions between stimulus waveform parameters, stimulation selectivity and overall neurophysiologic response (at the cellular, tissue and system level).
- Optimization of already existing and introduction of novel stimulation techniques, based on optimal stimulus waveform, considering both the beneficial and adverse stimulation effects as well as energy efficiency.

- Development of novel multiphysics simulation (*in silico*) models as well as realistic (*in vivo*) experimental models (through interdisciplinary collaborations) that would encompass combined neurophysiologic interactions.
- Development of innovative measurement and medical (therapeutic) equipment (which could be accomplished through collaboration with SME enterprises).
- Gained knowledge on possible adversity of certain waveforms would enable better protection of humans from unintentional exposure to EMFs.
- The outcomes of the proposed WM could be possibly used as a good basis for complex CNS stimulation procedures related to brain region selectivity and cortical/subcortical mapping, focal magnetic stimulation optimization, pain control during electroconvulsive therapy, etc.
- Finally, all these outcomes should lead to improved, optimized, safer, more efficient and less invasive, cost-effective therapeutic and diagnostic application, which is one of the basic impacts of the COST EMF-MED action.

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