

### *Commentary - The Ideal DBS System*

The proliferation of DBS systems allows for customization to meet the unique needs of the individual patient. However, the multiplicity of different systems, both current and anticipated, increases the complexity of deciding which to use. This monograph will not make any direct comparisons or recommendations because it is anticipated that new devices will become commercially available possibly with features that cannot be anticipated. Consequently, the ideal DBS system will be described to act as a benchmark for future comparisons.

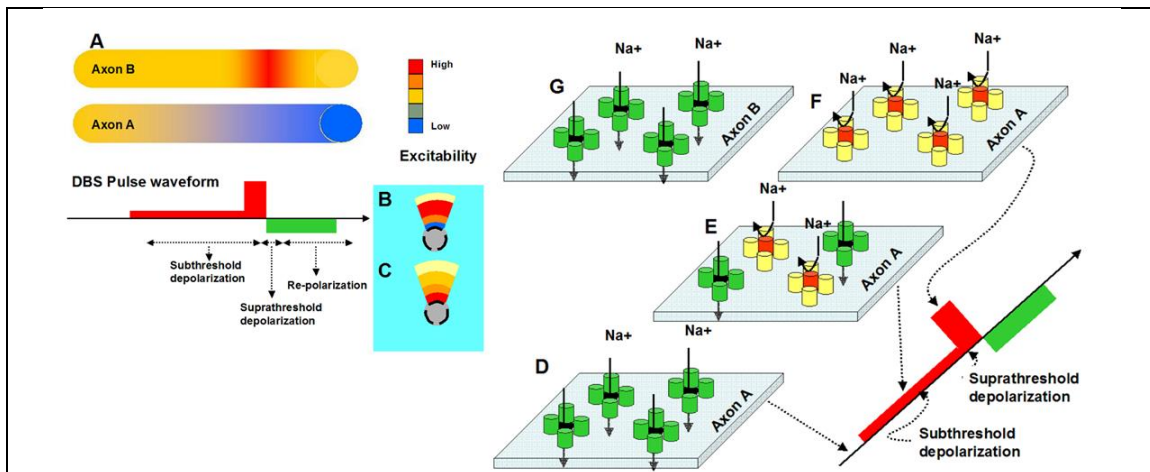
The ideal DBS system should provide constant-current stimulation. The advantages of a consistent clinical response in the face of changing impedances and the more effective stimulation pulse waveforms have been discussed previously (*see Chapter 2 - Principles of DBS Electronics, , Montgomery Jr. EB, Deep Brain Stimulation Programming: Mechanisms, Principles, and Practice, Oxford University Press 2016*). Further, even in those patients whose impedances stabilize some period of time after DBS lead implantation, different contacts on the same DBS lead can have widely varying impedances. This makes generalization based on the stimulation voltage necessary for effect or side effects on one electrode contact often cannot be applied to a different contract on the same DBS lead in the same patient.

The DBS system should allow for a precise sculpting of the electrical field and the ability to move the field in any direction. One approach would be to allow parsing different currents onto cathodes and anodes. Further, the DBS pulses for each of the different cathode and anode currents should be “physiologically” at the same time. This means that when two or more cathodes of different electrical currents are active the

effects are synergistic. It is not clear the interleaving of different pulses on different contacts on the same lead acts synergistically to produce a greater physiological effect than each of the pulses on each contact.

Current systems use a linear array of contacts (typically four) arranged as cylinders where the electrical contact spans the entire circumference. While the linear array allows for moving the electrical field up and down the long axis of the lead, they do not allow restriction of the electrical field in the plane orthogonal to the long axis of the lead. The ideal DBS lead would have segmented electrical contacts that would allow control of the electrical field in the plane orthogonal to the long axis of the DBS lead.

The ideal DBS system would allow leveraging various biophysical properties to achieve unique effects, for example, the ability to project the effective electrical field away from the electrode contact surface. For example, prolonged subthreshold depolarization results in inactivation of  $\text{Na}^+$  conductance channels, thereby preventing the generation of action potentials (*see Chapter 3 - Principles of Electrophysiology, Montgomery Jr. EB, Deep Brain Stimulation Programming: Mechanisms, Principles, and Practice, Oxford University Press 2016*). This phenomenon could be taken advantage of by inactivating axons relatively close to the electrode surface while axons further away still are sensitive to the DBS activation (**Figure 1**).



