Faculdade de Engenharia da Universidade do Porto

Towards adaptive Deep Brain Stimulation for Parkinson's disease: From research protocols implementation in clinical settings to the development of computational tools

Andreia Magalhães Oliveira



Programa Doutoral em Engenharia Biomédica

Supervisor:
Prof. Dr. Paulo de Castro Aguiar
Instituto de Investigação e Inovação em Saúde

Co-supervisors:
Prof. Dr. Andrea A. Kühn
Charité Universitätsmedizin- Berlin
Prof. Dr. Rui Vaz
Faculdade de Medicina da Universidade do Porto

14th October, 2024

Towards adaptive Deep Brain Stimulation for Parkinson's disease: From research protocols implementation in clinical settings to the development of computational tools

Andreia Magalhães Oliveira

Programa Doutoral em Engenharia Biomédica

Resumo

A estimulação cerebral profunda (ECP) do núcleo subtalámico é uma terapia recomendada em doentes com Doença de Parkinson (DP) avançada. Os seus benefícios e eficácia estão comprovados, melhorando a qualidade de vida dos doentes através da redução dos sintomas motores e não motores. O mecanismo por detrás do sucesso terapêutico da ECP permanece, em grande parte, desconhecido, e estão continuamente a encontrar-se desafios para alcançar os parâmetros ideais para a ECP. Um campo inovador é a ECP adaptativa *(aDBS)* com controlo em malha fechada, que integra inovações no desenvolvimento do dispositivo para ECP e na procura de biomarcadores patológicos. A aDBS visa proporcionar uma estimulação adaptada às necessidades dos doentes através de uma abordagem de medicina personalizada. Para alcançar a aDBS, precisamos de compreender melhor o mecanismo de ação da ECP assim como os seus parâmetros de estimulação. Com a possibilidade agora disponível de registar os *Local Field Potentials* (LFPs) no local de estimulação ou nas áreas vizinhas, surge uma nova oportunidade para explorar a atividade neuronal e o impacto da estimulação in vivo. Este trabalho foca-se nesta nova janela de ação e visa preparar ferramentas de suporte para a nova geração de ECP para DP com controlo em malha-fechada baseado em dados e procurando uma maior eficácia personalizada.

Começamos por apresentar uma revisão de literatura que explora a utilização de técnicas de Aprendizagem Automática (AA) no contexto da ECP para DP. As técnicas de AA estão na frente de desenvolvimentos como a identificação de biomarcadores eletrofisiológicos e o desenvolvimento de sistemas de controlo personalizados. Neste trabalho, exploramos como estas técnicas estão a ajudar a responder os desafios no desenvolvimento de ECP em malha fechada, particularmente na identificação de biomarcadores eletrofisiológicos.

De seguida, descrevemos o processo, desde a conceptualização até à implementação, de um protocolo de investigação atualmente operacional, com múltiplos atores envolvidos, para a análise de LFPs no contexto da DP. Foi desenvolvida e publicada uma *toolbox* computacional para visualização e análise de dados LFPs extraídos de neuroestimuladores. Pode ser usada de duas formas: através da interface do utilizador e como uma biblioteca de funções. O nosso objetivo era torná-la acessível e utilizável independentemente da experiência em programação do utilizador. A *toolbox*, DBScope, foi criada para promover o processo de tomada de decisão clínica e a identificação de biomarcadores clinicamente relevantes. São também discutidos casos de estudos com dados recolhidos deste protocolo e analisados com o DBScope, não só exemplificando a sua utilidade, mas iniciando a discussão do potencial científico do protocolo implementado.

Na última componente deste trabalho, aprofundámos a análise dos sinais das LFPs, em particular a variabilidade temporal do perfil espectral e os biomarcadores estabelecidos, como a banda beta. A nossa análise aplica técnicas exploratórias neste campo de análises, como os parâmetros de *Hjorth* e a entropia de *Shannon,* para descrever e fornecer *insights* sobre a não estacionaridade do sinal.

Neste trabalho multifacetado contribuímos em vários ângulos: na síntese de informação sobre o uso de AA no contexto de ECP, na implementação de protocolos de investigação longitudinais e multidisciplinares, ferramentas de análise e visualização em *open-access* para a comunidade de investigadores e clínicos, e *insights* sobre a dinâmica temporal de biomarcadores no domínio das frequências.

Abstract

Deep brain stimulation (DBS) of the subthalamic nucleus is a therapy applied in patients with advanced Parkinson's disease (PD). Its benefits and effectiveness are established, improving the quality of life of patients by reducing motor and non-motor symptoms. The mechanism behind the therapeutic success of DBS remains mostly unknown, and challenges to achieving optimal DBS therapy are emerging. One innovative field is adaptive Deep Brain Stimulation (aDBS) with closed-loop, which integrates innovations in the device's development for DBS and the search for pathological biomarkers. aDBS aims to provide stimulation that is adapted to the needs of the patients using a personalized medicine approach. To achieve aDBS, we need to better understand the mechanism of action of DBS and better orient and modulate the stimulation parameters. With the now available possibility to record Local Field Potentials (LFPs) at the site of stimulation or in the neighboring areas, a window into neuronal communication i*n vivo* emerges. This work acts on this window of action and aims to prepare the new generation of DBS for PD with data-driven feedback control for personalized improved effectiveness.

First, we present a literature review exploring the use of Machine Learning (ML) techniques in the context of DBS for PD. Machine Learning techniques are in the front of developments such as the identification of electrophysiological biomarkers and the establishment of personalized control systems. In the review, we explore how these techniques help overcome the challenges in the development of closed-loop DBS, particularly in defining electrophysiological biomarkers.

Secondly, we describe a research protocol, from conceptualisation to implementation, with multiple actors engaged, aiming to analyse LFPs in the context of PD. We then present a computational toolbox for visualisation and analysis of LFP data extracted from neurostimulators. It can be operated in two ways: via user interface and programmatically as a library function. We aimed to make it accessible and usable regardless of the user's programming background. The toolbox, DBScope, is set to promote the clinical decision-making process and identification of clinically relevant biomarkers. Additionally, we also discuss case studies from data collected in the protocol and analysed with DBScope, showcasing not only its utility but initiating the discussion of the scientific potential of the protocol implemented.

In the last part of this work, we delve into the analysis of the LFPs signals, in particular, the temporal variability of the spectral profile and established biomarkers such as the beta band. Our analysis applies unexplored techniques in the field, as Hjorth parameters and Shannon’s entropy, to describe and provide insights of the overlooked non-stationarity of the signal.

In this multifaceted work we contributed from various angles: with the synthesis of information regarding the use of ML in the context of DBS, the implementation of longitudinal and multidisciplinary research protocols, development of open-access tools for the broad community of researchers and clinicians, and insights on the conceptualization of spectral biomarkers.

Agradecimentos

As palavras não me surgem em quantidade. Quero acreditar que nos momentos certos, surgem em qualidade. E para mim, os agradecimentos, num único momento do tempo, são imperfeitos, incompletos. Acredito que estes, nesta única página e num momento, não serão exceção. Espero, ao longo destes anos, ter retribuído tudo de tão bonito que me foi dado. O carinho, o apoio, os abraços incontáveis e tantos outros sorrisos. E se não o fiz, espero ir a tempo, e além destas páginas.

Gostava de agradecer à equipa que me acompanhou estes anos. Aos meus orientadores e coorientadores, Paulo, Rui e Andrea, por partilharem comigo a sua experiência e me ajudarem a chegar até aqui. Ao NCN destes anos todos, Miguel, Zé, Joana, Cátia, Eduardo, Palma, Catarina, Rui, Beatriz, pelo companheirismo, pelas pequenas e grandes lições, pequenas e grandes discussões. Ao Domingos e à Ana pela amizade, e o apoio que sempre fez toda a diferença.

Aos meus amigos, que com medo de listagens vou omitir nomes, por todo o carinho, por todas as memórias, pelos anos e anos, e muitos mais pela frente de companheirismo e partilha. À Cris, Sara e Juliette, os meus portos-seguros, para os quais não chegam palavras. Foram anos ricos, de muitas pessoas a encherem-me de carinho desmedido, vindo de todos os cantos do mundo (até da Antártida!).

Ao Zé, que me mostrou todas as cores que a vida pode ter, que acalma todo o ruído em mim com o seu amor.

À minha família, aos meus avós, à tia Alice, aos meus pais, Justino e Emilia, e ao meu irmão André. Não podia ter mais sorte, não podia pedir mais. Tenho tanto orgulho em vocês, e espero conseguir fazer-vos orgulhosos também.

A tese dedico-a à Tia Graça, pela inspiração e o exemplo. Todos atravessamos as nossas tempestades, às vezes saímos delas e outras elas de nós: ficam as histórias da nossa passagem.

Table of Contents

RESUMO ..... **I**

ABSTRACT ..... **III**

LIST OF FIGURES ..... **X**

LIST OF TABLES ..... **XIX**

ABBREVIATIONS ..... **XX**

CHAPTER 1: INTRODUCTION **1**

1.1 Supervising team 2
1.2 Objectives 2
1.3 Contributions 4
1.4 Thesis Outline 5

CHAPTER 2: LITERATURE REVIEW AND STATE-OF-THE-ART **6**

2.1 Parkinson's Disease 6
2.1.1 Epidemiology *6*
2.1.2 Etiopathogenesis *7*
2.1.3 Clinical Presentation *8*
2.1.4 Diagnosis *9*
2.2 Treatment 10
2.2.1 Pharmacological Treatment *10*
2.2.2 Surgical Treatment *10*
2.2.3 Deep Brain Stimulation for Parkinson's Disease *10*
2.3 Deep Brain Stimulation 12
2.3.1 History *12*
2.3.2 Mechanisms *12*
2.3.3 Electrodes Design *14*
2.3.4 Target for DBS *14*
2.3.5 Biocompatibility *15*
2.3.6 Stimulation therapy adjustment *15*
2.3.7 The effect of varying parameters *16*
2.3.8 Advances in stimulation methods *17*
2.3.9 Biomarkers *18*
2.4 Adaptive and Closed-Loop DBS 22
2.4.1 Closed-Loop DBS *23*
2.4.2 aDBS Control Strategies *24*
2.4.3 Model-Based Algorithms for Optimizing DBS Therapy *25*
2.4.4 Stimulation Challenges *26*
2.4.5 Wearables *26*
2.4.6 Perspectives and Challenges for aDBS *26*
2.5 Percept PC 27
2.5.1 Signal processing parameters *30*
2.6 Conclusion 30

CHAPTER 3: MACHINE LEARNING CONTRIBUTIONS TOWARDS CLOSING THE LOOP FOR DBS **32**

3.1 Core concepts in Machine Learning 34
3.2 The quest for effective Biomarkers 38
3.2.1 Motor Biomarkers 39
3.2.2 Electrophysiology Biomarkers 40
3.2.3 Other Biomarkers 42
3.3 Bringing adaptive DBS to the clinic 43
3.3.1 Adaptive DBS control strategies 43
3.3.2 Amplitude modulation 44
3.3.3 Frequency and pulse-width modulation 45
3.3.4 Phase modulation 45
3.4 Open challenges in aDBS – Future Roadmap 45
3.5 Conclusion 47

CHAPTER 4: FRAMEWORK FOR ANALYSIS OF LOCAL FIELD POTENTIALS IN PARKINSON'S DISEASE: FROM CONCEPT TO IMPLEMENTATION 48

4.1 Ethics Approval 48
4.2 Conceptualization 48
4.3 Study Protocol: BrainSense streaming sessions with stimulation levels 49
4.3.1 Initial Notes 49
4.3.2 Preparation 49
4.3.3 Section 1: Defining the Patient's Baseline 49
4.3.4 Section 2: Stimulation Study in the Left Hemisphere without Movement - Tremor 49
4.3.5 Section 3: Stimulation Study in the Right Hemisphere without Movement - Tremor 50
4.3.6 Section 4: Stimulation Study in the Left Hemisphere without Movement - Rigidity 50
4.3.7 Section 5: Stimulation Study in the Right Hemisphere without Movement - Rigidity 50
4.3.8 Section 6: Stimulation Study in the Left Hemisphere with Movement - Open/Close Hand 50
4.3.9 Section 7: Stimulation Study in the Right Hemisphere with Movement - Open/Close Hand 50
4.3.10 Section 8: Final Stimulation Recording 51
4.4 Insights from implementation 51
4.5 Protocol management 51
4.6 Building a Database 52
4.7 Microlesion protocol 52
4.7.1 Adaptation of protocol and clinical circuit for Microlesion study 52
4.8 Conclusion 53

CHAPTER 5: DBSCOPE AS KEY TOOL FOR THE VISUALIZATION AND ANALYSIS OF SENSING DATA FROM DEEP BRAIN STIMULATION 54

5.1 Methods 55
5.1.1 Software 55
5.1.2 Sensing data 55
5.1.3 Ethics 55
5.1.4 Toolbox features 55
5.1.5 Objected-Oriented Programming 56
5.2 Results 56
5.2.1 User interface 56
5.2.2 Operational Workflow 57
5.3 Case-Studies 58
5.3.1 Case study: out-of-clinic recordings 60
5.3.2 Case study: in-clinic recordings 62
5.4 Discussion 64

5.5 Conclusion 66

CHAPTER 6: ANALYSIS OF TEMPORAL DYNAMICS IN THE SPECTRAL PROFILES OF LOCAL FIELD POTENTIALS RECORDINGS 67

6.1 Dataset processing 67
6.2 Analysis of the frequency spectrum 68
6.2.1 Methods 69
6.2.2 Results 70
6.2.3 Discussion 70
6.3 Study and application of Hjorth parameters 71
6.3.1 Methods 72
6.3.2 Results 73
6.3.3 Discussion 76
6.4 Short-term and long-term temporal dynamics of the spectral profile of the LFP recordings 77
6.4.1 Methods 78
6.4.2 Results 79
6.4.3 Discussion 82
6.5 Conclusion 83

CHAPTER 7: FINAL REMARKS AND CONCLUSIONS 84

7.1 What about the concept of biomarkers? 84
7.2 Personalized medicine and patient variability 84
7.3 Hardware versus software efforts 85
7.4 Data-driven explorations in the field 86
7.5 Future Steps 86
7.6 Last words 87

REFERENCES 89

ANNEXES 104

Chapter 3 - Supplementary Material 104
Ethics Committee Proposal 114
smartDBS: Participant Information 115
DBScope User Guide 116

List of Figures

Figure 1.1: Project host and co-host institutions.
In the first image of the left is the i3S, and in the middle picture the Centro Hospitalar Universitário de São João, both in Porto, Portugal. The last picture on the right are the facilities of Charité Universitätsmedizin Berlin, Germany.
.....2

Figure 2.1 Representation of a simplified schematic of the neuronal circuits involving the basal ganglia.
Anatomy and physiology of Parkinson's disease (PD) motor manifestations. A simplified schematic of the neuronal circuits involving the basal ganglia, thalamus, and cortex and their derangement in PD. For simplicity, only the direct pathway is shown. It normally functions to facilitate movements (left), but in PD the output is attenuated (right). The midbrain substantia nigra pars compacta (SNc) provide dopaminergic input to the putamen (Pu), which is excitatory to the direct pathway. The putamen inhibits (red) the globus pallidus interna (GPi), which subsequently inhibits the thalamus (Th). The thalamus projects excitatory input (green) to the motor cortex. In PD, degeneration within the SNc leads to net increased inhibition of the thalamocortical projection. The indirect pathway (not shown), including the globus pallidus externa (GPe) and subthalamic nucleus, is inhibited by SNc dopaminergic input and normally functions to repress movements, but its activity is enhanced in PD. Adapted from (Shulman, De Jager, & Feany, 2011).
.....7

Figure 2.2 Classical model of the Basal Ganglia.
The classical model (center) simplifies basal ganglia connectivity (left) by highlighting the role of dopamine on direct and indirect pathway activity and motor output. In the healthy condition (center), dopamine (blue) from the SNc to the striatum activates direct pathway (green) and inhibits indirect pathway (red) MSNs. This effect decreases GPi output, releasing inhibition on the thalamus and cortex and promoting movement. In the parkinsonian condition (right), loss of SNc dopamine causes hypoactivity of the direct pathway and hyperactivity of the indirect pathway that leads to excessive GPi output. As a result, over inhibition of the thalamus and cortex leads to a suppression of movement. Adapted from (McGregor & Nelson, 2019).
.....8

Figure 2.3 Infographic about clinical information of Parkinson's Disease.
Adapted from presentation at WhatElse seminar in October 2022, Porto, Portugal.
.....9

Figure 2.4 Electrode implantation Deep Brain Stimulation.
The lead for deep-brain stimulation is implanted in either the subthalamic nucleus or the internal segment of the globus pallidus. The lead passes through a burr hole in the skull. Attached to the lead is a connecting wire, which is tunnelled under the skin of the scalp and neck to the anterior chest wall, where it is connected to an impulse generator. Adapted from (Okun, 2012).
.....11

Figure 2.5 Networks Effects of Deep Brain Stimulation.
Deep-brain stimulation has broad effects on neural networks in addition to, or because of, its local influences. Motor pathways are complex, and their disturbance in Parkinson's disease is likewise far-ranging. Deep-brain stimulation modulates the feedback loops that ultimately determine motor control. Adapted from (Okun, 2012).
.....11

Figure 2.6 Electrification of decapitation in Bologna in 1802.
To left, the direct stimulation of the cortical surface is visible. From Plate IV in J. Aldini. Essai théorique et experimental sur le galvanisme. Paris: Fournier Fils, 1804; courtesy of the Accademia delle Scienze di Torino. Adapted from (Zago, Ferrucci, Fregni, & Priori, 2007).
……12

Figure 2.7 Local Effects of Deep Brain Stimulation.
The local effects of deep-brain stimulation tend to result in the inhibition of neuronal-cell bodies (–) and the excitation (+) of neighboring axons. In addition, astrocytes are stimulated to release calcium, which may lead to a release of glutamate (GLUT) and adenosine (ADO), as well as local increases in cerebral blood flow. Finally, there is evidence that deep-brain stimulation can induce local and possibly distal proliferation of neural precursor cells. Adapted from (Okun, 2012).
……13

Figure 2.8 Deep Brain Stimulation electrode configurations.
Dark grey regions correspond to electrode contacts that can be activated to deliver current. A) Common electrode configurations for DBS. B) Modes of stimulation according to the type of DBS system implemented. Adapted from (Krauss et al., 2021).
……14

Figure 2.9 Functional electrical stimulation parameters.
Pulse width, amplitude, and frequency define the muscles stimulated, force, and quality of the contraction. Adapted from (Marquez-Chin & Popovic, 2020).
……16

Figure 2.10 Illustrations showing how LFP is recorded during the 3 periods.
(Left) During the DBS surgery, LFP can be recorded through the explorative micro/macroelectrodes, which also record SUA to optimize lead localization. ECoG and EMG signals may be simultaneously collected for clinical and/or research usages. (Middle) During the perioperative period, normally 3–4 days after the surgery, LFP can be recorded through cables connecting leads to an external digital amplifier. (Right) The latest perceptive bidirectional neurostimulator makes long-term LFP recording possible. LFP signals can be recorded and transferred via Bluetooth wireless when patients are sitting, walking, sleeping, etc. LFP: local field potential; DBS: deep brain stimulation; SUA: single unit activity; ECoG: electrocorticography; EMG: electromyography. Adapted from (Zixiao Yin et al., 2021).
……19

Figure 2.11 Electrophysiological Biomarkers correlated with motor symptoms.
The concept of electrophysiological biomarker in the context of Parkinson's Disease comes naturally linked in finding biomarkers of (pathological) motor activity. An electrophysiological signal is processed to extract patterns that correlate to certain motor symptoms that can be modulated with deep brain stimulation.
……20

Figure 2.12 Exemplar plot of power spectrum analysis of STN LFP in PD patients.
The functions related to different frequency bands were labelled in both the physiological and pathological states. NBM: nucleus basalis of Meynert; PPN: Pedunculopontine nucleus; GPi: internal globus pallidus; LF: low frequency; HFO: high frequency oscillation. Adapted from (Zixiao Yin et al., 2021).
……22

Figure 2.13 Overview of open-loop DBS (a) versus closed-loop DBS (b).
In open-loop DBS (a), a neurologist manually adjusts the stimulation parameters every 3–12 months after DBS implantation. On the other hand, in closed-loop DBS (b), programming of the stimulation parameters is performed automatically based on the measured biomarker. c) Demonstration of two different brain states and the action of open-loop and closed-loop DBS. When the brain enters a specific state, it remains in that state for a short or long time. Closed-loop DBS gets deactivated when the brain enters the normal state. Open-loop DBS continues the stimulation regardless of the brain state. Adapted from (M. Parastarfeizabadi & Kouzani, 2017).
.....23

Figure 2.14 Percept PC neurostimulator with BrainSense Technology.
In this figure we have the representation of three key elements of the system: on the right, the smartphone given to the patient to manage stimulation programs (pre-defined by the clinician), and to log the 'Events' entries. In the middle, the neurostimulator to be implanted and on the left the clinicians table that allows to visualize the LFPs and to manage the parameters of stimulation (as in display in this picture). Adapted from the White Paper of the Percept PC Neurostimulator with Brain Sensing Technology from Medtronic.
.....28

Figure 3.1 A development framework for closed-loop control supporting adaptive Deep Brain Stimulation (aDBS).
The closed-loop control integrates three key components or units. The sensing unit refers to the sensing lead and signal acquisition. The processing unit refers to the stimulation strategy and model, and the supporting hardware characteristics. The stimulation model can rely on advanced algorithms based on machine learning (ML) methods. The stimulating unit refers to the stimulation parameters and the stimulating lead. For each unit, relevant associated parameters are presented.
.....33

Figure 3.2 Visual representation of the mentioned areas of machine learning.
The two main areas listed here are supervised and unsupervised learning (a third type is reinforcement learning but is outside the scope of this paper). On the top row, two methods of unsupervised learning (methods that look for hidden patterns or internal structures in the input, without pre-defined information about the output) are represented: clustering (a method that groups sets of data according to similarities or goals), here presenting three possible clusters, and dimensionality reduction (methods that search for a reduced set of variables describing the data), here considering two initial dimensions collapsed in one output variable. The bottom row refers to supervised learning (models that are trained on labelled, or annotated, datasets), presenting regression (which produces continuous outputs), and classification (which are associated with categorical/discrete outputs), both considering here two input variables.
.....35

Figure 3.3 Generic workflow associated with the application of supervised learning methods to achieve data-driven stimulation.
In light grey (top) is the development pipeline and in dark grey (below) is the deployment pipeline.
.....36

Figure 3.4 Schematic representation of a conventional adaptive deep brain stimulation algorithm compared to a machine learning-based adaptive deep brain stimulation system.
(A) Input signals are cortical ECoG and subcortical LFP brain signal recordings. New incoming data packets are pre-processed (e.g. normalization, referencing, artifact detection and subsequent rejection applied) and features are extracted (e.g. Fourier transformation, band power averaging and smoothing). The control algorithm is a simple threshold detection of a predefined feature: the brain state (e.g. pathological or non-pathological state) is predicted, and translated into a control command, such that the DBS stimulation parameters are adapted. (B)

Machine learning-based adaptive deep brain stimulation can use multimodal features to decode a variety of brain states (e.g. classification for decoding of tremor or regression for indication of severity of bradykinesia in PD). In addition to brain signals, the decoding model can also be re-adjusted based on the information delivered by the stimulation signal. Moreover, information from previous patients could be used to feed the decoding algorithms and potentially avoid time-consuming individual training sessions. Adapted from (T Merk et al., 2022).
.....38

Figure 3.5 Signal decomposition in the frequency domain.
(A) Decomposition of the time domain signal in its frequency components. (B) Raw signal and Fourier transform of Local Field Potentials (LFP). In the Fourier transform plot it is possible to identify the frequency composition of the signal. (C) Representation of three frequency bands of LFP signals: theta & alpha band (4-12Hz), beta band (13-35Hz) and gamma band (31-200Hz). Panel A adapted from: https://tex.stackexchange.com/questions/127375/replicate-the-fourier-transform-time-frequency-domains-correspondence-illustrati.
.....40

Figure 3.6 Application of machine learning towards adaptive deep brain stimulation using closed-loop control.
In the top panel, list of challenges at different stages of DBS therapy implementation where ML methods can play an important role. The diagram represents a closed-loop system for aDBS, based on LFPs sensing and electrophysiological biomarkers identification and interpretation.
.....43

Figure 3.7 Types of control mechanisms in Deep Brain Stimulation using electrophysiological signals as input.
Three standard control mechanisms for DBS: non-adaptive, adaptive with binary outputs, and adaptive with continuous outputs. Concerning an electrophysiological signal, the control system first reads the signal, and then decides on the stimulation pulse amplitude. In the case of non-adaptive DBS, this amplitude is constant, and it will be independent of the electrophysiological signal behaviour. When considering adaptive DBS, the amplitude will vary with the readings of the electrophysiological signal. In the case of binary control, a threshold for stimulation is defined, and every time the electrophysiological signal crosses above the threshold, the stimulation is turned ON and turned OFF when the signal shifts below the threshold. In the case of continuous control, the amplitude is being adapted to the continuous reading of the signal and varying according to this behaviour.
.....44

Figure 5.1 DBScope internal structure.
The toolbox was designed using an object-oriented programming framework. Upon initialization, the class NCNPERCEPT_BATCH separates the loaded files in patients (each containing one or several files). Each file gives rise to a NCNPERCEPT_FILE object. These objects contain six classes, each with its own properties and methods. Each class is named after the type of recording that it can access. The WEARABLES_EXTERNAL class handles additional data that is not present within the neurostimulator files and needs to be loaded separately afterward. COMMON_METHODS is an auxiliary class that runs background methods.
.....56

Figure 5.2 DBScope graphical interface.
The toolbox comprises a main interface that accommodates four sections. Each section gives access to part of the data contained in the loaded files. Within the Calibration Information and Online Streaming Sensing sections, the user can access secondary interfaces, that are used in artifact inspection and signal filtering, respectively. The main interface also contains a text area that displays information during user interaction. For instance, upon loading a file, it shows the available sensing modes
.....57

Figure 5.3 DBScope script example.
The initial steps involve initializing the mother object, NCNPERCEPT_BATCH, followed by the file(s) loading. Subsequently, one file is analysed considering three different streams of operations: Calibration System, for the display of the lead information; Chronic Sensing, for the visualization of the Timeline and circadian distribution; and Online Streaming Sensing, for the application of the ECG artifact cleaning algorithm and visualization of the data summary.
.....57

Figure 5.4 General workflow.
The user starts by loading one or multiple files. The user can always return to this step, with the option to save the current workspace. After loading the file(s), four streams of operations are available: System information, gives information about the patient, the device, and the in-clinic visit; Calibration Information deals with the recordings obtained when testing and setting the stimulation and sensing parameters, and has a secondary interface for artifact inspection; Chronic Sensing offers multiple visual and analytical functions for the Timeline and Events recordings; Online Streaming Sensing provides tools for visualization, artifact removal, filtering (using a secondary interface), and alignment with wearable data. Regardless of the chosen workflow, the user can always save the workspace (for more information, consult the DBScope documentation).
.....58

Figure 5.5 Overview of the toolbox outcomes.
(a) Snapshot of the text window displayed once a file is loaded. (b) Snapshot of the battery information. (c) Impedance information (monopolar and bipolar) for one hemisphere, accessible in the Calibration section. (d) Raw signal and Fast Fourier Transform (FFT) of a Survey recording. (e) Chronic data of one hemisphere, with the events marked by the patient. (f) FFT of 'Medication episodes marked in (e). (g) Data summary, containing the raw signal, the stimulation amplitude, the spectrogram, and the scalogram obtained with a wavelet method of an Online Streaming recording. (h) Spectrograms of the recording of (g) before and after a bandpass filter.
.....59

Figure 5.6 Power in alpha-theta and beta frequency bands of four different events.
Each graph has the minimum, 25th percentile, median, 75th, and maximum values for the four types of events: M – Medication; FS – Feeling stuck; FW – Feeling well; D – Dyskinesias. The asterisk marks the instances where dyskinesias are statistically different from at least one other event (ANOVA, $p<0.05$).
.....60

Figure 5.7 Case study of out-of-clinic data.
(a) Representation of Timeline and Events of the selected hemisphere. The recordings cover approximately one month in a conventional DBS protocol (continuous fixed stimulation amplitude). (b) Estimated circadian profile of the Timeline recording in (A). The LFP power is higher during waking hours. (c) Fast Fourier Transform (FFT) profiles for each of the recorded Events. The observed median profiles were similar, with the highest variation around the 15 Hz peak. (d) Daily distribution of 'Medication' and 'I feel stuck' episodes. Notice that distributions are similar, with three periods of higher incidence (6h, 11-12h, 20-21h). (e) Distribution of 'I feel stuck' events relative to

'Medication' events (triggered at zero). Interestingly, 'I feel stuck' episodes are mostly reported after 'Medication'. (f) Event-triggered average plots showing the power of the selected band in the proximity of 'Medication' and 'I feel stuck' episodes. The mean power decreases after the two events.
.....61

Figure 5.8 Case study of in-clinic recordings.
(a) Application of a customized filter to better highlight a band of interest (13-35 Hz). (b) Raw neuronal recording and time-frequency analysis aligned to therapy changes. Amplitude stepping induces changes both at the raw signal (abrupt magnitude rises) and scalogram (high low-frequency activity). Note that the y-axis of the scalograms has a logarithmic scale. (c) Example of a recording where both beta and theta-alpha activities are elevated. (d) Recording with cardiac artifacts before (top) and after (bottom) cleaning. (e) Recording with motion-induced artifacts. The artifacts span across the entire frequency spectrum, being more intense at the peaks in motion power and vanishing once the motion power is plotted over zero. (f) Cross-signal analysis for a titration recording during a motor task. Both stimulation and movement suppress beta-band activity.
.....62

Figure 5.9 Application of DBScope in a clinical evaluation.
Snapshot of the DBScope Morlet Wavelet function. In the absence of detected artifacts (highlighted in a red box), the raw data was selected. The plot displays a screenshot of the toolbox output, featuring the following: top row – raw LFP traces and stimulation; and bottom row – scalogram of the signal. Notably, the reduction of the beta band on the third level of stimulation is observable from the third to fifth stimulation levels, suggesting a response to the stimulation. (b) FFT of the selected sensing channel, 'ONE THREE RIGHT', with a clear peak in the low beta band. (c) Computation of the relative bandpower for the beta band (13-35Hz) reveals statistical significance (One-way ANOVA, $p<0.001$) among most stimulation levels. The statistical differences between stimulation levels are shown with the bars, where in this case there ceases to be a difference between the fourth and the fifth level.
.....63

Figure 5.10 Effect of stimulation in beta bands: UPDRS values and wavelets representation.
In this figure, we see two different recordings extracted from the protocol. On the top rows there is a representation of the raw signal of the LFPs (blue), with the representation of stimulation amplitude (orange), and the values from the UPDRS evaluation for resting tremor in each stimulation level. In the bottom rows, we have the wavelets representation of the corresponding recordings.
.....64

Figure 6.1 Nested structure for the LFP database.
This structure is organized in nested cells and created in MATLAB. The main cell is the Metric extracted, and the values of each cell are the metric computed for the signal that follows the structure tree up to the corresponding cell. For example, the cell LF of the structure on the right consists of the Metric for Patient 1, in the Stimulation OFF state of the left hemisphere and for the filtered signal in the low-frequency band (LF). This nested structure allows the manipulation of the data depending on the researcher's need (e.g. stimulation state or patient level).
LF – Low Frequency; B – Beta band; LG – Low Gamma band; SH – Stimulation subharmonic; HG – High Gamma band.
.....68

Figure 6.2 Visualization of spectrograms and wavelet transform.
In this figure, we see examples, for the same recording alongside the representation of the raw signal, of the two time-frequency methods most used to visualize the local field potentials and other electrophysiological time series. Due to the characteristics of the methods, the wavelet transform provides a more accurate definition of the bands compared to the spectrogram. This occurs because wavelets provide a multi-resolution analysis that

captures high-frequency details with fine time resolution to the low-frequency components with coarse time resolutions. This allows us to capture more transient features across the spectrum, compared to the spectrograms that are limited by a fixed size of window, and do balance time-frequency resolution across the signal. This visualization is an output of the DBScope.
.....69

Figure 6.3 Identifiable wavelets' temporal patterns.
In this figure, we showcase examples of the identifiable wavelets' temporal patterns through visual inspection.
A – Single, stable and well-defined band; B – Periodical hyperactivity across multiple bands; C – Periodic burst activity; D – Multiple, stable and well-defined bands; E – Presence of artefacts; F – No Pattern.
.....71

Figure 6.4 Parametric connections between time domain properties and spectral characteristics of an arbitrary signal.
Adapted from (Hjorth & Elema-Schönander, 1970).
.....72

Figure 6.5 Hjorth parameters computed during recordings.
In this figure, we visualize, for two recordings (A without stimulation and B with stimulation), the plot of the Hjorth parameter computed over time (seconds) for the signal filtered in the beta band. In the top rows, we have the plot of the Raw signal, the second top row of the computed bandpower, and then, by order, the Hjorth parameter Activity, the Hjorth parameter Mobility and the Hjorth parameter Complexity.
.....73

Figure 6.6 Correlation of variables with beta PSD.
In this figure we plot the correlation of all computed features with the beta bandpower. The correlation coefficients are in the x axis: in blue are represented the negative correlation coefficients, and in red the positive correlation coefficients.
.....74

Figure 6.7 Correlation of Hjorth parameters with UPDRS fold.
In this figure we plot the correlation of all computed features with the UPDRS fold. The correlation coefficients are in the x axis: in blue are represented the negative correlation coefficients, and in red the positive correlation coefficients.
.....75

Figure 6.8 Response of Hjorth Parameter to stimulation.
This figure shows how the Hjorth parameters respond to stimulation (from OFF stimulation state to ON state). Upwards arrows mean an increase in the parameter value, and downward arrows. The X shape indicates no shift. The dark blue arrows mean a significant statistical evolution ($p<0.05$), while the light blue arrows mean a non-statistically significant evolution.
.....76

Figure 6.9 Graphical representation of the role of short and long-term dynamics in DBS clinical evaluation
In this figure, we see a graphical representation of the role and impact of short- and long-term dynamics in clinical evaluation. Our case study focuses on a patient with Parkinson's Disease (PD) undergoing Deep Brain Stimulation (DBS) therapy. This patient requires stimulation adjustments tailored to their specific needs. Currently, these adjustments are made in clinical settings, utilizing electrophysiological data, motor information (e.g., wearables), and clinical information (e.g., UPDRS). The clinician or healthcare practitioner makes an informed decision on the

optimal parameters to minimize PD symptoms while avoiding adverse effects from stimulation. This evaluation is conducted at a specific clinical moment (single time-point evaluation). However, several temporal considerations are crucial: 1. The patient's needs evolve over different time frames, such as minutes and days. Therefore, an evaluation at a single moment might not provide the best stimulation parameters for the patient's overall needs; 2. Disease progression also modulates the patient's needs over time; 3. Both short- and long-term temporal dynamics affect the stimulation's efficacy and may influence the evolution of the patient's response to the therapy. These temporal dynamics impose limitations on choosing optimal parameters at a given time point.
.....78

Figure 6.10 Differences in spectral profiles within recordings.
This figure shows the spectral profiles, computed by the application of pwelch, considering different divisions (with no overlap) of one recording: (a) shows the pwelch applied to the entire recording, (b) to the first division of the recording, (c) to the second division of the recording and (d) to the third division of the recording. The beta band (13-35Hz) is highlighted in all plots.
.....79

Figure 6.11 Distribution of the low and beta band metrics in stimulation off and on conditions.
This figure shows the distribution of the selected metrics, Shannon's Entropy and STD for the filtered band (a) low beta and (b) high beta. In the top row of (a), we see the distribution of Shannon's Entropy for stimulation states off and on, and in the bottom row, we see the STD for the same conditions. Similarly, for (b), on the top row, we see the distributions of Shannon's Entropy and the bottom row of STD for both stimulation conditions.
.....80

Figure 6.12 Temporal populations and correlation to clinical information.
In this figure, we present two main insights: (a) and (b) showcase examples of temporal population clusters (utilising k-means imposing two clusters) applied to individual recordings from different patients. At the same time (c) and (d) depicts the relationship between the metrics and the Unified Parkinson's Disease Rating Scale (UPDRS) for all patients. Panel (a) illustrates an instance where the division between clusters is less distinct, while in (b), the clusters exhibit an apparent differentiation. Moving to (c), it becomes evident that intermediate UPDRS values correlate with a broader entropy distribution, indicating more significant temporal variability. In (d), the distribution of standard deviation (STD) is less heterogeneous across UPDRS scores.
.....81

Figure 6.13 Comparison of Entropy over follow up points.
This figure shows the distribution of Entropy for all patients, in stimulation OFF, over the follow-up times. Although there is a tendency from the 18 months forward to decreasing values, this is not statistically significative.
.....82

Figure 7.1 Practical approach to set up adaptive deep brain stimulation (DBS).
The implementation of adaptive deep brain stimulation (aDBS) for a given patient requires a stepwise procedure. This involves the assessment of the individual clinical and spectral characteristics for the identification of symptom-specific biomarkers. In principle and depending on the target biomarker, this assessment can be informative if conducted during different clinical conditions as well as OFF and ON continuous stimulation. Special consideration should be given to signal artifacts that could potentially interfere with a control system. Overall, the question should be answered whether aDBS is feasible to be applied unilaterally and/or bilaterally. There are different control policies that can be selected (also see Figs. 1 and 2) and the clinical and electrophysiological response during continuous DBS may inform the fine tuning of aDBS-specific stimulation parameter boundaries. As with conventional DBS, aDBS parameters need to be reassessed and tuned over time. Adapted from (W.-J. Neumann et al., 2023).
.....85

List of Tables

Table 2.1 BrainSense features detailed descriptions.
Adapted from the White Paper of the Percept PC Neurostimulator with Brain Sensing Technology from Medtronic.
.....28

Table 2.2 BrainSense Data Locations.
Adapted from the White Paper of the Percept PC Neurostimulator with Brain Sensing Technology from Medtronic.
.....30

Table 3.1 Tuneable Deep Brain Stimulation (DBS) parameters.
In this case, we are considering as target the subthalamic nucleus (STN) nucleus, but the same parameters can be applied to DBS with different target regions.
.....32

Tables 3.2-3.6- Publications included in this review, organized according to the treatment stage in DBS. Concerning the machine learning algorithms, the methods applied are mentioned as well as which model group they belong to, and the type of input data used. Acronyms: CT - Computerised Tomography; EEG - Electroencephalogram; EMG - Electromyography; LFP - Local Field Potentials; qEEG - Quantitative Electroencephalogram; MER - Microelectrode Arrays; MIR - Magnetic Resonance Imaging. Model Group: Cf - Classification; Ct - Clustering; DR/FS - Dimensionality Reduction/ Feature Selection. R/TS - Regression/ Time Series.
Table 3.2 Publications included in the review under the category “DBS therapy management”.
Table 3.3 Publications included in the review under the category “Detection/management of symptoms”.
Table 3.4 Publications included in the review under the category “Identification of Biomarkers”.
Table 3.5 Publications included in the review under the category “Peri-operative management”.
Table 3.6 Publications included in the review under the category “Signals decoding/encoding”.
.....104

Table 3.7 Machine Learning methods in DBS.
The methods are organized according to the following categories: Clustering (Ct) and Dimensionality Reduction / Feature Selection (DR/FS) for unsupervised learning; Classification (Cf) and Regression / Time Series (R/TS) for supervised learning. It should be noticed that some methods can be adapted to operate with different purposes. For example, recurrent networks can be used either in a context of classification or regression.
.....37

Table 3.8 Division of Local Field Potentials (LFP) in the frequency bands described in literature. (STN – Subthalamic nucleus)
.....40

Table 6.1 Derivation of Hjorth parameters.
Adapted from (Hjorth & Elema-Schönander, 1970).
.....71

Abbreviations

aDBS- Adaptive Deep Brain Stimulation
AP- Action Potentials
AR- Akinetic Rigid
BBB- Blood-Brain Barrier
CNN- Convolutional Neuronal Networks
CV- Coefficient of Variation
DBS- Deep Brain Stimulation
ECoG- Electrocorticography
EEG- Electroencephalogram
EMG- Electromyography
GPe- external Globus Pallidus
GPi- internal Globus Pallidus
IPG- Implantable Pulse Generators
LF- Low Frequency
LFP- Local Field Potentials
ML- Machine Learning
OOP- Object-Oriented Programming
OR- Operating Room
PD- Parkinson's Disease
PSD- Power Spectral Density
RF- Random Forest
SNc- Substantia Nigra pars compacta
STD- Standard Deviation
TD- Tremor Dominant
TSN- Science Communication Network
STN- Subthalamic nucleus
SVM- support vector Machines
UPDRS- Unified Parkinson's Disease Rating Scale
VTA- Ventral Tegmental Area

“Connaître, ce n'est point démontrer, ni expliquer. C'est accéder à la vision.”
Antoine de Saint-Exupéry

Chapter 1: Introduction

Deep brain stimulation (DBS) of the subthalamic nucleus (STN) is a therapy applied in patients with advanced Parkinson's Disease (PD). Its benefits and effectiveness are established, improving the quality of life of patients by reducing motor and non-motor symptoms. The mechanism, or mechanisms, behind the therapeutic success of DBS remains mostly unknown. Intended to act as a reversible lesion, DBS appears to produce a more complex physiological response beyond the local effect by disrupting outer circuits. There are emergent challenges to achieve the optimal DBS therapy. As there is a considerable interindividual variability of the symptoms and pathological traits, DBS needs to be both patient and electrophysiologically tailored, in the far spectrum of what personalized medicine approach is. Given the current reported adverse stimulation-induced side effects, affective, cognitive, and motor, a better understanding of its mechanisms is needed.

One innovative field is the adaptive Deep Brain Stimulation (aDBS) with closed-loop, which integrates innovations in the device's development for DBS and the search for pathological biomarkers. aDBS aims to provide stimulation adapted to the needs of the patients. To achieve aDBS, we need to better understand the mechanism of action of DBS, and better orient and modulate the stimulation. With the now available possibility to record Local Field Potentials (LFPs) at the site of stimulation, or in the neighboring areas, emerges a window into the neuronal communication *in vivo*. Study of such electrophysiological recordings provide valuable information not only towards aDBS, but also about associated pathologies.

In 2020, Medtronic ® launched the Percept PC neurostimulator with BrainSense ™ technology. This device performs DBS in an open-loop feedback approach. It is also capable of sensing, recording LFPs surrounding the sensing lead – making the mentioned window in neuronal communication accessible. Although it has a mechanism that allow to be used in a closed-loop control, such approach requires more study and validation. Extensive research on the safety and effectiveness of feedback control mechanisms is also still needed, and approval by health regulatory entities is yet missing. Nevertheless, it provides valuable data in paving the way to aDBS. Later, in 2023, the Percept RC started to be implemented. This neurostimulator has a rechargeable battery, unlike the precedent model, which also answers in the limitation of sensing by not impacting the absolute timespan of the battery.

The goal for this project was to prepare the new generation of DBS for PD with data-driven feedback control for personalized improved effectiveness. To do so, we:

- Developed a public domain (open-source) computational toolbox to import, visualize and analyse the neurostimulators' BrainSense data files;
- Assessed the predictive value of the electrophysiological signals by taking advantage of the Percept PC sensing features, in particular, in-clinic recordings;
- Explored signal structure and activity patterns in the recorded electrophysiological data, using traditional spectral analysis methods, and exploring the possibility of implementation of both unsupervised and supervise learning paradigms;
- Performed longitudinal studies of electrophysiological data on implanted PD patients.

This project combines both fundamental and clinical expertise: electrophysiology, neuroengineering and data analysis, together with two pillars of clinical neurosciences- neurosurgery and neurology. The project was carried at i3S, Centro Hospitalar Universitário de São João (CHUSJ) and Charité Universitätsmedizin- Berlin, under the supervision of Paulo Aguiar and the co-supervision of Rui Vaz and Andrea Kühn, from the respective institutions.

1.1 Supervising team

Paulo Aguiar (main supervisor) is a PI at i3S and leader of the Neuroengineering and Computational Neuroscience (NCN) research group. He has extensive experience in neuronal dynamics/biophysics, electrophysiology, and has developed widely used neuroinformatics tools. His research includes novel computational methods and advanced data analysis algorithms for neuroscience.

Rui Vaz (co-supervisor) is a neurosurgeon at CHUSJ and head of the Neurosurgery Department. He pioneered DBS stimulation surgeries in Portugal and coordinated the national team with the largest accumulated experience in this field. Until December 2022, he was also the head of the team responsible for the clinical follow up of patients with Parkinson Disease from CHUSJ. He has a PhD from the Faculty of Medicine of University of Porto, where he is a Professor of Neurosurgery.

Andrea Kühn (co-supervisor) is the head of Movement Disorders and Neuromodulation section at the Charité Universitätsmedizin in Berlin. She has a vast experience in the field of DBS and imaging in neurological disorders. Her latest works relate to the search of electrophysiological biomarkers for Parkinson's Disease, as well as the further understanding of the potential of DBS.

The combination of two major medical centres allowed us to address the need for significant amounts of data. The neurosurgery team provides support with their experience in implantation of Deep Brain Stimulators in Parkinson Disease patients and their follow up. The neurology team assists with the crucial understanding of experimental analysis and knowledge of Percept PC with BrainSense technology.



Figure 1.1: Project host and co-host institutions.
In the first image of the left is the i3S, and in the middle picture the Centro Hospitalar Universitário de São João, both in Porto, Portugal. The last picture on the right are the facilities of Charité Universitätsmedizin Berlin, Germany.

1.2 Objectives

Our work aimed to prepare the new generation of DBS for PD using data-driven feedback control in a multifaceted approach.

Our first contribution, **Publication I,** is a literature review exploring how machine learning techniques can contribute to the field of adaptive DBS, in particular for closed-loop control mechanisms, diving into the current examples in literature, the tendencies and challenges ahead.

The core of this work is sustained in the development and implementation of a **Research Protocol**, with a multidisciplinary team working with industry and clinicians. However, early in this process, it was clear that accessible and comprehensive computational tools to analyse and visualize BrainSense raw data were lacking.

Medtronic BrainSense information is stored in json files, downloadable from the clinical console, and stored with an established data structure. Two main types recording modes are possible in predefined frequency bands: continuous recordings and "streaming" periods recordings obtained during clinical sessions. Additionally, to that information, other components are available such as related to device and patient information. To access and work

with such files it is necessary to upload and open them in an adequate environment, which can be a demanding and time-consuming task.

Already available toolboxes for LFP recording analysis concerned mainly the visualization of the placement of electrode and the visual reconstruction of the DBS electric field. Some examples are:

- FastField (Baniasadi, Proverbio, Gonçalves, Hertel, & Husch, 2020): FastField is an open-source toolbox for DBS electric field and ventral tegmental area (VTA) approximation. The toolbox computes scalable electrical field approximations operating on the principle of superposition and VTA activation models.
- Lead-DBS (Horn & Kühn, 2015): This toolbox can be used to facilitate the reconstruction of the lead electrode trajectory and the contact placement. The electrode placement can be reconstructed and visualized based on the electrode-induced artifacts of post-operative magnetic resonance or CT images.
- BRAVO (Cagle et al., 2023): An open-source web interface for both clinicians and researchers to visualize electrophysiological data from Percept.

Aiming to address the gap for an accessible and easy-to-use toolbox, our contribution (running in parallel with the implementation of the research protocol) focused on developing computational algorithms to import, explore, visualize, and analyse BrainSense data files. The recordings used were extracted from the device Percept PC with BrainSense™ Technology, Medtronic ®. Specific methods were developed to preprocess the data (filtering, artifacts removal, visualization), to produce informative graphical representations (for both clinical and research contexts), and to analyse neurophysiological data (power spectral density- PSD, LFP signatures, among others). MATLAB was used, with a standalone app feature to run without needing programming prompts. The result is a versatile and powerful computational toolbox, released as open source, that supported the other thesis components and aiming to accelerate research on DBS in the wider community, regardless of the computational background of the operators.

The analysis of LFP data contained state-of-the art methods, as the following: application of Fourier transform, determination of power spectral density, analysis of spectrograms and interpretation of wavelets in different recordings contexts (Accolla et al., 2016; Geng et al., 2018; Lindén et al., 2011) Within this approach, methods such as Welch's, modified periodogram and wavelet transform are found (Geng et al., 2018; Kolb, Abosch, Felsen, & Thompson, 2017; Lempka & McIntyre, 2013; Maling, Lempka, Blumenfeld, Bronte-Stewart, & McIntyre, 2018; Miyagi et al., 2009; Welch, 1967).

To facilitate the interpretation of these analysis, visualization tools were implemented and integrated in the toolbox whenever possible and adequate. Examples of visualizations are the representation of PSD, and the behaviour of the LFP through different intervals of time (e.g., to study the circadian rhythm), and in particular, the Wavelet transform simultaneously with the raw signal and the levels of stimulation. This work is available now in as an **Open-Access Software** in GitHub and described in **Publication II.**

These new tools supported the work that followed, which focused on characterizing neural activity and building knowledge towards the identification of "biomarkers" for pathologic conditions. Here "biomarkers" are not molecular in nature and represent instead specific signal patterns and dynamics. The characterization of biomarkers is a key achievement (Simon Little et al., 2013). LFPs frequency bands are emerging as a promising biomarkers for aDBS in PD. LFPs result from the neural processes taking place in the extracellular space neighboring the sensing electrode (Kuo, White-Dzuro, & Ko, 2018). There are more than one possible locations of the electrode, such as the STN, and there will be different frequency bands in the LFP, such as the beta-band power, which are a suitable biomarker in PD (Simon Little et al., 2016, 2013). These components of the LFP power spectrum translate the firing pattern of specific subset neuronal populations, and reflect the synchronous activity in population of neurons (Brown et al., 2001; Kühn et al., 2005; Marsden, Ashby, Limousin-Dowsey, Rothwell, & Brown, 2020; A Priori et al., 2006). Moreover, the dynamic behaviour of LFP power spectrum components at the

stimulation location appears to correlate with symptoms of movement disorders (Kühn, Kupsch, Schneider, & Brown, 2006; Reck et al., 2009). Patients with PD have a heterogenous display of symptoms, which means that group-level neural markers such as beta band power of the STN may not be sufficient to achieve an efficient aDBS (Watts, Khojandi, Shylo, & Ramdhani, 2020). Several methods, both supervised and unsupervised, were tested to find the one with best quality measurements. With the identification and characterization of biomarkers, it becomes possible to manage the stimulation in response to its different states. This process aims to provide information to adjust the stimulation provided in the future, its directionality and target, culminating in a fine tailored DBS to the needs of the patients. This way, the absolute quantity of stimulation provided can reduced, as well as its adverse side effects, and the battery of the device, and lifespan, increased.

Studies show that frequency-specific effects can inform the frequency programming of STN-DBS in clinical use (Su et al., 2018). Combined with the known effects of DBS, an hypothesis is that DBS has a multimodal modulating effect in neuronal activity surrounding the site of stimulation (Hell, Palleis, Mehrkens, Koeglsperger, & Bötzel, 2019). The stimulation aims to responds to fluctuation in the dynamics of patient LFP data. Several parameters have been studies to identify the one with most significant improvement in motor symptoms. So far, the most promising parameters is the adjustment of stimulation frequency (Belasen et al., 2017; Moreau et al., 2008; T Xie, Kang, & Warnke, 2012), opposing to studies stating that stimulation amplitude is more critical (A. Eusebio et al., 2011; E. Moro et al., 2002; Whitmer et al., 2012). The variation of stimulation frequency is known to be essential for the therapeutic success of STN-DBS on motor symptoms in PD (Su et al., 2018). Consensus regarding the most beneficial frequency states that occurs at 130Hz (M. J. Birdno & Grill, 2008; Moreau et al., 2008). Building on the knowledge regarding PD biomarkers, and its behaviour, the modulation of stimulation will be dependent on the parameters selected.

Moreover, to assess the long-term effects of DBS, it is important to determine what outcome measures are more adequate (Limousin & Foltynie, 2019). Some of the most used are the effects of DBS on the severity of PD (UPDRS part II, III and IV, and available dyskinesia rating scales), on both on and off periods, and disease-specific PDQ39, quality of life and adverse outcomes (Limousin & Foltynie, 2019). The adverse outcomes assessment is mostly performed by the clinician. These effects, specially related to the stimulation, such as swallowing difficulties, dysarthria, freezing of gait and balance disturbances, are widely recognized. As PD progress spite the application of stimulation, the presence of adverse side effects adds complexity to the study of the disease progression and PD related symptoms evolution. With access to clinicians' notes, and the logged events, it will be possible to track the outcomes of the therapy throughout the time.

Our contribution towards the characterization of the "biomarkers" concept is twofold. First, we present case studies of analysis of BrainSense files in the context of DBS, exploring outputs and workflows of DBScope. These case studies show the potential that both in-clinic and out-clinic recordings have to feed in the characterization of pathological patterns, but as well stimulation responsive patterns. To note as well is that this accessibility of analysis paves the way for easier patient-specific characterization. This patient specific is also discussed in the second contribution, where an exploratory analysis of the temporality of the spectral profiles was conducted. Electrophysiological signals as the ones BrainSense are non-stationary, and these features areg not yet described and understood in the literature. In our results, we document this variability through different methods, such as Hjorth parameters and Shannon's entropy, opening further discussion on spectral features that can become electrophysiological biomarkers.

1.3 Contributions

The dissemination of this work occurred through:

- two top journal publications and presentations in international meetings:

    - **Machine learning for adaptive deep brain stimulation in Parkinson's disease: closing the loop** Oliveira, A.M., Coelho, L., Carvalho, E. et al. J Neurol (2023) doi.org/10.1007/s00415-023-11873-1
    - **DBScope as a versatile Computational toolbox for the visualization and analysis of sensing data from Deep Brain Stimulation,** Andreia M. Oliveira, Eduardo Carvalho, Beatriz Barros, Carolina Soares, Manuel Ferreira-Pinto, Rui Vaz, Paulo Aguiar. npj Parkinson's Disease, 2024, npj Parkinson's Disease doi:10.1038/S41531-024-00740-Z
- a computational toolbox available open source in GitHub (https://github.com/NCN-Lab/DBScope),
- a research protocol, currently in its second year and extending for another two years in a multidisciplinary team.

This work holistically invests in the information provided by the LFP recordings from BrainSense technology. DBS therapies have an increasing range of applications, but the understating of its mechanism is beyond complete. With these recordings, steps towards enlightenment on theses mechanisms can be taken. The possibility to have a window into in vivo human electrophysiological recordings during a pathologic process is of great value and can provide information that has the potential to change not only the approach to PD, but to many other disabling diseases.

1.4 Thesis Outline

In Chapter 1, we introduce the objectives of this work, as well as the contributions of this thesis. The background that sustains these objectives is presented in Chapter 2, where we provide a comprehensive literature review and state-of-the-art. Here, we dive into the pathophysiology of Parkinson's Disease and move further to present the field of Deep Brain Stimulation in the context of PD. We then explore the concept of biomarkers, finishing this segment by linking all topics approached together in a discussion surrounding aDBS.

The following chapters present the results of this work. In Chapter 3, we continue the discussion about aDBS and biomarkers, with a focus on the contributions that ML provides and its potential for shaping these two concepts in the near future. This chapter presents our **Publication I**. In Chapter 4, we move to an experimental setting and present the process of implementing a **clinical protocol** for the analysis of local field potentials, from its conceptualisation to implementation. During this stage of our work, we worked in parallel to achieve the results presented in Chapter 5, the **Publication II** and the **computational toolbox entitled DBScope**, which comes full circle with the presentation and discussion of case studies from data (LFPs recordings) resulting from the protocol explored in Chapter 4.

A further analysis of LFPs is presented in Chapter 6, in a novel approach to the spectral analysis in the context of DBS. We focus on the non-stationarity of this type of data and explore methods to characterise them and to spark discussion in the community about their potential to act as biomarkers, the same concept we started discussing early in Chapter 2.

Lastly, in Chapter 7, we provide a comment on the final remarks and conclusions, but as well a look into the future of the field of aDBS. Further sections for each chapter are found in the supplementary materials.

Chapter 2: Literature Review and State-of-the-Art

Electrical stimulation-based therapies are gaining increasing attention for the treatment of neurologic disorders. As an alternative to pharmacologic approaches, such as systemic drugs intake (frequently with adverse side-effects), electrical stimulation offers direct effect over neuronal electrical activity, with major improvements in the quality of life for many patients. This is particularly true for PD patients. As the second most common neurodegenerative disease, PD has a severe impact in society, further aggravated by an aging population. The neuropathology of PD is characterized by the loss of dopaminergic neurons and its cardinal symptoms are gait impairment, bradykinesia, tremor, and rigidity. Current medication for PD is symptom directed.

Surgical treatment is now well-established with the use of DBS. In this procedure, an electrode is placed invasively in the STN, providing continuous electrical stimulation. DBS produces dramatic results in reducing the called 'off' periods (periods when motor and nonmotor symptoms of PD re-emerge) and dyskinesias. Present DBS technology is far from perfect, and its research is an active field regarding innovation. Directed and adaptive DBS are gaining attention as both show improvements compared to previous continuous DBS. Closed-loop adaptive DBS becomes a possibility with neural activity recordings obtained directly from the target region. The complexity of neuronal signals/coding urges, however, the identification of activity patterns ("biomarkers") of the pathological electrophysiological states to better fit DBS. To achieve this, computational models of DBS is an approach of utmost importance.

These novel closed-loop DBS technologies aim to surpass present limitations both in physiological (reduction of side effects) and technical (extend battery life) domains. Other limitations, such as loss of effectiveness from continuous stimulation, is also an important aim. Medtronic, a leading company in DBS, announced in Q1 2020 the first EU approved neurostimulator with recording capabilities (Percept PC with BrainSense technology). Whereas the device is technologically prepared for closed-loop, it only works in open-loop: the proper feedback protocols still need investigation and validation. Nevertheless, they provide already invaluable neuronal activity data to clinicians and researchers.

The challenge now is to use the available physiological/pathological neuro-electrophysiological signals to develop new "intelligent" DBS technologies for PD. This will allow personalized and symptom-specific therapies through the exploitation of closed-loop mechanisms. The coordination between state-of-the-art machine learning (ML) methods, advanced data analysis and computer modelling, allied with detailed clinical information, plays here a fundamental role for future developments.

Noteworthy, the development of optimized feedback mechanisms in DBS has far-reaching applications beyond PD and movement disorders. Epilepsy syndromes and obsessive-compulsive disorders can also benefit from progress in feedback control protocols/mechanisms (noteworthy, Medtronic neurostimulator with BrainSense technology is also approved in the EU for these pathologies). In this chapter, we provide a narrative review on the status of the art of DBS for PD.

2.1 Parkinson's Disease

Parkinson's Disease is a progressive nervous system disorder that affects movement, with a significant impact worldwide. Understanding its epidemiology, etiopathology, and current treatments is fundamental to appreciate the challenges and innovations on its therapeutics.

2.1.1 Epidemiology

Parkinson's Disease is a neurodegenerative disease, the second neurodegenerative most common worldwide. It was first described clinically by James Parkinson, in 1917. It is estimated that 5 million persons worldwide, 1 million in Western Europe and 1 million in the United States suffers from PD (He et al., 2021). Both sexes, all races,

occupations, and countries are affected by this condition. With a mean age of onset of 60 years, its incidence increases with aging. However, there are cases reported in with disease onset in early 20s. The under-diagnosis of PD in elderly groups may influence the incidence studies (Ramirez-Zamora & Ostrem, 2018). It is estimated, based on the current and past demographics of the population, that the disease will see a dramatical increase in the upcoming decades (He et al., 2021).

2.1.2 Etiopathogenesis

The pathologic hallmarks of PD are degeneration of dopaminergic neurons in the substantia nigra pars compacta (SNc), reduced striatal dopamine and intracytoplasmic proteinaceous inclusions containing alpha-synuclein (Lewis bodies) (Kasper, Jameson, Fauci, Hauser, & Localszo, 2012) (Figure 2.1). But not only the dopamine system is affected. Cholinergic neurons of the nucleus basalis of Meynert, norepinephrine neurons of the locus coeruleus, serotonin neurons in the raphe nuclei of the brainstem, and neurons of the olfactory system, cerebral hemispheres, spinal cord and peripheral autonomic nervous systems are also altered in PD (He et al., 2021).

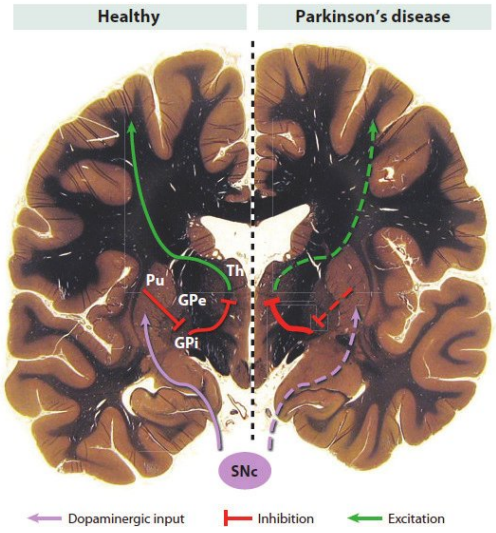


Figure 2.1 Representation of a simplified schematic of the neuronal circuits involving the basal ganglia.
Anatomy and physiology of Parkinson's disease (PD) motor manifestations. A simplified schematic of the neuronal circuits involving the basal ganglia, thalamus, and cortex and their derangement in PD. For simplicity, only the direct pathway is shown. It normally functions to facilitate movements (left), but in PD the output is attenuated (right). The midbrain substantia nigra pars compacta (SNc) provide dopaminergic input to the putamen (Pu), which is excitatory to the direct pathway. The putamen inhibits (red) the globus pallidus interna (GPi), which subsequently inhibits the thalamus (Th). The thalamus projects excitatory input (green) to the motor cortex. In PD, degeneration within the SNc leads to net increased inhibition of the thalamocortical projection. The indirect pathway (not shown), including the globus pallidus externa (GPe) and subthalamic nucleus, is inhibited by SNc dopaminergic input and normally functions to repress movements, but its activity is enhanced in PD. Adapted from (Shulman, De Jager, & Feany, 2011).

