bioRxiv preprint doi: https://doi.org/10.1101/2020.09.10.292284; this version posted September 11, 2020. The copyright holder for this preprint (which was not certified by peer review) is the author/funder. All rights reserved. No reuse allowed without permission.

DyNeuMo Mk-1: A Fully-Implantable, Motion-Adaptive Neurostimulator with Configurable Response Algorithms

Mayela Zamora, Robert Toth, Jon Ottaway, Tom Gillbe, Sean Martin, Moaad Benjaber, Guy Lamb, Tara Noone, Zachary Nairac, Timothy G. Constandinou, Jeffrey Herron, Ivor Gillbe, Stefan De Wachter, Charles H. Knowles, Tipu Z. Aziz, Alexander L. Green and Timothy Denison

***Abstract*—There is growing interest in using adaptive neuromodulation to provide a more personalized therapy experience that might improve patient outcomes. This paper describes the design of the 'DyNeuMo Mk-1', a fully-implantable, motion-adaptive research stimulator that titrates stimulation based on the patient's movement state (e.g. posture, activity, shock, free-fall). The design leverages off-the-shelf consumer technology that provides inertial sensing with low-power, high reliability and modest cost. We used a three-axis accelerometer and its embedded digital motion processor to enable real-time stimulation adaption based on configurable motion parameters. The algorithm configurability and expanded stimulation parameter space allows for a number of applications to be explored in both central and peripheral applications. The implantable system was designed, prototyped and verified using ISO 13485 design controls, including ISO 14971 risk management techniques to ensure patient safety, while enabling novel algorithms. With the design controls in place, first-in-human research trials are now being prepared to explore the utility of automated motion-adaptive algorithms. The design highlights how consumer electronics technology can be leveraged for efficient and reliable medical device development. The implantable system automatically provides activity- and posture-based responsive stimulation which can be configured by the clinician to optimize therapy. Intended applications include adaptive stimulation for movement disorders, synchronizing stimulation with circadian patterns, and reacting to transient inertial events such as shocks for urinary incontinence.**

***Index Terms*—Neural implants, Brain stimulation, Activity recognition, Accelerometers, Adaptive control, Closed loop systems, Design methodology, Risk analysis, Safety management.**

This work was supported by the John Fell Fund, the UK Medical Research Council and the Royal Academy of Engineering.

Mayela Zamora is with the Department of Engineering Science, University of Oxford, Oxford OX2 7DQ, UK. (e-mail: mayela.zamora@eng.ox.ac.uk)

Robert Toth is with the MRC Brain Network Dynamics Unit, University of Oxford, Oxford OX1 3TH, UK.

Jon Ottaway, Tom Gillbe, Guy Lamb, Tara Noone, and Ivor Gillbe are with Bioinduction Ltd, Bristol BS8 4RP, UK.

Timothy G. Constandinou is with the Department of Electrical and Electronic Engineering and the UK Dementia Research Institute (Care Research and Technology Centre), Imperial College London, London SW7 2AZ, UK.

Jeffery Herron is with the Department of Neurological Surgery, University of Washington, Seattle, WA 98195-6470 US.

Sean Martin, Alexander L. Green and Tipu Z. Aziz are with the Department of Neurosurgery, John Radcliffe Hospital, Oxford OX3 9DU, UK.

Stefan De Wachter is with the Department of Urology, University of Antwerp Hospital, 2650 Edegem, Belgium.

Charles H. Knowles is with the Barts and the London School of Medicine and Dentistry, Queen Mary University of London, London E1 2AT, UK.

Moaad Benjaber and Timothy Denison are with the Department of Engineering Science, and the MRC Brain Network Dynamics Unit, University of Oxford, Oxford OX1 3TH, UK. (e-mail: timothy.denison@eng.ox.ac.uk)

I. Introduction

The field of adaptive neuromodulation is an active area of development, with particular emphasis on the use of bioelectric signals to inform the control algorithm [1]. For example, the Neuropace RNS is approved in the U.S. for refractory epilepsy [2]. While promising, the ultimate benefit of the responsive stimulation for epilepsy is still debated, and refinement of the algorithmic approach is an active area of study [3]. Likewise, in the field of movement disorders, particularly Parkinson's disease, adaptive stimulation has shown promise for improving outcomes while lowering energy use [4], [5]. However, the signals recorded from sub-cortical targets are 1) relatively small (1 μVrms), 2) prone to artefacts from stimulation, cardiac signals and motion, and 3) the optimal configuration of algorithms are still debated and might prove complex for programming [6]. In addition, the resolution of small bioelectric signals in the presence of stimulation puts significant constraints on the relationship between sensing and stimulation electrodes, which can severely limit the therapy options [4], [5], [7], [8]; recent work to bypass these constraints potentially compromise the tissue-electrode interface's safety due to leakage currents and single-fault errors [9].

One alternative to strictly "neural closed-loop" methods is to use wearable sensors to determine an estimation of the patient or symptom state as a feed-forward method to adjust stimulation. The widespread adoption of inertial sensing in consumer wearable electronics has resulted in many features ideal for use in implantable closed-loop neuromodulation systems: 1) low power (order of 10 μW), 2) high reliability and shock immunity, and 3) embedded "digital motion classifiers" that facilitate motion classification [10]. Inertial sensing has already been applied in medical implants to automatically titrate stimulation. Notable examples include activity-based titration of cardiac pacemakers [11], and posture responsive adjustment of stimulation for spinal cord stimulation [12]. Investigational work using the Activa PC+S has also demonstrated the use of inertial sensing in deep brain stimulation (DBS) applications, with wrist-mounted inertial sensors being used to control stimulation in real-time in both essential tremor [13] and Parkinson's disease [14]. Despite the potential research and therapeutic opportunities allowable by integrating inertial closed-loop functionality into brain neuromodulation devices, there are no such devices broadly available for research.

In this paper, we introduce the Dynamic Neuro Modulator Mark 1 (DyNeuMo Mk-1), a cranial mounted motion-adaptive

bioRxiv preprint doi: https://doi.org/10.1101/2020.09.10.292284; this version posted September 11, 2020. The copyright holder for this preprint (which was not certified by peer review) is the author/funder. All rights reserved. No reuse allowed without permission.

