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Closing the loop for Deep Brain Stimulation implants enables personalized healthcare for Parkinson's disease patients

Wolfgang Eberle, *Senior Member, IEEE*, Julien Penders, and Refet Firat Yazicioglu

DEEP brain stimulation implants have improved life quality for more than 70,000 patients world-wide with diseases like Parkinson's, essential tremor, or obsessive-compulsive disorder where pharmaceutical therapies alone could not offer sufficient relief. Still, optimization and monitoring relies heavily on regular clinical visits, putting a burden on patient's comfort and clinicians. Permanent monitoring and combination with other patient health signals could ultimately lead to a personalized closed-loop therapy with remote quality monitoring. This requires technological improvements on the DBS implants such as integration of recording capabilities for brain activity monitoring, active low-power electronics, rechargeable battery technology, and body sensor networks for integration with e.g. gait, speech, and other vital information sensors on the patient's body and a link to a telemedicine platform using mobile technologies.

I. Challenges in Deep Brain Stimulation

Parkinson's disease (PD) is the second most common neurodegenerative disease, affecting more than 2 per 1000 people in Europe. This incidence increases to 1.6 to 1.8 per 100 people in persons over 65. It is estimated that 6.3 million people have PD worldwide. The age of onset is usually over 60, but it is estimated that one in ten are diagnosed before the age of 50.

For delivery of neurological care to people with Parkinson's disease, adequate human resources, medical, and rehabilitation facilities are required. The cost of care for an increasing number of cases will place an enormous burden on an already strained healthcare system. Drug-based therapies today are fighting against symptoms which are heavily patient-dependent. A personalized approach is required to optimize each patient's quality of life under this disease constraint, dealing with disease symptoms and therapy-dependent side effects such as speech, tremor, or gait deficiencies.

Deep brain stimulation (DBS) is a surgical treatment [1][2], typically used as a last resort when drug therapies are not effective anymore. It involves the implantation of usually 1 passive probe with e.g. four mm-size electrode sites in deeper brain regions, in the left and/or right hemisphere. Probes are connected with lead wires to an implant in the main body which contains stimulation electronics, short-range wireless communication for programmation and battery supply. Latest innovations include rechargeable batteries.

DBS can be used for more than PD therapy alone and has also found to be applicable in the therapy of depression, tremor, and obsessive-compulsive disorder (OCD). A hypothetic model for its functional principle has been put forward in [1] but DBS as such is not yet fully understood though its therapeutic successes are undoubted.

Besides the most widely used Medtronic Activa system, several other systems have been developed, partially approved, partially in various clinical stages of the approval chain. St. Jude Medical's Libra system has been approved in Europe in 2009 for use in Parkinson's disease. The Medtronic system has gained approval for OCD lately. Other companies working on DBS technology are Boston scientific (including Intelect), Neuropace, ANS (Germany), and 3WIN (Belgium). Several companies have recently merged or abandoned the development.

II. Technology Improvements

Today's DBS technology is strongly based on clinical implantation and pre-determination of stimulation settings. Changes in settings are under limited control of the patient and remote monitoring is not present. Hence, neither an alarm-based system informing a clinical observation centre nor closed-loop control adapting drug therapy and/or DBS settings to symptoms are available. There is a great potential of improvement here involving several key technologies:

- brain activity recording for assessment of stimulation efficiency and side effects,
- local feedback between recordings and stimulation,
- monitoring of symptoms and side effects through wearable sensors e.g. for speech or gait analysis,
- body area networks (BAN) for multiple sensor data collection,
- decision-taking and control based on multi-sensor data fusion,
- telemedicine for remote communication (alarm and/or control of settings).

This translates into innovation required on the probe side (improvement of spatial resolution and integration of bi-directional stimulation and recording), active implanted electronics, wearable sensors for voice and body

W. Eberle and R. F. Yazicioglu are with Imec, Leuven, Belgium (e-mail: wolfgang.eberle@imec.be, firat.yazicioglu@imec.be).
J. Penders is with Holst Centre / Imec, Eindhoven, The Netherlands (e-mail: julien.penders@imec-nl.nl).

movements, wireless BAN, multi-sensor algorithms, and mobile telemedicine technology.