Most PD cases (~85-90%) are sporadic, meaning the cause is unknown. There is evidence that environmental factors may have a role in the incidence of PD in patients older than 50 years, whereas for younger patients genetic factors are the most important (Kasper et al., 2012). However, no environmental factor has been proved to directly cause typical PD. Multiple specific mutations and gene associations regarding the cases of familial origin (10-15%) were identified. Genetic factors are also present in sporadic cases, with several cases of typical PD carrying the LRRK mutation (Kasper et al., 2012). One hypothesis is that PD is due to a "double hit", where an interaction between a gene mutation that induces susceptibility is coupled with exposure to an environmental factor, thus inducing epigenetic or somatic DNA alterations (Kasper et al., 2012).

The degraded motor function happens due to a series of neuronal circuits and loops linking the basal ganglia nuclei with cortical motor regions. The differential diagnosis reflects the damage to different components of the basal ganglia. The basal ganglia comprise subcortical nuclei including the striatum (putamen and caudate nucleus), STN

globus pallidus pars externa, globus pallidus pars interna, and the substantia nigra pars compacta. These regions are connected via direct and indirect pathways. The basal ganglia provide inhibitory tones to thalamic and brainstem neurons, which will connect to motor systems on the cerebral cortex and spinal cord controlling motor function. Decrease neuronal activity in the GPi and SNc is associated with facilitation of movement. The dopaminergic projects originating in the SNc neurons modulate neuronal firing and stabilization of the basal ganglia network. PD is characterized by a progressive degeneration of nigrostriatal dopaminergic neurons. There are dopamine denervation and loss of dopaminergic tone leading to an increase in the firing of neurons in the STN and GPi, with excessive inhibition of thalamus and decrease in the activation of cortical motor system, resulting in parkinsonism (Kasper et al., 2012).

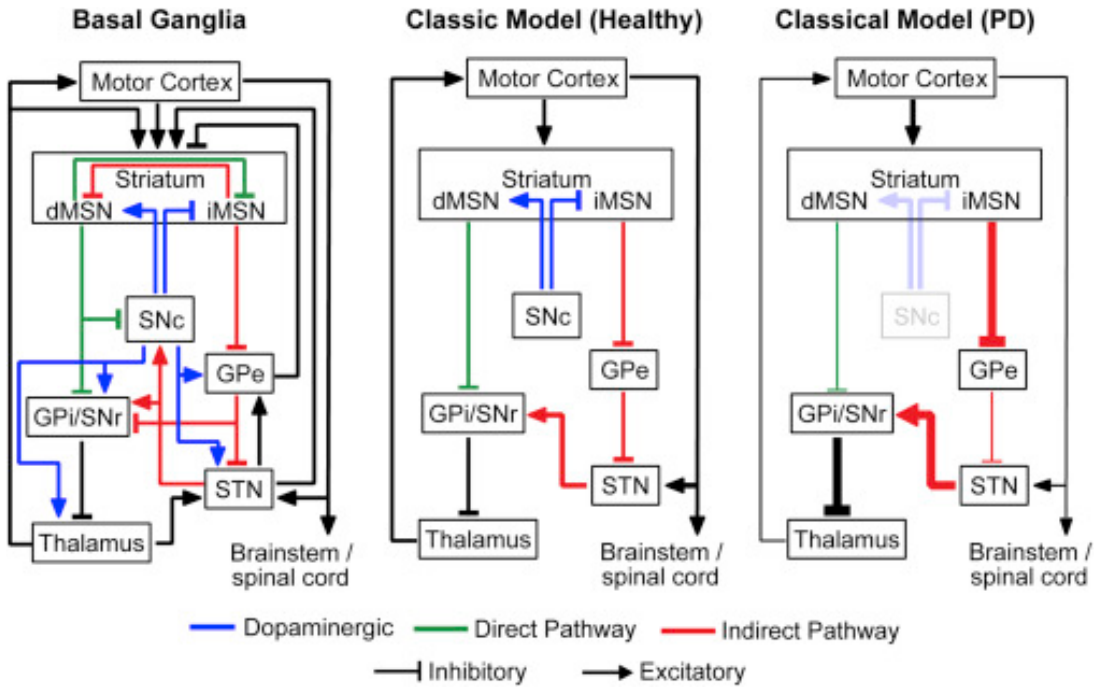


Figure 2.2 Classical model of the Basal Ganglia.

The classical model (center) simplifies basal ganglia connectivity (left) by highlighting the role of dopamine on direct and indirect pathway activity and motor output. In the healthy condition (center), dopamine (blue) from the SNc to the striatum activates direct pathway (green) and inhibits indirect pathway (red) MSNs. This effect decreases GPi output, releasing inhibition on the thalamus and cortex and promoting movement. In the parkinsonian condition (right), loss of SNc dopamine causes hypoactivity of the direct pathway and hyperactivity of the indirect pathway that leads to excessive GPi output. As a result, over inhibition of the thalamus and cortex leads to a suppression of movement. Adapted from (McGregor & Nelson, 2019).

2.1.3 Clinical Presentation

Parkinson Disease is characterized by rigidity, rest tremors, bradykinesia and gait impairment (Kasper et al., 2012). These features are considered “cardinal features”. Further features are freezing of gait, postural instability, speech impairment, autonomic and sensory alterations, cognitive impairment, dementia, among other less common (Kasper et al., 2012).



Figure 2.3 Infographic about clinical information of Parkinson's Disease.
Adapted from presentation at WhatElse seminar in October 2022, Porto, Portugal.

2.1.4 Diagnosis

When we talk about parkinsonism, we refer to a syndrome composed of bradykinesia associated with rigidity and/or tremor, which can be due to PD, but as well to other underlying diseases. Parkinsonism is not exclusive for PD (Kasper et al., 2012). However, PD is the most common reason for parkinsonism (~75% of de cases) (Kasper et al., 2012).

Originally, PD was seen as a pure movement disorder. It was composed of three cardinal signs: bradykinesia, rigidity, and tremor. Later was added postural instability. Currently, bradykinesia, rigidity and rest tremor remain as cardinal signs, and the symptom of bradykinesia must be associated with rest tremor, rigidity, or both (Kasper et al., 2012; Tysnes & Storstein, 2017). These signs allow to establish a clinical diagnosis. However, a considerable proportion of cases with clinical diagnosis failed to present the histopathology characteristic of PD. Even though that there has been progress in the definition of the diagnosis of PD, some uncertainty remains. In these new diagnostic criteria are now defined subcategories: supportive criteria, absolute exclusion and red flags, and the diagnosis of clinically established PD needs the presence of two supportive criteria, the absence of absolute exclusion criteria and red flags. The supportive criteria are motor and non-motor aspects of the disease, as effect of dopaminergic therapy, levodopa-induced dyskinesia, asymmetry in rest tremor, olfactory loss or positive test on cardiac sympathetic degeneration (Tysnes & Storstein, 2017). Absolute exclusion criteria are anti-dopaminergic therapy in place, cortical findings, cerebellar abnormalities, frontotemporal cognitive changes, slow progression, and supra nuclear gazer palsy (Tysnes & Storstein, 2017). Red flags are absence of progression, early gait impairment, early bulbar dysfunction, inspiratory respiratory dysfunction, severe autonomic failure in the first year of disease, reduced balance with recurrent falls, early antecollis, pyramidal trach signs, bilateral parkinsonism and absence of common non-motor features seen in PD (Tysnes & Storstein, 2017).

2.2 Treatment

2.2.1 Pharmacological Treatment

Levodopa, an amino acid precursor of dopamine, was introduced in late 1960s and is still a commonly used therapy for PD (Kasper et al., 2012). As dopamine cannot cross the blood-brain barrier (BBB), Levodopa was tested to treat PD. Levodopa is administered alongside a peripheral decarboxylase inhibitor which prevents the peripheral metabolism of dopamine. One of these combinations of active agents available is called Sinemet.

Alternatively, dopamine agonists act directly on dopamine receptors and, in comparison to levodopa, do not require metabolism. Its efficacy is not comparable to levodopa, but are less prone to induce dyskinesia, reason for which clinicians initiate therapy with dopamine antagonists, and supplement with Levodopa as required.

Two other pharmacologic therapies are available: the inhibitors of monoamine oxidase type B (MAO-B) and the COMT inhibitors. The inhibitors of MAO-B act by blocking the central dopamine metabolism, which will lead to the increase of the neurotransmitter (Kasper et al., 2012). COMT inhibitors increase the elimination half-life of levodopa, consequently enhancing brain availability (Kasper et al., 2012). Even with the available pharmacologic treatment, the disease progress into intolerable disability. The current agents available do not act as a neuroprotective therapy, which is the major unmet need.

2.2.2 Surgical Treatment

Most surgical procedures for PD nowadays use DBS. DBS will provoke reversible (to an extent dependent of the plasticity induced over time by DBS) alterations: stimulation has effect without making an irreversible major brain lesion. This is achieved, presumably, by the reduction of neural activity in tissue surrounding the electrode contact (Samii, Nutt, & Ransom, 2004). It is applied in PD, but as well other neurologic and psychiatric conditions such as epilepsy and obsessive compulsive disorder (Kasper et al., 2012). The mechanisms of DBS are not well understood, yet. One hypothesis, for PD, is the disruption of the abnormal signalling in PD associated with motor complications (Kasper et al., 2012). The stimulation can be adjusted in respect to electrode configuration, frequency, pulse duration and voltage. The aim is to maximize benefit and reduce adverse side effects tailored to each patient. In PD, DBS shows dramatic reduction of “off” periods and dyskinesias (Kasper et al., 2012). However, it does not show improvement or prevention on the development of features occurring that do not respond to treatment of levodopa. Side effects of DBS are related to the DBS system or the stimulation itself too. Regarding the DBS system, side effects include lead break, lead displacement, infection and skin ulcerations, surgical procedures, such as haemorrhage, infarction, and infections. In terms of the stimulation itself, side-effects include depression, ocular and speech impairment, muscle twitches and paraesthesia (Samii et al., 2004). Side effects related to stimulation can be reversed by the adjustment of stimulation. It is also important to mention that not all PD patients are candidates for DBS therapy.

The DBS currently implemented has different results according to the site of stimulation (Cagle et al., 2024). The unilateral thalamic DBS reduces contralateral tremor, but does not have an effect on other symptoms of PD. The stimulation of STN bilaterally improves bradykinesia, rigidity and tremor. The effects described allow the reduction of pharmacology therapy, consequently leading to the reduction of their side effects.

2.2.3 Deep Brain Stimulation for Parkinson’s Disease

Parkinson disease is one of the primarily clinical uses of DBS. A prerequisite for a successful DBS outcome is previous robust motor response to levodopa, and DBS is considered after patients develop disabling motor symptoms or dyskinesias with medical therapy in place (Svjetlana Miocinovic, Somayajula, Chitnis, & Vitek, 2013).The main targets for DBS in PD are the STN and the GPi (Siegfried & Lippitz, 1994). Initial studies favoured STN over GPi DBS, but currently the discussion between the most beneficial target for DBS is not yet closed. Even though that STN DBS continues to be preferred, GPi can be considered in PD patients presenting speech, cognitive

and mood disturbances, once STN DBS aggravates these symptoms (Follett et al., 2010). It has been show significant improvement of levodopa-related complications, as drug induced dyskinesia (Krack et al., 2003). In PD, however, DBS therapy is not risk and burden free. Surgery and implant related complications need to be made aware, as well as the need for follow up, patient support system and commitment to therapeutic plan.

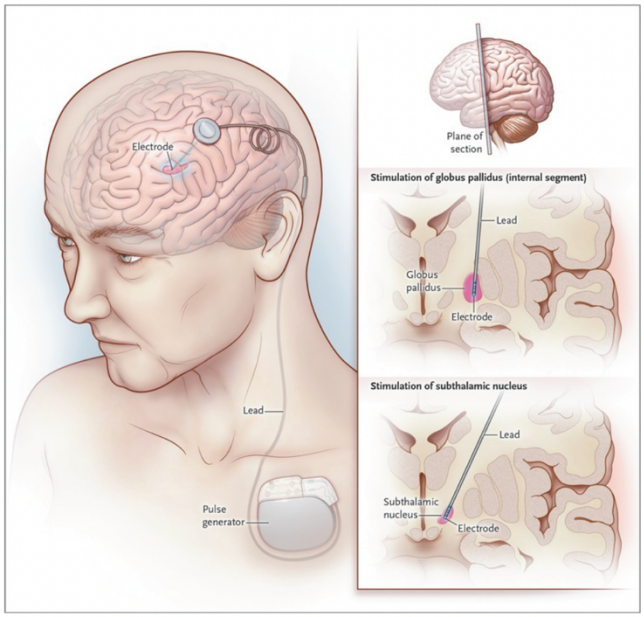


Figure 2.4 Electrode implantation Deep Brain Stimulation.
The lead for deep-brain stimulation is implanted in either the subthalamic nucleus or the internal segment of the globus pallidus. The lead passes through a burr hole in the skull. Attached to the lead is a connecting wire, which is tunnelled under the skin of the scalp and neck to the anterior chest wall, where it is connected to an impulse generator. Adapted from (Okun, 2012).

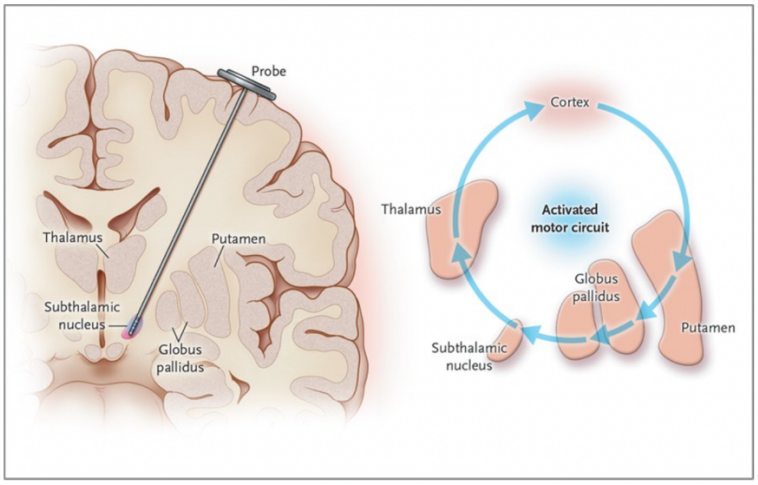


Figure 2.5 Networks Effects of Deep Brain Stimulation.
Deep-brain stimulation has broad effects on neural networks in addition to, or because of, its local influences. Motor pathways are complex, and their disturbance in Parkinson's disease is likewise far-ranging. Deep-brain stimulation modulates the feedback loops that ultimately determine motor control. Adapted from (Okun, 2012).

Animal and in vitro models for PD

PD progression involves multiple cellular pathways. Dopaminergic neuron death, with involvement of mitochondrial dysfunctions and reactive oxygen species generation, alpha-synuclein misfolding and deposition are two of the most studied. However, due to the complexity of brain organization, in vitro studies of such pathways in PD is a challenging endeavour (Raza, Anjum, & Shakeel, 2019). These challenges are enhanced by the scarce

availability of in vitro human neuronal tissue for studying the (electro)physiology of dopaminergic neurons. There are examples of human dopaminergic neuron containing cultures derived from pluripotent stem cells, neural stem cells and embryonic stem cells (Yoo et al., 2015; Yu et al., 2007). In vitro models mimicking PD characteristics in the extent of the possible techniques are highly valuable to understand cellular mechanisms as well as to identify future therapeutic targets (Martínez-Morales & Liste, 2012). Existing cellular models of PD allowed the better understanding of alfa-synuclein misfolding and aggregation process, mitochondrial impairments, fusion-fission dynamics, axonal transportation and bioenergetics (Alberio, Lopiano, & Fasano, 2012; Menezes, Tenreiro, Macedo, Santos, & Outeiro, 2015). One pre-clinical alternate is animal models mimicking PD symptoms and features (Raza et al., 2019). Although animal models with complete replication of the human PD features is not yet possible, animal models display the core pathological characteristics in humans with PD.

2.3 Deep Brain Stimulation

Deep Brain Stimulation is a neurosurgical procedure used for the treatment of movement disorders, such as Parkinson Disease, dystonia, and tremor. It allows targeted circuit-based neuromodulation. Innovations in this field are emerging as promising treatments for conditions beyond the movement disorders.

2.3.1 History

The first applications of DBS were intended to provoke irreversible lesions in a specific targeted region in the brain. They were based on the similarities between the effect of DBS on the clinical manifestations and surgical lesioning, upon the theory of basal ganglia functioning known as the “rate model” (Albin, Young, & Penney, 1989; Hess, Vaillancourt, & Okun, 2013). Nowadays, most experts believe that this approach has significant problems (Hess et al., 2013). With the introduction of reliable pulse generators appears the possibility to perform DBS without lesioning the target tissue (Krauss et al., 2021). DBS is approved by the Conformité Européene and the FDA as a standard of care for movement disorders, such as PD. DBS has also been used for other neurological conditions, such as epilepsy or psychiatric conditions, such as obsessive-compulsive disorder. With innovations from the field of pacemakers for cardiologic conditions, pulse generators for DBS evolved to small implantable devices. From the idea of a reversible effect, current vision of DBS is aiming towards the effect DBS as a complex agent present in process between inhibitory and excitatory mechanisms.

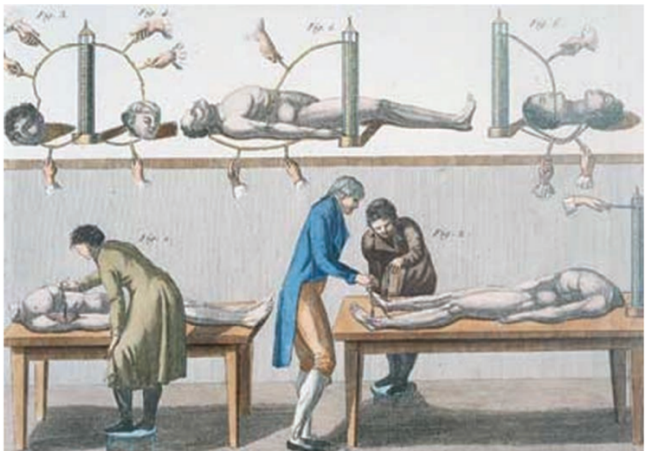


Figure 2.6 Electrification of decapitation in Bologna in 1802.
To left, the direct stimulation of the cortical surface is visible. From Plate IV in J. Aldini. Essai théorique et experimental sur le galvanisme. Paris: Fournier Fils, 1804; courtesy of the Accademia delle Scienze di Torino. Adapted from (Zago, Ferrucci, Fregni, & Priori, 2007).

2.3.2 Mechanisms

DBS appear to have several possible mechanisms to affect neuronal networks. Studies shows that DBS can have inhibitory and excitatory action. Local field potentials from during and after DBS surgery in humans and experimental lesioning in animals, together with computational models simulation basal ganglia networks, suggest

the presence of dysfunctional firing patterns within the basal ganglia networks, in comparison to absolute increase or decrease of the firing rates (Hess et al., 2013; C. McIntyre & Hahn, 2010). While there is an inhibition of neuronal cell bodies in the surroundings of the stimulation electrode, there are also efferent projections which will result in the activation of complex neural networks (Alexandre Eusebio, Cagnan, & Brown, 2012; Hess et al., 2013; E. B. Montgomery & Gale, 2008; Vitek, Zhang, Hashimoto, Russo, & Baker, 2012). Other proposed therapeutic mechanism is the direct suppression of local pathological neuronal activity, masking of pathological activity, and interactions with re-entrant nonlinear oscillations (Johnson, Miocinovic, McIntyre, & Vitek, 2008; E. B. Montgomery & Gale, 2008; Obeso et al., 2008). It is held that both the excitatory and inhibitory effects are secondary to DBS, and its hypothesized that synchronized oscillations have a critical role in the effects of DBS (Hess et al., 2013). However, it is important to consider that various simultaneous processes occur due to DBS stimulation.

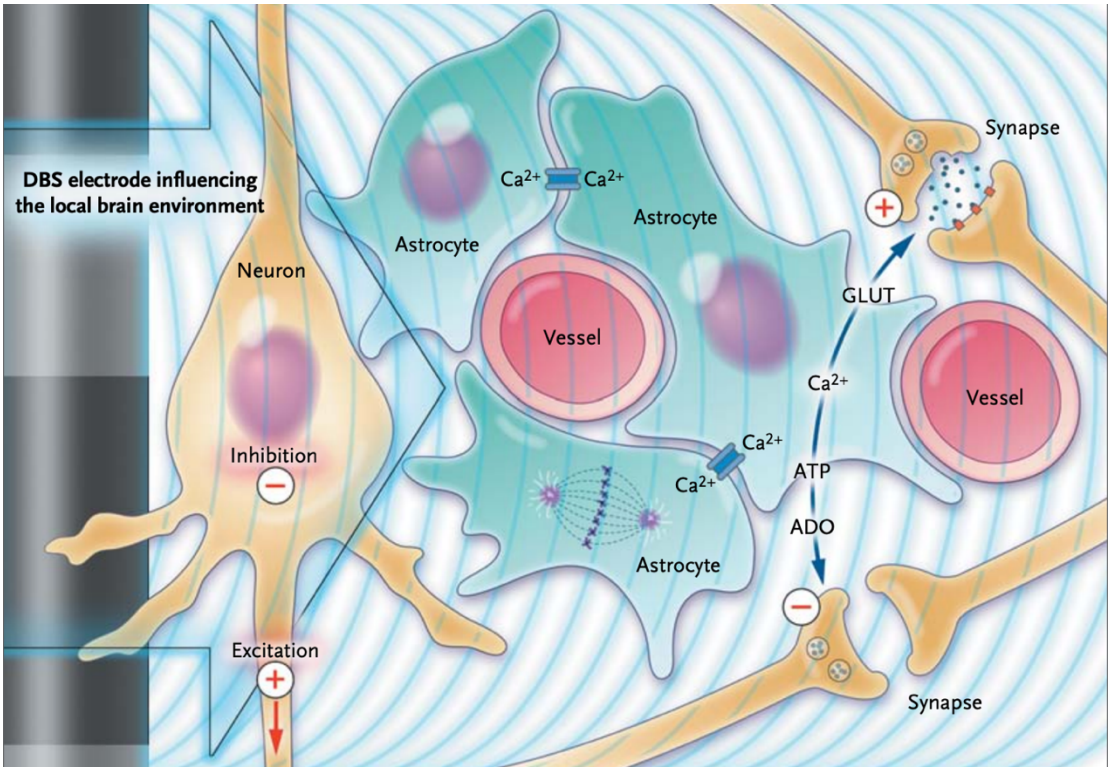


Figure 2.7 Local Effects of Deep Brain Stimulation.

The local effects of deep-brain stimulation tend to result in the inhibition of neuronal-cell bodies (–) and the excitation (+) of neighboring axons. In addition, astrocytes are stimulated to release calcium, which may lead to a release of glutamate (GLUT) and adenosine (ADO), as well as local increases in cerebral blood flow. Finally, there is evidence that deep-brain stimulation can induce local and possibly distal proliferation of neural precursor cells. Adapted from (Okun, 2012).

To fully understand how DBS affects the brain networks and their function, it is important to look into neural networks and neural cells and how they are affected by chronic stimulation. The components of neurons - dendrites, myelinated axons, neuronal cell bodies - have electrical properties that differ between each other. Studies point towards myelinated axons as the most likely target to be affected in standard stimulation parameters of DBS (Kringelbach, Jenkinson, Owen, & Aziz, 2007; Vedam-Mai et al., 2012). The different effects and their interaction will lead to a complex result where both inhibitory and excitatory processes occurring affect neuronal activity (Lozano et al., 2019; C. C. McIntyre, Savasta, Kerkerian-Le Goff, & Vitek, 2004). As for the inhibitory effect, this could be due to the indirect synaptic inhibition by activation of retrograde action potentials (AP) in the incoming axons, or the depletion of neurotransmitter in the outgoing axons resulted of the high-frequency synaptic firing (Benabid et al., 2009; Mateus et al., 2021; C. McIntyre & Hahn, 2010). The excitatory effect is dependent of the extension of the axons of the stimulated neuron, and if it is an excitatory or inhibitory neuron (C. C. McIntyre, Grill, Sherman, & Thakor, 2004).

The ideal DBS technology should be flexible in stimulating a smaller volume of a target region (high spatial resolution), stimulating preferentially axons mediating beneficial effects, avoid stimulating other axons of excitable elements which will translate in adverse side effects, eliminate or suppress the neuronal signal present in a pathologic network while not interfering with normal physiological network function. Stimulation techniques available were designed to counteract existing abnormal synchronization of neuronal activity. Neuronal populations have a complex behaviour in response of spike timing dependent plasticity (W. J. Neumann, Staub, et al., 2016). These responses will lead to states of strong or weak synapses, and synchrony. Referring to theoretical models, the desynchronization of stimulation leads to the reduction of neuronal coincidence rates, that are mediated by spike timing-dependent plasticity resulting in the decrease of synaptic strength.

2.3.3 Electrodes Design

As an invasive procedure, the goal of DBS is to use small electrodes to be placed intra-cortically and deliver electrical stimulation to targeted brain regions (Fig. 3). The concerns surrounding electrodes refer to its biocompatibility, durability, inertness, stability over time, conductivity, electrical properties, current delivery, surgical feasibility and spatial configuration (Krauss et al., 2021). Two additional characteristics include compatibility with MRI and the potential for sensing. The standard electrode is quadripolar, presenting four stimulation electrodes contacts, with 1,27mm in diameter (Krauss et al., 2021). The cylindrical contact is 1-5mm in lengths and the contacts are positioned 0.5 to 1.5mm apart. These standard configurations allow the electrical field to be shaped along the z axis of the lead due to integrated programming of various combinations of anodes and cathodes (Krauss et al., 2021).

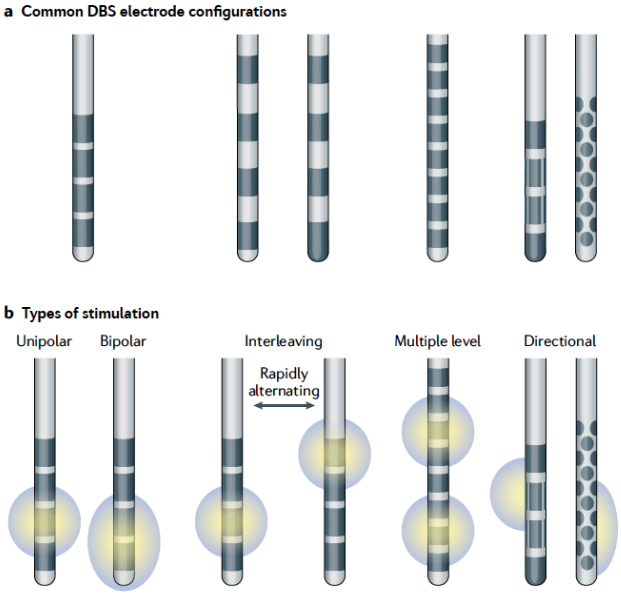


Figure 2.8 Deep Brain Stimulation electrode configurations.
Dark grey regions correspond to electrode contacts that can be activated to deliver current. A) Common electrode configurations for DBS. B) Modes of stimulation according to the type of DBS system implemented. Adapted from (Krauss et al., 2021).

2.3.4 Target for DBS

Insights about the basal ganglia role in the pathophysiology of the PD cardinal motor features, as well as the knowledge derived from lesioning techniques, led to the proposal of STN and GPi as targets for DBS in PD (Hartmann, Fliegen, Groiss, Wojtecki, & Schnitzler, n.d.). The most used is STN DBS, but there is improvement regarding both targets in symptoms such as bradykinesia, rigidity and tremor. Even though the motor symptoms of PD are the main target when applying STN DBS, there is also evidence of nonmotor improvements. Moreover, studies show beneficial effect of STN DBS in hyperdopaminergic behaviours and neuropsychiatric fluctuations,

which is possibly due to the reduction in dopaminergic medication (Lhommée et al., 2018; Merola et al., 2017). The comparison of the effect of STN and GPi DBS has not yet led to a conclusion on superiority of benefits between the two targets. Patients with high intake of dopaminergic medication, hyperdopaminergic behaviours and neuropsychiatric fluctuations prefer STN DBS, whereas for mild cognitive decline, predominance of axial symptoms and severe hyperkinesia GPi DBS is preferred (Ramirez-Zamora & Ostrem, 2018). Other targets are available, in particular for axial symptoms of PD, such as mesencephalic locomotor regions (Fasano, Aquino, Krauss, Honey, & Bloem, 2015). The impact of DBS of this target is not fully known, and further studies need to take place before its implementation in clinical practice.

2.3.5 Biocompatibility

One major concern regarding DBS is the biocompatibility of the device. As the electrode is invasively implanted, the interface between the electrode and the surrounding tissues evolves through time (W. J. Neumann, Staub, et al., 2016). Acutely, it is a foreign body that, progressing to chronic stage, will lead to protein absorption on electrode site and glial encapsulation of the electrode. Importantly, the ionic movement at the electrodes interface will influence the behaviour of the interface between electrode and tissue. Acute presence of idiopathic delayed-onset oedema surrounding the leads has been described (W. J. Neumann, Staub, et al., 2016). One important problem with the implementation is the inflammatory foreign body reaction which will influence the therapeutic effect of the electrode. In particular, the inflammatory response around the electrode will affect impedance through time (W. J. Neumann, Staub, et al., 2016). However, even considering such concerns, long-term DBS is considered safe to be applied.

2.3.6 Stimulation therapy adjustment

The therapy adjustment is performed by the clinician. The process starts with conventional initial settings of the DBS system, with the delivery of constant current or voltage through selected electrodes. Evaluating the clinical response and presence of adverse effect, the stimulation settings are adjusted in a trial-and-error approach. The process to achieve an adequate response takes weeks to months to be completed (C. F. Wang et al., 2017). Significant improvements should appear after 3 months of surgery, but it can take a year to reach optimal effect. Another important factor is the voltage that is required for stimulation. Usually, a mean of 3.0V is effective in obtaining an adequate clinical response in PD. However, electrodes implanted in different target regions such as the STN and the GPi have variable stimulation effects (C. F. Wang et al., 2017). The increase of voltage will reduce the battery life spam, increasing treatment cost and the need for more surgical procedures. As for the therapeutic frequency range typically use in DBS is from 80 to 185 Hz, and the stimulation current range from 1 to 10mA (Gubellini, Salin, Kerkerian-Le Goff, & Baunez, 2009; Vedam-Mai et al., 2012). Regardless on the initial approach, the adjustment of stimulation relies heavily on the subjective evaluation by the clinician during in-clinic sessions. To achieve a more objective and fit-for-patient parameter selection, closed-loop programming models need to be developed. These models adjust the stimulation parameters based on patients' characteristics and biomarkers. This approach will be discussed in following chapters. There is a wide range of characteristics that can be used as biomarkers to feed the feedback control such as electrical neural activity, posture and kinematics parameters, and biochemical measures (Svjetlana Miocinovic et al., 2013). Local field potentials can translate neural activity, and its measurement is possible through contacts of the DBS electrode with sensing capacities. LFP characteristics have the potential to translate the disease state and trigger appropriate stimulation (M. Birdno, Kuncel, Dorval, Turner, & Grill, 2008). However, the wide range of symptoms aimed to be treated with DBS may require a vast set of biomarkers as well, with pathological signatures and different response to stimulation settings. The topic of biomarkers will be covered in named section.

2.3.7 The effect of varying parameters

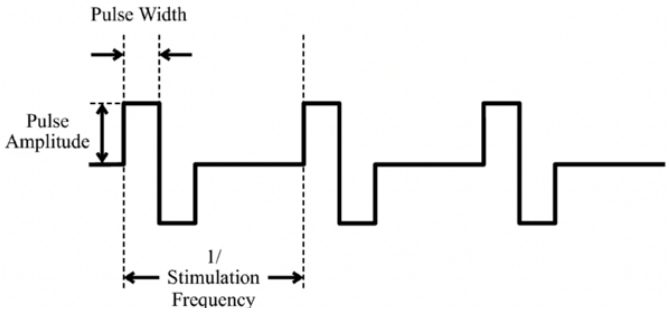


Figure 2.9 Functional electrical stimulation parameters.
Pulse width, amplitude, and frequency define the muscles stimulated, force, and quality of the contraction. Adapted from (Marquez-Chin & Popovic, 2020).

Stimulation Intensity

Stimulation intensity is the parameter with more significant effect in reducing Parkinsonian motor signs, and usually the most titrated parameter in the initial stages of STN DBS programming. Stimulation intensity can be achieved through managing the voltage or the current, which is related to the impedance. Side effects dependent of voltage mainly consist of motor or sensory symptoms, occurring mostly with progressive increase in voltage.

Frequency

Frequencies bellow 50Hz applied to STN DBS were shown not to have a clinical significant effect on motor signs in PD (Rizzone et al., 2001). There is also evidence that very low frequencies (5-10Hz) worsens motor symptoms, in particular bradykinesia, in comparison with no stimulation setting (E. Moro et al., 2002). In a study by Moro et al, frequencies over 50Hz improved bradykinesia and tremor, and frequencies above 33Hz improved rigidity (E. Moro et al., 2002). Improvements in cardinal motor signs was shown with increasing frequency, being significant between 50Hz and 230Hz, and the veiling of beneficial effects was in the range of 130-185Hz (E. Moro et al., 2002).

Pulse width

Conventional pulse widths used in STN DBS range from 60 to 450s duration (Dayal, Limousin, & Foltynie, 2017). To achieve a required clinical effect, when increasing the pulse width value, it is required to correspondingly lower the intensity of the stimulus. This results, with increasing pulse widths, in a narrower therapeutic window (Rizzone et al., 2001). The adverse effects seen are similar to those reported by the increase of stimulation intensity, such as muscle contractions, paraesthesia, dysarthria, and postural tremor.

Directional Steering

To perform directional stimulation, the conventional cylindrical electrode needs to be replaced with a segmented or multi-contact electrode. This allows that the selective activation of one or more contacts is used to produce a field of stimulation in a certain orientation that will target adjacent neural tissue more selectively (Contarino et al., 2014; Dayal et al., 2017; Pollo et al., 2014). Directional steering electrodes complement the advances of adaptive DBS. The three-dimensional configuration of the brain target is not spherical, neither it presents a regular shape that would match the spherical or ellipsoid conformation of the electric field that is generated by the DBS electrode (Hariz, 2014). Brain anatomy is irregular and heterogenous, with different reactions possible in response to electrical stimulation, and individualized. Hence, when considering directional steering, it is important to optimize at the best the target region, in way to maximize the effect on this target and minimize adverse effects in other regions not relevant for the therapy.

Interleaving stimulation mode

This mode of stimulation is an already available feature in currently used DBS systems which allows for independent and alternated stimulation of two contacts of the quadricular DBS lead, with different values of voltage and pulse width but presenting the same frequency (Hariz, 2014). It allows to deliver stimulation with different energies to neighboring anatomical structures. This is useful when adjacent anatomical structures requiring stimulation with different amplitudes, which is not possible with classical monopolar or bipolar stimulations. Often, it results in side effects from the too high stimulation in certain target areas adjacent to areas that required that level of energy to have good clinical results in the first place. These techniques has been applied to PD patients and have been reported to be successful (Baumann et al., 2012). However, programming of such techniques is far from simple, and increases the drain of the battery, hence reducing its lifespan.

2.3.8 Advances in stimulation methods

In the last years there was an increase in the advances regarding stimulation techniques. These include the introduction of regulated current implantable pulse generators (IPG) (Bour et al., 2015), and use of novel stimulation waveforms shape and temporal patterns of stimulation (W. J. Neumann, Staub, et al., 2016). These advances led to rethinking the current stimulation algorithms, and the development of new approaches towards DBS.

The shape of the stimulation waveform refers to the shape of the stimulation current as a function of time. It can affect both the number and type of neural elements activated with stimulation. A simulation pattern is created when waveforms of pulses are repeated at inter-pulse intervals. Symmetric biphasic pulses, in comparison to conventional asymmetric DBS waveforms, seem to produce greater reduction of motor symptoms in PD patients (W. J. Neumann, Staub, et al., 2016). Symmetric biphasic pulses are prone to activation of larger neural population in comparison to asymmetric pulses. This arrives due to both cathodic and anodic phases of the stimulus waveform polarity, the reversal of the standard pulse phase order, and the existing gap between the two phase of charge balanced biphasic pulse (W. J. Neumann, Staub, et al., 2016). When considering closed-loop delayed feedback, linear or nonlinear, the shape of the waveform can influence the desynchronization impact of DBS techniques.

Evidence indicates the temporal pattern of stimulation has impact in the clinical outcome of patients undergoing DBS, emphasizing this effect in PD (W. J. Neumann, Staub, et al., 2016). Having the selection of the optimal pattern in consideration creates a new important design challenge in accounting for the effect of the stimulation on symptoms, as the response may not be stable over time (W. J. Neumann, Staub, et al., 2016). It adds to the challenge the fact that the range of temporal patterns is wide, and the empirically identified as the most effective may not be indeed possible. With the optimization of the temporal pattern, a model of stimulation could address the challenge. However, to do so, it needs to be an established model for the patient that allows the loop to be applied as required. The delivery of brief high-frequency pulses train, known as coordinated reset stimulation, through different stimulation contacts, can cause acute desynchronization effects and unmeaning of abnormal synaptic connectivity and neuronal synchrony. After cessation of coordinated reset stimulation, it was shown that desynchronization accumulates and persists (W. J. Neumann, Staub, et al., 2016). These results indicate potential in temporal patterns towards enhancement of the efficiency of stimulation and symptom relief through the control of neural plasticity.

With the wider application of DBS, there is anticipation towards advances of the available technology (W. J. Neumann, Staub, et al., 2016). Regarding the electrode and the IPG, expected advances are related with their miniaturization, their large-scale and modernized production to reduce costs, multiple power sources within IPGs (enabling multiple independent current control), and enhancement of battery life as well as the possibility for recharging. Regarding safety of DBS, advances are aimed at improvement of compatibility with MRI systems, antibiotic impregnation to reduce infection rates, and protection from hacking (including brainjacking). Concerning optimized stimulation, advances aim at the use of varying interpulse intervals as well as coordinated reset. A

significant field of improvement in DBS technologies is related to adaptive DBS and closed-loop designs. These aim to provide a stimulation in response to local field potentials power spectra or bursting activity, as well as incorporate information of secondary sources as electromyographic recordings, body position or motion. Lastly, an important contribution to DBS techniques are the advances of neuroimaging to improve targeting, out of the scope of this work.

2.3.9 Biomarkers

Neuronal structures communicate between each other, but as well with other units such as muscular ones. These communications are governed by regulatory pathways, and in some cases of communication with muscular units, pathways for voluntary movement. Physiological components of such process entail neural oscillations. To study the relation of oscillations, present between two sources it is possible to apply several methods of analysis, such as coherence which will study their mutual dependence. It has been described the coupling of physiological oscillatory activity of cortical neurons with voluntary contractions of muscles, and their alteration status in pathologic states. These findings open the possibility to the identification of biomarkers of the corresponding pathologic states and symptoms. There is evidence that the cortico-basal-ganglia-thalamo-cortical networks manifest abnormal neural oscillations as a pathophysiologic marker for movement disorder (Piña-Fuentes et al., 2018). The identification of these oscillations can, in theory, be used as a biomarker towards the closed-loop signal-orientated delivery of adaptive DBS.

The adjustment of open-loop stimulation has several challenges, hindering the optimal therapy of DBS. To overcome these limitations, closed-loop DBS development is needed. To achieve closed-loop DBS, the concept of biomarkers is central. Various signals have been used as a feedback biomarker in closed-loop DBS systems, such as AP (Lettieri et al., 20122012; Boris Rosin et al., 2011), electrocorticography (ECoG) signals (Mahboubeh Parastarfeizabadi & Kouzani, 2017), local field potentials (Abosch et al., 2012; Giannicola et al., 2012; Simon Little et al., 2013; Alberto Priori, Foffani, Rossi, & Marceglia, 2013) and electroencephalogram (EEGs) (Swann et al., 2011). There is evidence from EEG recordings from PD patients that basal ganglia presents abnormal circuit functions, and the presence of high thalamocortical theta coherence (Sarnthein & Jeanmonod, 2007; Swann et al., 2011). The readings of biomarkers in EEG are a possibility, further enhanced by its non-invasiveness, but hindered by the signal low amplitude, low spatial resolution, high noise and artifacts sensitivity. ECoG are also an option, however, the distances of the sensing electrode from the source of networks disruption are limitative (Rouse et al., 2011). Adding to ECoG the limitation of the requirement for placement of subdural electrodes in the brain epidural or subdural spaces, making it an invasive procedure with yet low spatial resolution. APs have a high spatial resolution, making them a good candidate as biomarkers to use in adaptive DBS devices. However, there are limitations that affect its position as a good candidate as biomarkers. The continuous recording of APs may lead to cellular death and there is high demand for recalibration process in order to maintain the stability of the signal (János et al., 2013). The most used signal as biomarker in closed-loop DBS are the LFPs (Abosch et al., 2012; Simon Little et al., 2013; Alberto Priori et al., 2013). These signals are the extracellular recordings of potentials generated by propagation of APs through axons. Hence, although not having a high spatial resolution as the APs, they reflect the neuronal processes taking places in a local region in the neuronal extracellular space surrounding an electrode (Yoshinao Kajikawa, 2012). LFPs present advantages towards their use as biomarkers: the availability of electrodes with stimulation and sensing properties allow for the recording of LFPs and they achieve long-term stability at electrode-tissue interface (Simon Little & Brown, 2012). Several neurological conditions have already been studied with closed-loop DBS system operating with LFPs as biomarkers (Deeb et al., 2016).

Considering the different factors of a biomarker, its selection will depend on various characteristics, in context of disease and degree of impairment due to symptoms. Key features are the high signal-to-noise ratio recordings and the stability over the presence of external artifacts such as movement, specificity to ensure the correlation in time with the severity of the clinical symptoms, and high sensitivity (Piña-Fuentes et al., 2018; Z Yin et al., 2021).

Moreover, once a biomarkers is decided, it adds the necessity of full knowledge of their characteristics such as latency and duration, and velocity of reaction to electrical stimulation (Piña-Fuentes et al., 2018).

Although the primary focus is by default toward a single signal biomarker, the relation between two different sources signals that allow to study their oscillatory relation is also of valuable use for aDBS (Piña-Fuentes et al., 2018). Advancing beyond spectral analysis, evaluation of coherence and other statistic methods would contribute towards a more robust feedback implementation.

Local Field Potentials

The use of LFPs as a biomarker obeys the following process. The LFPs are processed by filtering of the recordings, and the posterior identification of the power changes in frequency bands are possible through spectral analysis (Piña-Fuentes et al., 2018). The analysis of LFP is commonly performed in a frequency-based approach. The bands are related to specific frequency intervals and associated with brain circuits and symptoms. It has been shown that one frequency band can be associated with more than one function, depending of the activated network in context (Z Yin et al., 2021). Context will depend on the pathology in cause, and the motor and nonmotor state. This approach allows for a comparison and discussion of results across neurophysiology experiments and analysis. For example, LFPs features aids in the classification of PD motor phenotypes. Studies have classified PD patients in two main groups in accordance with the main motor symptoms: tremor dominant PD (TD) and akinetic rigid PD (AR) (Z Yin et al., 2021). LFPs beta band features can be applied to differentiate both groups, as the suppression of beta band is present in AR patients during movements tasks, in opposition to their absence in TD patients (Quinn et al., 2015).

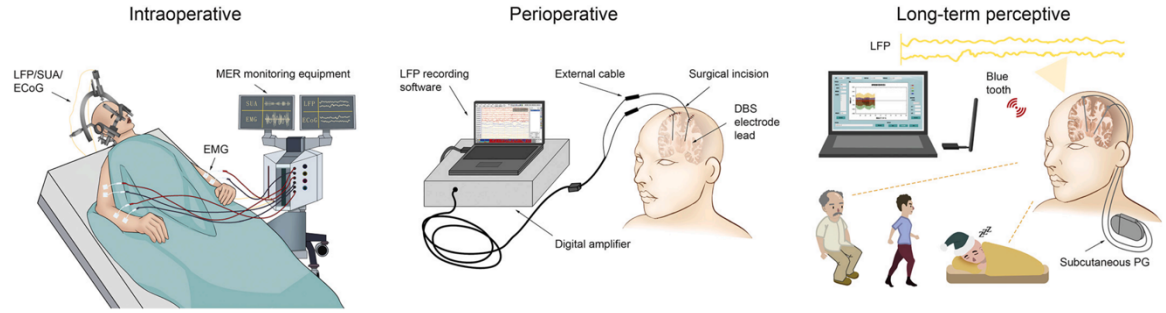


Figure 2.10 Illustrations showing how LFP is recorded during the 3 periods.
(Left) During the DBS surgery, LFP can be recorded through the explorative micro/macroelectrodes, which also record SUA to optimize lead localization. ECoG and EMG signals may be simultaneously collected for clinical and/or research usages. (Middle) During the perioperative period, normally 3–4 days after the surgery, LFP can be recorded through cables connecting leads to an external digital amplifier. (Right) The latest perceptive bidirectional neurostimulator makes long-term LFP recording possible. LFP signals can be recorded and transferred via Bluetooth wireless when patients are sitting, walking, sleeping, etc. LFP: local field potential; DBS: deep brain stimulation; SUA: single unit activity; ECoG: electrocorticography; EMG: electromyography. Adapted from (Zixiao Yin et al., 2021).

LFP sensing from basal ganglia structures can be recorded in three periods (Z Yin et al., 2021). The first period is related to the surgery of implantation. While optimization DBS lead localization, LFP can be recorded through the electrodes connected to the intraoperative monitoring equipment. However, the intraoperative recordings are a period where the patient is limited of free movement or of performing intricate tasks (M Rosa, Marceglia, Barbieri, & Priori, 2014). The second period arises just after implantation, before the lead's connection to the permanent IPGs, in a perioperative period of 3 to 4 days after surgery. Here, movement tasks are possible, and clinicians have opportunity to study the stimulation effects in the activities of the patient (Alonso-Frech et al., 2006; Christensen, Abosch, Thompson, & Zylberberg, 2019). As the leads are connected to external digital amplifiers, this window should not be overly extended to avoid intracranial infections. Lastly, DBS devices have the capability for sensing. This opens the third window for recording LFPs, in a chronic approach that can last years, allowing longer recordings with patients able to perform free movement and complex tasks.

With segmented contacts, it is possible to perform directional steering current in specific STN target regions (Pollo et al., 2014). However, this directional component adds another parameter for adjustment, increasing its time and complexity. LFP sensing allows to optimize this process as, for example, the choosing of a contact pair in maximal STN beta power is likely to result in better symptomatic control with the largest therapeutic window (G. Tinkhauser et al., 2018). Evidence also shows that stronger beta and gamma activity of a particular pair are likely closer to the pathological source (Nuri Firat Ince, Akshay Gupte, Thomas Wichmann, MD, James Ashe, MD, Thomas Henry, MD, Margaret Bebler, RN, CNS, Lynn Eberly, PhD, and Aviva Abosch, MD, 2015). The reduction of distance to the sources allows a reduction in the requirements of current.

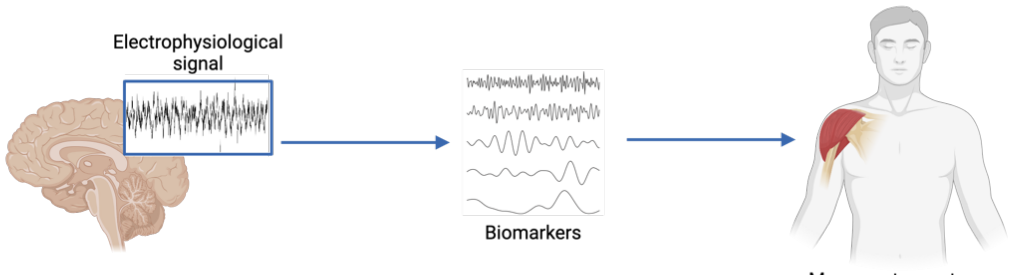


Figure 2.11 Electrophysiological Biomarkers correlated with motor symptoms.
The concept of electrophysiological biomarker in the context of Parkinson's Disease comes naturally linked in finding biomarkers of (pathological) motor activity. An electrophysiological signal is process to extract patterns that correlate to certain motor symptoms that can be modulated with deep brain stimulation.

LFP Frequency Bands

Delta bands (0.3Hz)

Literature related to delta band is scarce, with few studies reporting its effect. This could be due to its susceptibility to be filtered out or influenced by movement artifacts. In depth electrode recording, delta activity is identified in the nucleus basalis of Meynert for PD with dementia patients (Nazmuddin et al., 2018).

Theta (4-7Hz) and alpha (8-12Hz) bands

The components theta and alpha are often referred as low frequency (LF) (Wojtecki et al., 2017). STN LF oscillations have been studied in extensive non-motor domains such as cognition and emotion, economic decision making, impulse control, reward related processing, memory function, attention and consciousness, among others (Manuela Rosa et al., 2013; Zénon et al., 2016). For motor features in PD, there was an increase of LF activity in STN and GPi and alleviation of motor symptoms, after Levodopa intake or DBS stimulation (Silberstein et al., 2003).

LF activity has potential to be a biomarker in the adjustment of treatment dose as it was shown to correlate with degrees of dyskinesias (Alonso-Frech et al., 2006). Another potential use of LF is integrated with the evaluation of beta power. Off therapy states present LF STN power and high beta band power, which will induce to turn on the stimulation. The STN power may be transferred from the beta band to the LF band, leading to turning off the stimulation (Giannicola et al., 2012). This LF/beta band power ratio can be a tool to achieve closed-loop stimulation as it has advantages over the single use of beta band power. First, beta activity locates mainly in the dorsolateral STN, and LF is more widespread (the peak of its location is the ventromedial STN) (Horn, Neumann, Degen, Schneider, & Kühn, 2017; Trottenberg, Kupsch, Schneider, Brown, & Kühn, 2007). Having sensing from two locations as inputs for the closed-loop cycles allows to obtain optimized status of the pathological oscillations and improving stimulation efficacy. A second predicted advantage is to extend the control of motor symptoms as beta activity is more associated with rigidity and bradykinesia, and the LF band with the tremor frequency band (A. Eusebio et al., 2011; Giannicola et al., 2012). However, LF activity has been shown to increase in parkinsonian tremor and levodopa-induce dyskinesia, which can affect the adjustment of symptomatic control and the appearance of adverse side effects.

Beta bands: Low beta (13-20Hz) and high beta (21-35Hz) bands

Beta band is the most studied band as biomarker for aDBS design, once has been repeatedly shown its safety and effectiveness (Arlotti et al., 2018; Iturrate et al., 2019). Beta band power is shown to be abnormally high in the STN of PD patients which decrease during movement preparation and execution and showing a rebound once the movement is over (Brown et al., 2001; Kühn et al., 2006). The beta activity can be reduced by the intake of Levodopa. Suppression of beta band is associated with improvement of motor symptoms (Kühn et al., 2009; Oswal et al., 2016). Its increased state is suggested to be related to hypodopaminergic states (Brown et al., 2001; W. J. Neumann, Degen, et al., 2016). There are two main characteristics of beta band which makes it a good candidate as biomarker for aDBS and closed-loop stimulation. First, beta band is clinical relevant as it is associated with parkinsonian symptoms and is affected by medical therapy and DBS (Brittain & Brown, 2014). The second characteristic is the consistency of the band in long term recordings. The association between beta power and symptoms severity is maintained throughout the time, allowing a chronic assessment of the motor symptoms through STN LFP (W. J. Neumann et al., 2017). Nevertheless, LFP are not the only possible biomarker, as stated before. Single-unit activity, LF, gamma band activity, phase-amplitude couples between STN and the motor cortex can all be used integrated and provide variate feedback strategies to better accommodate aDBS. Moreover, LFP beta activity recordings can be smothered over short periods of time and processed to retain rapid fluctuation present in the signal (Krauss et al., 2021). The component heavily smothered tracks the dynamics related to pharmacologic therapy and motor on-off state changes, which, implemented in aDBS can reduce power requirements by ~50% and on-state dyskinesias (Krauss et al., 2021).

Beta band power can be divided in two bands according to their frequency: low beta (13-20Hz) and high beta (21-35Hz) bands. It is suggested that these bands have different functions (S. Little, Pogosyan, Kuhn, & Brown, 2012; van Wijk et al., 2016). Low beta activity is dominant in the STN, and associated with pathological oscillations (Tsiokos, Malekmohammadi, AuYong, & Pouratian, 2017). Low beta activity is more sensitive to medication than high beta band, and is significantly higher in untreated PD patients, associated with the disease severity of PD and appears to have intraregional (more local) role (W. J. Neumann, Staub, et al., 2016). On another hand, high beta band its hypothesized to have a longer distance role. The coupling between STN and cortex in the high beta band frequency could be a electrophysiological manifestation of the hyperdirect pathway, once there were shorter coupling delays between the STN and motor cortex in the high beta band in comparison to the low beta band (Alexander & Crutcher, 1990; Blumenfeld et al., 2017).

Beta activity were first identified in 1992 as short-long phasic bursts in primates (V.N. Murthy & Fetz, 1992; Venkatesh N. Murthy & Fetz, 1996). These burst are a physiological activity with roles in information transformation, and their presence, duration and size are affected by context (Torrecillos et al., 2018). Studies in PD patients that underwent aDBS commonly indicate that larger and longer burst are associated with pathological beta activity (Gerd Tinkhauser et al., 2017). Presence of abnormal beta bursts in PD is associated with the degree of motor symptoms and the severity of rigidity and can explain the impairment of motor capabilities better in comparison with average beta power (Roxanne Lofredi et al., 2019; Gerd Tinkhauser et al., 2017). Pathological beta bursts are explained by over-synchronization of neurons in the motor networks, locally but also involving dynamic long range synchronization (Gerd Tinkhauser et al., 2017). According to Hebb, synchronized neurons are more prone to fire together (Hebb, 1949), and the process of transferring different information individually decreases restricting the information-coding capacity of the circuit (Brittain & Brown, 2014). Pharmacological therapy with Levodopa and electrical stimulation can affect the STN beta burst from long to short duration, hinting about its physiological status (Gerd Tinkhauser et al., 2017). This can represent a target for aDBS since the detection of longer burst can act as a trigger to increase stimulation which would terminate these bursts, allowing the reduction of power requirements and adverse effects in comparison to conventional continuous stimulation (Krauss et al., 2021). As burst are affect by the administration of levodopa, combining DBS with Levodopa intake will lead to a less frequently triggered stimulation since it would be triggered by the final distribution of the bursts

(Manuela Rosa et al., 2015, 2017). However, the threshold for activation is dependent on the methods applied for their calculation which may result in burst differing its duration (Schmidt, Peters, Turner, & Grill, 2020).

Gamma band (31-200Hz)

The gamma band activity is seen as prokinetic, with a compensatory mechanism toward the akinetic role of beta activity (102,103). The onset of movement is identified as an increase in gamma power as well as during movement, and movement inhibition (Litvak et al., 2012; Roxanne Lofredi et al., 2018). Movement velocity is positively correlated with increase in the STN narrow gamma band, corresponding to 40-90Hz, power and negatively with parkinsonian motor symptoms (Roxanne Lofredi et al., 2018). Studies shows that synchronization of gamma power during movement is present in bursts, with the burst rate increasing in parallel with fast movements. In opposition to beta band, after administration of Levodopa there is an increase in gamma activity (Elben, Trenado, Vesper, Schnitzler, & Wojtecki, 2018; Roxanne Lofredi et al., 2018). On other perspective, low gamma activity (31-45Hz) is positively correlated with the severity of resting tremor, which can be affected by emotion, stress and the co-existence of dyskinesia and tremor in certain patients (Kühn et al., 2006). Another approach to control dyskinesia relies in the detection of rapid changes in gamma activity at the cortical level, once there the amplitude is larger and easier to distinguish from stimulation artifacts (Krauss et al., 2021).

High frequency oscillations (above 200Hz)

High frequency oscillations (HFO) were observed in STN of PD patients intra and post operatively (J. Wang et al., 2014). HFO are regarded as prokinetic, and STN activity increases at the onset of the movement and Levodopa administration (Alegre et al., 2012; Litvak et al., 2012). It is speculated that the components of high-frequency DBS for PD patients improves the motor impairment through the evocation of STN neural activities similar to HFO (Nicholas C. Sinclair et al., 2019).

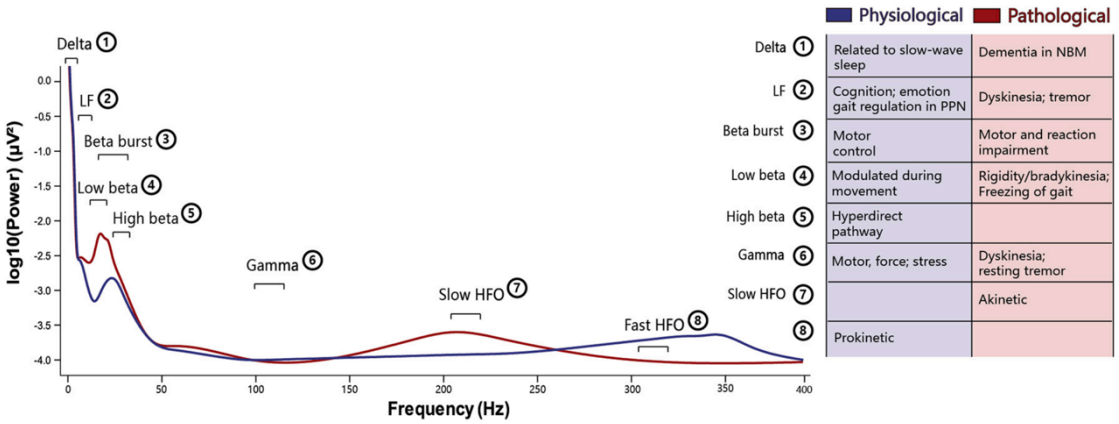


Figure 2.12 Exemplar plot of power spectrum analysis of STN LFP in PD patients.
The functions related to different frequency bands were labelled in both the physiological and pathological states. NBM: nucleus basalis of Meynert; PPN: Pedunculopontine nucleus; GPi: internal globus pallidus; LF: low frequency; HFO: high frequency oscillation. Adapted from (Zixiao Yin et al., 2021).

2.4 Adaptive and Closed-Loop DBS

Adaptive DBS (aDBS) is possible due to the integration of several advances in the DBS technology. It encompasses the study of biomarkers, the development of more effective leads, and the understanding of closed-loop mechanisms in model development for several pathological states. While advancements such as directional leads and adaptive stimulation are made available, the technology implemented is lagging in adequate programming for aDBS. Adaptive DBS aims to tailor stimulation delivery to the patient according to a biomarker signal which provides information about the clinical state and underlying neurophysiopathology. This approach will allow the minimization of side effects induced by stimulation and a personalized treatment adequate to patients' needs. Evidence shows that aDBS could control dyskinesias induced by Levodopa of implanted patients (Manuela Rosa et

al., 2017). Battery life span is a major concern in chronic DBS, and the optimization of stimulation delivery in aDBS could reduce battery usage. However, the chronic potential of aDBS still requires more research to tune according to possible confounders. Oedema and microlesion effects occur after implantation and can alter the nature of the recorded signals. The advancement in the field of available leads with directional steering capabilities allows to take advantage in shaping the electrical field used in DBS (Krauss et al., 2021). By providing stimulation to a more defined region, targeted, it reduces the side effects of ineffective stimulation and optimizes therapeutic windows. Studies show that adaptive stimulation, using feedback obtained from measurements of bands power from various channels with different directions and depths with a 32 contact DBS lead, directed to the highest activity in the beta band power was related with better outcomes in reducing symptoms as rigidity (Bour et al., 2015). The effect of exact location of electrodes or contacts are often not included in analysis of DBS results, which leads to the need to address this confounding in the real effect of DBS (Dayal et al., 2017).

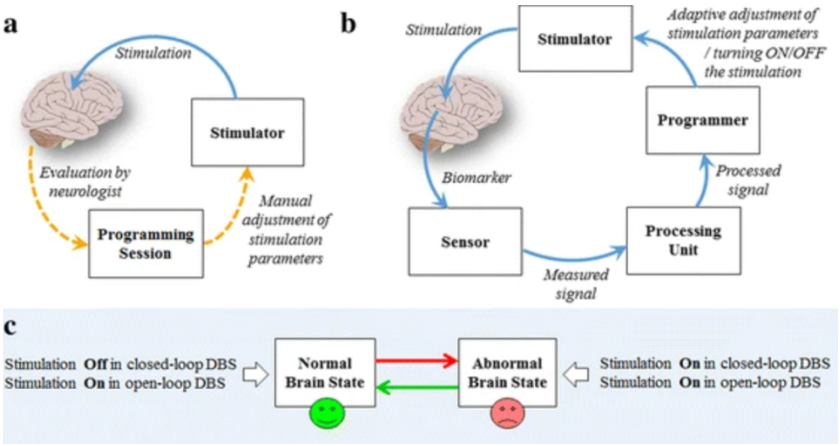


Figure 2.13 Overview of open-loop DBS (a) versus closed-loop DBS (b).
In open-loop DBS (a), a neurologist manually adjusts the stimulation parameters every 3–12 months after DBS implantation. On the other hand, in closed-loop DBS (b), programming of the stimulation parameters is performed automatically based on the measured biomarker. c) Demonstration of two different brain states and the action of open-loop and closed-loop DBS. When the brain enters a specific state, it remains in that state for a short or long time. Closed-loop DBS gets deactivated when the brain enters the normal state. Open-loop DBS continues the stimulation regardless of the brain state. Adapted from (M. Parastarfeizabadi & Kouzani, 2017).

