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17 Closed-loop Cortical Stimulation

As illustrated in previous chapters, in open-loop cortical stimulation, parameter adjustment is a labor-intensive, trial-and-error process based on the clinical response to the last setting. Once programmed, parameters remain constant until the next follow-up visit. These limits are due in part to the absence of a feedback control system, insufficient knowledge of mechanisms of action of ICS as well as the absence of appropriate bioinspired algorithms to implement these mechanisms and guide parameter determination. This situation is slowly changing with the introduction of so-called closed-loop systems. Closed-loop brain stimulation banks on neural activities recorded in the nervous system and analyzed online to deliver appropriate electrical stimulation (Fig.17.1). Closed-loop DBS is currently being tested with cortical recording and deep stimulation (Activa® PC+S DBS <http://newsroom.medtronic.com/phoenix.zhtml?c=251324&p=irol-newsArticle&id=1882373>). Also, closed-loop stimulation is FDA-approved for refractory epilepsy (Chapter 16; see also Berenyi et al 2012). During the last decade, patents have been filed (e.g. Beuter and Modolo 2009) and companies have been created to design and produce the next generation of intelligent neurostimulators. Neural stimulation is the last to benefit: closed-loop control has been known and used in engineering for many decades now. In the brain, the loop can be closed at relay points located deep in the brain or superficially on the cortex (Beuter and Modolo, 2012). The rationale for closing the loop at the cortical level is that both the cortex and deep nuclei (basal ganglia, thalamus) are part and parcel of the same large-scale network of interconnected structures and this network can be entrained from any point, including indeed the easily accessible cortical mantle (Canavero, 2011).

Certainly, the cortex presents an especially challenging locale. Each cortical area contains an unknown number of networks of interconnected neurons, with a complex integration of multiple information streams originating from both hemispheres. However, due to anatomical fanning-out, the modulation of a given brain network requires a larger area of stimulation at the cortical level than at deeper sites, suggesting that less focal currents need to be delivered for cortical stimulation to obtain efficacy, without producing adverse effects (Canavero 2011). Propagating waves of electrical activity mediate specific information at specific rhythms in different cortical regions (Patten et al., 2012), e.g. propagation of beta oscillations conveys motor information from M1 in humans (Takahashi et al., 2011). The interaction of the current delivered during cortical stimulation with such propagating waves carrying physiological information between cortical regions should be avoided. This is achievable: Brittain et al (2013) showed that transcranial alternating current stimulation (tACS) delivered over M1 at pathologic tremor frequency and phase-locked to the tremor signal induces phase cancellation of the tremor rhythm. The optimal suppressive phase alignment

produced 50% average reduction in resting tremor. Importantly, De Hemptinne et al (2013) observed that in patients with Parkinson's disease, the coupling between beta-phase and gamma-amplitude in M1 is exaggerated, and that this excessive coupling may be reduced by STN DBS. More specifically, peaks in gamma-amplitude in M1 are not only coupled but precede the beta-trough in the subthalamic nucleus, suggesting that M1 LFPs can be used as a control signal for automated programming of basal ganglia stimulators. Finally, the 3-D structure of the cortex with sulci and gyri results in a marked heterogeneity of neural fiber orientation, with the lowest activation threshold found at fiber endings or axonal bends, especially at the interface between the gray and white matter. This calls for neuroengineering modelization data to be integrated into the closed-loop neural analyzer ([Chapters 19-20](#)).

Fig. 17.1 : a schematic view of the components of a closed-loop neurostimulation system.

17.1 Biomarkers

Closed-loop brain stimulation works on the assumption that a very small number of high-dimensional parameters or biomarkers can be monitored and used to parameterize the algorithm implemented in the device controller (Winslow et al 2012). There is agreement today that Local Field Potentials (LFP) recorded with macroelectrodes can be used as a suitable control variable / biomarker (Priori et al., 2013; Winestone et al., 2012 and Little et al., 2013). In Parkinson's disease, LFPs oscillate at various frequencies that are correlated with the cardinal signs of the disease such as tremor,

rigidity, postural instabilities and akinesia. LFPs are robust, with reproducible time-domain, frequency-domain, linear and nonlinear features, and can be implemented on microchips (Priori et al., 2013); they can be monitored continuously during brain stimulation (Priori et al., 2005; Rossi et al., 2007; Rouse et al., 2011). The aim is to keep LFP parameters (e.g., global amplitude, spike or synchronized oscillation detection using high or low pass filtering, time-dependent spectral power in specific frequency bands) within a predetermined range, by automatically adjusting the stimulation parameters (frequency, amplitude, pulse width, cyclic or continuous stimulation, etc) to produce the desired effects, in a safe fashion and without interfering with propagating waves carrying physiological information (see above). Finally, LFP indices must correlate with the clinical (motor, cognitive, behavioral) state of the treated subjects. An appropriate battery of quantitative measures evaluating the evolution over time (weeks, months...) of the clinical symptoms must complement the classical clinical rating scales. In Parkinson's disease - for example- some LFP markers correlate with tremor, while others with bradykinesia, rigidity and even dyskinesias.