III. VARIATIONS ON CLOSING-THE-LOOP

Today's DBS therapy is essentially an open-loop technique using a fixed electrical stimulation pattern after a clinical calibration session. Settings are pre-determined per electrode side and can only be varied in a very limited way due to the missing feedback path. Hence, adaptations require a clinical reassessment.

Closed-loop control can be instantiated at three levels regarding the observation side:

- activity-based quasi-direct feedback: observation of the brain activity in the effected pathway, focusing on desired effects and e.g. undesired effects in neighboring regions. This requires the addition of recording sites, finer spatial resolution to distinguish the origin of brain activity, and technology for monitoring the recording during silent parts of the stimulation burst.

- symptom-based indirect feedback: observation of symptoms using non-invasive wearable sensors that trace symptoms such as speech, tremor, and gait anomalities.

- multi-sensor feedback: combining data from multiple sensors including brain activity to improve stability and reliability of the therapeutic decision-taking.

On the actuation side, both the release of drugs using e.g. implanted or intra-oral/palatal drug devices and the adaptation of stimulation parameters of DBS devices can be considered either alone or jointly.

Besides the technical innovation, it should not be forgotten that modifications towards closed-loop operation may also incur relevant changes in therapeutic procedures, liability for medical device manufacturers or physicians, as well as a fundamental change in clinical and ambulatory care [3].

IV. TECHNOLOGICAL CHALLENGES AND RISK ASSESSMENT

Modifications on medical devices require a careful risk assessment comparing the modifications and their potential risk against the benefits. In this respect, four major aspects can be seen here:

- Modification of the implanted probe technology,
- Modification of the signal processing electronics,
- Reliability of the closed-loop communication,
- Reliability and fallback mechanisms of the overall control software.

A. *Probe technology*

Figure 1 illustrates the current state-of-the-art probe technology as well as three potential evolutionary steps. In a first step (aDBS I), existing DBS probes may be enhanced by adding additional passive electrode sites able to record local field potential (LFP) information at a sub-mm resolution. In particular, packaging and material reliability will need to be reassessed here. A second option could be the implantation of additional read-out electrodes (aDBS II) which would require a modification of the surgical procedure and a reassessment of damage. A third option depends on the assessment of the prior options and may reveal the optimum electrode site topology and integrate the manufacturing process for stimulation and recording electrodes to minimize biocompatibility risks.

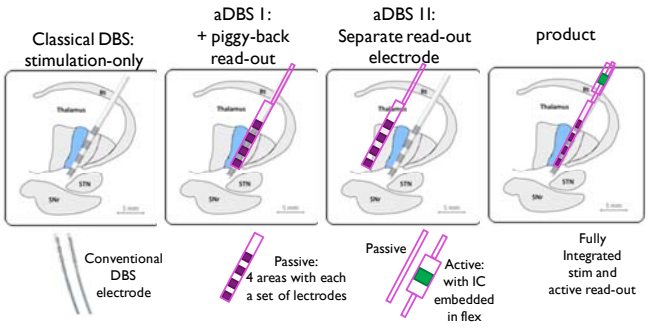

Fig. 1. Classical DBS probe technology (left) and increasingly more complex novel probes.

B. *Integration with active electronics*

Active electronics to improve the recording of the weak uV-mV level brain activity signals could be integrated *in situ* next to the recording electrodes. The benefit of low-power low-noise mixed-signal electronics on signal quality is undisputed. It allows for example the distinction of action potentials and local field potentials [4]. Improvements on low-power circuitry allow the long-term monitoring of various types of signals such as ECG, EEG, and EMG [5].

Under implant conditions however, this requires an assessment of compliance with frequently used imaging techniques such as magnetic resonance imaging (MRI). Long leads as well as active electronics can be damaged or induce unwanted signals during MRI.

