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XXXI CICLO DEL DOTTORATO DI RICERCA IN

NEUROSCIENZE E SCIENZE COGNITIVE

EFFECTIVE TELEMONITORING FOR THE OPTIMIZATION OF NEW DEEP BRAIN STIMULATION THERAPIES FOR PARKINSON'S DISEASE PATIENTS

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DOTTORANDO
MARCO PRENASSI

COORDINATORE
PROF. TIZIANO AGOSTINI

SUPERVISORE DI TESI
PROF. SARA MARCEGLIA

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Abstract

Introduction: Deep brain stimulation (DBS) outcomes could benefit from monitoring the fluctuation of Parkinson's disease symptoms in order to set the best stimulation parameters. A correct and constant monitoring of this time-frame is essential to regulate their therapies. The scope of this work is to develop and validate a system architecture to continuously monitor the patient through personally collected data. The implementation of this framework could also be used in a broader research perspective in which personally collected data and constant telemonitoring in ecological environment are needed. In addition, it could support the development and implementation of new DBS approaches aimed to real-time adapt DBS parameters according to the evaluation of the patient's clinical state (i.e., adaptive DBS, aDBS).

Methods: The implementation followed a three-step bottom-up approach. The first phase is fully patient centered: an Android App was developed paired to a smartwatch sensor to provide a clinical e-diary to be filled in by the patients at predefined times. The rationale was to gather data to verify whether this combination of two simple technologies was enough to collect information relevant for tracking patient's activity and symptoms in a stand-alone system strictly within a point-of-care perspective. A consumer-grade and a research-grade smartwatch were used to conduct the validation and two budget-grade mobile phones were used to test this initial setup. Two algorithms, the Bradykinesia Accelerometric Score (BAS) and Bradykinesia Index (BradIndex) were developed using the data collected through the smartwatches to estimate bradykinesia and then compared to Unified Parkinson's Disease Rating Scale part III (UPDRSIII), reported by neurologists. The second step involved the clinicians and the researchers: accelerometric data and diary data were integrated to neurophysiological data, in order to obtain a comprehensive view on the patient's state. Subthalamic nucleus local field potentials (STN LFPs) were recorded from the implanted DBS electrodes and integrated with the self-collected data. The LFPs, e-diary and accelerometric data integration were evaluated with a clinical index (UPDRSIII). The third step further expanded the system in a multi-centered study perspective: a web-based platform was developed to support data collection and analysis. The platform expanded the architecture of an already established technology in order to introduce a standards-based architecture aimed to implement a bidirectional exchange between patient-generated data and the clinical data repository. Use-case test were performed to assess the system. The validation study enrolled 13 Parkinson's disease patients undergoing DBS electrode implant surgery. During an 8 hours session, the patients were asked to fill in the e-diary and to wear the smartwatch. A clinician assessed their condition compiling a Unified Parkinson's Disease Rating Scale part III (UPDRSIII). After the 8 hour trial, a clinician asked the patients if the smartwatch was uncomfortable during the day.

Results: In total, of the 13 patients, 2 were dropped due to technical issues. The two algorithms provided significative inverse correlation with UPDRSIII evaluation (BAS: Pearson's correlation coefficient, 0.541, $p<0.004$; BradIndex: Pearson's correlation coefficient -0.500, $p < 0.0005$). The patient reported e-diary status provided significative correlation with the UPDRSIII assessment (Pearson's correlation coefficient -0. 7416, $p < 0.0005$) and also with the BradIndex accelerometric index (Pearson's correlation coefficient 0.6042, $p < 0.05$). LFP recordings were modulated during walking, with respect to talking and relaxing (beta power change from baseline during walking: -14%±4.212, talking:-11.2 %±2.724, and relaxing: -8.811%±2.418, one-way ANOVA $p<0.0001$). USE-CASE tests were performed to validate the overall architecture, denoting a good patient e-diary compliance (Of 140 diaries, 123 were compiled without null values) but a considerable accelerometer data loss caused by the consumer-grade smartwatch was observed.

Conclusions: This work provided good results supporting the use of consumer-grade devices (smartwatches and smarthphones) to allow DBS patient's telemonitoring. Personally-recorded data were successfully integrated with neurophysiological data, providing essential insights for the implementation of new aDBS therapy. The platform was able to support the study with meaningful results, the smartwatches were well tolerated, and the mobile app was used by the majority of patients to fill in the diary. The system could be therefore used in the future in the home environment to monitor PD patients with DBS implant, and to collect additional data for building up an holistic view on the patient's state.

Sommario

1 Introduction

The increasing number of patients, the high costs of management, and the slow and chronic progress of the disease that prevents patients to perform even simple daily activities, make Parkinson's Disease a complex pathology with high impact on society. In particular, patients implanted with Deep Brain Stimulation (DBS) electrodes face a highly fragile stabilization period, requiring specific support at home. Even though DBS improves PD symptoms, patients still experience clinical fluctuations that prevent them from performing the simplest daily activities. Moreover, the long-term DBS outcomes DBS depend on the development of unresponsive PD disturbances, related to disease progression that should be properly monitored to allow early recognition and treatment.

At home, patients require the full support of a family caregiver, who is not usually specifically trained to deal with PD progression and DBS, and relies mainly on personal experience. Moreover, whereas follow up visits for DBS patients are scheduled once or twice a year (and the reference center is often far from patient's house) the pathology is characterized by fluctuating conditions on daily time windows.

In addition, new DBS technologies, based on a closed-loop strategy that automatically changes DBS parameters according to the patient's clinical state assessed through the recording and analysis of local bioelectrical activity, are currently under development. Considering the expected beneficial impact on PD management of these new technologies, their validation in ecological conditions is crucial to close the gap between research prototypes and clinical practice.

Grounding on this rationale, the development and validation of a system architecture to continuously monitor the patient through personally collected data is the main focus of this thesis. The implementation of such framework is designed not only to serve the initial study, but also to be used in a broader research perspective where personally collected data and constant telemonitoring in ecological environment is needed.

In this first chapter a bird-eye view is presented of the Parkinson's Disease, showing the various symptoms and signs that could be tracked, and the various therapies that contribute to the disease fluctuations. At the end of the chapter is presented the closed-loop paradigm, in which a direct feedback to the therapy is applied monitoring a patient status control variable, and the various methodologies to assess this variable on Parkinson's disease patients.
In chapter 2 the specific objectives of this work are presented, the implementation steps to achieve a continuous, multi-source telemonitoring systems, and the main experimental protocol used to validate such system.
In chapter 3, 4, and 5 the implementations of these steps are presented, starting with the patient. A custom made mHealth app connecting to a wearable to assess accelerometric wrist data and to

administer self-reported questionnaire through the mobile device to actively monitor the hospitalized patients is shown.

In chapter 4 it is shown the integration of these self-collected data to the local field recordings, connecting our monitoring system to support the new adaptive deep brain stimulation device study.

In chapter 5 the expanded interconnected framework system is presented in a multi-centered study perspective, showing the components needed to manage workflow and clinical data in an anonymized standard based and modular architecture.

1.1 Parkinson's disease

Parkinson's disease (PD) is characterized by a neurodegeneration of dopaminergic neurons in substantia nigra pars compacta (SNc), a reduced striatal dopamine and intracytoplasmic proteinaceous inclusions known as Lewy bodies (Brust, 2006). While affecting primarily the dopamine system this degeneration alters also the cholinergic neurons of the nucleus basalis of Meynert (NBM), the norepinephrine neurons of the locus coeruleus (LC), the serotonin neurons in the raphe nuclei of the brainstem, and the neurons of the olfactory system, cerebral hemispheres, spinal cord and peripheral autonomic nervous system (Brust, 2006).

There are some genetic risk factors that have emerged in studies over the last decade: first degree family members of affected patient have a 2 to 3 fold increased risk to develop PD compared to general population or control (Lesage et al., 2005). Monogenetic causes of PD have been identified, primarily the leucine-rich repeat kinase (LRRK2) mutations (Lesage et al., 2005), but is generally considered that monogenetic causes may be involved less than 10% of the PD population but the cause of PD is unknown for most identified cases (Lill, 2016).

PD is the second commonest neurodegenerative disease, exceeded only by Alzheimer's disease, it is estimated that PD affects 1-2 per 1000 of the population at any time (Lill, 2016). PD prevalence is increasing with age and PD affects 1% of the population above 60 (Lill, 2016). PD affects men and women of all races, all occupations, and all countries. The mean age of onset is about 60 years, but cases can be seen in patients in their 20s, and even younger (Brust, 2006).

1.1.1 Symptoms and signs

The main symptoms of PD are rigidity, rest tremor, bradykinesia and gait impairment, known as the cardinal features (Brust, 2006). Additional motor features includes freezing of gait, postural instability, speech difficulty and also non-motor feature as mood disorders, sensory alterations, sleep dysfunction, dementia and cognitive impairment (Table 1).

Even if proper PD is the most common form (approximately 75% of cases), there are many pathologies with similar symptoms and the differential diagnosis of the symptom complex known as "Parkinsonism"

is wide and reflect the damage to different components of the basal ganglia (Brust, 2006). The basal ganglia circuit will be further described in the next paragraph.

Historically the diagnosis were based on the presence of three cardinal feature (tremor, rigidity and bradykinesia) but postmortem studies found that a 24% error rate with only these criteria (Hughes, Daniel, Kilford, & Lees, 1992). PD was subsequently associated more correctly with rest tremor, asymmetry and a good response to levodopa (U.K. brain bank criteria (Hughes et al., 1992)). The clinical diagnosis with these revised criteria is confirmed pathologically in 99% of cases. In difficult cases can be used also positron emission tomography (PET) and single-photon computed tomography (SPECT) to trace the uptake of striatal dopaminergic markers, but in routine clinical practice are rare occurrence (Brust, 2006).

Other forms of Parkinsonism often involves SNc and striatum and/or pallidum and as a group, they present symptoms of rigidity and bradykinesia, but they typically have a different clinical picture, reflecting the different pathologies. In the early stages these form of Parkinsonism may be characterized by early gait and speech impairment, absence of rest tremor, no asymmetry but they may show some modest benefit from levodopa making them hard to distinguish from PD.

Cardinal Features	Other Motor symptoms	Non-motor symptoms
Bradykinesia Rest tremor Rigidity Gait disturbance/postural instability	Micrographia Masked facies (hypomimia) equalize Reduced eye blink Soft voice (hypophonia) Dysphagia Freezing	Anosmia Sensory disturbances (e.g., pain) Mood disorders (e.g., depression) Sleep disturbances Autonomic disturbances: Orthostatic hypotension Gastrointestinal disturbances Genitourinal disturbances Sexual dysfunction Cognitive impairment/dementia

Table 1: Parkinson's Disease main features

In these cases, imaging is not usually helpful, as severe atypical forms may present a degeneration of dopamine neurons. A more useful approach is to detect the decreased activity in the GPi with an increased activity in the thalamus, shown through metabolic imaging (Brust, 2006)

In Table 2 the other forms of Parkinsonism are shown related to the symptoms, to give a brief overview of the other forms of Parkinsonism, all with overlapping symptoms.Atypical or secondary parkinsonism	Early speech and gait impairment (Atypical), poor or no response to an adequate trial of levodopa
Drug-induced parkinsonism	Exposure to neuroleptics
Wilson's disease, non-Wilsonian hepatolenticular degeneration	Liver disease
Dementia with Lewy bodies	Early hallucinations
Progressive supranuclear palsy (PSP)	Diplopia, impairment of down gaze
Dementia with Lewy bodies	Dementia as first symptom
Multi system atrophy – Parkinson type (MSA-p)	Prominent orthostatic hypotension
Multi system atrophy – Cerebellar type (MSA-c)	Prominent cerebellar signs
Essential tremor	High frequency (8-10 Hz) symmetric postural tremor with a prominent kinetic component

Table 2: Other forms of parkinsonism.