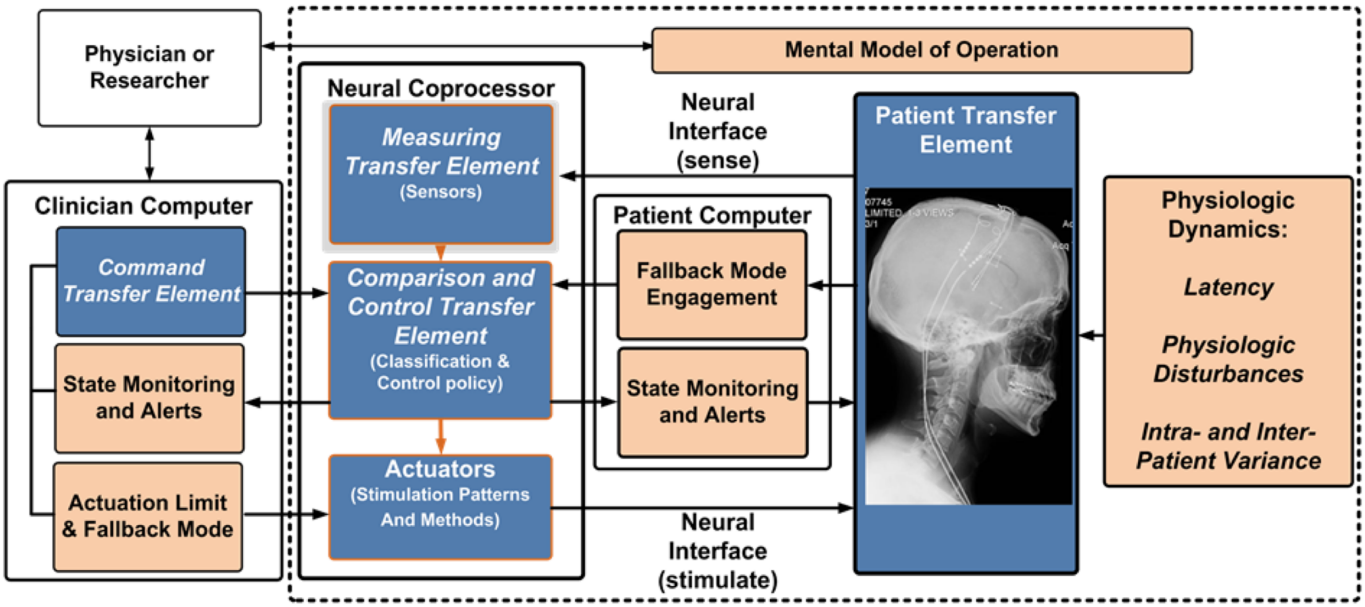

Fig. 1. System block-diagram using the IEC 60601-1-10 physiologic control framework. Blue boxes are derived from user needs, while tan boxes are derived from risk mitigations. Both sources of design inputs inform the system specifications for the DyNeuMo Mk-1. Reproduced with permission from [1].

neurostimulator for use in human investigational studies into inertial-sensing based closed-loop therapies, based on the Picostim system by Bioinduction [15].

Unlike classical DBS devices, implanted in the chest cavity with electrode leads routed through the neck, the DyNeuMo and predicate Picostim systems utilize a cranial mounted design. This approach has several advantages, summarized here from [15]. The surgical procedure is considerably simplified requiring only a single incision, reducing both surgical and infection risk for patients, while also improving the productivity of surgical teams. Avoiding tunnelling of leads through the neck significantly reduces the risk of lead wire breakage or fibrosis around the lead, a cause of stiffness and pain. Overall a cranial mounted device improves patient safety, while also significantly reducing expected treatment costs.

To support first-in-human research, we used ISO 13485–compliant design controls throughout the project. The paper will follow a similar structure to a typical medical device design flow, starting with the assessment of our device requirements motivated by anticipated user needs and risk management. We will then discuss in detail the implementation of our design before demonstrating the system's functionality through verification testing. Planned future research projects for system validation are presented, as well as a discussion of the advantages and limitations of the implemented approach. The inertial-focused research stimulator will expand the possible research space in human feasibility studies, providing an alternative method for adaptive, patient-specific therapies.

II. Design Inputs and Requirements

We designed the DyNeuMo Mk-1 to be used as a research system for exploring how we might improve therapies with automated algorithms. The system-level requirements are summarized in Table I.

As a first design requirement, our research tool must preserve the stimulation capabilities of predicate therapy systems, to ensure there is no compromise to clinical care options. This approach is consistent with other state-of-the-art research tools provided for therapy research [16], [17]. The DyNeuMo Mk-1 provides stimulation capability equivalent to predicate deep brain, chronic pain, sacral (incontinence), and gastric stimulators, based on publicly-available manufacturer specifications.

As a general research tool, we aim to support a variety of potential use-cases. Motion-based states of interest include tremor (oscillations), general activity, gait and freezing, absolute posture, falls, and transient shocks. The detection of these motion states can then be applied by researchers exploring improved therapies for postural and gait instability in Parkinson's disease, transient stress events in mixed incontinence, posture effects in orthostatic hypertension, and titration of stimulation through circadian (sleep-wake) cycles. In addition to automated stimulation titration, inertial sensing also provides diagnostic information on patient activity without an added instrument burden on the user. The sensor also provides an alternative input for the patient to discretely interact with their device through explicit motor inputs, such as tap-activation.

The practical implementation of a motion-adaptive stimulator motivates additional design requirements. To help train and program the classifier, we need a method to gather individual patient data and configure the algorithm classifier based on their specific characteristics. We also need to implement a control method to map motion classification to the desired stimulation state. To minimize the impact on device longevity or avoid increasing recharge burden, the addition of the algorithm must not significantly increase the power consumption compared to baseline therapy, e.g. roughly $< 400\,\mu W$ for Parkinson's disease bilateral stimulation. Finally, we need a safe verification process to confirm the functional operation of the motion-adaptive algorithm in each patient.

bioRxiv preprint doi: https://doi.org/10.1101/2020.09.10.292284; this version posted September 11, 2020. The copyright holder for this preprint (which was not certified by peer review) is the author/funder. All rights reserved. No reuse allowed without permission.