**Figure 1.** Example of leveraging biophysical properties to affect the shape and distribution of the DBS electric field. Effects of an initial subthreshold depolarization phase in the DBS pulse waveform allow reduction in the excitability of axons nearer the electrode contact while maintaining excitability of axons further from the electrode contact (A). With only a supra-threshold depolarization, the highest activation are axons near the electrode contact surface (C). The subthreshold pre-pulse allows the excitability to be “thrown” further away from the contact surface (B). Initially the  $\text{Na}^+$  conduction changes are active (capable of being opened) in both axons A and B (D). The low voltage subthreshold depolarization causes an inactivation of the  $\text{Na}^+$  conductance channels but only in axon A (E). By the time the supra-threshold depolarization phase occurs all the  $\text{Na}^+$  conductance channels in axon A are inactivated (F) and axon A cannot generate an action potential. The  $\text{Na}^+$  conductance channels in axon B are active (G) and can generate an action potential in response to the supra-threshold phase of the DBS pulse.

Other types of DBS pulse waveforms may selectively activate cell bodies or axons, which could allow better efficacy and fewer side effects in situations where either

the cell bodies or axons selectively cause either efficacy or side effects. Another property that could allow more selective activations of neurons is based on chronaxie, which, roughly, is the amount of electrical charged which is related to the duration of the stimulation cathode phase, necessary to cause an action potential. Axons are excited at short pulse widths than cell bodies or dendrites.

Another biophysical property that can be exploited is the refractory period that differs between axons, cell bodies and dendrites. If a pair of stimulation pulses is administered at an inter-pulse interval shorter than the refractory period, then the second of the pair of pulses will occur with the neuronal element is in its refractory period. The refractory period of a cell body or dendrite, for example 2 ms, is longer than that of an axon typically less than 1 ms. Thus, a pair of stimulation pulses with an inter-stimulus interval of 1 ms while have the effect of only 1 pulse for the cell body or dendrite while the pair of stimulation pulses will have the effect of two pulses on the axon.

The ideal IPG would allow for an arbitrarily wide range of stimulation patterns, from paired pulses as described above to “noisy” patterns with frequencies over a specific bandwidths. “Noisy” stimulation could improve the signal-to-noise ratio causes by disease that corrupts information processing within the brain or causes misinformation. While counter intuitive, adding noise to a poor signal-to-noise condition can actually improve the signal through a process called stochastic resonance.

The Systems Oscillators theory posits that different reentrant neural oscillators within the same network operate over different frequency bands. For example, the dysynaptic oscillator, the thalamo-cortical circuit, operates at approximately 147 Hz. DBS at this frequency can resonant amplify the signal in this frequency range just as the

oscillator in an AM radio amplifies, that is selects, the appropriate radio signal from the radio station. Different oscillators within the basal ganglia-thalamic-cortical system may require stimulation at different frequencies to resonant amplify the information carried within those specific oscillators. For example, the ability to recruit of motor units may require high frequency DBS to resonant amplification of the thalamic-motor cortical system in order to increase effort. However, the precise modulation of motor unit activity over the longer time course of a behavior may require DBS at lower frequencies. This may explain why low frequency DBS may be more helpful in gait and speech (*see Chapter 2 - Principles of DBS Electronics, Montgomery Jr. EB, Deep Brain Stimulation Programming: Mechanisms, Principles, and Practice, Oxford University Press 2016*). The ideal IPG would provide for DBS trains that could provide stimulation at multiple frequencies in an interleaved or multiplexed manner.

If neural systems physiology and pathophysiology research and research into the therapeutic mechanisms of action are supported and expanded, then the potential applications of nervous stimulation will increase. This could provide help to the countless number of patients not adequately responding to pharmacological therapies, which include stem cell and gene therapies. Advances in neural systems physiology and pathophysiology and into the therapeutic mechanisms of DBS could be translated into new engineering solutions that will become the basis for the ideal IPG of the future.

There are a number of practical issues that could be improved by future ideal IPGs. Therapeutic impedances and warnings could be more straightforward. Device and patient specific information allowing efficient use with respect to prolonging battery and recharge use would be appreciated. Rechargeable IPGs could reduce repeated surgical

trauma associated with battery replacement and reduce cost. However the ideal IPG would not allow a patient or caregiver to let the battery charge to run out. While external reminders would be helpful, they could easily be forgotten or ignored. An adequate warning device incorporated into the IPG itself, such a vibration, would be hard to ignore. Alternatively, the time course of IPG failure due to lack of recharge should be gradual so as to allow a gradual deterioration of the patients symptoms thereby reminding the patient and/or caregiver without endangering the patient. There have been case reports of serious sequela in patients with Parkinson's disease due to sudden device failure.

Miniaturization of the IPGs so that they could be placed in the head rather than in the chest would obviate the need for tunneling the extension wires and increase patient comfort. DBS systems that are not affected by the external electrical environment would uncomplicated patient's lives and medical care.

Given the increasing number of commercially available and anticipated DBS systems, particularly IPGs, it is difficult to provide information specific to each IPG that does not risk obsolescence. Further, comments about anticipated but not yet FDA approved IPGs would be to invite perhaps untoward interest by the FDA potentially reflected upon the manufacture.