Leaving the brain cortex and taking a deep dive inside the brain there is an area known as Basal Ganglia, here there are several nuclei that act as key regulators of motor and non-motor functions. The Basal ganglia is composed by the striatum, the globus pallidus internus (GPi) and externus (GPe), the substantia nigra pars compacta (SNc) and pars reticulate (SNr) and the subthalamic nucleus (STN) Figure 1.

The detailed functionality of basal ganglia is not completely understood and their functional significance is largely a matter of speculation. As shown in figure Figure 1, these structures forms a circuit that starts with the input from the associational cortex and goes to the putamen and caudate nucleus, to continue into the internal and external layers of the globus pallidus (GPi and GPe) and SNpr; both these structures project to the ventroanterior and ventrolateral (VA and VL) areas of the thalamus and at the end back to the motor cortex. There is also a second route from SNpr to the superior colliculus, mostly for head and eye movements (Carpenter & Reddi, 2012).

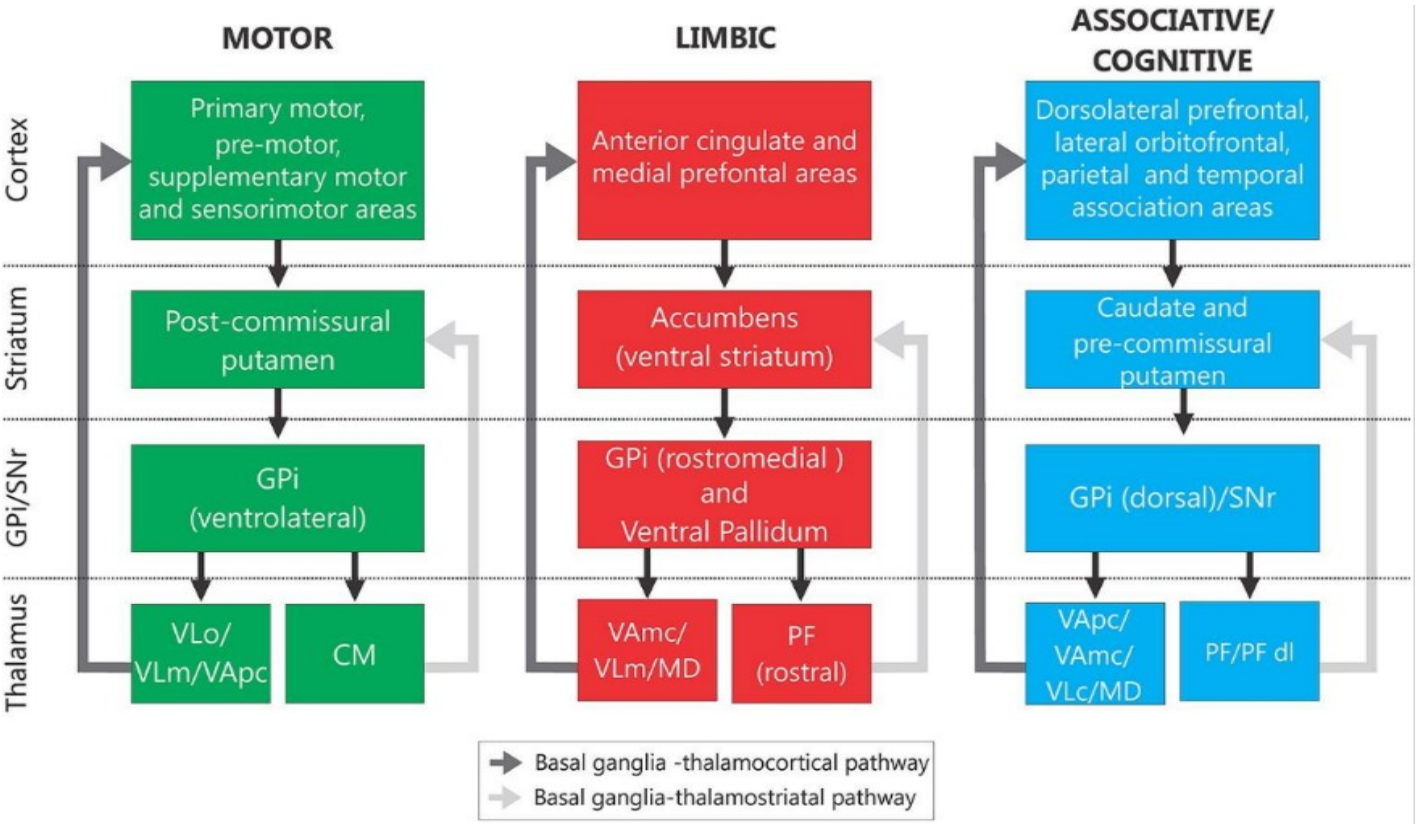


Figure 1 : Basal Ganglia motor circuit (modified from Galvan, Devergnas, & Wichmann, 2015).

The logical organization of these structures is shown in figure Figure 2.A. The inhibitory connections are shown with blue arrows, the excitatory in red arrows. It is shown that the striatum it is the major receiving hub and the GPi with the SNr are the major output regions that project to the thalamocortical and brainstem motor region. The connections between GPi and SNr are direct and indirect pathways.
The dopaminergic projections from SNc neurons serve to modulate neuronal firing and to stabilize the basal ganglia network.
When a patient suffers from PD, he is subject to a dopamine denervation in SN. In figure 2B what happen with a SNc in suboptimal conditions is shown, without the regulatory feedback functionality of SNc the inhibitory effect on GPe increases the excitatory output on STN that sends an inhibitory output from GPi and SNr. This results in an excessive inhibition of the thalamus, a reduced activation of the cortical motor system and thus the development of parkinsonian features. On the other hand, we can partially predict the dyskinesia resulting from a excessive activation of the thalamus by an insufficient firing from the GPi and SNr regions Figure 2.C (Brust, 2006), but experimental studies demonstrated that lesions in these structures could improve parkinsonism and dyskinesia. This discrepancy between the theoretical model and the practical outcomes is probably due not of the simple firing rate but instead of a more complex interference with abnormal firing pattern in circuit neurons (Munhoz, Cerasa, & Okun, 2014).

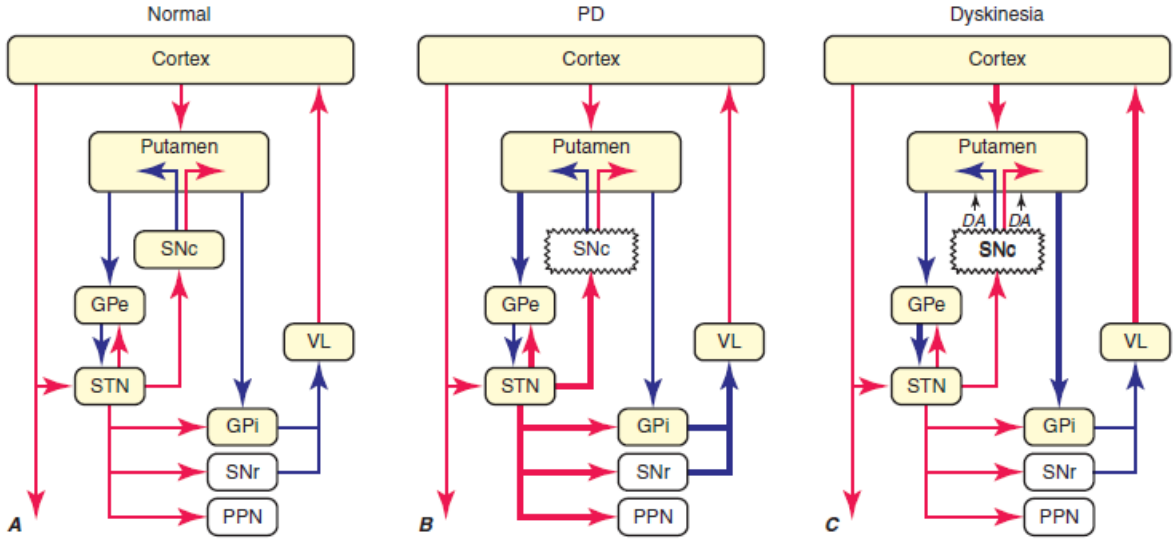


Figure 2: different basal ganglia motor circuit in a A, normal; B, bradykinetic and C, dyskinetic patient (modified from Obeso et al., 2008)

1.1.1.1 Cardinal Motor Symptoms

Bradykinesia:

The first use of the term "bradykinesia" was used by James Parkinson to describe one of the cardinal features of PD. Bradykinesia is now recognized as a motor dysfunction not only exclusive of PD disease but found in many movement disorders (Brust, 2006).

Akinesia and hypokinesia are often used as synonyms of bradykinesia but in reality they are different dysfunction and may not always be well correlated with each other.

Formally, akinesia refers to a poverty of spontaneous movement or associated movement; akinesia is related also to freezing and the prolonged time to initiate movement.

Hypokinesia refers to the length of the movements, smaller than desired.

Bradykinesia describes the slowness of a performed movement (Berardelli, Rothwell, Thompson, & Hallett, 2001).

True bradykinesia is different from simple slowness caused by decreased muscle power, spasticity or reduced motivation. Clinically, bradykinesia is assessed with repetitive movements, quick and wide as possible, these standardized movement, such as tapping thumb and index fingers, will be described in 1.1.2. The emergence of progressive slowness and hypokinesia might ultimately bring the movement to full arrest (freezing).

Clinical displays of bradykinesia can be hypomimia (termed the "poker face" in the milder stages, it is a decreased facial expression and eye blinking), softer voice (hypophonia) and micrographia (typical hypokinetic sign) and difficulty in swallowing.

Rigidity:

This term refers to an increased muscle tone during passive movement of limbs or neck. It involves the flexor and the extensor muscle group. This resistance does not increase with higher mobilization speed like spasticity caused by upper motor neuron lesions.

The classical "cog-wheel rigidity" can be felt when resting tremor coexist during passive limb mobilization, especially in the wrist. This rigidity can be increased by voluntary movement of other body parts (Froment's maneuver), that is useful to detect mild rigidity (Massano & Bhatia, 2012).

Rest tremor:

The tremor at rest is more specific to Parkinson's, even if the patient can show tremor with movement and also there are two other postural tremors for PD patients: one is the tremor at rest that persists with maintained posture (e.g. stretching out of the arms) and the other is clinically identical to essential tremor. Separation of these tremors is often difficult.