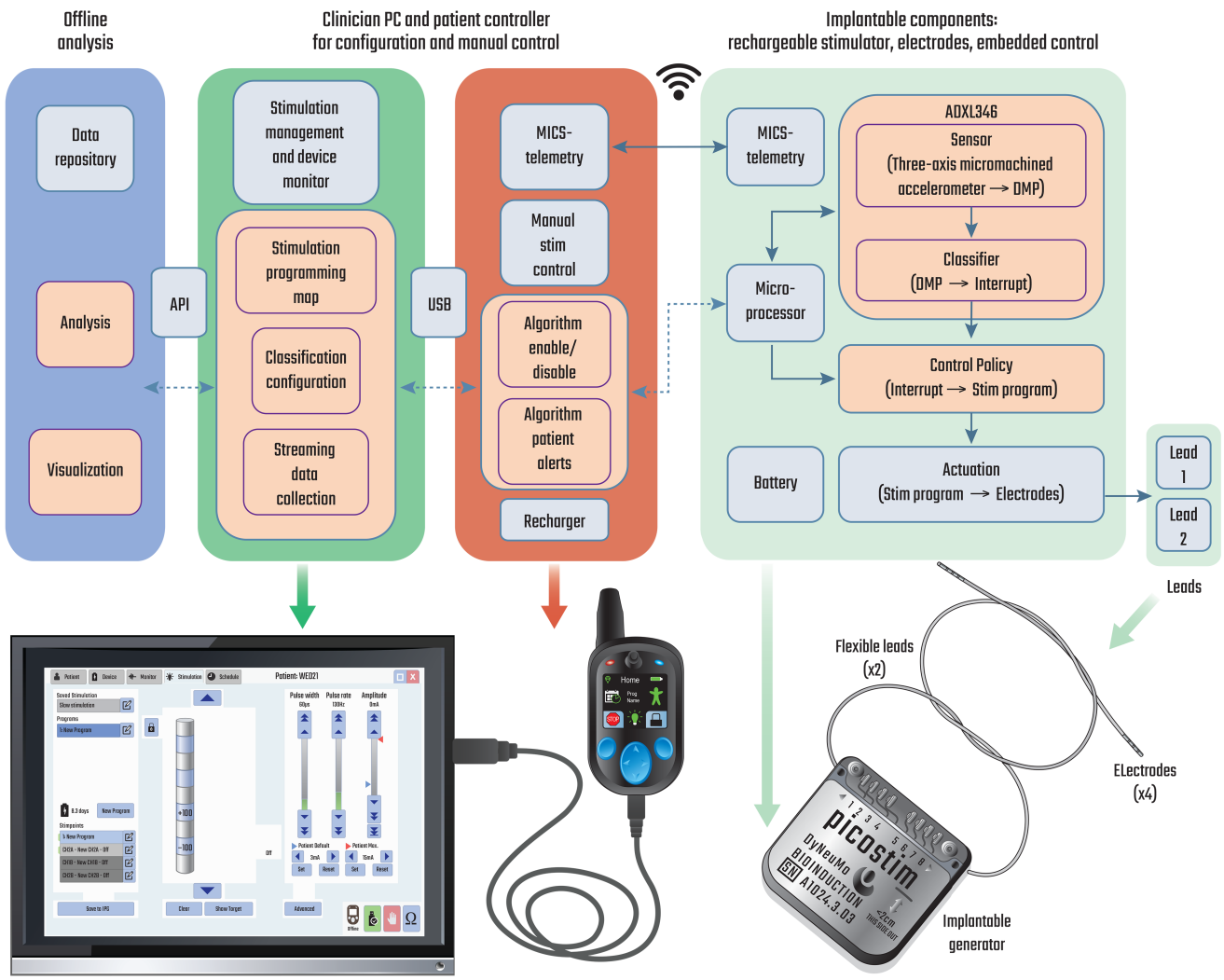

Fig. 2. Top: system block diagram for the DyNeuMo Mk-1 including the baseline functionality provided by the predicate Picostim (light blue) and the motion-adaptive algorithm additions (tan). Bottom: actual physical components for the DyNeuMo Mk-1 research system. Note that the research tool is observable through the firmware and software versions; mechanical components are largely reused. The USB connector between the patient programmer and tablet is for in-clinic programming. Research subjects use the handheld controller for at-home recharge and manual adjustments.

III. Risk Mitigations for Motion Adaptive Algorithms

In parallel with defining user needs for research, we followed the ISO 14971 risk management process to identify and address potential harms to the patients. Particular emphasis was placed on the automated algorithms, and the IEC 60601-1-10 was used as guidance for the design of physiologic control systems. Fig. 1 helps to illustrate the design considerations for closed-loop medical systems using this framework [1].

Using the physiologic control framework, we identified concerns and specified system mitigations. With an automated system, we need to limit stimulation to known-safe levels as the algorithm commands state changes. This "actuation limit" can be achieved by limiting the algorithm's access to specific pre-configured programs (patterns of stimulation) [18], [19]. The clinician-researcher then effectively defines a boundary on parameter states, with assurance that the algorithm never exceeds these limits. We also need to provide visibility to the users, both subject and clinician, on the immediate algorithm state. This observability was implemented on the patient controller with specific state alerts, including both the state of the algorithm (enabled/disabled) and the active stimulation program. All available states were also verified in software testing. Aligned with this specification, the patient controller also provides a mechanism to enable and disable the adaptive algorithm with a button press. Supporting the deactivation feature and stimulation limits, a pre-selected open-loop "fallback" program is also defined, which the stimulator defaults to upon manual exit of the algorithm [18]. Timing safeguards were also added including ramped transitions in intensity between stimulation programs (Fig. 6) to avoid subject discomfort such as paresthesia [20], and timing interlocks to avoid inadvertent rapid transitions at classification boundaries. As an additional safeguard out of precaution, we specified that the adaptive motion algorithm should be disabled during recharge to prevent changes in the stimulation program and ensure a known stimulation state is maintained throughout the process.

bioRxiv preprint doi: https://doi.org/10.1101/2020.09.10.292284; this version posted September 11, 2020. The copyright holder for this preprint (which was not certified by peer review) is the author/funder. All rights reserved. No reuse allowed without permission.

TABLE I
SYSTEM-LEVEL SPECIFICATIONS FOR THE DYNEUMO-MK1 INVESTIGATIONAL RESEARCH SYSTEM

User Needs	
Predicate Therapy Support	The research system must support existing stimulation parameters for therapy delivery (amplitude, frequency, pulse width)
Supported Therapy Research	Deep brain stimulation, chronic pain (spinal cord), incontinence and bladder control (sacral, pudendal nerve), gastroparesis (enteric)
Adaptive Sensing Scheme	Inertial accelerometer (three axis) – with DC accuracy for posture detection and AC capability for activity, tremor, gait, shocks and free-fall – flexibility for configuration to specific therapy needs
Algorithm Training Support	Ability to stream data for classifier training
Algorithm Power Allowance	The adaptive algorithm must draw no more than 20% of the nominal therapy power (e.g. 80 µW for deep brain stimulation)
Algorithm Latency	$<$ 20 ms from event detection to stimulation adjustment
Algorithm Verification	Minimal-risk verification procedure for the algorithm
Risk Mitigations	
Stimulation (Actuation) Limits	Pre-defined limits on the stimulation level to ensure patient safety; this includes transition ramps between stimulation program settings for tolerance (e.g. avoid paresthesia)
State Monitoring and Alerts	Algorithm state clearly shown on patient interface, ability to enable/disable with a button press; data logger for algorithm transitions for issue resolution
Fallback Mode	Pre-defined stimulation program for emergency exit from algorithm; disengagement of the automated algorithm during recharge
Physiological Dynamics	Stimulation timing interlocks to avoid inadvertent rapid transitions at classification boundaries

IV. SYSTEM DESIGN IMPLEMENTATION AND CONFIGURATION PROCESS

The DyNeuMo Mk-1 was implemented using the physiologic control model as the design framework (Fig. 1) [1]. To summarize the overall mental model of the design, our aim is to supplement the selection of stimulation parameters using manual and timer-scheduled adjustments with the addition of motion-adaptive changes. This can be considered an additional response loop that adjusts stimulation based on characteristic motion profiles. Using this abstracted framework, we summarize here the key attributes of the design, and how the user engages the adaptive stimulation functionality. The system block diagram is shown in Fig. 2 details the control and signal routing.

