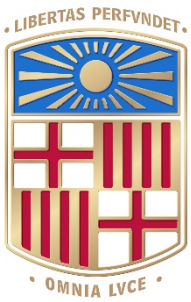

UNIVERSITAT DE BARCELONA

Final Degree Project

Biomedical Engineernig Degree

"Validation of the Guide XT software for patients with Parkinson's Disease undergoing STN-DBS in Hospital Clínic of Barcelona"

Barcelona, May 8, 2022

Author: Cristina María Pérez Miranda

Director/s: Dr. Pedro Roldán Ramos

Tutor: Dr. Pedro Roldán Ramos

Abstract

Parkison's Disease is the second most common neurodegenerative disorder worldwide and its prevalence is expected to grow as population ages. Deep brain stimulation is a well-established surgical treatment used as an alternative when medication is not effective. This neurosurgical procedure consists of the implantation of electrodes into specific targets within certain areas of the brain and on the electrical stimulation of these targets through the application of constant or intermittent electricity from an implantable pulse generator (IPG) to treat the movement disorders associated with Parkinson's Disease. Stimulation parameters setting is highly important in this surgical treatment. Programming deep brain stimulation is a challenging and time-consuming process since there is a huge number of possible parameters combinations.

Guide XT (Boston Scientific) is a 3-dimensional neuroanatomic visual software that automatically detects the position of the electrodes in the anatomy of the patient. It enables the visualization of the volume of tissue activated by simulating the stimulation field output. This can help to efficiently determine the most appropriate settings for each patient. The objective of this project is to compare the stimulation settings of the traditional trial-and-error method versus the Guide XT-assisted selection of parameters, to determine software reliability as a supporting tool in deep brain stimulation programming.

For the study, data from 37 patients who underwent bilateral subthalamic nucleus deep brain stimulation was collected. Stimulation settings from the first programming session and from the one month after the surgery visit was obtained. All patients were implanted with the Vercise Cartesia directional leads and the comparison and statistical analysis with respect to the stimulation parameters selected with Guide XT was performed in a jupyter notebook.

The highest value of the Cohen's kappa coefficient used to assess inter-rater agreement for the left side contact selection for those patients who did not present side effects in the first programming session was k=0.26. Nevertheless, the percentage of correspondence between contacts selection for both electrodes in the two programming sessions and selection based on software simulations was over 50% in all cases. Thus, it was concluded that the software is a reliable tool to be used in the clinical practice, even though a further analysis testing results in patients would be of interest.

Keywords: Parkinson's Disease, Deep Brain Stimulation, Guide XT, reliability, clinical practice

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Abbreviations

PD: Parkinson's Disease
HRQoL: Health-Related Quality of Life
NMSs: Non-Motor Symptoms
DBS: Deep Brain Stimulation
SN: Substantia Nigra
BG: Basal Ganglia
CNS: Central Nervous System
SNpc: Substantia Nigra pars compacta
CN: Caudate Nucleus
GP: Globus Pallidus
GPi: Globus Pallidus internal segment
GPe: Globus Pallidus external segment
SNpr: Substantia Nigra pars reticulata
STN: Subthalamic Nucleus
PPN: Pedunculopontine Nucleus
GBD: Global Burden of Disease
YLDs: Years Lived with Disability
IPG: Implantable Pulse Generator
Vim: Ventral intermediate nucleus
CT: Computed Tomography
MRI: Magnetic Resonance Imaging
CTi: intraoperative Computed Tomography
LFPs: Local Field Potentials
aDBS: adaptive Deep Brain Stimulation
VAS: Visual-Analog Scale
YLDs: Years Lived with Disability
MDSW: Medical Device Software
fMRI: functional Magnetic Resonance Imaging
VEsF: Volume of the Electrostatic Field

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1. INTRODUCTION

1.1 Motivation

Neurological disorders are currently the leading cause group of disability and the second leading cause of deaths around the world according to the Global Burden of Disease (GBD) study [1][2]; and within these disorders, Parkison's disease (PD) is the one that is experiencing the fastest growing [3].

PD is the second most common neurodegenerative disorder worldwide after Alzheimer's disease. It affects approximately 1-3% of the global population aged over 60 years [4-6] and is estimated to affect 10 million sufferers around the world [7]. The global incidence estimation of PD ranges from 5 to >35 new cases per 100.000 individuals yearly [4]. In Europe, prevalence and incidence rates for PD are estimated at approximately 108–257/100.000 and 11–19/100.000 per year, respectively [8].

The main risk factor for developing PD is age, so this neurodegenerative disorder becomes increasingly prevalent as the population ages. The average age at which PD appears is around 55 years, but most patients are aged between 50 and 80 years old [9]. Mortality is not increased in the first decade after disease onset, but increases thereafter, eventually doubling compared with the general population. Another important risk factor for the disease is male gender. PD is twice as common in men than in women in most populations [4] [10].

In the last years there have been a lot of improvements in healthcare that has led to longer survival of the global population, and given that this disease predominantly affects older adults, population aging is associated with an increase in PD prevalence over time. This means that worldwide aging populations, especially in economically developed countries, will increasingly need to develop strategies to meet the health care needs of individuals with PD [6]. The number of people with this disease is expected to double between 2005 and 2030 [4], so a progressive increase in the personal, societal and economic burden associated with PD is expected in the future as the world population ages.

Another important factor to take into account is the health-related quality of life (HRQoL), which is a multidimensional, self-reported measure of the impact that the disease has in patients' lives. Improving the HRQoL is the aim of healthcare in chronic diseases, especially in PD, in which HRQoL is determined by motor, non-motor symptoms (NMSs), and other social factors [11].

Since PD is having a huge impact in global society and its prevalence in our society is expected to continue growing as the population ages, it is crucial to have useful treatments and tools to help to reduce symptoms as much as possible, ensuring patients' HRQoL. With time, different methods have appeared to deal with motor symptoms, which are the most noticeable ones. Drugs are very helpful, but when they are not enough the alternative is often surgery. Deep Brain Stimulation (DBS) is a well-established treatment for advanced PD which has been shown to provide benefits for motor and non-motor symptoms signs, as well as improved quality of life [12-14]. In this surgical treatment, patients are implanted with electrodes (or leads) in specific brain areas to treat the characteristic shaking of PD and an impulse generator battery is implanted too.

After the surgery, the battery that supplies the energy to the electrodes must be programmed, and achieving an optimal electrical stimulus for each patient is a process that can be time-consuming. Improving DBS programming can result in a better performance of the DBS technique and also in

the symptoms treatment by reducing the number of visits to the doctor to readjust parameters, what leads to a better quality of life.

Nowadays there exist different visualization software platforms that can be used to assist neurologists to program these implanted batteries improving accuracy and performance, and reducing the programming time at the same time; but it is highly important to ensure that these softwares are truly helpful and that do not provide wrong estimations in order to avoid causing serious damages to patients. For this purpose, Hospital Clinic needs to validate a software that has been used since January 2021 and which could help in this programming task. Its validation will be done in the neurosurgery department office of the hospital taking different parameters from patients who have been diagnosed with PD and who have already undergone the DBS surgical procedure.

1.2 Objectives

It is important to bear in mind that after each DBS surgery, leads final position is not always exactly the same, it varies among patients and even among the same patient (each electrode will have a different position). These location variations are in the order of millimeters, and it is important to know that these small changes in the brain are highly significant, because if the electrode is placed a concrete distance further from the ideal target position (which is determined using a software), it could touch certain brain structures from the surroundings that are not of interest for this PD therapy. Furthermore, this could cause several damages if the stimulus applied by the electrodes is not correctly programmed for each patient.

Here lies the importance and also the need of using a software for DBS programming. The main aim of this project is to determine the reliability of the stimulation output simulations performed with the software Guide™ XT, from Boston Scientific, to aid in parameter selection during DBS programming. With this, it could be evaluated if Guide™ XT software is a useful tool for the clinical practice.

The main objectives of this project can be summarized in:

- Assess the software reliability when helping on determining the patient-specific optimal parameters for DBS programming based on post-operative imaging when compared to the traditional approach (trial and error method).

- Evaluate the real utility of the software to be used as a reliable tool in hospitals in DBS programming for patients with PD.

Other secondary objectives of this project are:

- Determine the optimal parameters that must be applied to each patient.

- Define the relationship between adverse effects and lead location.

1.3 Methodology

The methodology followed to develop this project has been detailed in figure 1. Tasks included in the flow diagram have been divided into different sections since there was a part of the project that

could not be performed by the author. These sections can be differentiated with the colors used to represent the project workflow. The final result has been marked in red.

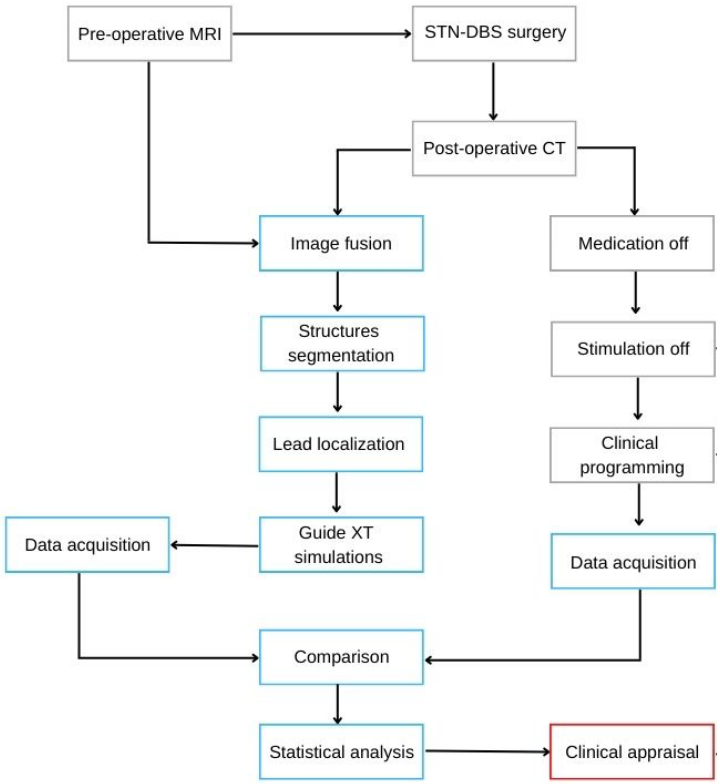


Figure 1. *Flow diagram of the software validation. Gray = part of the process not performed by the author; Blue = workflow; Red = outcome.*

For project development, some clinical imaging tests had to be performed to obtain the patient images needed for the simulations. These clinical tests were mainly MRI scans and CT scans, so they had to be performed by clinicians. The images obtained were used firstly to plan the surgery, and then to assess electrodes' final position after the surgical procedure. With these images, patient's 3D brain structures were reconstructed after image co-registration and lead localization, so a final display of electrodes position in the patient's anatomy could be seen.

For DBS programming, patients had to attend the visit in an off-medication state. This procedure was performed by clinicians in the hospital. When data from both software simulations and clinical programmings was collected, a database with this information was created. In the clinical programming section of the flow diagram, the different programming sessions performed between the first one and the last one from which data was collected are included.

With this information, a comparison of the values obtained and a statistical analysis was realized. From results obtained, a clinical appraisal was performed and software reliability was evaluated.

1.4 Scope and Span

In order to achieve the goals of this project, different analysis have been performed to evaluate the reliability of the software, using anonymous patient data such as pre and post-operative images, surgical information and intraoperative neuronavigation systems to assess leads position. All

mentioned before was used to set the parameters in DBS programming with the software. Most of the tasks were performed in the Department of Neurosurgery of Hospital Clinic de Barcelona. Concretely, specific data acquisition from patients and software implementation to plan the surgeries and later the DBS programming was done at the neurosurgery office. Final software evaluation was performed there also. In addition, some patients were visited to assist and visualize DBS programming procedure. Regarding the DBS surgical procedure, some surgeries were attended in the hospital to understand the whole process and the implementation of certain softwares related with the lead location assessment before and after the surgery.

The time period in which the project has been developed was from February 2022 to June 2022, and the timeline can be seen in the execution chronogram section (figure 24).

This project **includes** the following aspects:

- Evaluation of the side effects that patients undergoing DBS surgery can experience when programming is not correctly performed.
- Comparison between clinical and software-guided determination of the stimulation parameters.

On the other hand, this project **excludes**:

- Discussion of which is the most appropriate surgical target in DBS given that the procedure followed in Hospital Clinic is established to always perform a STN-DBS, so this is something that for the objectives of this project, is not needed to be discussed.
- Detailed description of the algorithms behind the software.
- Patient evolution after a month of the surgery.
- Assessment of software accuracy to determine electrodes' position in patient's anatomy, since this has been proved in other articles found in the literature.

1.5 Limitations

An important limitation that this project has is the time available to perform it. Given that it is a bachelor's thesis, there is a predetermined date to deliver it, so results must be obtained within this time period. Thus, the margin for correcting mishaps is small. In relation to data acquisition during project development, it must be taken into account that in order to have a standardized time period evaluation, only a one-month follow-up of the results from DBS surgery has been done. So changes in stimulation parameters or future possible problems after a month from the surgery have not been evaluated because it has been considered that this time period was enough to obtain reliable and trustworthy results. This decision has been made because otherwise those patients who underwent DBS surgery first would have had more time to reprogram and check DBS parameters, leading to probably better results than those who underwent DBS surgery later. So to standardize results, this decision was made.

Another important limitation that can be found in this project is that software reliability has not been compared with the other software that has been used in the hospital previously for the same purpose. Instead, software performance has been compared with results found in the literature.

On the other hand, regarding software validation, there are some external variables which do not depend on the software and that should be taken into account when analyzing the results, given that they could disrupt them due to the fact that these variables can affect the correct performance of DBS procedure, and if this technique does not work properly, neither will the software performance. These variables are:

- **Patient selection:** If any of the patients selected for this project was unsuitable to undertake the DBS treatment, then the battery programming will not be correct anyway because this patient was not supposed to undergo this surgery.

- **Surgical procedure and electrode placement:** If at the end of the surgery, the electrodes position is not correct, this could lead to adverse effects, giving rise to a bad performance of the software.

- **Adjustment of pharmacological therapy:** If the patient is taking drugs for PD treatment or for another reason meanwhile is subjected to the DBS procedure, this could affect the results.

- **Number of patients used for the software validation:** It may be not enough to perform an accurate software validation.

- It is important to perform **DBS programming** once the microlesion effects due to lead implantation trauma have disappeared, because this effect could confuse the initial results. In this study, for some patients it has not been possible to evaluate if this effect has altered the results because it has not passed enough time from the surgery.

- **Impedance fluctuations** in the tissue surrounding the DBS lead can also contribute to inaccurate assessment. Impedances are observed to be increased immediately after placement of a lead, as a consequence of edema, and they tend to decrease and stabilize over the first few weeks.

2. THEORETICAL BACKGROUND

2.1 Context

2.1.1 Parkinson's Disease

PD is a neurodegenerative brain disorder in which nerve cells from a part of the brain called substantia nigra (SN), which is localized in the basal ganglia (BG), become impaired and/or die. The BG is an area of the brain that controls movement and maintains body and limbs posture [9], and it is formed by different neuron clumps. When the brain sends a stimulus to move a muscle, this stimulus passes through the BG. In order to transmit this stimulus, neurons in the BG release an important neurotransmitter known as dopamine. So the gradual loss of neurons in the BG leads to a dwindling production of dopamine, which causes the characteristic movement problems of PD. Patients who have this brain disorder usually suffer trembling, stiffness, and difficulty with walking, balance, and coordination [15].

Given that there are no blood or laboratory tests to diagnose PD, diagnosis of this disorder is based on the patient's medical history and on neurological examinations, but it can be easily confused with other brain disorders which have similar symptoms.

Currently there is no cure for PD, so patients must be treated to slow down the neurodegenerative process. There exist different treatments available, such as medicines, physical and occupational therapies or surgery, which help to reduce the main symptoms and try to maintain quality of life for as long as possible. Patients are usually treated with Levodopa, the most effective medicine for PD given that it is the metabolic precursor of dopamine, so neurons use it to make dopamine and replenish the lack of this neurotransmitter in the brain. Levodopa is generally taken along with another medication called carbidopa, which is necessary to prevent or reduce the therapeutic side effects that Levodopa can cause resulting from dopamine decarboxylation.

PD motor symptoms severity can be evaluated using clinical scales such as the *Movement Disorder Society Unified Parkinson's Rating Scale part III (MDS-UPDRS-III*), which depend on the patient's status at the time of assessment and are limited by subjectivity [16].

2.1.2 Anatomical Brain Structures

As mentioned before, PD is a neurodegenerative disorder which affects the central nervous system (CNS), and within this system, there are certain brain structures which are more affected. The dopaminergic neurons lost in PD are generated in the substantia nigra pars compacta (SNpc), which is located in the BG. In order to better understand these brain structures and how they work, in figure 2 it is shown which are all the structures involved in the disease and where are they located.