An alternative is a bypass option which branches off from the regular stimulation path (Fig. 2); this branching can be active only during the acute implantation phase, can be chronic, or can be deactivated e.g. during MRI offering a more benign, less hazardous option. In such a scenario, even device separation could be partially maintained, requiring mainly an assessment of the probe and signal bridge safety.

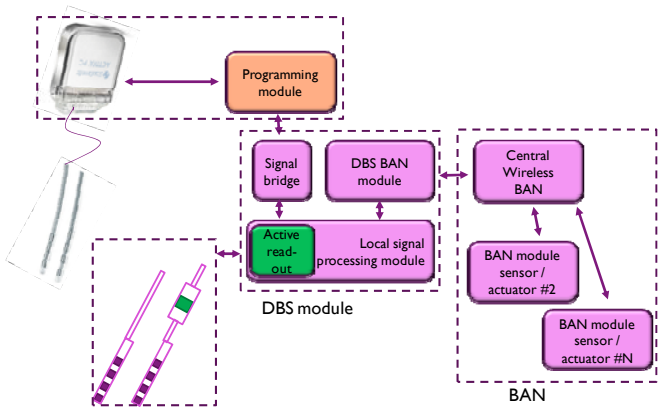

Fig. 2. System integration options with a signal bridge towards a classical stimulation implant. The rest of the system connects to a body area network and eventually other e.g. wearable sensors or actuators.

The DBS module can only include limited local signal processing (due to energy constraints) but this could enable already brain-activity based closed-loop control. If the BAN communication drops out, a first fall-back to brain-activity based closed-loop operation is possible. A second fall-back to standard open-loop operation would be possible by interrupting the signal bridge.

C. *Wireless BAN and mobile Health*

A low-power body area network allows data fusion integrating implanted and wearable sensor and actuator data. A major advantage is the removal of wires, crucial for implanted devices and essential for patient comfort in case multiple sensors need to be worn such as sensors for gait analysis. Centralization of data allows local personalized signal process but is still subject to limited computing and energy resources. Linking the BAN to mobile technologies (3G/4G etc) enables the full mobile health (mHealth) paradigm by connecting such a personalized Parkinson closed-loop system to 24/24 centers for alarm monitoring or clinical centres for long-term or computationally expensive data analysis. Even remote adaptation and follow-up of therapeutic parameters is possible.

For wearable monitoring, such wireless technology has already been demonstrated: A complete BAN connected to a mobile phone enabling reliable long-term ambulatory monitoring of various health parameters such as cardiac performance (ECG), brain activity (EEG), muscle activity (EMG), etc. Such BANs are miniaturized sensor networks, consisting of lightweight, ultra low-power, wireless sensor nodes which continuously monitor physical and vital parameters in a comfortable way for the patient (Fig. 3).

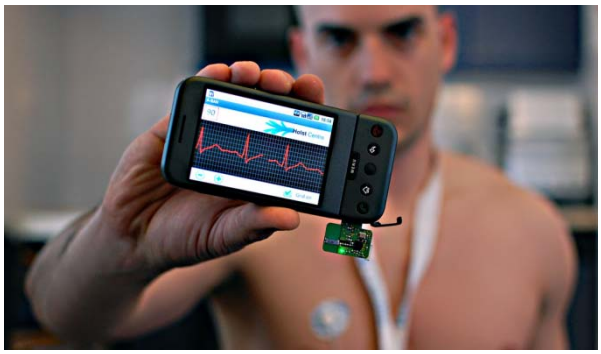

Fig. 3. Imec and Holst centre's Human++ BAN sensor network [6] connected to an Android mobile phone where data is collected, stored, processed, and sent over the internet or mobile network to make them available to authorized users such as a physician or patient monitoring centre.

V. Conclusions

Introducing technological innovations on probe technology, active electronics, signal processing algorithms, and wireless technology can drive further several closed-loop paradigms for deep brain stimulation therapies, allowing significantly better adaptation to personal patient needs, leading to a higher patient quality-of-life and driving down healthcare cost. A careful risk assessment is required for each technological modification, keeping in mind hazards and risks and offering fallback modes for safe device operation under all circumstances.

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