The inertial sensing is provided by an embedded ADXL346, an ultra-low power microelectromechanical system (MEMS) three-axis accelerometer manufactured by Analog Devices [21]. The classifier leverages the digital motion processor (DMP) embedded in the ADXL346. The DMP is configured through the clinician interface through a read/write register field. While this interface requires referring to the register table in the manufacturer-provided documentation [21] to fully utilize, it does provide full accessibility to the DMP, which was deemed desirable for research teams exploring custom algorithms. The sensing axis, combination of axes, thresholds, AC/DC coupling, and timing constraints for rules/threshold-based classification provided by the DMP are all accessible in the register field. To lower the user burden, a set of reference register tables is provided to facilitate DMP configuration using representative use cases for algorithms based on absolute posture, general activity/inactivity, and transient shocks.

The control policy is implemented by allowing the DMP to raise interrupts in the system. For this, DMP event marker signals are attached to digital inputs of the embedded microcontroller, and set as external interrupt sources. In the current design, two unique interrupts can be generated, based on the DMP register configuration (Fig. reffig3a). DMP interrupts are then able to select between two pre-configured stimulation programs to apply to the electrodes. The association between the stimulation program and the interrupt source is configured on the clinician's tablet programmer. In addition to the DMP-driven stimulation programs, the clinician also sets the default fallback program (per risk management) during configuration. The final control policy constraint is to ensure that the stimulation amplitude ramps during program transitions are acceptable to the patient; the ramp rate represents a user-controlled trade-off between side-effects, such as paresthesia and response time [22].

Given the multiple control inputs, we also needed to define the priority of changes being sent to the stimulation controller (Fig. 3b). Based on the analysis of use cases, we chose to use the latest command arising from either the motion classifier,

bioRxiv preprint doi: https://doi.org/10.1101/2020.09.10.292284; this version posted September 11, 2020. The copyright holder for this preprint (which was not certified by peer review) is the author/funder. All rights reserved. No reuse allowed without permission.

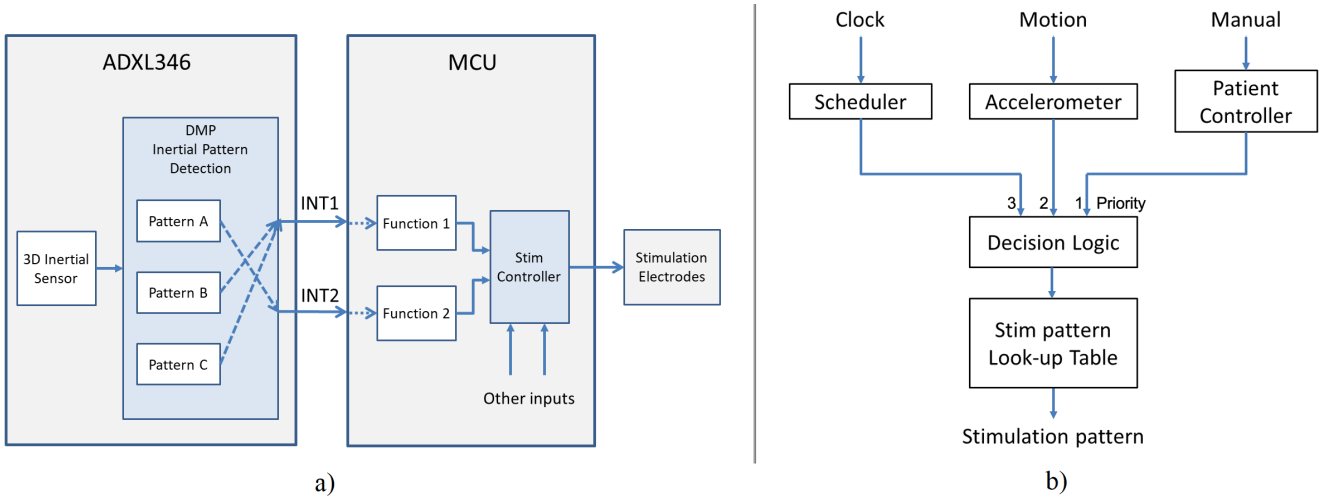

Fig. 3. Block diagrams showing (a) the pathway for the interrupts generated by the DMP and (b) the dynamic stimulation controller with its three types of inputs in increasing order of priority: fixed or scheduled, inertial detection, and manual control.

or manual intervention to determine the stimulation state. In addition to avoiding any confusion on prioritization, this approach also allows for an intuitive hierarchy of expected changes: fixed patterns of stimulation from the scheduler are overwritten by more frequent motion-based therapy fine-tuning, while manual intervention can always override these automated adjustments, including disabling them completely.

Once the motion-adaptive algorithm is configured, the verification of the automated system is supported through wireless telemetry to the patient programmer. When the motion-adaptive algorithm is activated with a button press, the screen indicator shows the current stimulation program in use. As the patient changes their motion state, the clinician-researcher can then verify that the expected stimulation program is activated by monitoring updates telemetered to the patient controller.

We also developed a system for classifier training and verification. The training module included real-time data streaming at 10 Hz through the MICS-band radio, while logging the accelerometer data to a file that can be used to determine register values for a motion-specific classifier. An example of the real-time streaming is provided in Fig. 4 which is compared to an external reference accelerometer. As illustrated in Fig. 5, the training module includes a wearable sensor that acts as a twin of the implant. The digital twin allows for register settings and classifier outcomes to be established before committing to the implant. Note that while streaming, the register table on the Clinician PC (tablet programmer) is also updated to display the implant's embedded classification state. The streaming rate was chosen to balance time resolution and power constrains.

V. System Verification

System verification ensures that the DyNeuMo Mk-1's motion adaptive algorithms have provided the desired automated stimulation adjustments, while not compromising the existing functionality of the Picostim. Most of the system hardware and software leverages the Picostim predicate, and verification testing protocols for functional areas such as stimulation, telemetry, and biocompatibility. The DyNeuMo Mk-1 incremental verification efforts focused on the accelerometer, firmware and software changes required to implement motion-adaptive stimulation.

We specifically focused on the expected use cases that leverage posture sensitivity, activity sensitivity, and tap/shock activation. Verification protocols demonstrated that the ADXL346 registers could be programmed appropriately for detection of specific inertial states, and that stimulation was then adjusted accordingly. For example, Fig. 6 shows a representative posture activation that occurs when a subject transitions from laying down to upright (at time t_1). Inertial transition points, timing interlocks, stimulation program mapping, and ramp rates were verified to operate as expected. Note that temporal responsiveness is fully programmable, as an example when a subject is laying down (at time t_2), the DMP could wait for several minutes to avoid symptoms while transitioning to sleep; however while standing up it could respond immediately to prevent falls. Other verification examples included activity vs inactivity (e.g. for essential tremor control or gait detection) by testing the AC-coupled accelerometer mode for classification. Finally, we verified tap/shock detection, which could be useful for transient events such as those related to urinary incontinence, or as a mechanical patient input that eliminates their need for interaction using the handheld controller. As illustrated in Fig. 7, the stimulator can respond in under 15 ms to a transient event, which falls within the reported acceptable latency for responding to mixed incontinence stress events [23]. The stimulation will stay active until the timing threshold for inactivity is met; in this case, one second. For improved specificity when required, the functionality of the double tap constraint, which can help prevent false positives, was also verified.