The BG or basal nuclei are a group of subcortical nuclei or masses of gray matter (collections of neuron bodies or somas) that are located at the CNS near the base of the brain (at the base of the forebrain and top of the midbrain), embedded deep within the cerebral hemispheres [17]. These nuclei are strongly interconnected with the cerebral cortex, thalamus, and brainstem [18], and are mainly involved in control of voluntary motor movements and in the selection and implementation of purposeful actions in response to external and internal signals. Furthermore, BG set the pattern for facilitation of voluntary movements and simultaneously inhibit competing or interfering movements. Besides this, they are also associated with the control of a wide variety of non-motor behaviors, spanning emotions, language, decision making, procedural learning, habit learning, conditional learning, eye movements, cognition and working memory [19] [20]. The BG unique spatial positions make them a proper candidate to interrelate between the cortical, limbic and

thalamic regions. These interactions mainly serve to balance, control, and integrate motor activities by receiving extensive inputs from both the cortex and thalamus, and returning output through projections yielded by the BG three major pathways linking the striatum to the BG output layer [21].

a) Basal Ganglia Components

The main brain structures included in the BG are the caudate nucleus (CN), the putamen and the nucleus accumbens (which collectively form the striatum), the globus pallidus (GP) including its internal segment (GPi) and external segment (GPe), the SN (its pars compacta [SNpc] and its pars reticulata [SNpr]), and the subthalamic nucleus (STN). The limbic portion of the BG is composed by the nucleus accumbens, ventral pallidum, and ventral tegmental area [19]. Each of these structures has a complex internal, anatomical and neurochemical organization:

- **Striatum:** It is the biggest subcortical mass in the brain (120 millions of neurons) and is a functional nucleus that is in contact with the ventricle. Striatum integrates information from different parts of the cortex, thalamus, pedunculopontine nucleus (PPN) and the dopamine system (SNpc and ventral tegmental area) [22]. This structure is usually divided into 2 sections:

    - Dorsal striatum (neostriatum): It is one of the primary input areas for the BG and contains the caudate and putamen. Fibers from the cerebral cortex, SN and thalamus all enter the BG via the dorsal striatum.

    - Ventral striatum: It contains the nucleus accumbens and is related with rewarding experiences. The nucleus accumbens seems to be involved in reinforcement, reward, and the progression from simply experiencing something pleasurable to seeking it out compulsively as part of an addiction. So the ventral striatum is activated when the person does something pleasurable. The nucleus accumbens receives fibers from the ventral tegmental area, which is a dopamine-rich structure in the midbrain. These fibers are part of a pathway called the mesolimbic dopamine pathway, which is a primary component of the reward system [23].

- **Globus pallidus (GP):** Ganglion with a light gray triangular shape with a thin layer of white matter in its middle that sometimes unites with the putamen to form the lentiform nucleus. The GP receives input from the striatum, and sends inhibitory output to a number of motor-related areas.

- **Subthalamic nucleus (STN):** It has small dimensions and is located under the thalamus, at the junction of the midbrain and diencephalon. The STN receives input mainly from the striatum and cerebral cortex and it contains glutaminergic neurons which project to the GPI. The glutamatergic neurons increase the activity of the GPi, which contains GABAergic neurons that, in turn, decrease the activity of the thalamus and inhibit movement. Lesions of the STN can disrupt the inhibition of movement by the GPi and results in hemiballismus [24].

- **Substantia nigra (SN):** It is located under the STN and is divided into 2 parts:

    - SNpc (densely packed nuclear region that contains dopaminergic neurons)

    - SNpr (with GABAergic neurons).

The fibers from the SN to the putamen, which make up a pathway called the nigrostriatal pathway, are thought to be especially important to movement and are severely affected by neurodegeneration in patients with PD [25]. The SNpc has neurons with neuromelanin as metabolic product of dopamine. The SN is the source of the striatal input of the neurotransmitter dopamine, which plays an important role in BG function.

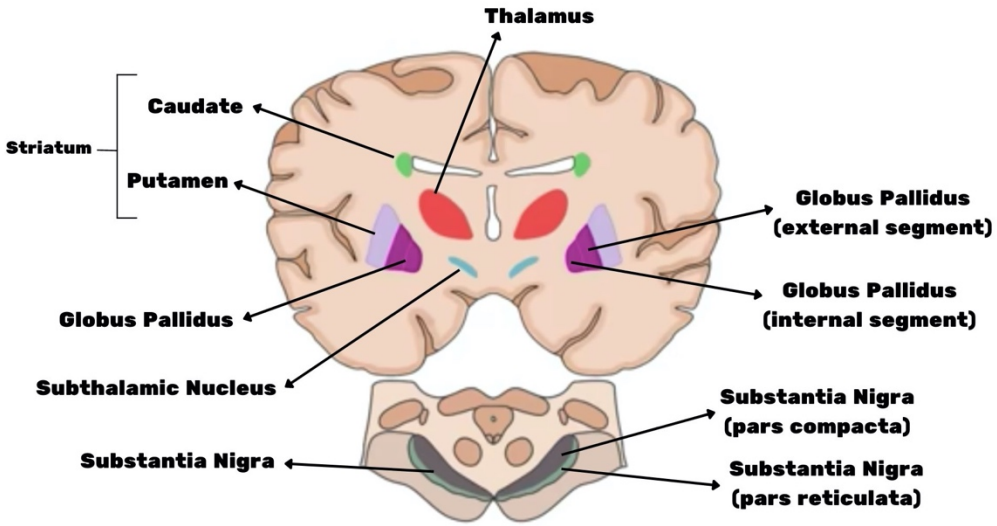


***Figure 2**. Brain structures involved in Parkinson's Disease. Components of the Basal Ganglia.*

The caudate and putamen are separated from one another by a white matter tract called the internal capsule. There are many strands of gray matter that cross the internal capsule, giving the structure a striped appearance. On the inner side of the internal capsule is the CN (nucleus of the tail) and on its outer side the putamen (shell-shaped nucleus), next to which is the GP. Located to the side of the GP, but further inward, is the STN and, below it, the SN [26].

Each nucleus that forms the basal nuclei is formed by different cell types, which have different functions, so each of them will receive different patterns of inputs and will have different synaptic organizations. The main input nuclei of the BG are the striatum and the STN, which receive the majority of the inputs from outside the BG, most of which emanate from the cerebral cortex. On the other hand, the bulk of outputs sent from the BG emerges from GPi and SNpr, which are the main output nuclei of the BG, and they send projections out from the BG to the cerebral cortex, mostly by way of the thalamus, as well as to nuclei in the brainstem. The thalamus distributes the processed information towards the cerebral cortex, specifically to prefrontal and premotor areas, which are the ones that have the function of action planning and execution [27]. GPi and SNpr are inhibitory to thalamic nuclei, superior colliculus, and the pedunculopontine area of the brainstem.

b) Basal Ganglia Circuit

As mentioned before, BG circuits are organized to select desired actions and to inhibit potentially competing unwanted actions. This is accomplished through a complex circuitry that is modified through development and learning. Mechanisms of neural plasticity underlying these modifications are increasingly understood, but new mechanisms continue to be discovered [28]. The model of BG circuits that will be explained below is the traditional circuit of "direct" and "indirect" pathways, which is the current circuit that is used to explain this mechanism. But as new discoveries are made, modifications on these pathways have been done.

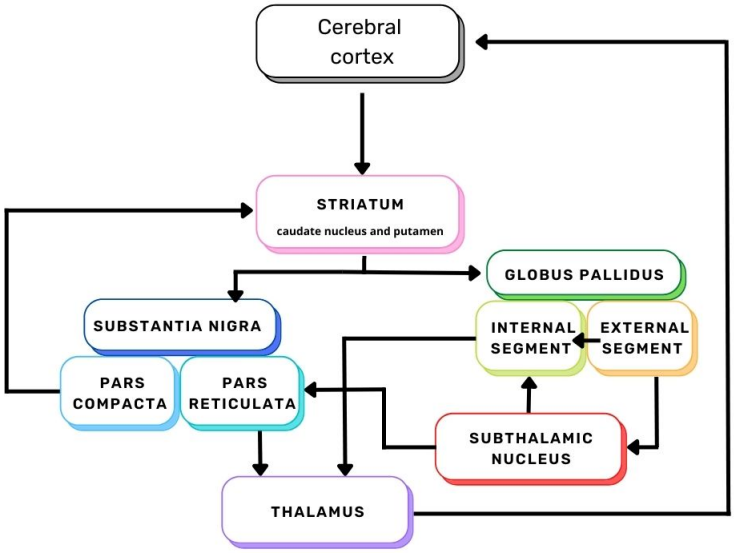


***Figure 3**. Basal ganglia circuit including direct and indirect pathway.*

According to the direct/indirect model, when a movement is desired, a signal to initiate the movement is sent from the cerebral cortex to the BG, typically arriving at the CN or putamen. Then, the signal follows a circuit in the BG known as the direct pathway, which leads to the silencing of neurons in the GP. This frees the thalamus from the inhibitory effects of the GP and allows movement to occur. There is also a circuit within the BG called the indirect pathway, which involves the STN and leads to the increased suppression of unwanted movements. It is thought that a balance between activity in these two pathways may facilitate smooth movement. All these connection networks and the modulation provided by the BG serves to achieve proper planning, initiation and finalization of voluntary movements, especially those movements with a complex cognitive dimension.

When a desired movement is initiated by a particular motor pattern generator in the cerebral cortex or brainstem, BG output neurons projecting to that generator decrease their discharge, thereby removing tonic inhibition and "releasing the brake" on that generator. BG output neurons projecting to other motor pattern generators, that are involved in competing actions, increase their firing rate and thereby apply the "brake" to those generators. In this way, competing actions are prevented from interfering with the one(s) selected. Thus, the output of the BG is inhibitory to posture and movement pattern generators. The result is the focused selection of desired actions and surrounding inhibition of competing actions. Disruption of the ability to facilitate desired movements and inhibit unwanted movements results in slow voluntary movements (parkinsonism), abnormal involuntary movement (chorea, dystonia, tics), or both.

The importance of BG in movement performance can be noticed when we look at cases where the BG have been damaged. In PD, dopaminergic neurons of the SN degenerate. When this happens, the ability of the BG to cause the release of inhibition necessary to make a movement may be impaired. This can cause individuals with PD to have difficulty initiating movements, resulting in some of the symptoms associated with PD like rigidity and slow movement.

2.1.3 Deep Brain Stimulation

When medication is not enough to treat the disease because it causes serious side effects to the patient or because it has become less effective and does not reduce Parkinson's symptoms properly, there is another treatment that can be used as an alternative: deep brain stimulation

(DBS). This surgical procedure is applied if the patient has the disease in an advanced state and does not present dementia or any psychiatric symptoms [29].

DBS is a neurosurgical procedure that consists on the implantation of electrodes (also called leads) into specific targets within certain areas of the brain and on the electrical stimulation of these targets through the application of constant or intermittent electricity from an implantable pulse generator (IPG) to treat the movement disorders associated with PD [30]. The leads are connected to the IPG through connecting wires that travel subcutaneously from the skull to the chest till reaching the IPG, as it can be seen in figure 4. The brain structures that are most commonly used as targets are the STN, the GPi or the ventral intermediate nucleus (Vim) of the thalamus. The aim of DBS is to modulate the activity of neurons located at these target regions, changing the extracellular potential of cells and fibers located nearby the leads by applying electric current. The stimulation of these targets can substantially reduce the main symptoms of PD such as rigidity, tremor and gait difficulties [31]. For example, STN-DBS suppresses spontaneous activity in the beta band and drives evoked resonant neural activity (ERNA) [32].

As these anatomic targets are typically on the order of millimeters, it is essential to perform the intervention with high precision, because a slight error in lead location can sometimes significantly impact clinical outcomes. This is the main reason why the use of certain tools such as stereotactic frames, interventional magnetic resonance imaging (iMRI), computed tomography scans (CT scans) and image-guided softwares is extremely important to set the brain coordinates and reach the target with high accuracy. With the help of all these instruments, intraoperative errors are significantly reduced, as well as the time required to perform the entire process.

Electrode implantation can be lateral or bilateral; that means that it can be stimulated only one side of the brain or both sides. Usually the procedure is done bilaterally and the ideal target is not defined given that DBS targeted at STN and GPi has been shown to have similar efficacy [33]; however, in a study where results were analyzed in the on-medication phase and in the off-medication phase, clinical improvements for STN and GPi were almost the same in the on-medication phase, but in the off-medication phase, Vim-targeted DBS was associated with better improvement in UPDRS scores [34]. In this project, all patients have undergone STN-DBS given that it is the procedure performed in Hospital Clínic of Barcelona (it is the most commonly performed surgery for PD).

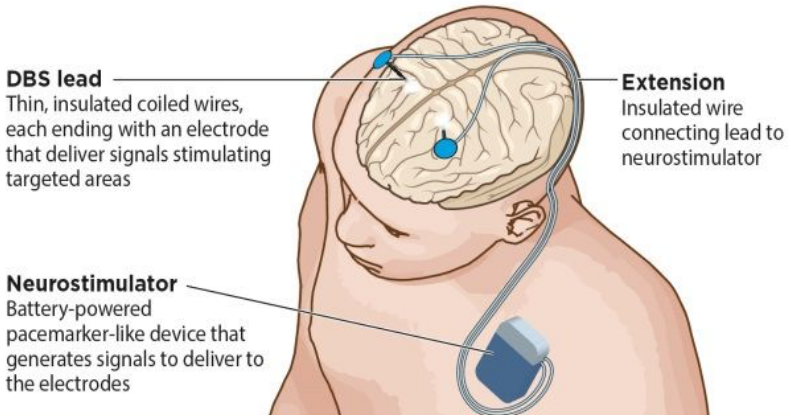


***Figure 4**. Bilateral deep brain stimulation [35].*

Once the implantation of the electrodes in the brain targets is done and the IPG is placed subcutaneously on the anterior chest wall, the DBS programming is performed by configuring the IPG stimulation parameters. The optimal parameters that have been found to effectively control the

motor symptoms are a voltage in the range 2.4 to 4.4 V, a high-frequency stimulation in the range 50 to 185 Hz and a pulse width in the range 67 to 138 s [36] [37].

DBS side effects include intraoperative and hardware related adverse events, worsening of cognitive function, psychiatric symptoms, and ocular and speech disturbances; moreover, motor signs that do not respond to Levodopa, such as freezing, falling and axial signs, do not show a marked improvement with DBS [38]. Anyway, DBS is effective for control of tremors that are refractory to dopaminergic medications, motor fluctuations, and Levodopa induced dyskinesia that are bothersome to patients. The success of DBS is dependent on many factors including appropriate selection of patients, accurate placement of DBS lead, and a thorough programming process to identify the optimal stimulation parameters [39]. In addition, this treatment is preferred to ablative procedures by many experts owing to its reversibility, programmability, and the ability to be safely performed bilaterally. Several randomized clinical studies have demonstrated the effectiveness of DBS surgery for control of PD symptoms [40].

a) Surgical Procedure

The DBS surgical procedure followed in Hospital Clínic of Barcelona is an MRI guided and image verified procedure, and will be described in the following section:

The first thing done when a patient with PD must undergo DBS surgical procedure is the surgical planning. For that, 2 weeks before the operation, a 3T magnetic resonance imaging (MRI) scan of the brain of the patient is obtained. With the Brainlab Elements software, a reconstruction of the brain of the patient is done with the MRI images, and a simulation of the optimal position in which the electrodes should be placed in that patient is performed over this reconstruction, so patient-specific anatomy is used for the surgery planning, which is a huge advantage. From this simulation, surgeons obtain the exact coordinates where the leads must be implanted, as well as the most suitable path to reach the target position taking into account the anatomy of the patient.

The day of the surgery, once the patient is under general anesthesia and before starting the procedure, a stereotactic frame (image 1) is attached to the head of the patient by using four spins that will be embedded into the skull. Using the stereotactic frame facilitates an accurate brain targeting given that it is measured in millimeters and will allow surgeons to implant the electrodes in the desired position because before placing the stereotactic frame around the head of the patient, they set the coordinates.

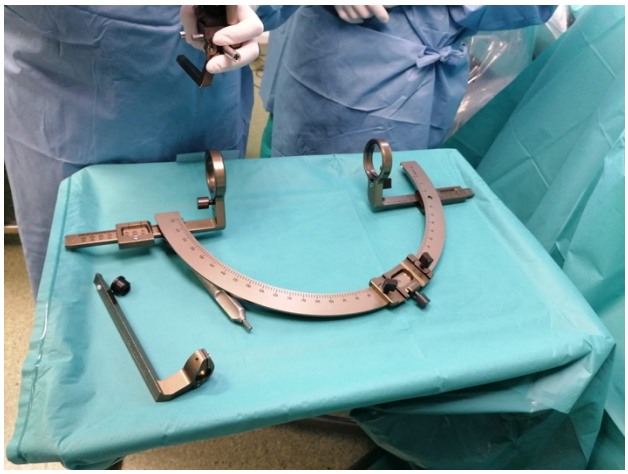


***Image 1**. Coordinates setting in the Leksell stereotactic Frame G before the surgical procedure.*

When the frame is correctly fixed to the skull, a support piece is coupled to it to keep the head of the patient in a comfortable position for the surgery. Then, a box-shaped localizing device is placed over the top of the stereotactic frame forming a cube around the head of the patient. This box has symmetric fiducial lines (radio-opaque marks) which allow the exact three-dimensional coordinates localization of the target area within the brain for that frame. The coordinate 100,100,100 corresponds exactly to the center of the head of the patient. Afterward, the O-arm TM, which is a mobile intraoperative CT (CTi) developed by Medtronic which allows a 2D/3D view of the anatomy of the patient in real time during the surgery, is placed around the head of the patient and it must be perfectly aligned with the cube mentioned before. To achieve this alignment, the O-arm TM laser is used.