This tremor one or more parts of the body and can be markedly asymmetrical. It is most typical with a flexion-extension of the elbow, the forearm pronation and supination, and the so-called "pin rolling", a movement of the thumb across the fingers. The frequency of rest tremor is 3 Hz to 7 Hz, but usually is between 4-5 Hz. The amplitude is quite variable, ranging from 1 to 10 cm or more wide. Tremor can also be present in the lower limbs, tongue and jaw, but full head tremor is unusual for PD patients. The tremor disappears with movement, but it may return with maintained posture. Usually it improves with the dopaminergic therapies (and others surgical means discussed later). In clinical practice, the best way to observe tremor is when the patient is occupied by a particular mental task, as counting down from 100 with eyes closed, this facilitates the limb muscle relaxation("Classification and Treatment of Tremor | JAMA | JAMA Network," n.d.).

Postural impairment:

Parkinsonian patients tend to stand stooped due to the loss of postural reflexes, with flexion of the hips and knees, and rounding of the shoulders.

A retrospective observational study showed that a third of patients with PD had a deformity of their limbs, neck, or trunk (Ashour & Jankovic, 2006). More severe abnormalities can occur in a subset of patients; these postural deformities include camptocormia, antecollis, Pisa syndrome and scoliosis

(Figure 3). The pathophysiology under these deformities is largely unknown and their management remains difficult.

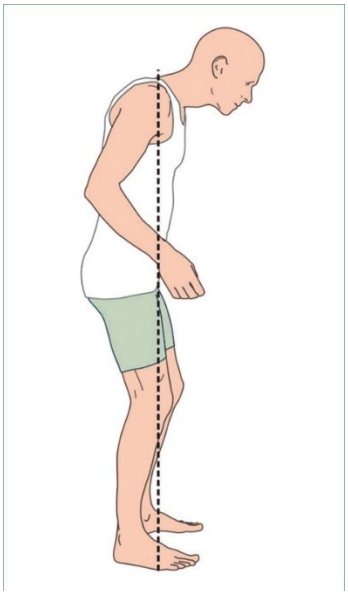


Figure 3: The classic 'stooped' appearance of PD with mild hip and knee flexion and rounding of the shoulders

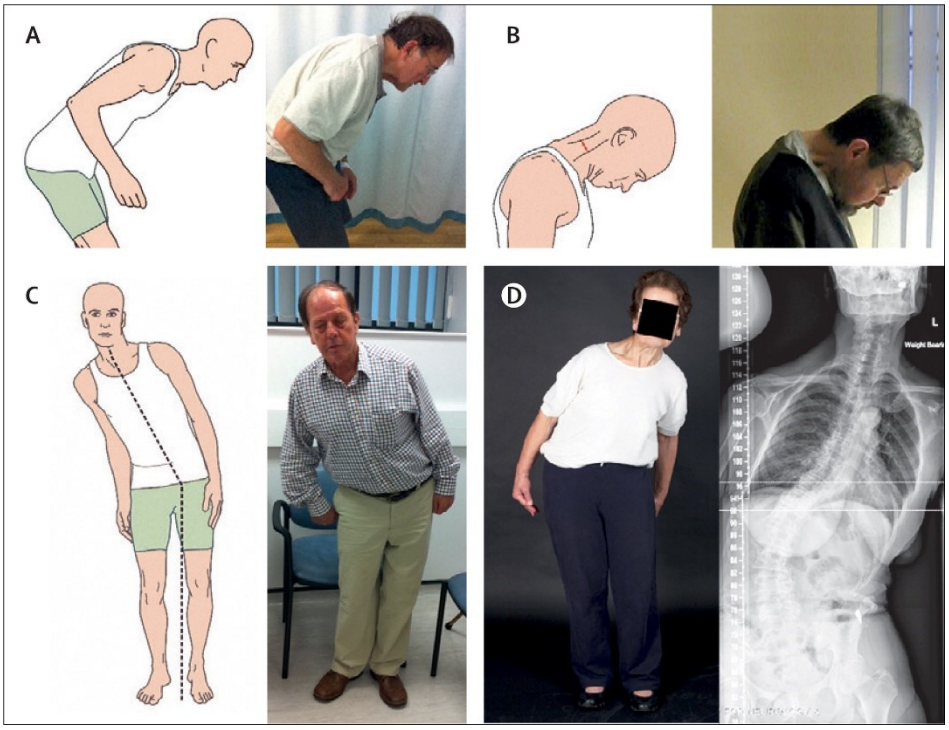


Figure 4: Sagittal plane deformities (A: camptocormia, B: antecollis) and coronal plane deformities (C: Pisa syndrome, D: scoliosis). Figure 3 and 4 (modified from Doherty et al., 2011)

Gait impairment:

Gait is a complex task and the PD motor dysfunction deeply affects this movement.

The gait in PD patients tends to be slow, imbalanced due to a narrow base and characterized by short shuffling steps. There is a decreased arm swing and the turning around is difficult, slow and performed with small steps. FOG can occur, especially if the environment is crowded or narrow. The festination, in which the patient involuntarily moves with short, accelerating steps, often on tiptoe, with the trunk flexed forward and the legs flexed stiffly at the hips and knees, and can be stopped encountering an obstacle or with the help of visual or auditory rhythmic cues (Suteerawattananon, Morris, Etnyre, Jankovic, & Protas, 2004). Imposing a cognitive load on the PD patient further worsens these condition, making the walking or turning difficult or even impossible especially with late PD. To evaluate these impairments one should observe the posture and gait on a corridor and while passing through narrow doorways or other obstacles. Another test is the "pull test", in which an examiner stands behind the patient and pulls his/her shoulder, then allowing him to step back in order to regain balance. If there is no postural response, even if the patient was previously warned of the pull, then the postural stability is compromised (Massano & Bhatia, 2012).

Dyskinesia:

This symptom is caused by the daily fluctuation in motor capability, due to the pharmacological treatment, common in PD patients. These fluctuations range from the wearing off phenomenon to sudden changes in mobility ("ON" and "OFF" states) producing great disability in addition to abnormal involuntary movements already onset. Accordingly with their timing with the pharmacological administration of dopaminergic treatment (mostly levodopa), these motor dysfunctions can be classified in three categories:

1. "Peak Dose" dyskinesias, occurring during the peak of therapeutic action of the levodopa or during the whole "ON" state ("square wave")
2. Diphasic dyskinesias: during the onset and the end of the "ON" state.
3. "OFF" state dyskinesias, it often takes the form of dystonic postures during periods of decreased mobility, more often in the morning before taking the first levodopa dose.

Levodopa induced dyskinesia can be also classified according to the type of movement:

1. Chorea: Chorea is a hyperkinetic movement disorder characterised by excessive spontaneous movements that are irregularly timed, randomly distributed and abrupt.
2. Blepharospasm is an abnormal contraction of the eyelid muscles.
3. Dystonia, characterized by painful, prolonged muscle contractions that cause involuntary repetitive twisting and sustained muscle contractions.
4. Myoclonus, a sudden, involuntary jerking of a muscle or group of muscles.
5. Tics, a habitual spasmodic contraction of the muscles, most often in the face.
6. Repetitive alternating movements (RAMS) in the limbs.

And other mixed movement disorders(Luquin, Scipioni, Vaamonde, Gershanik, & Obeso, 1992).

Current models of basal ganglia function and symptomatology of PD:

The standard "antagonist balance" model suggests that there are a direct and indirect pathway through the basal ganglia, the first is thought to facilitate movements and the latter is thought to suppress movements. This model states that the effect of dopamine is different between the two pathways due to the presence of different dopaminergic receptors in striatal neurons. The primary derangement in PD is a loss of dopaminergic neurons in the pars compacta and the substantia nigra and this reduce the activity in the direct pathway and excites the indirect pathway inhibiting movements (Gale, Amirnovin, Williams, Flaherty, & Eskandar, 2008).

A modification of the standard model, called center-surround model, suggests that the two pathways interact in a center-surround organization similar to the visual system. In the visual system, the center-surround system is thought to enhance contrast, for example to improve edge detection. In this model the basal ganglia focus on the desired action and the indirect pathway provides the inhibitory surround to suppress all the competing movements. In this model, GPi neurons with an inhibitory input from the direct pathway constitute the excitatory center.

The center-surround model is most effective in explaining the apparent excess of activity observed in hemiballismus (Gale et al., 2008).

More recent studies have emphasized the role of neuronal oscillations and increased synchrony in PD, even if the mere presence of oscillatory activity in the basal ganglia may not in itself be abnormal. However, in PD the abnormally high power of the beta-band oscillations may act to impede or obscure normal signals, therefore slowing or preventing movements, this behavior is described by the abnormal firing pattern model (Gale et al., 2008).

There is an emerging consensus that the anterior neostriatum is involved in learning new motor tasks and that dopamine plays an important role in this process (Bar-Gad, Morris, & Bergman, 2003).

The Learning Model suggests that the neostratium and, by extension, the rest of basal ganglia, plays a critical role in the reward-based learning. The phasic dopamine release potentiates particular corticostriatal synapses or circuits in an iterative process which selectively strengthens or weakens associations, both successful or not. This model explains some apparent paradoxes like the lesions of the motor thalamus that do not lead to hypokinetic symptoms as predicted by the standard model (Gale et al., 2008).

1.1.2 Clinical scales

To follow and assess a complex neurological disease as Parkinson's require a systematization of the diagnostic process, to make it reproducible across multi centered studies, physicians and make it accessible to clinicians with less expertise in PD diagnosis.
There are many clinical scales used to evaluate PD patients, a brief overview of some utilized by the trials presented further are discussed in this section.

1.1.2.1 UPDRS

In 1985 was founded the Movement Disorder Society (MDS), a not-for-profit organization, in 1992 merged with the international Medical Society for Motor Disturbances and lately, in 2013 it changes its name in "International Parkinson and Movement Disorder Society".
In 2001, the MDS sponsored a critique of the Unified Parkinson's Disease Rating Scale (UPDRS), originally developed in the 1980 and the most widely used clinical rating scale for PD . MDS lauded the strengths of the scale but found some ambiguities and weakness, and thus developed a new version to resolve the identified problems and incorporate a number of clinically pertinent PD-related problems poorly included in the original version.
This society is responsible for the updated Unified Parkinson's Disease Rating Scale (UPDRS).
The UPDRS is composed by four parts with a total summed score; with the updated scale there is an added section that integrates non-motor elements of PD:

I. Non-motor, experiences of daily living;
II. Motor experiences of Daily Living;
III. Motor Examination;
IV. Motor Complications.

All the items have five response options with scores that ranges from normal = 0, slight = 1, mild = 2, moderate = 3 and severe = 4. There are several questions in daily living parts (I and II) written as a patient/caregiver questionnaire. This test is tailored to an estimated 30-minute goal, with 10 minutes for the interview items of Part I, 15 minutes for Part III and 5 minutes for Part IV.
In a 2008 sponsored validation study (Christopher G. Goetz, Tilley, et al., 2008) the researchers administered the UPDRS test to 877 English speaking PD patients; this revised version correlated with the original UPDRS (rho = 0.96) and more importantly the results showed high internal consistency (Cronbach's alpha = 0.79-0.93). A 2012 independent Spanish study (Martinez-Martin et al., 2013) performed a cross-culturally adapted MDS-UPDRS Spanish version, administered to 435 PD patients showed a moderate floor effect for Part IV. MDS-UPDRS parts correlated well with other measures (i.e. PDQ-8, EQ-5D… etc.) for related constructs (>= 0.60), confirming the results of the original study.

