DEEP BRAIN STIMULATION – THE CHALLENGES AHEAD

T. Heida, J. Holsheimer, J.A.G. Geelen, P.H. Veltink
Dept. Biomedical Signals and Systems, Faculty EEMCS, University of Twente, P.O. Box 217, 7500 AE Enschede, The Netherlands

Parkinson's disease (PD) is characterized by progressive loss of dopamine neurons in the pars compacta of the substantia nigra, which results in reduced activity in the thalamus. Clinically effective deep brain stimulation (DBS) has been achieved with electrode contacts in the anterior-dorsal subthalamic nucleus (STN), globus pallidus internus (GPi) and ventral intermediate nucleus (Vim). Stimulation parameters (monopolar cathodic; 1-5 V amplitude; 60-200 μs pulse duration; 120-180 Hz frequency) have been established primarily by trial and error. Although DBS has substantially improved the suppression of symptoms in PD-patients: an average reduction of akinesia (42%), rigidity (49%), tremor (27%), the mechanism of DBS is still unclear and side-effects may occur (e.g. ocular deviation, hypophonia, speech disturbances). There is a lack of quantitative understanding of the influence of high-frequency stimulation on the neuronal elements surrounding the electrode and the neuronal systems involved.

Modeling DBS

The necessity of developing volume conduction and neuronal cell models has already been proved. However, many questions remain yet unanswered.

1. According to current models the fibers that respond to stimulation will generally be the largest (myelinated) axons closest to the cathode. Furthermore, only the membrane time constant of these fibers is small enough to ´follow´ the high stimulation frequency. But what happens to the smaller fibers in the near vicinity of the cathode?
2. Normally, monopolar cathodal stimulation is used. Does the spherically symmetric distribution of the stimulation area in monopolar stimulation favor the ability to control the direction of stimulation using e.g., an array of electrodes?
3. Due to the somatotopic organization of the STN and the small area that is affected by DBS only part of the functionality of the stimulated nucleus is influenced. Generally, the area of the STN that reduces rigidity of the limbs is targeted. Decreasing the anti-parkinson medication based on the symptomatology of the limbs, may result in underdosage with respect to e.g., speech function. What area(s) should be focused on?
4. What are the consequences of the differential stimulation effects occurring in the cell body and the axon of the same neuron, the anti- and orthodromic propagation of activation, and the effects of external stimuli on pre- and post-synaptic neuronal elements?
5. Volume conduction models as well as neuron models have important limitations. Volume conduction models generally include isotropic media, while the tissue surrounding the electrodes is (highly) anisotropic. Furthermore, the multiple actions of DBS, each with a different time course (e.g., alterations in tremor occur in seconds-to-minutes, followed by alteration in limb akinesia and rigidity in several minutes, and axial symptoms in hours) cannot be included.

Model validation

Model validation may benefit from the development of various quantitative and semi-quantitative experimental methods to measure several parameters involved in PD, e.g., bradykinesia, movement time, velocity of movement, reaction time, tremor, rigidity, dyskinesia, etc.
In several neurosurgical centers neuronal activity is registered during the positioning of the intracerebral electrodes. The main purpose of the procedure is to verify the target by its characteristic firing pattern. However, recordings close to the stimulation site may reveal important information for the validation of volume conduction and neuron models. In addition, it has been demonstrated that evoked potentials (EP) can be recorded at the scalp as a result of stimulation.

SOLVING UNSOLVED PROBLEMS

Model based research

- *Volume conduction model:* investigation of the neuronal region that is affected by stimulation. From anatomical studies the fiber diameter and fiber density and anisotropy near the electrode will be investigated, which may give an indication of the actual number of fibers that is affected by DBS since the position (and orientation) of the electrode(s) as well as the stimulation settings are of critical importance.
- *Neuron-model:* investigation of the effects of stimulation on neuronal elements within the region of the electrode based on anatomical studies.
- *System-model:* investigation of the neuronal systems that are directly or indirectly stimulated by DBS and which are involved in PD-symptoms.

Experimental research

Measurements of motor parameters in combination with EMG and EP recordings will be investigated. Research topics include:

- the somatotopic organization of the stimulated nucleus;
- side effects;
- transition from stimulation on an off;
- time-delay effects.