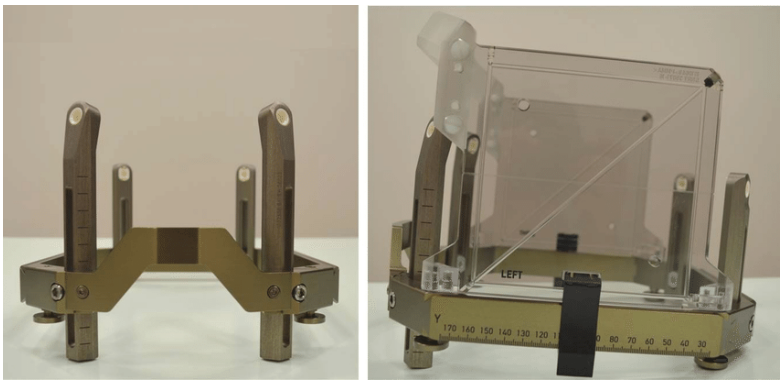


***Image 2**. Leksell stereotactic coordinate Frame G: (left) frame assembled with the curved front piece in the upwards position; (right) lateral view of the Leksell Frame G with the CT fiducial indicator box attached [41].*

Once the O-arm TM is correctly aligned with the fiducial indicator box, it is connected to a computer that has installed the StealthStation™ S8 Surgical Navigation System, a software developed by Medtronic, in which the pre-surgical brain reconstruction obtained 2 weeks before the surgery with the surgery planning has already been uploaded. After this, CT images are obtained with the O-arm TM in order to visualize the current state of the brain and evaluate if there have been changes. When the brain reconstruction with the CT images is obtained, then it is merged with the pre-surgical reconstruction used for the simulation in the surgical planning, and the software calculates the possible error that could have been produced during frame placement. Using the CT scans and the software, the surgeon plans the final target and trajectory of the electrodes.

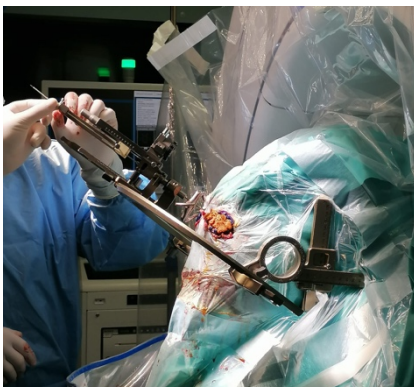


***Image 3**. Electrode implantation through a guide during the surgery.*

The coordinates obtained with the stereotactic O-arm TMimages are then translated into frame coordinates, and these ones must be rounded to entire or half numbers (.0 or .5) due to the Leksell´s frame characteristics. These are the coordinates where the leads will be placed and the trajectories that will follow. Apart from coordinates x, y and z, there are also the ring and the arc coordinates. Ring coordinates are the antero-posterior rotation angle coordinates from the arc; and the arc coordinates are the entrance coordinates of the arc to the head. Once all the coordinates are obtained, sterile draping is applied and the surgery commences.

The skin incision is made following the planned trajectory to expose the skull. Then, using a drill, a burr hole is made on the skull to allow electrodes to be passed through the brain. Bone wax is

applied to avoid craneal porous bone bleeding. After this, the fixation device that will keep the electrode in its position is placed. This fixation will be used also to cover the burr hole once the electrode is implanted. Through this hole, the electrode is inserted to a precise depth and angle into the brain based on the previously obtained stereotactic coordinate. The implantation is done using a specific holder device (micropositioner) guide which will guide the electrode to the desired position. This procedure can be seen in image 3.

To verify the correct lead location, the next step is to obtain another intraoperative image with the O-arm TM. For that, the new CT scan is merged with the one obtained at the beginning of the surgery (the pre-surgical MRI scan with the planning coregistered with the intraoperative CT scan). The reconstructed image obtained with the O-arm TM is uploaded to the software, and this one shows the accuracy of the electrode position with respect to the desired one (the position simulated in the surgery planning). If the accuracy of the electrode is submilimetric, the fixation cover is placed, and then the same procedure is repeated on the other side of the brain to place the second electrode.

When both electrodes are implanted and the wounds are closed, a tridimensional image of both electrodes is reconstructed over the last scan obtained with the O-arm TM to verify correct electrode position. This tridimensional scan will also be used extra-operatively to do the automatic segmentation of each electrode to evaluate the programming parameters that must be applied according to its position.

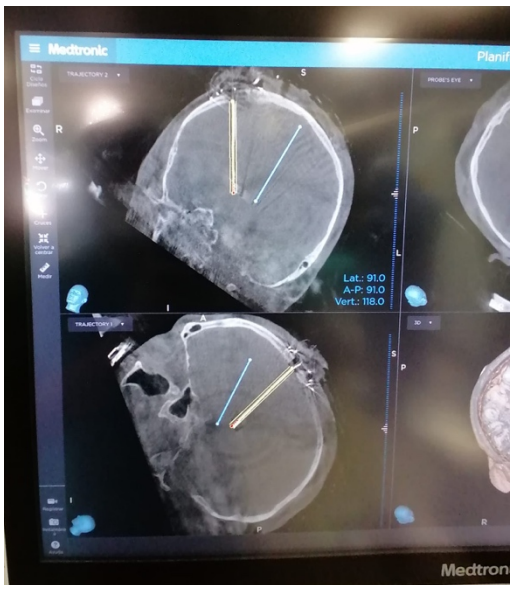


Image 4. *Assessment of electrode position After the implantation with the StealthStation S8 Surgical Navigation System.*

After all this procedure, the final step is to implant the battery source which will deliver the energy needed by the electrodes to perform the electrical stimulation. For that, a small incision in the anterior upper chest of the patient is done to locate the IPG. To connect the battery to the poles of the leads, another small incision in the head is done to pass the extension wires through the subcutaneous cellular tissue till the chest. Once the poles of the electrodes are connected to the battery poles, it must be checked that the circuit is closed. This is done via bluetooth with an iPad that connects to the battery. Once it is checked that all poles are correctly connected and that the circuit is closed, the wounds are closed and the surgery is finished.

b) Programming

DBS programming is typically done by a trained healthcare professional who traditionally is a neurologist and a specialized nurse. The traditional DBS programming method is based on a trial-and-error approach, often becoming a time-consuming process for both treating physicians and patients. The procedure followed in Hospital Clinic of Barcelona to perform DBS programming is described in this section.

Seven days after the surgery, the patient must go to the hospital after an overnight off-dopaminergic medication to assess the effects of DBS without the interference of medications [42]. In this first

programming visit after the surgery, a so-called “monopolar review” is done. The goal is to determine the therapeutic window for each electrode contact; that is the difference of electrical current values between the stimulation settings that provide maximum alleviation of motor symptoms and the settings for which the first stimulation-induced side effect appears. The wider this window, the more flexibility is offered to the patient for stimulation without causing side-effects [43]. The initial programming visit can often be long lasting nearly 60–90 minutes.

Initially, each electrode contact on the lead is tested in a monopolar configuration with the electrode as negative (cathode) and the neurostimulator case as positive (anode). With a fixed frequency and pulse width, each of the electrode contacts is separately examined with amplitude delivered at increasing increments of 0.5V or mA until there is elicitation of adverse effect (objective or subjective) that stays persistent with continued stimulation. This establishes a stimulation threshold for the adverse effects. Then the efficacy of stimulation at this contact is examined using an amplitude reduction by 0.1–1.0 V or mA below the stimulation threshold for side effects. As the amplitude is reduced, the lowest threshold for inducing the best clinical benefits is determined. The electrode contact with the widest therapeutic window (wider difference between the threshold for inducing side effects and the threshold for clinical benefits) is selected for chronic stimulation. Both clinical effects and side effects depend on the direction of spread of current stimulating the anatomical structures. If there is inadequate control of motor symptoms with single monopolar configuration, the next choice is to employ double monopolar stimulation with the two stimulation contacts as negative and the neurostimulator case as positive.

During the initial six months after surgery, patients are followed every month. Once the optimal programing settings are determined, patients are then followed on an annual basis for clinical performance, troubleshooting, and battery checks. An earlier follow-up is scheduled if the disease status worsens at a faster pace.

Stimulation parameters were set to 130 Hz and 60 μs by default, with increasing stimulation amplitude starting at 1 mA (with 0.5 mA increments). At each stimulation amplitude, the patient was tested for occurrence of side effects (almost exclusively muscle spasms).

c) Stimulation Parameters

The main stimulation parameters in DBS programming include the electrical current amplitude, the frequency, the pulse width and the contact of stimulation:

Amplitude: controls the intensity of the stimulation and is measured in mA.

Pulse Width: refers to the duration of each electrical pulse delivered and is in the order of μs.

Frequency: is the rate of stimulation employed in programming and is measured in Hz.

Contact of stimulation: It is the most important parameter since it determines with which part of the electrode will be applied the electrical current. The electrodes that are implanted the most in the hospital have 4 contact rings, and the two in the middle are split into 3 segments to allow current steering. The distribution of the contacts of one of the electrodes implanted remains as shown in figure 5. By convention, the contacts are numbered from ventral (1) to dorsal (8). Contacts 2/3/4 form the supraventral ring, and contacts 5/6/7 the subdorsal ring. The 4 contact rings clinical nomenclature is illustrated in figure 5 too.

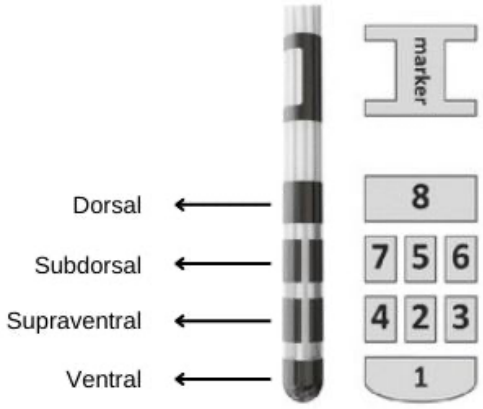


***Figure 5**. Vercise Cartesia™ directional lead contact distribution with the corresponding nomenclature for each contact ring. Contacts 2/3/4 and 5/6/7 are the directional contacts of the middle lead levels [44].*

In addition to these parameters, the **therapeutic window (TW**) is another parameter that is usually measured in DBS programming. Nevertheless, it was not considered for the study since it did not provide useful information to analyze. The therapeutic window is the difference of electrical current values between the stimulation settings that provide maximum alleviation of motor symptoms and the settings for which the first stimulation-induced side effect appears (e.g., eye deviation, muscle contraction, speech impairment). The wider this window, the more flexibility is offered to the patient for stimulation without causing side-effects [43].

d) Electrodes

Over the last years, several electrodes designs have been developed for DBS which have undergone modifications, improving their accuracy and efficiency by providing more freedom to target stimulation. Conventional electrodes used to provide circular current to the target and direction of the stimulus could not be directed (non-directional DBS).

In recent years, segmented leads have been developed, which are able to steer the field of stimulation from a concentric to eccentric shape relative to the vertical axis of the DBS lead. The appearance of directional leads have led to considerable improvements in DBS results owing to a better targeting of stimulation, allowing to direct the current not only in the vertical but also in the horizontal plane. With directional DBS (dDBS), the risk of stimulation-induced adverse effects is reduced and the clinical benefit of DBS is optimized.

In the following figure, it is shown a comparison between different types of non-directional leads and directional leads developed in the last years. The major difference relies on contacts distribution, which for the case of non-directional electrodes, they have 4-8 cylindric contacts at variable interspacings. On the other hand, some directional leads have the 2 cylindric contacts in the middle divided into three equal segments and span about 120º (the first two starting from the left in [B]); whereas the other one has a 40-contact lead design.

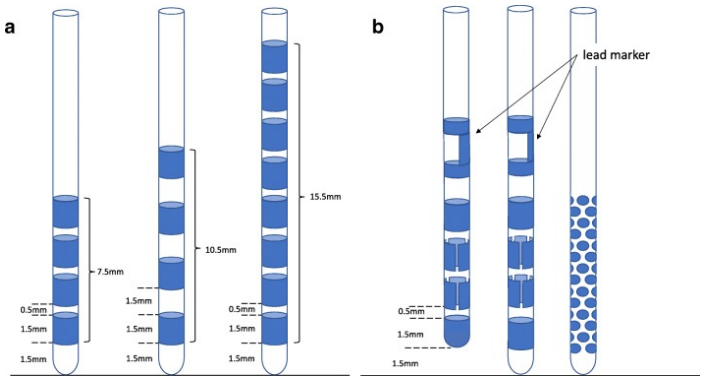


***Figure 6**. Overview of different electrode design schemes. (A) Scheme of the most common non-directional DBS electrodes developed by St. Jude Medical, Medtronic and Boston Scientific (from left to right, respectively). (B) Schematic drawing of 2 currently available directional DBS electrodes developed by Boston Scientific (left) and Medtronic (middle), and an electrode used so far only within studies from Medtronic (right) [45].*

The 2 commercially available directional DBS electrodes use either an "active tip" contact to allow more "downwards" current flow or a cylindric contact as the most distal. Both have a lead marker on top, which allows to control the rotational orientation via fluoroscopy.

In Hospital Clinic, since this year, directional leads have been used due to its advantages and better results. The most implanted one is the Medtronic SenSight B33005 since it allows brain activity recording; but the Vercise Cartesia™ Directional Lead (Boston Scientific) is implanted too in a smaller percentage.

Boston Scientific's Vercise Cartesia directional lead has 4 cylindrical contacts, and current steering is enabled due to the two contacts in the middle, that are divided into three equal segments.

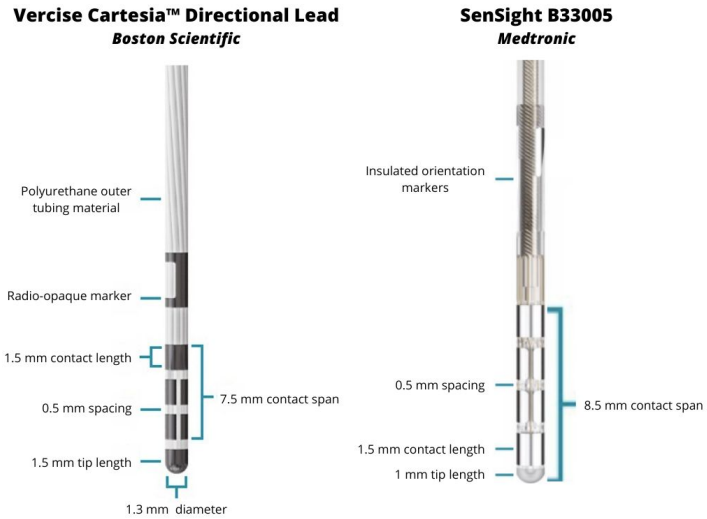


***Figure 7.** Feature comparison of the 2 most used electrodes in Hospital Clinic of Barcelona, the Vercise Cartesia™ Directional Lead (left) and the SenSight B33005 (right).*

Although the advent of directional DBS may allow for more precise and patient-tailored stimulation, the increasing number of contacts and possible stimulation settings introduce a higher degree of complexity that comes with a more expensive and complex postoperative management. Thus, technological tools would be warranted to identify effective parameter settings for each patient in advance [46].

2.2 Current situation

Initially, after surgery an extensive number of programming sessions used to be performed to define the most optimal stimulation parameters because DBS programming mainly relied on clinician's personal experience as no evidence-based guidelines were available. As a result, patients often underwent inconsistent and inefficient stimulation changes, as well as unnecessary visits. In addition, other sessions were very often organized during the follow-up visits in order to manage stimulation-induced side effects.

Over the last few years, several novel technologies have been developed regarding DBS therapy. Directional leads, long lasting and rechargeable batteries, intraoperative visualization tools, softwares that enable patient-specific anatomy reconstructions and alternative programming techniques are the most remarkable ones. For DBS programming in particular, current-based programming, interleaved programming, fractionated current, and directional current steering are important examples of alternative programming techniques.

The most talked-about topic to improve DBS programming is related to adaptive DBS (aDBS), which is based on neuronal signals recording through the chronically implanted electrodes as a feedback control to do an automatised adjustment of DBS parameters. This type of stimulation uses the spontaneous electrophysiological activity recorded in the brain, termed the local field potentials (LFPs), as a feedback signal. Particularly, oscillations in the beta frequency band has been proved to be an useful biomarker to assess bradykinesia and rigidity; and the amplitude of neural activity at tremor frequency (∼5 Hz) and its first harmonic (∼10 Hz), which has been recorded in the cortico-basal ganglia-cortical loop in tremulous PD patients, has been suggested also as a possible feedback signal for aDBS [47].

Currently, DBS programming still requires multiple patient visits, but the quality and duration of these visits has improved with time as new technologies have been developed for this purpose. Actually, there exist a variety of softwares developed by different companies that help clinicians in determining the optimal parameters of stimulation by allowing them to simulate the electrical field that would be induced under certain values and using patient-specific anatomy. These softwares are very useful as they save a lot of time on this procedure.

2.2.1 State of the art

Several attempts have been made recently to streamline DBS programming including but not limited to clinical algorithms, volume of tissue activated (VTA)-based software, functional magnetic resonance imaging (MRI)-based paradigms, and approaches using the patient's programmer. In this section, recent developments in relation with the alternative programming techniques mentioned above, as well as novel algorithms and softwares will be discussed, as they are important advances in the field of DBS programming.

DBS systems currently stimulate in an open-loop manner, meaning that stimulation parameters are pre-programmed and are not responsive to changes in the patient's clinical symptoms or in the underlying physiological activity. Although open-loop stimulation is state of the art, limitations like overall efficiency, reduction of efficiency over time or side-effects have become more obvious with growing clinical experience [48].

Therefore, adaptive closed-loop stimulation systems that apply disease-specific biomarkers, such as LFPs, are currently being actively examined to facilitate programming. However, the most suitable feedback signal still remains largely unknown [49]. Regarding this problem, there is a research group in Germany which is evaluating the PD patient's subjective judgment as a valid

feedback signal given that based on a previous study performed by the same group, it was found that there was no significant difference compared to standard programming. The intention of this investigation group is to evaluate a visual-analog scale (VAS) for remote DBS programming based on their results, which suggest that DBS patients are well able to adjust their IPG settings by themselves. This would allow DBS patients to perform the programming setting remotely, solving the problem of mobility that some patients have when they have to go to the programming visits, as well as the time saving that this approach provides. The effectiveness and safety of VAS-based remote DBS programming in PD would be performed by using a novel and recently introduced software platform (Abbott NeurosphereTM Virtual Clinic) that allows the programming through a smartphone-based video connection with the patient. Anyway, a validation of this approach is required given that it is still in a testing state.