In addition to algorithm functional performance, we also verified other system requirements such as power consumption, patient interface controls, and the human factors for algorithm programming. The power consumption of the MEMS sensor, including classification, is approximately 40 µW, or 10% of the nominal therapy for a Parkinson's or essential tremor patient. Note that this estimate does not include any potential energy savings by turning down stimulation at night

bioRxiv preprint doi: https://doi.org/10.1101/2020.09.10.292284; this version posted September 11, 2020. The copyright holder for this preprint (which was not certified by peer review) is the author/funder. All rights reserved. No reuse allowed without permission.

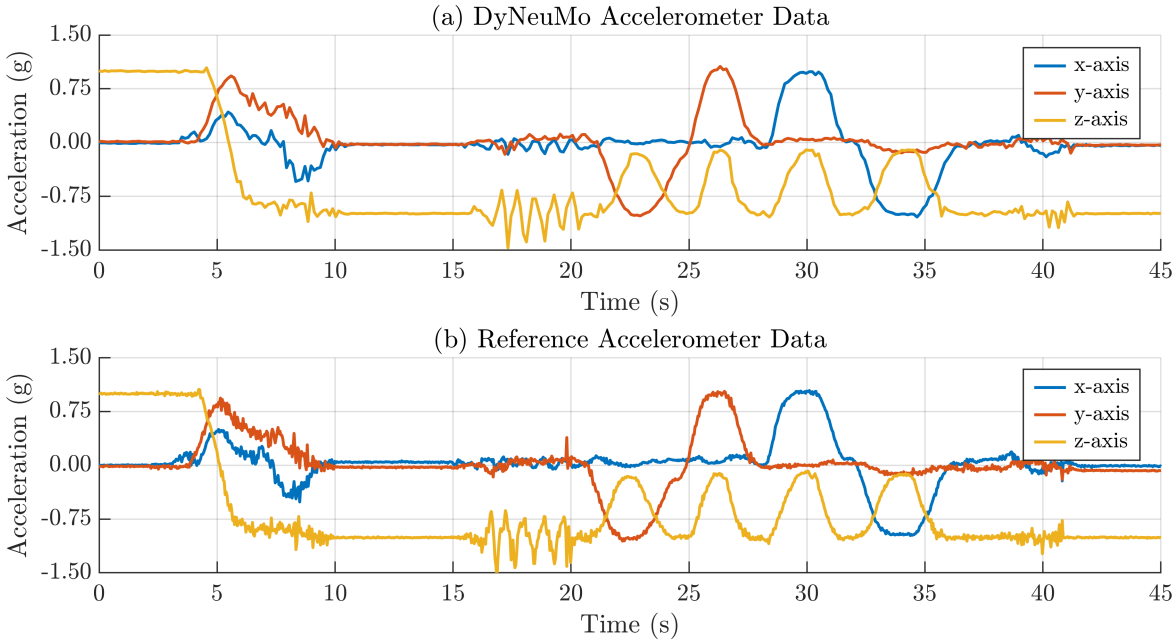

Fig. 4. Validation of the data stream used for gathering user specific training data for the classifier to recognize specific motion states. a) Data streamed from the DyNeuMo Mk-1 implantable system through the MICS-band radio, shown with interpolation. b) Reference accelerometer data used for external calibration. Note that the embedded accelerometer closely follows the reference, albeit at a lower sampling rate. Ultimate classifier specificity is limited using the DMP approach (see Section VII).

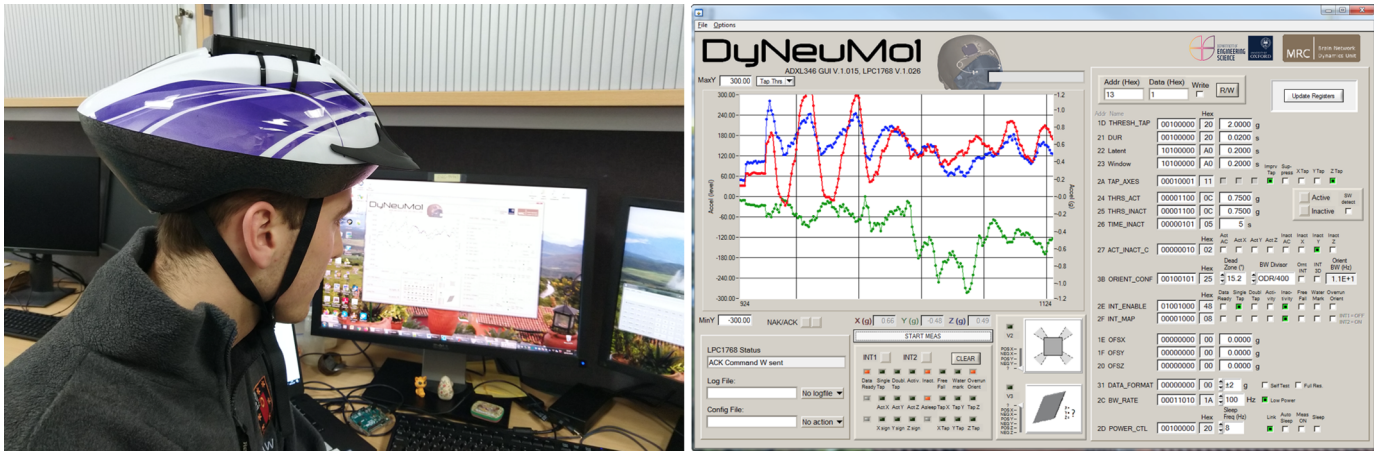

Fig. 5. Prototyping system for inertial measurements and classification. Left: the reference accelerometer can be mounted on different body locations for sensor measurements and classifier assessment; shown here on a bicycle helmet for assessing cranial placement. Right: user interface for displaying the signals, reading and writing registers, and assessing classifier outputs and interrupts.

or during periods of low activity. Other key performance results are summarized in Table II.

VI. System Validation Through Clinical Trials

We consider system validation to be addressed through research protocols targeting specific disease states. To facilitate these experiments, the DyNeuMo Mk-1 is being released as a research tool for the clinical neuroscience community including the design history files required to support investigational device approvals. In-line with our user requirements, we aim to support existing therapies that might benefit from motion-adaptive stimulation; if the algorithm is not successful, it can be disabled and the patient benefits at a minimum from the predicate therapy.

For the initial validation case, we are exploring the treatment of orthostatic hypertension, gait imbalance, and sleep disturbances using deep brain stimulation of the pedunculopontine nucleus [24], [25]. Our choice of this protocol is motivated by the relationship between inertial signal inputs, clinical state, and stimulation parameters that can be explored with motion-adaptive stimulation. Pending promising outcomes from this trial, we can expand out to other disease states where explicit mappings between inertial signals and desired stimulation exist, such as tremor, cervical dystonia, and urinary incontinence [14], [26].

bioRxiv preprint doi: https://doi.org/10.1101/2020.09.10.292284; this version posted September 11, 2020. The copyright holder for this preprint (which was not certified by peer review) is the author/funder. All rights reserved. No reuse allowed without permission.