2.4.1 Closed-Loop DBS

Closed-Loop DBS systems simultaneously record and provide stimulation to neural issue surrounding the lead and allows to an adjusted stimulation according to neural biomarkers that are disease specific. Optimization of closed-loop stimulation parameters can enhance the patients' therapeutic benefits and reduce side effects. Open-loop stimulation is programmed by the clinicians with the same goals but are far from producing the results closed-loop stimulations aims to. More that managing the parameters, this management should operate simultaneous to the stimulation delivery and in autonomous response to the information that the sensing probe is providing.

In some neurological diseases, the cause for pathologic symptoms is in the synchronization of populations of oscillatory neurons. In open-loop DBS, the stimulation may not yield desynchronization and the therapeutic effects may decrease over time (Volkmann, 2004). Several models have been developed in attempt to reestablish the desynchronized dynamics in network of oscillatory neurons. Due to neuronal plasticity, neuronal tissue reaction to a constant stimulation delivery may alter through time in response to external, environmental, or internal, disease progression, factors (Hunka, Suchowersky, Wood, Derwent, & Kiss, 2005). Neural plasticity is an important neuronal characteristic as it is related to the ability of neurons to adapt to change and endorsing new functional or structural states.

Closed-loop stimulation models with desynchronization protocols include single-site linear, multi-site linear, and non-linear delayed feedback stimulation techniques, operated in a demand-controlled approach or closed-loop (Popovych, Hauptmann, & Tass, 2005; Popovych, Lysyansky, Rosenblum, Pikovsky, & Tass, 2017; Popovych, Lysyansky, & Tass, 2017; Popovych & Tass, 2010; M. G. Rosenblum & Pikovsky, 2004; M. Rosenblum & Pikovsky, 2004). It was showed effective and robust desynchronization of STN GPi model neurons by combining the closed-loop DBS approach with desynchronization stimulation protocols (Popovych, Lysyansky, Rosenblum, et al., 2017; Popovych, Lysyansky, & Tass, 2017). To do so, they used linear and non-linear delayed feedback stimulation methods to a pulsatile closed-loop DBS.

Some of the closed-loop controllers only act in response to the parameters of the stimulation (commonly amplitude), or act in a ON/OFF control. This is an on-demand system that activates the DBS system to provide stimulation only when needed. To achieve this, a biomarker previously defined needs to be monitored continually. A threshold is set that, when the value of the biomarker crosses it, the system either turns on or off the stimulation. As discussed above, several studies focus on beta power as a biomarker for PD to design on-demand aDBS. Important to note that, while the biomarker might be shared through the same disease, the threshold is more likely to be different between patients. Other algorithms follow strategies different from the ON/OFF stimulation delivery. For example, an algorithm proposed by Rosa et al modifies the stimulation parameters continuously and linearly each second related to patients behaviour of LFP beta power (Manuela Rosa et al., 2015).

2.4.2 aDBS Control Strategies

The development of aDBS starts by the identification of biomarkers that will robust and safely indicate the optimal stimulation delivery timing. aDBS requires availability of IPGs with capacity of sensing, recording of signals, in order to conduct monitorization of the biomarkers to inform the stimulation parameter in an online manner (Arlotti et al., 2018). Important to note is that biomarkers are not required to be causal to the mechanisms of disease, rather show correlation with symptoms presence and severity and the evolute according to the course of disease (De Hemptinne et al., 2013; Kühn et al., 2006; W. J. Neumann et al., 2017; D. D. Wang et al., 2016). However, causal correlation is valuable once it allows the perception of changes prior to emergence of symptoms, providing a predictive potential over a responsive symptom management. As described in the Biomarkers section, a broad range of neural signals recordings have potential to be used as biomarkers for aDBS system, such as LFPs, Aps, ECoGs, and EEGs recordings.

The adjustment of stimulation intensity though titration of current and voltage is the mainstay for DBS programming, but it bears limitation due to the increasing stimulation. Hence, alternatives as aDBS emerge as an opportunity to optimize the control of stimulation, and the interplay of the different parameters for specific indicators increasingly stating their relevance (Dayal et al., 2017). The behaviour of long term aDBS, and the maintenance of the describes effects, is not assumed without uncertainty, based on the available evidence (Ricchi et al., 2012). Explanations for this unsolidity through time could be due to the wearing off and loss of efficacy of stimulation and disease progression counterbalancing the beneficial effects over time. The effect of exact location of electrodes or contacts are often not included in analysis of DBS results, which leads to the need to address this confounding in the real effect of DBS (Dayal et al., 2017). To achieve an efficient online control protocol of stimulation delivery, several factors must be taken in consideration. These facts are related to battery consumption, data computation and transfer, and modality and frequency of stimulation parameters. In another point of view, the full potential for clinical improvements with the application of aDBS system are related to electrode configurations such as the variation of amplitude, frequency, pulse-width of the stimulation train, characteristics that should be possible to modify in online aDBS system.

Amplitude-based aDBS

One of the pulse parameters that can be used to manage the control architecture in aDBS system is the amplitude (Herron et al., 2017, 2017; Simon Little et al., 2016, 2013; Malekmohammadi et al., 2016). The simplest paradigm

is to deliver the stimulation in ON/OFF phases of a predefined set of amplitude, frequency, and pulse width, but only when it is necessary (ON). The onset of stimulation should increase linearly, in a smooth ramp from zero towards the defined amplitude to avoid secondary paresthetic effects. The systems have been implemented in akinetic PD patient with the online analysis of beta-LFP amplitude and in tremor-dominant PD patients, through the use of ML algorithms on wearable sensors and electromyography *(*EMG) data (Basu, Graupe, Tuninetti, Shukla, Slavin, Metman, et al., 2013; Khobragade, Graupe, & Tuninetti, 2015; Simon Little et al., 2013). Instead of ON/OFF delivery of stimulation, other approaches apply an amplitude modulation through different designs: gradual and continuous (Vissani, Isaias, & Mazzoni, 2020). Gradual amplitude modulation consists of a closed-loop regulations aiming to maintain the amplitude between two defined values (upper and lower thresholds). A common sense on the values of the thresholds has not been yet achieved (Malekmohammadi et al., 2016; NC et al., 2018). Continuous amplitude stimulation is also based in a closed-loop regulation, but the control policy will be a continuous feedback signal proportional to the instantaneous values of the measured biomarker. The output amplitude will as immediately as possibly reflect the alterations of the input signal. This method was already implemented in akinetic PD patients using as a biomarkers STN LFP beta band amplitude (Arlotti et al., 2018; Manuela Rosa et al., 2015, 2017).

Phase-based aDBS

Stimulation at patients' tremor frequency induced transitory amplification and suppression on neural synchrony. By providing LF stimulation in the timing that most effectively suppressed the patients tremor, it is possible to reduce side effects and the amount of stimulation delivery without compromising clinical results. Other activities not phase-locked to the stimulation may remain without interference.

Adaptive modulation of stimulation frequency and pulse width

Frequency modulation in alliance with LFP features can be an alternative aDBS opposing to amplitude modulation. Modulation of frequency have the potential to integrate a feedback approach including the ability to decode behavioural states from sensing probes. Studies show that with the fitting features being extracted from the contacts STN LFP signals, it is possible to build a multi-variable multi-behavioural decoder (H M Golshan, Hebb, Hanrahan, Nedrud, & Mahoor M H, 2918). Certain behaviours, such as random movement class, although not related to a specific activity, are useful to train the classifier to recognize other tasks. There are also symptoms that do not response to conventional DBS, such as axial symptoms as freezing of gait, speech, swallowing. Studies suggest using low frequency DBS (50-80Hz) to treat these symptoms (Valldeoriola et al., 2019). However, over time the beneficial effects are not yet characterized as they appear to be inconsistent and can even led to worsening of appendicular symptoms (Zibetti et al., 2016). Regarding pulse width modulation, clinical benefits can be achieved with targeting selectively axons belonging to direct cortico-subthalamic pathway. With shorter pulse widths, therapeutic benefits can be increased, whereas battery consumption decreased (M. M. Reich et al., 2015).

Stimulation artifact suppression

Interference from the stimulation current pulses adds difficulty in the recording and processing of biomarkers due to differences in amplitudes for the stimulation pulses and the signal recorded (Rossi et al., 2007). In answer to this problem, Rossi at al proposed "Filter DBS", an artifact-free recording system (Rossi et al., 2007). The separation of stimulation artifacts and higher harmonics was possible by the implementation of a band pass filter. Another approach is post-filtering of the signal to remove the stimulations artifacts (Al-ani, Cazettes, Palfi, & Lefaucheur, 2011). In this process, the stimulation signal is subtracted from the recorded signal allowing the production of an artifact-free biomarker, however degrading the quality of the signal. Other works approach aDBS devices benefiting from LFP/ECoG sensors and integrated neural amplifiers (Stanslaski et al., 2012).

2.4.3 Model-Based Algorithms for Optimizing DBS Therapy

Computational models are a valuable tool to study neuroscience questions, allowing the research to deconstruct intricate systems in algorithms and sequence of steps fairly accurate. For DBS, this is no exception, with

computational models providing significative information regarding regions and pathways affected by this therapy. Most of models so far are based in retrospective analysis, in which collected known clinical outcomes are associated with model predictions, for regions and for pathways. In the past years, targeting algorithms have been proposed. Some are focused in optimizing electrode configurations, as monopolar and multipolar option of stimulation, and stimulation amplitude. Some examples are neural network classification based in volume of tissue activated morphologies, convex optimization for targeting axonal pathways, oriented-selective stimulation, and particle swarm optimization with objective functions. Other algorithms are focused in optimizing the pattern of stimulation, and shape and size of electrodes.

2.4.4 Stimulation Challenges

The pattern of stimulation is important either for open-loop and closed-loop DBS. Two types of pulses exist: monophasic, which are charge imbalanced, and biphasic, which can be charged imbalanced or charge balanced (Piallat et al., 2009). The characteristic of charge imbalanced translates in the formation of adverse chemical reactions at the electrode surface through time, hence, resulting in dangerous conditions for the brain tissue that can result in lesions. Passive and active charge balancing schemes can allow for charge-balanced pulses. Most available open and closed-loop DBS systems use a charged-balanced scheme. The temporal regularity of the stimulation pattern is also important regarding effectiveness of stimulation. There are two main perspectives: first, closed-loop DBS appears to deliver an temporal irregular scheme due to the adaptive variations is performing, and second, it has been reported that irregular patterns can reduce the therapeutic effects (Baker, Zhang, & Vitek, 2011; Dorval, Kuncel, Birdno, Turner, & Grill, 2010; M. G. Rosenblum & Pikovsky, 2004).

2.4.5 Wearables

To optimize DBS therapy, a discussion emerges about using complementary data. In particular, and as a considerable proportion of motor symptoms characterize PD, this data is to be data that evaluates the movement. Answering this, the devices that collect such data are classified as wearables. These devices are mainly used in the limbs and adapted for different purposes (Virbel-Fleischman et al., 2023). The main goal is to identify and characterize movement periods within pathological versus non-pathological movements and different types of movement. The hardware and software of such devices vary, with recent devices incorporating ML methods for identification, classification and prediction of movement periods. For example, considering the operative process, Geraedts presents a study that includes wearable sensor data to predict motor outcomes after surgery (V. Geraedts et al., 2023). Here, it is not a prediction of movement itself, but how movement information contributes to predicting a designated outcome. A more widespread use is, as mentioned, to directly characterise pathological movement and use that information to contribute to DBS and overall PD management. This includes quantification of gait impairment, bradykinesia, tremor and rigidity (Arrais et al., 2024; Akash Mishra et al., 2024; Múrias Lopes et al., 2020). However, the discussion also emerges in combining more than one symptom in the elopement of wearable-based models. Recent work takes a step further to use the information from wearables to quantify the effect of varying the parameters of DBS on constellation motor symptoms, using advanced ML techniques such as neural networks and decision trees (LeMoyne, Mastroianni, Whiting, & Tomycz, 2024). Furthermore, beyond characterizing and predicting symptoms, wearables also offer the potential for remote monitoring of PD symptoms. This opens up the possibility of an indirect approach to DBS, where the parameters of the wearables feed the stimulation system, adjusting the parameters according to the patient's needs. This not only provides a more personalized approach to DBS but also allows for continuous monitoring and adjustment of the therapy, potentially improving patient outcomes.

2.4.6 Perspectives and Challenges for aDBS

The advances in DBS systems aim to provide therapies with increasing efficiency and reduce to inexistent the side-effects. The development of devices with sensing capacity and electrodes with increase spatial selectivity are paving the way. Nevertheless, that are still concerns to face. As already explored, one challenge is the determination of a reliable biomarker of the clinical condition of the implanted patients. So far, the prime candidate appears to be LFP, and for PD there is a special focus in the beta band power. However, biomarkers as

LFPs, and others (APs, ECoGs and EEGs) are affected by the stimulation pulses. Therefore, additional techniques for artifact removing are also important to improve the sensing for the biomarker (Jankovic, 2008; Rossi et al., 2007; Stanslaski et al., 2012). This has added difficulty as there is a variety of diseases treated with DBS, and within the same condition, the phenotype of the patients differs, which would translate in the different biomarkers. Hence, to have maximum efficacy, aDBS requires to act in a personalized medicine approach. One hypothesis to overcome these challenges is a period in which each patient undergoes an initial calibration for aDBS therapy, where the parameters to feed in the control strategy are tuned (Vissani et al., 2020). Nevertheless, this process would still require the parameters to have a robust behaviour. Another factor to have in account is the importance of having a control system able to react to everyday actions and behaviours of the patients, automatically differentiating it from pathological manifestations (Vissani et al., 2020). Having this insight would allow, once more, to tune the optimal stimulation paradigm to better respond to the needs of the patients. In example, patients with tremor have less need to stimulation during sleep. Identifying and classify such behaviour allows to, in such periods, reduce the stimulation.

To achieve optimal aDBS outcome, besides electrodes location and biomarkers understanding, the type of control algorithm used is of upmost importance. Most used algorithms so far, for PD, predefines a threshold on beta or gamma band power, voltage linearly following the behaviour on the beta power or a dual threshold on beta power (Simon Little et al., 2013; NC et al., 2018; Manuela Rosa et al., 2015; Velisar et al., 2019). These parameters are lacking the inclusion of temporal dynamics of beta band power, which are likely to be better understood with the sensing capacities of newer implants.

Concern rises regarding closed-loop DBS about the size and weight of devices. These devices will have additional features, such as recording and programming circuits, that will add to the size and weight of the implant. These concerns increase its significance when considering long-term implants. The design of the implant cannot be a limitation to the patient to carry daily life activities, such as sleeping, walking, etc. Another challenge in the design of closed-loop DBS devices is the heat signature and energy consumption by the continuous activity it is performing, both for measuring and analysing data. As an intracortical implant, this challenge is crucial. Having a low power consumer balanced with capacity of re-chargeability and memory space will be a query to pursue for future devices (Dams et al., 2013; N. Verma et al., 2010). These constraints as led to the assessment of electronic alternatives, such as memristors and other neuromorphic devices, to produce low-power, small-sized, and computationally efficient implantable devices (Dias, Castro, Aroso, Ventura, & Aguiar, 2022).

Innovations in the digital field for clinical response prediction are key to synergically build effective aDBS systems. Having such technologies allows to input information in the system that would translate in a more adequate stimulation delivery, as well as reduce the programming time for DBS. There are tools available to help the visualization of the VTA in patient specific models. This particular type of data paved the road to the creation of probabilistic maps of clinical response, which can be applied to train ML algorithms (discussed further in the next chapter) designated for prediction clinical individual response to stimulation which specific parameters in a specific location (S. G. Reich & Savitt, 2019).

2.5 Percept PC

The neurostimulator from which the data will be collected is the Percept PC, with later recordings being done with the rechargeable version, the Percept RC. This device is developed and commercialized by Medtronic and includes a feature that records bioelectric data (passive brain sensing) of LFPs through one or two leads implanted in the brain, targeted at the area for PD symptoms management. However, there are other pathologies to which Percept PC can be the neurostimulator of choice, such as Epilepsy. The BrainSense technology, the collection of bioelectric data, has five sensing features: Survey, Setup, Timeline, Events and Streaming (Table 2.1 and 2.2).



Figure 2.14 Percept PC neurostimulator with BrainSense Technology.
In this figure we have the representation of three key elements of the system: on the right, the smartphone given to the patient to manage stimulation programs (pre-defined by the clinician), and to log the 'Events' entries. In the middle, the neurostimulator to be implanted and on the left the clinicians table that allows to visualize the LFPs and to manage the parameters of stimulation (as in display in this picture). Adapted from the White Paper of the Percept PC Neurostimulator with Brain Sensing Technology from Medtronic.

Feature	Purpose	Used
BrainSense Survey	Broad Spatial overview of LFPs signals measurable from both hemispheres of the patient with stimulation off.	In-clinic, with approximately 40 seconds measurement duration for each grouping of electrode level pairs chosen to survey and approximately 70 seconds measurement duration for each grouping of segment electrode pairs chosen to survey.
BrainSense Setup	To use BrainSense technology in all manners besides BrainSense Survey, the user must first setup LFP sensing using BrainSense Setup and select a frequency band of interest (approximately 5Hz wide) to track chronically for this patient.	In clinic, with approximately 90 seconds measurement for setup.
Brain Sense Timeline	Once BrainSense Setup has been completed, the Timeline is used to analyse the out-of-office data when the patient returns to the clinic. This is used to assess the data for changes in LFP activity that may occur over the course of a day(s).	Outside-clinic, records LFP data chronically for follow-up data analysis in-clinic via the Timeline view.

BrainSense Events	Once BrainSense Setup has been completed, BrainSense Events, a.k.a LFP snapshots can be recorded at a moment in time, showing the magnitude of the LFP signal over a range of frequencies. The LFP snapshot is recorded when the patient records an event as configured by the clinician. Used to assess the occurrence of clinician-defined events, and associate LFP activity with those events.	Outside-clinic, with approximately 30 seconds of LFP measurement directly after patient marking and event.
BrainSense Streaming	Once BrainSense Setup has been completed, the user can view the LFP power in a selected frequency band in real time, by streaming the data to the clinician tablet. This is used to observe changes in the LFP during active stimulation programming or while instructing and observing the patient performing activities. Moreover, Streaming can be used to collect time domain data from the selected channel(s) for offline analysis and signal processing.	In-clinic, with no limit on streaming measurement duration, with or without stimulation.

Table 2.1 BrainSense features detailed descriptions.
Adapted from the White Paper of the Percept PC Neurostimulator with Brain Sensing Technology from Medtronic.

Sensing Feature Data	Time Domain [LFP Magnitude (µVp) vs. Time]	Frequency Domain [Magnitude (µVp) vs. Hz]	Power Domain [LFP Power in Band vs. Time]	Channels per Hemisphere (1x4 lead)	Channels per Hemisphere (SenSight lead)	Stim: On or Off	Data Collection: In or Out of Clinic
BrainSense Survey							
On-screen	-	X	-	6	15	Off	In
Session Report	-	X	-				
BrainSense Data Viewer	-	X	-				
JSON Export	X	X	-				
BrainSense Survey Indefinite Streaming							
On-screen	-	-	-	3	3	Off	In
Session Report	-	-	-				
BrainSense Data Viewer	-	-	-				
JSON Export	X	-	-				
BrainSense Setup (Signal Check)							
On-Screen	-	X	-	3	3	Both	In
Session Report	-	-	-				
BrainSense Data Viewer	-	X	-				
JSON Export	X	X	-				
BrainSense Timeline Data							
On Screen (timeline)	-	-	X	1	1	Either	Out
Session Report	-	-	Summarized				
BrainSense Data Viewer	-	-	X				
JSON Export	-	-	X				
Events (LFP Snapshot)							
On Screen	-	X	-	1	1	Either	Out
Session Report	-	-	-				
BrainSense Data Viewer	-	X	-				
JSON Export	-	X	-				
BrainSense Streaming							
On-Screen	-	-	X	1	1	Either	In
Session Report	-	-	-				
BrainSense Data Viewer	-	-	X				
JSON Export	X	-	X				

Table 2.2 BrainSense Data Locations.
Adapted from the White Paper of the Percept PC Neurostimulator with Brain Sensing Technology from Medtronic.

2.5.1 Signal processing parameters

For most of our work, we will be working with the raw measured LFP signal downloaded from Percept. The recorded data is sampled at 250Hz and passed through the following filters: two low passes at 100Hz and two high passes (one at 1Hz and a second at a user-defined between 1 and 10Hz). Moreover, the clinician application will provide information about the presence of artefacts – a signal that is measured that does not correspond to an LFP signal. The nature of the artefact can be due to the ECG – system detecting the patient's heartbeat, identifiable in the LFP signal spectrogram as a large amplitude signal at ~1-2Hz. It can also be a motion artefact – the system that detects the patient's movements, that is visible in the raw signal as a very large amplitude signal, not periodic, during the times when the patient moved.

2.6 Conclusion

Deep Brain Stimulation implementation has a long history of success and pitfalls. Its application is widespread in the neurosciences, from neurodegenerative diseases to psychiatric conditions, as depression, to other neurologic conditions such as epilepsy. Combined, the prospective number of patients that could benefit from a well-tailored, widespread DBS therapy is tremendous. One of the conditions which can benefit from DBS is Parkinson's Disease. Parkinson's Disease is a highly debilitating condition, with no cure, and for which treatment is symptomatic and

does not change the progression of disease. Today, diagnosis such as PD have a tremendous impact on the life of patients, and their future.

With the advances of the technologies for DBS, new hopes emerge. The tailored therapy is no longer utopic, neither the long-term therapy, allowing patients to enjoy an extended quality of life. There are still challenges in understanding the exact mechanism of DBS, how to “read” the disease in the electrophysiologic communication, and how to make it widely available for the individual patient. This literature survey aimed to provide a comprehensive grasp on the main characteristics of DBS and its future.

Chapter 3: Machine Learning contributions towards closing the loop for DBS

Deep brain stimulation is a therapy applied in an increasing range of neurological disorders, including Parkinson's disease. Second to Alzheimer's disease, PD is one of the most common neurodegenerative diseases worldwide, with tremendous impact in society (He et al., 2021). Currently available pharmacological treatments for PD are symptom oriented and there are no disease modifying therapies. These treatments achieve symptomatic control in a considerable proportion of patients but there is still a significant number of patients for whom pharmacologic therapies are ineffective or insufficient, leaving DBS therapy as the remaining option.

For the implementation of DBS in PD patients, an electrode is surgically placed in the brain, providing electrical stimulation patterns to a specific target area (the STN or the GPi). In the initial setup after surgery, stimulation parameters are explored by the clinician in search for the configuration achieving the proper symptomatic control. Each parameter is tuned within a window of values where the intervention is potentially beneficial to the patient (for a brief overview of the tuneable parameters and their known effects see Table 3.1). Outside these subjective and patient dependent window's boundaries, the therapeutic effect is not as effective and adverse effects might occur. Information on the precise lead localisation, obtained via imaging techniques, is also often considered in this process. The stimulation parameters are adjusted by a trial-and-error approach, relying on qualitative evaluation of clinical responses (Mahboubeh Parastarfeizabadi & Kouzani, 2017; C. F. Wang et al., 2017). The parameters are then kept fixed for the time between consultations. Given the dynamic nature of PD symptoms, this canonical open-loop stimulation strategy is suboptimal, as the applied therapy does not automatically adapt to the patient's state nor condition evolution. Furthermore, its adverse effects (generally caused by the continuous stimulation with constant amplitude) are difficult to manage.

Parameter	Typical ranges and observations
Pulse amplitude	Most titrated parameter in the initial stages of STN DBS programming. Variation of 0.1-0.5V or 0.1-0.5mA are known to produce visible results.
Pulse frequency	Frequencies of 130Hz are often used as a starting point. Improvements in cardinal motor signs were shown with increasing frequency.
Pulse width	Conventional pulse widths used in STN DBS range from 60 to 450μs duration.
Directional steering	Maximizes the therapeutic response while minimizing adverse effects in other regions not relevant for the therapy management.
Interleaving simulation mode	Allows delivering stimulation with different energies to neighbouring anatomical structures.

Table 3.1 Tuneable Deep Brain Stimulation (DBS) parameters.
In this case, we are considering as target the subthalamic nucleus (STN) nucleus, but the same parameters can be applied to DBS with different target regions.

Progress towards optimized DBS (on both open and closed loop approaches) is challenged by the fact that there is still no clear understanding of its mechanisms of action on neuronal populations and circuits (Krauss et al., 2021;

W.-J. Neumann, Horn, & Kühn, 2023). While the exogenous electrical current applied by the electrode exerts direct effects on locally-residing cell bodies, which can be of inhibitory or excitatory nature, it also perturbs en passant axons, resulting in the modulation of complex neural networks (A Eusebio, Cagnan, & Brown, 2012; Hess, Vaillancourt, & Okun, 2013; E. B. Montgomery & Gale, 2008; Vitek et al., 2012). Indeed, multiple mechanisms of action are likely to occur simultaneously. On one hand, this adds complexity to our understanding of the modulation process but, on the other hand, it also opens alternative potential targets to explore as to improve the neuromodulation results. Possible therapeutic mechanisms involve the direct suppression of local pathological neuronal activity, masking of pathological activity, and interactions with re-entrant nonlinear oscillations (Johnson et al., 2008; Magarios-Ascone, Pazo, Macadar, & Buo, 2002; E. Montgomery, 2004; E. B. Montgomery & Gale, 2008; Obeso et al., 2008; Tai et al., 2003; Warren, Snyder, & Miocinovic, 2004).

Adaptive DBS (aDBS) emerges as a promising paradigm to achieve "smart" DBS systems (Figure 3.1). The principle behind this proposed approach is the optimization of stimulation parameters in direct response to the patient's electrophysiological state, achievable in a closed-loop configuration. Closed-loop control mechanisms are associated with algorithms capable of automatically regulating the system's parameters as to maintain a desired/predefined target state, without human interaction. For aDBS, this means that DBS stimulation parameters continuously adjust to the patient's varying needs. Considering the different possible strategies to close the loop in aDBS, the feedback systems directly based in neuronal signals are of particular interest. These feedback control systems become possible with real-time neuronal activity recordings obtained directly from the target region using dual function electrodes (providing concurrent stimulation and recording). Recent neurostimulators are modified to operate with these novel sensing electrodes capable of recording local field potentials (LFPs, extracellular potentials generated by the synchronized electrical activity of closely located neurons in the vicinity of an electrode (Y Kajikawa, 2012)) together with the delivery of stimulation. This direct access to the neuronal activity domain enables the potential identification of electrophysiological biomarkers linked to pathological states of the disease (here "biomarkers" are not molecular in nature but represent instead specific signal patterns). Monitoring these biomarkers (which may be patient specific) and exploring their variability enables the adaptation of different stimulation parameters according to the needs of each patient and in response to the disease progression over time. This leads to a potential increase in the quality of life of the patient whilst lowering the cumulative effect of therapy. Unfortunately, there are still challenges that must be overcome for the successful development and implementation of electrophysiology-based closed-loop aDBS. A significant part of these challenges is related to the complex signal analysis and to the stimulation modulation.

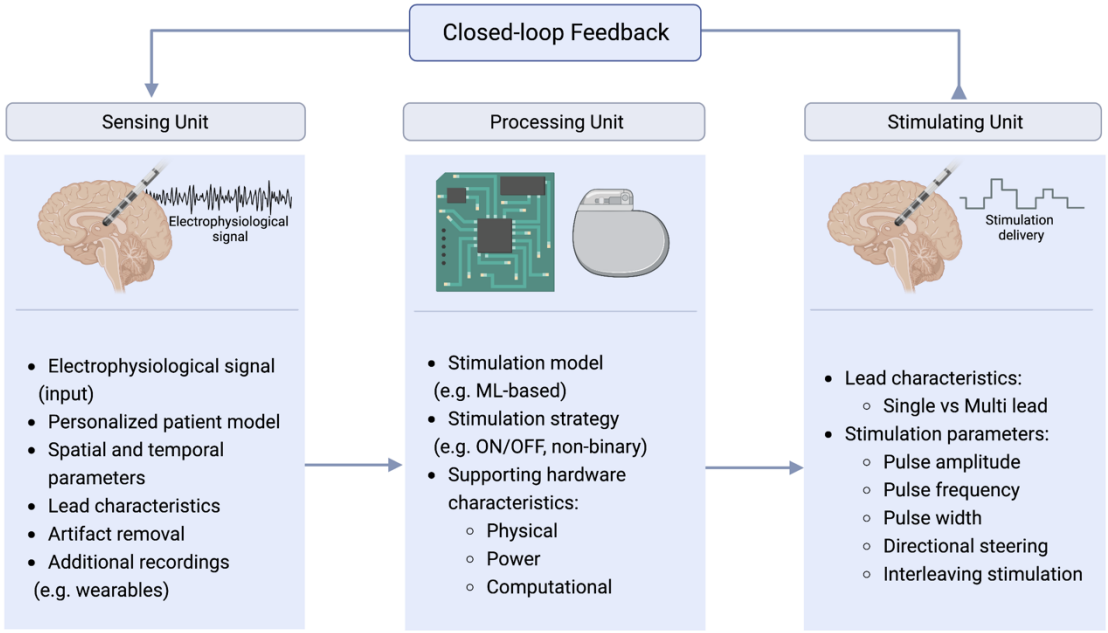


Figure 3.1 A development framework for closed-loop control supporting adaptive Deep Brain Stimulation (aDBS).
The closed-loop control integrates three key components or units. The sensing unit refers to the sensing lead and signal acquisition. The processing unit refers to the stimulation strategy and model, and the supporting hardware characteristics. The stimulation model can rely on advanced algorithms based on machine learning (ML) methods. The stimulating unit refers to the stimulation parameters and the stimulating lead. For each unit, relevant associated parameters are presented.

Machine Learning methods are rapidly growing in popularity as powerful computational tools to deal with the complex data from DBS and pave the way to "smart" systems. These methods can give computers the ability to learn and improve from accumulated data ("experience"), without the need to define algorithms or specific dependencies between variables. ML offers methods to explore complex structure and patterns in the data, that are not easily identifiable with traditional methods. Given its versatility, ML can be useful at different stages of the DBS therapy process such as patient selection (Castano-Candamil et al., 2019; Oliveira, MacHado, & Andrade, 2018), electrode placement during surgery (Kim et al., 2019; Ozturk et al., 2020; Valsky et al., 2020), prediction of outcome (Farrokhi et al., 2020; Park et al., 2021; Maxime Peralta, Haegelen, Jannin, & Baxter, 2021), and management of stimulation (Opri et al., 2020). The latter is linked to the identification of discriminatory electrophysiology biomarkers and associated modulation of stimulation parameters, crucial to the development of personalized and adaptive control systems for an effective symptom relief.

The application of ML towards the development of components of an aDBS system based on electrophysiology biomarkers is the focus of this review. We discuss the current strategies and challenges towards these "smart" closed-loop aDBS technologies and explore how ML can contribute to their development. In specific, we focus our attention to the use of ML for the identification and validation of biomarkers. PubMed was used for the literature analysis, focusing on publications with date ranging from 2015 to 2023. Further information regarding the included papers, such as the methods used and its contextualization in the DBS therapy, can be found in annex as tables 3.2-3.6. In the next section, we start by providing the core concepts and terminology of ML. We then move on to exploring the search for effective biomarkers, providing fertile ground to discuss different aDBS strategies and technologies. We close the review with the discussion of the road ahead for achieving aDBS with the application of ML.

3.1 Core concepts in Machine Learning

Machine learning methods are a large family of data-driven algorithms capable of automatically improving their ability to make decisions/predictions through accumulated data exposure ("experience"). The application of a ML methods often implies training a model with the available data, which is then tested and validated according to given performance criteria. Different metrics (defined according to the problem) are used to evaluate the performance of the model and select the most adequate for the task. There are three main types of methods used in ML. In supervised learning, the models are trained on annotated datasets (with labelled input-output correspondence). In unsupervised learning, methods look for hidden patterns or internal structures in the input, without pre-defined information about the output. Finally, in reinforcement learning a computational agent is trained based on policies ("rules") that reward desired actions and punish unwanted ones. Whereas reinforcement learning methods yield a relevant potential for training neuromodulation systems, they have not yet been employed in the context of DBS for PD (but see (Lu, Wei, Che, Wang, & Loparo, 2020)). As such, in this review we focus on unsupervised and supervised learning methods successfully used in DBS.

Unsupervised learning algorithms can help in dimensionality reduction (search for reduced set of variables describing the data), feature extraction (identifying what variables can be helpful for discrimination and what are redundant), and clustering (grouping sets of similar data according to similarities or goals). Such algorithms can be used per se to support decisions or, in combination with data representation techniques, to gain new insights (e.g. the number of classes contained in the data, how the data is distributed, and what patterns exist within the data) leading to a better selection of models in a subsequent processing stage (Figure 3.2).

Supervised learning algorithms require labelled data (for every input there must be a matching annotated output) and two data subsets should be defined: a training subset, for adjusting the model's parameters; and a testing subset, for model evaluation with data that was unseen during training (a validation subset may also be considered for adjusting the model's hyper-parameters). This division in training data and testing data is fundamental and addresses the ability of the model to generalize, i.e. preserve adequate performance with new non-annotated data. As real-world data is noisy (from both instrumental and physiological sources), there is the risk of attaining high performance levels in the training data but low levels in the new data (a situation called overfitting). Concerning the outputs (predictions) in supervised learning, so called regression methods produce continuous values whereas classification methods are associated with categorical/discrete outputs (Figure 3.2).

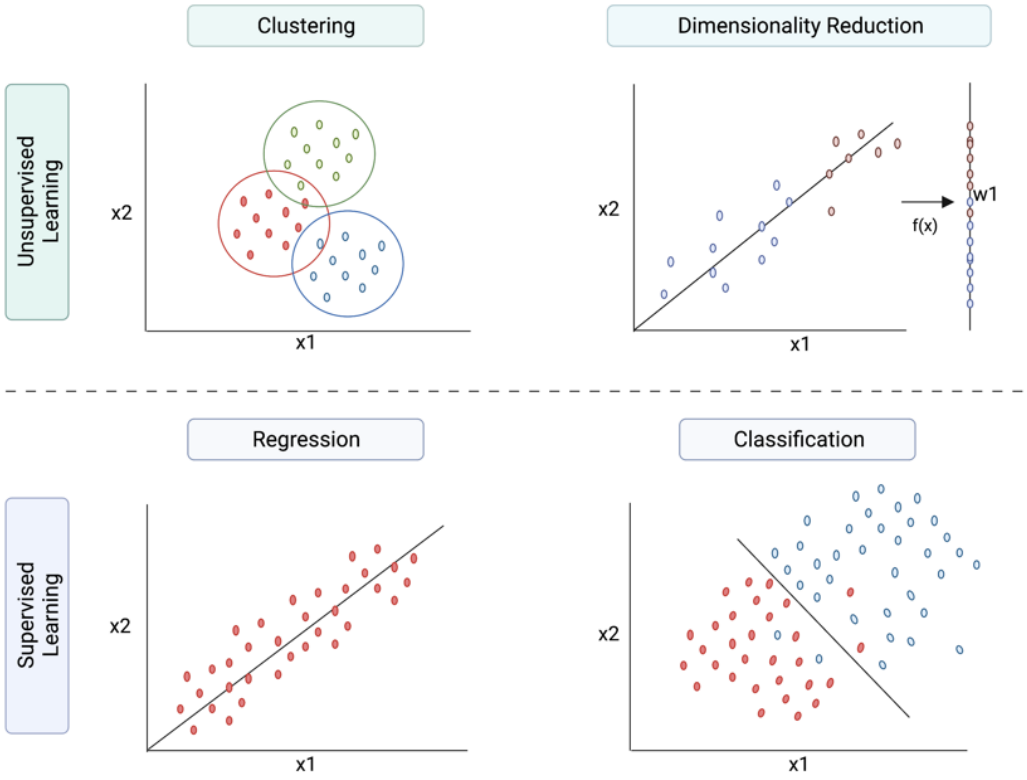


Figure 3.2 Visual representation of the mentioned areas of machine learning.
The two main areas listed here are supervised and unsupervised learning (a third type is reinforcement learning but is outside the scope of this paper). On the top row, two methods of unsupervised learning (methods that look for hidden patterns or internal structures in the input, without pre-defined information about the output) are represented: clustering (a method that groups sets of data according to similarities or goals), here presenting three possible clusters, and dimensionality reduction (methods that search for a reduced set of variables describing the data), here considering two initial dimensions collapsed in one output variable. The bottom row refers to supervised learning (models that are trained on labelled, or annotated, datasets), presenting regression (which produces continuous outputs), and classification (which are associated with categorical/discrete outputs), both considering here two input variables.

A generic workflow to support the development of classification (and detection) methods in the context of data-driven stimulation is presented in Figure 3.3.

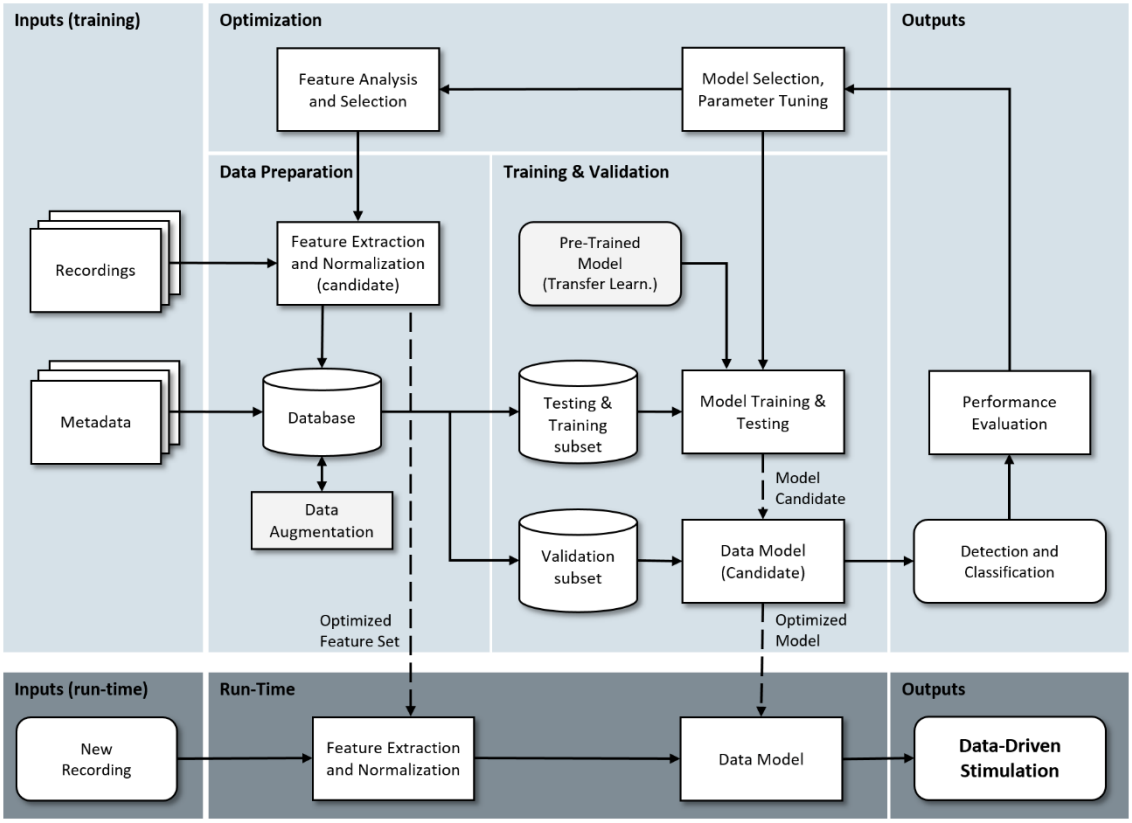


Figure 3.3 Generic workflow associated with the application of supervised learning methods to achieve data-driven stimulation.
In light grey (top) is the development pipeline and in dark grey (below) is the deployment pipeline.

A particular ML method called deep learning has gained considerable relevance, due to its ability to provide good estimates even when facing unstructured high dimensionality data. This method is inspired by the dynamics of biological neurons and uses nodes (neuron analogues) which are combined in large architectures with several sequential layers to provide the output. The number of elements per layer, the number of layers, and the behaviour of each layer (e.g., fully connected, convolutional, recurrent) are some of the parameters that can be adjusted to fit the network to the data/problem. Despite the widespread use of these techniques, the high amount of data that is required for training and the “black box” model that is obtained in the end are strong caveats of deep neural networks. Nevertheless, visualization tools, data augmentation and transfer learning are techniques that can help solving these issues.

Both supervised and unsupervised ML methods, in a variety of different algorithms, have already been effectively used with DBS data (table 3.7). In all these methods, the quality of the data deserves special attention: incorrect or poor-quality data (e.g., outliers, wrong labels, noise), if not properly cared for, will lead to under-optimized models and to unsatisfactory results. In the ML context, the discussion is often focused on the decision of the model and on what performance metrics to be considered during the development phase. In a clinical setting, the relative impact between false positive predictions and false negative predictions is an important issue on the choice of performance metrics.

Since these approaches are "data-driven", it is essential to ensure the quality of the supporting data, used in the training phase, and to monitor the operation, in the deployment phase (Figure 3.4). Training datasets should be sufficiently diverse to guarantee that a wide range of operational situations are anticipated. The amount of data should be sufficient to ensure a reasonable fit of the model parameters, and should be balanced across classes, so that trends or decision bias do not arise. Regarding the operational phase, it is important to guarantee that safety limits are established, and that regulatory and contingency mechanisms are foreseen.

Type/Purpose		Method name
Unsupervised	Clustering	Gaussian mixture model; K-means
	Dimensionality Reduction / Feature Selection	Linear discriminant analysis (LDA); Principal component analysis (PCA): kernel PCA; t-distributed stochastic neighbour embedding (t-SNE)
	Classification	AdaBoost; Decision Tree (DT): Oblique DT; Gradient Boosting Machine: XGBM, Extreme gradient boosted trees; Hidden Markov Model (HMM); K-nearest neighbour (KNN); Logistic Regression (LR): L1 logistic / LASSO; L2 logistic / Ridge; Naïve Bayes (NB): Conditional model and Gaussian; Neural Networks (NN): Multilayer perceptron, Shallow NN, Convolutional NN (CNN), Deep NN, LAMSTAR NN, Recurrent Networks; Random Forest (RF): unsupervised RF; Support-vector machine (SVM): SVM based on linear and Radial Basis Function (RBF) kernels
Supervised	Regression / Time Series	Granger causality; Linear Regression; Kalman filters; Recurrent networks; Volterra kernels

Table 3.7 Machine Learning methods in DBS.

The methods are organized according to the following categories: Clustering (Ct) and Dimensionality Reduction / Feature Selection (DR/FS) for unsupervised learning; Classification (Cf) and Regression / Time Series (R/TS) for supervised learning. It should be noticed that some methods can be adapted to operate with different purposes. For example, recurrent networks can be used either in a context of classification or regression.

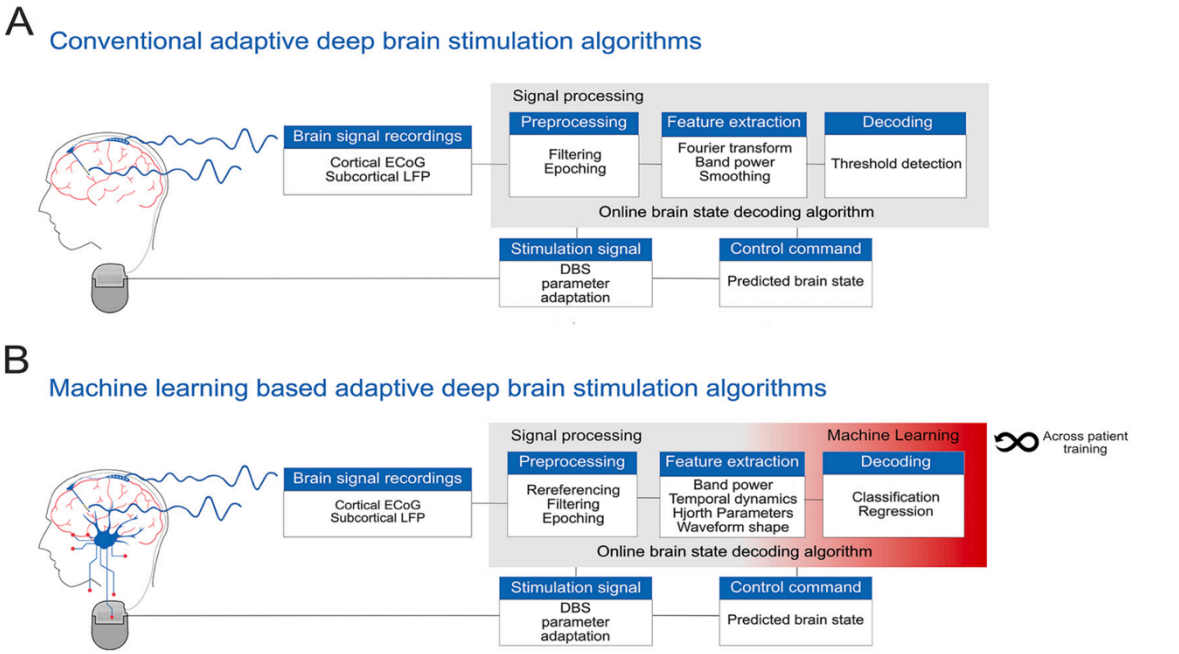


Figure 3.4 Schematic representation of a conventional adaptive deep brain stimulation algorithm compared to a machine learning-based adaptive deep brain stimulation system.
(A) Input signals are cortical ECoG and subcortical LFP brain signal recordings. New incoming data packets are pre-processed (e.g. normalization, referencing, artifact detection and subsequent rejection applied) and features are extracted (e.g. Fourier transformation, band power averaging and smoothing). The control algorithm is a simple threshold detection of a predefined feature: the brain state (e.g. pathological or non-pathological state) is predicted, and translated into a control command, such that the DBS stimulation parameters are adapted. (B) Machine learning-based adaptive deep brain stimulation can use multimodal features to decode a variety of brain states (e.g. classification for decoding of tremor or regression for indication of severity of bradykinesia in PD). In addition to brain signals, the decoding model can also be re-adjusted based on the information delivered by the stimulation signal. Moreover, information from previous patients could be used to feed the decoding algorithms and potentially avoid time-consuming individual training sessions. Adapted from (T Merk et al., 2022).

3.2 The quest for effective Biomarkers

The concept of biomarkers plays a central role in the development of feedback control systems for aDBS. A biomarker refers to a characteristic in a physiological signal, such as a specific pattern or component, which correlates to a certain pathological state. Different motor or electrophysiological signals, such as EEG signals and LFPs, have shown potential for biomarker identification, and consequently closing the loop in aDBS (Abosch et al., 2012; Giannicola et al., 2012; Lettieri et al., 2012; Mahboubeh Parastarfeizabadi & Kouzani, 2017; Alberto Priori et al., 2013; B Rosin et al., 2011; N.C. Sinclair et al., 2018; Swann et al., 2011; C Wiest et al., 2023). LFPs present interesting advantages over EEG due to the source location and data fidelity, a possibility given the now available electrodes with combined stimulation and sensing properties, and appropriate long-term stability at the electrode-tissue interface (Simon Little & Brown, 2012). Different neurological conditions have already been studied in the context of closed-loop DBS systems using LFPs as biomarkers (for an overview, see (Deeb et al., 2016)).

Several aspects come to play in the identification of effective biomarkers and their selection is determined by the disease context and symptom manifestation. Key features to consider during the selection of either single- or multi-dimensional biomarkers are the high signal-to-noise ratio of the recordings and the stability over the presence of external artifacts. These artifacts can be caused by non-pathological functions, such as intentional movement. In fact, one issue with the use of beta-band subcortical oscillations as a biomarker in PD is that they are also involved in the modulation of voluntary movement (Deeb et al., 2016). Naturally, important features also include the sensitivity and the specificity of the biomarkers, to ensure the correlation in time with the severity of the clinical symptoms (Piña-Fuentes et al., 2018; Zixiao Yin et al., 2021). Independently of the source/type of the

physiological signal, the search for strong correlations between signal features and pathological states is a challenging analytical task, in which ML methods can have an important contribution.

3.2.1 Motor Biomarkers

With motor symptoms being a hallmark of PD, several studies have focused on assessing strong correlations between motor features and clinical states (Busch et al., 2023). Given that motility is an intrinsic feature of the human experience, it is crucial to understand what constitutes a pathological motor pattern and how it differs from normal motor activity, be it volitional or not. A common source for the study of motor data are the so called wearables: sensors that can be worn and provide detailed motor/physiological information about the patient (D, Member, Mastroianni, D, & D, 2020). This objective information serves as a valuable addition to the clinical data when assessing symptoms and their response to stimulation, enhancing confidence in the chosen stimulation parameters. By providing objective measurements, it also alleviates the workload on the clinicians. One of the major advantages of wearables is that they can be easily integrated in ordinary devices, such as smartwatches or rings. For instance, Powers et al developed a motor fluctuations monitor for Parkinson's disease algorithm, integrating long term data collection from smartwatches, capable of evaluating tremor severity and the presence of dyskinesia (Powers et al., 2021). Additional information on movement (e.g. extracted from smartphones) can also emerge from crowd-generated data as a proxy for wearables, as shown by Zhang et al. In their work, convolutional neuronal networks (CNN) and random forest (RF) applied to smartphone accelerometer and gyroscope recordings were used to differentiate PD from control subjects (Zhang, Deng, Li, Albin, & Guan, 2020). Alternatively, Kleinholdermann et al explored the use of non-invasive movement recordings to predict the best DBS settings (Kleinholdermann, Bacara, Timmermann, & Pedrosa, 2023). In their work, RF models were trained to learn the relation between electrode settings, clinical ratings, and movement features (extracted from wearables). Their work shows not only that movement features were able to predict the clinical mobility (correlations up to r=0.68 between the predicted and true values), but also that these features predicted the optimal DBS parameters (r=0.8).

Discrimination between PD and healthy subjects is also possible using information from wearables placed on a single arm with the implementation of the K-nearest neighbours (KNN) algorithm, providing a quantitative assessment of bradykinesia, rigidity and tremor (Huo et al., 2020). Moreover RF algorithms using 3D gait data and motor readout signals have been used to show that a standing up test can be used to distinguish PD OFF DBS patients from healthy subjects; also, foot and lower leg kinematics are better in classifying motor anomalies than other gait analysis segments (Kuhner et al., 2017, 2020). This contributes not only to the diagnosis of PD, but also to the monitoring of the symptom progression and response to treatment. Different approaches for monitoring symptoms, combining sensors for motion, muscle activity and force, were presented by Angeles et al and Tahafchi et al (Angeles, Tai, Pavese, Wilson, & Vaidyanathan, 2017; Tahafchi et al., 2017). These studies used, respectively, K-nearest neighbours and support vector machines methods to predict motor symptom severity and Freezing of Gait (FoG) events. Liu et al took advantage of yet another RF model to classify FoG states based on the Codamotion 3-D movement capture system and synchronized intracranial EEG data, further broadening the understanding of movement dynamics and contributing to bridging the gap between peripheral and intracranial signals (Liu et al., 2022).

It is important to recall that DBS is not a substitute to pharmacologic treatment, but rather a complementary therapy. Consequently, monitoring response to medication should also be considered when designing aDBS systems. In this respect, Khodakarami et al applied linear regression models to predict the motor symptom state based on the response to the first morning dose of levodopa (Khodakarami et al., 2020).

The ability to detect and analyse motor patterns (directly or indirectly) may turn out to be an indispensable component of aDBS systems, capable of adjusting function over different time horizons and symptom intensities. Yet, one should not forget that the symptoms measured by wearables are but a peripheral manifestation of a

neurological condition. Furthermore, the location of the wearable will affect the extracted features, and there is not a consensus on the best approach for these measurements. The information of wearables alone is, most likely, not sufficient to fulfil the needs of aDBS implementation: some of the neurological traits may not translate into noticeable motor manifestations and have non-motor implications on the patients.

3.2.2 Electrophysiology Biomarkers

Electrophysiology signals coming from the stimulated neuronal populations can be explored either in the time domain (amplitude as a function of time) or in the frequency domain (decomposition in its frequency components; Figure 3.5). The latter, often studied using spectral analysis, is generally preferred not only because it facilitates both noise and artifact identification and reduction, but also because it allows the decomposition of the signal in pre-defined frequency bands (Table 3.8) (Piña-Fuentes et al., 2018).

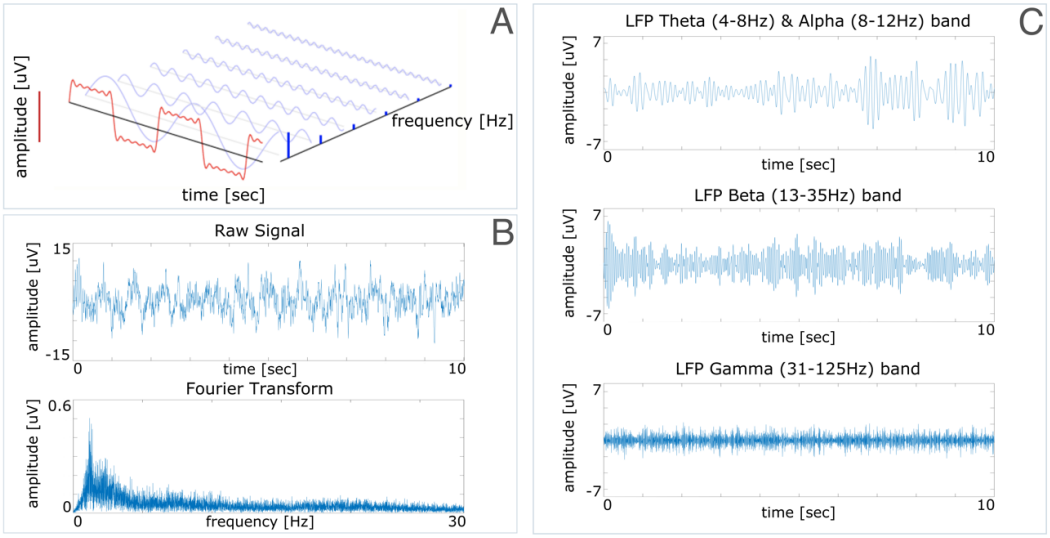


Figure 3.5 Signal decomposition in the frequency domain.
(A) Decomposition of the time domain signal in its frequency components. (B) Raw signal and Fourier transform of Local Field Potentials (LFP). In the Fourier transform plot it is possible to identify the frequency composition of the signal. (C) Representation of three frequency bands of LFP signals: theta & alpha band (4-12Hz), beta band (13-35Hz) and gamma band (31-200Hz). Panel A adapted from: https://tex.stackexchange.com/questions/127375/replicate-the-fourier-transform-time-frequency-domains-correspondence-illustrati.

Variations in the power of these bands have been associated (correlated) with different PD symptoms, showing their potential to work as biomarkers for pathologic events (Zixiao Yin et al., 2021). However, accounting for the complexity of neuronal dynamics, reducing the biomarker to a frequency band's power may leave out useful information (Belova, Semenova, Gamaleya, Tomskiy, & Sedov, 2023). Here, ML can help to uncover patterns that traditional signal processing tools do not.

Band (range)	Description
Delta bands (0.3Hz)	Literature related to delta band is scarce.
Theta (4-7Hz) & Alpha (8-12Hz) bands	STN low frequency (LF) oscillations have been studied in extensive non-motor domains. LF/Beta band power ratio has advantages over the single use of beta band power.

Beta bands (13-35Hz)	Beta band is the most studied band as biomarker for "smart" DBS design. Suppression of beta band is associated with improvement of motor symptoms.
Gamma band (31-200Hz)	The gamma band activity is seen as prokinetic, with a compensatory mechanism toward the akinetic role of beta activity.
High frequency oscillations (above 200Hz)	High frequency oscillations are regarded as prokinetic, and STN activity increases at the onset of the movement and Levodopa administration.

Table 3.8 Division of Local Field Potentials (LFP) in the frequency bands described in literature. (STN – Subthalamic nucleus)

Electrophysiology datasets (and LPFs datasets in particular) are often small, structured, and noisy. Consequently, specific techniques have been developed to circumvent these challenges. For example, these datasets are amenable to gradient-boosted tree learning, a popular ML method for prediction. Hirschmann et al effectively used this method to demonstrate that neuronal oscillations in LFPs provide accurate predictions of motor symptom improvements following DBS (Jan Hirschmann, Steina, Vesper, Florin, & Schnitzler, 2022). In addition to signal band power, the signal coherence between subthalamic and parietal regions was shown to have relevant predictive power of DBS' therapeutic efficacy. With their approach, it was possible to study not only the predictive capability of the LFPs, but also which features would contribute more to a potential clinical application (among the best being the sub-thalamic high beta power). Additionally, logistic regression was able to identify periods when patients have rest tremor using LFPs from the subthalamic nucleus (S. A. Shah, Tinkhauser, Chen, Little, & Brown, 2018). Two studies with LFPs, using neuronal networks and hidden Markov model classifiers were also successful in decoding movement and laterality (the side in motion), as well as tremor prediction (J. Hirschmann, Schoffelen, Schnitzler, & van Gerven, 2017; Islam, Mamun, & Deng, 2017).

Another approach to classification of human behaviour with LFPs signals and considering five tasks (speech, finger movement, mouth movement, arm movement, and random segments), was possible using support vector machines (SVM) (H. Golshan et al., 2018). In Golshan et al, more complex methods such as CNNs were used to classify the human behaviour using the time-frequency representation of STN-LFPs within the beta frequency range (Hosein M. Golshan, Hebb, & Mahoor, 2020). Interestingly, even simpler classification methods, such as the naïve Bayes classifier, can extract valuable information from LFPs. For example, LFPs dynamics on specific frequency bands (alpha and beta) allow accurate prediction of intentional limb movements, ahead of their execution (Khawaldeh et al., 2020). Further combinations of ML techniques with Kalman filters applied to LFPs allowed the identification of biomarkers such as the power in the high beta frequency band, high gamma frequency band, and low beta frequency band for tremor detection (Yao, Brown, & Shoaran, 2020).

It is also worth mentioning that potential biomarkers can be explored in a variety of neuronal activity metrics. This includes synchronization levels and long-term correlations between neuronal signals from different sources (e.g., different hemispheres or intracerebral/peripheral). For example, SVMs algorithms and Gaussian Naïve Bayes models have been applied to LFPs recordings to decode movement behaviour using frequency dependent neural synchronization and inter-hemispheric connectivity features (Mamun et al., 2015). Recent literature emerged on the value of evoked resonant neural activity (ERNA) signals as potential biomarkers, however, its use is still under validation (N.C. Sinclair et al., 2018; C Wiest et al., 2023).

Finally, it should be highlighted that the search for personalized biomarkers is gaining some traction. This is not surprising, given that the disease manifests and evolves differently in each patient. The "one size fits all" approach is being replaced by tailoring the treatment according to individual needs. Mohammed et al implemented patient

specific features extraction in combination with adaptive SVM classifiers (Mohammed, Zamani, Bayford, & Demosthenous, 2015). The outcome of this method provided individualized features and a classifier for each patient. This highlights the importance to account for the heterogeneity of symptoms across patients and tones-down the expectation on finding reliable population-wide neuronal markers. On a similar note, supervised methods were used for the identification of individual neural markers of hand motor performance in PD patients undergoing DBS. In this study, patient specific markers provided improved decoding accuracy compared to group-level (Castaño-Candamil et al., 2020).

3.2.3 Other Biomarkers

Besides affecting motor control, PD is also characterized by a myriad of non-motor symptoms, such as speech alteration and insomnia, highly debilitating and often hard to diagnose and manage. These symptoms could also, in principle, support relevant biomarkers. However, the identification and monitoring of non-motor symptoms poses serious challenges, due to their subjective nature. An even higher level of complexity is attained if one intends to correlate these symptoms with intracranial electrophysiology signals from sensing electrodes. Regarding non-motor symptoms that can be monitored, two groups are highlighted here: speech and voice alterations, and sleep and cognition.

Speech and voice features can provide additional digital biomarkers as well as valuable information for the screening of PD patients. Given the complexity of these signals, ML methods have also been used for this type of analysis. In Braga et al, speech recordings in uncontrolled background conditions were used to identify PD patients and to estimate early signs of PD using ML regression models (Braga, Madureira, Coelho, & Ajith, 2019). On another approach, by extracting paralinguistic features of voice recordings, Tracy et al explored the possibility to predict PD severity, using both classification and regression methods However, no clinical validation was provided in the study (Tracy, Özkanca, Atkins, & Hosseini Ghomi, 2020).

Within non-motor symptoms, both sleep quality and cognition worsen with progressing PD. They are particularly challenging to address, even when using ML algorithms since the collected data has a strong level of subjectivity inherent to the available assessment tools (A. Verma et al., 2023). However, the study of electroencephalographic recordings shows potential to extract biomarkers for post-operative cognitive decline deterioration (V. J. Geraedts et al., 2021; Victor J. Geraedts et al., 2021). Using LFPs recordings during wakefulness and nocturnal polysomnography sleep monitoring as inputs to SVMs and decision tree algorithms, Chen et al showed that it is possible to classify sleep stages in PD (Chen et al., 2019).

Clinical information (admission details and UPDRS-III evaluations) has proven helpful in the prediction of PD progression and its response to therapy. For example, Khojandi et al have used preoperative PD rating scores and clinical characteristics to feed a RF algorithm to predict the appropriate DBS stimulation frequency (either 60 Hz or 130-185 Hz) for a given patient (Khojandi, Shylo, Mannini, Kopell, & Ramdhani, 2017). In the context of PD but not directly related to DBS, Shamir et al present a proof-of-concept of a clinical decision support system that applies ML techniques such as SVMs and RF to clinical data in order to assist in treatment management (Shamir, Dolber, Noecker, Walter, & McIntyre, 2015).