In another proof-of-principle pilot study it was shown that currently available LFP-based technology can be used to confirm the efficacy of different programming parameters when tested by the patients themselves outside the hospital setting at home [50].

On the other hand, some groups have developed tools to perform a more specific programming, like the Toronto Western Hospital, which in 2016 developed four algorithms tailored to an individualized approach to managing symptoms associated with DBS and disease progression in patients with PD [51]. Another research study published recently the potential use of functional magnetic resonance imaging (fMRI) as a predicting tool of DBS parameters. In this study a machine learning algorithm was developed, based on the characteristic fMRI brain response pattern to clinically optimal stimulation, to predict the optimal vs. non-optimal stimulation parameters of 39 PD patients with a priori clinically optimized DBS [52]. This approach could be interesting for the future of DBS programming, but further validation with additional studies is needed.

Future advances in DBS technology such as closed loop DBS will increase battery life and advances in DBS programming like remote and Internet based programming will increase patient comfort and convenience [53].

3. MARKET ANALYSIS

As mentioned in the previous section, advances in technology have led to the appearance of new softwares and algorithms developed to help in DBS programming. In this section it will be done a thorough global market analysis of the current technologies used nowadays for this purpose.

3.1 Historical Evolution

Formerly, when there were no softwares for DBS programming, in order to visualize the leads after the surgery, patients had to be taken to do an MRI and with the image obtained, clinicians had to evaluate visually the leads position and DBS programming was performed under their criteria. This was not usually done by clinicians and programming was exclusively based on a trial-and-error technique in which in each visit, stimulation parameters were changed and evaluated to see if there were improvements or if they produced secondary effects. This process used to take a lot of time and in addition this was a problem for those patients who lived far away from the centers where programming was performed. If side effects were encountered at a low therapeutic window, or no clinical benefit was obtained, then an MRI was performed to verify the position of the electrodes.

With time, different tools and softwares have appeared to help clinicians in this task, helping them to visualize leads position. The first softwares used to locate leads in the patient image according to a neuroanatomy atlas, but this was not very reliable. As technology advances, new softwares have appeared that use post-operative patient-specific images, which is a huge advantage given that it allows to visualize leads location, and compare it with the pre-operative image where the leads position was programmed before the surgery. This allows clinicians to estimate the errors in leads position that have been produced during the surgery, and also to evaluate the actual location of the electrodes and take it into account to find the optimal stimulation parameters that must be applied by each lead.

3.2 Global Market Leaders

Most of the companies that are currently developing softwares to provide help in DBS programming are from North America, who dominated the DBS devices market with a share of 51.9% in 2020. This is due to an increase in FDA approvals for DBS devices in clinical applications. However, Asia is expected to significantly lead the market for DBS devices in the future from 2021 to 2028. This is attributed to the rising prevalence of neurodegenerative disorders coupled with unmet demand for effective and long-term solutions. The rising awareness about neurological disease treatment options and improvements in the clinical development framework of emerging economies is expected to drive the market for DBS devices in this region. Moreover, the presence of high growth opportunities in developing countries such as Japan, China and India are likely to contribute to market growth [54].

3.3 Target Sectors

In the past years, among neurological disorders PD is the one which has undergone the fastest growth in prevalence and disability [55] and according to the GBD study, its incidence was 1.02 million people in 2017, reporting 6.1 million cases of PD globally in 2016 [56].

As mentioned in the introduction, PD is a neurological disorder that affects elder people; therefore, as the world population grows and ages, its prevalence will continue to increase. In a study made in more than 200 countries it was shown that most of them have an upward trend in PD burden, being the United States of America, Norway and Germany some of the countries with a high socio-demographic index that showed a more pronounced upward trend [55].

Another important factor related with the disease and the global population growth is the years lived with disability (YLDs), which is an index measuring the average lifespan of incident cases until rehabilitation or death, and the disability due to that status. YLDs is a widely used index evaluating the health loss caused by PD, and it is highly related with patients quality of life. Improving patient quality of life as much as possible is one of the main aims of healthcare, so a huge investment in PD is expected in the future to achieve this goal. In fact, the global DBS devices market size was valued at USD 1.12 billion in 2020 and is expected to expand at a compound annual growth rate (CAGR) of 9.3% from 2021 to 2028 [54].

So one of the main target sectors for DBS programming softwares are those well-developed countries where PD incidence is high and is expected to continue growing. These softwares will target those patients with PD that must undergo DBS surgery. Another important risk factor for this disease, in addition to age, is male gender. So elder people and mostly men will be the focus for this type of softwares.

The places where these softwares will be used are mainly hospitals and centers where DBS programming is performed, so these are other target sectors where they would be implemented, and the intended users are healthcare professionals educated for the planning and execution of DBS procedures. These are, in general, neurosurgeons and neurologists.

3.4 Key Players

Currently there are different companies and startups who have developed similar tools (softwares and algorithms) to help in DBS programming. The four main companies that have developed these softwares are Medtronic, Boston Scientific, St. Jude Medical (Abbott) and Aleva Neurotherapeutics S.A. Softwares developed by each of these companies are described below, as well as other softwares from smaller companies and startups.

The SureTune™ 4 software has been developed by **Medtronic**. This software enables the creation of patient-specific anatomy and lead location and orientation which then can be pulled into the DBS by the Clinician Programmer for a visually informed programming session, helping to streamline the directional lead programming workflow. It includes patient-specific anatomy segmentation tools based on the use of the Bardinet algorithm to automatically fit the YeB Atlas to a patient MRI T1 or T2 image. In addition, manual segmentation tools allow further refinement if needed. Regarding the lead placement and orientation, it allows to automatically position and orient a patient lead within a post-operative CT or an O-arm TM image.

SureTune™ 4 also allows to import data into the Clinician Programmer for a customized and visually-informed programming session. Through the integration of information from planning to programming it enables a more optimal DBS therapy management. Before launching the SureTune™ 4 software, Medtronic had developed other versions of this software before. So this company has large years of experience on this type of softwares development, which makes them a powerful competitor in this sector.

***Figure 8**. SureTune™ 4 software user interface [57].*

Another huge company that has developed different tools for this purpose is **Boston Scientific Corporation** (Valencia, CA, United States). The latest software that this company has launched is the Guide™ XT. This software was developed in association with Brainlab AG, a software-driven medical technology company that contributes to the improvement of patient treatment planning and surgical navigation. This exclusive collaboration between Brainlab and Boston Scientific offers a comprehensive portfolio where all the elements needed for patients and clinicians to perform DBS are covered. The Guide™ XT software was the first DBS visualization system built for directionality, which uses stimulation field and patient-specific anatomy modeling. This technology provides clinicians with 3D image planning capability and, when used together with the Vercise™ DBS system, it allows clinicians to personalize and optimize DBS treatment [58]. The software is based in part on Xerces C++3.1.1, developed by the Apache Software Foundation, and also on the work of the Independent JPEG Group [59]. Guide™ XT has been intended to display medical images and simulate stimulation output. It includes functions for image manipulation and 3D visualization of reconstructions and volume rendering. Features include the display of a simulated DBS lead from a patient's CT scan compared to an anatomical atlas.

Furthermore, in April 2022 the FDA approved a new software from Boston Scientific Corporation, the Stimview™ XT, which adds 3D image guidance to the process.

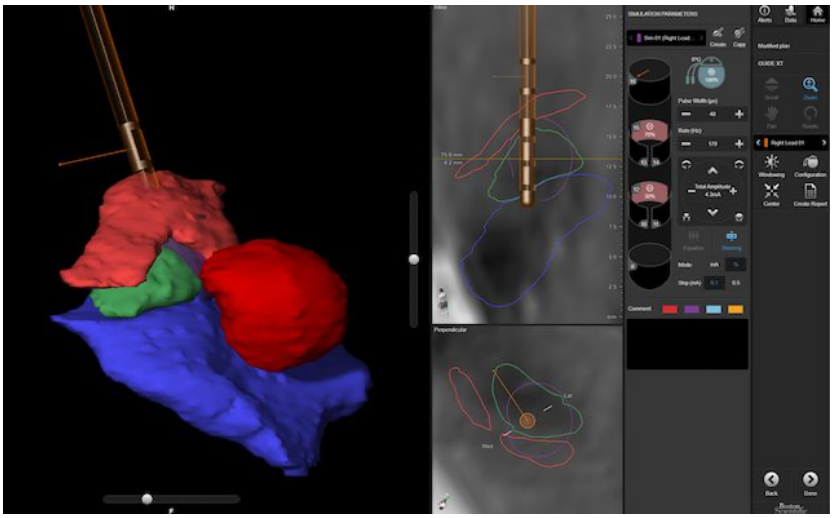


***Figure 9**. Patient lead visualization with the Boston Scientific Guide™ XT software [60].*

The St. Jude Medical Infinity™ DBS system (now called Abbott's Infinity™ DBS system) features an industry-leading DBS iOS software wireless platform and Apple mobile digital devices as

programming platforms [61] that are combined with directional lead technology. This software has been developed by the company **St. Jude Medical**, which now belongs to **Abbott**, and it has been designed to streamline therapy management for a discreet and personalized experience for patients. The Abbott's Infinity™ DBS system includes segmented, directional lead technology which has been designed to steer the current towards the desired anatomical targets and it is the first wireless iOS software DBS mobile platform that offers efficient and personalized therapy management with reduced risk of adverse effects.

***Figure 10**. Abbott's Infinity™ DBS system [61].*

The directSTIM™ DBS system developed by **Aleva Neurotherapeutics S.A**. includes 12 electrode directional leads, 12 contact extensions and 2 x 12 channels IPG with independent current sources. It also includes a clinician programmer which allows to configure the IPG and tailor stimulation parameters according to the patient response and symptoms. This company together with NeuroPace, Inc. are considered innovators in the DBS devices market owing to the good price-performance propositions of the offered products, as well as to how advanced they are technologically.

Other powerful softwares and algorithms that are used for DBS programming are:

- **Lead-DBS:** It is a toolbox which facilitates DBS electrode reconstructions and computer simulations based on post-operative MRI and CT imaging. Lead-DBS was initially developed at the Movement Disorders Unit of Andrea Kühn, by the Department of Neurology, Charité – University Medicine (CCM), Berlin, Germany. Since 2016, development continues among researchers from various institutions and since 2019, development is coordinated from the Network Stimulation Laboratory in Berlin. This toolbox is made available to the public in the form of an open-source Matlab repository [63] and works within Matlab >2014b. It needs statistics and imaging toolboxes as well as SPM12 installed [9] [64]. Lead-DBS is an open-source software which is constantly being updated.

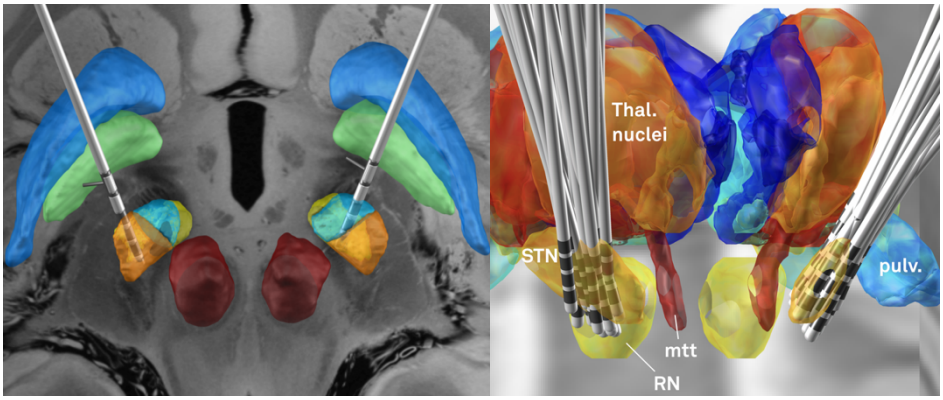


***Figure 11**. Electrodes reconstruction with Matlab Lead-DBS software [64].*

- **CranialVault Cloud (Cranial Cloud):** Developed by the spinoff Neurotargeting LLC out of Vanderbilt University, it consists on a network of nodes, each with the capability to store and process data, that share the same spatial normalization processes, thus guaranteeing a common reference space [65]. The CranialVault is the only system that can be distributed and combines patient's image data, data that can be localized within them such as micro-electrode recordings, patient's response to stimulation, implant location and any demographic or disease-related information. The CranialVault system normalizes the patient's data onto a common reference system using the patient MRI images and registration algorithms. Once normalized, the data can be analyzed through various queries.

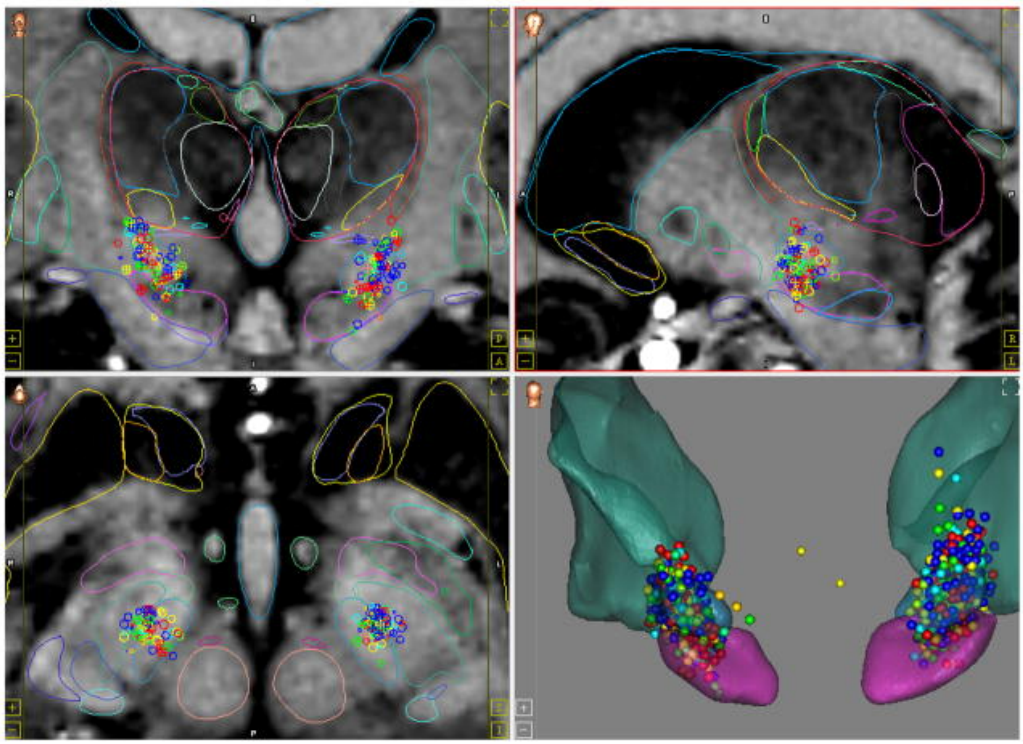


***Figure 12.** CranialVault Atlas module visualization interface [65].*

3.5 Future Opportunities

Advances in technology are bringing a wide variety of possibilities which will lead to future improvements in DBS programming and software development. As mentioned before, the DBS devices market is expected to grow in the coming years as the need to treat PD patients will

increase according to the growing incidence of the disease. This will allow current companies to develop new novel devices and also to improve the actual ones, as well as to the emergence of new companies looking for opportunities inside the sector.

In addition, DBS programming softwares have been launched to the market in the recent years, therefore these tools are still in their infancy. So here there is a huge field in which companies can focus on improving what they have already developed and where the opportunities to innovate and grow are boundless.

Technological advancements in DBS technologies are anticipated to create growth opportunities in this market. These technological improvements include robot-assisted implantation, improved microelectrode designs, multi-target stimulation, rechargeable implantable pulse generators, and personalized directed programming [54]. Regarding possible future improvements of these softwares, development of tools that allow remote and internet based programming are likely in order to resolve the issues of unnecessary programming visits and patient displacement in the near future. Furthermore, as the newest electrodes released to the market are able to record electrical activity in the brain, a possible future opportunity could be developing a software capable of reading this physiological activity and predict the optimal stimulation parameters according to the patient's brain activity in the target area. And a future improvement to this possible software could be that in addition to predicting the stimulation parameters, the software were able to select which contacts are more suitable for the stimulation according to the electrical activity recorded.

4. CONCEPTION EGINEERING

Different approaches have been evaluated to accomplish the aim of this project. In this section, an analysis of the different possible solutions that were contemplated has been done.

4.1 Study Requirements and Features Setting

4.1.1 Patient Selection

First of all, the number of patients needed to perform a reliable study had to be defined. Looking at the literature it was found that authors of similar studies usually collect data from between 9 and more than 50 patients. Regarding the number of patients selection, the alternatives were data collection from around 10, 30 or 50 patients. To make this choice, time available to collect data had to be taken into account, as well as the additional time that would be needed to perform the corresponding simulations for each patient.

In addition to the number of patients, another requirement that was evaluated was the type of electrode with which patients were implanted. As mentioned before, in Hospital Clinic surgeons use both the SenSight B33005 from Medtronic and the Vercise Cartesia from Boston Scientific. Both of them are directional leads, and with the Guide XT software it is possible to simulate the two types of electrodes. However, since the software is from Boston Scientific, simulations performed for electrodes from this company are more accurate. Guide XT provides the option to select the type of electrode that has been implanted among the different leads developed by Boston Scientific (directionals or non-directionals). Simulations performed for Medtronic electrodes are accurate when representing lead position with respect to patient anatomy; but if stimulation parameters output is simulated, software outcome will not be consistent with real stimulation output since the electrode simulated does not have the same contact distribution as the real one.