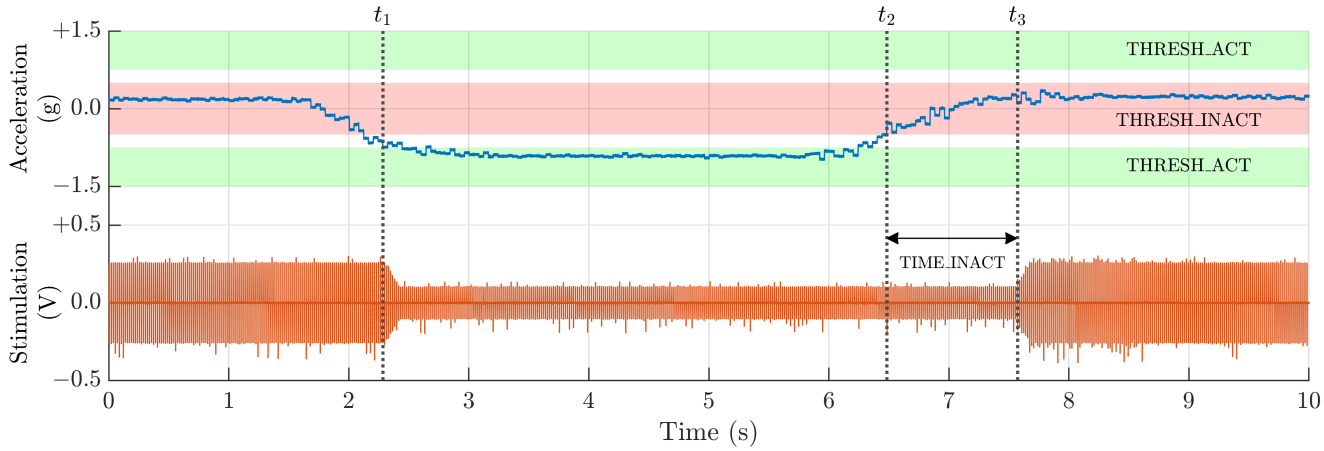

Fig. 6. Data from the posture algorithm verification showing a stimulation transition including transition ramps and adjustable response timing. Note that activity response is immediate (t_1), while detection of an inactivity event requires acceleration staying within the inactivity band for an adjustable interval t_2–t_3 (nominally one second in this example).

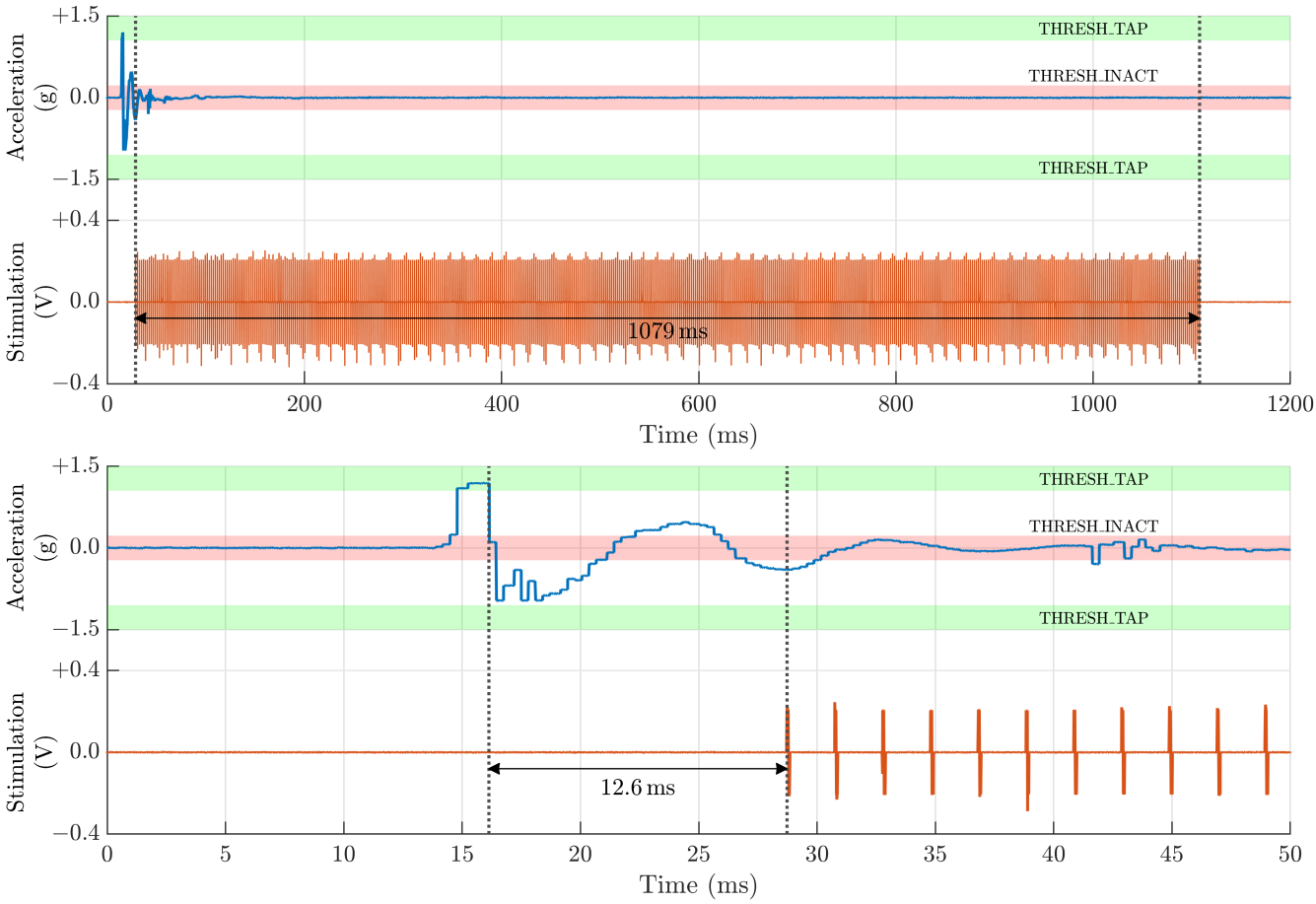

Fig. 7. Timing characterization for stimulation. Top panels: the initiation of stimulation due to a transient shock, that ceases after a programmed second of inactivity. Bottom panels: Resolving the response time to the shock, which shows stimulation initiating roughly 12.6 ms after detection.