1.1.2.2 Rush-DRS

In a 1994 Goetz et al. proposed a revised Obeso dyskinesia scale to create an objective rating scale for dyskinesia assessment during activities of daily living (ADL). They videotaped PD patients asked to perform three tasks: walking, putting on a coat and lifting a cup to the lips for drinking. The raters had to observe the types of dyskinesia and rate the patient's worst function between chorea, dystonia and other dyskinetic movements in combination. The severity rating code was: 0, absent; 1, minimal severity, no interference with voluntary motor acts; 2, dyskinesias may impair voluntary movements but patient is normally capable of undertaking most motor acts; 3, intense interference with movement control and ADL are greatly limited; 4, violent dyskinesias, incompatible with any normal motor task (C. G. Goetz et al., 1994).

1.1.2.3 UDysRS

The Unified Dyskinesia Rating Scale (UDysRS) was developed by Goetz et al. (Christopher G. Goetz, Nutt, & Stebbins, 2008) to rate PD-dyskinesias. The UDysRS is composed by four parts:

I. Historical Disability (patient perceptions) of On-Dyskinesia impact;
II. Historical Disability (patient perceptions) of Off-Dystonia impact;
III. Objective Impairment (dyskinesia severity), anatomical distribution over seven body regions and type (choreic or dystonic) based on four activities observed or video-recorded;
IV. Objective Disability based on Part III activities.

The clinimetric testing involved 70 patients and 20 movement disorder expert that rated videotaped examinations. Internal consistency was good (alpha: 0.915, 0.971) for all the subsections, interrater reliability was acceptable and likewise for intrarater reliability, except for the right leg.

1.1.3 Patient Diaries

Due to the advancement of the PD and the fluctuations of symptoms through the day a patient diary is a useful tool to track the progression of the disease. Patients self-report their daily symptoms at specified intervals through their "ON" and "OFF" state The only two PD diaries reccomendedby the MDS Task Force on Rating Scales are the Parkinson Disease Home Diary (PD-HD) and the Core Assessment Program for Surgical Interventional Therapies in Parkinson's Disease (CAPSIT-PD) discussed further (Antonini et al., 2011). Their assessment, to be meaningful, requires the presence of motor fluctuation.

Parkinson Disease Home Diary (PD-HD): PD-HD was developed to track not only the overall "ON" and "OFF" time, but also the so called "bad" time due to unwanted dyskinesia during "ON" state. The diary Figure 5 is composed by 5 items (Asleep, OFF, ON without dyskinesia, ON with non-troublesome dyskinesia, ON with troublesome dyskinesia) and divided by 30 minutes time slot during the day. It separates the ON time in 3 parts regarding dyskinesia severity to provide a more accurate reflection of clinical response than change in off time alone. It includes clear instruction to the patients.

PARKINSON'S DISEASE DIARY

NAME_____ DATE_____

Instructions: For each half-hour time period place one check mark to indicate your predominant status during most of that period.
ON = Time when medication is providing benefit with regard to mobility, slowness, and stiffness.
OFF = Time when medication has worn off and is no longer providing benefit with regard to mobility, slowness, and stiffness.
Dyskinesia = Involuntary twisting, turning movements. These movements are an effect of medication and occur during ON time.
Non-troublesome dyskinesia does not interfere with function or cause meaningful discomfort. **Troublesome dyskinesia** interferes with function or causes meaningful discomfort.
Tremor is shaking back and forth and is not considered dyskinesia.

time	asleep	OFF	ON without dyskinesia	ON with non-troublesome dyskinesia	ON with troublesome dyskinesia
6:00 AM					
:30					
7:00 AM					
:30					
8:00 AM					
:30					
9:00 AM					
:30					
10:00 AM					
:30					
11:00 AM					
:30					
12:00 PM					
:30					
1:00 PM					
:30					
2:00 PM					
:30					
3:00 PM					
:30					
4:00 PM					
:30					
5:00 PM					
:30					

time	asleep	OFF	ON without dyskinesia	ON with non-troublesome dyskinesia	ON with troublesome dyskinesia
6:00 PM					
:30					
7:00 PM					
:30					
8:00 PM					
:30					
9:00 PM					
:30					
10:00 PM					
:30					
11:00 PM					
:30					
12:00 AM					
:30					
1:00 AM					
:30					
2:00 AM					
:30					
3:00 AM					
:30					
4:00 AM					
:30					
5:00 AM					
:30					

Figure 5: Parkinson's Disease - Home Diary (PD-HD)

The Test-retest reliability of this diary is good and increased with the increasing number of days it was filled. The issues with this half an hour diaries is compliance, dropping beyond the third day (Hauser, Deckers, & Lehert, 2004).

1.1.3.1 CAPSIT-PD

The Core Assessment Program for Surgical Interventional Therapies in Parkinson's Disease (CAPSIT-PD) is a four item motor condition diary filled every 30 minutes. The recommendation suggest to filing it daily for 1 week every month. Motor conditions item are defined as:

1- *OFF:*
    a. *Poor or no Effect of antiparkinsonian drugs difficulties in moving;*
    b. *Difficulties in moving;*
    c. *Slowness, stiffness*
    d. *Tremor*
2- *Partial OFF or Transition State:*
    a. *Some effect of antiparkinsonian drugs;*
    b. *Condition in between "OFF" and "ON";*
    c. *Symptoms as in "OFF", but mid;*
3- *ON:*
    a. *Good effect of antiparkinsonian drugs;*
    b. *Able to move without disabling slowness or stiffness;*
4- *ON with Dyskinesias :*
    a. *"ON" phases complicated by involuntary, irregular, twisting, and/or jerky movements.*

Further studies conducted with this diary suggested that good patient's training yield better results. The study suggested that even 4 items are too much, a three item diary (without the "Transition State" item) is better, unless extensive training of the patients. Like the PD-HD the representativeness of diary derived data can be challenged if administered for only small time periods(Reimer, Grabowski, Lindvall, & Hagell, 2004).

1.1.4 Towards an electronic diary for the future

The advent of new technologies brings the opportunity to expand the current capabilities of paper-format diaries adding the possibility to integrate the data with personal time-wise information, personalized questionnaires and automatic notification. This increase may capture a wider range of motor, non-motor and circadian complex fluctuation. MDS technology Task Force and the MDS Rating Scales Program Electronic Development Ad-Hoc Committee recently brainstormed on a set of desirable characteristics towards the developmental steps for a more technologically savvy diary to support both clinical trials and clinical practice ("PD Diary," 2018). The desirable characteristics of an e-Diary are:

1. Phenomena recognition: a diary must focus on capturing key symptoms and signs that correlate with the clinically pertinent fluctuations in motor a non-motor function.

2. Patient language: patient must understand the meaning of the definition and trained to possess some health literacy.

3. Administration and data collection: frequency of assessment and method of state determination must be clearly stated and achieved with good compliance and minor errors.

4. Diary format and data visualization: the patient interface need to be clear and ideally include a visual feedback to stimulate long term compliance of the diary.

5. Data and clinimetric properties:

Data: action-dependent (active input by the patients, e.g. questionnaires or tasks) and action-independent measurements (wearables data sensors and other passive forms of data collection)
Clinimetric properties: Validate internal consistency (Cronbach's alpha), construct validity (convergent, divergent, known groups), patient-clinician agreement, predictive validity calculations, and factorial analysis, among other methods.

6. Technology-based objective measures: providing a updating-evolving questionnaire that can be administered remotely and also remote or wearable sensor that can provide complementary action-dependent and action-independent objective measures.

1.2 Therapies

1.2.1 Levodopa

Between 1910 and 1913 Torquato Torquati isolated the L-isomer of the amino acid D, L-dihydroxyphenyalanine (L-DOPA) from seedlings of Vicia faba, soon after, in 1913 Markus Guggenheim established the chemical structure. In 1938 Peter Holtz converted the inert levodopa to the biologically active catecholamine dopamine (DA). In 1957 Kathleen Montagu and soon after Weil-Malherbe and Bone discovered the occurrence of DA in the mammalian brain. It was Carlsonn, then, in 1957 that showed the beneficial effects of levodopa in the reserpine induced Parkinsonism in rabbits (Hornykiewicz, 2010). Hornykiewicz in 1960 demonstrated that brains of patients with PD had a profound loss of DA in the caudate nucleus and the putamen, and suggested a dopaminergic treatment. DA is not capable of crossing the blood-brain barrier, so levodopa was chosen instead. In 1967, Cotzias introduced the chronic, high dose, oral levodopa regimen, which is the most effective therapy for PD patients (Hornykiewicz, 2010), so effective that, as noted before, the ineffective response to L-DOPA causes the diagnosis to questioned.
Levodopa is administered with a peripheral decarboxylase inhibitor to prevent the peripheral metabolism and the development of nausea and vomiting caused by dopamine receptors in areas not protected by the blood-brain barrier (Brust, 2006).
Common pharmalogical forms are Madopar (L-DOPA and benserazide), Sinemet (L-DOPA e carbidopa). Levodopa can also be administered in controlled release formulations. Levodopa is still considered the

golden standard against new PD therapies,, and no current medical or surgical treatment provides antiparkinsonian benefits superior of this treatment (Brust, 2006).

This therapy has still important limitations due to side effects as vomiting, nausea and orthostatic hypotension and usually it cannot adequately control autonomic dysfunction, sleep disorders, dementia and freezing of gait (FOG).

Dopaminergic medications used in the treatment of patients with Parkinson's disease are associated with non-motor behavioral side-effects, such as impulse control disorders, also known as behavioral addictions. Levodopa-induced dyskinesias occur in up to 80% of patients with Parkinson's after a few years of chronic treatment. Impulse control disorders, including gambling disorder, binge eating disorder, compulsive sexual behavior, and compulsive shopping occur in about 17% of patients with Parkinson's disease on dopamine agonists. These behaviors reflect the interactions of the dopaminergic medications with the individual's susceptibility, and the underlying neurobiology of Parkinson's disease (Voon et al., 2017).

Most importantly, L-DOPA induces motor complications due the fluctuation of the motor response causing involuntary movements, called dyskinesias (Brust, 2006).

A dyskinesia is typically a transient, stereotypic, rhythmic movement, predominant but not limited to the lower extremities. Levodopa has a relatively short half-life (60 to 90 minutes) but its benefits are long-lasting when initially administered. In the long run, however, it develops a wearing-off effects, and the duration of the benefits of a single dose tends to approaches the half-life of the drug (Figure 6). In addition, many patients develop dyskinesia, especially near the peak of the plasma concentration (approximately 30 minutes after the administration).

In the late stages of Parkinson patients may cycle between so called “ON” state and “OFF” state. In “OFF” state the patients suffer from severe parkinsonism (bradykinesia, rest tremor, rigidity…) and in “ON” state the patient may swing between nearly asymptomatic motor condition to disabling dyskinesias. The dyskinesias are not only related to the peak dose, but they can be also related to the initial and final (wear off) phase of the levodopa, those are called “diphasic dyskinesias”.

These states can have other causes besides insufficient (or too much) L-DOPA delivery (such as transient FOG), but the mostly the motor fluctuations can be explained by a not stable L-DOPA concentration in the brain areas. L-DOPA is administered orally and achieving a drug intake that reaches regularly the brain is problematic because the gastrointestinal tract is not well suited for optimizing the drug uptake(LeWitt, 2015).

Even with a well-deserved “gold standard” status, L-DOPA treatment needs to be supported by other means, especially in the late stages of the disease.