4.1.2 Programming time period

An important parameter that had to be decided for the study was the time period in which data was going to be collected. Patient data from different programming sessions should be gathered to perform a further comparison. The different time periods evaluated were:

- One-week patient follow-up: data collection only from the first programming session (performed by the neurology service one week after the surgery).
- One-month patient follow-up: data collection from the first programming visit after the surgery and from the programming session performed one month after the surgery.
- Three-month patient follow-up: data collection from the first programming session and from the one month, two months and three months visits after the surgery.
- Six-month patient follow-up: data collection from the first programming visit, from the programming session three months after the surgery and from the six months visit after the surgery.

Time Period	Programming sessions data collection	Advantages	Disadvantages
1 week follow up	First programming session	Comparison between data from software simulation and data from the first attempt to set the optimal	Data from only the first programming session can be unreliable since stimulation parameters are usually

		stimulation parameters would be interesting.	modified after this session due to anatomical changes in the brain. This data is not enough to do a further analysis.
1 month follow up	• First programming session • 1 month after the surgery	Stimulation parameters after 1 month from the surgery are not usually modified in most patients. An analysis about how these parameters have changed with respect to the first programming session could be performed.	An analysis of future modifications in stimulation parameters could not be assessed.
3 months follow up	• First programming session • 1 month after the surgery • 2 months after the surgery • 3 months after the surgery	With this extensive amount of data, consecutive stimulation parameters modifications within this time period could be evaluated .	Time-consuming process due to the large amount of data that should be acquired in a relatively short time period. Changes in stimulation parameters may not be that important within short time periods.
6 months follow up	• First programming session • 3 months after the surgery • 6 months after the surgery	With this huge amount of data, it could be done a thorough analysis of how the stimulation parameters have varied during a long time period.	It should be evaluated if long-term stimulation parameters modifications are relevant for this study. Less patients could be included in the study.

***Table 1**. Different options for the time period follow up.*

4.2 Data Collection

4.2.1 Database platform

To perform the study, patient information had to be noted down and stored somewhere to perform the further analysis, as well as the data obtained from software simulations. Thus, the creation of a database was needed. The different platforms evaluated for this purpose were mainly a word document or an excel sheet.

4.2.2 Clinical data

For the information that was going to be collected from clinical outcome, an analysis of all the possible parameters that could result of interest for the study was performed. The information from patients that was thought to be useful, based on similar studies from the literature, was:

- **Age**
- **Sex**
- **Disease Duration:** How many years has the patient been with the disease until the surgery date.
- **Patient ID:** To have a way of identifying patients for the subsequent simulation's performance.
- **Surgery date:** To have a control of on which day were patients implanted (necessary for simulations).
- **DBS lead:** The type of electrode with which patients were implanted.
- **Location of stimulation contact**: Which of the contact rings was used for DBS programming.
- **Stimulation amplitude:** How many mA were applied for each electrode.
- **Frequency**
- **Pulse Width**
- **Side Effects** (after each programming session)
- **Final programming date:** To calculate the time period between the first programming session and the last one assessed.
- **Unified Parkinson's Disease Rating Scale (UPDRS-III):** Pre-operative and post-operative values of this test, since it is a reliable way to assess patients' motor symptoms evolution.
- **The Parkinson's Disease Questionnaire (PDQ-39):** Pre-operative and post-operative values of this test to assess the quality of life evolution of PD patients regarding their social situation.

4.2.3 Software data

Regarding the data that was going to be obtained from the simulations, the purpose was to compare it with the values obtained from the clinical outcome. Therefore, information obtention of some of the parameters selected for data extraction from the clinical outcome was evaluated, but further information could be obtained from simulations. The data that could be useful to perform the comparison and obtain results from software performance assessment was the following:

- **Ideal stimulation contact:** This could be assessed by a surgeon or any clinician who has knowledge about how to perform DBS. For stimulation contact selection, the clinician should look at the electrode position with respect to patient brain structures reconstruction and evaluate which contact would be better for the stimulation.

- **Electrode position:** To evaluate if the electrode has been placed correctly after the surgery and take it into account when performing the stimulation output simulation. This information could be useful to perform a further analysis.
- **Stimulation amplitude:** This parameter could be decided by a clinician to perform an optimal stimulation.
- **Frequency**
- **Pulse Width**

Selection of the most suitable stimulation parameters for each patient required the help of a clinician with knowledge on DBS, since the author did not have the experience needed to make this decision.

4.3 Data Analysis Environment

From data collected, a thorough analysis could be performed to assess software usefulness when selecting stimulation parameters based on simulations. In addition, different results related with clinical outcomes could be obtained. In order to perform these data analysis and extract results from them, different environments were evaluated to achieve this purpose: Excel, Anaconda Navigator, Matlab and R Studio. Each of them is described below.

Excel is a software program developed by Microsoft that uses spreadsheets to organize numbers and data with formulas and functions. It enables users to format, organize and calculate data easily and also to perform fast calculations and to obtain statistical graphs from data. In addition, it is very visual because the user can see the data introduced and work over it when applying the formulas. The main uses of Microsoft Excel include data entry and management, charting, graphing and programming, among others. It features computation capabilities, graphing tools and a macro programming language called Visual Basic for Applications (VBA) [66].

Anaconda Navigator is a desktop graphical user interface included in Anaconda® distribution that allows users to launch applications and manage conda packages, environment, notebooks and channels easily without the need of using command-line commands in the computer [67]. This graphical user interface includes different applications in which users can write codes in one of the most common programming languages: Python, an open source tool which includes a huge variety of packages such as Numpy, Matplotlib or Pandas that allow to manage data and perform statistical analysis. The advantage of Anaconda Navigator is that by using these applications, for example Jupyter Notebook or Spyder, the user can run the code and visualize data easily.

Matlab is a programming and numeric computing platform used widely for data analysis [68]. It includes a set of toolboxes that combined with its array-based language allow users to manage data and obtain graphic results. To use this programming platform, an annual license is needed.

R Studio is a free, open source environment developed for the programming language R, which is focused on data science. It includes tools for plotting, history, debugging and workspace management, and it is used for statistical data analysis and graphical representation. This tool allows the combined use of the programming languages R and Python [69].

4.4 Statistical Analysis

Data analysis requires a set of different statistical tests to quantitatively evaluate and show results. Since most parameters assessed were categorical, the statistical tests that could be applied for data to obtain precise results were:

- **Chi-squared test (X2 test):**
  It is a non-parametric statistical test applied for categorical variables. This test assesses if there exists a statistical relationship between two categorical variables by comparing observed results with expected results [70]. The most common chi-squared type used widely is the Pearson's chi-squared test (test of independence), which evaluates how likely it is that any observed difference between sets of categorical data is due to chance. For this, the test assumes that null hypothesis is true (H0), which states that there is no association between the given variables (they are statistically independent). If p-value is 0.05, H0 is accepted, but if it is under this value, H0 is rejected and H1, which states that there is association between variables, is accepted. The formula to measure chi-square is the following:

  $$x^2 = \frac{(O-E)^2}{E} \quad \text{where} \quad E = \frac{RT*CT}{Total}$$

  These values are obtained from a contingency table that contains the frequency distribution of the given variables.

- **Wilcoxon paired signed rank test:**
  Non-parametric statistical test used to compare paired data samples. It computes the difference between each set of matched pairs and then compares sample median against a hypothetical median [71]. The null hypothesis of this test assumes that sample distributions are equal. To be effective, the test requires at least 20 observations in each data sample [72]. As in the chi-squared test, if p-value is 0.05, H0 is accepted.

- **Cohen's kappa coefficient (k):**
  Statistical metric used to assess the agreement between two observers by measuring the inter or intra-rater reliability for categorical items [73]. Cohen's kappa is a quantitative measure of this reliability, corrected by the frequency in which raters coincide by chance. A value of 0 means that there is random agreement among raters and there can be negative values, which means that there is less agreement than the random chance. A score of 1 would mean complete agreement among raters [74].

4.5 Proposed Solution

After evaluating the different options to perform this project, the final decision to validate the Guide XT software included the following conditions:

The number of patients included in the study would range between **30 and 50 patients**, as it was considered to be a good sample number.

For patient selection, only those implanted with **Vercise Cartesia Boston Scientific leads** were included in the study. This condition of eligibility was imposed to simplify results and ensure they were reliable, as the software only gives the option to simulate electrodes from its own company.

Regarding the programming period assessment, the **1-month follow up** option was considered to be enough to perform the comparison between different programming sessions, as assessing only the first programming was not very reliable and doing 3 or 6-months follow up was unnecessary. In addition, a long time period assessment implied excluding patients from the study owing to the fact

that the hospital started to implant directional leads less than two years ago, so the number of patients that could be assessed was limited and only the latest have these leads implanted.

The platform chosen to create the database was **Microsoft Excel** due to the tools and facilities it provides to deal and manage such amounts of data.

From all the information mentioned above that could be collected from patients, patient ID, surgery date and final programming date were discarded since this information was not considered to be useful to obtain any result. The type of lead was also removed since all patients were implanted with the same type of electrode. The UPDRS-III and PDQ-39 values were also discarded since the main aim of the project was not assessing patients' symptoms evolution, but software reliability, so these values did not provide useful information for the study. From data collected from simulations, all the parameters mentioned above were included. Current steering application was included in both databases to perform a comparison of this variable later.

The environment chosen to perform the data analysis and obtain results was **Anaconda Navigator**, given that it included all the necessary tools and packages needed to achieve the objectives of this project. In addition, the difference with the results that could have been obtained using Matlab or R Studio was not significant, and no additional installation was needed since the author had it already installed on its own computer.

The statistical test applied for certain results was the **Cohen's kappa coefficient**, as it was considered to be the one that best suited the desired results.

5. DETAIL ENGINEERING

In this section it is described the work undertaken to assess the utility of the software Guide XT for clinical purposes. As it has been mentioned beforehand, the main aim of this project was to evaluate the reliability of the Guide XT as a supporting tool when determining the stimulation parameters in DBS programming. For that, stimulation parameters from patients who had already undergone DBS were collected, and then for each patient a simulation of stimulation output with the most optimal parameters was performed using the software.

Once data from patients and from the software was collected, a thorough analysis was carried out to obtain the correspondence between the clinical outcome and the software performance. The most important aspect to consider was the concordance between the stimulation parameters set by clinicians that did not cause side effects to patients, and the stimulation parameters selected using software simulations. From here, it was possible to determine the usefulness of the software to avoid the time-consuming trial and error programming method performed in the hospital.

Furthermore, other interesting results could be obtained from data collected such as the relationship between electrode position and the presence of side effects, or the number of patients whose electrode stimulation contacts were changed between the first programming and the one-month follow-up programming. All these relationships are shown in the results section with its corresponding statistical data.

5.1 Patient data collection

For the study, data from 37 patients with PD (26 males [70.3%] and 11 females [29.7%]) who underwent bilateral STN-DBS surgical procedure at Hospital Clínic of Barcelona was collected. All patients were implanted with Vercise Cartesia directional lead (Boston Scientific) and surgeries were performed between January 2021 till April 2022. The IPG was from the Vercise™ DBS system (Boston Scientific) and it was implanted in the subclavicular region during the same procedure. Data collection time period was limited to patients implanted in the last 2 years owing to the fact that the hospital started to implant patients with directional electrodes in 2021, so it was not possible to acquire data from more patients.

The mean age of patients at the time of the surgery was of 57 8.5 years (mean SD) for males, and of 55 9.6 years for females. The average disease duration of the entire population was of 11.6 4.2 years.

The stimulation contact rings used for each patient on each side of the brain are described in table 2, where a differentiation between the contact rings used in the first programming and in the one-month follow up programming session has been done. These stimulation contacts were chosen by clinicians applying the trial-and-error method for both visits.

	Programming visit	**1st Programming**		**1 month follow up Programming**	
	Brain side	**Left**	**Right**	**Left**	**Right***
Contact ring	*Ventral*	7 (18.92 %)	5 (13.51%)	9 (24.32%)	4 (10.81%)

	Supraventral	25 (67.57%)	26 (70.27%)	20 (54.05%)	23 (62.16%)
	Subdorsal	5 (13.51%)	5 (13.51%)	8 (21.62%)	9 (24.32%)
	Dorsal	0 (0%)	1 (2.70%)	0 (0%)	0 (0%)

Table 2. *Stimulation contact rings used by clinicians in both programming visits through the trial and error programming method. *There was a patient in the one-month follow up programming who underwent bipolar stimulation for the right electrode, and the stimulation contact rings used where the ventral and supraventral ones, being this bipolar stimulation a 2.70% of the total.*

To obtain all data from patients, the clinical history of each of them had to be reviewed one by one, looking for the dates of each programming session (the first one, 7 days after the surgery, and the second one, 30 6 days after the surgery). In order to acquire this data without having access to patients personal information, the patient ID clinical number was used.

5.2 Stimulation field simulation

To perform the corresponding simulations of the stimulation output with the Guide XT software, a reconstruction of the anatomy of the patient had to be done for each subject. From here, localization of the implanted DBS leads could be done and a simulation of them was displayed. Here is where the stimulation field simulation was performed after introducing the desired stimulation parameters. Since knowledge about neuroanatomy and DBS is required to decide which are the most optimal stimulation parameters for each patient, the help of clinicians (specially surgeons and neurologists) was necessary to perform the simulations.

The entire procedure about how the simulations were performed and all the steps followed to obtain the electrodes display from patients' anatomy images has been explained in this section. In addition, it is highly important to understand the Guide XT workflow and where the software is located, so the environment where the software is utilized has been described.

5.2.1 Guide XT workflow

As previously mentioned, Guide XT is a commercially available software that has been developed for visualization of DBS leads and also for simulation of stimulation outcome. The software is based on patient-specific anatomy reconstructions from preoperative MRI images coregistered with postoperative CT scans to provide 3D simulations of stimulation fields. Therefore, it can be an useful tool to aid in DBS programming as it allows patient's anatomical structures visualization to restrict the volume of the electrostatic field (VEsF) to the STN. With this, it could be avoided the stimulation of surrounding structures involved in the appearance of stimulation-induced side effects.

The typical Guide XT workflow includes the use of required and also optional applications that are compatible with the software. These additional applications are included in the Brainlab Elements® (Brainlab AG, Munich, Germany) medical software, and are compatible with the Guide XT due to the fact that this software is integrated into the Brainlab Elements workflow. The collaboration between both companies has led to the appearance of a software that includes all the necessary tools to cover the key elements of DBS. Brainlab Elements is composed of complementary software modules that all together provide the needed tools to assist in the entire process of DBS.

In figure 13 the additional tools that can be used in the Guide XT workflow are shown. In the upper part is where patient data necessary to perform the reconstructions can be selected. For some patients, image fusion, brain structures segmentation and lead localization were already done because surgeons sometimes use the software to evaluate if electrodes have been correctly placed after the surgery. When this is the case, data is automatically saved as a "plan", so when someone accesses patient data again, it appears the saved plan indicating the data that has been utilized for the reconstructions.

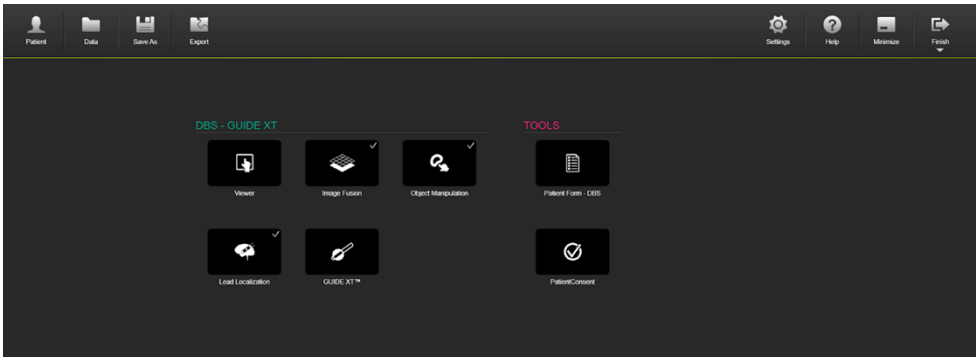


***Figure 13**. Brainlab Elements DBS section main page showing Guide XT workflow.*

To perform the simulations, for the case of those patients that had a plan already created, by selecting this plan in the patient data option and then entering inside each application of the Guide XT workflow to ensure that everything was correctly done, then the final step was to enter inside the "Guide XT™" application. For all other patients, the entire Guide XT workflow shown in figure 13 had to be performed.

a) Patient data selection

Necessary data that had to be selected to obtain patient-specific anatomy reconstruction from clinical tests were:

- A preoperative 3D Sagittal T2-FLAIR 3T-MRI scan from the day before the surgery (MRI / FLAIR-FatSp (3D Sag T2 FLAIR Cube))
- A preoperative 3D Sagittal T1-MRI scan with contrast (MRI / T1 (3D Sag T1 MP-RAGE + CTE))
- A preoperative stereotactic CT scan (CT / CT-CA)
- A postoperative CT scan from the day of the surgery

As patients usually undergo these tests several times, for each patient there were repeated tests with different number of cuts. The criteria to decide which tests were going to be utilized was to choose the ones that had been done later in time, and from these ones, those that had a bigger number of cuts.

b) Brain anatomy reconstruction (Image fusion)

Once the necessary images were selected, the reconstruction of the anatomy of the patient could be performed. For that, the "Image Fusion" option was utilized. Here, the software automatically merged the different image sets (MRI scans and CT scans). This process takes some time, and when co-registration is done, the software asks for the user's acceptance of the final result.