All things considered, biomarkers with high specificity and sensitivity will have a crucial role in the multiple stages of PD management: either as immediate sources of clinical information or as the means for more effective DBS protocols. Wearables, and other sources of peripheral signals related to PD symptoms, are an important strategy to provide information on the patient's clinical state. However, the use of additional external hardware can be uncomfortable for the patient and unnecessary/redundant if neuronal (electrophysiology) biomarkers can provide equivalent information. ML techniques have been successfully applied in the study of the PD symptomatology, especially in intracranial electrophysiological signals. The ideal closed-loop control systems would probably rely solely on intracranial signals, and, in this sense, the use of LFPs related signals, captured by modern DBS systems,

may be the best solution. LFP analysis should consider not only isolated values of the parameters (single or combined) but also their long-term temporal evolution and intrinsic patterns, both in physiological and pathological states. These provide a better understanding of the patient's state, leading to the design of better control strategies. A clinically validated classification system based solely on intracranial signals has not yet been achieved, but the first steps have been taken. Although early DBS literature aimed towards the finding of generalized biomarkers for PD, recent works are increasingly adopting a personalized framework, giving primacy to individual-specific biomarkers.

3.3 Bringing adaptive DBS to the clinic

Adaptive DBS systems must simultaneously monitor (record) physiological signals and provide stimulation to the neuronal targets, while adjusting the stimulation parameters according to disease specific biomarkers reflecting the current state of the patient (Binder et al., 2023; Radcliffe et al., 2023). It is worth mentioning that the neuronal tissue response to electrical stimulation may fluctuate over time as a result of external (environmental) or internal (disease progression) factors (Hunka et al., 2005). Efficacy of aDBS is further challenged by neuronal plasticity, which is thought to contribute to the loss of therapeutic effect over time in an open-loop framework.

Three main components are required for an aDBS system with closed-loop control using LFPs biomarkers (Figure 3.6): the neurostimulator (controllable pulse generator) that provides the stimulation, a lead that delivers the stimulation and simultaneously records the LFPs, and a processing unit that reads and interprets the biomarkers present in the LFPs and decides the appropriate stimulation response. Recent technological advances in the neurostimulation devices expanded the range of tunable parameters beyond the typical pulse parameters (amplitude, frequency, and pulse-width). For example, with the availability of new leads with directional stimulation capabilities, it is also possible to shape the electrical field used in DBS (Bour et al., 2015; Krauss et al., 2021; Rammo et al., 2021; Sabourin et al., 2020; Schnitzler et al., 2021). All these parameters can be contemplated, a priori, usable by ML algorithms for closed-loop aDBS.

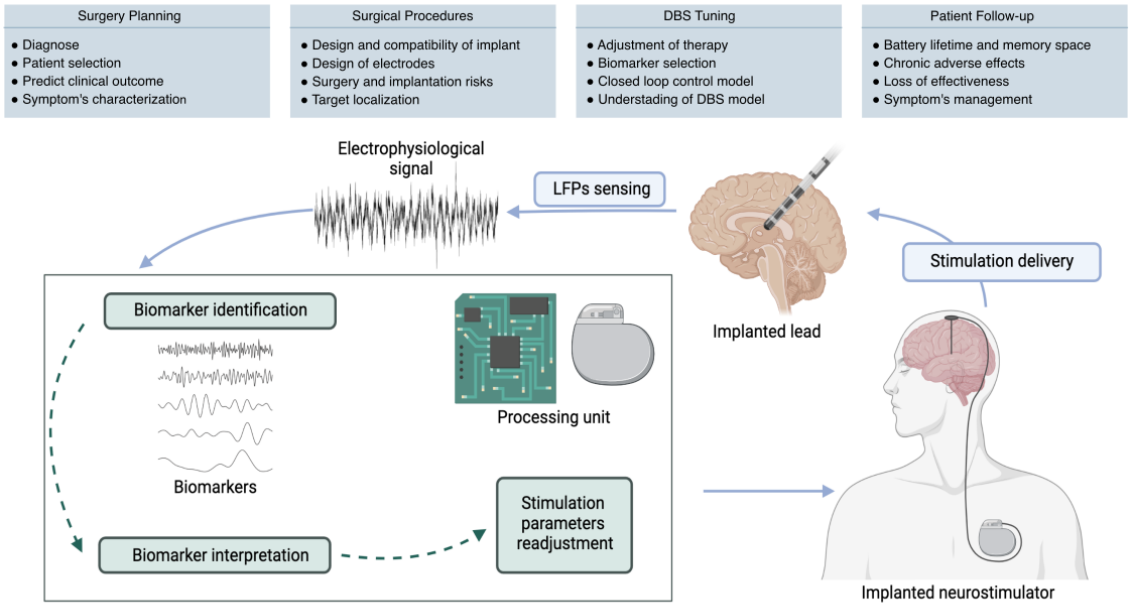


Figure 3.6 Application of machine learning towards adaptive deep brain stimulation using closed-loop control.
In the top panel, list of challenges at different stages of DBS therapy implementation where ML methods can play an important role. The diagram represents a closed-loop system for aDBS, based on LFPs sensing and electrophysiological biomarkers identification and interpretation.

3.3.1 Adaptive DBS control strategies

Adaptive DBS requires IPGs with signal sensing and recording capabilities, in addition to the stimulation delivery, in order to conduct biomarkers monitoring and generate the stimulation protocols in an real-time manner (Arlotti

et al., 2018; Sarica et al., 2021). Biomarkers are not required to be causally linked to the disease mechanisms, but rather to show strong correlation with symptom onset and severity, and to be sensitive or adaptive to the disease progression (De Hemptinne et al., 2013; Kühn et al., 2006; W. Neumann et al., 2017; Wang, DD et al., 2016). Nevertheless, a causal relation would be ideal since it allows the identification of changes prior to the onset of symptoms, enabling a predictive approach rather than a responsive one. A common strategy in neuromodulation that employs preventive (and predicted) measures is the delayed feedback control method, entailing closed-loop techniques designed to desynchronize abnormal neuronal activity. Aiming at the suppression of pathological collective synchrony, effective and robust desynchronization of STN GPi model neurons has been shown by stimulation protocols based on delayed feedback control (Popovych, Lysyansky, Rosenblum, et al., 2017; Popovych, Lysyansky, & Tass, 2017). The latency of the response is also an important factor to account for. Current neurotechnologies allow for virtually instantaneous and continuous adaptation of the stimulation parameter to the monitored biomarkers (Simon Little et al., 2013). However, it is yet not clear how refined should the temporal resolution for aDBS be, considering the optimization of therapeutic effect and the parallel computational requirements. In Rosa et al, stimulation intensity was linearly adjusted every second, in proportion to LFP beta power. Despite only being deployed in one patient, this approach improved symptom control (Manuela Rosa et al., 2015). In Little et al, ON/OFF stimulation was adjusted continuously in a closed-loop system with improvements on motor symptoms in an eight-patient cohort (Simon Little et al., 2013).

3.3.2 Amplitude modulation

Amplitude is one of the pulse parameters that can be used to modulate the stimulation in aDBS systems (Basu, Graupe, Tuninetti, Shukla, Slavin, L, et al., 2013; Khobragade et al., 2015; Simon Little et al., 2013) (Figure 3.7). The simplest paradigm consists in the delivery of stimulation with a predefined non-null amplitude only when necessary (ON/OFF controller). Other paradigms modulate the amplitude in different ways: gradually (or, step-wise) and continuously (Vissani et al., 2020). During gradual amplitude modulation, the amplitude is maintained between two defined discrete values and varies in a step-like fashion (Malekmohammadi et al., 2016; Swann et al., 2011). In continuous modulation, the amplitude of the stimulation varies (proportionally, in general) according to a reference signal/biomarker. The output amplitude reflects, with minimal delay, the alterations of the input signal (Arlotti et al., 2018; Manuela Rosa et al., 2015, 2017).

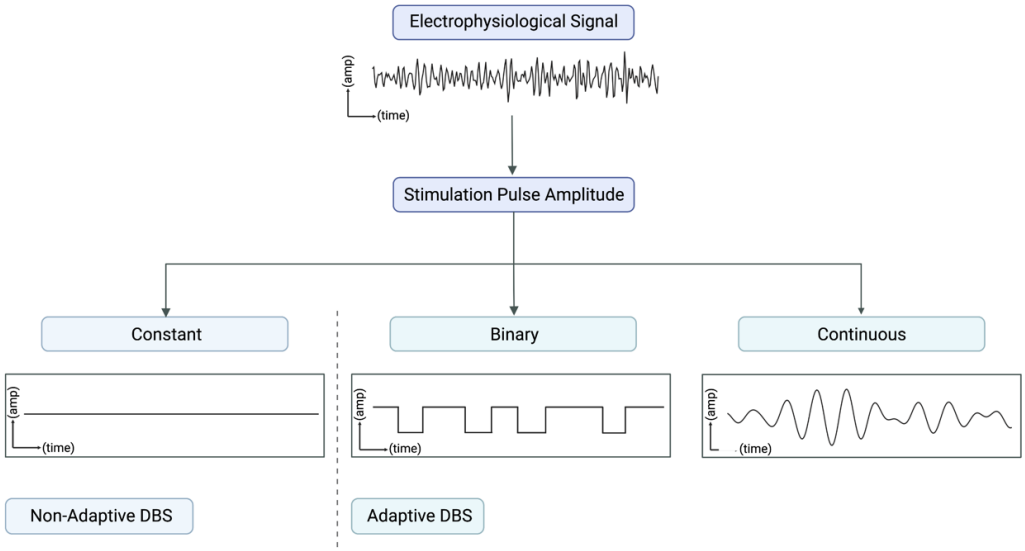


Figure 3.7 Types of control mechanisms in Deep Brain Stimulation using electrophysiological signals as input.
Three standard control mechanisms for DBS: non-adaptive, adaptive with binary outputs, and adaptive with continuous outputs. Concerning an electrophysiological signal, the control system first reads the signal, and then decides on the stimulation pulse amplitude. In the case of non-adaptive DBS, this amplitude is constant, and it will be independent of the electrophysiological signal behaviour. When considering adaptive DBS, the amplitude will vary with the readings of the electrophysiological signal. In the case of binary control, a threshold for stimulation is defined, and every time the electrophysiological signal crosses above the threshold, the stimulation is turned ON and turned OFF when the signal shifts below the threshold. In the case of continuous control, the amplitude is being adapted to the continuous reading of the signal and varying according to this behaviour.

3.3.3 Frequency and pulse-width modulation

Changes in the frequency and pulse duration of the stimulation have an impact on the neuronal response and can be used in a closed-loop context. Although the involved biological mechanisms remain unclear, high-frequency stimulation (>100Hz) generally produces better therapeutic results than low-frequency stimulation (Baizabal-Carvallo & Alonso-Juarez, 2016; Tao Xie et al., 2017). The initial parameters for frequency and pulse-width are often in the ranges of 130-180 Hz and 60-90 µs, respectively. The fact that different symptoms respond better to specific frequency intervals is taken into account when setting parameterizations for personalized treatments (Koeglsperger, Palleis, Hell, Mehrkens, & Bötzel, 2019). Recent studies have explored the use of shorter pulse widths, which appear to offer comparable therapeutic effects with better energy management and reduced adverse effects (Steigerwald et al., 2018). Changes in the pulse-width have also been shown to provide clinical benefits by exciting brain sites more selectively (Akbar et al., 2016; Steigerwald et al., 2018).

3.3.4 Phase modulation

A core concept supporting phase-based aDBS is the hypothesis that the precise timing of stimulation is important for its effectiveness. This is particularly relevant in the context of trying to suppress pathological collective synchronization across neuronal populations. In this approach, the stimulation signal is derived from the phase response curve of the monitored neuronal population. Under this hypothesis, adapting the stimulation at the timing that most effectively suppresses the patients tremor, appears to reduce side effects and the amount of stimulation delivered, without compromising clinical results (Popovych et al., 2005; Popovych, Lysyansky, Rosenblum, et al., 2017; Popovych, Lysyansky, & Tass, 2017; Popovych & Tass, 2010).

Concluding, one should emphasize that pioneering studies using ML to support real-time data analysis in closed-loop control strategies for aBDS in PD have already started to emerge. In Gilron et al, subcortical and cortical oscillatory signatures of motor state were used as control signals to achieve a fully embedded adaptive DBS, working outside clinical settings. Both supervised and unsupervised ML methods were implemented to assess the possibility for using i) oscillatory phenomena in PD to decode motor fluctuations; and ii) multiple recording sites to improve the classification of an individual's motor state (Gilron, Little, Perrone, Wilt, de Hemptinne, Yaroshinsky, Racine, Wang, Ostrem, Larson, Doris D. Wang 1, Nick B. Galifianakis2, Ian O. Bledsoe2, Marta San Luciano2, et al., 2021)(Sarikhani et al., 2022). In other movement disorders, such as essential tremor, ML-based stimulation protocols were already successfully applied (Opri et al., 2020). Notwithstanding, two main concerns persist. The first has to do with the computational cost of some of these algorithms. Given the power limitations of the current processing, aDBS is advised to operate on low complexity algorithms. Secondly, the development of such system will require progressive iteration, starting from works such as the one present by Gilron et al, and learning from the protocols applied to other pathologies.

3.4 Open challenges in aDBS – Future Roadmap

As already explored, one of the major challenges of aDBS is the identification and validation of reliable biomarkers with high specificity and sensitivity (A Mishra, Shah, McBriar, Zamor, & Mammis, 2023; A. Shah et al., 2023). The recent developments in sensing technology widens the opportunity to understand how the electrophysiology at the site of stimulation evolves with the pathology. In this regard, LFPs from neurons in the stimulated regions are a prime candidate for the identification of biomarkers. For better analysis of the electrophysiological signal, novel

techniques for artifact removal are important to improve the robustness of LFP-based biomarkers (Rossi et al., 2007; Stanslaski et al., 2012). In the established literature, attention has been devoted to the LFPs' beta band power but as addressed earlier, other frequency bands such as alpha and gamma also convey valuable information regarding the patient's clinical state. Representations outside the frequency domain should be better explored as features in the time domain may prove useful for defining biomarkers.

Furthermore, the variability on disease and symptoms presentation across patients motivated an attention on personalized therapies, to which individualized biomarkers and algorithms incorporating learning capabilities are necessary. To have maximum efficacy, "smart" DBS is required to act as a personalized medicine approach. Since "smart" controllers require a training stage (either to learn from scratch or adapt), one solution is to have a period in which each patient undergoes an initial calibration for aDBS therapy, where the control strategy parameters are tuned (Vissani et al., 2020). Another factor to consider is the importance of having a control system that can react to patients' everyday actions and behaviours, automatically differentiating normal patterns from pathological activity. For both these requirements, machine learning emerges as a powerful tool to discriminate the (pathological) signatures specific for each patient, a feature hardly achievable by other methods. Still, clinical expertise remains as an unreplaceable component, especially in initial parameterization and tuning of DBS, as symptoms exhibit rich and dynamic symptomatology in time scales that range from minutes to days/months.

Machine learning is already promoting advances in DBS (M Peralta, Jannin, & Baxter, 2021). However, ML methods also have limitations and constraints that should be kept in mind. Some classes of methods require large datasets and high-performance hardware for training the models, and the resulting black-box models are still met with caution. Moreover, often the labelled datasets are established in highly specific contexts, which limits the potential generalization of the extracted features. ML's need for high quantity/high quality data can be met with sharing open and curated databases, allowing the replication and the exploration of published results in a collaborative scientific effort. To evaluate and compare the existing methods across studies, a consensus on the parameters by which performance is measured is needed. There is also a lack of long-term recorded data, hindering our knowledge on the long-term loss of therapeutic efficacy and rise of adverse effects. Moreover, the current computational requirements for closed-loop systems (model training, deployment, and algorithm implementation), may delay its implementation in IPGs for real-time therapy management.

The hardware requirements for closed-loop DBS running ML methods also raise attention as the novel computational features on these neurostimulators can add to the size and weight of the implant. Another challenge is the heat signature and energy consumption under their continuous activity, covering data acquisition, processing, and stimulation. Having a low power consumption balanced with rechargeable battery capacity and increased memory storage are requirements of future devices (Dams et al., 2013; Krauss et al., 2021; N. Verma et al., 2010). Currently, researchers are investigating electronic alternatives, such as memristors and other neuromorphic devices, aiming to achieve low-power, small-sized, and computationally efficient implantable devices (Dias, Castro, Aroso, Ventura, & Aguiar, 2022). Another comment goes to the importance of developing simulation environments and biophysical models of closed-loop stimulation to design and test aDBS systems before their implementation in vivo (Fleming, Dunn, & Lowery, 2020; Jovanov et al., 2018).

Lastly, as ML becomes increasingly integrated into clinical practice, with aDBS being just one example, it is important to assess the impact of these methodologies on the clinical workflow. On one hand, the use of ML in therapies enhances the concept of personalized medicine but a clear understanding of these technologies is not integrated into clinical training (as it primarily falls within the realm of computational fields). By fostering a multidisciplinary environment, combining clinical and computational expertise, collaborative efforts can be made towards the effective development of aDBS. Moreover, as these technologies scale up, continuous data management and algorithm tuning becomes crucial, highlighting the need for established cooperation between clinical, engineering, and computational sciences.

To progress towards adaptive DBS, we must conceptualize it from the start as a multifactorial system. The challenges in this field are many, from hardware constraints to software needs, requirements of high amounts of data and the development of personalized models with clinical validation. Nevertheless, the technology has shown promising results and the associated improvements in the patients' quality of life should encourage the device manufacturers to continue pushing for aDBS systems.

3.5 Conclusion

This work reviews the available research on ML implementation towards aDBS in PD. Its implementation is possible throughout all the stages of DBS therapy, and towards biomarker identification/selection- that may be patient-specific - and to post-operative DBS programming, using biomarker levels and adjusting many stimulation parameters. The latter may particularly benefit from ML application, due to its ability to perform complex mappings between stimulation parameters and biomarkers information. Nevertheless, there are still many open challenges that need to be addressed regarding the use of ML on aDBS. Large datasets and long-term studies, carefully planned and collected, are needed for accurate model development. The application of ML extends to the IPG hardware management whose battery duration, memory space and computational power may also benefit from its use. A key challenge is the pressing need for a better fundamental understanding of PD and of the DBS physiological mechanisms. Although ML methods provide powerful descriptive models to deal with complex data and systems, alone they are not sufficient to obtain the optimal aDBS system, presenting the need to a multidisciplinary effort, entailing computational and clinical sciences. Nevertheless, these technologies have shown potential to improve patients' quality of life. This fact alone should encourage the investment in future aDBS, not only for PD but for other neurologic disorders.

Chapter 4: Framework for analysis of Local Field Potentials in Parkinson's Disease: from concept to implementation

This part explores the work developed in partnership with CHUSJ, focused on two major components: a protocol for data acquisition with PD patients from CHUSJ and toolbox for data analysis of local field potentials from the same patients, to be shared in open source for researchers /clinicians working with the same data types (discussed in the next chapter). Along the way, the project evolved from a PhD project to two independent projects with self-funding: smartDBS and the study of Microlesion effects by CHUSJ.

4.1 Ethics Approval

A key component for the implementation of a research protocol with patients was the submission of the protocol and further required information to the Ethics Committee of CHUSJ for approval. There are some key features of the project worth mentioning. First, the data to be used was considered secondary data. The patient is implanted with a neurostimulator for DBS therapy in the context of PD, evaluated and decided by the medical team. After implantation, the patient has a series of follow-up appointments throughout the years, in which the stimulation is adjusted to the patient's needs. It is at these moments that the data collection is performed. At the time of the medical appointment, the patients are exposed to the research protocol and asked for consent to participate. Prior to consent, efforts are made to ensure that patients are fully informed and capable of this decision. If consent is given, the recordings performed will be included in the research protocol. The research protocol provides insights discussed with the medical team, in addition to the research outcomes. The primary goal of the data collected is clinical improvement, and it does not augment the patient's risk. The whole process is optimized to take as little time as possible to avoid any discomfort to the patient and reduce the patient's visits to the hospital. All patients included are 18 years old, and the selection process is operated based on the principles of justice and equity in access to health. In all processes, the respect for the liberty and autonomy of the patients is preserved. The ethics approval request is on the following pages. In the end of 2022, an updated request was submitted under the umbrella of smartDBS.

4.2 Conceptualization

As the Percept is a neurostimulator with LFP recording capability with diverse features and at the time of the start of this thesis several patients had already been successful implanted, we decided to design a research protocol that did not disrupt the clinical practice to provide insights for better management of therapy. The goals are to address each patient individually to contribute to its personalized stimulation titration, explore the correlation between LFPs and motor symptoms, provide insights to advise on the neurostimulator parameterization, contribute to the characterization of electrophysiological biomarkers of pathological symptoms and conduct a long-term evaluation study of electrophysiological data in PD. To do so we understood that we would need to develop a long-term protocol for the creation of a database structured to answer to these questions. In in-clinic settings, specialized clinicians already explored the stimulation parameters, such as current amplitude, frequency and pulse width. The evaluations at time were based on subjective metrics, such as the UPDRS, so we aimed to contribute to a new paradigm using LFP recordings and evaluation as complementary information.

In the first stage, we designed a data acquisition protocol integrating clinical and data information to a systematic and objective assessment of the parameter configuration with combined information from electrophysiological data and preliminary wearables data. After iterations and from the later established protocol with the INESCTEC, their wearables systems are now in use. These are four devices, iHandU, working in pairs (two per upper limb – on in the index finger and another in the palm of the hand), adapted for this protocol (Múrias Lopes et al., 2020). Prior to the implementation of 2023, the protocol was testing in clinic, under the supervision of clinicians, to ensure an effective data acquisition in routine clinical settings and troubleshooting the operationalization. After these months of iterations, a final version was implemented in January 2023.

4.3 Study Protocol: BrainSense streaming sessions with stimulation levels

4.3.1 Initial Notes

- The current protocol poses no risks to the participant, utilizing data collected from the BrainSense technology, which aims to mitigate the patient's symptoms and provide information for better titration of the stimulation.
- Simultaneously with the registration of the neurostimulator signal, the investigator should continuously record the patient's motor and non-motor symptoms throughout the sections with wearables (iHandU) signals.
- To maintain consistency between the neurostimulator's temporal record and the data from the accelerometer, whenever both are used, the recording should begin with the induction of an artifact. This artifact is obtained by touching the neurostimulator with the hand wearing the accelerometer.
- Two sets of accelerometer systems will be used to monitor the movement on both the ipsilateral and contralateral sides of stimulation.
- Stimulation thresholds are set before the session begins, according to the therapeutic range defined for the patient.
- If a patient does not tolerate a stimulation levels, the protocol is stopped, and no further levels are attempted.

4.3.2 Preparation

- Whenever possible, the patient should not take their usual PD medication on the day of the session (to be agreed upon with the attending physician and the patient).
- The accelerometer sensors should be adjusted before the session begins.
- Before starting the session, test signal acquisition of:
    - Neurostimulator.
    - Accelerometer (left and right).
    - Video signal (this signal is anonymized with an algorithm for blurring the faces that appear in the video, and it is only intended to use in cases were synchronization between LFPs and wearables is not possible through other methods).
- Signing of informed consent.

4.3.3 Section 1: Defining the Patient's Baseline

- No stimulation in both hemispheres.
- Patient at rest.
- Induction of artifact at the beginning of the recording.
- Duration: 1 minute.
- Movement: no active/passive movement, evaluating resting tremor on both sides as indicated in the UPDRS part III.

4.3.4 Section 2: Stimulation Study in the Left Hemisphere without Movement- Tremor

- One streaming session of ~5 minutes.
- No initial stimulation in both hemispheres, and right hemisphere stimulation is kept off throughout the section.
- Patient at rest.
- Increase stimulation in the left hemisphere after measuring tremor (UPDRS), with stimulation increments defined for each patient.
- Increase stimulation every 50 seconds after reaching the stimulation threshold.
- Movement: no active movement, evaluating resting tremor on the right side as indicated in the UPDRS part III.

4.3.5 Section 3: Stimulation Study in the Right Hemisphere without Movement- Tremor

- One streaming session of ~5 minutes.
- No initial stimulation in both hemispheres, and left hemisphere stimulation is kept off throughout the section.
- Patient at rest.
- Increase stimulation in the right hemisphere after measuring tremor (UPDRS), with stimulation increments defined for each patient.
- Increase stimulation every 50 seconds after reaching the stimulation threshold.
- Movement: no active movement, evaluating resting tremor on the left side as indicated in the UPDRS part III.

4.3.6 Section 4: Stimulation Study in the Left Hemisphere without Movement- Rigidity

- One streaming session of ~5 minutes.
- No initial stimulation in both hemispheres, and right hemisphere stimulation is kept off throughout the section.
- Increase stimulation in the left hemisphere after measuring rigidity (UPDRS), with stimulation increments defined for each patient.
- Increase stimulation every 50 seconds after reaching the stimulation threshold.
- Movement: no active movement, evaluating wrist rigidity on the right side as indicated in the UPDRS part III.

4.3.7 Section 5: Stimulation Study in the Right Hemisphere without Movement- Rigidity

- One streaming session of ~5 minutes.
- No initial stimulation in both hemispheres, and left hemisphere stimulation is kept off throughout the section.
- Increase stimulation in the right hemisphere after measuring rigidity (UPDRS), with stimulation increments defined for each patient.
- Increase stimulation every 50 seconds after reaching the stimulation threshold.
- Movement: no active movement, evaluating wrist rigidity on the left side as indicated in the UPDRS part III.

4.3.8 Section 6: Stimulation Study in the Left Hemisphere with Movement- Open/Close Hand

- One streaming session of ~5 minutes.
- No initial stimulation in both hemispheres, and right hemisphere stimulation is kept off throughout the section.
- Increase stimulation in the left hemisphere after active movement, with stimulation increments defined for each patient.
- Increase stimulation every 50 seconds after reaching the stimulation threshold.
- Movement: Evaluating bradykinesia with open/close hand test on the right side as indicated in the UPDRS part III.

4.3.9 Section 7: Stimulation Study in the Right Hemisphere with Movement- Open/Close Hand

- One streaming session of ~5 minutes.
- No initial stimulation in both hemispheres, and left hemisphere stimulation is kept off throughout the section.
- Increase stimulation in the right hemisphere after active movement, with stimulation increments defined for each patient.

- Increase stimulation every 50 seconds after reaching the stimulation threshold.
- Movement: Evaluating bradykinesia with open/close hand test on the left side as indicated in the UPDRS part III.

4.3.10 Section 8: Final Stimulation Recording

- Both hemispheres stimulation set at clinical stimulation parameters.
- Patient at rest.
- Duration: 1 minute.
- Movement: no active/passive movement, evaluating resting tremor on both sides as indicated in the UPDRS part III.

4.4 Insights from implementation

The process of conceptualization of this protocol started in 2021 when there was a need for a structured collection of data while minimizing the time patients would have to be at the hospital. In parallel, the process of this data collection and the tasks required are insightful for the evaluation of the patient and already provided information that was fed to clinical decisions taken during the execution of the protocol (as, for example, report of side effects of stimulation and response to untested levels). But, as expected, to achieve a fully operational protocol, it was needed a designing and redesigning process up to the point of implementation that required dialogue with the clinicians with expertise in PD, as well as colleagues from other engineering fields. First, it was clear that being PD a movement disorder, additional information from the limbs would be important to add. In particular, the characteristic finger movement, as if 'counting coins', of Parkinson's Disease leads us to agree on having, on both sides, sensors in the hand (that was decided to be located at the palm) and in the index fingers. The selection of the tasks was also agreed in iteration with the clinicians, under the insight that tasks have specific latency times in answering to stimulation. In answer to this, we included intervals of 50 seconds to mitigate and detect the effect of simulation in the LFPs and motor components. Moreover, it was important to annulate the interhemispheric coherence effect, and hence, the scalability of the steps of stimulation is done separately, with no stimulation on the contralateral side. This allows us to study the effect of the hemisphere stimulation change on the ipsi and contralateral hemisphere. Currently, 1.5 years of protocol have already provided some insights into the operationality of such protocols. One of our concerns was to minimize the length of the protocol as motivation and willingness to collaborate decreased in proportion to the length of the protocol. An optimal agreement in two baselines – no stimulation and clinical stimulation – was agreed upon with sections testing the tasks: tremor, rigidity and bradykinesia of upper limbs. This provides a substantial amount of information in the context of the PD motor symptoms while keeping the protocol sustainable and tolerable for the patients without disrupting the clinical appointment dynamics.

4.5 Protocol management

A key task I performed during these years was the management of the implementation and operationalization of the protocol. The protocol is established in a partnership with several actors: the Neuroengineering and Computational Neuroscience Lab, with the expertise in the protocol operationalization; the team at CHUSJ composed by neurosurgeons and neurologists with surgical and clinical expertise, the Centre for Biomedical Engineering Research at INESCTEC, with the expertise in the wearable sensors, and the Medtronics, the industry making Percept available that supports us in each session. Not only for the conceptualization and updates of the protocol all these actors are required, but to the operationalization each session, to ensure patient safety and coherence between all the devices. A normal moment of protocol would have a clinician from CHUSJ, a member for the NCN lab and a member from Medtronic. Sporadically, to update and troubleshoot the wearable system, a member of INESCTED team would also be present. This is coordinated with the patient and its routine appointment. The process requires sensibility to the needs of each actor, as well as adaptability, to minimize any constraint and ensuring that each session schedule takes place without disrupting the routines of the patient.

4.6 Building a Database

Up to the writing of this thesis, the protocol implemented has 14 subjects and 31 recordings, all patients were ON medication. Inclusion criteria were DBS therapy with Percept PC for less than 3 years. Exclusion criteria were inability to understand protocol and significant non-motor impairment (in particular, cognitive impairment). However, from April 2024 forward, with the new Percept rechargeable, 1-2 patients are being added each month. In balance, patients completing three years post-operation are removed from the study. As the study is expected to last more than two years, patients from 2024 will complete three years of follow-up, which will be the maximum follow-up limit, as the time points being further than that would not have enough representation for data analysis. Moreover, with the progress of disease and therapy, patients develop cognitive symptoms that make the sensing procedures less tolerable.

An important contribution of our work is, consequently, building a database of recordings comprising three main data types: LFPs, wearables signals and clinical information. In accordance with the ethical protocol, a pipeline to ensure anonymization was first built. The second main component of this process was the development of an immediate pre-processing pipeline, applied in a short period right after the recording, to ensure that 1) the recordings were error-free and if errors occur (such as a mislabelling of the type of recording) they were corrected or labelled and 2) organize the recordings in an workable and sustainable structure for future use of the database built. Storing such databases was conducted offline in secure hard drives. The process resulted in a second database, a workable database, where the signal available was anonymized, pre-processed and organized in a standardized structure.

4.7 Microlesion protocol

In the context of DBS, a widely described but understood effect is the Microlesion effect. It is an improvement in the motor symptoms after implantation surgery, before any electrical stimulation provided, and fades in a time span lasting from day to approximately a month (Aygun, Dere, Yildiz, Temel, & Kocabicak, 2019; Jech et al., 2012; Mestre, Lang, & Okun, 2018; Okun et al., 2012). During this period, patients require a lower dose of medication to manage their symptoms. However, when this effect wears off, symptoms return as well as the need for medication, now adjusted with stimulation therapy. One important feature is that this effects is an indicator of the STN being successfully targeted in the implantation surgery, and a predictor of long-term efficacy of therapy (Lange et al., 2023; Maltête et al., 2008; Tykocki, Nauman, Koziara, & Mandat, 2013). The pathophysiology of this phenomena has not yet been described, but it is believe to result from the electrode-induce local damage, inflammation and microglia activation (Vedam-Mai, Baradaran-Shoraka, Reynolds, & Okun, 2016).

Building on the already established protocol and this mentioned concept, a second protocol was designed with the aim to characterize the electrophysiological signature of the microlesion period (from 1-day to 1-month post-op). The goals are to identify the neuronal activity biomarkers of this stage of good symptomatic control as well as their evolution. As there is no electrical stimulation, it is also possible to evaluate the effect of medication intake on the STN activity and correlate the STN activity with the symptoms.

4.7.1 Adaptation of protocol and clinical circuit for Microlesion study

As for the clinical routine during this period, patients are discharged three days after implantation surgery, with electrical stimulation switched off, and these parameters will be kept during this first post-operative month. After a month, patients are re-admitted, and the electrical stimulation is initiated after parameterization of the optimal settings by a neurologist.

Data will be collected in three phases, and the protocol is adapted to two of the phases.

- First hospital admission, after the general anaesthesia recovery, the LFP timeline features will be initiated and maintained throughout the hospital stay.

- At one day post-operative, an adaptation of the protocol will be performed. This protocol consists in four steps and is performed entirely on off state stimulation: two baseline recordings with no tasks while evaluating resting tremor – one at the start and other at the ending of the session, two tasks' recordings, one per hemisphere, executing the tasks of finger tapping and open-close hand.
- During the first month between hospital admissions, the timeline feature is kept.
- At one-month post-operative, there is a second hospital admission, and the adapted protocol is once more performed.

With this adaptation, it is expected to test the following hypothesis: 1) is the pure physical presence of electrodes (without delivering stimulation) within the STN sufficient to transiently improve symptoms during a period of days to weeks? And is the intrinsic STN physiology transiently modified during this time? And 2) Is the microlesion effect reflected in acute disease-related phenomena, such as periods of the day of transient symptom worsening or the response to medication intake? At the time of this submission, the data collection phase is still in place.

4.8 Conclusion

In summary, we implemented a structured research protocol to contribute to the field of aDBS. Although not exclusively analytical, the challenges that occurred were nevertheless less impactful. In particular, having a solid research structure will have a major impact in future work. As we are doing a clinical protocol with patients, the ethics submission and approval were thorough and detailed, ensuring the ethical principles and the correct conduct of the protocol in all phases. A second important feature is its multidisciplinary team, which includes engineering, analytical, clinical, and commercial actors in the same discussion space. This ensures the best clinical interaction with the patient whilst fomenting state-of-the-art research that is possible to be escalated to commercial settings. This way, we return again to the patients and close the loop of the societal impact of research. Another interesting component of this work is that due to the successful implementation, new adapted protocols were implemented in the same field but for different research questions. What this shows is that this work is not only an end game in itself but as well a foundation for more research questions to be explored.

Chapter 5: DBScope as key tool for the visualization and analysis of sensing data from Deep Brain Stimulation

Deep Brain Stimulation is an established practice for the treatment of neurologic diseases and shows promising prospects for psychiatric conditions (Krauss et al., 2021; S Miocinovic, Somayajula, Chitnis, & Vitek, 2013). It involves the delivery of electrical stimulation to targeted brain regions, that vary in respect to the disease in question (He et al., 2021; Johnson et al., 2008; Okun, 2012). While the exact mechanisms of action underlying DBS remain unknown, evidence supports its capacity to modulate neural circuits locally and non-locally (Chiken & Nambu, 2016; Johnson et al., 2008). Current DBS therapies are delivered in a continuous and open-loop fashion: using a trial and error approach, the clinician selects the best performing stimulation parameters (i.e., a combination of higher symptom mitigation with lower incidence of adverse effects) from established therapeutic parameter ranges (Dayal et al., 2017; Moldovan et al., 2018; M. Parastarfeizabadi & Kouzani, 2017); after selection, the parameters are kept until the following clinical session, where they are re-adjusted.

Medtronic, a leading company in DBS, announced in 2020 the first US/EU approved neurostimulator with the ability to chronically sense local field potentials during stimulation (Percept PC) (Goyal et al., 2021). Since then, clinicians and researchers have been integrating the retrieval of the recorded sensing data (using a 'programming' tablet) into their practices, although with clinicians doing so in a more gradual manner. This inclusion has been key in increasing our understanding of disease-related brain activity patterns, their temporal evolution, and their modulation in response to therapies. In addition, it also gave the opportunity to unveil new electrophysiological biomarkers and ultimately bring the implementation of adaptive stimulation therapies closer to clinical practice (Feldmann et al., 2022; W.-J. Neumann, Gilron, Little, & Tinkhauser, 2023; Thenaisie et al., 2021). Recently, Netoff's Lab published their work in how Percept PC can be used for thalamic stimulation in epilepsy(Sanger et al., 2024). Nonetheless, the current visualization tools accessible on the clinician's tablet are limited: they fall short in fully exploiting the information embedded within the recordings and are ill-suited for longitudinal analyses (reviewing current and previous data). Consequently, clinicians and researchers have been compelled to seek and develop custom-made software to handle the files exported from the tablet.

Until recently, very few toolboxes were created for this purpose and addressed only simple extraction and visual methods for specific types of recordings (Sieger, Neumann, & Tinkhauser, 2022; Stam et al., 2023; Thenaisie et al., 2021). Among these resources, the Perceive toolbox stands out for its capability to import Percept PC recordings and make the data available in MATLAB (MathWorks, Natick, MA), allowing the user to interact with the data programmatically (Sieger et al., 2022). It is also capable of exporting the data in a format compatible with Fieldtrip, an open-source toolbox that is commonly used for MEG, EEG and iEEG analysis (Oostenveld, Fries, Maris, & Schoffelen, 2011). Still, all these toolboxes provide limited intrinsic functionality and require expertise in programming, a deterrent factor for many clinicians/researchers working on DBS. Moreover, the use of tools tailored to other electrophysiological signals fails to fully leverage the specificities of DBS data. These shortcomings have recently been challenged by a new open-source platform called BRAVO (Brain Recording Analysis and Visualization Online), which using a web-based interface offers visual tools for DBS data analysis (Cagle et al., 2023). While this platform addresses the 'parsing challenge' and allows the concurrent analysis of several files, its use poses technical challenges (requires configuration of a Linux server), and special attention regarding clinical data sharing/security (non-local data analysis).

In short, there is still a pressing need for easy-to-use yet versatile tools that facilitate the visualization and analysis of the data downloaded from currently available neurostimulators. To answer this need, we developed a free open-source toolbox, named DBScope, that imports data from neurostimulation devices and can be operated in two ways: via user interface and programmatically, as a library of functions. In this way, it can be used by both clinicians during clinical sessions (for instance, to visually inspect data from the current or previous in-clinic visits), and by researchers in their research pipelines (e.g., for pre-processing, feature extraction and biomarker search).

At this stage, DBScope contains a parser for the Percept PC device, but as other devices with sensing capabilities become available, other data parsers can be included. All in all, the DBScope toolbox is set to facilitate the clinical decision-making process and the identification of clinically relevant biomarkers.

5.1 Methods

5.1.1 Software

DBScope was developed with MATLAB 2022b (MathWorks, Natick, MA), a well-established scientific programming language with several built-in tools, ranging from signal analysis to user interface creation.

5.1.2 Sensing data

The initial motivation for the toolbox stemmed from an interest in conducting in-depth analysis on the files extracted from the Medtronic's Percept PC setup. Besides information regarding the in-clinic visit, the patient and the neurostimulator, these files contain two main groups of recordings: the in-clinic recordings, which are subdivided in Survey, Setup, and Streaming sensing modes; and the chronic (or out-of-clinic) recordings, containing the Timeline and the Events sensing modes (up to 60 days for the Percept PC device).

5.1.3 Ethics

Fully anonymized recordings from patients already implanted with the Percept PC neurostimulator with sensing capabilities were used to develop, test and validate the DBScope toolbox. We have obtained informed consent from the patients and the study received authorization (reference CE 233/2023) from the Ethics Committee of CHUSJ, Portugal. As such, this clinical dataset is not shared. However, a fully anonymized recording is provided with the DBScope toolbox for testing purposes.

5.1.4 Toolbox features

The DBScope toolbox was designed with a set of core features in mind: 1) interactivity, as to ensure that users with little to no programming experience could use it in their practices; 2) reusability, so that users with some programming experience could easily create or adapt the tools to better fit their research questions; 3) integration, to allow the simultaneous analysis of both different signals (in cases where motor data is also acquired) and multiple files (for longitudinal studies); 4) customization, to the extent that each sensing mode should have tailored methods. We used an Object-Oriented Programming (OOP) paradigm to facilitate the fulfilment of these requirements (Figure 5.1). Specific functions in DBScope were derived from pre-existing open-source computational toolboxes: the extraction of LFP and stimulation information methods are based on the analogous functions present in the Thenaisie et al. toolbox; the electrocardiographic (ECG) artefact cleaning tool was extracted from the Perceive toolbox. Regarding exportation, the toolbox offers two options: 1) a MATLAB file organized in the DBScope internal structure; and 2) a set of MATLAB files that are compatible with FieldTrip, each corresponding to one type of sensing mode.

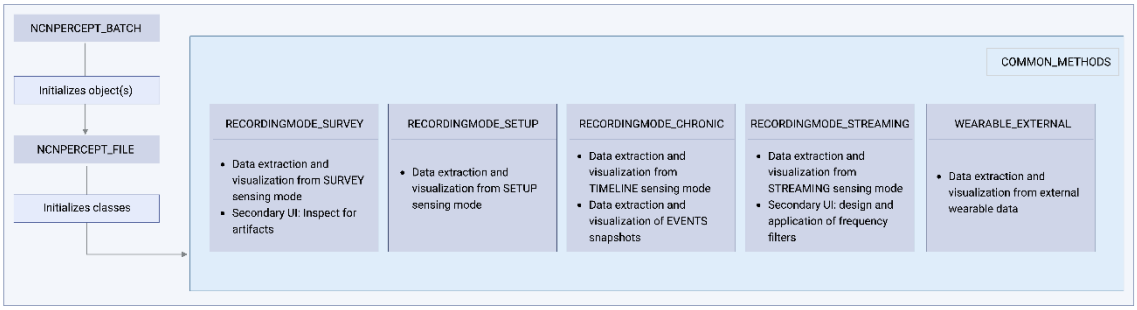


Figure 5.1 DBScope internal structure.

The toolbox was designed using an object-oriented programming framework. Upon initialization, the class NCNPERCEPT_BATCH separates the loaded files in patients (each containing one or several files). Each file gives rise to a NCNPERCEPT_FILE object. These objects contain six classes, each with its own properties and methods. Each class is named after the type of recording that it can access. The WEARABLES_EXTERNAL class handles additional data that is not present within the neurostimulator files and needs to be loaded separately afterward. COMMON_METHODS is an auxiliary class that runs background methods.

5.1.5 Objected-Oriented Programming

OOP is a strategy that allows to create applications modelled on real-world objects and hierarchical structures. It uses objects, classes and data structures, to provide robust application that follow the order of hierarchical relations imposed by the programmer. One characteristic of the data extracted from Percept that made us chose this paradigm was the similar data structures from different origins, for example, time domain from distinct sensing features, and that was important to ensure that in the application there would not be the possibility to call the wrong data structure by accident. This way, we made use of two principal features of OOP: inheritance and encapsulation. Starting with the later, it allows for methods to be available within a class and cannot be used by other class. For example, if we are working in streaming data, we cannot call methods to be applied to survey data. And inheritance means that lower-level class can inherit methods from upper classes, but this is customizable. For example, there are methods form COMMON_METHODS that all classes can access, however, we can also hide those methods and select with methods from the upper class can each lower-class access. This allow us to have background methods that are required to each class operational without interfering with the encapsulation of each class.

5.2 Results

5.2.1 User interface

Integrating information from multiple types of recordings can be troublesome and time-consuming. To facilitate this process, we developed a user interface (Figure 5.2), which provides a graphical environment for data analysis and exploration. This inclusion is mainly addressed to an audience with no previous experience in programming, that is keen on including DBS data analysis into their clinical or research routines. Nevertheless, the toolbox also enables experienced programmers to create their own scripts, adapting or creating new functions to better fit their research questions (Figure 5.3).

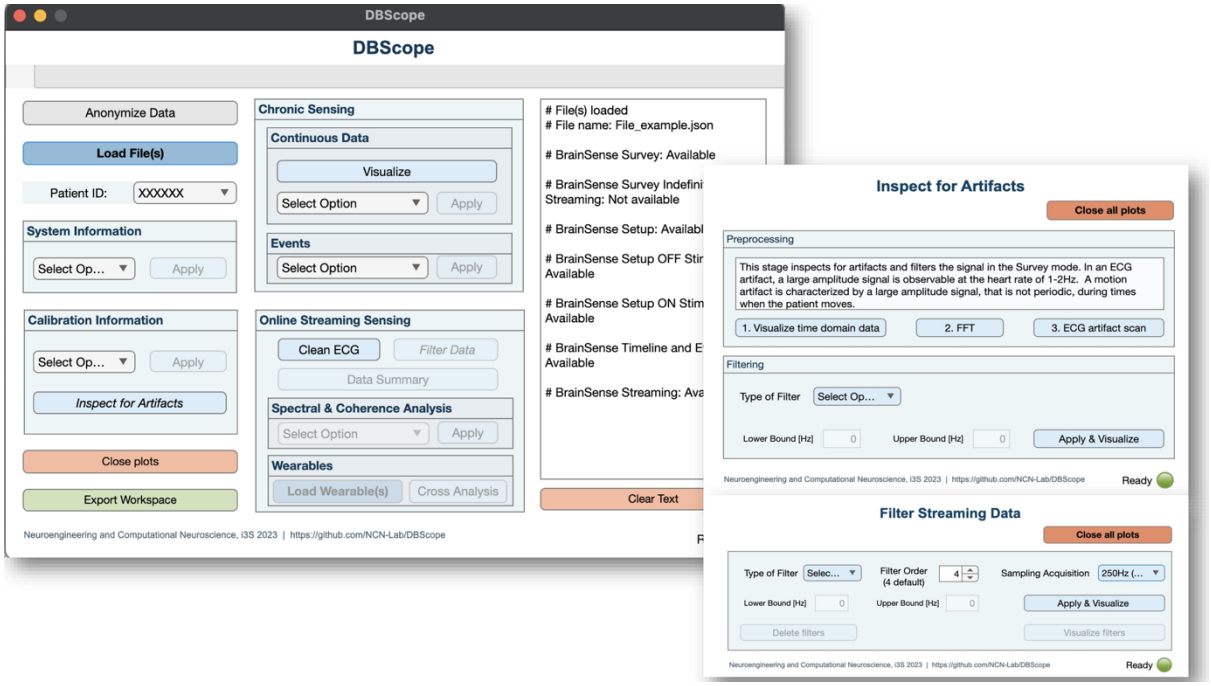


Figure 5.2 DBScope graphical interface.

The toolbox comprises a main interface that accommodates four sections. Each section gives access to part of the data contained in the loaded files. Within the Calibration Information and Online Streaming Sensing sections, the user can access secondary interfaces, that are used in artifact inspection and signal filtering, respectively. The main interface also contains a text area that displays information during user interaction. For instance, upon loading a file, it shows the available sensing modes.

```
%% DBScope example script
% Initialize object
obj = NCNPERCEPT_BATCH;
[ status, text ] = obj.open_batch_files();
% Exemplify with one file
patient = 1; file = 1;
% Disp Lead Information
text = obj.ncnpercept_patient{patient}{file}.getLeadConfig();
% Chronic - Timeline
obj.ncnpercept_patient{patient}{file}.chronic_obj.plotLFPTrendLogs();
% Chronic - Circadian Distribution
obj.ncnpercept_patient{patient}{file}.chronic_obj.plotCircadian();
% Online Streaming - ECG Artifact Cleaning
obj.ncnpercept_patient{patient}{file}.streaming_obj.cleanECG(250);
% Online Streaming - Data Summary
obj.ncnpercept_patient{patient}{file}.streaming_obj.plotSummaryStreaming(1);
```

Figure 5.3 DBScope script example.

The initial steps involve initializing the mother object, NCNPERCEPT_BATCH, followed by the file(s) loading. Subsequently, one file is analysed considering three different streams of operations: Calibration System, for the display of the lead information; Chronic Sensing, for the visualization of the Timeline and circadian distribution; and Online Streaming Sensing, for the application of the ECG artifact cleaning algorithm and visualization of the data summary.

5.2.2 Operational Workflow

The first step in DBScope is to load the files of interest. The toolbox is capable of handling one or multiple files from the same patient, facilitating combined/aggregated analysis as required. Once the files are loaded, four main streams of operations are suggested (Figure 5.4), considering the sensing modes present in the loaded file(s):

- System Information provides information on the neurostimulator, the patient, and the in-clinic visit.

- Calibration Information gives access to the impedance tests, to the Survey and Setup recordings, and to a secondary interface for artifact exploration.
- Chronic Sensing offers visualization and analytical tools for the Timeline and Events recordings.
- Online Streaming Sensing draws on four main functionalities: 1) an ECG cleaning algorithm; 2) a filtering tool that calls a secondary interface; 3) spectral and correlation tools; and 4) a tool for visual cross-analysis with wearable data. For the latter, the user must load the corresponding wearable data files, in a CSV format (for more information, consult the DBScope documentation). During visualization, the toolbox automatically aligns the wearable recordings with the streaming recordings using the marked timestamps.

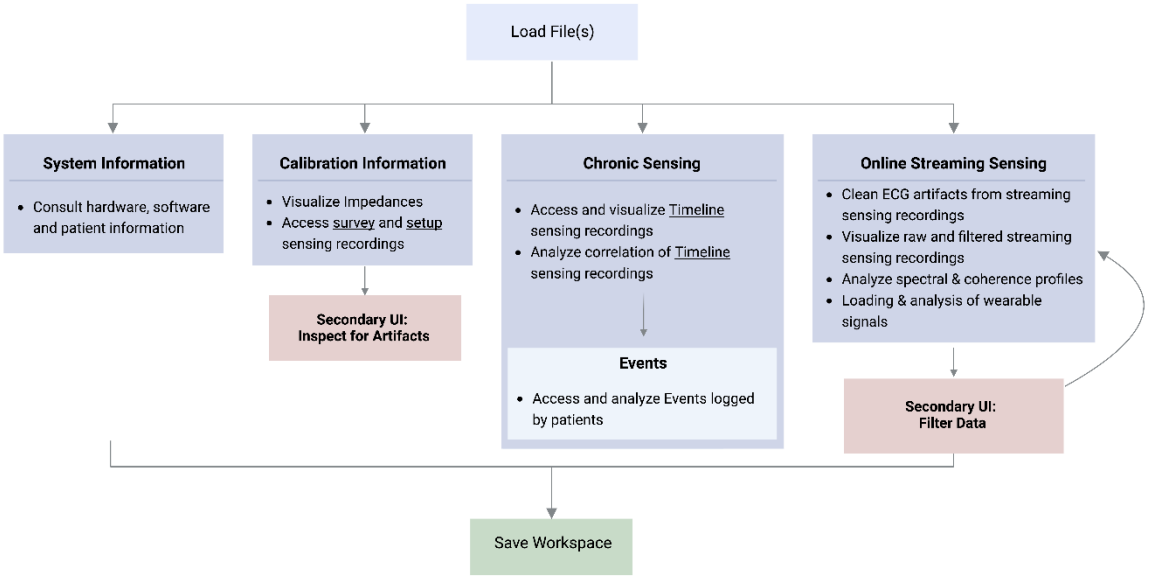


Figure 5.4 General workflow.
The user starts by loading one or multiple files. The user can always return to this step, with the option to save the current workspace. After loading the file(s), four streams of operations are available: System information, gives information about the patient, the device, and the in-clinic visit; Calibration Information deals with the recordings obtained when testing and setting the stimulation and sensing parameters, and has a secondary interface for artifact inspection; Chronic Sensing offers multiple visual and analytical functions for the Timeline and Events recordings; Online Streaming Sensing provides tools for visualization, artifact removal, filtering (using a secondary interface), and alignment with wearable data. Regardless of the chosen workflow, the user can always save the workspace (for more information, consult the DBScope documentation).

5.3 Case-Studies

To exemplify the application of the toolbox and showcase some of its features (Figure 5.5).

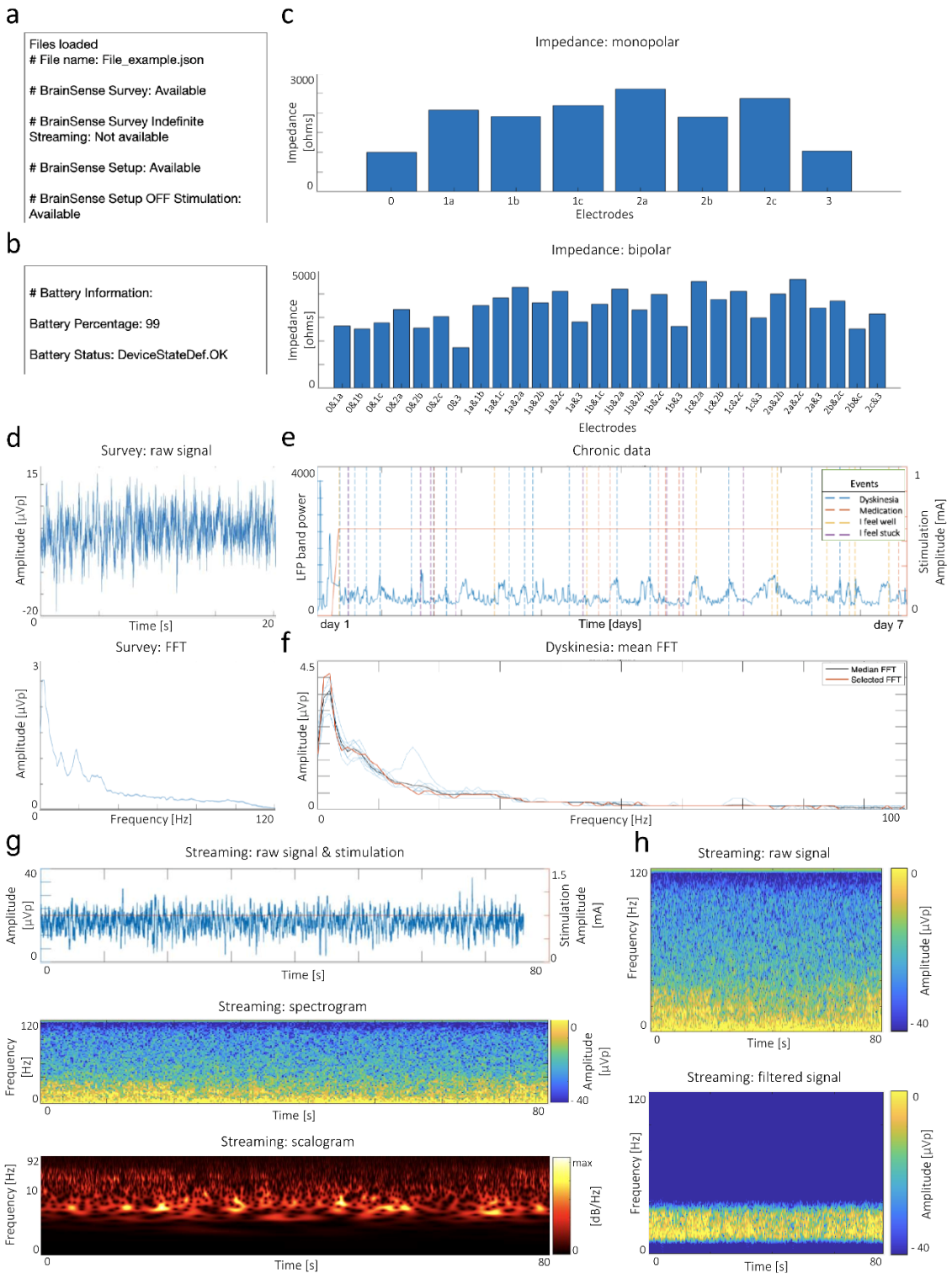


Figure 5.5 Overview of the toolbox outcomes.

(a) Snapshot of the text window displayed once a file is loaded. (b) Snapshot of the battery information. (c) Impedance information (monopolar and bipolar) for one hemisphere, accessible in the Calibration section. (d) Raw signal and Fast Fourier Transform (FFT) of a Survey recording. (e) Chronic data of one hemisphere, with the events marked by the patient. (f) FFT of 'Medication episodes marked in (e). (g) Data summary, containing the raw signal, the stimulation amplitude, the spectrogram, and the scalogram obtained with a wavelet method of an Online Streaming recording. (h) Spectrograms of the recording of (g) before and after a bandpass filter.

We present two case studies: the first about the long-term LFP dynamics (up to a month) of out-of-clinic recordings; the second about the LFP dynamics in shorter time scales (in the domain of minutes) of in-clinic recordings.

5.3.1 Case study: out-of-clinic recordings

This case study investigates a single hemisphere of one patient. Circadian and diurnal power fluctuations within the preselected frequency band can be observed throughout the entire 34-day Timeline recording (Figure 5.7A-B). While beta power exhibits a consistent reduced magnitude overnight (which is indicative of sleep time), most fluctuations occur during daytime and increase in range over the recording period. The latter phenomenon may be explained by the fact that the implantation took place two weeks prior to the recording and the tissue around the implant was still stabilizing (i.e., inflammatory response, oedema, and scar tissue formation persisted). This patient's Events recordings include 'Medication', 'I feel well', 'I feel stuck', and 'Dyskinesias' episodes (Figure 5.7C). Dyskinetic episodes are characterized by lower theta-alpha and beta powers (Figure 5.6).

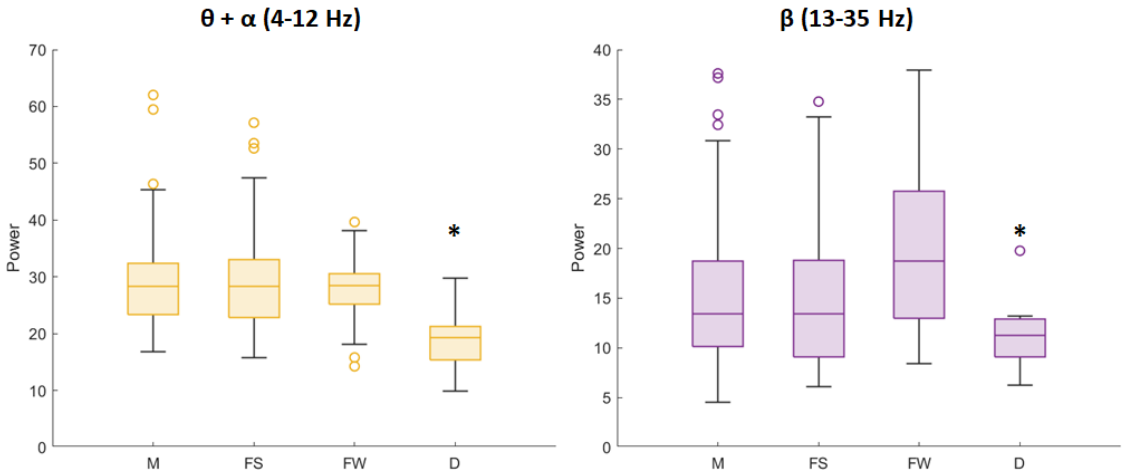


Figure 5.6 Power in alpha-theta and beta frequency bands of four different events.
Each graph has the minimum, 25th percentile, median, 75th, and maximum values for the four types of events: M – Medication; FS – Feeling stuck; FW – Feeling well; D – Dyskinesias. The asterisk marks the instances where dyskinesias are statistically different from at least one other event (ANOVA, $p<0.05$).

The daily distribution of 'I feel stuck' episodes contain multiple periods of higher incidence, which are aligned with the medication intake distribution (Figure 5.7D). Interestingly, most 'I feel stuck' episodes appear immediately after medication (Figure 5.7E). While the inverse relationship would be expected (i.e., medication would decrease rigidity), it is possible that the patient was using the medication schedule as a cue to report the immediately preceding rigidity states.

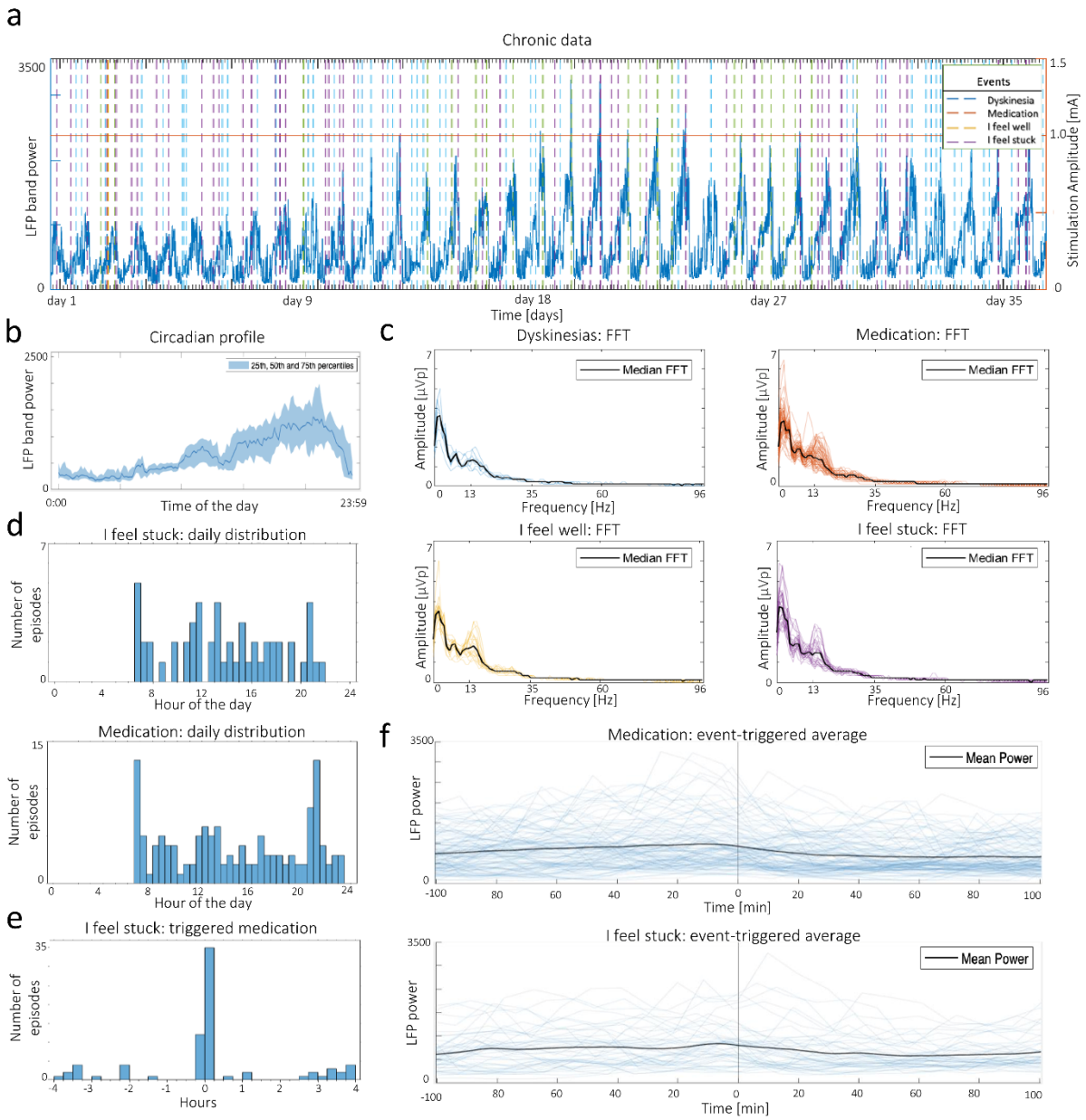


Figure 5.7 Case study of out-of-clinic data.
(a) Representation of Timeline and Events of the selected hemisphere. The recordings cover approximately one month in a conventional DBS protocol (continuous fixed stimulation amplitude). (b) Estimated circadian profile of the Timeline recording in (a). The LFP power is higher during waking hours. (c) Fast Fourier Transform (FFT) profiles for each of the recorded Events. The observed median profiles were similar, with the highest variation around the 15 Hz peak. (d) Daily distribution of 'Medication' and 'I feel stuck' episodes. Notice that distributions are similar, with three periods of higher incidence (6h, 11-12h, 20-21h). (e) Distribution of 'I feel stuck' events relative to 'Medication' events (triggered at zero). Interestingly, 'I feel stuck' episodes are mostly reported after 'Medication'. (f) Event-triggered average plots showing the power of the selected band in the proximity of 'Medication' and 'I feel stuck' episodes. The mean power decreases after the two events.