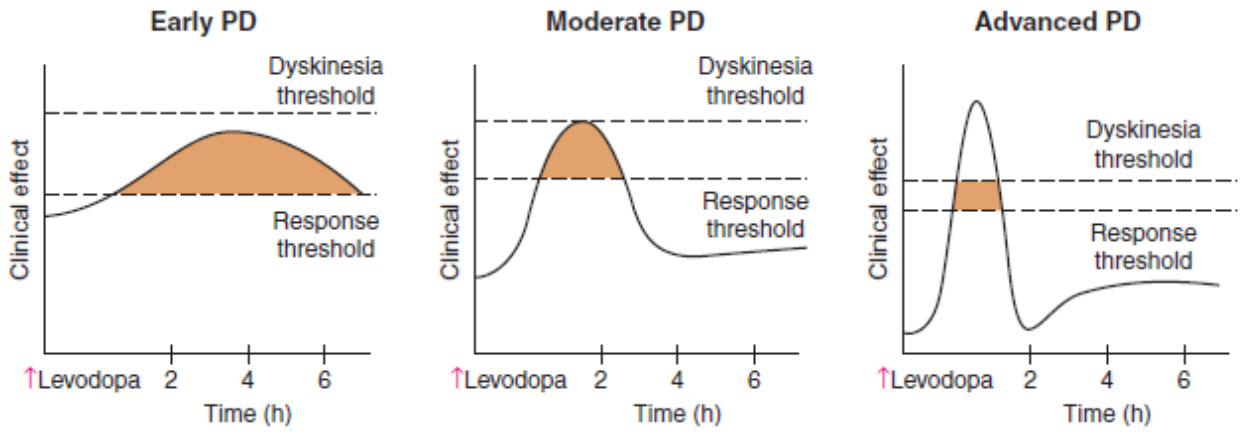


Figure 6: hourly fluctuation of dopamine treatment in PD in early, moderate and advanced stages. The brown area between the threshold is the ON status, when the optimal clinical effect is reached

1.2.2 Dopamine Agonists

This class of drugs acts directly on dopamine receptors and do not require to metabolize an active product and do not undergo oxidative metabolism. Broadly speaking, these therapies do not have the same comparable efficacy as levodopa; they only were used to complement the therapy. They are used primarily to reduce OFF time in fluctuating patients, and to reduce dyskinesia. Many physicians initiate the therapy with dopamine agonists but in the later stages levodopa is required for virtually all patients. Side effects include vomiting, nausea, orthostatic hypotension; hallucinations and cognitive impairment are more common with dopamine agonists(Brust, 2006).

1.2.3 MAO-B inhibitors

They are inhibitors of monoamine oxidase type B, it blocks the central dopamine metabolism and thus increasing synaptic concentration of the neurotransmitter. Clinically MAO-B inhibitors provide modest antiparkinsonian benefits when used as monotherapy in early disease, they reduce “off” time when used as an adjunct to levodopa in patients with motor fluctuations.

1.2.4 COMT INHIBITORS

Inhibitors of Catechol-O-methyltransferase (COMT) enhance the levodopa brain availability. It prolongs “ON” time in fluctuating patients and lessen the “OFF” time. Side effects of COMT inhibitors are vomiting, nausea and increased dyskinesia.

1.2.5 Surgical Treatment

Surgical lesions were proven beneficial for more than a century. How specified earlier, lesions placed in the GPi improves rigidity, bradykinesia and tremor. Pallidotomy is associated with an improvement on contralateral dyskinesia, however, bilateral lesions are associated with dysarthria, dysphagia and impaired cognition so it is not advised for patients with bilateral disease.

Since 2009 emerged a new less invasive technique to perform a pallidotomy: Magnetic Resonance guided focused ultrasound (MRgFUS). A recent study concluded a phase I of a clinical trial that performed unilateral MRgFUS pallidotomy to 10 patients with a success rate of 80%. Two patients were discarded due to insufficient temperature rise in the surgery and no visible lesion through temperature map, 1 successful patient suffered from unusual side effect of the sonication: dysarthria and grade III right motor hemiparesis but he fully recovered two days later.

The clinical outcomes, with a follow up of six months, showed an improvement both in "OFF" state (32.2 % in UPDRS part III score, $p = 0.018$) and especially in dyskinesias in "ON" state (52.7% in UDysRS score, $p = 0.017$, in the 6 month follow-up it becomes 42.7%, $p = 0.046$) (Jung et al., 2018).

1.2.6 Deep Brain Stimulation (DBS)

DBS is a neuromodulatory technique that consists of low impedance electrodes, permanently implanted in a subcortical nucleus, connected to a subcutaneous stimulator delivering current impulses with a frequency between 100 and 200 Hz (usually 130 Hz), impulse width between 60-210 μs and voltage range between 1-3.5 V (Volkmann, Herzog, Kopper, & Deuschl, 2002). The functional stimulation target is pathology specific and is shown in Table 3. For PD is usually the STN (Carpenter & Reddi, 2012), but also globus pallidus (Kosutzka et al., 2018).

Despite being invasive, DBS was successfully applied to Parkinson's disease, essential tremor, dystonia, Tourette syndrome and other neurological disorders.

DBS in PD requires usually a robust motor response to levodopa (except for tremor-predominant PD), and stimulation is considered only after the patients develop disabling dyskinesias and motor fluctuations while receiving medical therapy. STN and GPi are the most commonly used target, at first electrode placement in STN was favored because yielded a greater improvement in motor score than GPi, later studies proven GPi DBS effective even if the STN remains the preferred target. GPi DBS can be considered in patients with speech, cognitive and mood disturbances, as STN DBS can sometimes worsen these symptoms.

DBS-STN improves "OFF" state motor symptoms, ranged between 30% and 55% persisting at 5-year evaluations and shows a general improvement of rest tremor, rigidity, gait and lib akinesia ("Five-Year Follow-up of Bilateral Stimulation of the Subthalamic Nucleus in Advanced Parkinson's Disease | NEJM," n.d.),(Krack, Martinez-Fernandez, Del Alamo, & Obeso, 2017). More than 50% reduction in on time with

dyskinesias (Deuschl et al., 2006) and decrease of levodopa-induced dyskinesias by almost 70% (Kleiner-Fisman et al., 2006).

Primary dystonia	Gpi	Effective
Secondary dystonia	GPi	Debated
Essential tremor	Thalamus STN	Effective
Tourette syndrome	CM-Pf-VO CM-Pf Gpi Accumbens	Good results still under consideration
Depression	Ipothalamus	Experimental therapy
Obsessive-compulsive disorder	Ipothalamus	Experimental therapy
Headache	Ipothalamus	Experimental therapy
Epilepsy	Amygdale	Experimental therapy
Alzheimer disease	Ipothalamus	Experimental therapy
Parkinson's disease	STN GPi Vim PPN	Effective Effective Effective Experimental therapy

Table 3: DBS treatment, divided by pathology and anatomical location. (Carpenter & Reddi, 2012)

This procedure also improves some axial scores, in particular postural stability and speech(Romito & Albanese, 2010), and the overall quality of life (Deuschl et al., 2006).

However, over time, patients who have DBS often develop levodopa-resistant symptoms including FOG, postural instability, and cognitive decline (Bronstein et al., 2011a), (Krack et al., 2017) and stimulation-related side effects aggravated in the long-term and are not always reversible with reprogramming (Krack et al., 2017). STN-DBS can worsen speech and gait in some patients and depression and impulsivity have been reported following DBS and may represent a consequence of stimulation (Bronstein et al., 2011a).

DBS, due to the invasive surgery, also include risk of hemorrhage and infection, a risk of mechanical failure of the electrodes and the stimulator. It require a stabilization period (between 2 weeks and one month after the surgery) and frequent follow-up visits.

All the other adverse effects are typically transient and reversible (Miocinovic, Somayajula, Chitnis, & Vitek, 2013). The cost of the device and the battery replacement are another important factor.

History of DBS	
1890	Horsley performed extirpation of the motor cortex for treatment of athetosis.
1947	Spiegel et al. described a stereotactic frame.
1950	Spiegel et al. made lesions in patients with PD to interrupt pallidofugal fibers causing improvement in bradykinesia, rigidity and tremor.
1950s	Hassler, Riechert, Talairach et al. treated Parkinsonims with lesions in the VL thalamic nucleus. Cooper attempted to section the cerebral peduncle but inadvertently interrupted the anterior choroidal artery and was forced to ligate it, leading to disappearance of rigidity and tremor with preserved motor and sensory function.
1963	Albe Fessard et al. reported that stimulation in the area of ventrointermediate nucleus of the thalamus at frequencies of 100-200 Hz improved tremor in patient with parkinsonism.
1969	Levodopa was introduced, parkinsonian symptoms were improved, and stereotactic surgery fell out of favor.
1987	Benabid and colleagues heralded the modern era of DBS through their publication of thalamic DBS contralateral to thalamotomy in patients with tremor.
1989-1990	Albin et al. and DeLong introduced a model of basal ganglia function based on the hypothesis that there were segregated circuits within the basal ganglia thalamocortical network, each serving a different function.
1992	Laitinen and colleagues reintroduced the Leksell pallidotomy technique for patients with advanced PD along with severe adverse effects from levodopa therapy.
1998	Documentation of safety and efficacy of bilateral STN BDS by Limousin et al., including its potential for reducing the dose of dopaminergic medications in patients with advanced PD.

2000	Coubes et al. presented data for GPi BS in treatment of dystonia.

Table 4: History of DBS (Miocinovic et al., 2013).

The primary effect of DBS is to produce action potentials in the axons, as these have the lowest threshold for activation (Montgomery, 2016), however this action potential is propagated both orthodromically and antidromically, in the latter case influencing a collateral branch, becoming a orthodromically conducted action potential. Thus, the indirect postsynaptic events can invoke both temporal and spatial summation as potential mechanism of action. To be effective for the temporal summation the DBS pulses must be given in a time frame where the effects of the prior pulse has not been dissipated in the neurons' transmembrane electrical potentials (Montgomery, 2016). The DBS pulse also affect spatial summation regarding the standard electrodes used, multiple times larger than the axons in their vicinity; thus, it is likely that many axons are activated and they may converge on the same neuron, producing spatial summation (Montgomery, 2016).

The operation mechanism for DBS is mainly uncertain (Chiken & Nambu, 2016).

A computational model made by Santaniello et al. Assumes that DBS may depolarize presynaptic terminals along with efferent axons from the stimulated site, this depolarization can lead to an activation of cortical, thalamic, and striatal neurons, even though with a very low probability, and the stimuli delivered to each neuron have a stochastic distribution. This study further suggests that the antidromic activation elicited by DBS (with impulses > 100 Hz) might provide a contribution to the suppression of the beta oscillations by involving different structures (striatum, cortex, etc.) simultaneously(Santaniello, Montgomery, Gale, & Sarma, 2012).

A hypothesis called "disruption hypothesis", suggests that an abnormal information flow is isolated by the high frequency stimulations as a result of DBS dissociation effect between input and output, however still needs preclinical validation (Chiken & Nambu, 2016). Another review (Herrington, Cheng, & Eskandar, 2016) present several non-exclusive mechanism: local and network-wide electrical and neurochemical effects of stimulation, modulation of oscillatory activity, synaptic plasticity and, potentially, neuroprotection and neurogenesis. In table 4 a brief history of DBS is reported.