17.2 Bioinspired Modeling

Computational models of neuronal networks based on real neural circuits have become necessary tools to implement closed-loop brain stimulation (Feng et al., 2007; Schiff and Sauer, 2008; Schroll and Hamker, 2013). In the context of movement disorders, the cortical-basal ganglia-thalamo-cortical network has been addressed and modeled with a view to quell pathological activity (Rubin and Terman 2004, Pascual et al 2006, Modolo et al 2008, Modolo and Beuter, 2009ab, Modolo et al., 2009; Modolo et al., 2010abc, Modolo et al., 2012). In a multiscale biologically inspired model, Modolo et al. (2010b) proposed a method for selectively modulating cortical rhythms using a neural field approach. Continuous neural field theory provides a realistic representation of coarse-scale dynamics of cortical tissue in which non-local interactions occur with time delays and a variety of external inputs. The descriptive and, more importantly, the predictive value of neural field models have been extensively demonstrated. In this model, cortical tissue is considered as a two-dimensional continuous sheet of tissue (as opposed to a sheet of discrete elements, i.e., single neurons are densely packed), as justified by the high density of neurons in cortical tissue (Young et al., 2013); interconnected neural masses i.e., aggregates of neurons containing excitatory and inhibitory neurons, are considered as equivalent to cortical macrocolumns, and cortical tissue is described as synaptically-coupled cortical columns. Thus, a neural field is a continuous entity composed of neural masses with a connectivity function depending on the distance between two neural masses. Summation is performed over the neural field using delayed integro-differential neural field equations. Spike propagation delays and conduction speed of

the fibers are taken under consideration. The general form of the function sums two exponential functions depending on the spatial range of the fibers and the strength of excitatory/inhibitory connections and gives rise to four possible connectivity patterns: local excitation, local inhibition, local excitation with lateral inhibition, and local inhibition with lateral excitation. Based on this model, the authors propose to use a two-dimensional electrode array both for cortical recording and stimulation, using a stimulation signal that is autoadaptive both in space and time. In this approach, the activity of artificial neural masses is linked with that of cortical columns, emulating cortical dynamics. The scale of the model (mesoscopic) is therefore compatible not only with the meaningful scale for information coding in M1, but also with the scale at which flat electrodes can provide stimulation to the tissue. Assumptions are made, such as considering that the connectivity function is identical in each spatial position (i.e., translationally invariant function). Also, the value of the neural field reflects the mean depolarization of cell membranes. Therefore it is assumed that all neurons in a given neural mass have a similar membrane potential. This model must be improved to include the contribution of axonal activation by electrical stimulation, and also to convert the calculated signal to a charge-balanced signal required in clinical practice to avoid brain tissue damage (see also Hess, 2013).

17.3 Underlying Physiological Control Mechanisms

As pointed out above, one direct consequence of our limited understanding of the mechanisms involved in brain stimulation is that it constrains our capacity to manipulate and control the system. One alternative comes from computational modeling (Winslow et al 2012). As a mechanism can be defined as an “*active structure that performs functions, produce regularities, underlie capacities or exhibit phenomena; doing so in virtue of the organized interaction among the mechanism’s component parts, and the processes or activities these parts carry out*” (Kaplan, 2011, p 347-348), a model has explanatory power only insofar as it “maps out” aspects of the causal structure of that particular mechanism (so-called Model-Mechanism-Mapping, 3M). However, this 3M does not require a perfect correspondence or isomorphic mapping between model and mechanism, but rather it requires that some of the variables (at least one) correspond to some (at least one) identifiable component part and causal dependencies among components in the mechanism responsible for producing the target phenomenon. If this minimal degree of model-mechanism correspondence is obtained, it can be said that the model is endowed with explanatory power, and the injection of sufficient explanatory power in the model provides potentially exploitable information for manipulation and control, leading to individually tailored stimulation protocols. More to the point, the explanatory power of the Modolo et al. (2010b)’s model, although limited, comes from the fact that an artificial module mimics to some extent the behavior of the biological cortical tissue, as both are