VII. Limitations of the DyNeuMo Mk-1 adaptive algorithm

The DyNeuMo Mk-1 does have significant limitations worth noting; these are both technical and physiological. Perhaps most importantly, the current embodiment limits the measurement of motion to the device implantation site. In the case of a cranially-mounted system such as the predicate Picostim for deep brain stimulation, the specific measurement of hand tremor is therefore not supported; a more general correlation with general motion is required, which limits the specificity of the adaptive algorithm. An additional specificity error arises from the measurement limitations of a three-axis accelerometer. Specifically, the DMP can be confounded when estimating

bioRxiv preprint doi: https://doi.org/10.1101/2020.09.10.292284; this version posted September 11, 2020. The copyright holder for this preprint (which was not certified by peer review) is the author/funder. All rights reserved. No reuse allowed without permission.

TABLE II
TECHNICAL SPECIFICATIONS FOR THE DYNEUMO-MK1 INVESTIGATIONAL RESEARCH SYSTEM

Sensor Characteristics	
Inertial sensing	3-axis accelerometer, sensitive to 4 mg activity variations; dynamic range programmable ± 2 g to ± 16 g; typical sampling rate is 50 Hz
Stimulation Characteristics	
Channel Access	8 independent electrodes, typ. arrangement is 2 leads $\times$ 4 electrodes
Stimulation overview	2 independent channels, current-controlled, charge-balanced monophasic / symmetric biphasic with programmable interphasic delay
Multiplexing	Full matrix configuration across electrodes (inc. the case reference)
Stimulation magnitude	0–15 mA (0.05 mA increments) and 0–450 µs pulse width, fractionalized distribution available for guarded cathodes, etc; programmable and independent ramp rates
Recharge characteristics	Programmable passive and active recharge, with variable recharge ratio
Stimulation frequency	1–500 Hz frequency stimulation; can go sub-Hz with cycling enabled; independent frequencies available across stimulation channels
Stimulation cycling	Adjustable cycle timing for enabling burst stimulation
Stimulation programs	Up to 8 independent programs can be configured in the IPG and accessed by algorithms or patient controller
Algorithm Characteristics	
Motion Classification	Absolute orientation, activity vs non-activity (parameterized), shocks and free-fall detection
Stimulation Control policy	Detected classification states mapped to pre-configured stimulation programs with pre-specified transition ramp rate. Two independent stimulation programmes tied to motion states, and a default fall-back.
Risk mitigations	Algorithm implementation aligns to 60601-1-10 specifications for physiologic control loops (e.g. limits, alerts, data logs, fallback modes)
Other System Characteristics	
Battery capacity, recharge cycle	50 mAh 3.6 V Lithium Ion, minimal fade, < 2 h recharge
Mechanical Characteristics	Cranial-mount, 7.4 cc titanium package, with 2 leads for 4 contacts/lead, typical bal-seal style modular fixation system
Telemetry/External Sensor and Stimulation Synchronisation	MICS-band radio, > 1 m distance, with hand-held module
MRI compatibility (in process)	MRI conditional imaging for 1.5 T and 3 T imagers
Electrodes	Modular design with ability to customize lead length and electrode spacing; currently supports brain stimulation and peripheral extradural electrodes and cuffs
Clinician programmer	Standard consumer tablet running Windows 10

posture by the superposition of linear acceleration with the gravitational field. This concern can be addressed somewhat by adjustment of the time and level constraints before generating an interrupt, but this mitigation is a trade-off with transition latency. While a gyroscope might help improve specificity, it also requires significantly more power than most therapies due to the principles of MEMS-based Coriolis sensing. Finally, our use of interrupt source to determine the stimulation program currently limits us to transitions between two stimulation states. If this is found to be severely limiting, we could perform more advanced interrupt masking and explore adaptive DMP register adjustments in the future. As one example of physiological limitations, the time dynamics between stimulation and physiological response need to align with the adaptive algorithm capabilities. For example, if stimulation requires extended time to take effect, then the utility of adaptive stimulation titration might be limited. At this time, we believe that several clinically-meaningful adaptive algorithms can be implemented with the first generation research tool, and we can refine future designs based on relevant clinical experience.

bioRxiv preprint doi: https://doi.org/10.1101/2020.09.10.292284; this version posted September 11, 2020. The copyright holder for this preprint (which was not certified by peer review) is the author/funder. All rights reserved. No reuse allowed without permission.

VIII. Summary

There is growing interest in adaptive medical devices, particularly using neuromodulation, to improve therapies by automatically adjusting stimulation based on clinically-relevant physiological features. In response to the worldwide demand for research tools to support clinical studies into adaptive neuromodulation techniques, we have developed a fully-implantable medical device that responds to inertial signals. The advantages of our approach are that it is 1) relatively easy to configure the classifier for clinically-relevant states, 2) relatively inexpensive to manufacture, and 3) highly reliable as a method. The limitations of this approach include limited specificity for detection away from the implant location, and confounds from superimposed motion when posture measurement is the goal. Even with these limitations, intertial sensing could be a practical solution for several unmet needs, which can be validated in first-in-human studies using the DyNeuMo Mk-1 research system. It could also serve as a secondary input to improve the performance of alternative methods using bioelectrical signals. As consumer electronics and the internet-of-things continue to evolve, we believe future medical devices will benefit from continued adoption of mainstream technology, which will provide meaningful clinical solutions with favourable economics and reliability.

Acknowledgment

The authors would like to thank Josephine Blyth for testing the reference accelerometer on a bicycle helmet.

Disclosures

The University of Oxford has research agreements with Bioinduction Ltd. Tim Denison also has business relationships with Bioinduction for research tool design and deployment.

References

[1] A. Gunduz, E. Opri, R. Gilron, V. Kremen, G. Worrell, P. Starr, K. Leyde, and T. Denison, "Adding wisdom to 'smart' bioelectronic systems: a design framework for physiologic control including practical examples," *Bioelectron. Med.*, vol. 2, no. 1, pp. 29–41, Mar. 2019.

[2] F. T. Sun and M. J. Morrell, "The rns system: responsive cortical stimulation for the treatment of refractory partial epilepsy," *Expert Rev. Med. Devices*, vol. 11, no. 6, pp. 563–572, Nov. 2014.

[3] A. Schulze-Bonhage, "Long-term outcome in neurostimulation of epilepsy," *Epilepsy Behav.*, vol. 91, pp. 25–29, Feb. 2019.

[4] S. Little, A. Pogosyan, S. Neal, B. Zavala, L. Zrinzo, M. Hariz, T. Foltynie, P. Limousin, K. Ashkan, J. FitzGerald, A. L. Green, T. Z. Aziz, and P. Brown, "Adaptive deep brain stimulation in advanced parkinson disease: Adaptive dbs in pd," *Ann. Neurol.*, vol. 74, no. 3, pp. 449–457, Sep. 2013.

[5] A. Priori, G. Foffani, L. Rossi, and S. Marceglia, "Adaptive deep brain stimulation (adbs) controlled by local field potential oscillations," *Exp. Neurol.*, vol. 245, pp. 77–86, Jul. 2013.