1.3 Closed Loop treatment

The broad overview of symptoms, signs and therapies present a clear challenge: managing the daily fluctuation caused by the progress of the disease and the long term levodopa administration. The therapies can be tailored but they require a continuous back-and-forth of the patient to the physician to assess their symptoms and consequently modify the prescription.

In other fields there are devices capable of sensing the patient physiology and responding accordingly. In the cardiac field the pacemaker is used for over 50 years and in diabetic field new automatic insulin pumps are becoming a commercial reality ("Premarket Approval (PMA)," 2018).

These devices require a two steps cycle: assessing the new patient condition and modifying the therapy accordingly: this is the "Closed-Loop" paradigm. The challenges of this approach are divided in two main concerns:

1. Administering a real-time responsive therapy.
2. Find one or more easily accessible and reliable control variables.

1.3.1 Administering a real-time responsive therapy

Electronic technology has, from its creation, the capability of being responsive: sensor inputs are translated in actuator/emitter action in simple or complex patterns, normally with a near immediate latency. Thus, electronic implants are the best candidates to enforce a responsive therapy. The most common electronic implant in PD treatment is DBS, even if right now conventional DBS (cDBS) is delivered with constant parameters, regardless of the motor state of the patient, not having a true symptomatic control. DBS still requires periodical reprogramming: it is proven (Bronstein et al., 2011b), (Yu & Neimat, 2008), (Kupsch et al., 2011) that change DBS parameters can reverse several adverse effects, e.g. dyskinesia. In cDBS the reprogramming process can be cumbersome for the patient: it requires multiple post-operative visits, in which an experienced clinician evaluates the patient and then recalibrates the therapy. The reprogramming process is dependent on the various DBS reprogrammable parameters: contact number, frequency, impulse width and stimulus amplitude and on every visits they all must be regulated to minimize the adverse effects and maximize the clinical benefits.
There are many combinations of these parameters (e.g. 4 contacts for STN, about 100 Hz with 10 Hz steps range, 0 to 8 Volt amplitude range with 0.5 Volt steps and 60 to 120 μs pulse width range with 10 μs steps makes for more than 7000+ possible combinations) and the assessment of the effectiveness of these combinations is time consuming; for this reason, the multiple post-operative visits and the inherent slowness of these operations still qualify cDBS as an Open-Loop process.

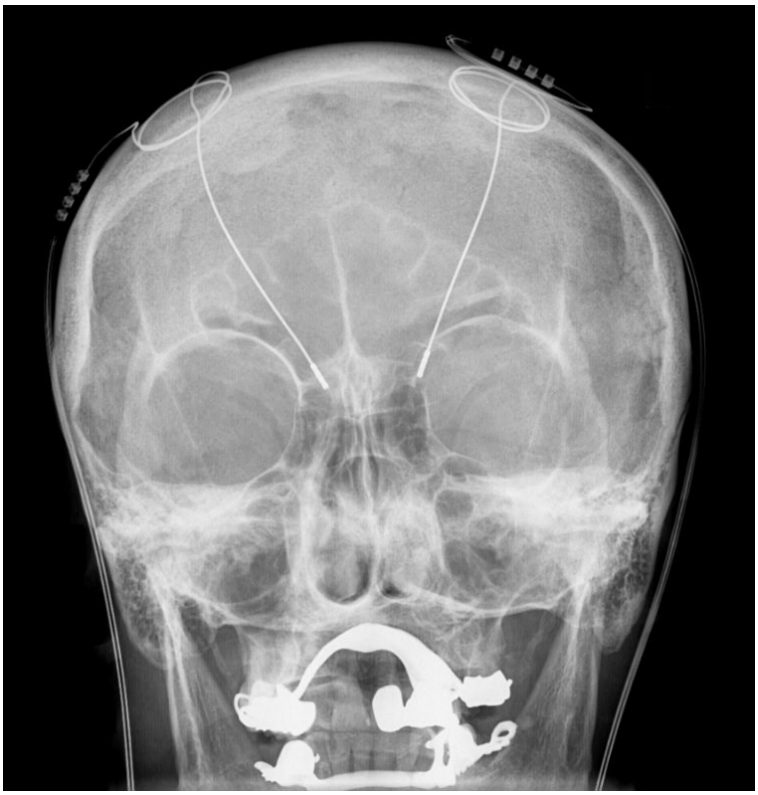


Figure 7: Deep Brain Stimulation electrodes implanted in the STN. ("Tiefe Hirnstimulation bei Morbus Parkinson: Sondenverlauf in Projektion auf den Schädel auf einer Röntgenaufnahme" by Hellerhoff is licensed under the Creative Commons Attribution-Share Alike 3.0 Unported license).

Therefore, DBS is the perfect candidate to implement a solid Closed-Loop paradigm, exploiting the natural technology responsiveness to automatically regulate parameters using one or more combined control variables, i.e. variables that tracks the patients status, which can be correlated with the patient clinical conditions to achieve measurable clinical benefits for the patient. This approach was called adaptive DBS (aDBS) and is composed by sensors that feeds the signal to a signal processing unit connected to the controller circuit which adapts the DBS settings and vary the stimulation accordingly.

1.3.2 Possible control variables

As stated before the control variables are fundamental in this systems, stimulation parameters must be modified only when the patient needs them and without the direct supervision of a clinician.
There may be many questions to answer when choosing a control variable, in this work we have chosen to answer the following, based on our experience:

A. *Is the implant acceptable by the patients?*

   New implants are likely to cause more discomfort to the patient, and not always they are worth the possible benefits of the new therapy.

B. *Do they correlate with the clinical state?*

A strong correlation with the clinical state of as many patients as possible is essential to develop a reliable and economically viable system.

C. *They require active participation from the patient?*

These variables can be acquired in an action-dependent or action independent manner, i.e. questionnaires and tasks or autonomous "passive" acquisition respectively.

D. *Is the system customizable?*

Even with a good point B. there is always a lot of variability between patients and also they have different needs, so it is important to tailor the acquiring system to different type of subjects.

E. *Do they imply changes in the surgical procedure?*

New surgical procedure means new risks and a lack of trained doctors, old and established procedure are usually a lot safer and error free.

F. *Does the system consume more battery?*

The majority of the closed-loop systems are implantable or wearables, so it is important that they last long, to limit the risk of not having the system online where it is needed and to not harass the patient with continuous battery changes / recharges.

In the following sections we present the main technologies considered as control variables for the closed-loop DBS.

1.3.3 Wearable body sensors

In recent years wearable technology had been growing and expanding more and more, it had some setbacks but the big technology companies press on (Bradshaw, 2017) focusing more on health and fitness as a new primary target of this technology. New FDA approved devices are starting to appear into the commercial market (Bradshaw, 2018) to support real clinical applications. Commercial-grade multipurpose wearables (especially smartband and smartwatches) have penetrated the health research with increased frequency since 2014; the acceptability and effectiveness in supporting health are still being validated in larger studies focusing on patients with the condition targeted by this devices (Reeder & David, 2016).

These observations suggest their possible application to measure controlled variables for closed-loop DBS.

Wearables sensors are a high frequency, high volume and high dimensional type of data:
High frequency: a normal smartwatch or smartphone can generate 100 or more samples per second only in kinematic data.
High dimensionality: this data can be taken by multiple sensors (e.g. accelerometric, gyroscopic and magnetic data) and this means high volume (high frequency samples per seconds of tri-axial multisensor data: in our example 100 samples/s * 3 axis * 3 sensor type = 900 scalar values every second).
PD classical data is collected in a substantial time frame mostly in a "snapshot" of the patient during the ambulatory visit or during a limited hospital period. PD wearable data is not static and is not subjective to different physician. Of course clinical data have merits: a clinical rater taken by a professional synthetizes an enormous amount of sensory information mediated by the experience of the assessing doctor that can seek out dynamically other confirmatory data to have a broad and holistic diagnosis of the patient condition. A wide multi-sensor approach integrated with extensive self-reported data and elaborated in a sophisticated manner may approximate a clinical rater, supporting the decisions of the physician or at least giving him/her new useful data of the day-by-day condition of the patient.
In March 2015 one of the biggest observational studies of the recent years was released: mPower (Bot et al., 2016), a smartphone-base data gathering developed using Apple's ResearchKit library, the main objective of the study was to evaluate the feasibility of remotely collecting frequent information about the daily changes in symptom severity and their sensitivity to medication in PD. In Table 5 the proposed tasks are shown, some supported by multi-item questionnaires and some supported by the internal iPhone sensors.

Task name	**Type of task and schedule**	**unique participants**	**unique tasks**
Demographics	Survey—once	6,805	6,805
PDQ8	Survey—monthly	1,334	1,641
UPDRS	Survey—monthly	2,024	2,305
Memory	Activity—3 times a day	968	8,569
Tapping	Activity—3 times a day	8,003	78,887
Voice	Activity—3 times a day	5,826	65,022
Walking	Activity—3 times a day	3,101	35,410

Table 5: Data available for each survey and activity completed by study participants from (Bot et al., 2016).

1.3.3.1 Kinematic sensors

Data acquired by Inertial Measurement Units (IMU) includes tri-axial accelerometric, gyroscopic and magnetic information by one or multiple sensors on limbs or other body part (e.g. abdomen or waist). This kinematic data (especially accelerometric and gyroscopic information) can be used to estimates

the patient motor condition autonomously or within prescribed precise self-administered tasks. The simplest symptom estimation that can be achieved with IMU is tremor at rest detection, for example, Haddock et al., 2018 (Haddock et al., 2018) controlled DBS stimulation using tremor kinematic data associated with PD and essential tremor (ET). DBS parameters were changed automatically through a direct computer interface sensing the wrist motion through an IMU sensor. The sensing device was a smartwatch, capable of reporting IMU data and also patient self-reported adverse effects. Other motor symptoms are bradykinesia, dyskinesia e FOG, real time classification of these symptoms are not trivial due to advanced computation related to the broad spectrum of possible activities that these symptoms manifest (reading, talking, walking, eating), e.g. REMPARK project is dedicated to the real-time assistance of these patient through automatic detection of these symptoms by wearable accelerometric sensors. It also features an automatic audio cue to recover from festination, an application of the closed-loop paradigm through sensory stimulation ("REMPARK: Personal Health Device for the Remote and Autonomous Management of Parkinson's Disease (REMPARK)," 2018),(Samà et al., 2012). Usually an IMU sensor acquires from 50 to 200 samples/seconds of a tri-axial multi sensor data, with accelerometer and gyroscopic range well within the limits of normal usage (e.g. STMicro LSM303DLHC accelerometer: ± 2g; Invensense MPU9150 gyroscope: ± 500 deg/s; STMicro LSM303DLHC magnetometer: ± 1.9Ga, all of them have 16 bits, signed quantization).

1.3.3.2 Sound (voice) sensor

Volume of the voice and articulation of speech are important features changed by PD fluctuations, in a 2014 study (Tsanas, Little, Fox, & Ramig, 2014) they trained a classifier to discriminate sustained vowel phonation (/a/) in "acceptable" (by a trained clinician) and "unacceptable" categories to follow a specific PD treatment. The automation of these voice evaluating exercises, according to this study, frees the patient from sustained clinician support, boosting the comfort of the patient (these exercises can be taken directly at home) and freeing the clinician schedule from those support tasks. The study was relatively small (13 patients), but with tools like "mPower" (Bot et al., 2016) the sample pool can be expanded even further, even if not clearly targeted specifically to the rehabilitation tasks.