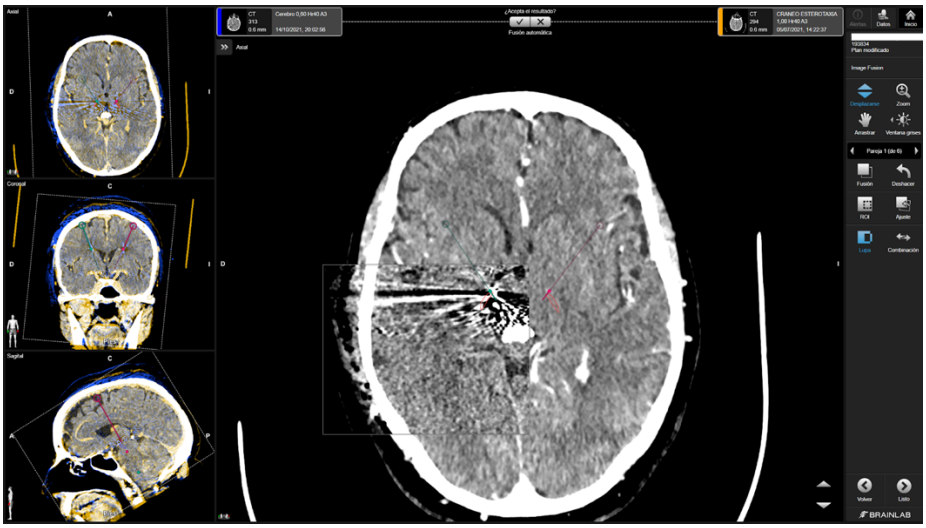


***Figure 14**. End of the image fusion process after automatic images co-registration.*

c) Brain structures segmentation

Following the Guide XT workflow, the next step was to select the brain structures desired to be visualized in the simulation. For those patients that had a plan previously made, these objects were already created and the only thing that needed to be done was to select them.

For patients who did not have a plan, these objects had to be created. As this step required including the surgical planning and performing a series of tasks that were out of the scope of this project, the help of a specialist was necessary. Once the neurosurgeon finished all these tasks, the brain structures of interest were selected, and the software created the objects by performing an automated brain segmentation. This process usually takes a lot of time, so performing it for each patient was time consuming. For all patients, the objects created were for the STN, the substantia nigra and the red nucleus Software used anatomical mapping for brain structures segmentation.

d) Leads Localization

The final step needed before performing the simulations was to localize the implanted electrodes in the patient's anatomy. This was an easy procedure as the software detected in a fast and automatic way both electrodes, creating at the end of the process two objects, one for each electrode (left and right). At this point of the Guide XT workflow is where the type of lead could be defined. The software gives the option to choose between a Boston Scientific standard lead (non-directional), which corresponds to the DB-2201 name, or the directional one. Since all patients included in the study were implanted with the Vercise Cartesia directional lead, the DB-2202 option was selected, which corresponded to the directional lead.

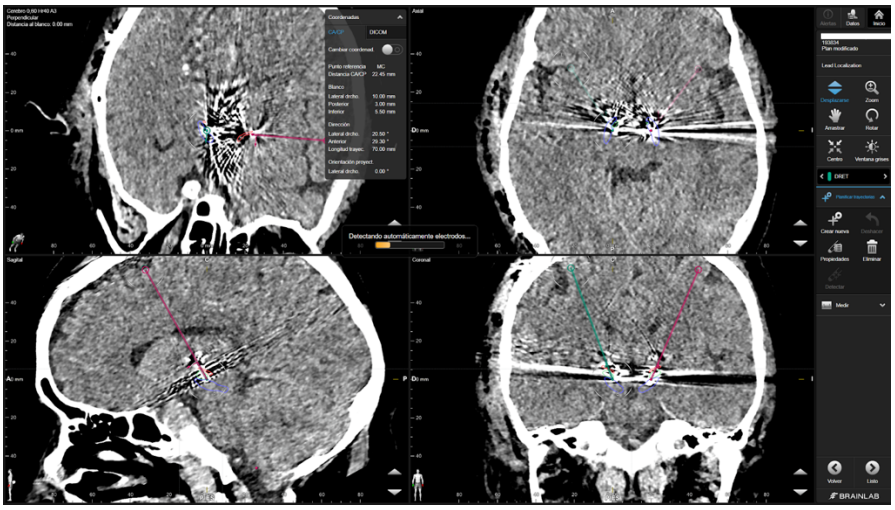


***Figure 15**. Software performance during lead localization process. Each electrode is represented with a different color.*

e) Simulation of stimulation output

When all the necessary data to display the 3D reconstruction of electrodes in the patient's anatomy was selected, the software was ready to perform the simulations. By entering in the Guide XT™ application, the software asks the user to select the desired electrodes to be visualized. For the study, both electrodes were selected. Guide XT displays leads individually, so only one electrode can be visualized on the screen at a time.

On the screen it is displayed at the left the 3D brain structures simulations with the implanted electrode. As it can be seen in figure 16, the lead position can be perfectly visualized so the surgical outcome can be assessed looking at this simulation. Additional image information is shown next to these reconstructions, where an inline and a perpendicular view is displayed.

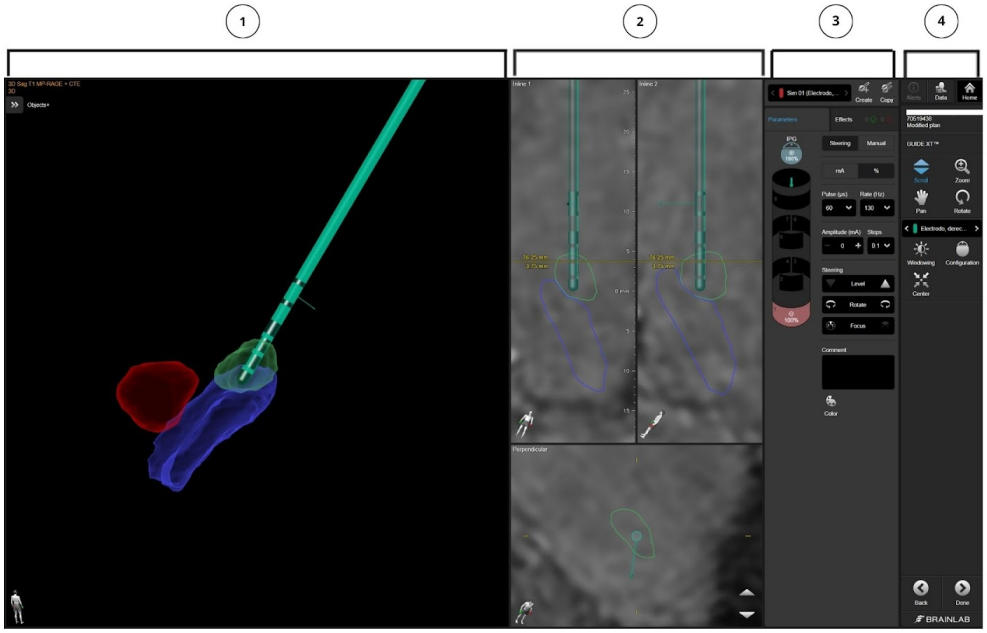


***Figure 16**. Standard layout of Guide XT software. (1) 3D structures display; (2) Inline and Perpendicular view that show additional information; (3) Simulation toolbar; (4) Toolbar.*

As this is an interactive simulation, 3D structures could be rotated in any of the 3D axes to obtain the desired view of the structures. This action was possible using the Scroll button of the toolbar (4). In addition, structures could be seen closer or further with the help of the Zoom button located in the toolbar too.

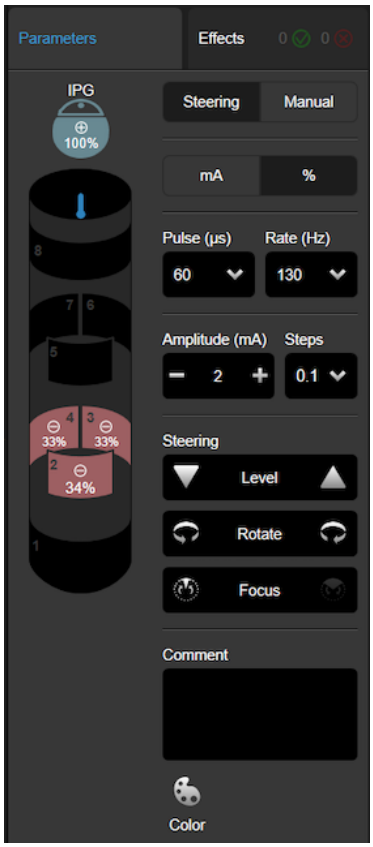
To perform the stimulation field simulation, the desired parameters for which the stimulation output was going to be simulated were set in the simulation toolbar (3). The criteria followed to set these parameters for each electrode of each patient was the following:

1. Select the most optimal stimulation contacts taking into account the electrode position with respect to the STN. The most suitable region to stimulate was the dorsal part of the STN.

2. Set the most appropriate electrical field stimulation amplitude (in mA) that encompassed the maximum of the desired target without stimulating the surrounding brain structures.

3. Evaluate for each case if bipolar stimulation was needed (i.e., using more than one stimulation contact).

4. Assess the need to steer the current (directionality of the stimulation field).



To select the stimulation contact/s, by clicking on the contacts of interest it was enough. By default, current is distributed equally among the entire ring. To steer current in the z axis, by clicking the arrows in the Level option inside the Steering section this was achieved. For current steering in the x and y axes, the Rotate and Focus options were used. By clicking the contacts in the second and third level of the electrode, these ones were selected or discarded, so current steering was also achieved.

The simulation of the stimulation output was displayed in the 3D reconstruction when current amplitude was set. This was done by selecting the desired value in the Amplitude (mA) option, and could be done manually or using the + and - buttons.

For all patients, pulse width and frequency rate values were the same, 60 s and 130 Hz, respectively. These values were set in the Pulse (s) and Rate (Hz) options.

***Figure 17**. Simulation toolbar display while stimulation parameters setting.*

An example of a stimulation field simulation after setting the most optimal parameters can be seen in figure 18, where first it is shown the electrode without electrical current, and then the 3D simulation of stimulation output.

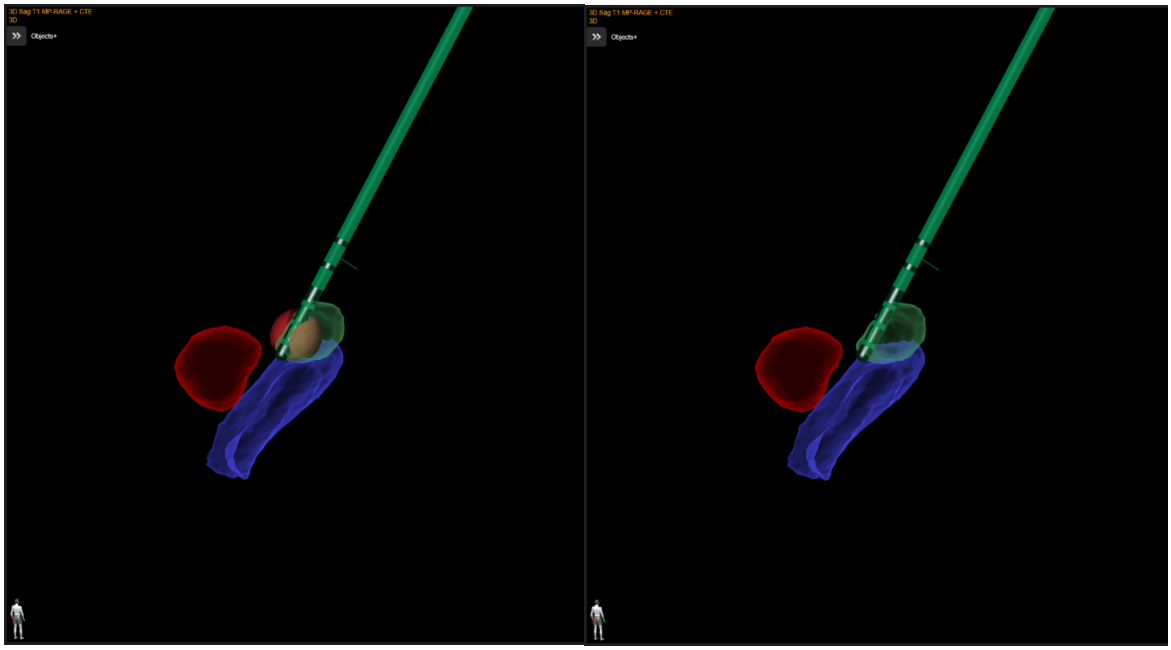


***Figure 18**. Right electrode display within the 3D brain structures (left); current steering simulation where the supraventral contact has been used (right).*

5.3 Software performance assessment (Data analysis)

The analysis performed to evaluate the utility of the software as a supporting tool in the stimulation parameters setting is detailed in this section. The main aim was to assess software's reliability by comparing the stimulation parameters selected based on the simulations, with the parameters selected by neurologists through the traditional trial and error method.

Moreover, since a large amount of data was collected from patients, a further analysis was performed for different factors from which interesting results could be extracted. The data analysis performed to obtain all the results for this study is described below.

Data loading

First of all, as both patient and software data were collected in an excel sheet, all data was loaded as different pandas dataframes (one for patient data and another one for software data) in a jupyter notebook. For the whole data analysis, the following open-source python libraries were needed:

- *pandas*
- *numpy*
- *matplotlib.pyplot*
- *statistics*
- *seaborn*
- *sklearn.metrics*

In addition, *collections* and *scipy.stats* modules where needed too.

General information statistics

From each dataframe, the desired columns for the analysis were selected and saved in different variables. General information statistics such as the percentage of men and women included in the study, their average age, the average of disease duration in years and the standard deviation of all

these values was extracted. Furthermore, the electrode contacts used for stimulation on each side of the brain for the first programming, the one-month follow up programming and the ones selected with the software were counted, as well as the number of cases for which current steering was applied.

Stimulation parameters comparison

Once the data above was extracted, a comparison between the lead contacts used in each programming, and between the contacts selected in the two programming sessions and the contacts selected with the software was performed. The same comparison was done for the electrical current amplitude, and for this stimulation parameter the variation between these values was computed too.

Side effects appearance

Another important factor to analyze was the appearance of side effects after each programming session. The number of patients who presented adverse effects in each session was counted. These effects that PD patients suffered as a consequence of DBS programming were classified and counted for each session, as well as the percentage that they represented for the study population. The variation of side effects between both programming sessions for each patient was assessed too, as well as the number of patients who improved, worsened or remained the same.

Relationship between side effects and electrode position

One of the factors that was considered most interesting to be analyzed was the possible relationship between the electrode position in patient's anatomy with respect to the STN and the appearance of adverse effects. This could be assessed thanks to the well-defined and clear software 3D simulation of electrodes inside brain structures. The different positions in which electrodes could remain were classified as follows:

- **Lateral**: If electrode was placed in the most lateral part of the STN.
- **Medial:** If electrode was placed outside STN towards the inner part of the brain.
- **Anterior:** If electrode was placed in the anterior part of the STN.
- **Posterior**: If electrode was placed in the posterior part of the STN.
- **Optimal:** If electrode was perfectly positioned.

The correlation between the different electrode positions for each side of the brain with the appearance of side effects in the first and the one-month follow up programming was computed and represented on a heat map. In addition, the total number of electrodes that remained in a certain position and caused side effects in any of the programming visits was counted and represented in a frequency table. With this table, it was also possible to assess the number of misplaced and well-placed electrodes that caused adverse effects.

Software vs. Clinical parameters comparison for successful results

Finally, an interesting result that could reflect in a good way the usefulness of the software as a supporting tool in DBS programming was the correspondence between the stimulation parameters set by neurologists for those patients who did not present side effects and the parameters selected using the software simulations. For this, the number of contact leads that matched with the contacts selected using the simulations was counted for each side of the brain and for each programming visit, and percentages were obtained too. To measure software reliability quantitatively, Cohen's kappa coefficient was computed to assess the degree of agreement between clinical outcome and parameters selection based on software simulations.

5.4 Results

The results obtained for each of the factors described in the previous section are shown below.

5.4.1 Software correspondence with clinical outcome

Current Steering

The percentage of cases in which current steering was applied for the 37 patients is shown in figure 19. This value is represented for the three different scenarios where this option could be used.

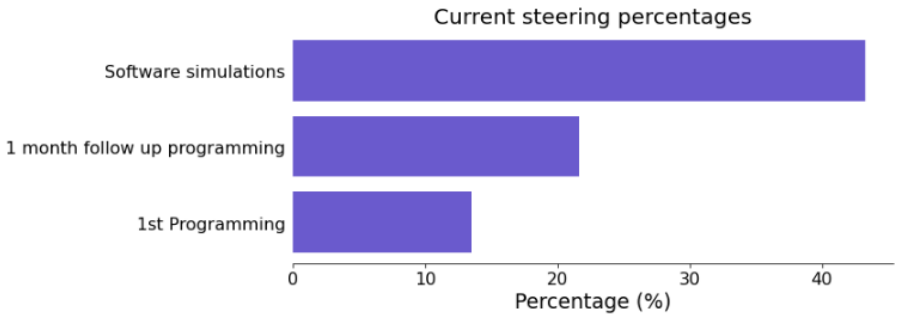


***Figure 19**. Electrical current steering percentages for the three different scenarios where this option could be applied (1st programming session, 1 month follow up programming and Software simulations).*

The percentage of patients in which current is steered increases less than a 10% between the first programming session (13.51%) and the one-month follow up one (21.62%). Nevertheless, the greatest increase in current directionality usage is when stimulation output simulations are performed, representing 43.24% of the total.