[6] N. C. Swann, C. de Hemptinne, S. Miocinovic, S. Qasim, J. L. Ostrem, N. B. Galifianakis, M. S. Luciano, S. S. Wang, N. Ziman, R. Taylor, and P. A. Starr, "Chronic multisite brain recordings from a totally implantable bidirectional neural interface: experience in 5 patients with parkinson's disease," *J. Neurosurg.*, vol. 128, no. 2, pp. 605–616, Feb. 2018.

[7] S. Stanslaski, P. Afshar, P. Cong, J. Giftakis, P. Stypulkowski, D. Carlson, D. Linde, D. Ullestad, A.-T. Avestruz, and T. Denison, "Design and validation of a fully implantable, chronic, closed-loop neuromodulation device with concurrent sensing and stimulation," *IEEE Trans. Neural Syst. Rehabil. Eng.*, vol. 20, no. 4, pp. 410–421, Jul. 2012.

[8] M. Arlotti, L. Rossi, M. Rosa, S. Marceglia, and A. Priori, "An external portable device for adaptive deep brain stimulation (adbs) clinical research in advanced parkinson's disease," *Med. Eng. Phys.*, vol. 38, no. 5, pp. 498–505, May 2016.

[9] A. Zhou, S. R. Santacruz, B. C. Johnson, G. Alexandrov, A. Moin, F. L. Burghardt, J. M. Rabaey, J. M. Carmena, and R. Muller, "A wireless and artefact-free 128-channel neuromodulation device for closed-loop stimulation and recording in non-human primates," *Nat. Biomed. Eng.*, vol. 3, no. 1, pp. 15–26, Jan. 2019.

[10] G. Appelboom, E. Camacho, M. E. Abraham, S. S. Bruce, E. L. Dumont, B. E. Zacharia, R. D'Amico, J. Slomian, J. Y. Reginster, O. Bruyère, and E. S. Connolly, "Smart wearable body sensors for patient self-assessment and monitoring," *Arch. Public Health*, vol. 72, no. 28, Dec. 2014.

[11] K. den Dulk, L. Bouwels, F. Lindemans, I. Rankin, P. Brugada, and H. J. Wellens, "The activitrax rate responsive pacemaker system," *Am. J. Cardiol.*, vol. 61, no. 1, pp. 107–112, Jan. 1988.

[12] D. M. Schultz, L. Webster, P. Kosek, U. Dar, Y. Tan, and M. Sun, "Sensor-driven position-adaptive spinal cord stimulation for chronic pain," *Pain Physician*, vol. 15, no. 1, pp. 1–12, Jan. 2012.

[13] J. A. Herron, M. C. Thompson, T. Brown, H. J. Chizeck, J. G. Ojemann, and A. L. Ko, "Chronic electrocorticography for sensing movement intention and closed-loop deep brain stimulation with wearable sensors in an essential tremor patient," *J. Neurosurg.*, vol. 127, no. 3, pp. 580–587, Sep. 2017.

[14] M. Malekmohammadi, J. Herron, A. Velisar, Z. Blumenfeld, M. H. Trager, H. J. Chizeck, and H. Brontë-Stewart, "Kinematic adaptive deep brain stimulation for resting tremor in parkinson's disease: Letters: New observations," *Mov. Disord.*, vol. 31, no. 3, pp. 426–428, Mar. 2016.

[15] Bioinduction Ltd. (2019) Picostim. Accessed: 29 Aug. 2020. [Online]. Available: https://bioinduction.com/the-solution/

[16] A. G. Rouse, S. R. Stanslaski, P. Cong, R. M. Jensen, P. Afshar, D. Ullestad, R. Gupta, G. F. Molnar, D. W. Moran, and T. J. Denison, "A chronic generalized bi-directional brain–machine interface," *J. Neural Eng.*, vol. 8, no. 3, p. 036018, Jun. 2011.

[17] S. Stanslaski, J. Herron, T. Chouinard, D. Bourget, B. Isaacson, V. Kremen, E. Opri, W. Drew, B. H. Brinkmann, A. Gunduz, T. Adamski, G. A. Worrell, and T. Denison, "A chronically implantable neural coprocessor for investigating the treatment of neurological disorders," *IEEE Trans. Biomed. Circuits Syst.*, vol. 12, no. 6, pp. 1230–1245, Dec. 2018.

[18] N. C. Swann, C. de Hemptinne, M. C. Thompson, S. Miocinovic, A. M. Miller, R. Gilron, J. L. Ostrem, H. J. Chizeck, and P. A. Starr, "Adaptive deep brain stimulation for parkinson's disease using motor cortex sensing," *J. Neural Eng.*, vol. 15, no. 4, p. 046006, Aug. 2018.

[19] P. Afshar, A. Khambhati, S. Stanslaski, D. Carlson, R. Jensen, D. Linde, S. Dani, M. Lazarewicz, P. Cong, J. Giftakis, P. Stypulkowski, and T. Denison, "A translational platform for prototyping closed-loop neuromodulation systems," *Front. Neural Circuits*, vol. 6, 2013.

[20] J. A. Herron, M. C. Thompson, T. Brown, H. J. Chizeck, J. G. Ojemann, and A. L. Ko, "Cortical brain–computer interface for closed-loop deep brain stimulation," *IEEE Trans. Neural Syst. Rehabil. Eng.*, vol. 25, no. 11, pp. 2180–2187, Nov. 2017.

[21] Analog Devices. (2009) ADXL346, revision C. Accessed: 29 Aug. 2020. [Online]. Available: https://www.analog.com/media/en/technical-documentation/data-sheets/ADXL346.pdf

[22] B. D. Swan, L. B. Gasperson, M. O. Krucoff, W. M. Grill, and D. A. Turner, "Sensory percepts induced by microwire array and dbs microstimulation in human sensory thalamus," *Brain Stimul.*, vol. 11, no. 2, pp. 416–422, Mar. 2018.

[23] I. Nissenkorn, M. Shalev, P. Radziszewski, P. Dobronski, A. Borkowski, and P. R. de Jong, "Patient-adjusted intermittent electrostimulation for treating stress and urge urinary incontinence," *BJU Int.*, vol. 94, no. 1, pp. 105–109, Jul. 2004.

[24] I. Arnulf, M. Ferraye, V. Fraix, A. L. Benabid, S. Chabardès, L. Goetz, P. Pollak, and B. Debû, "Sleep induced by stimulation in the human pedunculopontine nucleus area," *Ann. Neurol.*, vol. 67, no. 4, pp. 546–549, Apr. 2010.

[25] C. Huang, H. Chu, Y. Zhang, and X. Wang, "Deep brain stimulation to alleviate freezing of gait and cognitive dysfunction in parkinson's disease: Update on current research and future perspectives," *Front. Neurosci.*, vol. 12, p. 29, Feb. 2018.

[26] C.-H. Kuo, G. A. White-Dzuro, and A. L. Ko, "Approaches to closed-loop deep brain stimulation for movement disorders," *Neurosurg. Focus*, vol. 45, no. 2, p. E2, Aug. 2018.