1.3.3.3 EEG, surface EMG, ECG and others noninvasiveness sensor-to-skin devices

Figure 8: portable EEG sensor, clinical grade on the left and consumer grade on the right (MUSE, https://choosemuse.com/, November 2018).

In recent years more and more commercially available and portable EEG sensors are being developed for neuroscience fields and the general market Figure 8. In their studies, Handojoseno et al. used a 4-channel wireless and portable EEG machine to predict FOG in PD patients. These studies use power spectral density (PSD) and wavelet energy, two not too computational heavy processes, as a potential biomarker for FOG with a resulting sensitivity, for 16 patients, of 86.0%, a specificity of 74.4% and an accuracy of 80.2% (Handojoseno et al., 2014), (Handojoseno et al., 2015). These systems have still big limitations primarily due to the small amplitude of signal involved, a lot of artefacts and noise due to movement and the relative encumbrance of multiple sensor system, also, given the wear location, the head, they tend to be very showy and not always really aesthetically pleasing.

1.3.3.4 Superficial Electromyography (sEMG):

sEMG was proven reliable to differentiate normal subjects with PD patients (Meigal et al., 2009) and to differentiate ET and PD (Ruonala et al., 2013), also, using both support vector machine and dynamic neural networks they may be used to discriminate dyskinesia combined with accelerometric data while performing unscripted and unconstrained activities of daily living (Cole, Ozdemir, & Nawab, 2012). FOG was also studied with ECG and skin-conductance (SC) sensors (Mazilu et al., 2015). In this study they used an anomaly-based algorithm with the data provided by the two sensors: they predicted 71.3% of

184 FOG events from 11 subjects with an average of 4.2 seconds before the episode. The drawbacks of sEMG, ECG and SC are similar to EEG: artefacts due to movements, encumbrance and distress to the patient, and the forced skin contact, often with the adjunct of wet conductive gel.
The wearable noninvasive category does not modify the surgery procedure (question: E) and the system are usually very customizable (question: D) but the system is still an adjunct to the patient, can be relatively uncomfortable as EEG or EMG portable apparatus or nearly invisible because it is integrated in a common smartphone, still they require to be carried on (question: A), used and recharged (question: F). Moreover a lot of these methodologies assess only one aspect of PD, bradykinesia, FOG, dyskinesia or non-motor symptoms (question: B) and most studied methodologies requires the active participation of the patient.

1.3.3.5 Mobile Apps

A special addendum in the "wearables" category are the mobile apps. According to the United States Federal Drug Administration definition:

> *"Mobile apps are software programs that run on smartphones and other mobile communication devices. They can also be accessories that attach to a smartphone or other mobile communication devices, or a combination of accessories and software. Mobile medical apps are medical devices that are mobile apps, meet the definition of a medical device and are an accessory to a regulated medical device or transform a mobile platform into a regulated medical device."("Mobile Medical Applications," 2018)*

Mobile applications can act as a hub to different connected sensors (wearables and smartphone internal sensors like camera or accelerometer), elaborate data, connect with cloud system to exploit more powerful calculating power and also offer a familiar interface with the patient to administer questionnaires and tasks.

1.3.4 Local Field potentials

Multiple neighboring neurons generate a potential that is the sum of the electrical activity in the area, this extracellular voltage is the composed by action potential and graded potentials and it is a direct result of synaptic interaction. This electrical activity can be recorded by a microelectrode within the neuronal tissue, measuring the local field potential (LFP) in the area. A good low impedance acquisition tip and a low pass filter below 300 Hz can characterize the neuron activity within 3 mm its location, at this distance is possible to observe only ionic activity, the action potential activity contribute to LFP only below 350 μm (Legatt, Arezzo, & Vaughan, 1980), (Juergens, Guettler, & Eckhorn, 1999). In a study by Priori et al. (A. Priori et al., 2004) LFP recorded in the STN of PD patients showed an high power in the

beta band (13 Hz to 30 Hz) activity in OFF state caused by orphenadrine, and then, administrating levodopa and apomorphine, a clear spectral density power change, the beta decreased and the low frequency increased. The correlation between strong synchronization of STN LFP alpha/beta band (8-35 Hz) and the motion condition of a PD patient are generally accepted (Brown, 2003), (Marceglia et al., 2007), (Rosa et al., 2011), (Whitmer et al., 2012), (Little & Brown, 2012),(Quiroga-Varela, Walters, Brazhnik, Marin, & Obeso, 2013), (Stein & Bar-Gad, 2013), (Yang, Vanegas, Lungu, & Zaghloul, 2014) in particular new control variables were taken using beta band power amplitude relatively slow variations: LFP beta band calculated in 50 s smoothed windows (Arlotti et al., 2018), and, recently, fast beta bursts detection (Tinkhauser et al., 2017), (Tinkhauser et al., 2018). Nevertheless LFP are hard to detect for every patients, (Giannicola et al., 2010), even if a new study could find alpha/beta oscillations of >98% of patients. Drawbacks from LFPs are the not complete capture of all main symptoms of PD: tremor assessment is debated (Shreve et al., 2017), (Meidahl et al., 2017) also, in a recent study (Wang et al., 2018), they recorded the oscillatory activity in the globus pallidus in PD patients and isolated dystonia and found disease-specific patterns of elevated oscillatory synchronization and in coherence between pallidum and motor cortex, proposing an alternative coherence based method to assess these changes. A study (L. A. Johnson et al., 2016) argues that the voluntary movement also dynamically modulates beta activity. Another study (Hell, Plate, Mehrkens, & Bötzel, 2018) shows how high beta (20-30 Hz) and bilateral oscillatory connectivity, and also burst amplitude and burst lifetime are reduced during gait so alpha, beta and gamma are modulated and locked to the gait cycle, arguing that these changes are related to movement induced artifacts.

Despite these challenges, LFP has the major advantage that it could be recorded directly through the already available classic DBS electrodes (Figure 10). The normally implanted electrodes have 4 different leads, to better targeting the site with the major positive clinical outcome selecting the right electrode. The remaining electrodes could be used to record the LFP near the stimulating area (e.g. STN), but the stimulation artefact must be suppressed. To do so a special device is required, a recording device capable of measuring the signal filtering out the stimulation artefacts, this device is a special DBS filter, presented in a study (L. Rossi et al., 2007) and successfully patented (US8078281B2, 2011). The study presented in this thesis uses this device to record LFP from the patient and also administering DBS treatment.

Using the same electrodes of the classical DBS (cDBS) does not change the surgical procedure, this solves the primary concern of the other invasive control methodologies (FSCV, SUR, and ECoG).

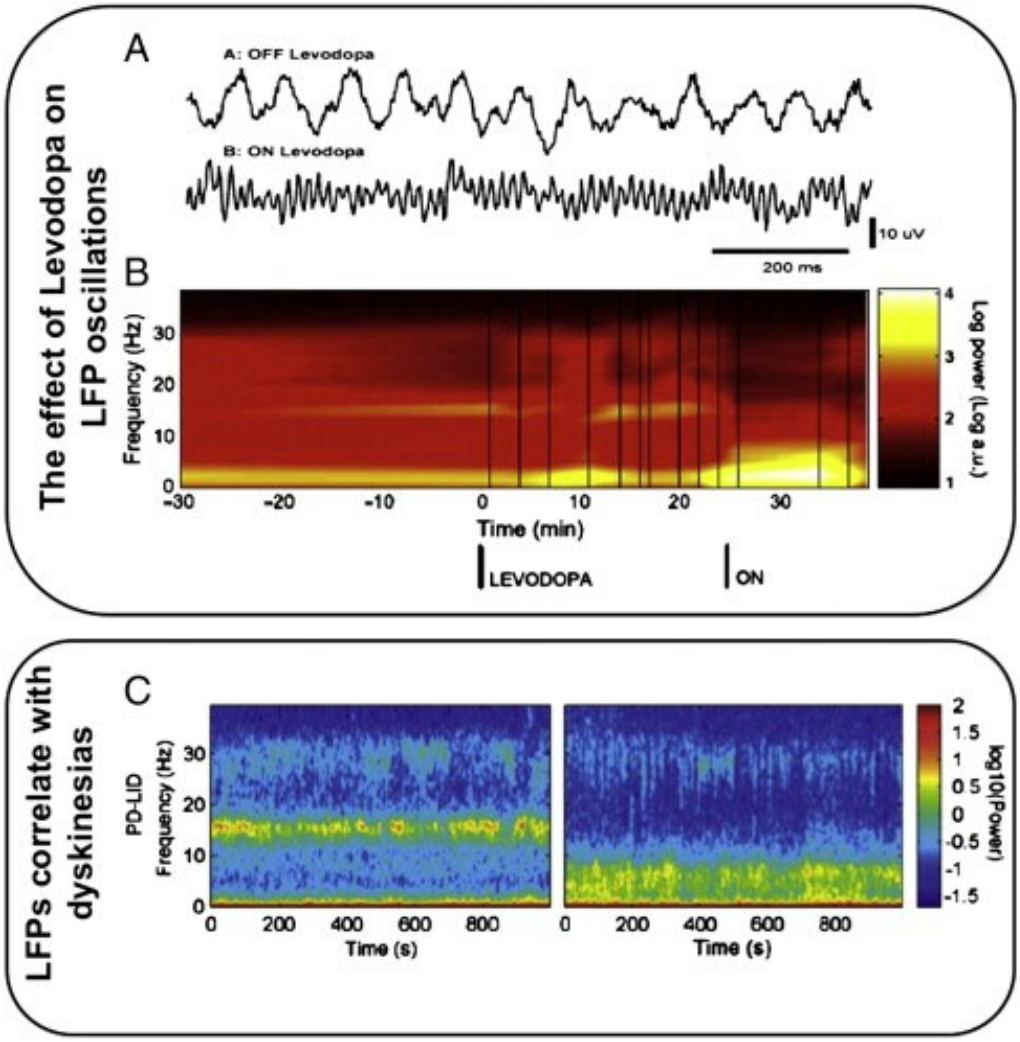


Figure 9: A: LFP response to L-DOPA intake; B: Spectrograms of high spectral Beta power (left) related to no dyskinesia status to low frequency power increase (right) related with a dyskinetic status.