Post-medication power shows a consistent decrease within a few minutes of medication intake (Figure 5.7F). This phenomenon aligns with the known suppression of beta activity induced by Parkinsonian medication and supports the usefulness of this frequency band in investigating the wear-off effect. This decrease is also seen after 'I feel stuck' episodes, which is not surprising given the temporal relationship with medication episodes (Figure 5.7E)

5.3.2 Case study: in-clinic recordings

This case study explores the streaming recordings of multiple patients. Scalograms, obtained with a wavelet transform method, exhibit bands with heightened activity for many patients (Figure 5.8A, top plots). To enable easier analysis and interpretation aligned with clinical observations, a filtering tool can be applied to highlight and isolate these bands (Figure 5.8A, bottom plots). Instead of merely displaying the overall power of the selected band (like the 'programming' tablet), it exhibits distinct frequency variations within the band. Moreover, it provides greater flexibility by allowing the highlighting of multiple bands, which is advantageous in situations where monitoring a single band may not be sufficient for therapy evaluation (e.g., when the theta-alpha bands are also elevated, Figure 5.8C).

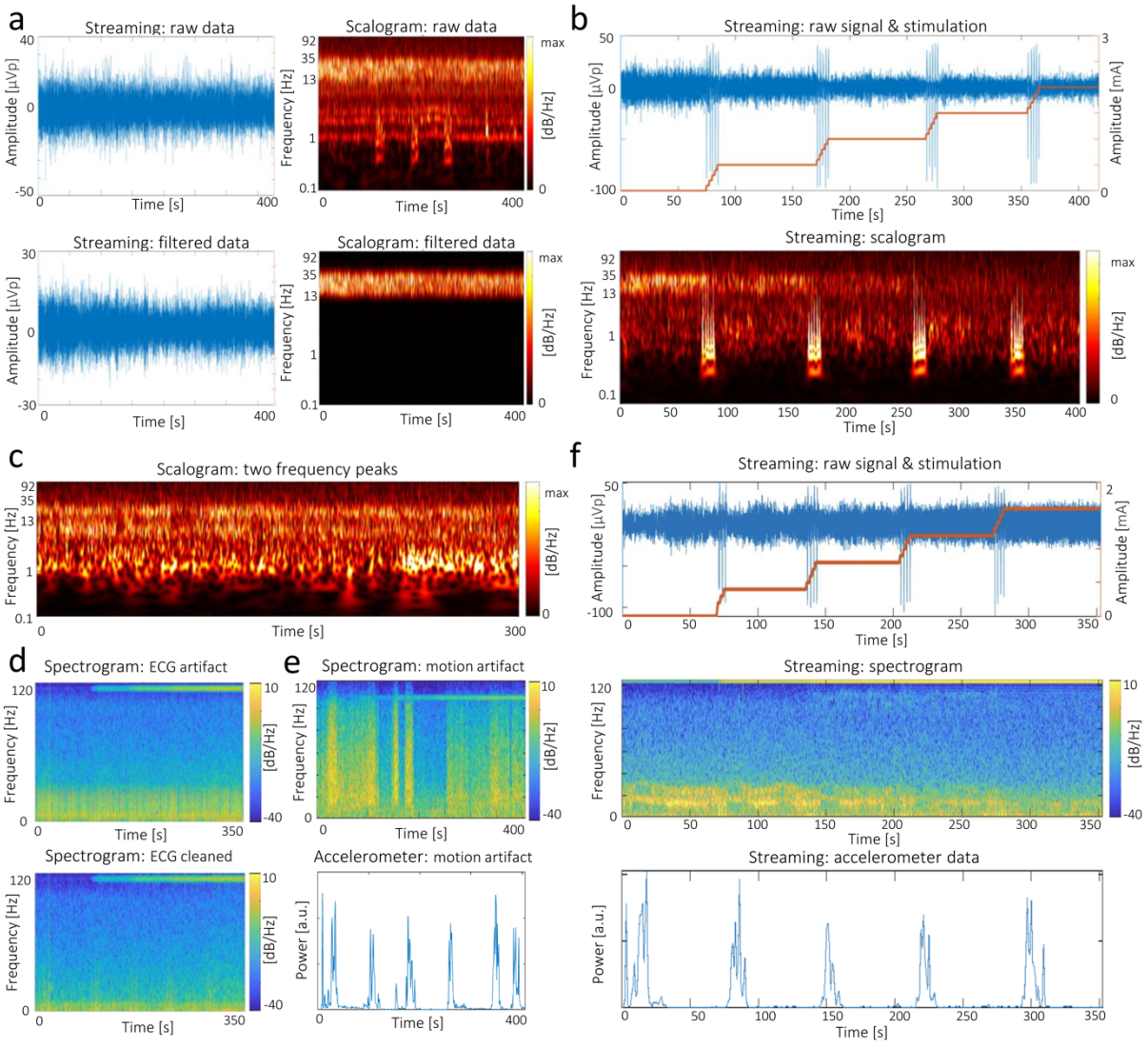


Figure 5.8 Case study of in-clinic recordings.
(a) Application of a customized filter to better highlight a band of interest (13-35 Hz). (b) Raw neuronal recording and time-frequency analysis aligned to therapy changes. Amplitude stepping induces changes both at the raw signal (abrupt magnitude rises) and scalogram (high low-frequency activity). Note that the y-axis of the scalograms has a logarithmic scale. (c) Example of a recording where both beta and theta-alpha activities are elevated. (d) Recording with cardiac artifacts before (top) and after (bottom) cleaning. (e) Recording with motion-induced artifacts. The artifacts span across the entire frequency spectrum, being more intense at the peaks in motion power and vanishing once the motion power is plotted over zero. (f) Cross-signal analysis for a titration recording during a motor task. Both stimulation and movement suppress beta-band activity.

In many of the recordings, the stepping of stimulation amplitude resulted in abrupt rises of the LFP signal, evident by an increase in lower frequency oscillations (Figure 5.8B). This phenomenon has an artefactual nature and has

been previously reported in Percept PC patients (Hammer, Kochanski, Starr, & Little, 2022). Incidentally, artifacts in DBS are common and can arise from various sources, including cardiac activity (Figure 5.8D, top plot), motion (Figure 5.8E), and stimulation itself. Furthermore, it is not uncommon for a signal to be contaminated by multiple types of artifacts. In some recordings, the ECG cleaning tool can successfully remove the ECG artifact (Figure 5.8D, bottom plot).

In some patients, an increase in stimulation amplitude results in beta-band activity suppression both at rest (additional case study, Figure 5.9) and during motor performance (Figure 5.8F). Additionally, desynchronization of beta activity is shown to occur at lower stimulation amplitudes during a motor task involving the opening and closing of the contralateral fist.

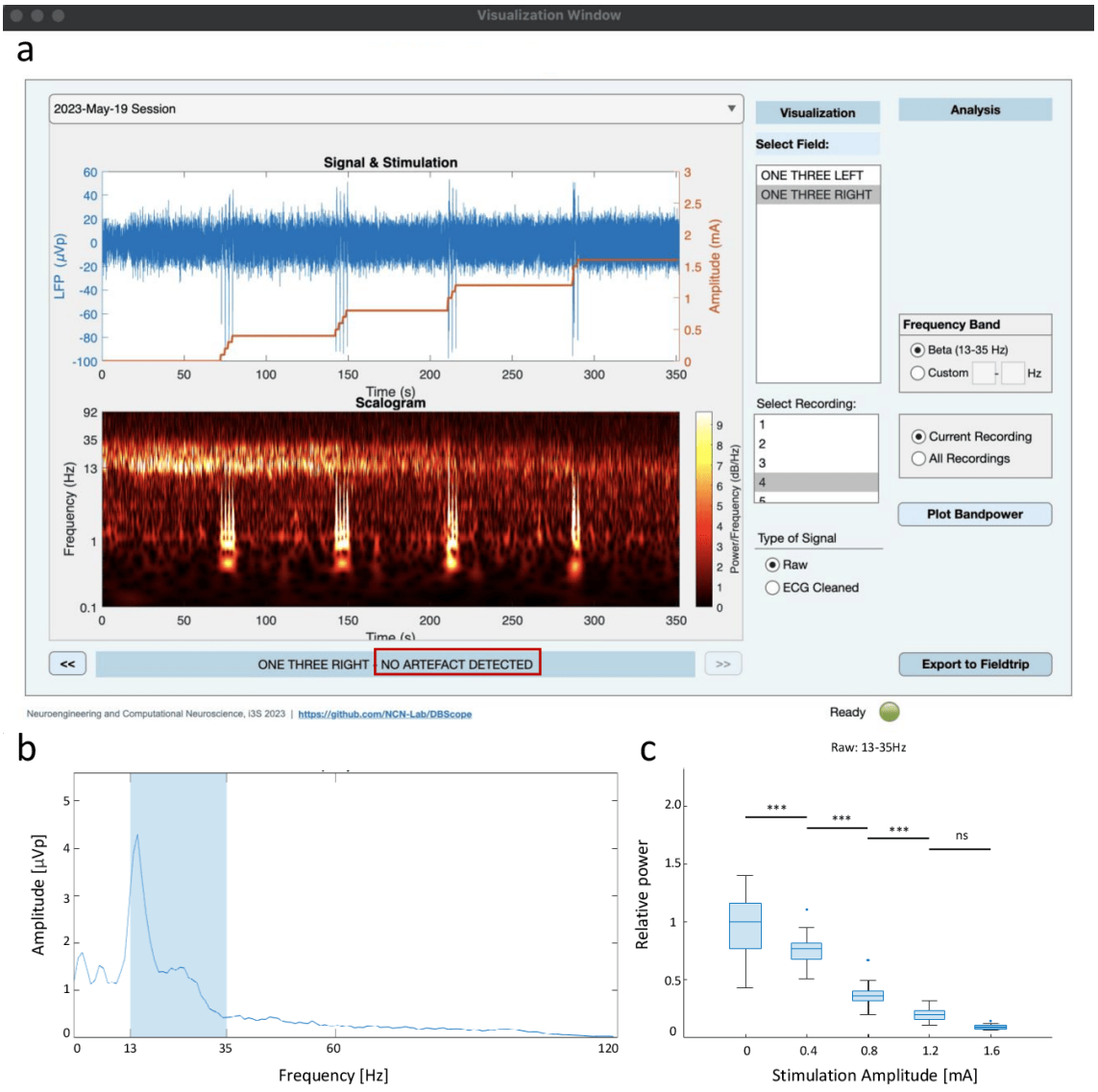


Figure 5.9 Application of DBScope in a clinical evaluation.
Snapshot of the DBScope Morlet Wavelet function. In the absence of detected artifacts (highlighted in a red box), the raw data was selected. The plot displays a screenshot of the toolbox output, featuring the following: top row – raw LFP traces and stimulation; and bottom row – scalogram of the signal. Notably, the reduction of the beta band on the third level of stimulation is observable from the third to fifth stimulation levels, suggesting a response to the stimulation. (b) FFT of the selected sensing channel, 'ONE THREE RIGHT', with a clear peak in the low beta band. (c) Computation of the relative bandpower for the beta band (13-35Hz) reveals statistical significance (One-way ANOVA, $p<0.001$) among most stimulation levels. The statistical differences between stimulation levels are shown with the bars, where in this case there ceases to be a difference between the fourth and the fifth level.

Considering that the hallmark of movement evaluation in the clinics is the UPDRS III scale (Society, n.d.), we explored the correlation of UPDRS values with the extinction of beta bandpower (Figure 5.10). Between stimulation levels, we compared the intervals with folds in the UPDRS (increase or decrease) and a statistically significant change in the bandpower in beta, where > 86% of the patients had no correlation. In our cohort a change in the bandpower appears not to be directly correlated with the clinical response, and vice versa. Nevertheless, not being correlation opens the potential for complementary information on having both methodologies to evaluate the patient.

By visualizing the wavelets of the recording with the variation of stimulation amplitude, our goal was to describe how the spectral profile answered to stimulation. Again, in the examples of Figure 5.10, we see an extinction of beta band (which we are assuming as a response to stimulation in the second level of stimulation). The location of the extinction of the spectral bands has potential information towards suggesting situations of over or understimulation.

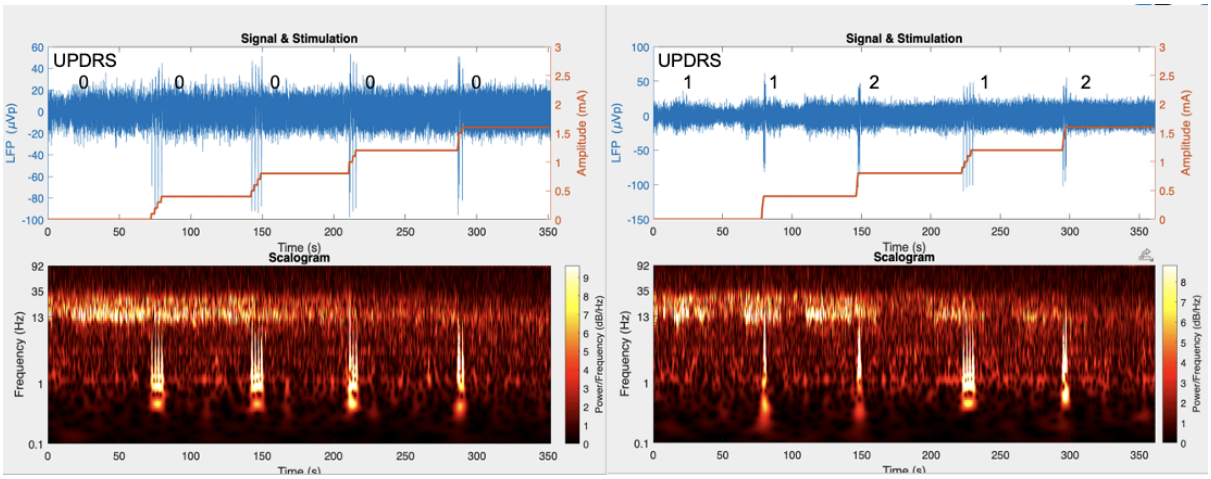


Figure 5.10 Effect of stimulation in beta bands: UPDRS values and wavelets representation.
In this figure, we see two different recordings extracted from the protocol. On the top rows there is a representation of the raw signal of the LFPs (blue), with the representation of stimulation amplitude (orange), and the values from the UPDRS evaluation for resting tremor in each stimulation level. In the bottom rows, we have the wavelets representation of the corresponding recordings.

5.4 Discussion

In this work, we address the need of accessible and comprehensive analytical tools for the DBS therapies. We present a toolbox with an intuitive user interface that allows both clinicians and researchers to access and explore intricate electrophysiological data. To the best of our knowledge, no other toolbox offers a comparable range of functions in terms of both extent and variety, together with ease to run/setup and customize (but see (Cagle et al., 2023)). Among these functions, we would like to emphasize the inclusion of an ECG cleaning tool and the capability to visualize streaming recordings with data obtained from wearable devices. Furthermore, the toolbox operates without the need for an internet connection and patient data is not required to be stored on a server. While we acknowledge that a central database may be desirable in a healthcare setting, it is also true that it imposes additional technical/security measures regarding the sharing of personal data.

To standardize some of the most performed analyses of the field, we designed a novel structure of classes and developed a diverse repertoire of functions within each class. Some of these functions were adapted from existing toolboxes, notably in the detection and cleaning of cardiac artifacts. By adopting an object-oriented programming framework, we were able to produce a toolbox that can analyse multiple files in a simple and intuitive workflow. This is desirable not only from a software design perspective, but also from a scientific perspective, where longitudinal, multi-signal and multi-patient analyses are relevant (Chen et al., 2020; Feldmann et al., 2022; Gilron, Little, Perrone, Wilt, de Hemptinne, Yaroshinsky, Racine, Wang, Ostrem, Larson, Wang, et al., 2021).

In the context of LFPs for improving DBS therapy, as has been mentioned, the spectral composition of the signal is a cornerstone of the topic of biomarkers. However, one key point that emerged in the literature before establishing the biomarkers was how to visualize the spectral profile of recordings. Two main methods are called upon: spectrogram and wavelets. The spectrogram is a 2D plot where the x-axis is the time and the y-axis represents the frequency, with the colour at each point representing the amplitude of a particular frequency-time. To compute this representation, first, the signal is computed in small segments, and then a Fourier Transform is applied to each segment, converting the signal from the time domain to the frequency domain. As mentioned, the colour implicates the amplitude of a particular frequency-time, meaning the magnitudes of the Fourier coefficients. As for the Wavelet transform, the main difference is that, unlike the Fourier method, instead of sine and cosine functions to decompose the signal in its frequency domain, it applies wavelets, which are small wave-like oscillations with localization in time and frequency. This allows the resolution of the signal to be adapted for different frequency intervals. First, a wavelet is chosen, which will be manipulated to create a set of wavelets with different scales. The signal is convolved with these wavelets and produces coefficients that represent the signal composition at the different scales. This allows for better temporal resolution in short-duration events and high-frequency resolution for longer events. In particular, we are interested in the location performance of the methods and the identification of the frequency intervals that have activity or patterns. Hence, due to the balance that the wavelet provides, this method is more localized in time and frequency, making it a better selection of methods for non-stationary signals such as LFPs.

To illustrate the application of DBScope, we presented case studies complemented with additional visualizations that concentrate on out-of-clinic and in-clinic recordings. All in-clinic are more commonly used in the context of Percept PC, as they offer a higher temporal resolution. Nevertheless, out-of-clinic recordings still provide an invaluable glimpse into real-world settings, where data-driven DBS therapies aim to actuate. In fact, we observed that chronic data contains valuable information, such as the patients' circadian patterns, which exhibit longer temporal dynamics. These patterns are challenging to identify in in-clinic recordings but are discernible in long-term ones. At the same time, it was possible to study the response of the LFP to specific occurrences, such as medication intake or rigidity episodes. While the marking of medication episodes showed potential in monitoring the wear-off effect, other events were reported less times and typically coincided with medication intake, suggesting that the patient was reporting retroactively. Regarding the in-clinic recordings, the toolbox offered clear visualizations that facilitated the identification of both artifacts and clinically relevant frequency bands. Additionally, the possibility of aligning streaming recordings with wearable data proved to be a relevant addition to DBScope, enabling the investigation of movement-related modulations.

Future developments aim to address two challenges. The first lies in the search for biomarkers. Defining a biomarker, or library of biomarkers, is an essential, albeit complex, step for the development of patient- and symptom-specific DBS therapies (Feldmann et al., 2022; Guidetti et al., 2021; Timon Merk et al., 2022). A direct mapping between brain activity and reported symptoms is seldom possible, due to the subjective and elusive natures of the latter. In these cases, a second signal, more interpretable and highly linked with the symptom type, is often introduced to facilitate the mapping process. For instance, accelerometery data is widely used to link electrophysiological signals with motor symptoms. Considering this, we have already included the functionality to load accelerometery data into DBScope and are actively developing additional methods to leverage the information contained in these signals. The second challenge stems from the fact that LFP are prone to artifacts of different origins, such as cardiac, movement, and stimulation. Although current devices have implemented artifact cleaning algorithms, not all artifacts can be reliably identified and effectively cleaned. DBScope currently enables artifact screening in an iterative process, where the user alternates between visualization and filtering/cleaning steps. However, this approach is time-consuming and ineffective when the entire frequency spectrum is affected. In this respect, we are invested in the development of algorithms that not only automatically detect the source of these artifacts, but also clean them accordingly.

In the first outcomes of our protocol that resulted in the case studies, further questions emerged. First, we have the possibility to study the effect of stimulation changes per level, which allows us to describe cases of under and overstimulation, useful information for the clinician to titrate the therapy to better fit the patient's needs. As the evaluation is a single point (to be discussed in the following chapters), additional electrophysiological insights can be important to adequately address the fluctuating needs of the patients in opposition to the moment of the evaluation. Moreover, it is undeniable that each patient has its own spectral profile and, consequently, response to stimulation. This emphasizes the direction towards personalized and complementary biomarkers– instead of one single biomarker, the conjugation of electrophysiological, clinical and movement information.

One of our major goals was to create the conditions for the DBS community to adopt and easily contribute to the enhancement of this toolbox, in response to advancements and discoveries in DBS research. For this reason, DBScope is “open source” and is accessible through an online repository. The dependence on MATLAB was circumvented with the creation of standalone applications for both Microsoft Windows and macOS operative systems. These standalone applications, also available in the online repository (“Release” section), allow DBScope to be used without having to install MATLAB (royalty-free). We firmly believe that these types of initiatives are key in fostering the emergence of novel methods for clinical integration. Although we are currently working on updates, we encourage the clinical and research communities to adapt the tools and algorithms already available in DBScope and to share their insights, becoming part of this joint effort to improve the DBS therapy.

Although DBScope succeeded on many fronts, it bears some limitations. Presently, the toolbox operates exclusively on files extracted from Medtronic's Percept PC setup. As new devices with sensing capabilities have since emerged (Medtronic’s Summit RC+S and Newronika’s AlphaDBS), we are considering the development of specific parsers to accommodate them. DBScope is also reliant on commercial software (MATLAB). However, it should be noted that universities and research institutes often offer campus-wide licenses to their members.

5.5 Conclusion

DBScope is an open-source computational toolbox to import, visualize and analyse files from the Percept PC device (Medtronic, BrainSense Technology). The toolbox can be used programmatically or through an interface for users without programming experience. This way, it can be directly integrated into the clinical and research practices, whilst remaining adaptable to one’s research questions. Its functionalities are up to date with current literature standards for the evaluation of LFP in DBS. Moreover, future updates are in store. Overall, DBScope is a versatile tool focused on the widespread improvement of data-driven DBS therapies, by expanding the accessibility of the data and by promoting new forms of analysing the complexity of DBS data.

Chapter 6: Analysis of temporal dynamics in the spectral profiles of Local Field Potentials Recordings

In the following chapter, we will focus on analysing the temporal dynamics of the spectral profiles of LFPs. This signals are often characterized by a non-stationarity behaviour which remains undescribed in the literature. The work presented in this chapter relies on applying different methods to capture this behaviour, in particular, by the application of Hjorth parameters, continuous parameters (e.g. bandpower) analysis or structural versus non-structural metrics (such as STD and Shannon's entropy).

6.1 Dataset processing

For the following analysis, patients with PD diagnostic were included (Elena Moro & Lang, 2006), from Charité-Universitätsmedizin Berlin hospital centre. The neuromodulator chosen for DBS therapy was the Percept PC. Recordings were performed using the streaming sensing mode that has a sampling frequency of 250Hz. The recordings were selected based on the criteria of no medication and a follow-up period of more than three months. The reason for choosing recordings without medication but keeping both stimulation levels was to focus the analysis on studying the effect of stimulation without the interference of medication while keeping the option to study the effect of disease progression (medication off and stimulation off). Future work could involve conducting the same analysis considering the effect of medication. The rationale for selecting recordings performed after a three month post-operative follow-up period was to exclude the microlesion effect (Tykocki et al., 2013).

For each recording, the resting periods were extracted. This was performed by using videos taken during the recordings as an anchor to the temporal synchronisation. Each time an LFP recording was performed, the researcher displayed the timestamp on the camera. By calculating the seconds in the video showing movement/ no movement period, the corresponding interval was possible to compute considering the timestamp shown on the LFP recording management tablet. This allowed for the manual removal or selection of periods without movement. Then, the raw data and spectral profiles (wavelet transform) were used to evaluate the quality of the recording and the presence of artefacts. Recordings with artefacts, such as ECG, stimulation, or other interferences, were excluded based on visual inspection.

As we intended to perform a cross-patient analysis, we applied the min-max normalisation method to all the recordings included. Min-max normalisation rescales the values of a dataset to a fixed range, which we chose as [0, 1] or [-1, 1]. We chose this method as it preserved the relationships between data points that could be related to the temporal profile that we wished to preserve. The data was filtered into the following frequency bands: 0-125Hz (total), 5-13Hz (low frequency), 13-20Hz (low beta), 20-35Hz (high beta), 13-35Hz (beta), 35-60Hz (low gamma), 60-65Hz (stimulation subharmonic), and 65-98Hz (middle gamma), using a Butterworth band-pass of fourth order filter. The most challenging step was the structural organisation of the data to proceed with the analysis in a systematic and efficient way. We converged to the following structure, built with the objects from DBScope that allowed to adapt into new structures regarding the hierarchical level of intended analysis (for example, patient-level versus stimulation type).

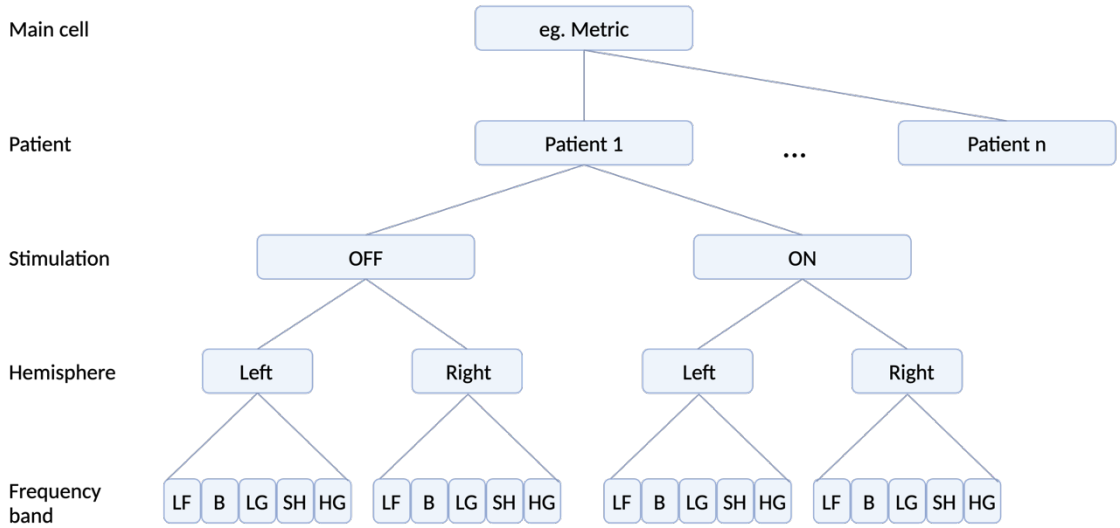


Figure 6.1 Nested structure for the LFP database.
This structure is organized in nested cells and created in MATLAB. The main cell is the Metric extracted, and the values of each cell are the metric computed for the signal that follows the structure tree up to the corresponding cell. For example, the cell LF of the structure on the right consists of the Metric for Patient 1, in the Stimulation OFF state of the left hemisphere and for the filtered signal in the low-frequency band (LF). This nested structure allows the manipulation of the data depending on the researcher's need (e.g. stimulation state or patient level).
LF – Low Frequency; B – Beta band; LG – Low Gamma band; SH – Stimulation subharmonic; HG – High Gamma band.

6.2 Analysis of the frequency spectrum

Once the dataset was created, the first step we took was to apply spectral analysis methods that provide information well described in the literature: frequency power. By doing that, we saw an opportunity to research these profiles in different domains, such as the temporal profile not yet described in the literature.

As seen in the previous chapter, the literature is well established in the correlation of frequency bands with motor symptoms, and it is starting to move beyond that towards a multifactorial concept of electrophysiological biomarkers. The importance of correlating frequency bands, and hence for us to start there, is that it is a well-established practice of electrophysiological analysis (transform a time series into a spectral profile) that already has been shown correlation with clinical symptoms and, hence, provides a reproduceable insight on the relationship of motor control and disorders (R Lofredi et al., 2023). The value of this analysis can be applicable in both research and clinical settings, from diagnosing to monitoring and treatment optimization. In the context of motor control and movement disorders, the bands that have been in the spotlight occur in the beta rhythms spectrum (13-35Hz), but the gamma bands are also emerging as important actors (Bočková et al., 2024; Mathiopoulou et al., 2024). When discussing an electrophysiological biomarker, and in the context of these bands, we build on assumptions of abnormalities manifested by certain variations of their power (increased or decreased) (Averna et al., 2023). For example, an optimal Parkinson's treatment will lower the beta band, which otherwise would be increased in the context of PD, a behaviour we deem pathological. By tracking these fluctuations over time, valuable clinical information can already be extracted to motor disorders and the effectiveness of the treatments, be it medication or DBS.

The selected method for the study of the frequency profiles was the wavelet transform, as it is a powerful tool that can analyse more accurately the time-frequency balance variations of power of a time series (Karthick, Wan, An Qi, Dauwels, & King, 2020; Sil et al., 2023). In opposition to the Fourier Transform or the Power Spectral density methods, which only provide frequency information for the entire signal used as in input and assume stationarity of the signal, the wavelet transform also provides information on the time domain and, hence, the possibility to analyse non-stationary signals. Although the frequency-only methods are widespread, it is natural that literature starts to focus on methods such as wavelet transforms since electrophysiological signals (such as LFPs) are non-

stationary. By applying the wavelet transform, we get information for the different frequency components and how they vary across time points, providing insight into the evolution of the frequency profiles. Ideally, one could extract features of these profiles, such as patterns or trends, to potentially to act as biomarkers.

Our aim was then to apply wavelets and visualise and characterise any visible patterns over time with high accuracy. Our interest in temporal variability, in conclusion from what has been mentioned, comes from its potential to enhance DBS efficacy and treatment optimisation and personalisation. It is well known that the needs of patients are patient-specific, but they fluctuate over time, particularly in this topic. And different time periods, more locally, from daily needs to the scale of months and years, are influenced by the disease progression and loss of efficacy of stimulation. Moreover, the temporality can feed into innovations directly in stimulation protocols, as well as for the development of technology such as the next generations of neurostimulators and electrodes. Similarly to the importance of the frequency bands and how their power is studied, understanding the temporality of the signals can also impact the understanding of DBS as the modulator of neural synchrony and the roots of that causality: what does stimulation do?

6.2.1 Methods

For this analysis, we developed scripts in MATLAB using functions from the DBScope toolbox library. For the power spectral density analysis, the preferred method was the PWelch method (*pwelch* function). Additionally, spectrograms were generated to provide a comparative method option as opposed to the wavelet transform method. Wavelet transform was applied using the continuous 1-D wavelet transform method, and the wavelet chosen was the Morlet. The classification of the patterns on the wavelets was done visually, aiming to identify any features that could be characterised in time, particularly considering the known concept of high activity of selected frequency bands.

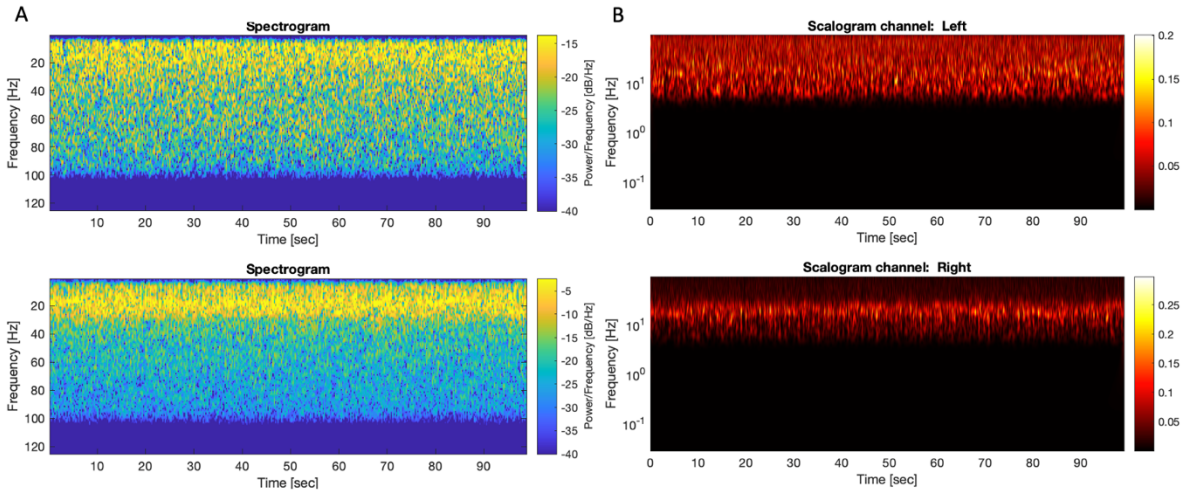


Figure 6.2 Visualization of spectrograms and wavelet transform.
In this figure, we see examples, for the same recording alongside the representation of the raw signal, of the two time-frequency methods most used to visualize the local field potentials and other electrophysiological time series. Due to the characteristics of the methods, the wavelet transform provides a more accurate definition of the bands compared to the spectrogram. This occurs because wavelets provide a multi-resolution analysis that captures high-frequency details with fine time resolution to the low-frequency components with coarse time resolutions. This allows us to capture more transient features across the spectrum, compared to the spectrograms that are limited by a fixed size of window, and do balance time-frequency resolution across the signal. This visualization is an output of the DBScope.

6.2.2 Results

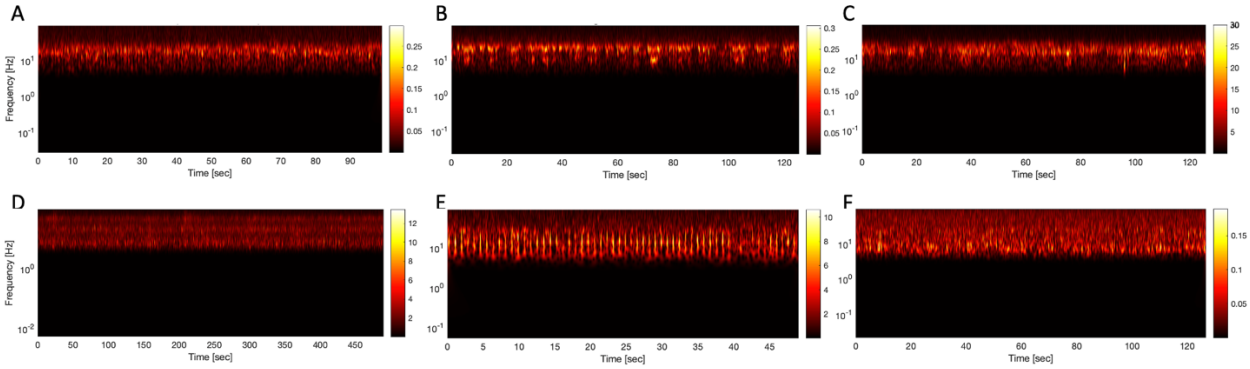


Figure 6.3 Identifiable wavelets' temporal patterns.
In this figure, we showcase examples of the identifiable wavelets' temporal patterns through visual inspection.
A – Single, stable and well-defined band; B – Periodical hyperactivity across multiple bands; C – Periodic burst activity; D – Multiple, stable and well-defined bands; E – Presence of artefacts; F – No Pattern.

As the first step, we performed a visual analysis of the wavelets for all the recordings. In particular, our attention was on the bands well-established in the literature, such as the beta band. Indeed, various recurrent patterns were identified within the electrophysiological recordings:

- Single, stable and well-define band: these are frequency bands, predominantly in the beta frequency range, that appears well defined across the recording. This suggest an unmodulated pathological process, which can be the target of the stimulation titration in DBS.
- Periodical hyperactivity across multiple bands: these patterns indicate periods of activity across frequency bands that are less stable and not defined in the affect band limits. Such variability raises the question of what process underlining could affect several bands simultaneously and the transient nature of these processes. In these types of discussions, it is important to highlight that on these visualizations of the frequency profiles, we capture both pathologic and physiological processes, as well as micro, meso, and macro-phenomenon. These patterns can be affected by these two perspectives: 1) such a wide-range pattern can hint at a physiological process; 2) Or could it hint at the original effect, from local scales to macro scales?
- Periodic burst activity: another pattern of transient hyperactivity, but within the limits of the frequency bands. In this case, this pattern is described in the literature as bursts of activity, which means sustained hyperactivity of a particular frequency band over a designed interval of time (Anderson et al., 2020). It is often correlated with pathological symptoms manifestation in the patient.
- Similarly to the first pattern, there is also the occurrence of multiple, stable and well-defined bands. The co-occurrence of bands is becoming more studied in the recent years.
- Presence of artifacts: in some recordings, is it possible to visually identify the present of artifacts such as stimulation, ECG and movement artifacts. While simulation and ECG artifacts are visually identifiable, at time movements artifacts need to be confirmed with additional data, being the recordings from wearables or videos.
- No pattern: additionally, there were recordings without a discernible pattern of behaviour. The recordings are, nevertheless, important, as they could represent the baseline profile of the physiological state – which, in this case, occurs in the process of Parkinson's Disease.

6.2.3 Discussion

The patterns persisted on the signals before and after applying normalization to the signals, which hints that they are not artefacts of the signal magnitude but intrinsic to its temporal evolution. In the consistency of pathological and physiological phenomena across different patients' conditions, is important to consider:

- A stable and consistent pattern has the potential to be a reliable biomarker for pathological or physiological processes.
- The temporal dimension of the spectral profiles is key to better addressing the stimulation needs of a patient, increasing the robustness of spectral features.
- The patterns identified in the wavelet transform visualization reflect the temporal dynamics that have only been briefly described in the literature.

6.3 Study and application of Hjorth parameters

In 1970, Hjorth suggested a set of three statistical tools for the analysis of electrophysiological time series, such as the EEG (Hjorth & Elema-Schönander, 1970). The aim of these parameters was to provide, in a quantitative approach, insights into the dynamics and characteristics of these signals and, consequently, the neural activity. Since our goal is to understand the dynamics of these time series, we decided to apply these parameters to our recordings as metrics for the temporal profile of the frequency bands.

The parameters are three, with sequential complexity (Table 6.1 and Figure 6.4):

- Activity, the first parameter, is the variance of the signal reflecting its power. A higher value of activity indicates a greater variance and signal power, which could mean a more intense neural activity within a particular frequency band that is not stable in amplitude.
- Mobility, the second parameter, describes how rapidly is the signal change over time. The calculation consists of the square root of the ratio of the variance of the first derivative of the signal to the variance of the original signal. Obtaining higher mobility values indicates a faster change or higher frequencies within the signal. Mobility is of particular interest because it targets the temporal changes contained within a frequency band, which is relevant to the goal of this work.
- Complexity, the third and last parameter, provides information on the similarity of the signal to a pure sine wave, considering frequency changes. It compares the mobility of the first derivative of the signal to that of the original signal. A higher value of complexity indicates more intricate signal structures and temporal variability, which can identify complex patterns of neural activity.

TABLE I

Derivation of parameters

Frequency		Time
Spectral moment	Parameter definition	Time operation
m_0	$m_0 = \text{activity} = \sigma_a^2$	$f(t)$
$m_1 = 0$	—	—
m_2	$(m_2/m_0)^{\frac{1}{2}} = \text{mobility} = \sigma_d/\sigma_a$	$\mathrm{d}(f)/\mathrm{d}t$
$m_3 = 0$	—	—
m_4	$\frac{(m_4/m_2)^{\frac{1}{2}}}{(m_2/m_0)^{\frac{1}{2}}} = \text{complexity} = \frac{\sigma_{dd}/\sigma_d}{\sigma_d/\sigma_a}$	$\frac{\mathrm{d}^2(f)}{\mathrm{d}t^2}$
$m_5 = 0$	—	—
$m_6, m_8, \ldots$	....	....

Table 6.1 Derivation of Hjorth parameters.
Adapted from (Hjorth & Elema-Schönander, 1970).

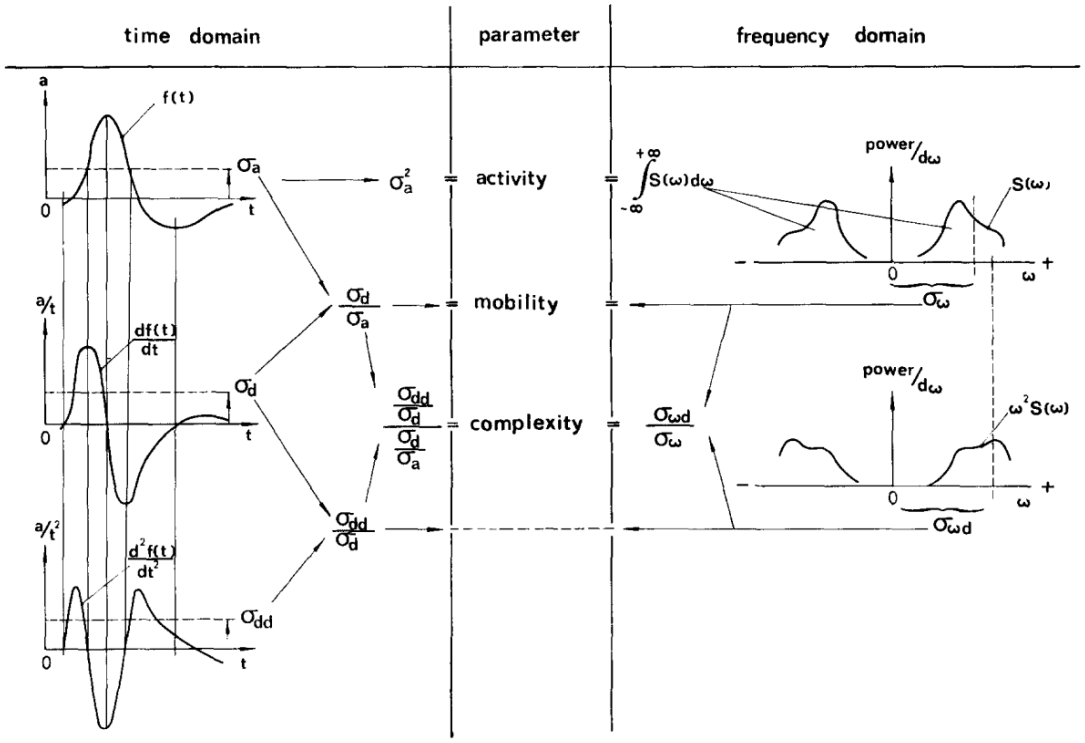


Figure 6.4 Parametric connections between time domain properties and spectral characteristics of an arbitrary signal.
Adapted from (Hjorth & Elema-Schönander, 1970).

In terms of statistical relevance, Hjorth parameters serve as a descriptive method to quantify aspects of the signal analysis. These parameters can be used for inference and hypothesis testing on these dynamics by employing statistical tests to assess the difference in the parameters between designed conditions.

To perform the analysis, we applied to parameters to signal in divisions (interval) with a selected moving window and 50% overlap. Choosing an appropriate window size was crucial: smaller windows captured local phenomena but introduced significant noise, while wider windows captured slower oscillations but also potentially smoothed out local details of interested. We tested sizes of 1, 5, 20 and 30 seconds, and while balancing these factors selected the 5 seconds window size that seemed to capture relevant temporal dynamics while minimizing noise interference.

6.3.1 Methods

For each recording we applied the three parameters to each interval of the recordings and then computed overall Mean, Max, and Coefficient of Variation (CV) of the parameters extracted. The CV quantifies the variability relative to the mean. To validate the relevance of Hjorth parameters and ensure they provided non-redundant information comparing to other established biomarkers, we performed correlation with beta bandpower. Another critical checkpoint to understand the relevance of potential biomarkers was its relation to the UPDRS. This correlation provided insights on the relation of the patterns to clinical symptom as well as indirectly to the effect of stimulation. That way, we could understand the novelty of the information provided, while also test its sensitivity to the neural activity in the designated frequency band. To compare how the Hjorth parameters behaved regarding the effect of stimulation, we applied Generalized Linear Mixed Models. Our goal was to accommodate the model for both fixed and random effects, important in complex data structures as these ones.

6.3.2 Results

We can clearly see that the relationship between activity and bandpower exhibits a consistent pattern across all the bands, differing in magnitude (Figure 6.5).; however, this relation is absent in the unfiltered signal. This leaves out a question of how filtering impacts / unravels the temporal dynamics – or other neural dynamics being captured by the Hjorth parameters. Another thing noticed is the insensitivity of mobility and complexity parameters to artefacts, seen when, for the same recordings, one compares their plots for the recording with artefacts and the recording without the artefact, and there is no alteration of the pattern. This could hint that mobility and complexity are candidates for providing a robust measure, which would be crucial in a system such as aDBS that often suffers from artefacts of several natures. Of note is the apparent difference and complementarity of the information Hjorth parameters have the potential to uncover when considering the dynamics of the neural activity.

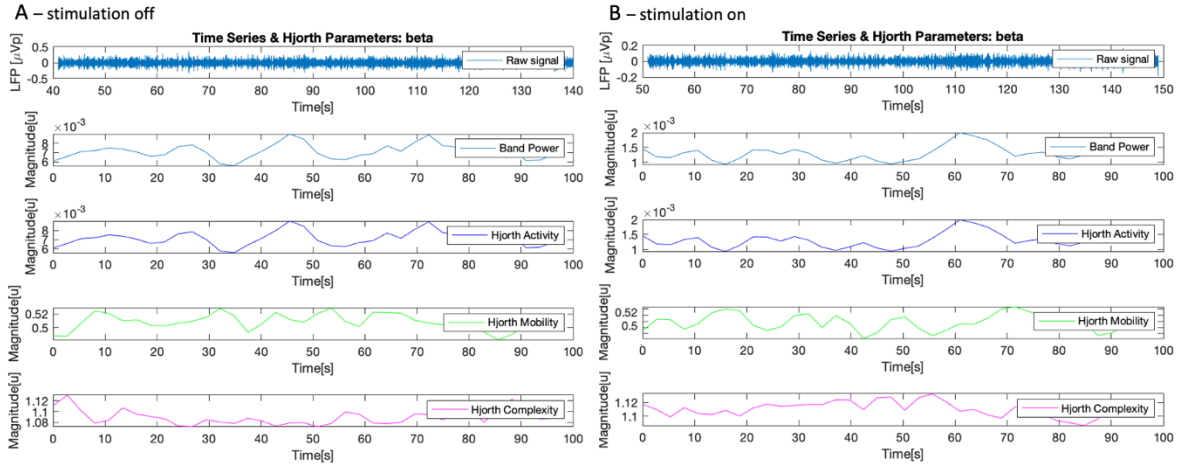


Figure 6.5 Hjorth parameters computed during recordings.
In this figure, we visualize, for two recordings (A without stimulation and B with stimulation), the plot of the Hjorth parameter computed over time (seconds) for the signal filtered in the beta band. In the top rows, we have the plot of the Raw signal, the second top row of the computed bandpower, and then, by order, the Hjorth parameter Activity, the Hjorth parameter Mobility and the Hjorth parameter Complexity.

Then, we correlated the features with the spectral power of the beta band (Figure 6.6). We selected the features with a $p < 0.05$ for the effect of stimulation and also correlated with the fold of UPDRS from between the states of no stimulation and the states of stimulation on of the protocol (Figure 6.7)., Besides the features related with the beta band in Figure 6.6, there was no substantial correlations.

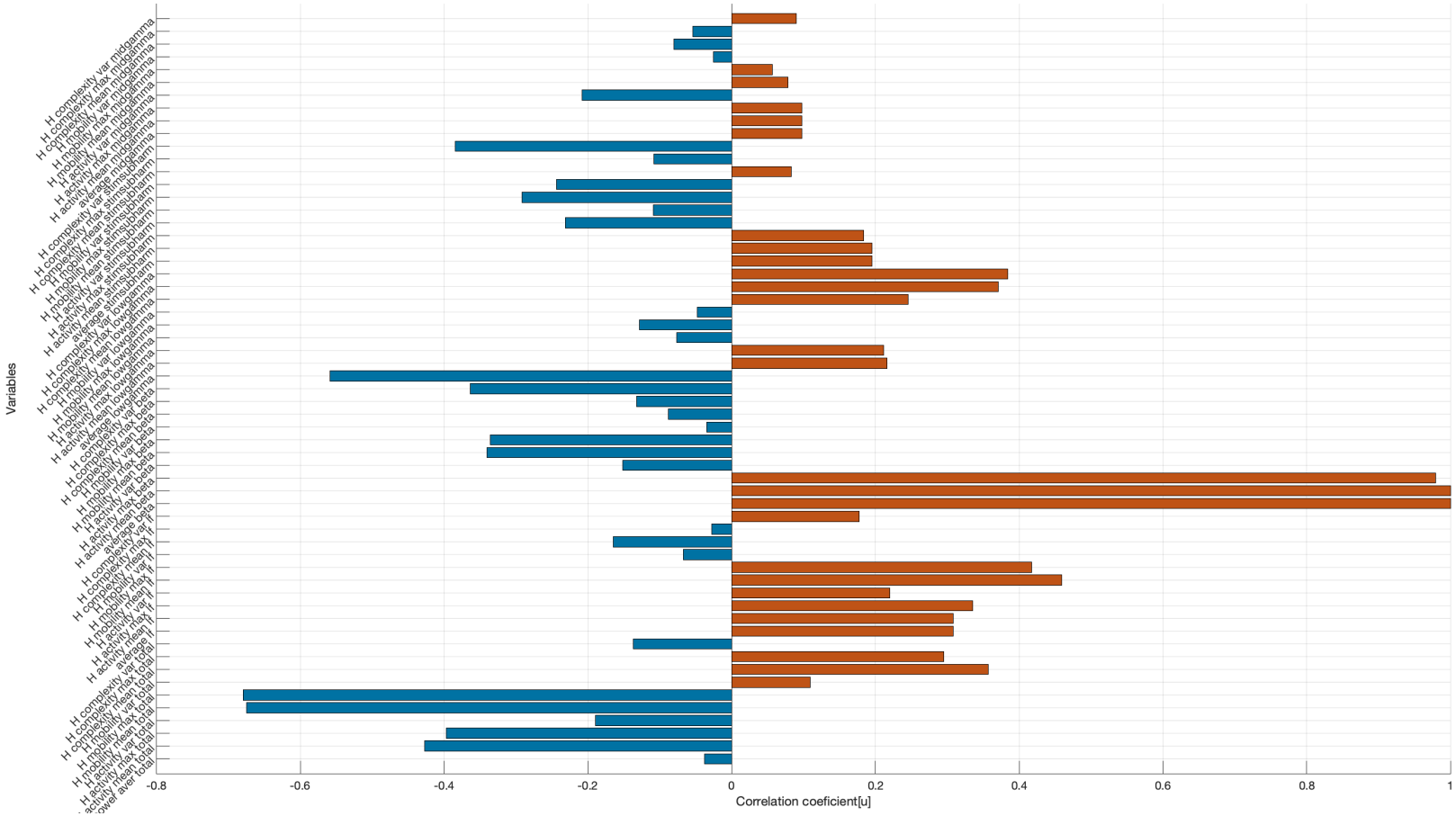


Figure 6.6 Correlation of variables with beta PSD.

In this figure we plot the correlation of all computed features with the beta bandpower. The correlation coefficients are in the x axis: in blue are represented the negative correlation coefficients, and in red the positive correlation coefficients.

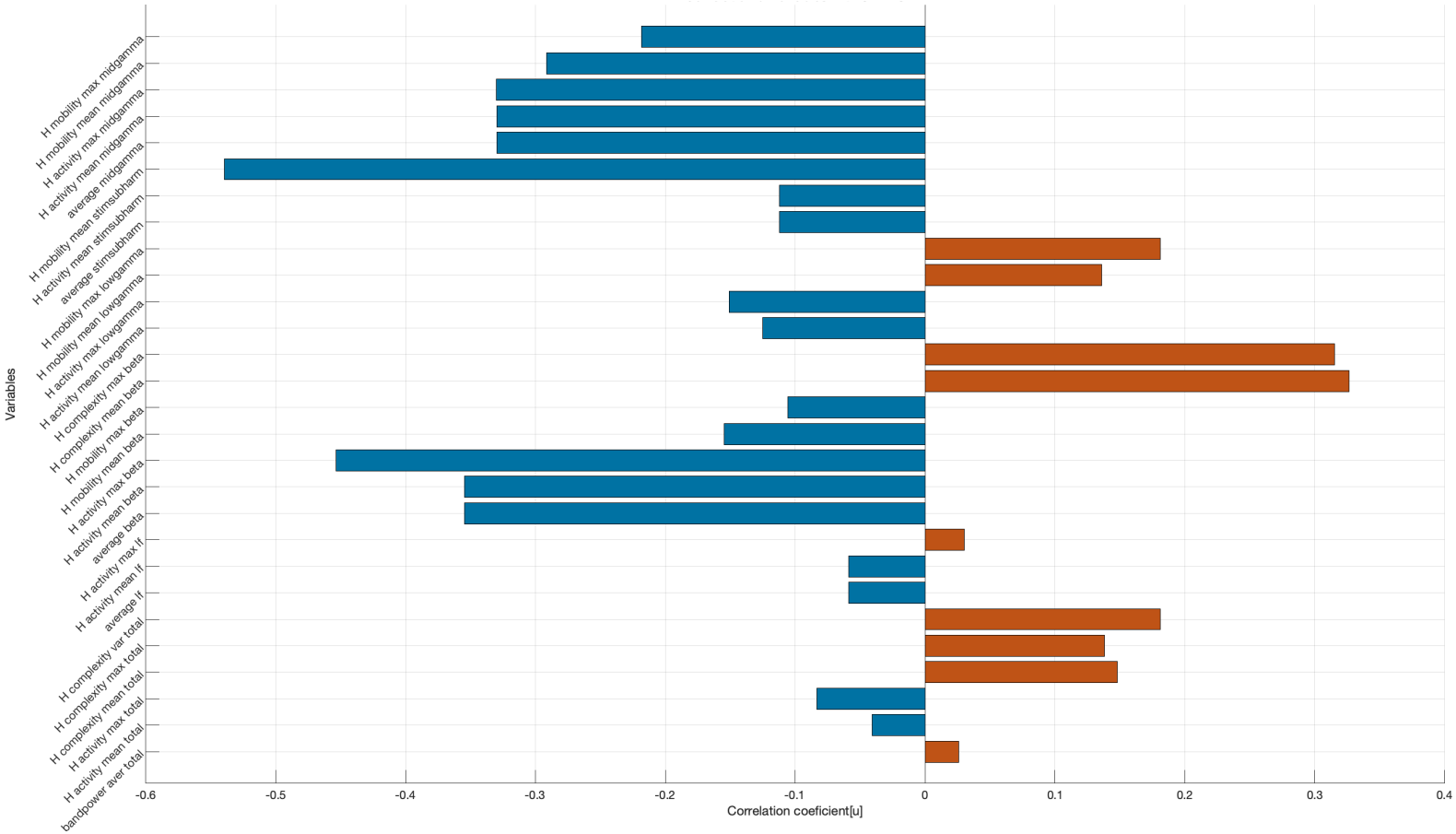


Figure 6.7 Correlation of Hjorth parameters with UPDRS fold.

In this figure we plot the correlation of all computed features with the UPDRS fold. The correlation coefficients are in the x axis: in blue are represented the negative correlation coefficients, and in red the positive correlation coefficients.

Alongside a statistical difference in the effect of stimulation, it was of interest to understand the directionality of this effect: Does the parameter increase or decrease with stimulation? (Figure 6.8) Hence, for each of the frequency bands we evaluated, we had the following results:

- For the unfiltered signal, we observed statistically significant effects in activity (variance) and complexity (signal content), with a trend towards higher values in both parameters.
- For the low frequencies, we found a significant decrease in activity, indicating lower variance compared to the unfiltered signal.
- In the beta band, there were significant decreases in activity (variance) and mobility (local dynamics), coupled with an increase in complexity (signal content).
- In the low gamma and stimulation subharmonic bands, there was a decreased activity and increased mobility.
- In the mid gamma band, there was a decrease in activity alongside an increase in mobility.

It is relevant to note that these patterns were consistent across the dataset, emphasizing the robustness of these frequency-specific effects on Hjorth parameters in characterizing neural signal dynamics.

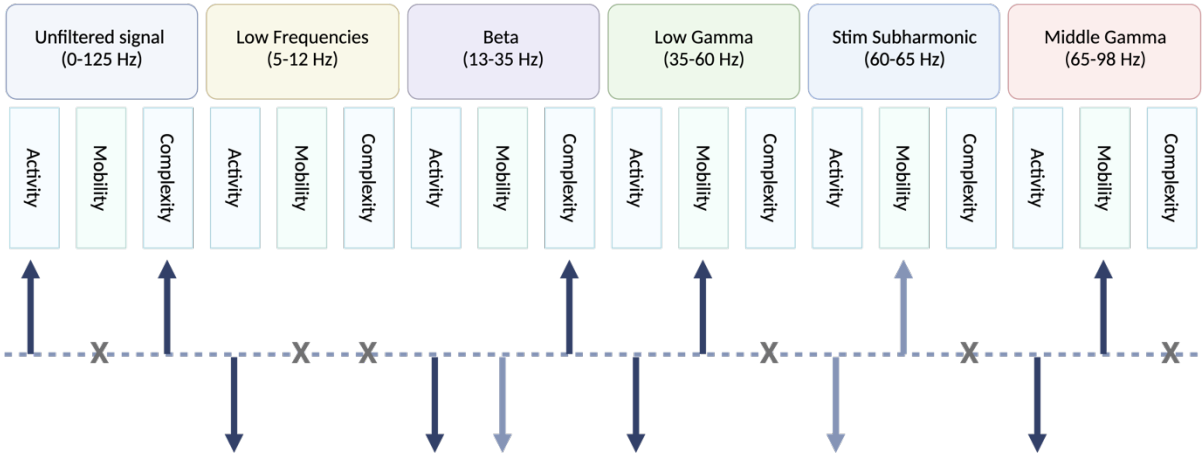


Figure 6.8 Response of Hjorth Parameter to stimulation.
This figure shows how the Hjorth parameters respond to stimulation (from OFF stimulation state to ON state). Upwards arrows mean an increase in the parameter value, and downward arrows. The X shape indicates no shift. The dark blue arrows mean a significant statistical evolution ($p<0.05$), while the light blue arrows mean a non-statistically significant evolution.

6.3.3 Discussion

In our analysis, we implemented a novel quantitative approach to study the dynamics of the neural signals: the application of Hjorth parameters- Activity, Mobility and Complexity. In our approach, to assess their potential as biomarkers, we focus on testing the effect of stimulation in such parameters, as well as their relationships to two established hallmarks in the literature: beta band power (as an electrophysiological signature) and the UPDRS (and the clinical information). In this analysis, we focus on short-term dynamics, as the parameters were calculated in divisions of the recordings and not the complete recording over time. A few insights we would like to propose considering each parameter:

- Activity: This parameter measures the power of the signal and is correlated with the beta bandpower. Its variation with stimulation reflects the overall activity level.
- Mobility: It captures the frequency-related changes in the signal, capturing its shift over time. It is a promising biomarker to understand how these neural dynamics change due to stimulation.
- Complexity: It assesses the complexity or irregularity of the signal waveform, reflecting transient modifications in the rhythmic patterns due to stimulation.

From our exploratory results, we see potential in these parameters, with some characteristics to highlight. First, it is apparent robustness to artefacts, particularly mobility and complexity. Moreover, mobility appears to eliminate trends present in the bandpower and activity, while complexity has the potential to reveal signal dynamics blind to the other parameters. While the computation of the parameters is hierarchical, each parameter has hints of impact on capturing different neural signal dynamics, working in complementarity.

In conclusion, this exploratory work consisted of the application of the Hjorth parameters, combined with statistical methods, to understand its potential to study neural dynamics in the DBS context. The parameters answer to the presence of stimulation and, therefore, hints that these temporal dynamics do so too. Further validation of these parameters is required, but there is potential to contribute to the advancing of the neural dynamics underlying neurological disorders.

6.4 Short-term and long-term temporal dynamics of the spectral profile of the LFP recordings

The advances in DBS are driven by progress in understanding brain disorders, innovations in hardware, such as neurostimulators and electrodes, and stimulation systems, such as closed-loop systems. These innovations promise to enhance DBS efficacy in the long term (Dayal et al., 2017; Goyal et al., 2021; Krauss et al., 2021). Consequently, DBS acts in the modulation of neural synchrony with an impact in clinical settings, which spans from preoperative planning and target confirmation to postoperative stimulation optimisation (W.-J. Neumann et al., 2023). However, and consequently derived from the previous discussions, the timing for clinical evolution and stimulation readjustment does not always reflect the primary needs of patients in their daily lives and its fluctuations (Zhang, Deng, Li, Albin, & Guan, 2020).

Moreover, the emergence and establishment of ML techniques applied to DBS (Maxime Peralta, Jannin, & Baxter, 2021) raises questions about how to select the features from the signal, even when focusing on the spectral profile, that are informative of the patient evolution, and to what extent can we understand them beyond the algorithm's "black box" (Peterson et al., 2022; Christoph Wiest et al., 2023). In this gap emerges the opportunity to further deepen our understanding of these spectral biomarkers and understand how their temporal variability in neural activity impacts clinical insights and treatment efficacy. For temporal variability in spectral profiles, we refer to the evolution of spectral power distribution over time, both within the same recording (short-term) and between follow-up moments (long-term) (Figure 6.9). This understanding is crucial for clinical evaluations and further understanding of the processes underlying specific increases in bandpower.