Stimulation contacts

The most important values to analyze in this project were the stimulation parameters selected during the different programming sessions and the ones selected based on the software simulations. In table 2, the stimulation contacts selected for each patient for each case are summarized. The variation of electrode contacts selection among the two programming sessions and with respect to the values obtained from the simulations is shown in figure 20.

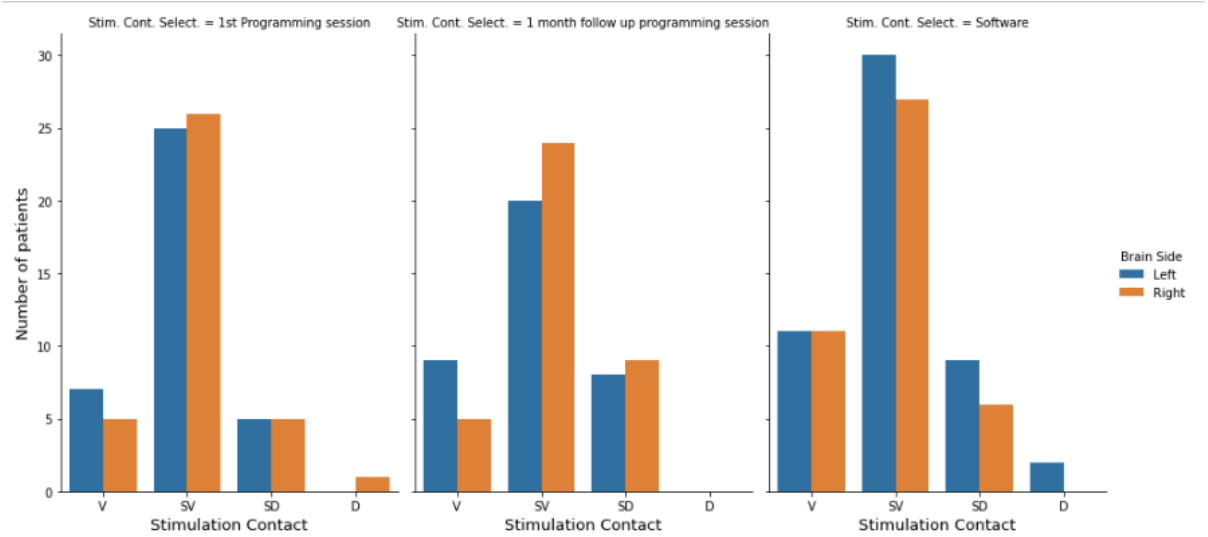


Figure 20. *Histogram showing the number of patients in which each stimulation contact was selected for DBS programming in the first programming session (left), the one-month follow up programming (middle) and using software simulations (right). Stim. Cont. Select.: Stimulation Contact Selection; V: Ventral; SV: Supraventral; SD: Subdorsal; D: Dorsal.*

The supraventral contact (SV) is the most used in the majority of patients, for both sides of the brain. It is important to highlight that for the case of contact selection based on software simulations, the number of patients for which each electrode was selected is bigger since bipolar stimulation was applied in more patients.

The percentage of left lead contacts that varied between first stimulation and stimulation after a month of the surgery was 27.03%, where the number of ventral and subdorsal contacts increased. The variation in the right lead contacts was 24.32%, increasing the number of subdorsal leads. Variation percentages when contacts were compared with the ones selected based on software simulations were higher.

For the left side, the percentage of patients in which stimulation contacts did not coincide with the ones selected using software simulations was 56.76%, and for the right side 62.16%. The variation among the programming session one month after surgery and the software simulations was 67.57% and 72.97% for the left and right side electrodes, respectively.

Stimulation amplitude

The average values of stimulation amplitude applied clinically for each side of the brain are detailed in table 3, as well as the corresponding standard deviation. Average stimulation amplitudes set based on software simulations are described in this table too.

Programming visit	**1st Programming**		**1 month follow up Programming**		**Software Simulations**	
Brain side	**Left**	**Right**	**Left**	**Right**	**Left**	**Right**
Mean (mA)	2.0	2.1	2.7	2.8	1.9	2.0
Standard Deviation	0.71	0.73	0.65	0.73	0.61	0.81

***Table 3**. Stimulation amplitude mean values and standard deviation applied for both hemispheres clinically and selected using Guide XT.*

The percentage of patients whose left-side-electrode stimulation amplitude was modified between the two programming sessions is 78.38% of the 37 included in the study, and for the right-side-electrode 86.49%. These percentages remained almost the same for the comparison between the stimulation amplitude set in the first programming session and the software simulations based ones, being 75.68% for the left side and 86.49% for the right side. The comparison between the one-month follow up programming session and the values obtained from the simulations resulted in that 86.49% of patients suffered a variation of stimulation amplitude for both hemispheres.

5.4.2 Side effects appearance

The adverse effects suffered by patients after both programming sessions can be divided into two groups:

- PD-associated side effects: It includes bradykinesia, tremor, hypophonia, rigidity, bloquing, imbalance and paresthesia. Patients who presented these PD characteristic adverse effects used to be due to a lack of stimulation.

- DBS-induced side effects: Dyskinesia, dysarthria (related with capsular effect, which is one of the worst DBS-associated side effects that doctors try to avoid the most), shuffling, dizziness and algia. These adverse effects can appear as a consequence of stimulation.

From one programming session to the other, 78.38% of patients suffered variations in their side effects. In the figures below it is detailed the percentage of patients that suffered each of the possible adverse effects.

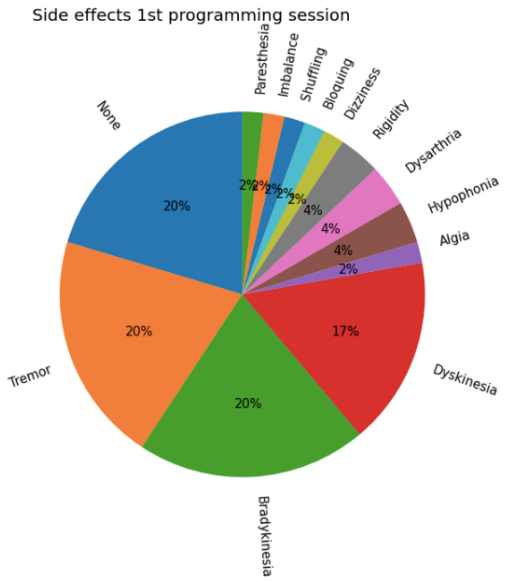


***Figure 21**. Pie chart for side effects after 1st programming session*

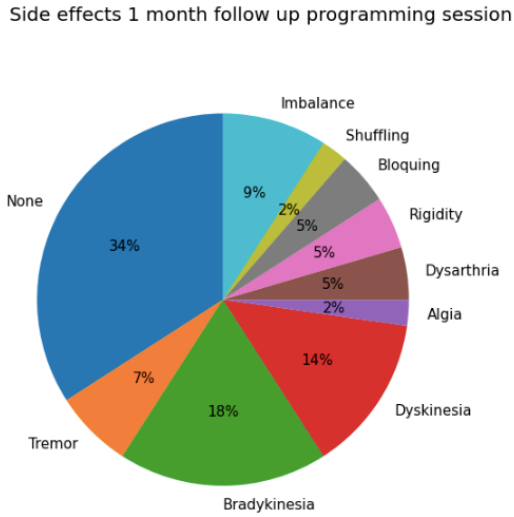


***Figure 22**. Pie chart for side effects after 1 month follow up programming session*

In the first programming session, from the 37 patients included in this study, only 11 did not present side effects after stimulation. For the 1 month follow up programming session this number increased to 15. From the 37 patients, 10 experienced an improvement in side effects (they went

from having any adverse effect to having none), 6 got worst (they went from having no side effects to having any) and 21 remained the same (16 presented side effects after both programming sessions and the other 5 did not have any adverse effect in any moment). In 3 of the 6 patients who got worse, stimulation contacts were changed from the first programming to the second one; and the same in 3 out of the 10 who improved.

Regarding the possible correlation between electrodes' position and the appearance of side effects, it was found that position of electrodes in the right hemisphere of the brain was slightly related with the appearance of side effects in the first programming session. This small correlation can be seen in the figure below.

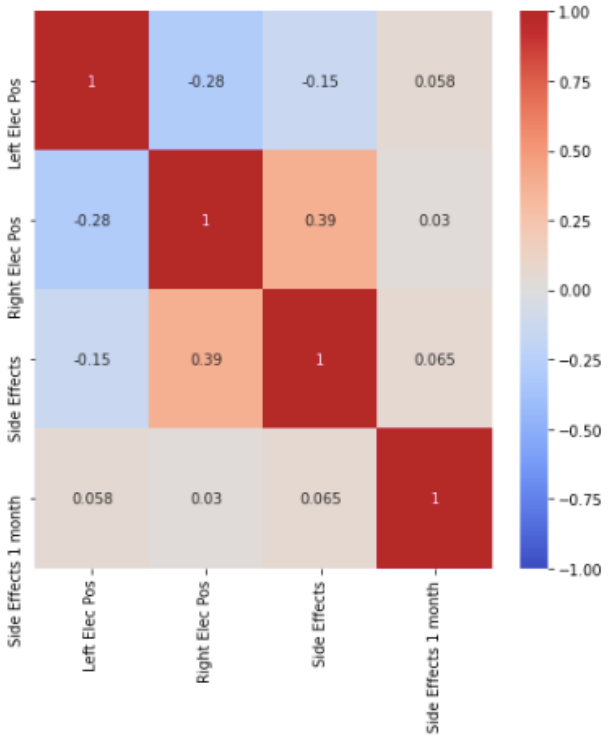


***Figure 23**. Heatmap representing the correlation between electrodes' position on each side of the brain and the presence of adverse effects.*

Evaluating the values obtained in figure 23, for electrodes in the left hemisphere there is almost no correlation with side effects in any of the programming sessions, and for the right hemisphere this small correlation decreases till 0 for the programming session 1 month after the surgery.

Table 4 shows the number of patients who presented side effects for each lead position.

Side Effects	No		Yes		Total
Side Effects 1 month	No	Yes	No	Yes	
Electrode Position					
Anterior	0	0	0	1	1
Lateral	1	0	0	0	1
Medial	3	5	6	8	22
Optimal	6	7	14	22	49
Posterior	0	0	0	1	1
Total	10	12	20	32	74

***Table 4**. Frequency table representing for each electrode position, the number of electrodes that were related with side effects or not (n=74). First row ('Side Effects') classifies patients according to whether they presented adverse effects in the first programming session or not. Second row ('Side Effects 1 month'), classifies patients who did not have adverse effects in the first programming session into the first two columns depending on if they presented side effects or not in the second programming visit. The ones who had adverse effects in the first programming session are classified into the third and fourth column.*

In this table it can be seen that from the 74 implanted electrodes, 49 remained in an optimal position after surgery, 22 remained medial with respect to the STN, and the other 3 remained anterior, lateral and posterior, respectively. Most of the optimal electrodes are related with side effects, as well as more than a half of the medial ones.

5.4.3 Software appraisal

To evaluate software reliability to select the optimal stimulation parameters, especially the contact leads which are the most important ones, the correspondence between the stimulation contacts selected for those patients who did not present side effects in both programming sessions with the contacts selected using software simulations was assessed. This correspondence is reflected in table 5.

	Correspondence Software vs. Clinical outcome			
	1st Programming session		1 month follow up programming session	
Electrode side	**Left**	**Right**	**Left**	**Right**
Coincidence percentage	72.73%	54.55%	66.67%	53.33%

***Table 5.** Percentage of correspondence between lead contacts selected clinically and lead contacts selected based on software simulations for those patients who did not present adverse effects in any of the programming sessions.*

For all cases, the percentage of correspondence is over 50%, meaning that selection of stimulation contacts based on software simulations could be helpful in most patients. For the left-side electrode contacts, correspondence turned out to be higher, especially for contacts selected in the first programming session.

The Cohen's kappa coefficient used to test inter-rater reliability resulted in a value of k= 0.26 for agreement between stimulation contacts in the left side of the brain selected in the first programming session and with the software. A value of k= -0.14 was obtained for the right side; and for the other programming session, values of k = 0.12 and k = 0.05 were obtained for stimulation contacts in the left and right side of the brain, respectively.

5.5 Discussion and clinical convenience

An analysis of the results obtained in this study has been performed in this section.

Regarding the application of current steering, results showed that using software simulations the number of patients on which directionality was decided to be more suitable was noticeably higher. This difference with respect to the two programming visits could be explained by the fact that when performing simulations, perfection in stimulation output is sought as it can be visualized at the moment. However, when clinicians perform monopolar stimulation through trial-and-error technique, most times with normal stimulation parameters side effects do not appear. Since the objective of DBS is to reduce PD symptoms without causing adverse effects to patients, if normal stimulation provides good results, there is no need to complicate stimulation output.

For the same reason, the percentage of patients in whom stimulation contacts did not match with the ones selected using software simulations was also high. In some cases, a different contact from the most optimal one can work properly if the other stimulation parameters are correctly adjusted. Performing image-based programming, bipolar stimulation could be more suitable for some patients, but it is not necessarily the only possible solution. The supraventral contacts were the ones most chosen by clinicians in all cases owing to the position in which electrodes usually remain with respect to the STN after the surgery.

The stimulation amplitude is a parameter that was interesting to analyze, but its relevance in stimulation outcome is not as important as that of stimulation contacts. Small variations in amplitude are not usually noticeable. This is the reason why among programming sessions and with software simulations, variations in stimulation amplitude for each electrode were so large. Relationship between stimulus amplitude and side effects appearance was not assessed for the same reason.

From the heatmap that correlates electrodes' position on each brain hemisphere with the presence of side effects, the only noticeable correlation was between electrodes placed in the right side of the brain and the side effects from the first programming session. However, this correlation was very small so a reliable conclusion cannot be obtained from this figure.

In table 4, the number of optimal electrodes that were related with side effects in both programming sessions resulted to be very large. This could be for different causes, but it is important to consider that for side effects assessment, it was not possible to differentiate between side effects caused by electrodes on each side of the brain separately since this information was not available in patients' clinical histories. Therefore, in many patients where one electrode was optimal and the other one was not, both electrodes were associated with the presence of side effects.

From table 5 it can be concluded that Guide XT can be a reliable tool to assist clinicians in DBS programming as results show that for most patients, the stimulation contacts selected with the software coincided with the ones selected clinically that did not cause side effects. In addition, Guide XT usage would have been very helpful to prevent 6 of the 11 patients who initially did not present side effects from appearing later. In 3 of the 6, the stimulation contact was changed in the second programming session, whereas the stimulation contacts from the other 5 (from the 11) were not changed and these patients remained without side effects afterwards.

With respect to Cohen's kappa coefficients, the values obtained were very low, a fact that was not expected since the correspondence percentages were higher. An explanation to these bad results in inter-rater agreement could be that the amount of data to be compared was short.

6. EXECUTION CHRONOGRAM

6.1 Project Structure

This project has been structured into 10 different sections.

First of all, an introduction describing the main objectives and the scope and limitations of the project was detailed. Then, a theoretical background was written to describe the environment in which the project was developed. This included PD (with the affected neurological pathway), DBS and the state of the art technologies developed to aid in DBS programming. A description of the currently available softwares that are used nowadays to support in DBS programming was performed in the Market analysis section. After this, in the Conception engineering section, the different solutions contemplated were described, followed by a complete description of the proposed solution in the Detail Engineering section. In the latter, the final results are shown and discussed. In the next section, Execution chronogram, the different tasks performed to develop this project are displayed in a GANTT diagram. Then, the technical and economical feasibility of the project are discussed, including a SWOT analysis, followed by the regulations and legal aspects section. Finally, the conclusions and future perspectives are exposed.

6.2 GANTT Diagram

The time curse followed to perform all the tasks needed to develop this project is detailed in figure 24.

The documentation part was highly important since a huge knowledge about PD and DBS was crucial to have a strong basis regarding the project environment. The writing part of the project document was performed during almost all the time course, except for a few weeks.

After project proposal and once the objectives were defined, literature review (documentation part) took a long time period since many information regarding PD and the DBS technique had to be clarified, as well as different aspects regarding software usage and environment. When enough information was collected, the theoretical background section was started to be written firstly.

Data collection and software simulations took almost 2 months owing to the time required to read all patients clinical histories and, especially, performing software simulations. This stage was very important since from this data the statistical analysis was going to be performed.

Finally, after the comparison between software simulations and the clinical outcome was realized, and after all the statistical data was obtained, the final step was to finish project writing by evaluating the clinical appraisal.