governed by similar “equations” (neural field on one side and cortical dynamics on the other side) and obey the same physical principles at a similar spatial scale. Global oscillations are modulated by a closed-loop stimulation signal triggered by, and calculated as a function of, the local mean membrane potential. Therefore, there is some correspondence between the model and the physiological system regarding the closed-loop stimulation current, i.e., the mean membrane potential, large-scale neuronal oscillations and the spatial scale at which these phenomena occur. The model predicts that to be efficient, the stimulation signal needs to be at the same frequency as the targeted pathological rhythm with a time delay dependent on neuroanatomical properties of cortical tissue. This model successfully predicts that a tremor reduction will occur with neuromodulation and recent work by Brittain et al. (2013) (see above) supports the prediction of the model (see also Nevado-Holgado et al., 2014 for new insights into the basal ganglia function).

17.4 Technological Issues

Closed-loop cortical stimulation has been advanced by recent hardware and software developments and by the emergence of novel tools to control neuronal activity with high precision in space and time. The convergence of mathematical modeling with neuro-engineering is likely to provide a new window of opportunity on disease and therapeutic mechanisms, which can be exploited for the design of next-generation “smart” neurostimulators. These devices need to be implementable in terms of size and external controllers. Various types of neuronal closed-loop controllers exist (Echaz et al 2009) including ‘*triggered open-loop controllers*’ (such as responsive neurostimulation used to treat epilepsy) in which sensors are used to start and stop the stimulation, ‘*continuous feedback controllers*’ using regular sensing to monitor the stimulation, ‘*adaptive controllers*’ using feedback signals from sensors to continually adapt the stimulation parameters, and finally ‘*learning/intelligent controllers*’. The latter outperform all others in their ability to adjust automatically and intelligently the parameters of stimulation using fine-grained feedback (Echaz et al., 2009) and are suitable for implementation in cortical closed-loop systems.

A major issue has to do with the electrodes. Current electrodes used for cortical stimulation are not suitable for closed-loop control. Their number is too small, their size too large, and their spacing not appropriate. This is why new matrices of flexible flat electrodes are being designed (see also de Hemptinne 2013 for long-term cortical recording). Computer-based models can be used to optimize electrode placement, polarity, and geometry and to modulate efficiently the excitation properties of cortical networks (Wongsarnpigoon and Grill, 2011). Shape and rigidity of flat, flexible chronic electrode arrays suited to cortical anatomy (sulci/gyri) are becoming available, but issues remain: how to anchor them and the extent of coverage of the cortical target.

Determination of stimulation parameters is suboptimal in current open-loop systems, but novel optimization techniques have been developed that predict parameters by combining concepts of neural network modeling with nonlinear control engineering (Davidson et al., 2014). Electrodes enabling high fidelity recording with short latency are also used to deliver appropriate stimulation after reducing stimulus artifacts (Rossi et al., 2007; Al-Ani et al. 2011). The mechanisms of artifact reduction by the instrumentation must be considered (Kent and Grill, 2012). In the future a new technique, i.e., fast-scan cyclic voltammetry, could become available to wirelessly monitor and measure the production of neurotransmitters in the brain and become a concrete biological feedback to deliver precise stimulation (Van Gompell et al., 2010).

17.5 Conclusion

Cortical closed-loop neuromodulation aims at reshaping specific frequency bands without interfering with healthy physiological functioning through the development of hybrid in silico/biological coadaptive symbiotic systems. In particular, this exploits instantaneous brain activity recordings, applying an appropriate stimulation algorithm and delivering activity-dependent neuromodulation in real time contingent upon the recorded neural activity via multiple flat electrodes placed over the dura of the subject. That being said, the next generation of hardware and software integrating bioinspired algorithms will soon be available. Furthermore, it will become possible to test-simulate stimulation algorithms. Lastly, communication with the implanted device will be performed by a wireless system built to send and receive data from inside and outside the body at high speed (which would avoid current equipment implantation). Some work is still required to implement and monitor the parameters of LFPs, calibrate the stimulation parameters to the patient's individual needs and quantify the evolution of symptoms over the long run.

The possibility of adjusting parameters automatically via an adaptive system while minimizing electric stimulation delivered to brain tissues to control aberrant brain rhythms caused by the disease represents a true alternative option to current open-loop systems. Closed-loop cortical stimulation may take another few years before it enters the clinic, but when it does, it will increase the number of patients treated, improve their quality of life, and decrease the cost of the surgical intervention and the number of follow-up visits.

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