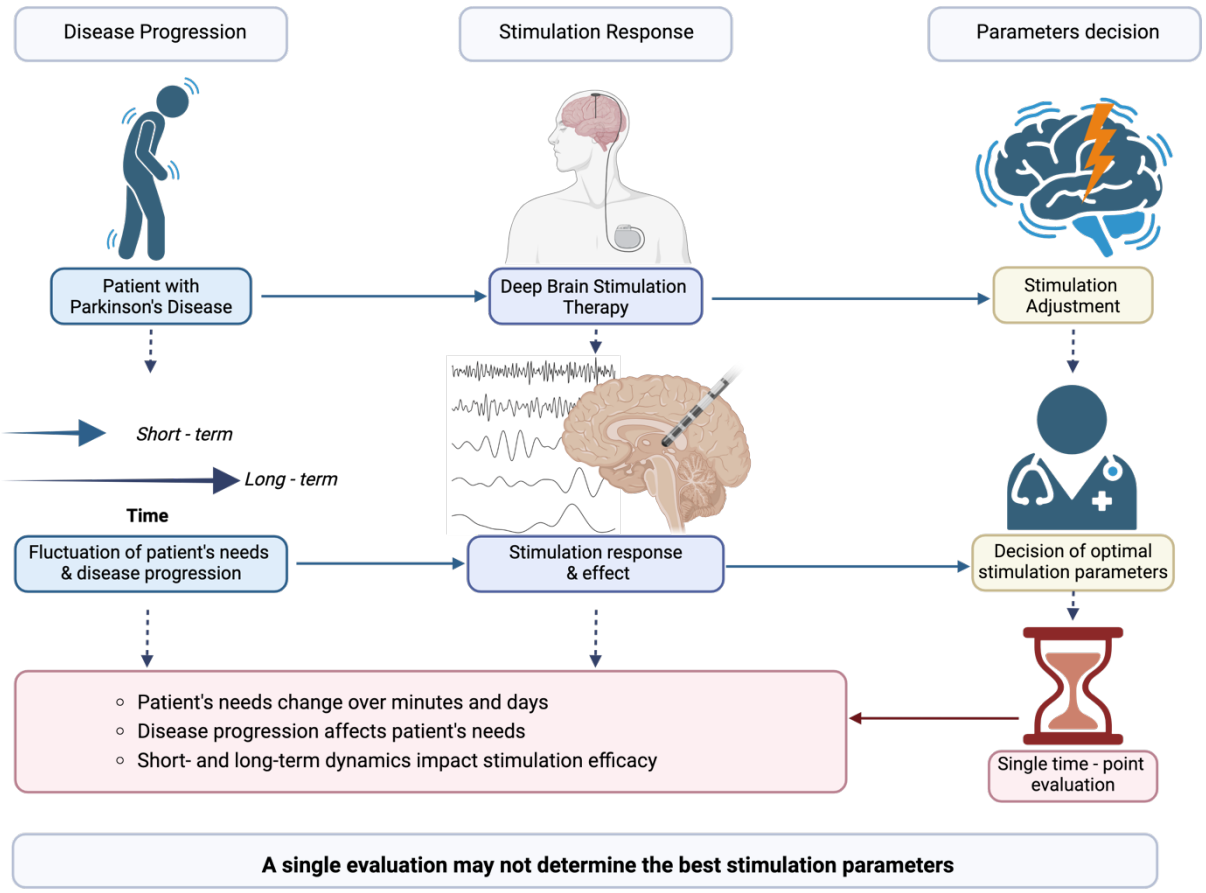


Figure 6.9 Graphical representation of the role of short and long-term dynamics in DBS clinical evaluation
In this figure, we see a graphical representation of the role and impact of short- and long-term dynamics in clinical evaluation. Our case study focuses on a patient with Parkinson's Disease (PD) undergoing Deep Brain Stimulation (DBS) therapy. This patient requires stimulation adjustments tailored to their specific needs. Currently, these adjustments are made in clinical settings, utilizing electrophysiological data, motor information (e.g., wearables), and clinical information (e.g., UPDRS). The clinician or healthcare practitioner makes an informed decision on the optimal parameters to minimize PD symptoms while avoiding adverse effects from stimulation. This evaluation is conducted at a specific clinical moment (single time-point evaluation). However, several temporal considerations are crucial: 1. The patient's needs evolve over different time frames, such as minutes and days. Therefore, an evaluation at a single moment might not provide the best stimulation parameters for the patient's overall needs; 2. Disease progression also modulates the patient's needs over time; 3. Both short- and long-term temporal dynamics affect the stimulation's efficacy and may influence the evolution of the patient's response to the therapy. These temporal dynamics impose limitations on choosing optimal parameters at a given time point.

6.4.1 Methods

For this work, the dataset consisted of recordings from 34 Parkinson's disease patients, conducted under medication-off conditions with neurostimulation either off or on at varying intensities (0mA, 1mA, and 2mA) while the patients were at rest. The follow-up evaluations were performed at postoperative appointments, at time points 3, 12, 18, 24, and 36 months. The number of times points for each patient varied. All patients were implanted with the neurostimulator Percept PC neurostimulator by Medtronic. The recordings were performed using the streaming method to acquire local field potentials with a sampling frequency of 250Hz.

If the temporal dynamics of the spectral profiles existed, the methods applied aimed at illustrating their impact from different perspectives considering their response to stimulation. To do so, we organized our analysis into four key points: 1) How can we describe the temporal dynamics? 2) How do the temporal dynamics change in the presence of stimulation? 3) How do the temporal dynamics evolve? 4) Do these dynamics correlate with UPDRS scores?

For the study of the metrics to be selected, we first applied the Welch method (pwelch) to the signal sliding windows, each with a 5-second width and 50% overlap. The sliding window size was determined by comparing visualizations of co-recordings from different hemispheres, selecting the shortest window that displayed simultaneous oscillations not attributable to noise.

Various metrics were tested, and we chose Shannon's entropy and standard deviation (STD) to proceed with the analysis due to their effectiveness in capturing variations in the spectra. First, metrics were applied to the complete recordings, and k-means clustering imposing two clusters was used to confirm the presence of distinct temporal populations. Then, the same clustering method was applied to the sliding window outputs per patient and recordings. The distribution of the metrics of all sliding windows and their response to stimulation was shown through histograms. Additionally, the correlation with UPDRS values in stimulation-off states was analysed and plotted.

6.4.2 Results

When visualizing a recording divided in intervals (Figure 6.10), we noticed that the profile varied depending on the time window from which it was computed—whether in shorter intervals or as a whole. This behaviour, in parallel with the previous analysis, triggered the focus to the temporal variability of the spectral profiles. Even within brief 2-minute recordings, there were noticeable differences in the profile's characteristics across the segments.

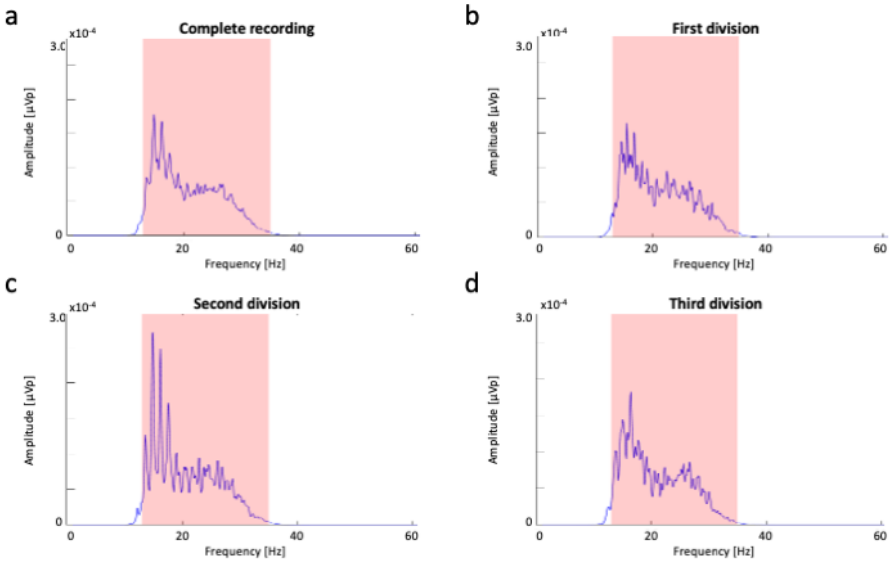


Figure 6.10 Differences in spectral profiles within recordings.
This figure shows the spectral profiles, computed by the application of pwelch, considering different divisions (with no overlap) of one recording: (a) shows the pwelch applied to the entire recording, (b) to the first division of the recording, (c) to the second division of the recording and (d) to the third division of the recording. The beta band (13-35Hz) is highlighted in all plots.

Given temporal dynamics, our approach to capturing them focused on two key metrics: standard deviation and Shannon's entropy. By incorporating these metrics, we gain the ability not only to intervene directly in the temporal domain but also to analyse the information transfer underlying this temporal evolution. Our selection process for these metrics was guided by the goal of encompassing a variety of distribution profiles, as illustrated in Figure 6.10. Furthermore, through empirical validation, as depicted in Figure 6.11, we have demonstrated the capability of these combined metrics to identify populations exhibiting particular combinations of dynamic traits.

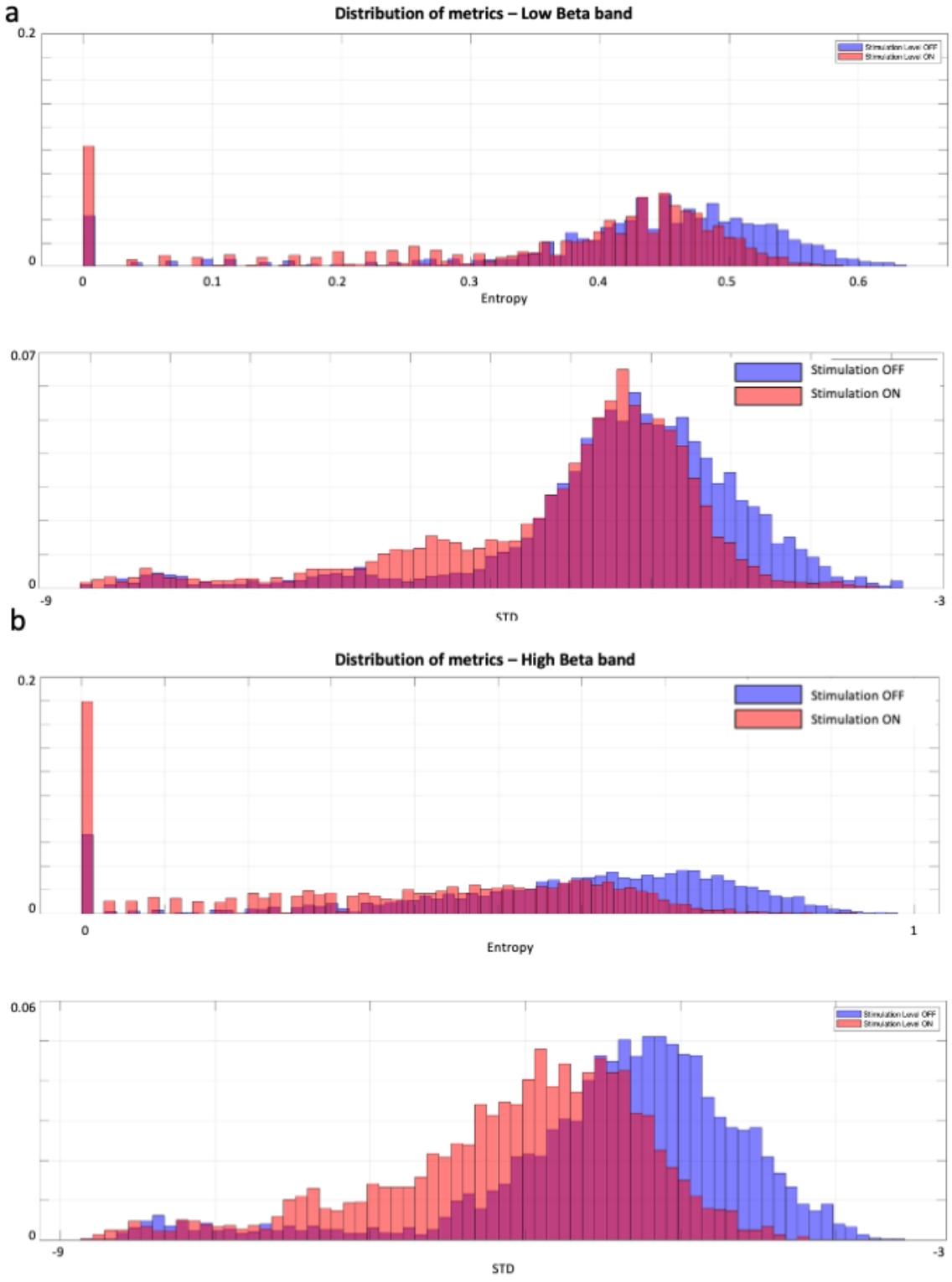


Figure 6.11 Distribution of the low and beta band metrics in stimulation off and on conditions.
This figure shows the distribution of the selected metrics, Shannon's Entropy and STD for the filtered band (a) low beta and (b) high beta. In the top row of (a), we see the distribution of Shannon's Entropy for stimulation states off and on, and in the bottom row, we see the STD for the same conditions. Similarly, for (b), on the top row, we see the distributions of Shannon's Entropy and the bottom row of STD for both stimulation conditions.

The histograms for the off-stimulation condition reveal that the high beta band has a flatter entropy distribution (Figure 6.11). Still, the values are generally higher compared to the low beta band. The STD distributions for both the high and low beta bands are similar. However, combining both bands into the total beta band increases the

STD. Entropy is higher when considering the total beta band. In contrast, the low-frequency bands exhibit shallow STD values. Analysis of histograms under stimulation reveals distinctive patterns across frequency bands (Figure 6.11). In the low frequencies, there is a decrease in STD, as well as an increase in entropy, indicative of a shift towards higher variability (the distribution shifts to the right). Conversely, in the high beta band, there is a decrease in STD and a distribution towards lower entropy levels. For the low beta band, while there is a decrease in STD, it is not as pronounced as in the high beta band, and entropy experiences a decline. Interestingly, when considering the total beta band, the STD reduces by half, resulting in a flattening entropy distribution towards lower levels.

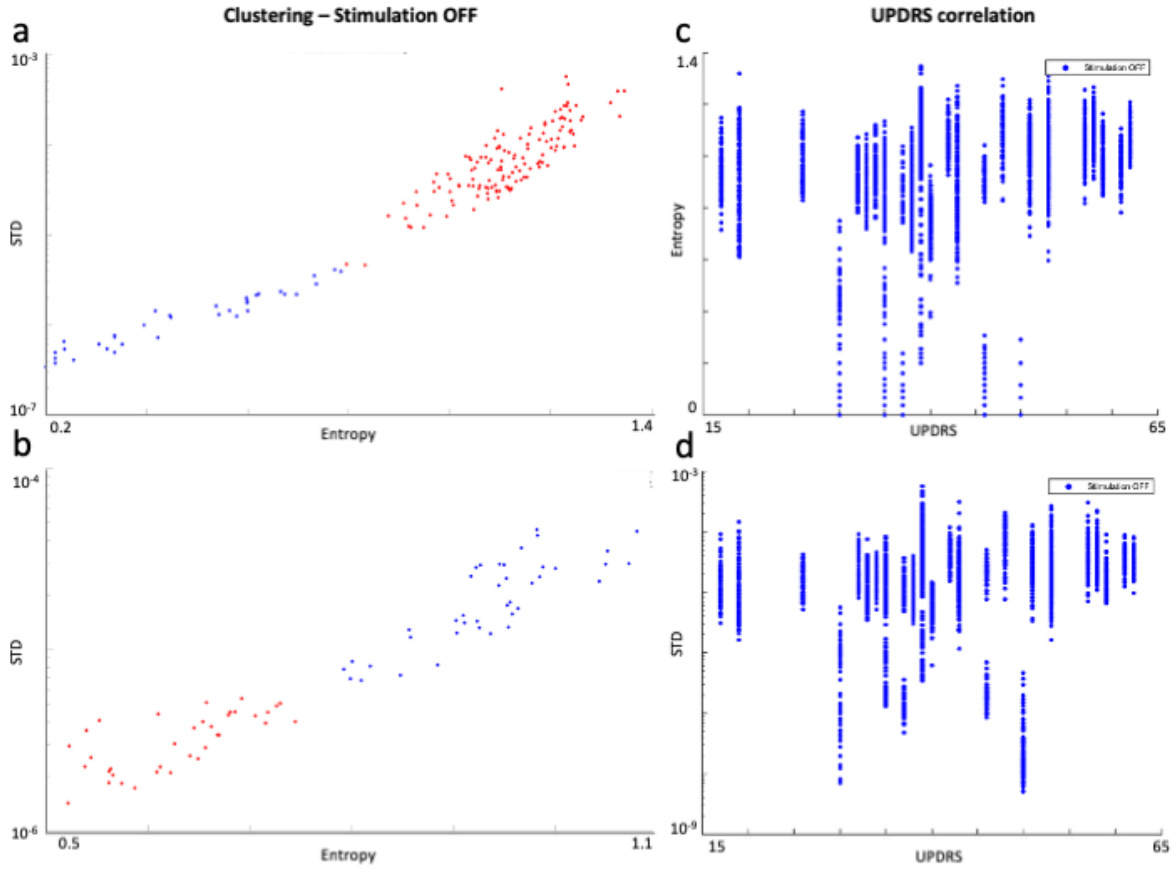


Figure 6.12 Temporal populations and correlation to clinical information.
In this figure, we present two main insights: (a) and (b) showcase examples of temporal population clusters (utilising k-means imposing two clusters) applied to individual recordings from different patients. At the same time (c) and (d) depicts the relationship between the metrics and the Unified Parkinson's Disease Rating Scale (UPDRS) for all patients. Panel (a) illustrates an instance where the division between clusters is less distinct, while in (b), the clusters exhibit an apparent differentiation. Moving to (c), it becomes evident that intermediate UPDRS values correlate with a broader entropy distribution, indicating more significant temporal variability. In (d), the distribution of standard deviation (STD) is less heterogeneous across UPDRS scores.

In examining clusters at varying degrees of separation (Figure 6.12 (a) (b)), the recordings show two distinct clusters. However, when the separation is less pronounced, the dynamics distribution reveals a spectrum of populations where the extremes distinctly represent two separate temporal behaviours. The transitional region exhibits characteristics corresponding to neither end, suggesting a nuanced shift or potentially representing a different set of evolving dynamic states. No direct correlation with UPDRS values off stimulation is apparent (Figure 6.12 (c) (d)).

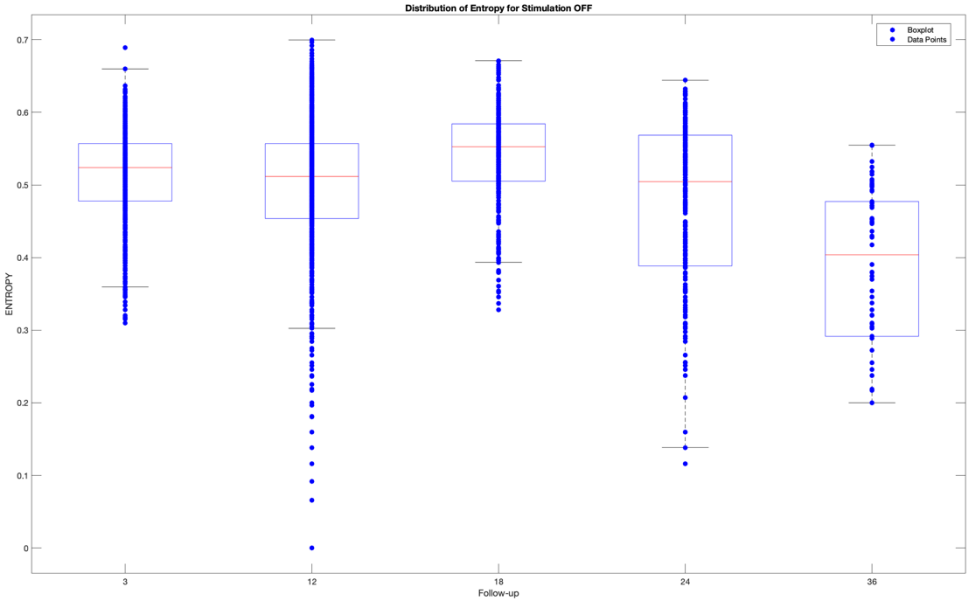


Figure 6.13 Comparison of Entropy over follow up points.
This figure shows the distribution of Entropy for all patients, in stimulation OFF, over the follow-up times. Although there is a tendency from the 18 months forward to decreasing values, this is not statistically significative.

Considering the distribution of metrics over follow-up times, there was not a visible trend for all patients. However, upon closer examination on a per-patient basis, these distributions appear to present a variable progression, suggesting that the metrics are not inherently stable over time for individual patients (Figure 6.13). This variability underscores the dynamic nature of the metrics within the context of each patient's unique physiological and treatment response profile.

6.4.3 Discussion

The central question of this study revolves around the dynamic nature of spectral profiles in the context of aDBS developments. Currently, the traditional DBS approach risks overlooking the temporal fluctuations in patients' states. One strategy to address this issue is to conduct multi-time point evaluations for the stimulation titration, providing for a more comprehensive understanding of spectral profiles in correlation with symptoms by including a temporal dimension in the assessment. However, pragmatically, the clinics routines do not have the capacity to accommodate such practices. However, in the realm of aDBS, this operational interval is a concept already in discussion, and of high importance (van Wijk, Bie, & Beudel, 2023). It shouldn't be too short, risking missing crucial temporal variations in spectral profiles and the evolving power of monitored bands. Similarly, it shouldn't be too long, potentially overlooking critical change intervals. Finding this balance ensures that aDBS systems effectively capture the dynamic nature of neural activity and optimise therapeutic outcomes.

Our results reinforce the assumption that temporal dynamics of the spectral profile exist and can be captured from different perspectives. Moreover, these dynamics answer to stimulation, which is crucial for understanding the effects of DB. Considering the histograms under off-stimulation conditions, there are distinct behaviours of both metrics for each division of the beta band. This underscores the importance of exploring the combined effect of studying the total beta band alongside the division high and low beta bands separately. Moreover, we show in our results that temporal and informational features decrease in magnitude with stimulation, suggesting that stimulation may act as a temporal stabiliser and noise reducer of underlying processes, particularly the high beta band.

Through cluster analysis, we identified varying degrees of separation as in a spectrum that reveals two clear populations. However, in the cases of less distinct separation, the distribution is sparse, and the poles of the distribution correspond to the same as in the well-defined cases, revealing a spectrum of temporal behaviour between two mains. This highlights the diverse temporal behaviours captured within recordings. We then have two evident populations, mainly characterized by with low and high metrics values, and a transition establishing a dynamic distribution of the recordings evolving from one end to the other. Shannon's entropy enriched the analysis as the dynamics affect information flow, which is crucial in clinical terms, and conversely, how temporal evolution relates to information transfer. The fact that it is also affected by stimulation suggests its effect on information transfer and noise interference.

Regarding box plots over time, while no discernible trend for all patients is observed, it does not necessarily imply stability. Temporal profiles vary between follow-ups for individual patients, suggesting that temporal dynamics are indeed unstable over time. This aligns with the current literature towards personalised biomarkers and patient profiles. Adding the correlation with UPDRS values to the discussion as a clinical proxy, no direct correlation is observed in the off-stimulation. However, interestingly, the intermediate to higher UPDRS values exhibit a sparser distribution of metric values for both. This suggests heterogeneity among patients with less extreme UPDRS scores. Indeed, the population in the study is considerably distributed regarding UPDRS. But, more significant for the discussion is that the absolute scoring of UPDRS is not necessarily generalised for the constellation of the patient's symptoms, as patients with similar scoring have different distributions of symptoms. In line with this, published works show that neuronal oscillations do not only predict DBS outcomes but are informative about motor symptom mechanisms (Jan Hirschmann, Steina, Vesper, & Florin, 2022; Mathiopoulou et al., 2024; Reakkamnuan, Kumarnsit, & Cheaha, 2023). Future work aims to provide a more accurate description of the population clustered in symptom types to understand if their temporal profiles can be distinguishable between them, scoring the need to explore electrophysiological profiles' correlation with symptoms further.

6.5 Conclusion

The findings in this chapter underscore the non-stationarity nature of spectral profiles, highlighting their potential to help improve aDBS in a personalized approach. A deeper understanding of the beta band's dynamics is crucial in the framework of its division in low and high for fine-tuning treatments. However, our study presents two main limitations. We converged to two metrics to determine how to describe these temporal dynamics, but more approaches could capture different perspectives of these same dynamics. Furthermore, it is essential to clarify how the temporal domain of the spectral profile evolves with and is related to motor symptoms.

Chapter 7: Final Remarks and Conclusions

One is left to think how after a period such as this PhD project there are more questions left than the ones answered. Indeed, that is part of the scientific progress, alongside answering questions- raising them. This work is no exception. A key characteristic of this work is its multifaceted nature. Science occurs at different streams, all feeding the same river: development of tools, synthesis of information, analysis, project management, science communication and many others. This project spans several facets with a common goal, to contribute to the field of aDBS. So let us walk through these contributions and which questions we left to answer.

7.1 What about the concept of biomarkers?

One central concept of the discussion from the beginning to its end is the concept of biomarkers. Currently centred in spectral bands (but slowly moving away from this), the key is to identify and validate biomarkers with high specificity and sensitivity. Having neurostimulators with enhanced sensing capabilities that allow for different sensing features allows us to do so. Moreover, discussing the concept of defining a biomarker is, in a sense, related to discussing the pathophysiology of the disease and of the stimulation effect – still unknown. LFP signals are a two-way street: on the one hand, they provide us with in-loco insights into what is occurring in the focus of therapy, but on the other hand, it is a noisy and complex signal. Moreover, a key challenge in such signals is the presence of several artefacts: movement, ECG, and unknown even. Hence, this endeavour of biomarker establishment is anything but complex. The way forward is to break down its complexity and move from correlation towards causality. The most established biomarkers are based on the correlation of the presence of motor symptoms with hyperactivity in this frequency band. With newer technologies, such as Machine Learning methods and combined sensing of motor and electrophysiology, the field can move towards establishing its causality. Moreover, representation outside the frequency bands should be explored as a feature that has the potential to build on the concept of biomarkers.

In each step of our work, we gravitate around the concept of biomarkers. First, by synthesising the current literature on how Machine Learning is contributing to it. Then, a research protocol that builds a database that allows researchers to pursue such a quest was implemented, and a computational toolbox with the tools to facilitate such research questions released. And later, on a disruptive approach by exploring the non-stationarity of the spectral profile as complementary information to the already established knowledge of beta band as a biomarker.

7.2 Personalized medicine and patient variability

With the increase of LFP data from patients, an emerging insight is that there is variability in disease and symptom presentation across patients. This is motivating the attention towards the design of personalised therapies such as aDBS and, in this, the concept that perhaps biomarkers should be individually tailored. Indeed, the goal of aDBS is to move to an automated system that requires a training stage in which each patient undergoes an initial calibration for aDBS therapy, such as the tuning of parameters. This automated system also needs to be adaptable to the fluctuations of patients' actions and behaviours, and it needs to identify which variations represent a need for change in stimulation and which are physiological or to be disregard by the system. For these computational and system needs, ML techniques can be a powerful tool to discriminate patterns specific to patients, complementary to clinical expertise, which is always an irreplaceable component for the safety of patients. In Figure 7.1, Neumann raises an interesting concept of aDBS compatibility assessment, where there is a stage for the assessment of the feasibility of aDBS. This is crucial in clinical tools; that is, regardless of how powerful an analytic result is, how does the implementation in clinics proceed? But assuming the feasibility, we then enter the realm of DBS tunning with the control policy selection, the parameter space adjustment and the aDBS system that, to close the loop, feed back into the biomarker assessment and tuning to keep adjusting the parameterisation. All this pipeline is nested in the clinical practice and workflow. And a clear understanding of these technologies is not currently integrated in the clinical training, traditionally done in the computational and technological fields. A note

then on the continuous need for establishing cooperation between clinical and computational fields, as well as multi-sector training.

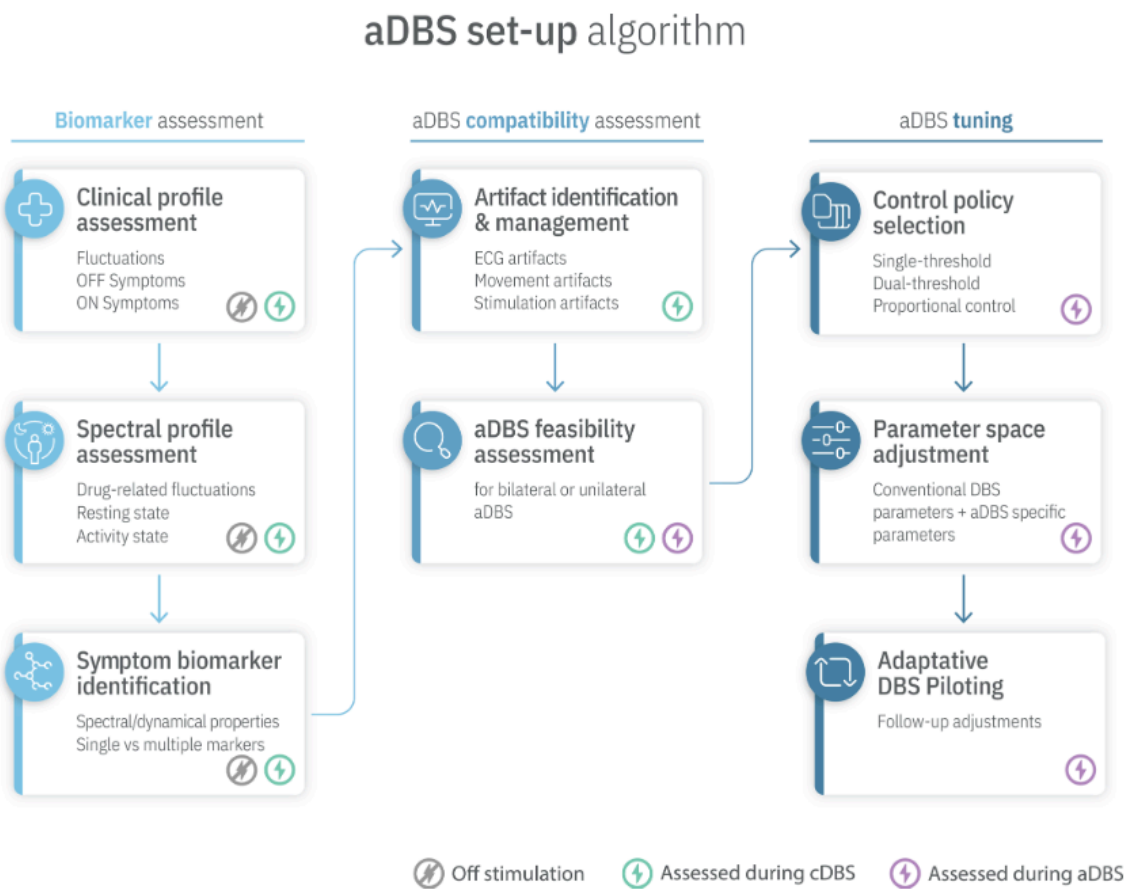


Figure 7.1 Practical approach to set up adaptive deep brain stimulation (DBS).
The implementation of adaptive deep brain stimulation (aDBS) for a given patient requires a stepwise procedure. This involves the assessment of the individual clinical and spectral characteristics for the identification of symptom-specific biomarkers. In principle and depending on the target biomarker, this assessment can be informative if conducted during different clinical conditions as well as OFF and ON continuous stimulation. Special consideration should be given to signal artifacts that could potentially inter-fere with a control system. Overall, the question should be answered whether aDBS is feasible to be applied unilaterally and/or bilaterally. There are different control policies that can be selected (also see Figs. 1 and 2) and the clinical and electrophysiological response during continuous DBS may inform the fine tuning of aDBS-specific stimulation parameter boundaries. As with conventional DBS, aDBS parameters need to be reassessed and tuned over time. Adapted from (W.-J. Neumann et al., 2023).

There is an emergence of richer and more complete datasets of LFPs in the context of PD and other diseases. Their computational needs ask for a high quantity/high quality data, which is often difficult to do single-centred. This problem can be answered by building open and curated databases, fostering collaboration and synergies for the community. These databases need to be consensual and standardized, which requires metrics to evaluate and maintain such structures.

7.3 Hardware versus software efforts

Systems such as the ones expected of aDBS will have needs concerning hardware and software. The hardware has, from the start, such delicate characteristics as it is implanted in patients, and hence, features such as weight, size and heat signature must be highly optimised. Expensive and complex computational methods, brought under the spectral analysis of the signal alone or combined approaches with machine learning, must be balanced with this hardware features. In answering to this, rechargeable batteries that already exist are a partial solution that allow

for increased computational power without the cost of life span of the neurostimulator, but still disregards heat and energy consumption signatures.

The multifactorial community engaging in the field, with different background brings to the table methods that become complementary. As seen in this work, there has been an effort for the publication of toolbox and platforms that make the computational analysis of this complex signals available to the entire community. These tools, as the DBScope, can be a starting point for researchers and clinicians to contribute to the research efforts.

7.4 Data-driven explorations in the field

Simultaneously, for an aDBS system, we are in an era of data-driven parameterisation. In clinics, testing the stimulation values while sensing the LFPs and additional data allows us to describe and characterize the response to stimulation and feed the shift from correlation to causation. All these efforts then culminate in ensuring that, be it at a time point or in a continuous system, the decision of alteration is based on data-driven validated conclusions.

Exploratory works such as the one we developed with the application of the Hjorth parameters and selected metrics showed potential to study neural dynamics in the DBS context. As any new implementation of methods in the field, further validation of these parameters is required, but there is potential to contribute to the advancing of the neural dynamics underlying clinical disorders. In our work, particularly, our research highlights the dynamic nature of spectral profiles in DBS and aDBS, emphasising the temporal variability of spectral characteristics. We reveal temporal fluctuations through Shannon's Entropy and STD analyses, suggesting personalised treatment potential. While limitations exist, our findings underscore the importance of understanding these dynamics in tailoring interventions for neurological disorders like Parkinson's. Acknowledging and leveraging them pave the way for more effective and individualised treatment strategies, ultimately enhancing patient care. By acknowledging the temporal evolution of spectral profiles, we can expand the scope of potential biomarkers. This perspective opens new avenues for investigating disease progression and the efficacy of therapeutic interventions.

7.5 Future Steps

It is with excitement that we arrive at this part. To achieve aDBS, we need to understand the causal mechanisms of DBS and deconstruct the pathophysiology of PD, all while promoting hardware and software developments. But progress is made in smaller steps, and what follows are the ones I consider should be the next to be taken – some more particular to aDBS, some in a zoomed-out view that indirectly impacts aDBS.

Temporal features

As we have seen in our work, there is an untackled potential in the temporal domain of the signal. In our work, we focused on the spectral temporality of the signal and took only the first steps. We have seen that there is information to be extracted from this approach to the analysis, but a lot more needs to be done. Our main challenge was to define a metric to characterize the temporal variability. Once certain metrics show variability, as we have seen, one can dive into the characterization of the signal over time between patients, stimulation states and movement states. This will provide additional information on which steps to take next in order to understand the impact of these temporal dynamics in the context of PD.

Effect of stimulation

We designed our protocol to study the effect of stimulation in the LFP while simultaneously studying the motor symptoms. However, due to the constraints of having a balance between a comprehensive but tolerable protocol, the characterization of the effect of each type of movement is limited to the interval post-stimulation of 45 seg-1min. More prolonged effects are not evaluated. More focused protocols to characterize specific movement types, for example, one protocol dedicated fully to rigidity would contribute to the overarching literature on movement disorders and towards aDBS.

Moreover, a key topic of interest regarding the stimulation effect is how the electrophysiological signal answers to the variation in stimulation. Similarly to the quest to characterize temporal dynamics, it would be interesting to move the analysis of stimulation answer away from the spectral domain and compare how other features of the signal answer to stimulation. However, the spectral domain should still be considered. One remark so far on our protocol was that the spectral answer to stimulation often was uncorrelated with the clinical variation of the symptoms. Hence, there is this knowledge gap in the relation of spectral behaviour and translation to symptoms that is not described or understood. It would be interesting to isolate these particular moments of recording, where the response of the LFPs and clinical scoring are not correlated, compare it with the recordings where this correlation exists and focus in understanding the root of this difference.

Longer rhythms of the disease

With the option to record out-of-clinic signals, we can study longer rhythms, such as the circadian rhythm. This is of particular interest to build predictive models of the stimulation needs without needing to access continuous signals. As these databases are still being built, in particular after the Percept RC was implemented (with Percept PC that had a no rechargeable battery there was a concern with battery longevity that is not in place with the new rechargeable devices) the community can now characterize long-term rhytms (longer than in-clinic identifiable patterns) in correlation with clinical information (such as medication and specific symptoms exacerbation).

Indirect impact on aDBS

So far, we've discussed direct matters in the field of aDBS. But as we know, science is not built in silos, and our knowledge will only be limited by not zooming out and looking at the bigger picture. Here, I would like to make a few remarks. First, it is essential to note that we were focused on movement symptoms for the bulk of this work. However, PD also has cognitive symptoms that progressively become more predominant for future research, and to fully achieve an optimal aDBS system, the cognitive aspects of PD must be incorporated into the models. Another clinical aspect of PD often overlooked but that is emerging is the impact of microbiome on the incidence and progression of PD. This opens the question to, as in this axis of brain-GI track, which other impacts beyond the brain can DBS have? Can we consider that the brain area limits the broad macro scale of effects, or should we look into other effects and causal chains? In my opinion, we should, but it does not substitute the need to understand the more local effects better. And lastly, something that indirectly affects all fields research is the publishing bias towards positive results. In this quest towards biomarkers particularly it is a damaging situation, as publishing negative results can lead to optimising the time and effort of peers working in the same questions, ultimately making the community more effective. More and more, this is being discussed, and it is always an important remark to remember.

7.6 Last words

To progress towards aDBS, a multifactored system should be conceptualized from the start. There are many challenges in the field: hardware constraints, software needs, data requirements, and the development of personalized models with clinical validation. But despite the challenges, promising steps have been taken. These steps translate into improvements in patients' quality of life that encourage the industry, the academy, and several other actors to continue investing in aDBS.

In this multifaceted work, we were able to contribute from different angles and strategies:

- Synthesizing information;
- Implementing sustainable research protocols that continue after this work is completed and foster advances and new protocols by themselves;
- Providing open-access tools for the broader community of researchers and clinicians;
- Offering insights on the conceptualization of spectral biomarkers.

All in all, we hope that our contributions pave the way for researchers to achieve the shared goals of an optimized and comprehensive aDBS system.

References

Abosch, A., Lanctin, D., Onaran, I., Eberly, L., Spaniol, M., & Ince, N. F. (2012). Long-term recordings of local field potentials from implanted deep brain stimulation electrodes. *Neurosurgery*, *71*(4), 804–814. https://doi.org/10.1227/NEU.0b013e3182676b91

Accolla, E. A., Herrojo Ruiz, M., Horn, A., Schneider, G. H., Schmitz-Hübsch, T., Draganski, B., & Kühn, A. A. (2016). Brain networks modulated by subthalamic nucleus deep brain stimulation. *Brain*, *139*(9), 2503–2515. https://doi.org/10.1093/brain/aww182

Akbar, U., Raike, R. S., Hack, N., Hess, C. W., Skinner, J., Martinez-Ramirez, D., … Okun, M. S. (2016). Randomized, Blinded Pilot Testing of Nonconventional Stimulation Patterns and Shapes in Parkinson's Disease and Essential Tremor: Evidence for Further Evaluating Narrow and Biphasic Pulses. *Neuromodulation: Technology at the Neural Interface*, *19*(4), 343–356. https://doi.org/10.1111/ner.12397

Al-ani, T., Cazettes, F., Palfi, S., & Lefaucheur, J. P. (2011). Automatic removal of high-amplitude stimulus artefact from neuronal signal recorded in the subthalamic nucleus. *Journal of Neuroscience Methods*, *198*(1), 135–146. https://doi.org/10.1016/j.jneumeth.2011.03.022

Alberio, T., Lopiano, L., & Fasano, M. (2012). Cellular models to investigate biochemical pathways in Parkinson's disease. *FEBS Journal*, *279*(7), 1146–1155. https://doi.org/10.1111/j.1742-4658.2012.08516.x

Albin, R., Young, A., & Penney, J. (1989). The functional anatomy of basal ganglia disorders. *Trends Neurosci.*, (12), 366–375.

Alegre, M., López-Azcárate, J., Alonso-Frech, F., Rodríguez-Oroz, M. C., Valencia, M., Guridi, J., … Obeso, J. A. (2012). Subthalamic activity during diphasic dyskinesias in Parkinson's disease. *Movement Disorders*. https://doi.org/10.1002/mds.25090

Alexander, G. E., & Crutcher, M. D. (1990). Functional architecture of basal ganglia circuits: neural substrates of parallel processing. *Trends in Neurosciences*, *13*(7), 266–271. https://doi.org/10.1016/0166-2236(90)90107-L

Alonso-Frech, F., Zamarbide, I., Alegre, M., Rodríguez-Oroz, M. C., Guridi, J., Manrique, M., … Obeso, J. A. (2006). Slow oscillatory activity and levodopa-induced dyskinesias in Parkinson's disease. *Brain*, *129*(7), 1748–1757. https://doi.org/10.1093/brain/awl103

Anderson, R., Kehnemouyi, Y., Neuville, R., Wilkins, K., Anidi, C., Petrucci, M., … Brontë-Stewart, H. (2020). A novel method for calculating beta band burst durations in Parkinson's disease using a physiological baseline. *Journal of Neuroscience Methods*, *343*(109911). https://doi.org/0.1016/j.jneumeth.2020.108811

Angeles, P., Tai, Y., Pavese, N., Wilson, S., & Vaidyanathan, R. (2017). Automated assessment of symptom severity changes during deep brain stimulation (DBS) therapy for Parkinson's disease. *IEEE International Conference on Rehabilitation Robotics*, 1512–1517. https://doi.org/10.1109/ICORR.2017.8009462

Arlotti, M., Marceglia, S., Foffani, G., Volkmann, J., Lozano, A. M., Moro, E., … Priori, A. (2018). Eight-hours adaptive deep brain stimulation in patients with Parkinson disease. *Neurology*, *90*(11), e971–e976. https://doi.org/10.1212/WNL.0000000000005121

Arrais, A., Vieira, R., Dias, D., Soares, C., Massano, J., & Silva Cunha, J. (2024). A Wearable Quantified Approach to Parkinson's Disease Gait Motor Symptoms. *IEEE 22nd Mediterranean Electrotechnical Conference (MELECON), Porto, Portugal*, 791–796. https://doi.org/10.1109/MELECON56669.2024.10608760

Averna, A., Debove, I., Nowacki, A., Peterman, K., Duchet, B., Sousa, M., … Tinkhauser, G. (2023). Spectral Topography of the Subthalamic Nucleus to Inform Next-Generation Deep Brain Stimulation. *Movement Disorders*, *38*(5), 818–830. https://doi.org/10.1002/mds.29381

Aygun, D., Dere, U., Yildiz, O., Temel, Y., & Kocabicak, E. (2019). Characterizing the Intraoperative Microelectrode Recording-Induced Microlesion Effect on Motor Symptoms in Patients with Parkinson's Disease Undergoing Deep Brain Stimulation of the Subthalamic Nucleus. *Turk Neurosurg*, *29*(3), 430–433. https://doi.org/10.5137/1019-5149.JTN.24348-18.3

Baizabal-Carvallo, J. F., & Alonso-Juarez, M. (2016). Low-frequency deep brain stimulation for movement disorders. *Parkinsonism and Related Disorders*, *31*, 14–22. https://doi.org/10.1016/j.parkreldis.2016.07.018

Baker, K. B., Zhang, J., & Vitek, J. L. (2011). Pallidal stimulation: Effect of pattern and rate on bradykinesia in the non-human primate model of Parkinson's disease. *Experimental Neurology*, *231*(2), 309–313. https://doi.org/10.1016/j.expneurol.2011.06.012

Baniasadi, M., Proverbio, D., Gonçalves, J., Hertel, F., & Husch, A. (2020). FastField: An open-source toolbox for efficient approximation of deep brain stimulation electric fields. *NeuroImage*, *223*(September), 2–11. https://doi.org/10.1016/j.neuroimage.2020.117330

Basu, I., Graupe, D., Tuninetti, D., Shukla, P., Slavin, K. V, L, M., & Corcos, D. (2013). Pathological tremor prediction

using surface electromyogram and acceleration: potential use in 'ON–OFF' demand driven deep brain stimulator design. *J Neural Eng.*, *10*(3), 036019.

Baumann, C. R., Imbach, L. L., Baumann-Vogel, H., Uhl, M., Sarnthein, J., & Sürücü, O. (2012). Interleaving deep brain stimulation for a patient with both Parkinson's disease and essential tremor. *Movement Disorders*, *27*(13), 1700–1701. https://doi.org/10.1002/mds.25221

Belasen, A., Rizvi, K., Gee, L. E., Yeung, P., Prusik, J., Ramirez-Zamora, A., … Pilitsis, J. G. (2017). Effect of low-frequency deep brain stimulation on sensory thresholds in Parkinson's disease. *Journal of Neurosurgery*, *126*(2), 397–403. https://doi.org/10.3171/2016.2.JNS152231

Belova, E., Semenova, U., Gamaleya, A., Tomskiy, A., & Sedov, A. (2023). Excessive α-β Oscillations Mark Enlarged Motor Sign Severity and Parkinson's Disease Duration. *Mov Disord.* https://doi.org/10.1002/mds.29393

Benabid, A. L., Chabardes, S., Torres, N., Piallat, B., Krack, P., Fraix, V., & Pollak, P. (2009). *Functional neurosurgery for movement disorders: a historical perspective*. *Progress in Brain Research* (Vol. 175). Elsevier. https://doi.org/10.1016/S0079-6123(09)17525-8

Binder, T., Lange, F., Pozzi, N., Musacchio, T., Daniels, C., Odorfer, T., … Capetian, P. (2023). Feasibility of local field potential-guided programming for deep brain stimulation in Parkinson's disease: A comparison with clinical and neuro-imaging guided approaches in a randomized, controlled pilot trial. *Brain Stimulation*, *16*(5), 1243–1251. https://doi.org/10.1016/j.brs.2023.08.017

Birdno, M. J., & Grill, W. M. (2008). Mechanisms of Deep Brain Stimulation in Movement Disorders as Revealed by Changes in Stimulus Frequency. *Neurotherapeutics*, *5*(1), 14–25. https://doi.org/10.1016/j.nurt.2007.10.067

Birdno, M., Kuncel, A., Dorval, A., Turner, D., & Grill, W. (2008). Tremor varies as a function of the temporal regularity of deep brain stimulation. *Neuroreport*, *19*, 599–602. https://doi.org/10.1097/WNR.0b013e3282f9e45e.Tremor

Blumenfeld, Z., Koop, M. M., Prieto, T. E., Shreve, L. A., Velisar, A., Quinn, E. J., … Brontë-Stewart, H. (2017). Sixty-hertz stimulation improves bradykinesia and amplifies subthalamic low-frequency oscillations. *Movement Disorders*, *32*(1), 80–88. https://doi.org/10.1002/mds.26837

Bočková, M., Lamoš, M., Chrastina, J., Daniel, P., Kupcová, S., Říha, I., … Rektor, I. (2024). Coupling between beta band and high frequency oscillations as a clinically useful biomarker for DBS. *Npj Parkinson's Disease*, *10*(40). https://doi.org/10.1038/s41531-024-00656-8

Bour, L. J., Lourens, M. A. J., Verhagen, R., De Bie, R. M. A., Van Den Munckhof, P., Schuurman, P. R., & Contarino, M. F. (2015). Directional recording of subthalamic spectral power densities in Parkinson's disease and the effect of steering deep brain stimulation. *Brain Stimulation*, *8*(4), 730–741. https://doi.org/10.1016/j.brs.2015.02.002

Braga, D., Madureira, A. M., Coelho, L., & Ajith, R. (2019). Automatic detection of Parkinson's disease based on acoustic analysis of speech. *Engineering Applications of Artificial Intelligence*, *77*(May 2018), 148–158.

Brittain, J. S., & Brown, P. (2014). Oscillations and the basal ganglia: Motor control and beyond. *NeuroImage*, *85*(Pt 2), 637–647. https://doi.org/10.1016/j.neuroimage.2013.05.084

Brown, P., Oliviero, A., Mazzone, P., Insola, A., Tonali, P., & Di Lazzaro, V. (2001). Dopamine dependency of oscillations between subthalamic nucleus and pallidum in Parkinson's disease. *Journal of Neuroscience*. https://doi.org/10.1523/jneurosci.21-03-01033.2001

Busch, J., Kaplan, J., Bahners, B., Roediger, J., Faust, K., Schneider, G., … Kühn, A. (2023). Local Field Potentials Predict Motor Performance in Deep Brain Stimulation for Parkinson's Disease. *Movement Disorders*, *38*(12), 2185–2196. https://doi.org/10.1002/mds.29626

Cagle, J., de Araujo, T., Johnson, K., Yu, J., Fanty, L., Sarmento, F., … Hemptinne, C. (2024). Chronic intracranial recordings in the globus pallidus reveal circadian rhythms in Parkinson's disease. *Nature Communications*, *15*, 4602. https://doi.org/10.1038/s41467-024-48732-0

Cagle, J., Johnson, K., Almeida, L., Wong, J., Ramirez-Zamora, A., Okun, M., … Hemptinne, C. (2023). Brain Recording Analysis and Visualization Online (BRAVO): An open-source visualization tool for deep brain stimulation data. *Brain Stimulation*, *16*(3), 793–797. https://doi.org/10.1016/j.brs.2023.04.018

Castano-Candamil, S., Piroth, T., Reinacher, P., Sajonz, B., Coenen, V. A., & Tangermann, M. (2019). An Easy-to-Use and Fast Assessment of Patient-Specific DBS-Induced Changes in Hand Motor Control in Parkinson's Disease. *IEEE Transactions on Neural Systems and Rehabilitation Engineering*, *27*(10), 2155–2163. https://doi.org/10.1109/TNSRE.2019.2941453

Castaño-Candamil, S., Piroth, T., Reinacher, P., Sajonz, B., Coenen, V. A., & Tangermann, M. (2020). Identifying controllable cortical neural markers with machine learning for adaptive deep brain stimulation in Parkinson's disease. *NeuroImage: Clinical*, *28*(February), 102376.

Chen, Y., Gong, C., Hao, H., Guo, Y., Xu, S., Zhang, Y., … Li, L. (2019). Automatic Sleep Stage Classification Based on

Subthalamic Local Field Potentials. *IEEE Transactions on Neural Systems and Rehabilitation Engineering*, *27*(2), 118–128. https://doi.org/10.1109/TNSRE.2018.2890272.Automatic

Chen, Y., Gong, C., Tian, Y., Orlov, N., Zhang, J., Guo, Y., … Li, L. (2020). Neuromodulation effects of deep brain stimulation on beta rhythm: A longitudinal local field potential study. *Brain Stimulation*, *13*(6), 1784–1792. https://doi.org//10.1016/j.brs.2020.09.027

Chiken, S., & Nambu, A. (2016). Mechanism of Deep Brain Stimulation:Inhibition, Excitation, or Disruption? *The Neuroscientist*, *22*, 313–322. https://doi.org/10.1177/1073858415581986

Christensen, E., Abosch, A., Thompson, J. A., & Zylberberg, J. (2019). Inferring sleep stage from local field potentials recorded in the subthalamic nucleus of Parkinson's patients. *Journal of Sleep Research*, *28*(4), 1–6. https://doi.org/10.1111/jsr.12806

Contarino, M., Bour, L., Verhagen, R., Lourens, M., de Bie, R., Van Muckhof, P., & Schuurman, P. (2014). Directional steering: A novel approach to deep brain stimulation. *Neurology*, *83*, 1163–1169.

D, R. L. P., Member, S., Mastroianni, T., D, D. W. M., & D, N. T. M. (2020). Parametric evaluation of deep brain stimulation parameter configurations for Parkinson ' s disease using a conformal wearable and wireless inertial sensor system and machine learning. *IEEE*, 3606–3611.

Dams, J., Siebert, U., Bornschein, B., Volkmann, J., Deuschl, G., Oertel, W. H., … Reese, J. P. (2013). Cost-effectiveness of deep brain stimulation in patients with Parkinson's disease. *Movement Disorders*, *28*(6), 763–771. https://doi.org/10.1002/mds.25407

Dayal, V., Limousin, P., & Foltynie, T. (2017). Subthalamic nucleus deep brain stimulation in Parkinson's disease: The effect of varying stimulation parameters. *Journal of Parkinson's Disease*, *7*(2), 235–245. https://doi.org/10.3233/JPD-171077

De Hemptinne, C., Ryapolova-Webb, E. S., Air, E. L., Garcia, P. A., Miller, K. J., Ojemann, J. G., … Starr, P. A. (2013). Exaggerated phase-amplitude coupling in the primary motor cortex in Parkinson disease. *Proceedings of the National Academy of Sciences of the United States of America*, *110*(12), 4780–4785. https://doi.org/10.1073/pnas.1214546110

Deeb, W., Giordano, J. J., Rossi, P. J., Mogilner, A. Y., Gunduz, A., Judy, J. W., … Okun, M. S. (2016). Proceedings of the fourth annual deep brain stimulation think tank: A review of emerging issues and technologies. *Frontiers in Integrative Neuroscience*, *10*(NOV2016). https://doi.org/10.3389/fnint.2016.00038

Dias, C., Castro, D., Aroso, M., Ventura, J., & Aguiar, P. (2022). A memristor-based neuromodulation device for real-time monitoring and adaptive control of in vitro neuronal populations. *ACS Appl Electron Mater*, *4*(5), 2380–2387.

Dorval, A. D., Kuncel, A. M., Birdno, M. J., Turner, D. A., & Grill, W. M. (2010). Deep brain stimulation alleviates parkinsonian bradykinesia by regularizing pallidal activity. *Journal of Neurophysiology*, *104*(2), 911–921. https://doi.org/10.1152/jn.00103.2010

Elben, S., Trenado, C., Vesper, J., Schnitzler, A., & Wojtecki, L. (2018). Human subthalamic oscillatory dynamics following somatosensory stimulation. *Clinical Neurophysiology*, *129*(1), 79–88. https://doi.org/10.1016/j.clinph.2017.10.015

Eusebio, A., Thevathasan, W., Doyle Gaynor, L., Pogosyan, A., Bye, E., Foltynie, T., … Brown, P. (2011). Deep brain stimulation can suppress pathological synchronisation in parkinsonian patients. *Journal of Neurology, Neurosurgery and Psychiatry*. https://doi.org/10.1136/jnnp.2010.217489

Eusebio, Alexandre, Cagnan, H., & Brown, P. (2012). Does suppression of oscillatory synchronisation mediate some of the therapeutic effects of DBS in patients with Parkinson's disease? *Frontiers in Integrative Neuroscience*, *6*(JULY 2012), 1–9. https://doi.org/10.3389/fnint.2012.00047

Farrokhi, F., Buchlak, Q. D., Sikora, M., Esmaili, N., Marsans, M., McLeod, P., … Carlson, J. (2020). Investigating Risk Factors and Predicting Complications in Deep Brain Stimulation Surgery with Machine Learning Algorithms. *World Neurosurgery*, *134*, e325–e338.

Fasano, A., Aquino, C. C., Krauss, J. K., Honey, C. R., & Bloem, B. R. (2015). Axial disability and deep brain stimulation in patients with Parkinson disease. *Nature Reviews Neurology*, *11*(2), 98–110. https://doi.org/10.1038/nrneurol.2014.252

Feldmann, L. K., Lofredi, R., Neumann, W.-J., Al-Fatly, B., Roediger, J., Bahners, B. J., … Kühn, A. A. (2022). Toward therapeutic electrophysiology: beta-band suppression as a biomarker in chronic local field potential recordings. *Npj Parkinson's Disease*, *8*(44). https://doi.org/10.1038/s41531-022-00301-2

Fleming, J. E., Dunn, E., & Lowery, M. M. (2020). Simulation of Closed-Loop Deep Brain Stimulation Control Schemes for Suppression of Pathological Beta Oscillations in Parkinson's Disease. *Frontiers in Neuroscience*, *14*. https://doi.org/10.3389/fnins.2020.00166

Florin, E., Erasmi, R., Reck, C., Maarouf, M., Schnitzler, A., Fink, G. R., & Timmermann, L. (2013). Does increased gamma activity in patients suffering from Parkinson's disease counteract the movement inhibiting beta

activity? *Neuroscience*, *237*, 42–50. https://doi.org/10.1016/j.neuroscience.2013.01.051
Follett, K. A., Weaver, F. M., Stern, M., Hur, K., Harris, C. L., Luo, P., … Reda, D. J. (2010). Pallidal versus Subthalamic Deep-Brain Stimulation for Parkinson's Disease. *New England Journal of Medicine*, *362*(22), 2077–2091. https://doi.org/10.1056/nejmoa0907083
Geng, X., Xu, X., Horn, A., Li, N., Ling, Z., Brown, P., & Wang, S. (2018). Intra-operative characterisation of subthalamic oscillations in Parkinson's disease. *Clinical Neurophysiology*, *129*(5), 1001–1010. https://doi.org/10.1016/j.clinph.2018.01.075
Geraedts, V. J., Koch, M., Contarino, M. F., Middelkoop, H. A. M., Wang, H., van Hilten, J. J., … Tannemaat, M. R. (2021). Machine learning for automated EEG-based biomarkers of cognitive impairment during Deep Brain Stimulation screening in patients with Parkinson's Disease. *Clinical Neurophysiology*, *132*(5), 1041–1048.
Geraedts, V., van Vugt, J., Marinus, J., Kuiper, R., Middelkoop, H., Zutt, R., … Contarino, M. (2023). Predicting Motor Outcome and Quality of Life After Subthalamic Deep Brain Stimulation for Parkinson's Disease: The Role of Standard Screening Measures and Wearable-Data. *Journal of Parkinson's Disease*, *13*(4), 575–588. https://doi.org/10.3233/JPD-225101
Geraedts, Victor J., Koch, M., Kuiper, R., Kefalas, M., Bäck, T. H. W., van Hilten, J. J., … Tannemaat, M. R. (2021). Preoperative Electroencephalography-Based Machine Learning Predicts Cognitive Deterioration After Subthalamic Deep Brain Stimulation. *Movement Disorders*, *36*(10), 2324–2334. https://doi.org/10.1002/mds.28661
Giannicola, G., Rosa, M., Servello, D., Menghetti, C., Carrabba, G., Pacchetti, C., … Priori, A. (2012). Subthalamic local field potentials after seven-year deep brain stimulation in Parkinson's disease. *Experimental Neurology*, *237*(2), 312–317.
Gilron, R., Little, S., Perrone, R., Wilt, R., de Hemptinne, C., Yaroshinsky, M. S., … Gregory A. Worrell 3, Vaclav Kremen 3, David A. Borton 4, T. D. and P. A. S. 1. (2021). Long-term wireless streaming of neural recordings for circuit discovery and adaptive stimulation in individuals with Parkinson's disease. *Nature Biotechnology*, *39*, pages1078–1085.
Golshan, H., Hebb, A., Hanrahan, S., Nedrud, J., Mahoor, M. H., Golshan, H. M., … J, N. J. and M. M. H. (2018). A hierarchical structure for human behavior classification using STN local field potentials. *J Neurosci Methods.*, *293*, 254–63.
Golshan, Hosein M., Hebb, A. O., & Mahoor, M. H. (2020). LFP-Net: A deep learning framework to recognize human behavioral activities using brain STN-LFP signals. *Journal of Neuroscience Methods*, *335*(January), 108621.
Goyal, A., Goetz, S., Stanslaski, S., Oh, Y., Rusheen, A. E., Klassen, B., … Lee, K. (2021). The development of an implantable deep brain stimulation device with simultaneous chronic electrophysiological recording and stimulation in humans. *Biosens Bioelectron*, *176*(1128888). https://doi.org/10.1016/j.bios.2020.112888
Gubellini, P., Salin, P., Kerkerian-Le Goff, L., & Baunez, C. (2009). Deep brain stimulation in neurological diseases and experimental models: From molecule to complex behavior. *Progress in Neurobiology*, *89*(1), 79–123. https://doi.org/10.1016/j.pneurobio.2009.06.003
Guidetti, M., Marceglia, S., Los, A., Harmsen, I. E., Meoni, S., Foffani, G., … Priori, A. (2021). Clinical perspectives of adaptive deep brain stimulation. *Brain Stimulation*, *1238–1247*. https://doi.org/10.1016/j.brs.2021.07.063
Hammer, L., Kochanski, R., Starr, P., & Little, S. (2022). Artifact Characterization and a Multipurpose Template-Based Offline Removal Solution for a Sensing-Enabled Deep Brain Stimulation Device. *Stereotact Funct Neurosurg*, *100*(3), 168–183. https://doi.org/10.1159/000521431
Hariz, M. (2014). Deep brain stimulation: New techniques. *Parkinsonism and Related Disorders*, *20*(SUPPL.1), S192–S196. https://doi.org/10.1016/S1353-8020(13)70045-2
Hartmann, C., Fliegen, S., Groiss, S., Wojtecki, L., & Schnitzler, A. (n.d.). An update on best practice of deep brain stimulation in Parkinson's disease Christian J. Hartmann , Sabine Fliegen, Stefan J. Groiss, Lars Wojtecki. *Ther Adv Neurol Disord*, *12*, 1–20.
He, S., Baig, F., Mostofi, A., Pogosyan, A., Debarros, J., Green, A. L., … Tan, H. (2021). Closed-Loop Deep Brain Stimulation for Essential Tremor Based on Thalamic Local Field Potentials. *Movement Disorders*, *36*(4), 863–873. https://doi.org/10.1002/mds.28513
Hebb, D. O. (1949). *The Organization of Behavior*. New York: Wiley.
Hell, F., Palleis, C., Mehrkens, J. H., Koeglsperger, T., & Bötzel, K. (2019). Deep brain stimulation programming 2.0: Future perspectives for target identification and adaptive closed loop stimulation. *Frontiers in Neurology*. https://doi.org/10.3389/fneur.2019.00314
Herron, J. A., Thompson, M. C., Brown, T., Chizeck, H. J., Ojemann, J. G., & Ko, A. L. (2017). Chronic electrocorticography for sensing movement intention and closed-loop deep brain stimulation with wearable

sensors in an essential tremor patient. *Journal of Neurosurgery*, *127*(3), 580–587. https://doi.org/10.3171/2016.8.JNS16536

Hess, C., Vaillancourt, D., & Okun, M. (2013). The temporal pattern of stimulation may be important to the mechanism of deep brain stimulation. *Bone*, *247*, 296–302. https://doi.org/10.1016/j.ol.2013.02.001.The

Hirschmann, J., Schoffelen, J. M., Schnitzler, A., & van Gerven, M. A. J. (2017). Parkinsonian rest tremor can be detected accurately based on neuronal oscillations recorded from the subthalamic nucleus. *Clinical Neurophysiology*, *128*(10), 2029–2036.