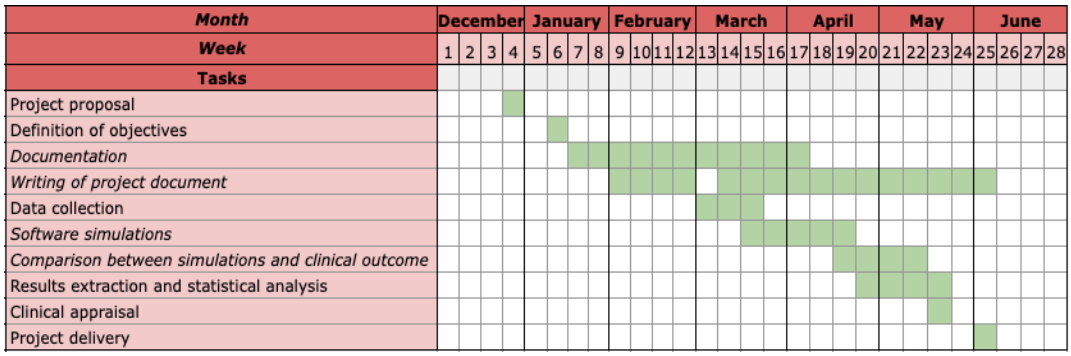


Figure 24. *GANTT diagram of the entire project*

7. TECHNICAL AND ECONOMICAL FEASIBILITY

7.1 Technical Feasibility

This project was carried out at Hospital Clinic of Barcelona working with the neurosurgery team. This service had the software installed on one of its department computers, so for this project, free access to the software was provided. In addition, the hospital counts with all the equipment necessary to obtain the MRI and CT images with which the software made the reconstructions. The only technical aspect to take into account is that as the intended environment in which the software should be used is a computer in a hospital (in a doctor's office and/or in an operating room environment), and that the computer used to support the software must accomplish the following specifications:

	Minimum
Processor	4 logical cores (e.g. Intel Core i5 with or comparable processor)
Memory	4 GB
Graphics Card	DirectX 10.1 compatible 512 MB graphics memory
Screen Resolution	1280 x 1024
Color Depth	24bit
Disk Space	20 GB

Table 6. *Hardware requirements specifications [59].*

7.1.1 SWOT Analysis

In the following table, an assessment of the Strengths, Weaknesses, Opportunities and Threats (SWOT) of this project has been done.

SWOT ANALYSIS

	Strengths	Weaknesses
Internal	• Opportunity to work with the software in the hospital • Availability of huge amounts of data from different patients • Professional team of neurosurgeons giving advice and support to the project • Strong theoretical background of project situation • Ability to easily adapt to changes and extract clear conclusions from results • Full understanding of project environment through visualization of the entire process (surgical procedure, DBS programming)	• Data collected from two years (could be more extensive) • Non-extended use of the software by the neurology team • Limited time for project development
	Opportunities	**Threats**
External	• Usage of the results obtained for a further analysis • Development of ideas for future software improvements • Automatic prediction of optimal stimulation parameters • Self-regulation of stimulation based on brain activity recordings	• Availability of other free online open-source softwares for the same purpose • Strong competitors working on similar softwares development • Fast technological advances which can lead to an early software obsolesce

Table 7. *SWOT analysis of the project.*

Strengths

The main strengths of the project have been highlighted, which are an intrinsic factor that contribute to its success. During project development, it was crucial to have the software Guide™ XT in the hospital in order to avoid unnecessary displacements. As a consequence, this gave rise to the opportunity of working with the neurosurgery team from Hospital Clínic, who helped during the process of performing the simulations by providing their professional advice. In addition, a thorough theoretical background was done owing to the importance of understanding the entire process to prove the relevance that the use of the software can have a positive outcome, as well as its clinical impact. As the main objective of this project was to validate the clinical use of this software by evaluating the reliability of its simulations to determine the stimulation parameters, evidence of its usefulness for this purpose has been provided.

Weaknesses

It is also important to mention the weaknesses this project presents, as they are internal aspects that could contribute for future improvements if taken into consideration. Firstly, data from more patients could have been collected to obtain more reliable results and perform a more extensive study. But the main weakness of this project was that objectives were not well-defined from the beginning, so there were different moments during project development in which tasks were not clear at all. This led to misunderstandings due to a bad communication in the first stages of the project that affected the entire process. Nevertheless, this (contratiempos) were solved and final results could be obtained.

Opportunities

During the study, a variety of future opportunities came up that could be considered to develop new projects. These opportunities come from ideas that emerged during project development or from findings in the literature, and are related with improvements that could be done to the software itself, or to future tools that could be developed for the same purpose. These possible improvements focus mainly on automatic prediction of stimulation parameters using artificial intelligence algorithms, based on MRI and CT images, or on performing an intuitive DBS programming in which the software were able to regulate parameters according to electrodes recordings.

Threats

An analysis of the possible threats must be done, but it is important to keep in mind that they are unavoidable because they are an external factor. The existence of other companies which have developed similar softwares for the same purpose can suppose a threat to the study because these softwares could have a better performance, but that is something out of the scope of this project. The usage that the hospital gives to the software is also important, because otherwise this study would be senseless. But the most important threat for this project are the technological advances. The high speed with which new technologies are emerging can entail an early software obsolescence

7.2 Economical Feasibility

Total economical costs of this project have been detailed in this section. For the analysis, a distinction between the material part (hardware, software and image acquisition) and the non-material part (human resources) has been done.

On the one hand, the average annual salary for a Trainee Software Tester in Spain is around 21.000€/year [75]; that is 10.94€/hour worked. As this bachelor's thesis has a duration of 300 hours (12 ECTS = 300 hours), the total amount of money destined to human resources for this project would be 300 hours x 10.94€/hour = 3.282 €. In addition to this cost, it must be taken into account the equipment needed to support the software, which has been described previously in the Technical feasibility section. The computer used in the Department of Neurosurgery of Hospital Clinic to work with the Guide XT is an HP which has a cost of 1934.79 €.

Regarding the Guide XT, since the software is integrated inside the Brainlab Elements, the cost of the latter is the one that must be counted, which has a cost in the market of 49.000 €/year. Nonetheless, as the software was provided by the hospital, its cost will not be taken into account. On the other hand, the Anaconda Navigator is an open source environment so it has no cost, and the Microsoft Excel has an annual license of 69€ [76]. However, as the license for this software was provided by the university, it did not imply any cost for the project.

Finally, another fundamental element for this study were the MRI and CT images used to perform the reconstructions, as well as the data from patients to do the analysis. As these images and information were provided by the hospital too, they had no cost.

The total costs of the entire project (without considering that the university provided the Microsoft Excel licence and supposing that hospital had to pay for the software and the computer) have been summarized in the following table.

		Product	Cost	Total
Material	Hardware	HP Computer	1934,79 €	1934,79 €
	Software	Brainlab Elements	49.000 €	49.034,50 €
		Anaconda Navigator	0 €	

		Microsoft Excel license	34,50€ (half year)	
	Image acquisition	MRI scans	0 €	0 €
		CT scans	0 €	
Non-material	Human resources	Trainee Software Tester	3.282€	3.282 €
Total cost of the project:				54.251,29 €

Table 8. *Total cost of the entire project.*

8. REGULATIONS AND LEGAL ASPECTS

As the validation of this software has been made for the Hospital Clinic of Barcelona (Spain), the legal aspects of this project must follow the spanish regulations.

First of all, the data acquired for this study was from real patients from the Hospital Clinic of Barcelona, thus it was essential to keep the information anonymous, according to the Ley Orgánica 3/2018, de 5 de diciembre, de Protección de Datos Personales y garantía de los derechos digitales [77], which was published in the BOE nº. 294, 06/12/2018. Specifications about how to treat health data are indicated in the Disposición adicional decimoséptima. Tratamientos de datos de salud section, which includes some points from the Reglamento (UE) 2016/679 [78]. In this section it is stated that data can be used if it is for a biomedical research purpose, fulfilling the condition that it must be previously anonymized and without the possibility of obtaining real personal data from patients.

Taking into account that the intended purpose of the Guide™ XT software defined by the manufacturer is to be used as a planning tool for the programming of DBS, then according to the European Commission it is considered as a medical device software (MDSW). In the Guidance on Qualification and Classification of Software in Regulation (EU) 2017/745 – MDR and Regulation (EU) 2017/746 – IVDR [79], it is defined that a requisite for a software to be classified as a MDSW is that it must have a medical purpose on its own. So as a MDSW, the Guide™ XT must fulfill the same legislation as any other medical device, which is defined in the Regulation (EU) 2017/745, that aims to ensure the smooth functioning of the internal market as regards medical devices [80]. In addition, there is the IEC 62304, a standard which specifies the requirements that must be fulfilled to develop a MDSW [81].

On the other hand, in 2012, Boston Scientific Corporation received the CE Mark for the Vercise DBS device system; and regarding the software-specific legal aspects, the legal manufacturer of Guide™ XT software is Boston Scientific Neuromodulation Corporation [59].

9. CONCLUSIONS AND FUTURE PERSPECTIVES

From this study it can be concluded that the Guide XT software is a reliable tool that could be used in hospitals to aid in DBS programming when selecting the stimulation parameters. Using the software, the programming sessions would be more effective, and neurologists would save time since they would not need to stimulate contact by contact trying to see which has a better performance. Thus, DBS programming softwares show a promising capability to predict the best level and directional contact/s as well as stimulation settings, and could be used to optimize programming with segmented lead technology.

As a future direction, it would be interesting to use recording electrodes to read the electrical activity from the STN and the surrounding structures and that the software were able to regulate the stimulus through an adaptative stimulation. Latent features derived from different signal sources could be used to establish a feedback driven stimulation algorithm based on the analysis of behavioral and physiological data and a suitable control mechanism. If these parameters that come from different sources (such as kinematic and electrophysiological measurements and other sensor like electromyography) were integrated, patient state, adverse effects appearance and underlying neural activity could be learned and classified through the implementation of machine learning algorithms.

On the other hand, it would be interesting to implement a function where the software, based on artificial intelligence algorithms, were able to predict which are the most optimal stimulation parameters that should be applied to each patient. This could be done based on electrode's position with respect to the STN.

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11. ANNEX

Patient data

	Patient	Gender	Age	Disease Duration (yr)	L.S.C. (L)	L.S.C. (R)	Direc. (1st programm)	L.S.A. (1st Progam)	R.S.A. (1st Progam)	Side Effects (1st programm)	L.S.C. (L) - 1 month	L.S.C. (R) - 1 month	Direc. (1 month)	L.S.A. (1 month)	R.S.A. (1 month)	Side Effects (1 month)
0	1	M	43	12	SV	V	No	2.5	2.5	Bradykinesia and Paresthesia	SD	SV	No	3.0	3.0	Soft Dysarthria and Bradykinesia
1	2	M	66	23	SV	SV	No	3.0	3.0	Dyskinesia, Imabalance and Hypophonia	SV	SV	No	2.5	2.5	Soft Dyskinesia
2	3	M	71	8	V	V	No	1.5	2.0	Soft Dyskinesia	V	V	No	1.5	1.5	None
3	4	M	70	16	V	D	No	3.0	3.0	None	V	SD	No	3.0	3.0	Freezing
4	5	M	53	7	SV	SV	No	1.5	1.5	Bradykinesia and Tremor	SV	SV	No	2.2	2.2	Bradykinesia and Tremor
5	6	M	59	12	SV	SV	Yes	2.5	2.0	Bradykinesia and Tremor	SV	SV	Yes	2.7	2.2	None
6	7	M	59	5	SV	SV	No	2.0	2.0	None	SV	SV	No	2.2	2.2	None
7	8	F	36	24	V	SV	No	1.5	2.0	Bradykinesia	SV	SV	No	3.0	3.0	Rigidity and Freezing
8	9	M	54	15	V	V	No	2.5	2.0	Tremor and Shuffling	V	SV	No	4.2	2.0	None
9	10	M	64	16	SV	SD	No	2.0	2.5	Bloquing, Bradykinesia and Soft Dysarthria	SD	SD	Yes	3.5	3.5	None
10	11	M	61	10	SV	SV	No	2.0	2.0	Bradykinesia	SV	SV	No	3.0	2.8	None
11	12	M	50	8	SD	SV	No	3.0	2.0	Bradykinesia, Tremor and Rigidity	V	SV	No	1.8	2.0	Dyskinesia
12	13	F	68	14	V	V	No	1.0	3.0	Dyskinesia	V	SD	No	1.5	3.5	Soft Dyskinesia
13	14	F	58	12	V	SV	No	2.5	3.0	None	V	SV - V	No	2.8	3.8	Shuffling and Pain
14	15	M	43	10	SD	SD	Yes	2.0	3.0	Tremor	SD	SD	Yes	2.0	3.3	Rigidity and Tremor
15	16	M	67	9	SV	SV	No	2.0	2.0	None	SV	SV	No	2.0	2.0	Dyskinesia

16	17	F	58	14	SV	SV	No	2.0	2.0	Dyskinesia	SV	SV	Yes	2.6	1.9	None
17	18	M	56	8	V	SD	No	1.5	1.5	Dyskinesia	V	SD	No	3.4	3.7	None
18	19	F	68	11	SV	SV	No	2.0	2.5	Bradykinesia and Tremor	SV	SV	No	2.5	3.0	Imbalance
19	20	M	70	17	SV	SV	Yes	1.0	2.5	Algia (pain)	SD	SV	Yes	2.6	3.2	Imbalance
20	21	M	65	9	SV	SV	No	2.5	2.0	None	SV	SV	Yes	3.0	2.5	Bradykinesia
21	22	M	59	7	SV	SV	No	2.3	2.0	Bradykinesia and Dyskinesia	SD	SD	No	3.4	2.3	Bradykinesia
22	21	F	64	8	SV	SV	No	3.5	2.0	Tremor	SV	SV	No	3.5	2.0	None
23	22	M	54	12	SV	SV	No	2.0	2.2	None	SV	SV	No	2.0	3.0	Bradykinesia, Imbalance, Dysarthria and Dysphagia
24	25	F	51	10	SD	SV	No	2.0	2.0	None	SD	SV	No	2.5	2.5	None
25	26	M	56	10	SV	SV	No	2.0	2.0	None	V	V	No	3.4	3.7	Bradykinesia
26	27	F	45	11	SV	SV	No	2.0	2.0	None	SV	SV	No	2.4	2.6	None
27	28	F	58	10	SV	SV	No	0.5	0.5	Bradykinesia and Tremor	SV	SV	No	2.5	3.0	Soft Bradykinesia and Dyskinesia
28	29	M	43	12	SV	SV	No	3.0	4.5	Dizziness and Rigidity	SV	SV	No	3.0	4.6	Dystonia
29	30	M	64	19	SV	SV	Yes	3.5	3.2	Hypophonia, Dysarthria, Bradykinesia and Dyski...	SV	V	Yes	3.5	4.0	Bradykinesia
30	31	M	49	9	SV	SV	No	2.0	1.5	Tremor	V	SV	No	3.3	2.0	Imbalance
31	32	F	58	10	SV	SD	No	1.5	2.5	None	SV	SD	No	2.4	4.0	None
32	33	M	50	15	SD	SD	No	1.5	1.5	Tremor	SD	SD	No	3.0	2.8	None
33	34	M	44	10	SV	SV	No	0.9	0.5	Tremor	SD	SD	No	1.7	1.7	Tremor
34	35	F	46	12	SV	SV	No	1.9	1.3	Dyskinesia	SV	SV	No	2.5	2.2	Dyskinesia
35	36	M	55	8	SD	V	Yes	2.0	1.3	Dyskinesia	SV	V	Yes	2.8	2.5	None
36	37	M	54	6	SV	SV	No	0.7	2.3	None	SV	SV	No	1.2	3.5	None

Software data

	Patient	Left Elec Pos	Right Elec Pos	L.S.C. (L)	L.S.C. (R)	Direc.	Amp (L)	Amp (R)
0	1	Medial	Optimal	V	V	No	2.0	2.5
1	2	Optimal	Medial	SV	V	No	1.6	1.3
2	3	Optimal	Medial	V	V	No	1.5	2.5
3	4	Optimal	Medial	V	SV	No	2.0	2.5
4	5	Optimal	Optimal	V/SV	V/SV	No	1.6	1.2
5	6	Medial	Optimal	SV	SV	No	1.5	1.5
6	7	Medial	Optimal	SV	V	Yes	2.0	1.5
7	8	Anterior	Posterior	V/SV	SV	Yes	1.5	1.3
8	9	Optimal	Optimal	SV/SD	SV	No	1.3	2.0
9	10	Medial	Optimal	SV	SV	Yes	3.0	2.7
10	11	Optimal	Optimal	SV	SV	No	3.0	2.5
11	12	Medial	Medial	SD/D	SV/SD	Yes	3.0	3.0
12	13	Optimal	Medial	V/SV	V	Yes	1.3	1.5
13	14	Optimal	Medial	SV/SD	SV/SD	Yes	2.6	3.7
14	15	Optimal	Optimal	SV	SV	No	2.5	1.5
15	16	Optimal	Medial	SV	SD	Yes	2.0	2.0
16	17	Optimal	Optimal	V/SV	SV	No	1.2	1.0
17	18	Optimal	Medial	SV	SV	Yes	1.5	1.2
18	19	Optimal	Medial	SD/D	SV	Yes	1.0	1.5
19	20	Medial	Medial	SV	SV	No	2.0	1.9
20	21	Medial	Medial	SV	V	No	1.5	2.0
21	22	Optimal	Optimal	SV	SV	No	1.5	1.5
22	23	Optimal	Optimal	SV	V	No	1.5	1.0
23	24	Optimal	Optimal	SV	SV	No	2.0	3.0
24	25	Optimal	Optimal	SV	SV	Yes	3.0	3.2
25	26	Optimal	Optimal	SV	SV	No	1.5	1.5
26	27	Optimal	Medial	V/SV	V/SV	Yes	1.1	1.3
27	28	Optimal	Optimal	V/SV	V/SV	No	2.0	1.5

28	29	Optimal	Optimal	V/SV	V	No	3.0	4.0
29	30	Optimal	Optimal	SV	SV	No	1.3	1.4
30	31	Optimal	Optimal	SV/SD	SV/SD	Yes	2.0	1.8
31	32	Optimal	Lateral	SV	SV	Yes	2.5	4.0
32	33	Medial	Optimal	SV/SD	SV	No	2.0	1.5
33	34	Optimal	Optimal	SV/SD	SV/SD	Yes	1.2	1.5
34	35	Optimal	Optimal	SD	SD	No	1.2	2.0
35	36	Medial	Optimal	SV/SD	SV	Yes	2.5	2.5
36	37	Optimal	Medial	V	SV	Yes	1.0	1.1