Hirschmann, Jan, Steina, A., Vesper, J., Florin, E., & Schnitzler, A. (2022). Neuronal oscillations predict deep brain stimulation outcome in Parkinson's disease. *Brain Stimulation*, *15*(3), 792–802. doi: https://doi.org/10.1016/j.brs.2022.05.008

Hjorth, B., & Elema-Schönander, A. (1970). EEG analysis based on time domain properties. *Electroencephalography and Clinical Neurophysiology*, (29), 306–310. https://doi.org/doi:10.1016/0013-4694(70)90143-4.

Horn, A., & Kühn, A. A. (2015). Lead-DBS: A toolbox for deep brain stimulation electrode localizations and visualizations. *NeuroImage*. https://doi.org/10.1016/j.neuroimage.2014.12.002

Horn, A., Neumann, W. J., Degen, K., Schneider, G. H., & Kühn, A. A. (2017). Toward an electrophysiological "Sweet spot" for deep brain stimulation in the subthalamic nucleus. *Human Brain Mapping*, *38*(7), 3377–3390. https://doi.org/10.1002/hbm.23594

Hunka, K., Suchowersky, O., Wood, S., Derwent, L., & Kiss, Z. (2005). Nursing time to program and assess deep brain stimulators in movement disorder patients. *J Neurosci Nurs.*, *37*, 204–210.

Huo, W., Angeles, P., Tai, Y. F., Pavese, N., Wilson, S., Hu, M. T., & Vaidyanathan, R. (2020). A Heterogeneous Sensing Suite for Multisymptom Quantification of Parkinson's Disease. *IEEE Trans. Neural Syst. Rehabil. Eng.*, *28*, 1387–1406.

Islam, M., Mamun, K., & Deng, H. (2017). Decoding of Human Movements Based on Deep Brain Local Field Potentials Using Ensemble Neural Networks. *Computational Intelligence and Neuroscience*, *176*(3), 139–148. https://doi.org//j.parkreldis.2018.04.009.Deep

Iturrate, I., Martin, S., Chavarriaga, R., Orset, B., Leeb, R., Sobolewski, A., … Millán, J. del R. (2019). Beta-driven closed-loop deep brain stimulation can compromise human motor behavior in Parkinson's Disease. *BioRxiv*. https://doi.org/10.1101/696385

Jankovic, J. (2008). Parkinson's disease: Clinical features and diagnosis. *Journal of Neurology, Neurosurgery and Psychiatry*, *79*(4), 368–376. https://doi.org/10.1136/jnnp.2007.131045

János, A., Mark, L., Wasim, Q., Sydney, C., Emad, E., Gerhard, F., & et al. (2013). Intra-day signal instabilities affect decoding performance in an intracortical neural interface system. *J Neural Eng*, *10*.

Jech, R., Mueller, K., Urgošík, D., Sieger, T., Holiga, S., Růžička, F., … Růžička, E. (2012). The subthalamic microlesion story in Parkinson's disease: electrode insertion-related motor improvement with relative cortico-subcortical hypoactivation in fMRI. *PLoS One,* *7*(11), e49056. https://doi.org/10.1371/journal.pone.0049056

Johnson, M. D., Miocinovic, S., McIntyre, C. C., & Vitek, J. L. (2008). Mechanisms and Targets of Deep Brain Stimulation in Movement Disorders. *Neurotherapeutics*, *5*(2), 294–308. https://doi.org/10.1016/j.nurt.2008.01.010

Jovanov, I., Nauman, M., Kumaravelu, K., Lesi, V., Zutshi, A., Grill, W. M., & Pajic, M. (2018). Learning-Based Control Design for Deep Brain Stimulation. *Proceedings - 9th ACM/IEEE International Conference on Cyber-Physical Systems, ICCPS 2018*, 349–350. https://doi.org/10.1109/ICCPS.2018.00048

Kajikawa, Y, & Schroeder, C. (2012). How local is the local field potential? Yoshinao. *Neuron*, *72*(5), 847–858. https://doi.org/10.1016/j.neuron.2011.09.029.

Karthick, P., Wan, K., An Qi, A., Dauwels, J., & King, N. (2020). Automated detection of subthalamic nucleus in deep brain stimulation surgery for Parkinson's disease using microelectrode recordings and wavelet packet features. *Journal of Neuroscience Methods*, *343*(1), 108826.

Kasper, D., Jameson, J., Fauci, S., Hauser, S., & Localszo, J. (2012). Harrison's Principles of Medicine, *Vol II*.

Khawaldeh, S., Tinkhauser, G., Shah, S. A., Peterman, K., Debove, I., Khoa Nguyen, T. A., … Brown, P. (2020). Subthalamic nucleus activity dynamics and limb movement prediction in Parkinson's disease. *Brain*, *143*(2), 582–586. https://doi.org/10.1093/brain/awz417

Khobragade, N., Graupe, D., & Tuninetti, D. (2015). Towards fully automated closed-loop deep brain stimulation in parkinson's disease patients: A LAMSTAR-based tremor predictor. *Conf. Proc. IEEE Eng. Med. Biol. Soc.*, 2616–2619.

Khodakarami, H., Ricciardi, L., Contarino, M. F., Pahwa, R., Lyons, K. E., Geraedts, V. J., … Horne, M. (2020). Erratum: Prediction of the levodopa challenge test in Parkinson's disease using data from a wrist-worn

sensor (Sensors, (2019) 19, 23, 10.3390/s19235153). *Sensors (Switzerland)*, *20*(15), 1–2. https://doi.org/10.3390/s20154167

Khojandi, A., Shylo, O., Mannini, L., Kopell, B. H., & Ramdhani, R. A. (2017). Stratifying Parkinson's Patients With STN-DBS Into High-Frequency or 60 Hz-Frequency Modulation Using a Computational Model. *Neuromodulation*, *20*(5), 450–455. https://doi.org/10.1111/ner.12607

Kim, J., Duchin, Y., Shamir, R. R., Patriat, R., Vitek, J., Harel, N., & Sapiro, G. (2019). Automatic localization of the subthalamic nucleus on patient-specific clinical MRI by incorporating 7 T MRI and machine learning: Application in deep brain stimulation. *Human Brain Mapping*, *40*(2), 679–698. https://doi.org/10.1002/hbm.24404

Kleinholdermann, U., Bacara, B., Timmermann, L., & Pedrosa, D. J. (2023). Prediction of Movement Ratings and Deep Brain Stimulation Parameters in Idiopathic Parkinson's Disease. *Neuromodulation*, *26*, 356–363.

Koeglsperger, T., Palleis, C., Hell, F., Mehrkens, J., & Bötzel, K. (2019). Deep Brain Stimulation Programming for Movement Disorders: Current Concepts and Evidence-Based Strategies. *Frontiers in Neurology*, *10*. https://doi.org/10.3389/fneur.2019.00410

Kolb, R., Abosch, A., Felsen, G., & Thompson, J. A. (2017). Use of intraoperative local field potential spectral analysis to differentiate basal ganglia structures in Parkinson's disease patients. *Physiological Reports*, *5*(12), 1–14. https://doi.org/10.14814/phy2.13322

Krack, P., Batir, A., Van Blercom, N., Chabardes, S., Fraix, V., Ardouin, C., … Pollak, P. (2003). Five-Year Follow-up of Bilateral Stimulation of the Subthalamic Nucleus in Advanced Parkinson's Disease. *New England Journal of Medicine*, *349*(20), 1925–1934. https://doi.org/10.1056/nejmoa035275

Krauss, J. K., Lipsman, N., Aziz, T., Boutet, A., Brown, P., Chang, J. W., … Lozano, A. M. (2021). Technology of deep brain stimulation: current status and future directions. *Nature Reviews Neurology*. https://doi.org/10.1038/s41582-020-00426-z

Kringelbach, M. L., Jenkinson, N., Owen, S. L. F., & Aziz, T. Z. (2007). Translational principles of deep brain stimulation. *Nature Reviews Neuroscience*, *8*(8), 623–635. https://doi.org/10.1038/nrn2196

Kühn, A. A., Kupsch, A., Schneider, G. H., & Brown, P. (2006). Reduction in subthalamic 8-35 Hz oscillatory activity correlates with clinical improvement in Parkinson's disease. *European Journal of Neuroscience*, *23*(7), 1956–1960. https://doi.org/10.1111/j.1460-9568.2006.04717.x

Kühn, A. A., Trottenberg, T., Kivi, A., Kupsch, A., Schneider, G. H., & Brown, P. (2005). The relationship between local field potential and neuronal discharge in the subthalamic nucleus of patients with Parkinson's disease. *Experimental Neurology*. https://doi.org/10.1016/j.expneurol.2005.02.010

Kühn, A. A., Tsui, A., Aziz, T., Ray, N., Brücke, C., Kupsch, A., … Brown, P. (2009). Pathological synchronisation in the subthalamic nucleus of patients with Parkinson's disease relates to both bradykinesia and rigidity. *Experimental Neurology*, *215*(2), 380–387. https://doi.org/10.1016/j.expneurol.2008.11.008

Kuhner, A., Schubert, T., Cenciarini, M., Wiesmeier, I. K., Coenen, V. A., Burgard, W., … Maurer, C. (2017). Correlations between motor symptoms across different motor tasks, quantified via random forest feature classification in Parkinson's disease. *Frontiers in Neurology*, *8*(NOV), 1–9. https://doi.org/10.3389/fneur.2017.00607

Kuhner, A., Wiesmeier, I. K., Cenciarini, M., Maier, T. L., Kammermeier, S., Coenen, V. A., … Maurer, C. (2020). Motion Biomarkers Showing Maximum Contrast Between Healthy Subjects and Parkinson's Disease Patients Treated With Deep Brain Stimulation of the Subthalamic Nucleus. A Pilot Study. *Frontiers in Neuroscience*, *13*(February), 1–10. https://doi.org/10.3389/fnins.2019.01450

Kuo, C. H., White-Dzuro, G. A., & Ko, A. L. (2018). Approaches to closed-loop deep brain stimulation for movement disorders. *Neurosurgical Focus*. https://doi.org/10.3171/2018.5.FOCUS18173

Lange, S., Kremer, N., van Laar, T., Lange, F., Steendam-Oldekamp, E., Oterdoom, D., … Drost, G. (2023). The Intraoperative Microlesion Effect Positively Correlates With the Short-Term Clinical Effect of Deep Brain Stimulation in Parkinson's Disease. *Neuromodulation*, *26*(2), 459–465. https://doi.org/10.1111/ner.13523

LeMoyne, R., Mastroianni, T., Whiting, D., & Tomycz, N. (2024). Deep Brain Stimulation with Machine Learning Classification Through Conformal Wearables. In: Wearable and Wireless Systems for Healthcare II. Smart Sensors, Measurement and Instrumentation. *Springer, Singapore.*, *49*. https://doi.org/10.1007/978-981-97-4635-4_13

Lempka, S. F., & McIntyre, C. C. (2013). Theoretical Analysis of the Local Field Potential in Deep Brain Stimulation Applications. *PLoS ONE*, *8*(3). https://doi.org/10.1371/journal.pone.0059839

Lettieri, C., Rinaldo, S., Devigili, G., Pauletto, G., Verriello, L., Budai, R., … Eleopra, R. (2012). Deep brain stimulation: Subthalamic nucleus electrophysiological activity in awake and anesthetized patients. *Clinical Neurophysiology*, *123*(12), 2406–2413. https://doi.org/10.1016/j.clinph.2012.04.027

Lhommée, E., Wojtecki, L., Czernecki, V., Witt, K., Maier, F., Tonder, L., … Speelman, H. (2018). Behavioural

outcomes of subthalamic stimulation and medical therapy versus medical therapy alone for Parkinson's disease with early motor complications (EARLYSTIM trial): secondary analysis of an open-label randomised trial. *The Lancet Neurology*, *17*(3), 223–231. https://doi.org/10.1016/S1474-4422(18)30035-8

Limousin, P., & Foltynie, T. (2019). Long-term outcomes of deep brain stimulation in Parkinson disease. *Nature Reviews Neurology*, *15*(4), 234–242. https://doi.org/10.1038/s41582-019-0145-9

Lindén, H., Tetzlaff, T., Potjans, T. C., Pettersen, K. H., Grün, S., Diesmann, M., & Einevoll, G. T. (2011). Modeling the spatial reach of the LFP. *Neuron*, *72*(5), 859–872. https://doi.org/10.1016/j.neuron.2011.11.006

Little, S., Pogosyan, A., Kuhn, A. A., & Brown, P. (2012). Beta band stability over time correlates with Parkinsonian rigidity and bradykinesia. *Experimental Neurology*, *236*(2), 383–388. https://doi.org/10.1016/j.expneurol.2012.04.024

Little, Simon, Beudel, M., Zrinzo, L., Foltynie, T., Limousin, P., Hariz, M., … Brown, P. (2016). Bilateral adaptive deep brain stimulation is effective in Parkinson's disease. *Journal of Neurology, Neurosurgery and Psychiatry*, *87*(7), 717–721. https://doi.org/10.1136/jnnp-2015-310972

Little, Simon, & Brown, P. (2012). What brain signals are suitable for feedback controzl of deep brain stimulation in Parkinson's disease? *Annals of the New York Academy of Sciences*, *1265*(1), 9–24. https://doi.org/10.1111/j.1749-6632.2012.06650.x

Little, Simon, Pogosyan, A., Neal, S., Zavala, B., Zrinzo, L., Hariz, M., … Brown, P. (2013). Adaptive deep brain stimulation in advanced Parkinson disease. *Annals of Neurology*. https://doi.org/10.1002/ana.23951

Litvak, V., Eusebio, A., Jha, A., Oostenveld, R., Barnes, G., Foltynie, T., … Brown, P. (2012). Movement-related changes in local and long-range synchronization in parkinson's disease revealed by simultaneous magnetoencephalography and intracranial recordings. *Journal of Neuroscience*, *32*(31), 10541–10553. https://doi.org/10.1523/JNEUROSCI.0767-12.2012

Liu, D. F., Zhao, B. T., Zhu, G. Y., Liu, Y. Y., Bai, Y. T., Liu, H. G., … Zhang, J. G. (2022). Synchronized Intracranial Electrical Activity and Gait Recording in Parkinson's Disease Patients With Freezing of Gait. *Frontiers in Neuroscience*, *16*(March), 1–11. https://doi.org/10.3389/fnins.2022.795417

Lofredi, R, Okudzhava, L., Irmen, F., Brücke, C., Huebl, J., Krauss, J., … Kühn, A. (2023). Subthalamic beta bursts correlate with dopamine-dependent motor symptoms in 106 Parkinson's patients. *Npj Parkinson's Disease*, *9*(2). https://doi.org/10.1038/s41531-022-00443-3

Lofredi, Roxanne, Neumann, W. J., Bock, A., Horn, A., Huebl, J., Siegert, S., … Kuühn, A. A. (2018). Dopamine-dependent scaling of subthalamic gamma bursts with movement velocity in patients with Parkinson's disease. *ELife*. https://doi.org/10.7554/eLife.31895

Lofredi, Roxanne, Tan, H., Neumann, W. J., Yeh, C. H., Schneider, G. H., Kühn, A. A., & Brown, P. (2019). Beta bursts during continuous movements accompany the velocity decrement in Parkinson's disease patients. *Neurobiology of Disease*, *127*(February), 462–471. https://doi.org/10.1016/j.nbd.2019.03.013

Lozano, A. M., Lipsman, N., Bergman, H., Brown, P., Chabardes, S., Chang, J. W., … Krauss, J. K. (2019). Deep brain stimulation: current challenges and future directions. *Nature Reviews Neurology*. https://doi.org/10.1038/s41582-018-0128-2

Lu, M., Wei, X., Che, Y., Wang, J., & Loparo, K. A. (2020). Application of Reinforcement Learning to Deep Brain Stimulation in a Computational Model of Parkinson's Disease. *IEEE Transactions on Neural Systems and Rehabilitation Engineering*, *28*(1), 339–349. https://doi.org/10.1109/TNSRE.2019.2952637

Magarios-Ascone, C., Pazo, J. H., Macadar, O., & Buo, W. (2002). High-frequency stimulation of the subthalamic nucleus silences subthalamic neurons: A possible cellular mechanism in Parkinson's disease. *Neuroscience*, *115*(4), 1109–1117. https://doi.org/10.1016/S0306-4522(02)00538-9

Malekmohammadi, M., Herron, J., Velisar, A., Blumenfeld, Z., Trager, M. H., Chizeck, H. J., & Brontë-Stewart, H. (2016). Kinematic Adaptive Deep Brain Stimulation for Resting Tremor in Parkinson's Disease. *Movement Disorders*, *31*(3), 426–428. https://doi.org/10.1002/mds.26482

Maling, N., Lempka, S. F., Blumenfeld, Z., Bronte-Stewart, H., & McIntyre, C. C. (2018). Biophysical basis of subthalamic local field potentials recorded from deep brain stimulation electrodes. *Journal of Neurophysiology*, *120*(4), 1932–1944. https://doi.org/10.1152/jn.00067.2018

Maltête, D., Derrey, S., Chastan, N., Debono, B., Gérardin, E., Fréger, P., … Hannequin, D. (2008). Microsubthalamotomy: an immediate predictor of long-term subthalamic stimulation efficacy in Parkinson disease. *Mov Disord*, *23*(7), 1047–1050. https://doi.org/10.1002/mds.22054

Mamun, K. A., Mace, M., Lutman, M. E., Stein, J., Liu, X., Aziz, T., … Wang, S. (2015). Movement decoding using neural synchronization and inter-hemispheric connectivity from deep brain local field potentials. *Journal of Neural Engineering*, *12*(5). https://doi.org/10.1088/1741-2560/12/5/056011

Marquez-Chin, C., & Popovic, M. (2020). Functional electrical stimulation therapy for restoration of motor function after spinal cord injury and stroke: a review. *Biomed Eng Online*, *19*(1), 34.

https://doi.org/10.1186/s12938-020-00773-4
Marsden, J., Ashby, P., Limousin-Dowsey, P., Rothwell, J., & Brown, P. (2020). Coherence between cerebellar thalamus, cortex and muscle in man. Cerebellar thalamus interactions. *Brain*, *123*(7), 1459–1470.
Martínez-Morales, P. L., & Liste, I. (2012). Stem cells as in vitro model of Parkinson's disease. *Stem Cells International*, *2012*. https://doi.org/10.1155/2012/980941
Mateus, J., Lopes, C., Aroso, M., Costa, A., Gerós, A., Pereira, A., … Aguiar, P. (2021). In vitro neuronal networks show bidirectional axonal conduction with antidromic action potentials effectively depolarizing the soma. *BioRxiv*. Retrieved from doi: https://doi.org/10.1101/2021.03.07.434278
Mathiopoulou, V., Habets, J., Feldmann, L., Busch, J., Roediger, J., Kim-Behnke, J., … Kühn, A. A. (2024). DBS-induced gamma entrainment as a new biomarker for motor improvement with neuromodulation. *Preprint*. https://doi.org/10.1101/2024.04.25.24306357
McGregor, M., & Nelson, A. (2019). Circuit Mechanisms of Parkinson's Disease. *Neuron*, *101*(6), 1042–1056. https://doi.org/10.1016/j.neuron.2019.03.004
McIntyre, C. C., Grill, W. M., Sherman, D. L., & Thakor, N. V. (2004). Cellular Effects of Deep Brain Stimulation: Model-Based Analysis of Activation and Inhibition. *Journal of Neurophysiology*, *91*(4), 1457–1469. https://doi.org/10.1152/jn.00989.2003
McIntyre, C. C., Savasta, M., Kerkerian-Le Goff, L., & Vitek, J. L. (2004). Uncovering the mechanism(s) of action of deep brain stimulation: Activation, inhibition, or both. *Clinical Neurophysiology*, *115*(6), 1239–1248. https://doi.org/10.1016/j.clinph.2003.12.024
McIntyre, C., & Hahn, P. (2010). Network perspectives on the mechanisms of deep brain stimulation. *Neurobiol. Dis*, *38*, 329–337.
Menezes, R., Tenreiro, S., Macedo, D., Santos, C. N., & Outeiro, T. F. (2015). From the baker to the bedside: Yeast models of parkinson's disease. *Microbial Cell*, *2*(8), 262–279. https://doi.org/10.15698/mic2015.08.219
Merk, T, Peterson, V., Köhler, R., Haufe, S., Richardson, R., & Neumann, W. (2022). Machine learning based brain signal decoding for intelligent adaptive deep brain stimulation. *Experimental Neurology*, *351*, 113993. https://doi.org/10.1016/j.expneurol.2022.113993
Merola, A., Romagnolo, A., Rizzi, L., Rizzone, M. G., Zibetti, M., Lanotte, M., … Lopiano, L. (2017). Impulse control behaviors and subthalamic deep brain stimulation in Parkinson disease. *Journal of Neurology*, *264*(1), 40–48. https://doi.org/10.1007/s00415-016-8314-x
Mestre, T., Lang, A., & Okun, M. (2018). Factors influencing the outcome of deep brain stimulation: Placebo, nocebo, lessebo, and lesion effects. *Mov Disord*, *31*(3), 290–296. https://doi.org/10.1002/mds.26500
Miocinovic, Svjetlana, Somayajula, S., Chitnis, S., & Vitek, J. L. (2013). History, applications, and mechanisms of deep brain stimulation. *JAMA Neurology*, *70*(2), 163–171. https://doi.org/10.1001/2013.jamaneurol.45
Mishra, A, Shah, H., McBriar, J., Zamor, C., & Mammis, A. (2023). Local Field Potentials in Deep Brain Stimulation: Investigation of the Most Cited Articles. *World Neurosurgery*, *17*(100140). https://doi.org/10.1016/j.wnsx.2022.100140
Mishra, Akash, Bajaj, V., Fitzpatrick, T., Watts, J., Khojandi, A., & Ramdhani, R. (2024). Differential Responses to Low- and High-Frequency Subthalamic Nucleus Deep Brain Stimulation on Sensor-Measured Components of Bradykinesia in Parkinson's Disease. *Sensors*, *24*(13), 4296. https://doi.org/10.3390/s24134296
Miyagi, Y., Okamoto, T., Morioka, T., Tobimatsu, S., Nakanishi, Y., Aihara, K., … Sasaki, T. (2009). Spectral analysis of field potential recordings by deep brain stimulation electrode for localization of subthalamic nucleus in patients with parkinson's disease. *Stereotactic and Functional Neurosurgery*, *87*(4), 211–218. https://doi.org/10.1159/000225974
Mohammed, A., Zamani, M., Bayford, R., & Demosthenous, A. (2015). Patient specific Parkinson's disease detection for adaptive deep brain stimulation. *Proceedings of the Annual International Conference of the IEEE Engineering in Medicine and Biology Society, EMBS*, *2015-Novem*, 1528–1531. https://doi.org/10.1109/EMBC.2015.7318662
Moldovan, A., Hartmann, C., Trenado, C., Meumertzheim, N., Slotty, P., Vesper, J., … Groiss, S. (2018). Less is more - Pulse width dependenttherapeutic window in deep brain stimulation for essential tremor. *Brain Stimulation*, *11*, 1132–1139. https://doi.org/10.1016/j.brs.2018.04.019
Montgomery, E. (2004). Dynamically Coupled, High-Frequency Reentrant, Non-linear Oscillators Embedded in Scale-Free Basal Ganglia-Thalamic-Cortical Networks Mediating Function and Deep Brain Stimulation Efiects. *Nonlinear Studies*, *11*(3).
Montgomery, E. B., & Gale, J. T. (2008). Mechanisms of action of deep brain stimulation (DBS). *Neuroscience and Biobehavioral Reviews*, *32*(3), 388–407. https://doi.org/10.1016/j.neubiorev.2007.06.003
Moreau, C., Defebvre, L., Destée, A., Bleuse, S., Clement, F., Blatt, J., … D, D. (2008). STN-DBS frequency effects on freezing of gait in advanced Parkinson disease. *Neurology*, *71*, 80–84.

Moro, E., Esselink, R. J. A., Xie, J., Hommel, M., Benabid, A. L., & Pollak, P. (2002). The impact on Parkinson's disease of electrical parameter settings in STN stimulation. *Neurology*, *59*(5), 706–713. https://doi.org/10.1212/WNL.59.5.706

Moro, Elena, & Lang, A. E. (2006). Criteria for deep-brain stimulation in Parkinson's disease: review and analysis. *Expert Review of Neurotherapeutics*, *6*(11). https://doi.org/10.1586/14737175.6.11.1695

Múrias Lopes, E., Vilas-Boas, M., Dias, D., Rosas, M., Vaz, R., & Cunha, J. (2020). IHandU: A novel quantitative wrist rigidity evaluation device for deep brain stimulation surgery. *Sensors*, *20*(2), 331. https://doi.org/10.3390/s20020331

Murthy, V.N., & Fetz, E. E. (1992). Coherent 25- to 35-Hz oscillations in the sensorimotor cortex of awake behaving monkeys. *Proc. Natl. Acad. Sci. U. S. A.*, (89), 5670–5674.

Murthy, Venkatesh N., & Fetz, E. E. (1996). Oscillatory activity in sensorimotor cortex of awake monkeys: Synchronization of local field potentials and relation to behavior. *Journal of Neurophysiology*, *76*(6), 3949–3967. https://doi.org/10.1152/jn.1996.76.6.3949

Nazmuddin, M., Oterdoom, D., van Dijk, J., van Zijl, J. C., Kampma n, A. K., G., D., … Beudel, M. (2018). Oscillatory activity and cortical coherence of the nucleus basa lis of Meynert in Parkinson's diseas e dementia. *Parkinsonism Relat. Disord.*, *52*, 102–106.

NC, S., de Hemptinne, C., Thompson, M. C., Miocinovic, S., Miller, A. M., Gilron, R., … Starr, P. A. (2018). Adaptive deep brain stimulation for Parkinson's disease using motor cortex sensing. *J. Neural. Eng.*, *15*.

Neumann, W.-J., Gilron, R., Little, S., & Tinkhauser, G. (2023). Adaptive Deep Brain Stimulation: From Experimental Evidence Toward Practical Implementation. *Movement Disorders*, *38*(6). https://doi.org/10.1002/mds.29415

Neumann, W.-J., Horn, A., & Kühn, A. A. (2023). Insights and opportunities for deep brain stimulation as a brain circuit intervention. *Trends in Neurosciences*. https://doi.org/10.1016/j.tins

Neumann, W. J., Degen, K., Schneider, G. H., Brücke, C., Huebl, J., Brown, P., & Kühn, A. A. (2016). Subthalamic synchronized oscillatory activity correlates with motor impairment in patients with Parkinson's disease. *Movement Disorders*. https://doi.org/10.1002/mds.26759

Neumann, W. J., Staub-Bartelt, F., Horn, A., Schanda, J., Schneider, G. H., Brown, P., & Kühn, A. A. (2017). Long term correlation of subthalamic beta band activity with motor impairment in patients with Parkinson's disease. *Clinical Neurophysiology*. https://doi.org/10.1016/j.clinph.2017.08.028

Neumann, W. J., Staub, F., Horn, A., Schanda, J., Mueller, J., Schneider, G. H., … Kühn, A. A. (2016). Deep brain recordings using an implanted pulse generator in Parkinson's disease. *Neuromodulation*, *19*(1), 20–23. https://doi.org/10.1111/ner.12348

Nuri Firat Ince, Akshay Gupte, Thomas Wichmann, MD, James Ashe, MD, Thomas Henry, MD, Margaret Bebler, RN, CNS, Lynn Eberly, PhD, and Aviva Abosch, MD, P. (2015). Selection of Optimal Programming Contacts Based on Local Field Potential Recordings From Subthalamic Nucleus in Patients With Parkinson's Disease, *19*(2), 161–169. https://doi.org/10.1227/01.NEU.0000372091.64824.63.Selection

Obeso, J. A., Marin, C., Rodriguez-Oroz, C., Blesa, J., Benitez-Temiño, B., Mena-Segovia, J., … Olanow, C. W. (2008). The basal ganglia in Parkinson's disease: Current concepts and unexplained observations. *Annals of Neurology*, *64*(SUPPL. 2), 30–46. https://doi.org/10.1002/ana.21481

Okun, M. (2012). Deep-brain stimulation for Parkinson's disease. *N Engl J Med*, *367*(16), 1529–1538.

Okun, M., Gallo, B., Mandybur, G., Jagid, J., Foote, K., Revilla, F., … Group, S. D. S. (2012). Subthalamic deep brain stimulation with a constant-current device in Parkinson's disease: an open-label randomised controlled trial. *Lancet Neurol, 11*(2), 140–149. https://doi.org/10.1016/S1474-4422(11)70308-8

Oliveira, F. H. M., MacHado, A. R. P., & Andrade, A. O. (2018). On the Use of t -Distributed Stochastic Neighbor Embedding for Data Visualization and Classification of Individuals with Parkinson's Disease. *Computational and Mathematical Methods in Medicine*, *2018*(Article ID 8019232). https://doi.org/10.1155/2018/8019232

Oostenveld, R., Fries, P., Maris, E., & Schoffelen, J. (2011). FieldTrip: Open Source Software for Advanced Analysis of MEG, EEG, and Invasive Electrophysiological Data. *Computational Intelligence and Neuroscience*. https://doi.org/2011:156869

Opri, E., Cernera, S., Molina, R., Eisinger, R. S., Cagle, J. N., Almeida, L., … Gunduz, A. (2020). Chronic embedded cortico-thalamic closed-loop deep brain stimulation for the treatment of essential tremor. *Sci Trans Med*, *12*(572).

Oswal, A., Beudel, M., Zrinzo, L., Limousin, P., Hariz, M., Foltynie, T., … Brown, P. (2016). Deep brain stimulation modulates synchrony within spatially and spectrally distinct resting state networks in Parkinson's disease. *Brain*, *139*(5), 1482–1496. https://doi.org/10.1093/brain/aww048

Ozturk, M., Telkes, I., Jimenez-Shahed, J., Viswanathan, A., Tarakad, A., Kumar, S., … Ince, N. F. (2020). Randomized, Double-Blind Assessment of LFP Versus SUA Guidance in STN-DBS Lead Implantation: A Pilot

Study. *Frontiers in Neuroscience*, *14*(June), 1–12. https://doi.org/10.3389/fnins.2020.00611
Parastarfeizabadi, M., & Kouzani, A. (2017). Advances in closed-loop deepbrain stimulation devices. *J. NeuroEngineering Rehab.*, *14*. https://doi.org/10.1186/s12984-017-0295-1
Park, K. H., Sun, S., Lim, Y. H., Park, H. R., Lee, J. M., Park, K., … Paek, S. H. (2021). Clinical outcome prediction from analysis of microelectrode recordings using deep learning in subthalamic deep brain stimulation for Parkinson's disease. *PLoS ONE*, *16*(1 January), 1–15.
Peralta, Maxime, Haegelen, C., Jannin, P., & Baxter, J. S. H. (2021). PassFlow: a multimodal workflow for predicting deep brain stimulation outcomes. *International Journal of Computer Assisted Radiology and Surgery*, *16*(8), 1361–1370. https://doi.org/10.1007/s11548-021-02435-9
Peralta, Maxime, Jannin, P., & Baxter, J. S. H. (2021). Machine learning in deep brain stimulation: A systematic review. *Artificial Intelligence in Medicine*, *122*(102198). https://doi.org/10.1016/j.artmed.2021.102198
Peterson, V., Merk, T., Bush, A., Nikulin, V., Kuhn, A., Neumann, W., & Richardson, R. (2022). Movement decoding using spatio-spectral features of cortical and subcortical local field potentials. *Experimental Neurology*, *359*(114261).
Piallat, B., Chabardès, S., Devergnas, A., Torres, N., Allain, M., Barrat, E., & Benabid, A. L. (2009). Monophasic but not biphasic pulses induce brain tissue damage during monopolar high-frequency deep brain stimulation. *Neurosurgery*, *64*(1), 156–162. https://doi.org/10.1227/01.NEU.0000336331.88559.CF
Piña-Fuentes, D., Beudel, M., Little, S., van Zijl, J., Elting, J. W., Oterdoom, D. L. M., … Tijssen, M. A. J. (2018). Toward adaptive deep brain stimulation for dystonia. *Neurosurgical Focus*, *45*(2), 1–8. https://doi.org/10.3171/2018.5.FOCUS18155
Pollo, C., Kaelin-Lang, A., Oertel, M. F., Stieglitz, L., Taub, E., Fuhr, P., … Schüpbach, M. (2014). Directional deep brain stimulation: An intraoperative double-blind pilot study. *Brain*, *137*(7), 2015–2026. https://doi.org/10.1093/brain/awu102
Popovych, O. V., Hauptmann, C., & Tass, P. A. (2005). Effective desynchronization by nonlinear delayed feedback. *Physical Review Letters*, *94*(16), 2–5. https://doi.org/10.1103/PhysRevLett.94.164102
Popovych, O. V., Lysyansky, B., Rosenblum, M., Pikovsky, A., & Tass, P. A. (2017). Pulsatile desynchronizing delayed feedback for closed-loop deep brain stimulation. *PLoS ONE*, *12*(3), 1–29. https://doi.org/10.1371/journal.pone.0173363
Popovych, O. V., Lysyansky, B., & Tass, P. A. (2017). Closed-loop deep brain stimulation by pulsatile delayed feedback with increased gap between pulse phases. *Scientific Reports*, *7*(1), 1–14. https://doi.org/10.1038/s41598-017-01067-x
Popovych, O. V., & Tass, P. A. (2010). Synchronization control of interacting oscillatory ensembles by mixed nonlinear delayed feedback. *Physical Review E - Statistical, Nonlinear, and Soft Matter Physics*, *82*(2), 1–7. https://doi.org/10.1103/PhysRevE.82.026204
Powers, R., Etezadi-Amoli, M., Arnold, E., Kianian, S., Mance, I., Gibiansky, M., … Ullal, A. (2021). Rob Powers et al. ,Smartwatch inertial sensors continuously monitor real-world motor fluctuations in Parkinson's disease. *Sci. Transl. Med.*, *13*(eabd7865). https://doi.org/10.1126/scitranslmed.abd7865
Priori, A, Ardolino, G., Marceglia, S., Mrakic-Sposta, S., Locatelli, M., Tamma, F., … Foffani, G. (2006). Low-frequency subthalamic oscillations increase after deep brain stimulation in Parkinson's disease. *Brain Res Bull*, *71*(149–154).
Priori, Alberto, Foffani, G., Rossi, L., & Marceglia, S. (2013). Adaptive deep brain stimulation (aDBS) controlled by local field potential oscillations. *Experimental Neurology*, *245*, 77–86.
Quinn, E. J., Blumenfeld, Z., Velisar, A., Koop, M. M., Shreve, L. A., Trager, M. H., … Brontë-Stewart, H. (2015). Beta oscillations in freely moving Parkinson's subjects are attenuated during deep brain stimulation. *Movement Disorders*. https://doi.org/10.1002/mds.26376
Radcliffe, E., Baumgartner, A., Kern, D., Borno, M., Ojemann, S., Kramer, D., & Thompson, J. (2023). Oscillatory beta dynamics inform biomarker-driven treatment optimization for Parkinson's disease. *Journal of Neurophysiology*, *129*(6), 1492–1504. https://doi.org/10.1152/jn.00055.2023
Ramirez-Zamora, A., & Ostrem, J. L. (2018). Globus pallidus interna or subthalamic nucleus deep brain stimulation for Parkinson disease a review. *JAMA Neurology*, *75*(3), 367–372. https://doi.org/10.1001/jamaneurol.2017.4321
Rammo, R. A., Ozinga, S. J., White, A., Nagel, S. J., Machado, A. G., Pallavaram, S., … Walter, B. L. (2021). Directional Stimulation in Parkinson's Disease and Essential Tremor: The Cleveland Clinic Experience. *Neuromodulation*, 1–7.
Raza, C., Anjum, R., & Shakeel, N. ul A. (2019). Parkinson's disease: Mechanisms, translational models and management strategies. *Life Sciences*, *226*(January), 77–90. https://doi.org/10.1016/j.lfs.2019.03.057
Reakkamnuan, C., Kumarnsit, E., & Cheaha, D. (2023). Local field potential (LFP) power and phase-amplitude

coupling (PAC) changes in the striatum and motor cortex reflect neural mechanisms associated with bradykinesia and rigidity during D2R suppression in an animal model. *Progress in Neuropsychopharmacology & Biological Psychiatry*, *127*(110838). https://doi.org/10.1016/j.pnpbp.2023.110838

Reck, C., Florin, E., Wojtecki, L., Krause, H., Groiss, S., Voges, J., … Timmermann, L. (2009). Characterization of tremor-associated local field potentials in the subthalamic nucleus in Parkinson's disease. *Eur J Neurosci.*, *29*(599–612).

Reich, M. M., Steigerwald, F., Sawalhe, A. D., Reese, R., Gunalan, K., Johannes, S., … Volkmann, J. (2015). Short pulse width widens the therapeutic window of subthalamic neurostimulation. *Annals of Clinical and Translational Neurology*, *2*(4), 427–432. https://doi.org/10.1002/acn3.168

Reich, S. G., & Savitt, J. M. (2019). Parkinson's Disease. *Medical Clinics of North America*, *103*(2), 337–350. https://doi.org/10.1016/j.mcna.2018.10.014

Ricchi, V., Zibetti, M., Angrisano, S., Merola, A., Arduino, N., Artusi, C. A., … Lanotte, M. (2012). Transient effects of 80 Hz stimulation on gait in STN DBS treated PD patients: A 15 months follow-up study. *Brain Stimulation*, *5*(3), 388–392. https://doi.org/10.1016/j.brs.2011.07.001

Rizzone, M., Lanotte, M., Bergamasco, B., Tavella, A., Torre, E., Faccani, G., … Lopiano, L. (2001). Deep brain stimulation of the subthalamic nucleus in Parkinson's disease: Effects of variation in stimulation parameters. *Journal of Neurology Neurosurgery and Psychiatry*, *71*(2), 215–219. https://doi.org/10.1136/jnnp.71.2.215

Rosa, M, Marceglia, S., Barbieri, S., & Priori, A. (2014). Local field potential and deep brain stimulation (DBS). *Encyclopedia of Computational Neuroscience.*, *Springer N*, 1–20.

Rosa, Manuela, Arlotti, M., Ardolino, G., Cogiamanian, F., Marceglia, S., Di Fonzo, A., … Priori, A. (2015). Adaptive deep brain stimulation in a freely moving parkinsonian patient. *Movement Disorders*, *30*(7), 1003–1005. https://doi.org/10.1002/mds.26241

Rosa, Manuela, Arlotti, M., Marceglia, S., Cogiamanian, F., Ardolino, G., Fonzo, A. Di, … Priori, A. (2017). Adaptive deep brain stimulation controls levodopa-induced side effects in Parkinsonian patients. *Movement Disorders*, *32*(4), 628–629. https://doi.org/10.1002/mds.26953

Rosa, Manuela, Fumagalli, M., Giannicola, G., Marceglia, S., Lucchiari, C., Servello, D., … Priori, A. (2013). Pathological gambling in Parkinson's disease: Subthalamic oscillations during economics decisions. *Movement Disorders*, *28*(12), 1644–1652. https://doi.org/10.1002/mds.25427

Rosenblum, M. G., & Pikovsky, A. S. (2004). Controlling Synchronization in an Ensemble of Globally Coupled Oscillators. *Physical Review Letters*, *92*(11), 1–4. https://doi.org/10.1103/PhysRevLett.92.114102

Rosenblum, M., & Pikovsky, A. (2004). Delayed feedback control of collective synchrony: An approach to suppression of pathological brain rhythms. *Physical Review E - Statistical Physics, Plasmas, Fluids, and Related Interdisciplinary Topics*, *70*(4), 11. https://doi.org/10.1103/PhysRevE.70.041904

Rosin, Boris, Slovik, M., Mitelman, R., Rivlin-Etzion, M., Haber, S. N., Israel, Z., … Bergman, H. (2011). Closed-loop deep brain stimulation is superior in ameliorating parkinsonism. *Neuron*, *72*(2), 370–384. https://doi.org/10.1016/j.neuron.2011.08.023

Rossi, L., Foffani, G., Marceglia, S., Bracchi, F., Barbieri, S., & Priori, A. (2007). An electronic device for artefact suppression in human local field potential recordings during deep brain stimulation. *Journal of Neural Engineering*, *4*(2), 96–106. https://doi.org/10.1088/1741-2560/4/2/010

Rouse, A. G., Stanslaski, S. R., Cong, P., Jensen, R. M., Afshar, P., Ullestad, D., … Denison, T. J. (2011). A chronic generalized bi-directional brain-machine interface. *Journal of Neural Engineering*. https://doi.org/10.1088/1741-2560/8/3/036018

Sabourin, S., Khazen, O., DiMarzio, M., Staudt, M. D., Williams, L., Gillogly, M., … Pilitsis, J. G. (2020). Effect of Directional Deep Brain Stimulation on Sensory Thresholds in Parkinson's Disease. *Frontiers in Human Neuroscience*, *14*(June), 1–8. https://doi.org/10.3389/fnhum.2020.00217

Samii, A., Nutt, J., & Ransom, B. R. (2004). Parkinson's disease. *The Lancet*, *363*, 1783–1793.

Sanger, Z., Henry, T., Park, M., Darrow, D., McGovern, R., & Netoff, T. (2024). Neural signal data collection and analysis of Percept™ PC BrainSense recordings for thalamic stimulation in epilepsy. *Journal of Neural Engineering*, *21*(1). https://doi.org/10.1088/1741-2552/ad1dc3

Sarica, C., , Iorio-Morin, C., Aguirre-Padilla, D., Najjar, A., Paff, M., Fomenko, A., … Kalia, S. (2021). Implantable Pulse Generators for Deep Brain Stimulation: Challenges, Complications, and Strategies for Practicality and Longevity. *Frontiers in Human Neuroscience*, *15*, 489.

Sarikhani, P., Ferleger, B., Mitchell, K., Ostrem, J., Herron, J., Mahmoudi, B., & Miocinovic, S. (2022). Automated deep brain stimulation programming with safety constraints for tremor suppression in patients with Parkinson's disease and essential tremor. *J Neural Eng*, *19*(4). https://doi.org/10.1088/1741-2552/ac86a2

Sarnthein, J., & Jeanmonod, D. (2007). High thalamocortical theta coherence in patients with Parkinson's disease.

Journal of Neuroscience, *27*(1), 124–131. https://doi.org/10.1523/JNEUROSCI.2411-06.2007

Schmidt, S. L., Peters, J. J., Turner, D. A., & Grill, W. M. (2020). Continuous deep brain stimulation of the subthalamic nucleus may not modulate beta bursts in patients with Parkinson's disease. *Brain Stimulation*, *13*(2), 433–443. https://doi.org/10.1016/j.brs.2019.12.008

Schnitzler, A., Mir, P., Brodsky, M. A., Verhagen, L., Groppa, S., Alvarez, R., … Vesper, J. (2021). Directional Deep Brain Stimulation for Parkinson's Disease: Results of an International Crossover Study With Randomized, Double-Blind Primary Endpoint. *Neuromodulation*, 1–12.

Shah, A., Nguyen, T., Peterman, K., Khawaldeh, S., Debove, I., Shah, S., … Tinkhauser, G. (2023). Combining Multimodal Biomarkers to Guide Deep Brain Stimulation Programming in Parkinson Disease. *Neuromodulation: Technology at the Neural Interface*, *26*(2), 320–332. https://doi.org/10.1016/j.neurom.2022.01.017

Shah, S. A., Tinkhauser, G., Chen, C. C., Little, S., & Brown, P. (2018). Parkinsonian Tremor Detection from Subthalamic Nucleus Local Field Potentials for Closed-Loop Deep Brain Stimulation. *Proceedings of the Annual International Conference of the IEEE Engineering in Medicine and Biology Society, EMBS*, *2018-July*(0), 2320–2324. https://doi.org/10.1109/EMBC.2018.8512741

Shamir, R., Dolber, T., Noecker, A., Walter, B., & McIntyre, C. (2015). Machine learning approach to optimizing combined stimulation and medication therapies for Parkinson's disease. *Brain Stimul.*, *8*(6), 1025–1032.

Shulman, J., De Jager, P., & Feany, M. (2011). Parkinson's Disease: Genetics and Pathogenesis. *Annual Review of Pathology: Mechanisms of Disease*, *6*, 193–222. https://doi.org/10.1146/annurev-pathol-011110-130242

Sieger, T., Neumann, W., & Tinkhauser, G. (2022). Perceive Toolbox.

Siegfried, J., & Lippitz, B. (1994). Bilateral chronic electrostimulation of ventroposterolateral pallidum: A new therapeutic approach for alleviating all parkinsonian symptoms. *Neurosurgery*, *35*(6), 1126–1130. https://doi.org/10.1227/00006123-199412000-00016

Sil, T., Hanafi, I., Eldebakey, H., Palmisano, C., Volkmann, J., Muthuraman, M., … Peach, R. (2023). Wavelet-Based Bracketing, Time–Frequency Beta Burst Detection: New Insights in Parkinson's Disease. *Neurotherapeutics*, *20*(6), 1767–1778.

Silberstein, P., Kühn, A. A., Kupsch, A., Trottenberg, T., Krauss, J. K., Wöhrle, J. C., … Brown, P. (2003). Patterning of globus pallidus local field potentials differs between Parkinson's disease and dystonia. *Brain*. https://doi.org/10.1093/brain/awg267

Sinclair, N.C., McDermott, H. J., Bulluss, K. J., Fallon, J. B., Perera, T., Xu, S. S., … Thevathasan, W. (2018). Subthalamic nucleus deep brain stimulation evokes resonant neural activity. *Ann Neurol*, *83*, 1027–1031.

Sinclair, Nicholas C., McDermott, H. J., Fallon, J. B., Perera, T., Brown, P., Bulluss, K. J., & Thevathasan, W. (2019). Deep brain stimulation for Parkinson's disease modulates high-frequency evoked and spontaneous neural activity. *Neurobiology of Disease*, *130*, 384–388. https://doi.org/10.1016/j.nbd.2019.104522

Society, M.-I. P. and M. D. (n.d.). MDS-Unified Parkinson's Disease Rating Scale (MDS-UPDRS). Retrieved from https://www.movementdisorders.org/MDS/MDS-Rating-Scales/MDS-Unified-Parkinsons-Disease-Rating-Scale-MDS-UPDRS.htm

Stam, M., van Wijk, B., Sharma, P., Beudel, M., Piña-Fuentes, D., de Bie, R., … Buijink, A. (2023). A comparison of methods to suppress electrocardiographic artifacts in local field potential recordings. *Clinical Neurophysiology*, *146*, 147–161. https://doi.org/10.1016/j.clinph.2022.11.011

Stanslaski, S., Afshar, P., Cong, P., Giftakis, J., Stypulkowski, P., Carlson, D., … Denison, T. (2012). Design and validation of a fully implantable, chronic, closed-loop neuromodulation device with concurrent sensing and stimulation. *IEEE Transactions on Neural Systems and Rehabilitation Engineering*. https://doi.org/10.1109/TNSRE.2012.2183617

Steigerwald, F., Timmermann, L., Kühn, A., Schnitzler, A., Reich, M. M., Kirsch, A. D., … Volkmann, J. (2018). Pulse duration settings in subthalamic stimulation for Parkinson's disease. *Movement Disorders*, *33*(1), 165–169. https://doi.org/10.1002/mds.27238

Su, D., Chen, H., Hu, W., Liu, Y., Wang, Z., Wang, X., … Feng, T. (2018). Frequency-dependent effects of subthalamic deep brain stimulation on motor symptoms in Parkinson's disease: a meta-analysis of controlled trials. *Scientific Reports*, *8*(1), 1–9. https://doi.org/10.1038/s41598-018-32161-3

Swann, N., Poizner, H., Houser, M., Gould, S., Greenhouse, I., Cai, W., … Aron, A. R. (2011). Deep brain stimulation of the subthalamic nucleus alters the cortical profile of response inhibition in the beta frequency band: A scalp EEG study in parkinson's disease. *Journal of Neuroscience*, *31*(15), 5721–5729. https://doi.org/10.1523/JNEUROSCI.6135-10.2011

Tahafchi, P., Molina, R., Roper, J. A., Sowalsky, K., Hass, C. J., Gunduz, A., … Judy, J. W. (2017). Freezing-of-Gait detection using temporal, spatial, and physiological features with a support-vector-machine classifier. *Proceedings of the Annual International Conference of the IEEE Engineering in Medicine and Biology Society,*

EMBS, (352), 2867–2870. https://doi.org/10.1109/EMBC.2017.8037455

Tai, C.-H., Boraud, T., Bezard, E., Bioulac, B., Gross, C., & Benazzouz, A. (2003). Electrophysiological and metabolic evidence that high-frequency stimulation of the subthalamic nucleus bridles neuronal activity in the subthalamic nucleus and the substantia nigra reticulata. *The FASEB Journal*, *17*(13), 1820–1830. https://doi.org/10.1096/fj.03-0163com

Thenaisie, Y., Palmisano, C., Canessa, A., Keulen, B. J., Capetian, P., Jiménez, M. C., … Contarino, M. F. (2021). Towards adaptive deep brain stimulation: Clinical and technical notes on a novel commercial device for chronic brain sensing. *Journal of Neural Engineering*, *18*(4). https://doi.org/10.1088/1741-2552/ac1d5b

Tinkhauser, G., Pogosyan, A., Debove, I., Nowacki, A., Shah, S. A., Seidel, K., … Schuepbach, M. (2018). Directional local field potentials: a tool to optimize deep brain stimulation. *Mov. Disord*, *33*(1), 159–164.

Tinkhauser, Gerd, Pogosyan, A., Little, S., Beudel, M., Herz, D. M., Tan, H., & Brown, P. (2017). The modulatory effect of adaptive deep brain stimulation on beta bursts in Parkinson's disease. *Brain*. https://doi.org/10.1093/brain/awx010

Torrecillos, F., Tinkhauser, G., Fischer, P., Green, A. L., Aziz, T. Z., Foltynie, T., … Tan, H. (2018). Modulation of beta bursts in the subthalamic nucleus predicts motor performance. *Journal of Neuroscience*. https://doi.org/10.1523/JNEUROSCI.1314-18.2018

Tracy, J. M., Özkanca, Y., Atkins, D. C., & Hosseini Ghomi, R. (2020). Investigating voice as a biomarker: Deep phenotyping methods for early detection of Parkinson's disease. *Journal of Biomedical Informatics*, *104*(March 2019), 103362.

Trottenberg, T., Kupsch, A., Schneider, G. H., Brown, P., & Kühn, A. A. (2007). Frequency-dependent distribution of local field potential activity within the subthalamic nucleus in Parkinson's disease. *Experimental Neurology*, *205*(1), 287–291. https://doi.org/10.1016/j.expneurol.2007.01.028

Tsiokos, C., Malekmohammadi, M., AuYong, N., & Pouratian, N. (2017). Pallidal low β-low γ phase-amplitude coupling inversely correlates with Parkinson disease symptoms. *Clinical Neurophysiology*, *128*(11), 2165–2178. https://doi.org/10.1016/j.clinph.2017.08.001

Tykocki, T., Nauman, P., Koziara, H., & Mandat, T. (2013). Microlesion Effect as a Predictor of the Effectiveness of Subthalamic Deep Brain Stimulation for Parkinson's Disease. *Stereotact Funct Neurosurg*, *91*(1), 12–17.

Tysnes, O. B., & Storstein, A. (2017). Epidemiology of Parkinson's disease. *Journal of Neural Transmission*, *124*(8), 901–905. https://doi.org/10.1007/s00702-017-1686-y

Valldeoriola, F., Muñoz, E., Rumià, J., Roldán, P., Cámara, A., Compta, Y., … Tolosa, E. (2019). Simultaneous low-frequency deep brain stimulation of the substantia nigra pars reticulata and high-frequency stimulation of the subthalamic nucleus to treat levodopa unresponsive freezing of gait in Parkinson's disease: A pilot study. *Parkinsonism and Related Disorders*, *60*(September 2018), 153–157. https://doi.org/10.1016/j.parkreldis.2018.09.008

Valsky, D., Blackwell, K., Tamir, I., Eitan, R., Bergman, H., & Israel, Z. (2020). Real-time machine learning classification of pallidal borders during deep brain stimulation surgery. *J Neural Eng*, *17*(1), 016021.

van Wijk, B. C. M., Beudel, M., Jha, A., Oswal, A., Foltynie, T., Hariz, M. I., … Litvak, V. (2016). Subthalamic nucleus phase-amplitude coupling correlates with motor impairment in Parkinson's disease. *Clinical Neurophysiology*, *127*(4), 2010–2019. https://doi.org/10.1016/j.clinph.2016.01.015

van Wijk, B. C. M., Bie, R. M. A. de, & Beudel, M. (2023). A systematic review of local feld potential physiomarkers in Parkinson's disease: from clinical correlations to adaptive deep brain stimulation algorithms. *Journal of Neurology*, *270*, 1162–1177. https://doi.org/10.1007/s00415-022-11388-1

Vedam-Mai, V., Van Battum, E. Y., Kamphuis, W., Feenstra, M. G. P., Denys, D., Reynolds, B. A., … Hol, E. M. (2012). Deep brain stimulation and the role of astrocytes. *Molecular Psychiatry*, *17*(2), 124–131. https://doi.org/10.1038/mp.2011.61

Vedam-Mai, V., Baradaran-Shoraka, M., Reynolds, B., & Okun, M. (2016). Tissue Response to Deep Brain Stimulation and Microlesion: A Comparative Study. *Neuromodulation*, *19*(5), 451–458. https://doi.org/10.1111/ner.12406

Velisar, A., Syrkin-Nikolau, J., Blumenfeld, Z., Trager, M. H., Afzal, M. F., Prabhakar, V., & Bronte-Stewart, H. (2019). Dual threshold neural closed loop deep brain stimulation in Parkinson disease patients. *Brain Stimulation*. https://doi.org/10.1016/j.brs.2019.02.020

Verma, A., Yu, Y., Acosta-Lenis, S., Havel, T., Sanabria, D., Molnar, G., … Johnson, L. (2023). Parkinsonian daytime sleep-wake classification using deep brain stimulation lead recordings. *Neurobiol Dis.* https://doi.org/176:105963

Verma, N., Shoeb, A., Bohorquez, J., Dawson, J., Guttag, J., & Chandrakasan, A. P. (2010). A micro-power EEG acquisition SoC with integrated feature extraction processor for a chronic seizure detection system. *IEEE Journal of Solid-State Circuits*, *45*(4), 804–816. https://doi.org/10.1109/JSSC.2010.2042245

Virbel-Fleischman, C., Mousin, F., Liu, S., Hardy, S., Corvol, J., Benatru, I., … Grabli, D. (2023). Symptoms assessment and decision to treat patients with advanced Parkinson's disease based on wearables data. *Npj Parkinsons Dis*, *9*(45). https://doi.org/10.1038/s41531-023-00489-x

Vissani, M., Isaias, I. U., & Mazzoni, A. (2020). Deep brain stimulation: A review of the open neural engineering challenges. *Journal of Neural Engineering*, *17*(5). https://doi.org/10.1088/1741-2552/abb581

Vitek, J., Zhang, J., Hashimoto, T., Russo, G., & Baker, K. (2012). External pallidal stimulation improves parkinsonian motor signs and modulates neuronal activity throughout the basal ganglia thalamic network. *Exp. Neurol.*, *233*(581–586).

Volkmann, J. (2004). Deep brain stimulation for the treatment of Parkinson's disease. *J Clin Neurophysiol*, *21*, 6–17.

Wang, DD, D., Hemptinne, C., Miocinovic, S., Qasim, S., Miller, A., Ostrem, J., … Starr, P. (2016). Subthalamic local field potentials in Parkinson's disease and isolated dystonia: An evaluation of potential biomarkers. *Neurobiol Dis*, *89*, 213–222. https://doi.org/10.1016/j.nbd.2016.02.015

Wang, C. F., Yang, S. H., Lin, S. H., Chen, P. C., Lo, Y. C., Pan, H. C., … Chen, Y. Y. (2017). A proof-of-principle simulation for closed-loop control based on preexisting experimental thalamic DBS-enhanced instrumental learning. *Brain Stimulation*, *10*(3), 672–683. https://doi.org/10.1016/j.brs.2017.02.004

Wang, J., Hirschmann, J., Elben, S., Hartmann, C. J., Vesper, J., Wojtecki, L., & Schnitzler, A. (2014). High-frequency oscillations in Parkinson's disease: Spatial distribution and clinical relevance. *Movement Disorders*, *29*(10), 1265–1272. https://doi.org/10.1002/mds.25962

Warren, G., Snyder, A., & Miocinovic, S. (2004). Deep brain stimulation creates an informational lesion of the stimulated nucleus. *NeuroReport*, *15*(7), 1137–1140.

Watts, J., Khojandi, A., Shylo, O., & Ramdhani, R. A. (2020). brain sciences Machine Learning ' s Application in Deep Brain Stimulation for Parkinson ' s Disease : A Review.

Welch, P. D. (1967). The Use of Fast Fourier Transform for the Estimation of Power Spectra: A Method Based on Time Averaging Over Short, Modified Periodograms. *IEEE Transactions on Audio and Electroacoustics*. https://doi.org/10.1109/TAU.1967.1161901

Whitmer, D., de Solages, C., Hill, B., Yu, H., Henderson, J. M., & Bronte-Stewart, H. (2012). High frequency deep brain stimulation attenuates subthalamic and cortical rhythms in Parkinson's disease. *Frontiers in Human Neuroscience*, *6*(JUNE 2012), 1–18. https://doi.org/10.3389/fnhum.2012.00155

Wiest, C, He, S., Duchet, B., Pogosyan, A., Benjaber, M., Denison, T., … Tan, H. (2023). Evoked resonant neural activity in subthalamic local field potentials reflects basal ganglia network dynamics. *Neurobiol Dis.*, *178*(106019.).

Wiest, Christoph, Torrecillos, F., Pogosyan, A., Bange, M., Muthuraman, M., Groppa, S., … Tan, H. (2023). The aperiodic exponent of subthalamic field potentials reflects excitation/ inhibition balance in Parkinsonism. *ELife*, *12*(e82467). https://doi.org/10.7554/eLife.82467

Wojtecki, L., Hirschmann, J., Elben, S., Boschheidgen, M., Trenado, C., Vesper, J., & Schnitzler, A. (2017). Oscillatory coupling of the subthalamic nucleus in obsessive compulsive disorder. *Brain*. https://doi.org/10.1093/brain/awx164

Xie, T, Kang, U., & Warnke, P. (2012). Effect of stimulation frequency on immediate freezing of gait in newly activated STN DBS in Parkinson's disease. *J Neurol Neurosurg Psychiatry*, *83*, 1015–1017.

Xie, Tao, Padmanaban, M., Bloom, L., MacCracken, E., Bertacchi, B., Dachman, A., & Warnke, P. (2017). Effect of low versus high frequency stimulation on freezing of gait and other axial symptoms in Parkinson patients with bilateral STN DBS: A mini-review. *Translational Neurodegeneration*, *6*(1). https://doi.org/10.1186/s40035-017-0083-7

Yao, L., Brown, P., & Shoaran, M. (2020). Improved detection of Parkinsonian resting tremor with feature engineering and Kalman filtering. *Clinical Neurophysiology*, *131*(1), 274–284.

Yin, Zixiao, Zhu, G., Zhao, B., Bai, Y., Jiang, Y., Neumann, W. J., … Zhang, J. (2021). Local field potentials in Parkinson's disease: A frequency-based review. *Neurobiology of Disease*, *155*, 105372. https://doi.org/10.1016/j.nbd.2021.105372

Yoo, J., Noh, M., Kim, H., Jeon, N. L., Kim, B. S., & Kim, J. (2015). Nanogrooved substrate promotes direct lineage reprogramming offibroblasts to functional induced dopaminergic neurons. *Biomaterials*, *45*, 36–45. https://doi.org/10.1016/j.biomaterials.2014.12.049

Yu, J., Vodyanik, M. A., Smuga-Otto, K., Antosiewicz-Bourget, J., Frane, J. L., Tian, S., … Thomson, J. A. (2007). Induced pluripotent stem cell lines derived from human somatic cells. *Science*, *318*(5858), 1917–1920. https://doi.org/10.1126/science.1151526

Zago, S., Ferrucci, R., Fregni, F., & Priori, A. (2007). Bartholow, Sciamanna, Alberti: Pioneers in the Electrical Stimulation of the Exposed Human Cerebral Cortex. *The Neuroscientist*, *14*(5), 521–528.

https://doi.org/10.1177/1073858407311101
Zénon, A., Duclos, Y., Carron, R., Witjas, T., Baunez, C., Régis, J., … Eusebio, A. (2016). The human subthalamic nucleus encodes the subjective value of reward and the cost of effort during decision-making. *Brain*, *139*(6), 1830–1843. https://doi.org/10.1093/brain/aww075
Zhang, H., Deng, K., Li, H., Albin, R. L., & Guan, Y. (2020). Deep Learning Identifies Digital Biomarkers for Self-Reported Parkinson's Disease. *Patterns*, *1*(100042). https://doi.org/10.1016/j.patter.2020.100042
Zibetti, M., Moro, E., Krishna, V., Sammartino, F., Picillo, M., Munhoz, R. P., … Fasano, A. (2016). Low-frequency Subthalamic Stimulation in Parkinson's Disease: Long-term Outcome and Predictors. *Brain Stimulation*, *9*(5), 774–779. https://doi.org/10.1016/j.brs.2016.04.017

Annexes

Chapter 3- Supplementary Material

Tables 3.2-3.6- Publications included in this review, organized according to the treatment stage in DBS. Concerning the machine learning algorithms, the methods applied are mentioned as well as which model group they belong to, and the type of input data used. Acronyms: CT- Computerised Tomography; EEG- Electroencephalogram; EMG - Electromyography; LFP- Local Field Potentials; qEEG- Quantitative Electroencephalogram; MER- Microelectrode Arrays; MIR- Magnetic Resonance Imaging. Model Group: Cf- Classification; Ct- Clustering; DR/FS- Dimensionality Reduction/ Feature Selection. R/TS- Regression/ Time Series.

Table 3.2 Publications included in the review under the category "DBS therapy management".

DBS therapy management					
Author & Year	Stage	Goal	Input/Type of data	Model Group	Model used
Castano-Candamil et al, 2019	Planning	Propose of a fine motor function assessment framework for capturing transient DBS-induced changes.	Copy-drawn test	DR/FS	LDA
Boutet et al, 2021	Release	Examine if machine learning could predict the benefits in specific Parkinsonian signs when informed by precise locations of stimulation.	Unified Parkinson's Disease Rating Scale (UPDRS-III)	Cf	SVM
Lu et al, 2020	Surgery	Describe and predict regions of therapeutic tissue activation.	MER	Cf, R/TS	L1 LASSO, SVM
LeMoyne et al, 2020	Tuning	Study of deep brain stimulation amplitude parameters.	Wearables	Cf	NN, Multilayer Perceptron
Mohammed et al, 2020	Tuning	Present an approach that uses machine learning models to estimate the symptom severity of patients and adjust therapy accordingly.	LFPs	Cf, Ct	SVM, GMM

Table 3.3 Publications included in the review under the category “Detection/management of symptoms”.

Detection/management of symptoms					
Author & Year	Stage	Goal	Input/Type of data	Model Group	Model used
Liu et al, 2022	Planning/Tuning	Describe a synchronized intracranial electroencephalogram recording and motion capture system.	EEG, Codamotion System.	Cf	RF
Oliveira et al, 2018	Planning	Discriminating neurologically healthy individuals from those suffering from PD (treated with levodopa and DBS).	Wearables & EMG	Cf, DR/FS	SVM, PCA, Sammon's mapping, t-SNE
Kuhner et al, 2017	Release	Extract global motor performance measures covering different everyday motor tasks as a function of a clinical intervention.	Wearables	R/TS, Cf	RF
Kuhner et al, 2020	Release	Distinguish between healthy and PD subjects with DBS STN ON / OFF by identifying motion features and develop biomarkers for detecting and monitoring PD patients' motor symptoms.	3D gait analysis	Cf	Weak classifier, Meta-Classifier AdaBoost
Angeles et al, 2017	Tuning	Present a sensor system that can quantify the three cardinal motor symptoms of PD - rigidity, bradykinesia, and tremor.	Wearables	Cf	DT, SVM, KNN
Braga et al, 2019	Tuning	Detect early signs of PD through free speech in uncontrolled background conditions.	Speech recordings	Cf	RF, SVM, NN

Chen et al, 2019	Tuning	Investigate the sleep-stage classification based on LFPs in STN.	LFPs	Cf	SVM, DT
Geraedts et al, 2021	Tuning	Develop an automated machine learning model based on preoperative EEG data to predict cognitive deterioration 1 year after STN DBS.	qEEG	Cf	RF w/ Bayesian optimization
Habets et al, 2020	Tuning	Development of at machine learning logistic regression prediction model to generate probabilities for experiencing week motor response one year after surgery.	Preoperative variables	R/TS	LR
Hirschmann et al, 2022	Tuning	To predict motor symptoms improvement from STN power and subthalamo-cortical coherence.	MEG, LFPs	Cf	Extreme-gradient Boosted Trees
Huo et al, 2020	Tuning	Present a new wearable device for Parkinson's diagnosis.	Wearables	Ct, Cf	1-NN, Multilayer Perceptron, AdaBoost classifier
Khobragade et al, 2015	Tuning	Apply the LAMSTAR (Large memory storage and retrieval) neural network for prediction of onset of tremor in PD patients to allow for on-off adaptive control of DBS.	Surface EMG, wearables	Cf	NN
Khodakarami et al, 2019	Tuning	Ascertain whether an ambulatory wearable device could predict the response to levodopa from the response to the first morning dose.	Wearables	R/TS, Cf	LR, SVM, RBF kernel, Gradient Boosting DT

Kleinholdermann et al, 2023	Tuning	Assess the benefits of non-invasive movement recordings to predict best DBS settings.	Wearables	R/TS	RF
Livi et al, 2016	Tuning	Discrimination and characterization of Parkinsonian rest tremors.	Laser based tremor frequency measurement	DR/FS, Cf	SVM
Liu et al, 2021	Tuning	Investigate whether substantia nigra susceptibility features derived from radiomics with machine learning can predict motor outcome of STN-DBS in PD.	MRI	R/TS	LR
Mohammed et al, 2015	Tuning	Create a patient customized detector for PD.	LFPs	Cf	SVM
Park et al, 2021	Tuning	Predict motor function improvement by applying DL techniques to MER.	MER	Cf	DL
Peralta et al, 2021	Tuning	Propose a machine learning-based method able to predict many DBS clinical outcomes for PD.	Clinical data, MRI	Cf	ANN, SVM
Shah et al, 2018	Tuning	Investigate the use of a logistic regression-based classifier to identify periods when PD patients have rest tremor by exploiting Local Field Potentials recorded with DBS STN.	LFPs	R/TS	LR

Shamir et al, 2015	Tuning	Implementation of a clinical decision support system that incorporates patient-specific details on both stimulation and medication.	Clinical Data	Cf	SVM, NB, RF
Tahafchi et al, 2017	Tuning	Propose of a FoG-detection method that captures temporal, spatial, and physiological features and uses a SVM to classify freezing episodes.	Wearables & EMG	Cf	SVM
Tracy et al, 2020	Tuning	Explore voice for early detection of PD and its potential as a deep phenotype for PD.	Voice recordings	R/TS	L2 Ridge regularized logistic regression, random forest, gradient boosted decision trees.
Yao et al, 2020	Tuning	Detect resting episodes in PD.	LFPs	Cf, R/TS, Ct, DR/FS	Kalman filtering, LR, SVM, LDA, Multilayer Perceptron, KNN, Extreme-gradient Boosted Trees, RF

Table 3.4 Publications included in the review under the category “Identification of Biomarkers”.

Identification of Biomarkers					
Author & Year	Stage	Goal	Input/Type of data	Model Group	Model used
Geraedts et al, 2021	Tuning	Explore electroencephalography signals as biomarker of cognition using a Machine Learning pipeline.	EEG	R/TS	RF
Hirschmann et al, 2017	Tuning	Tremor detection based on LFP based biomarkers.	LFPs	Cf	HMM
Khojandi et al, 2017	Tuning	Develop a computational model which stratifies patients based on symptomatology into different frequency settings.	Preoperative MDS-Unified Parkinson’s Disease Rating Scale III scores.	Cf	RF, SVM, NN
Wang 2022	Tuning	Comparison of resting state cortical connectivity between the off and off stimulation states and to healthy controls.	MDS-Unified Parkinson’s Disease Rating Scale, LFPs	Cf	RF, SVM
Zhang et al, 2020	Tuning	To extract digital biomarkers of PD from crowd-sourced movement records.	Wearables	Cf, DR/FS	Deep CNN

Table 3.5 Publications included in the review under the category “Peri-operative management”.

Peri-operative management					
Author & Year	Stage	Goal	Input/Type of data	Model Group	Model used
Baumgarten et al, 2016	Release	Propose of a pre-operative predictive model of PTSE.	Clinical data, MRI, CT	Cf	ANN
Chen et al, 2021	Release	Investigate the association between brain morphology and initial STN-DBS efficacy.	CT, LFPs, MRI	Cf	SVM
Cao et al, 2019	Surgery	Online identification of functional regions in deep brain stimulation based on an unsupervised random forest with feature selection.	MER	R/TS	RF
Hosny et al, 2021	Surgery	Delineation of the neurophysiological borders of the STN along the electrode trajectory developed.	MER	Cf	CNN
Kim et al, 2019	Surgery	Automatic localization of the subthalamic nucleus on patient specific clinical MRI.	MRI	R/TS	Regression
Khosravi et al, 2020	Surgery	Presents an objective approach to help the surgical team in localizing the STN in real-time.	MER	Cf, R/TS	SVM, LR, KNN, DT, CNN
Ozturk et al, 2020	Surgery	Compare the clinical benefit from SUA- versus LFP-based implantation using intraoperative online LFP processing.	LFPs	DR/FS	LDA

Valsky et al, 2017	Surgery	Present machine learning classification procedures that utilize MER power spectra and allow for real time and high accuracy discrimination between STN and substantia nigra pars reticulata.	MER	Cf	SVM, HMM
Valsky et al, 2020	Surgery	Propose a real-time machine learning classification of pallidal borders during deep brain stimulation surgery.	MER	Cf	HMM, L1 LASSO
Farrokhi et al, 202	Tuning	Investigate preoperative clinical risk factors and predict adverse outcomes.	Clinical and demographic characteristics	Cf, R/TS	LR, XGBM, NN

Table 3.6 Publications included in the review under the category “Signals decoding/encoding”.

Signals decoding/encoding					
Author & Year	Stage	Goal	Input/Type of data	Model Group	Model used
Zhu et al, 2020	Planning	Enable resource-efficient classification on a neural implant.	LFPs	Cf	Oblique DT
Camara et al, 2019	Release	Study of the non-linear dynamical behaviour of STN-LFPs of Parkinsonian patients.	LFPs, EMGs	Cf	Recurrence Networks
Castaño-Candamil et al, 2020	Tuning	Identifying controllable cortical neural markers.	Copy-drawn test, EEG	DR/FS, Cf, R/TS	LDA, source power co-modulation (SPoC), common spatial patterns (CSP)
Gilron et al, 2021	Tuning / Release	Long-term wireless streaming of neural recordings for aDBS.	LFPs	Ct	Unsupervised clustering
Golshan et al, 2018	Tuning	Present a human behaviour classification using LFP signals recorded from STN.	LFPs	Cf	SVM
Golshan et al, 2020	Tuning	Classify human behaviour using the time-frequency representation of STN-LFPs within the beta frequency range.	LFPs	Cf	CNN
Islam et al, 2017	Tuning	Explore deep brain LFPs for robust movement decoding of PD and Dystonia patients.	LFPs	Cf	NN

Khawaldeh et al, 2020	Tuning	Test the hypothesis that increased synchronization denoted by beta bursting might compromise information coding capacity in basal ganglia networks.	LFPs	Cf	NB
Manum et al, 2015	Tuning	Decode movement related behaviours from the recorded LFP activity.	LFPs	Cf	GNB, SVM

Ethics Committee Proposal

Parecer da Comissão de Ética do

Centro Hospitalar Universitário de São João / Faculdade de Medicina da Universidade do Porto

Título do Projeto: Towards effective feedback control in deep brain stimulation: combining brain sensing neurostimulators, detailed clinical information and machine learning techniques for improved Parkinson's disease data-driven treatments.

Nome da Investigadora principal: Dra. Andreia Oliveira.

Onde decorre o estudo: No Serviço de Neurocirurgia do CHUSJ. Apresentou declaração do Prof. Doutor Rui Vaz, que será o profissional de ligação e orientador.

Objetivos do estudo: Avaliar o valor preditivo dos dados eletrofisiológicos retirando vantagem da capacidade do Percept PC para registos de eventos específicos. Explorar a estrutura do sinal e os padrões de atividade nos dados registados, com técnicas de aprendizagem supervisionada e não supervisionada. Monitorização das mudanças no estado da atividade e dos perfis circadianos que possa suportar a modelação do protocolo de estimulação.

Conceção e pertinência do estudo: As tecnologias de estimulação cerebral profunda acarretam diversos desafios que limitam a operabilidade dos neuroestimuladores, assim como efeitos secundários adversos que não podem ser menosprezados. A presente investigação prevê resultados relacionados com a melhoria da eficácia dos protocolos de estimulação, de modo a diminuir as suas implicações negativas.

Benefício/risco: Benefício potencial para a sociedade através da evolução do conhecimento científico neste domínio.

Confidencialidade dos dados: Os dados são anonimizados devendo ser garantida a sua total confidencialidade.

Respeito pela liberdade e autonomia do sujeito de ensaio: Dada a total anonimização dos dados é legítimo presumir o consentimento dos participantes.

***Curriculum* da investigadora**: Adequado à investigação.

Data previsível da conclusão do estudo: Setembro de 2024

Conclusão: Proponho um parecer favorável à realização deste projeto de investigação.

Porto, 23 de outubro de 2020

O Relator da CE, Prof. Doutor Rui Nunes

smartDBS: Participant Information

The objective of this study is to develop more effective and personalized Deep Brain Stimulation (DBS) therapies used for the treatment of neurological and psychiatric disorders, such as Parkinson's Disease (PD). This study is integrated into subsequent Neurology consultations for the evaluation of DBS therapy and is conducted for an indefinite period. The target population is individuals diagnosed with PD, undergoing DBS, after informed, clarified, and free consent.

Three types of signals will be recorded simultaneously during the consultation:
1. Signals from the brain: extracted through the clinician's tablet connected to the patient's neurostimulator.
2. Movement signals: sensors placed on both hands, on the index finger, and on the palm of the hand.
3. Video recording: to complement the recording of motor symptoms and for synchronization purposes.

The protocol consists of 8 stages:
1. Baseline recording: without stimulation.
2. Resting tremor study in response to variation: left hemisphere.
3. Resting tremor study in response to variation: right hemisphere.
4. Rigidity study in response to variation: left hemisphere.
5. Rigidity study in response to variation: right hemisphere.
6. Bradykinesia study in response to variation: left hemisphere.
7. Bradykinesia study in response to variation: right hemisphere.
8. Baseline recording: therapeutic stimulation.

Estimated session duration: 35-40 minutes.

DBScope User Guide

DBScope
Visualization and Analysis of DBS data from Percept PC

Toolbox for import, preprocessing, visualization and analysis of Deep Brain Stimulation sensing recordings extracted from Medtronic's Percept PC

Andreia M. Oliveira, Eduardo Carvalho, Beatriz Barros & Paulo Aguiar
Faculty of Engineering of University of Porto (FEUP)
Neuroengineering and Computational Neuroscience (NCN) Lab,
I3S – Instituto de Investigação e Inovação em Saúde
Porto, Portugal
[pauloaguiar@i3s.up.pt]
Feb 2024

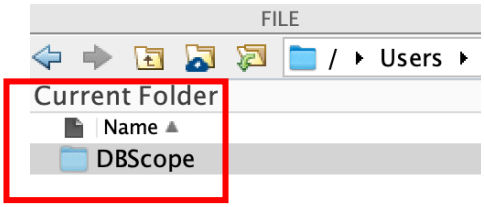
Installation

If you are only interested in DBScope's graphical user interface, you just need to install the standalone application (available for MSWindows and macOS). Just download the standalone application from this link: https://github.com/NCN-Lab/DBScope/releases

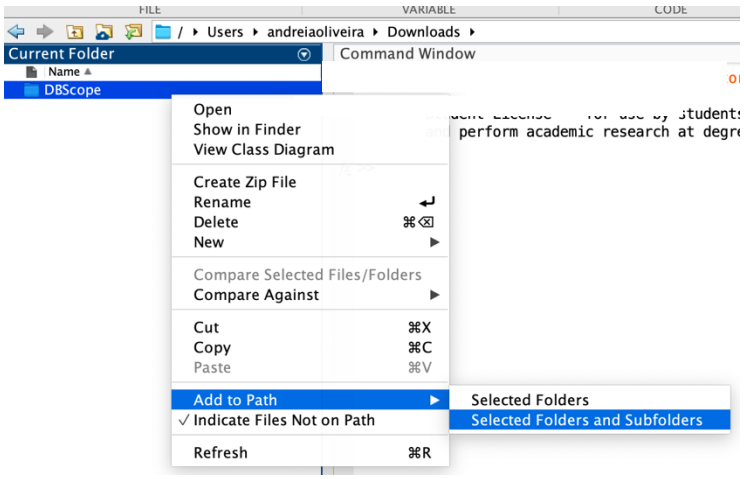
To access all the functionalities of DBScope (programming mode), download the open-source DBScope package from this link: https://github.com/NCN-Lab/DBScope

For the programming mode, you need to have MATLAB installed. The toolbox requires MATLAB versions R2021 and upwards. MATLAB is a paid application, but very frequently available in universities and research institutes.

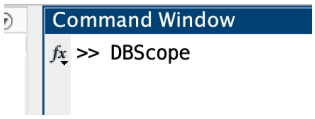
Once you have MATLAB installed, open the programming environment. Open the directory in the folder containing the DBScope package:



Then, add the 'DBScope' to path, by selecting the option 'Add to Path > Select Folders and Subfolders':



From this moment on, the toolbox is operational. You can access the tools directly via command window, or through the User Interface. To open the User Interface, run the command:
>> DBScope



Input files

The input data of the toolbox are the .json files directly extracted from the clinical console of the Percept PC.

DBScope Package

The DBScope toolbox was built for the import, preprocessing, visualization and analysis of Deep Brain Stimulation sensing recordings extracted from Medtronic's IPG- Percept PC. The files contain several types of recordings corresponding to the sensing modes available. The Percept PC has four main sensing modes: survey and setup, for in-clinic parameterization of the leads for sensing and stimulation; streaming, for in-clinic recordings; and timeline with events, for out-of-clinic recordings, containing snapshots of events logged by the patient.

Besides the graphical user interface that allows to easily access the information available in the data structure, the tools can be accessed programmatically (script and command window), bypassing the user interface. A step-by-step guide for these functionalities will be described below, with examples.

Main graphical user interface

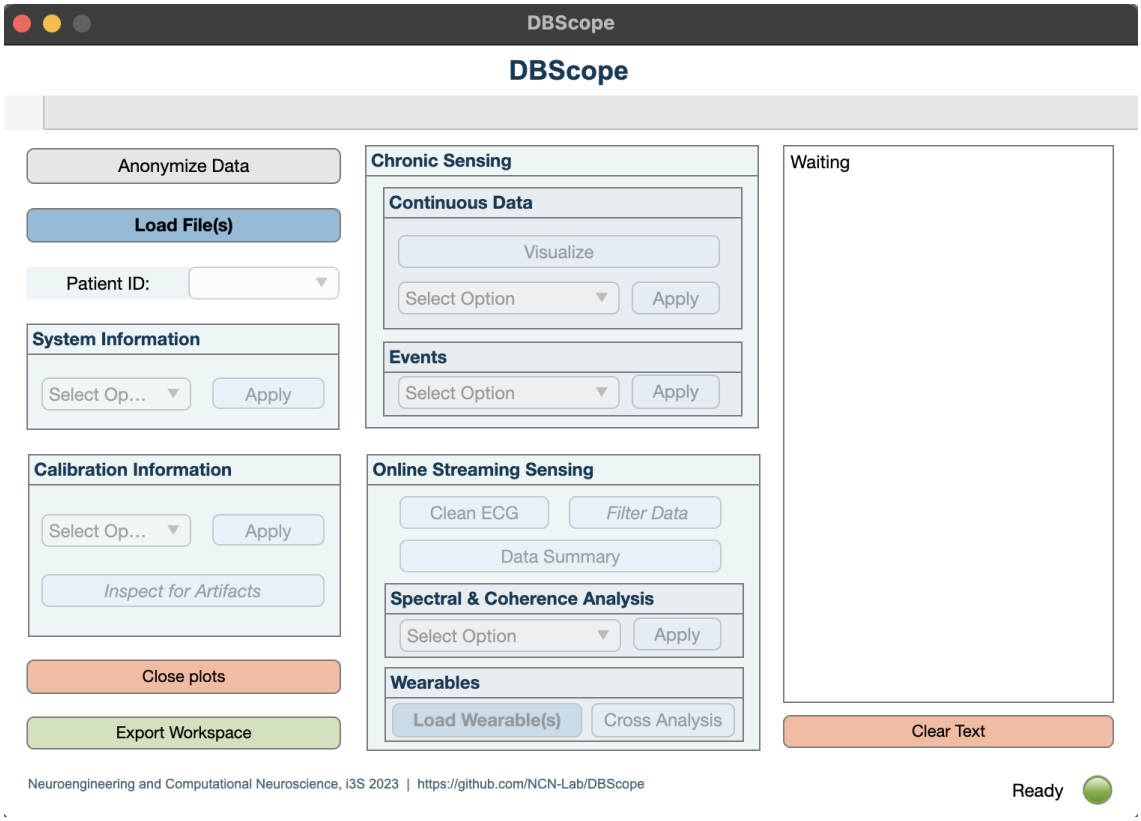
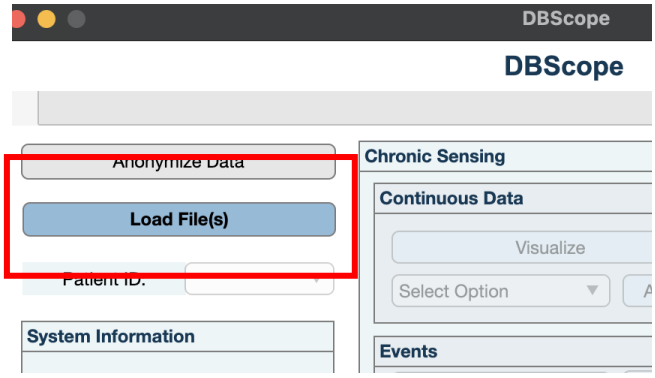


Figure 1. DBScope: Toolbox for import, preprocessing, visualization and analysis of Deep Brain Stimulation sensing recordings extracted from Medtronic's Percept PC – main window.

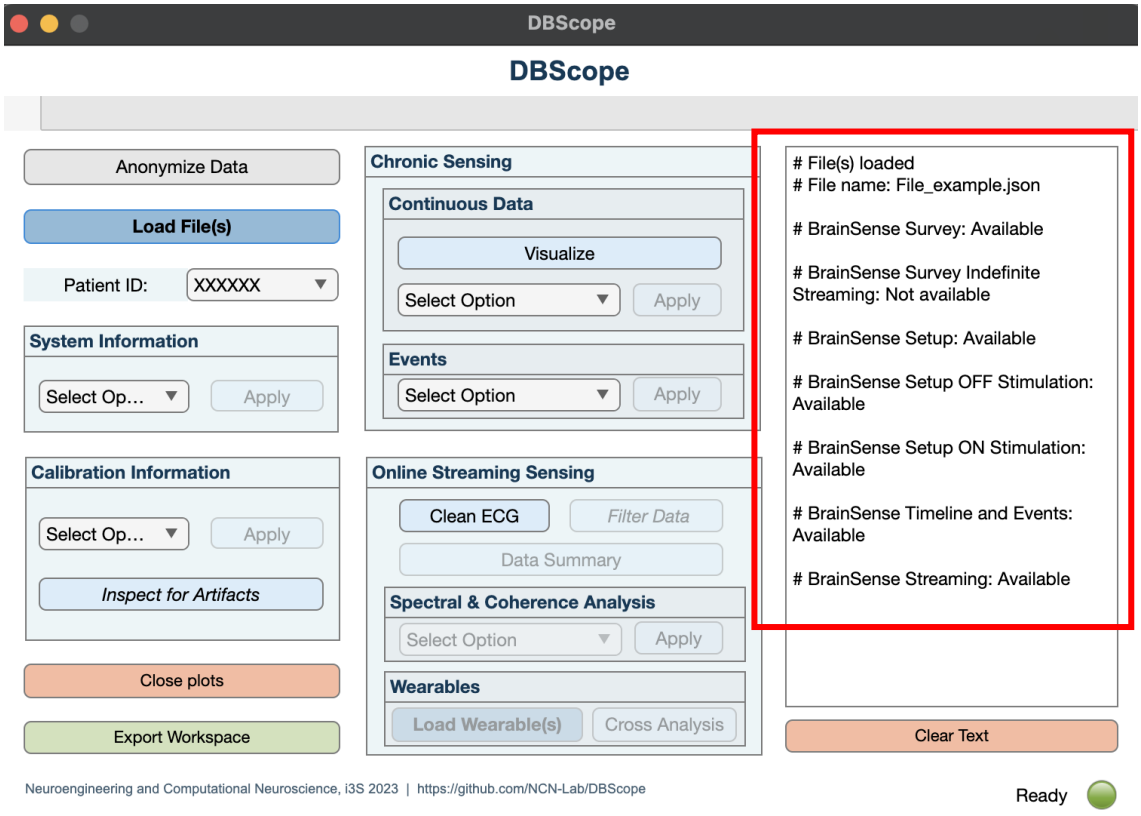
The toolbox can operate either on single file or multiple files (multi-selected or by uploading a folder). It also possible to upload previously recorded workspaces in .mat format.

A note on the visualization window: as each visualization window is independent, is it possible to open and operate several visualization windows simultaneously.

To load the file(s) click on the button 'Load File(s)' and select the process and files to upload.



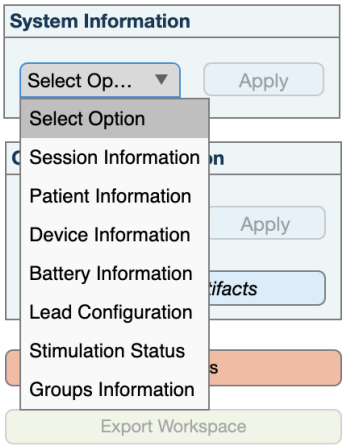
Once the file(s) is(are) uploaded, a message will appear in the text box with the information of which sensing recordings modes are available:

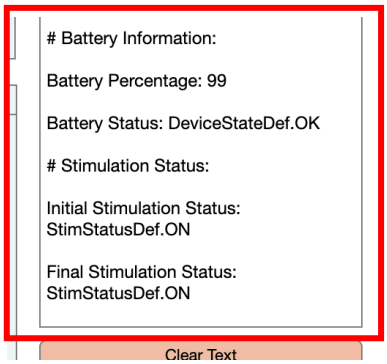


Depending on the sensing modes in the files, the following features are available: System Information, Calibration Information, Chronic Sensing and Online Streaming Sensing.

System Information

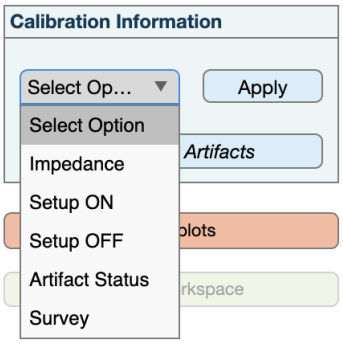
Here, the user can access system, patient, and hardware information. The information will be displayed in the text window on the right.

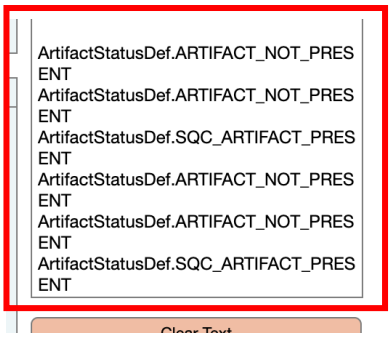


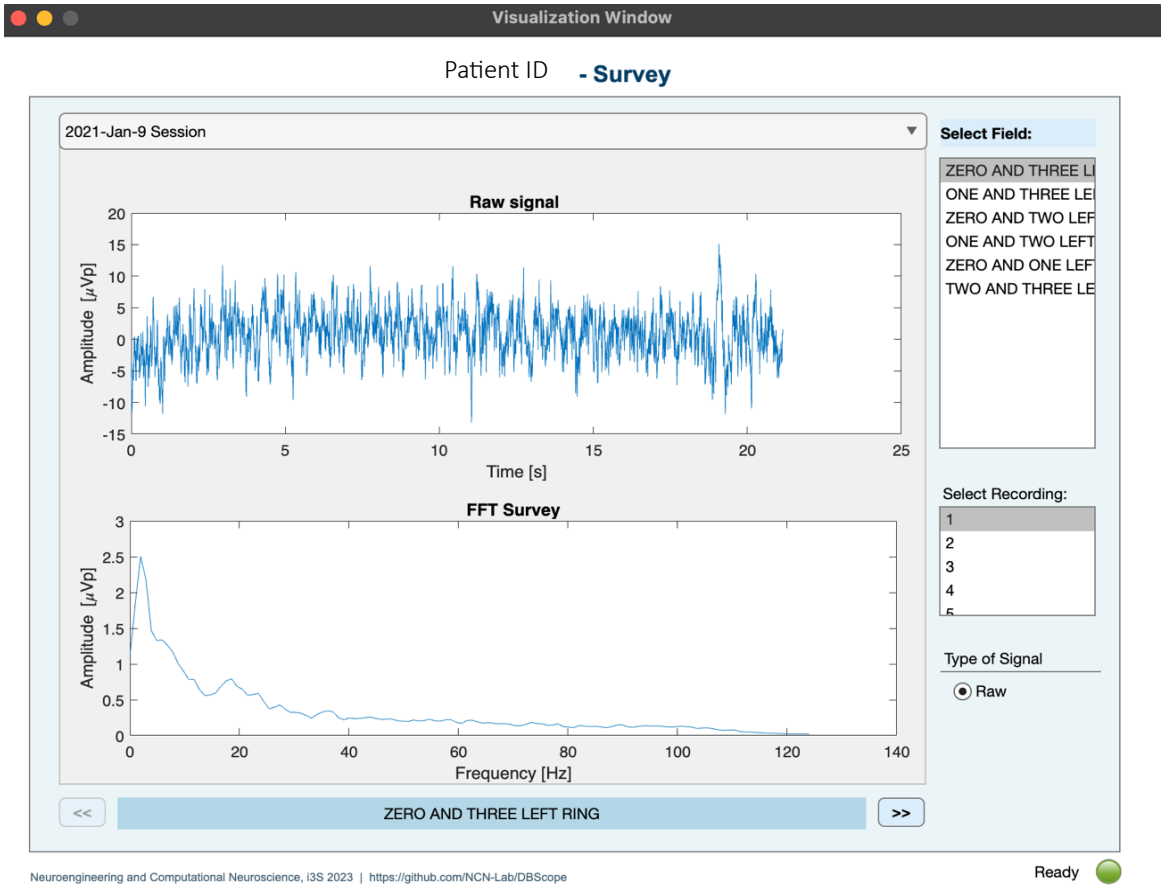


Calibration Information

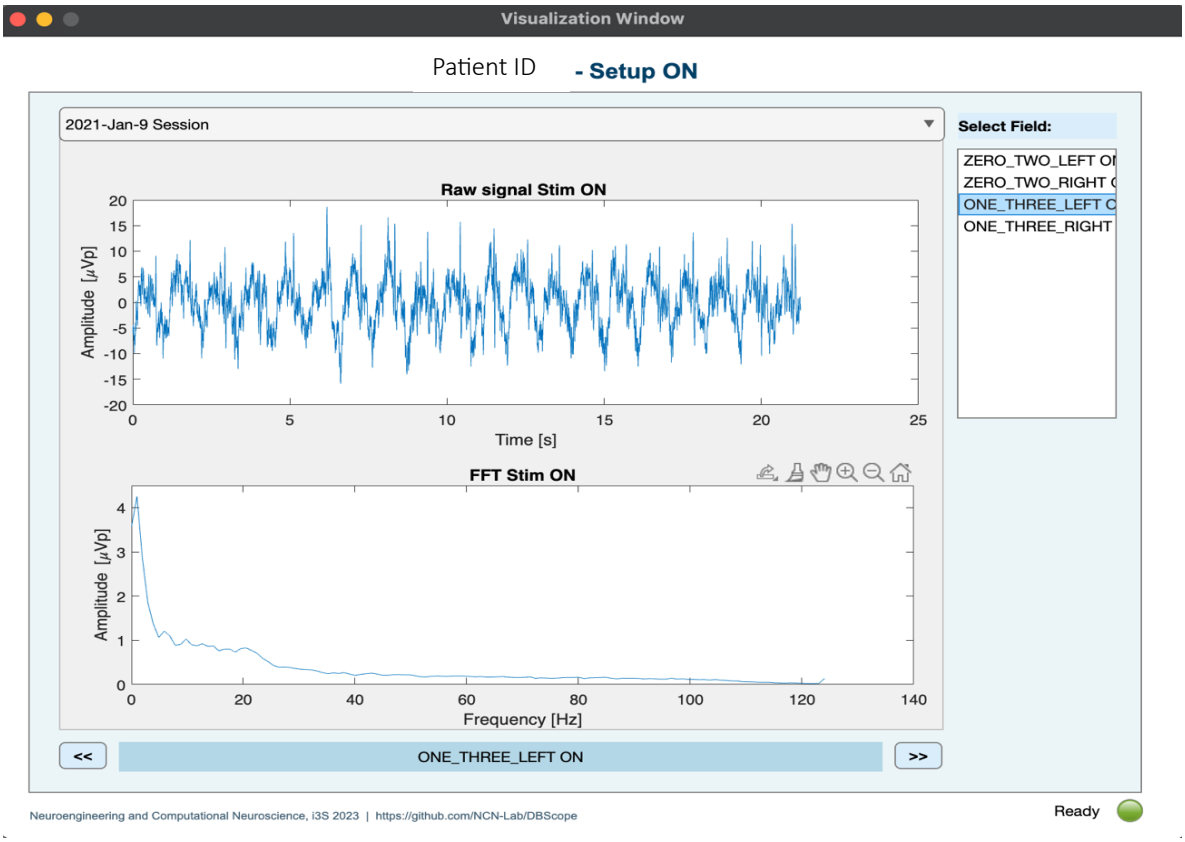
In this section, the user can access information about calibration. This includes the impedance tests performed in clinic, the presence of artifacts, and plots of the recordings from the recording modes Survey, Setup and Indefinite Streaming (if available in file(s)). The information about the presence of artifacts detected by the IPG will be made available in the text window.





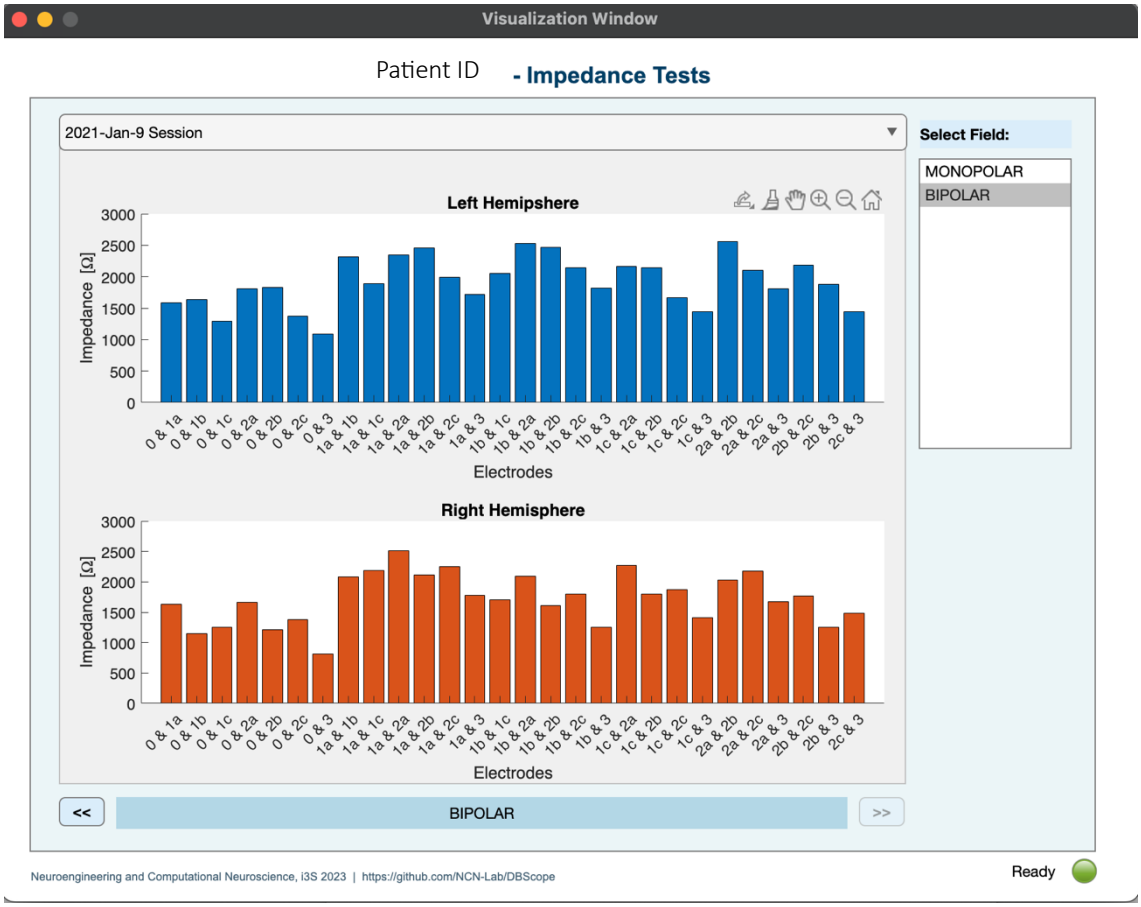


[Example of Survey recording visualization.]



[Example of Setup Stimulation ON recording visualization.]

Impedance



[Example of Impedance visualization.]

Inspect for Artifacts

A secondary User Interface is available at 'Inspect for Artifacts'. This feature allows the user to visualize the survey signals both in the time and frequency domains, and to design custom filters, that may help in the manual inspection for artifacts.

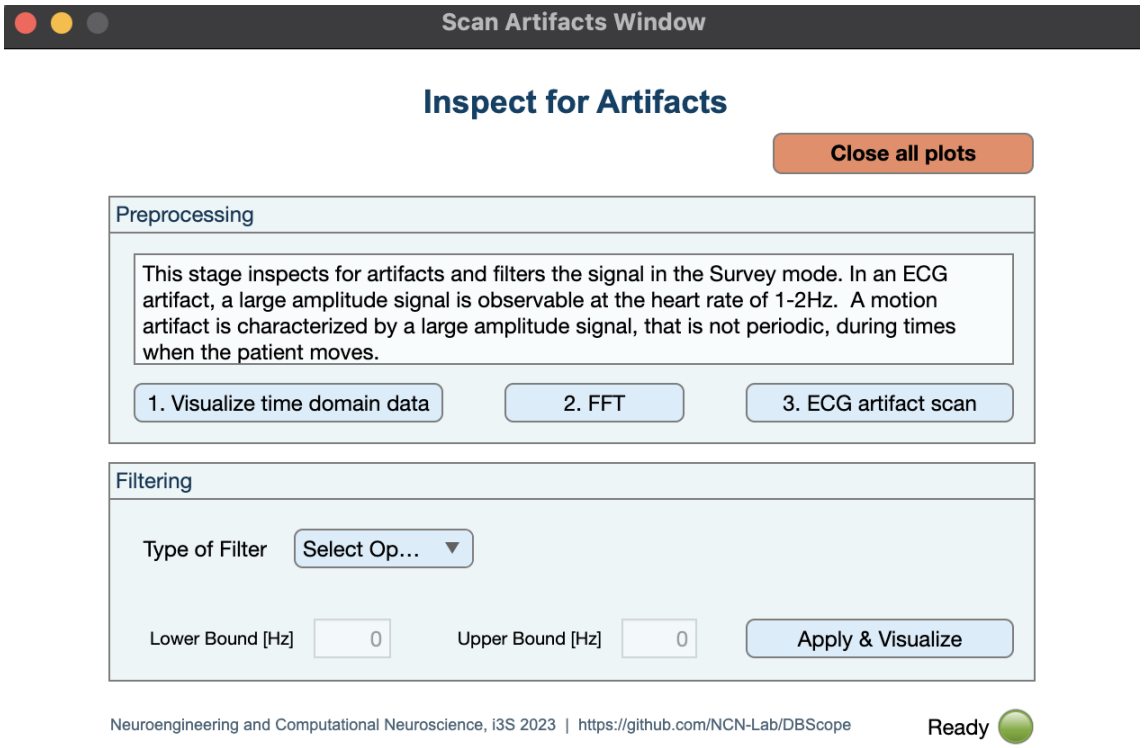


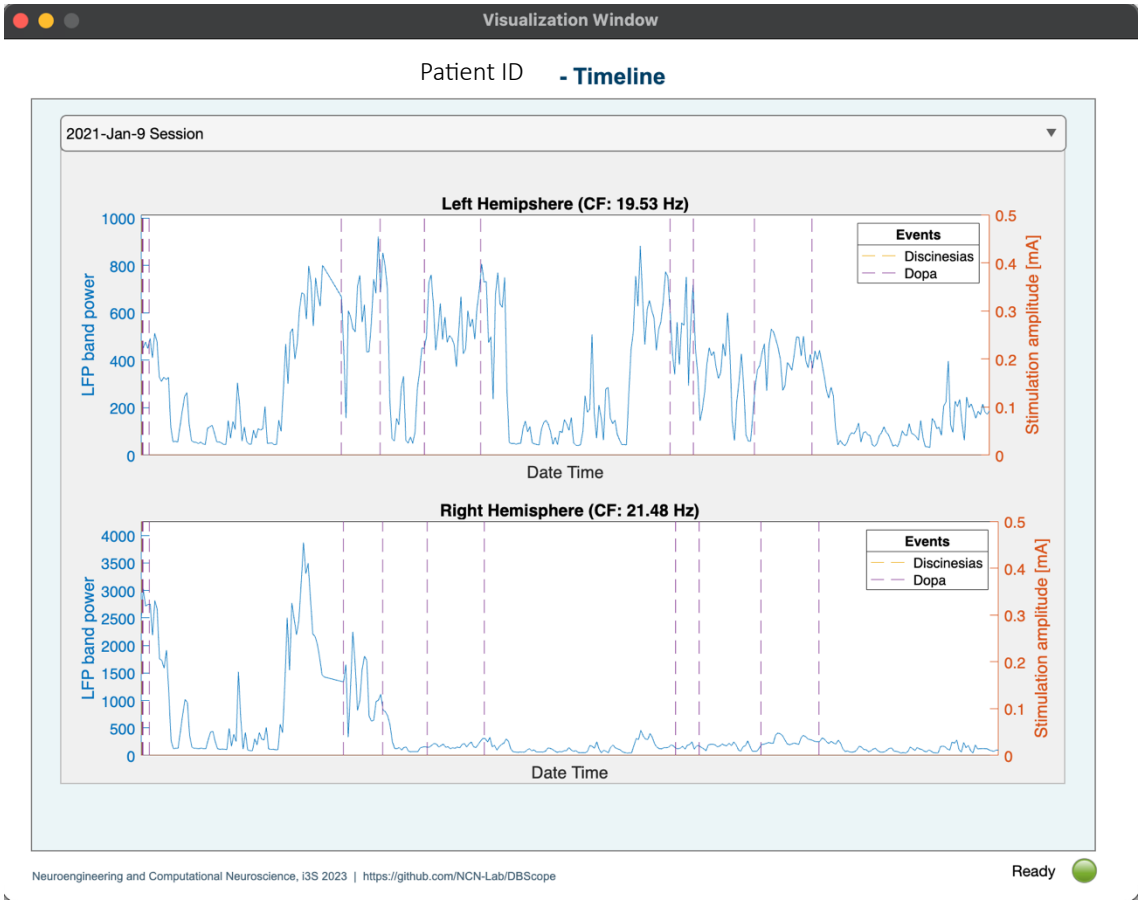
Figure 2: DBScope: Toolbox for the inspection of artifacts in survey sensing recordings – secondary window.

Chronic Sensing

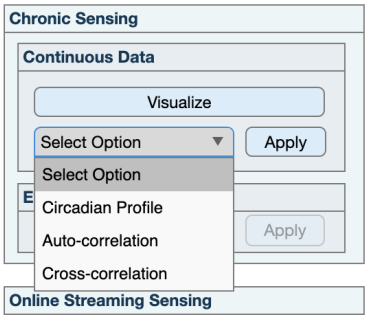
In the section for chronic sensing recordings, one can access two main types of data: timeline and events snapshots.

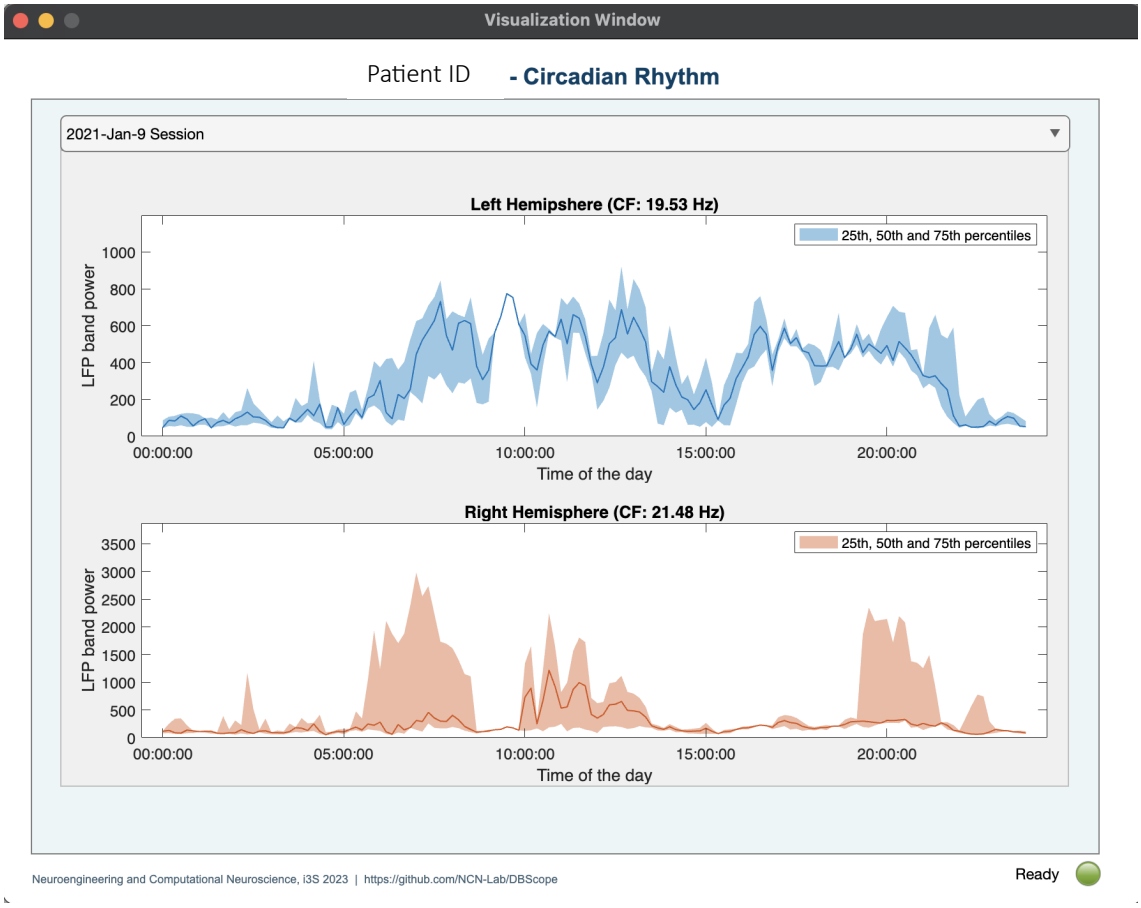
Timeline

Timeline recordings can be plotted at the button 'Visualize':



The user can also perform further analysis on chronic data:

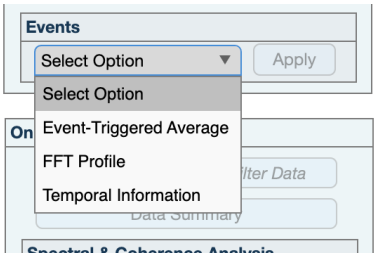


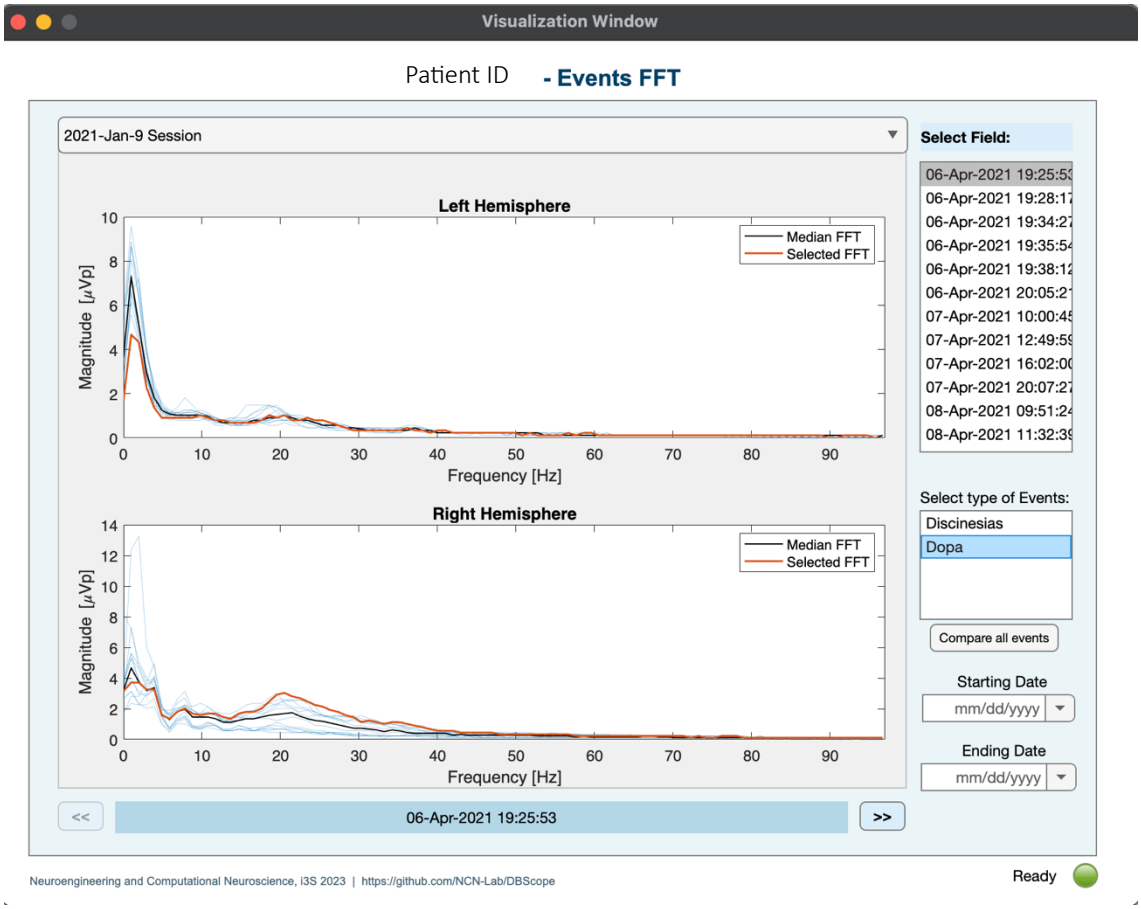


[Example of Circadian Profile visualization.]

Events

A second type of chronic recordings are the events logged by the patients. For the events, the following analyses are available: the Fast Fourier Transform (FFT) per event, Event-Triggered average, and the information of their temporal dynamics.



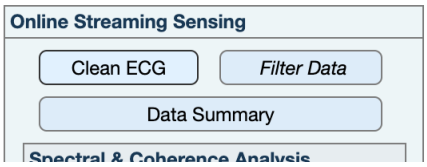


[Example of Events FFT visualization.]

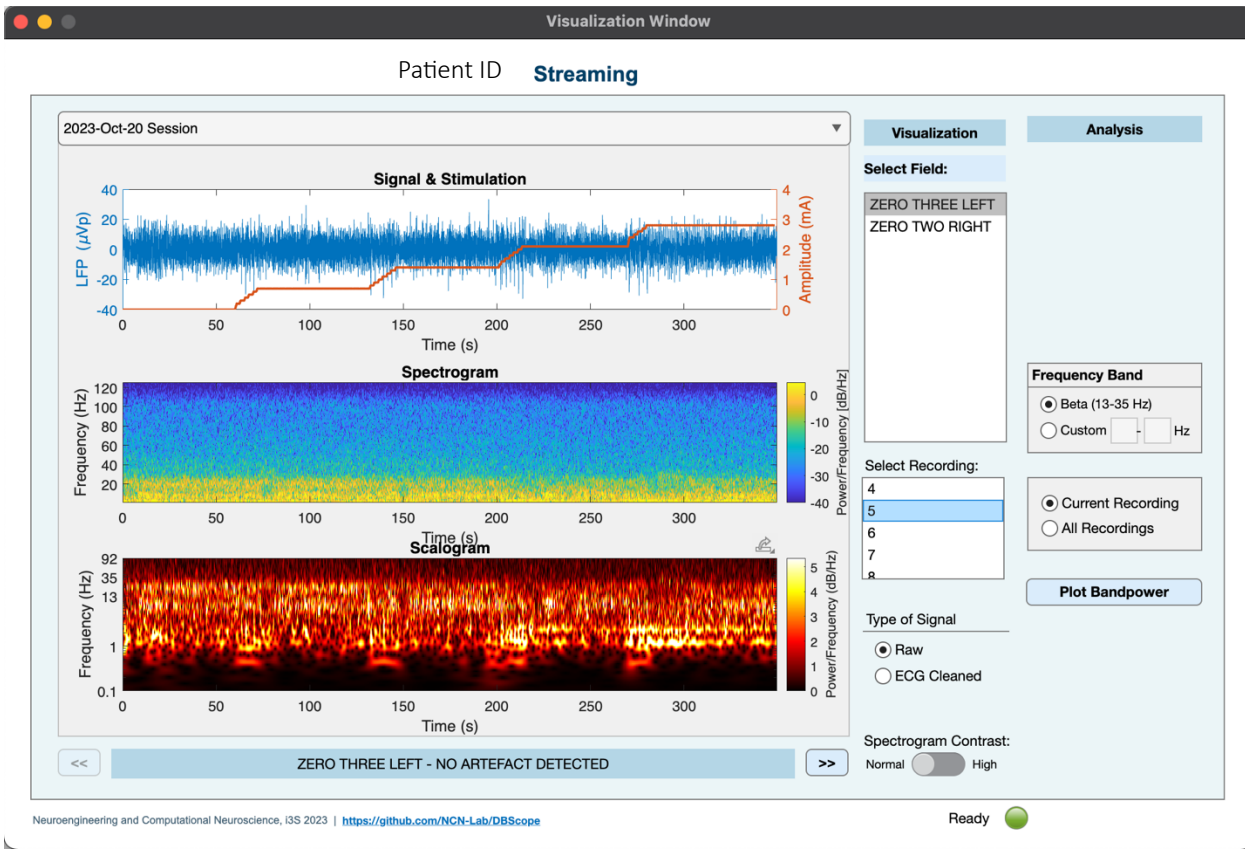
Depending on the characteristics of the recordings, it is possible, in the visualization window, to change files, define a temporal window, select the event type, and individual recordings.

Online Streaming sensing

For the online (in-clinic) streaming recordings, a first step is required: cleaning potential ECG artifacts (button 'Clean ECG'). From here onwards, two types of data will be available for plotting and analysis: raw or the ECG-cleaned signals.



After 'Clean ECG', the user can 1) filter the data; 2) plot a 'Data Summary ', which shows, in the same visualization window, the plot of raw signal, its spectrogram and corresponding Wavelet Transform; and 3) make use of different Spectral and Coherence Analysis tools.



[Example of Data Summary visualization.]

Depending on the characteristics of the recordings, it is possible, in the visualization window, to change files, electrode pairs and recordings. For example, in the visualization above the file is 'File_example', the recording is the '1', and the field (electrode pair) is 'ZERO TWO RIGHT'.

Filter data

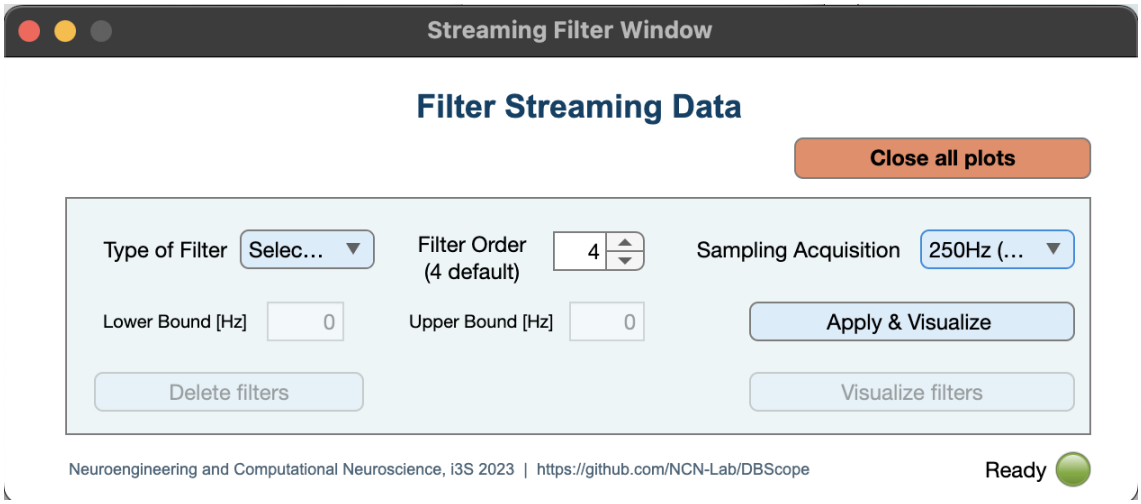
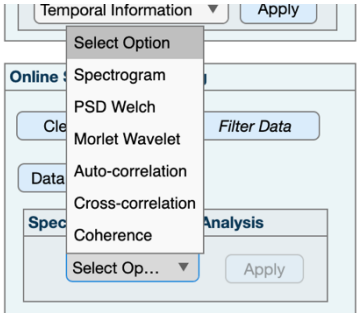


Figure 3: DBScope: Toolbox for filter design and application in streaming sensing recordings – secondary window.

In this secondary window, the user can define the type of filter (low pass, high pass, stopband and bandpass), and its boundaries (below the Nyquist frequency of 125Hz). It is possible to test an unlimited number of filters, as well as delete previous filtering iterations. The output of this process will then be available in the main GUI.

Spectral and Coherence Analysis



The set of tools available in the Spectral and Coherence Analysis tools can be applied to either the raw, the ECG-cleaned or the filtered data.

External Wearables



The set of tools available in the Wearables section allows for the load and cross visualization of the wearable data, simultaneously to the visualization of the corresponding streaming recordings.

Loading of wearable data

The data must be in a .CSV file named:

WearableID _PatientID_Task_TitrationInfo_SamplingFreq_StartDatetime('yyyy-MM-ddTHH-mm-ss').csv
Example: 'DorsalLeft_12345_OpenClose_RightTitration_100_2023-05-19T08-58-05.csv'

The first column of the file must contain the datetime in a ".net" format @UTC + 0:
Number of "clock ticks" since 1-Jan-0001 00:00:00 UTC, representing a Microsoft® .NET timestamp where each clock tick is 100 ns.

Besides the datetime column, the file can contain as many columns as you wish. Each column will be treated as a separate signal. For instance, you can have the 3-axis acceleration and 3-axis magnetometer values within the same file. Note that DBScope will use the name of the columns to identify the signals within its data structure.

When in the presence of metrics with different sampling frequencies, choose the higher sampling frequency and fill the other values with NaN:

1	time	total_acc	total_acc_power
2	638200896040100000	NaN	NaN
3	638200896040200000	NaN	NaN
4	638200896040300000	1.00950273821584	NaN
5	638200896040400000	1.00796206052089	NaN
6	638200896040500000	1.01701394986963	NaN
7	638200896040600000	1.00377437452695	NaN
8	638200896040700000	1.00599844258228	NaN
9	638200896040800000	1.01399387544742	NaN
10	638200896040900000	1.01965266999158	NaN

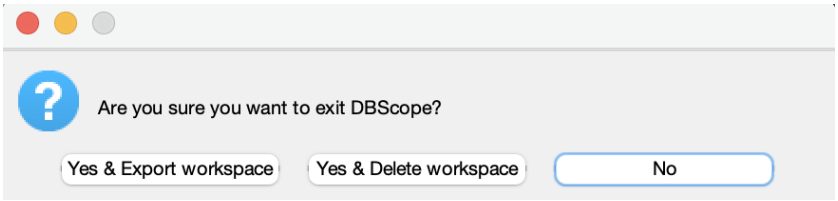
Cross Analysis

When performing cross-signal analysis, DBScope will automatically select the wearable recordings that overlap the currently selected Streaming recording. The signals are aligned and limited by the Streaming recording datetime window, so that wearable recordings that start before or end after the Streaming recording are only partially shown.
NOTE: Make sure that the neurostimulator and wearables are synchronized.

Export Workspace & Close App

The user can also save his analysis with the 'Export Workplace' button. This step allows to save the current operational workplace in a .mat file.

Finally, when closing the app, the following prompt window will appear:



Here, the user can select to leave the app- and export or delete the current workspace-, or to continue in the app.

Contact Us

For questions / comments, please send us an email to:

amoliveira@i3s.up.pt or pauloaguiar@i3s.up.pt