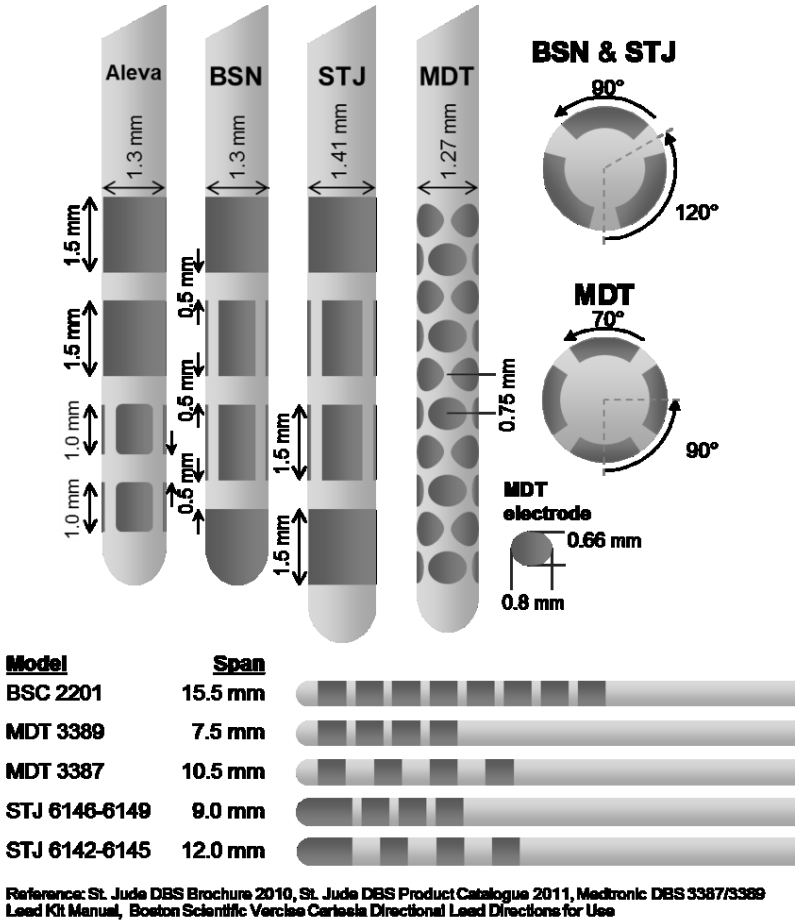


Figure 10: DBS models, on the top four St. Jude electrodes and on the bottom five Medtronic electrodes (Modified from P. J. Rossi et al., 2016).

1.3.5 Other biological and bioelectrical measures:

1.3.5.1 Fast-Scan Cyclic Voltammetry:

Voltammetry is a class of methods to analyze chemical compounds by measuring the current that pass through them when a voltage potential is varied, it is a potentiodynamicelectrochemical measurement. Cyclic Voltammetry works cycling through two different voltage potential and measuring the hysteresis current cycle through the analyte. The voltammogram is the plot of the current passing through the analyte and the voltage difference.

Fast-scan cyclic voltammetry (FSCV) is a high scanning rate cyclic voltammetry, this allows the rapid acquisition of a voltammogram within fraction of seconds (usually about 10 Hz). This high rate acquisition allows to trace dopamine into the brain and following dopaminergic projections is possible to see the balance of dopamine release and dopamine reuptake. The framework to interpret these evoked dopamine responses resides in the Michaelis-Menten model (M-M) (K. A. Johnson & Goody, 2011). The M-M assume that the dopamine release rate is constant during the stimulation and that the dopamine reuptake occurs through dopamine transporters within the M-M model of enzyme kinetics. Improved methodologies to be used as DBS control variable has been developed, as an improved version

of the M-M model to simulate heterogeneous regional dopamine responses following manipulation of duration, frequency and dopamine pharmacology (Harun, Grassi, Munoz, Torres, & Wagner, 2015). In another study (Shon et al., 2010) with a large animal model (pig), they simulate the human STN-DBS neurosurgery and used a FSCV with a carbon-fiber microelectrode (CFM) implanted into the striatum to monitor the dopamine release evoked by electrical stimulation at a human DBS electrode implanted into the STN. Optimal dopamine release in the striatum of the pig was obtained with frequency into the therapeutic range of human DBS (120-180 Hz). A study (Chang et al., 2013) tested a LFP closed loop DBS on the rat brain, demonstrating the release of dopamine during a DBS stimulation with various frequencies, as shown in Figure 11.

These studies shows that with dedicated measuring electrodes it is possible to use the voltage cycle directly generated by the DBS stimulation to trace the dopamine in the brain and use it as a control variable.

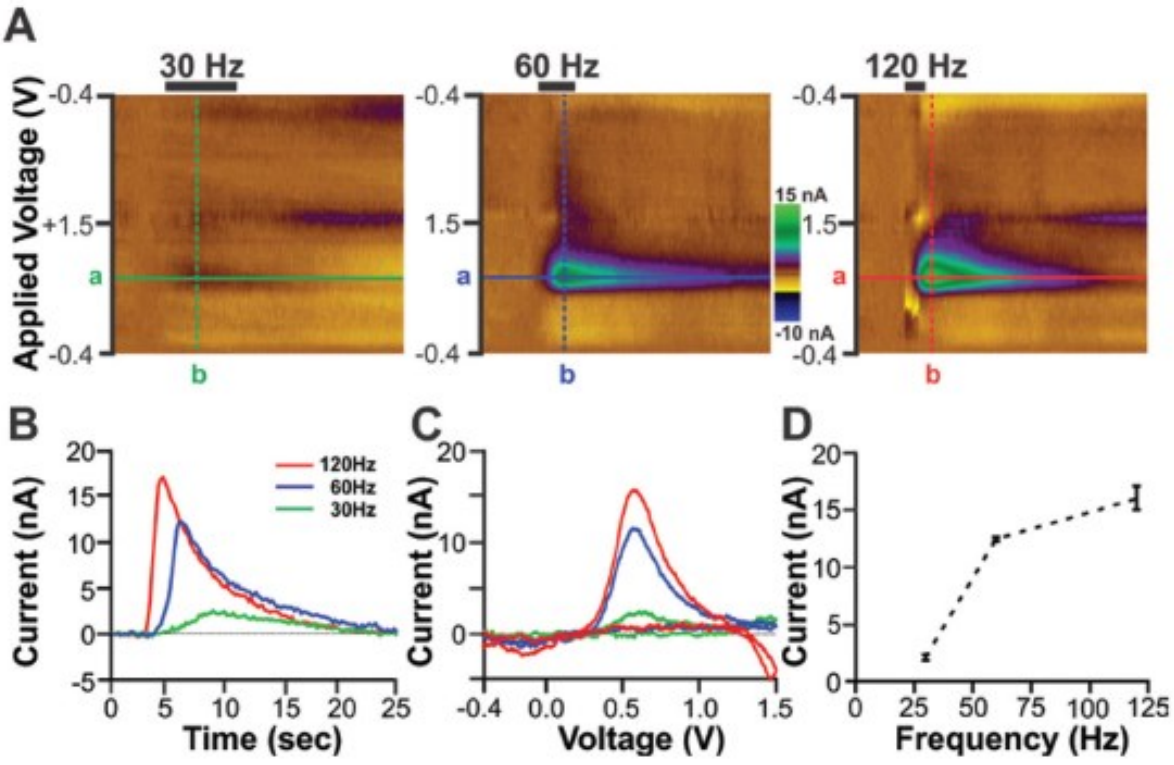


Figure 11: Voltammogram of dopmanine release in the STN (Modified from Chang et al., 2013).

1.3.5.2 Single unit recording (SUR):

Single unit action potentials (AP), induced change in electrical potential of a neuron, could be isolated and studied with SUR using microelectrodes applied directly in various area of the brain. A study (Brown, 2003) reveal the presence of two principal modes of synchronized activity within the human subthalamo-pallidal-thalamo-cortical circuit under 30 Hz and above 60 Hz during the execution of tasks

(i.e. a joystick maneuver task). These two frequency modes are inversely affected by movement, consistent with opposing actions, and differentially expressed according to the prevailing level of dopaminergic activity. In another study (Lettieri et al., 2012) they used the microelectrode placed in STN during DBS implantation surgery to extract neurophysiological data (spike number, mean firing rate, pause and burst index) during both local and general anesthesia (the patients had undergone re-implantation of the electrodes), even if in this case the aim of this practice was to provide a better stereotactic guidance in patient on general anesthesia.

1.3.5.3 Electrocorticography (ECoG):

ECoG is an invasive technique that uses an array of electrodes placed directly on the surface of the brain to record the local electrical activity of the cerebral cortex. The corticobasal pathways hyperactivity is an hallmark of PD (Janssen et al., 2014) and the lack of shielding role of dopamine between cortical to subcortical structures could be the cause of undamped and unstable motor control by the patient (Canessa et al., 2016). This cortical activity could be measured with ECoG and, even if it lacks the information of basal ganglia, study shows that could be used as a control variable: in nonhuman primates they applied a subdural grid on the motor cortex, assessing beta-activity of the area (Rosin et al., 2011). ECoG was also used to monitor dyskinesia and gait parameters (e.i. speed and duration) or even speech recognition(Swann et al., 2016), (McCrimmon et al., 2018), (Herff & Schultz, 2016). Through ECoG was possible to see a decreased of beta phase-amplitude coupling (PAC) the motor cortex during rest tremor (Qasim et al., 2016) and also bradykinesia in akinetic patients (de Hemptinne et al., 2015). Drawbacks from this method are the cortical bet-PAC is altered by movement preparation and execution (de Hemptinne et al., 2015) and also the particular PAC method and his time-frequency analysis could introduce artefacts due to armonic and nonsinusoidal neural dynamics in PD patients (Pittman-Polletta, Hsieh, Kaur, Lo, & Hu, 2014).
A big concern, also, resides in the invasiveness of the subdural electrodes grid, and the risks of hemorrhage and infection caused by the implantation surgery,

On answering the initial questions about FSCV, SUR and ECoG is possible to say that even if the system correlate with the physical state and the system does not require the patient participation, the battery consumption, the customization and the toleration by the patient are debatable but the hardware addition to the DBS systems surely encumbers more the patient and the additional power request of the system. More importantly, the main drawback of these systems is the alteration of the surgical procedure and the addition of new implants to the patient. Modifying a safe and long established surgical procedure adding other subcranial to subcutaneous permanent invasive electrodes to the patient may pose significant health risks.

1.3.6 Other forms of closed-loop in PD

Closed-loop system could also be used to detect festination and falling, in the first case providing a haptic/auditory feedback to help the patient to recover an effective gait, if this is not enough and they fall they could communicate with caregiver support to provide help ("REMPARK: Personal Health Device for the Remote and Autonomous Management of Parkinson's Disease (REMPARK)," 2018).

1.4 Point of Care Research

Point of Care Research (POC-R) is a new approach to study design that embeds trials into clinical care(Sara Marceglia, D'Antrassi, Prenassi, Rossi, & Barbieri, 2018). It is uniquely positioned to pragmatically compare two or more approved treatment options or strategies that are considered to be equivalent (in equipoise). Recruitment and randomization are accomplished at decision points in clinical care. Customized order-entry screens in the VA electronic medical record (EMR) allow for minimal disruption. A provider selecting between available treatments, who has no preference for one over the other, is prompted to learn more about the study. After reviewing a brief summary of the trial, the provider may give permission for the research team to approach the patient for consent to participate. Those patients who consent to be randomized are assigned to a treatment arm, and orders for the assigned treatment appear in the EMR. At this point, care returns to the clinical provider, who continues to treat the patient without deviation from usual care or interruption by research staff. Patients who do not agree to randomization may choose to allow their clinical data to be utilized. Study data collection is accomplished by automatically extracting information from the EMR, and includes clinical endpoints, deviations from treatment protocols, and patient compliance.

2 Objectives

2.1 Rationale: the need of monitoring PD patients

Controlling fluctuations, especially in the later stages of the disease, is crucial for PD patients. Constant feedbacks are required to change the therapies in a responsive manner. DBS, even with the possibility of been nearly real-time responsive, is, right now, relegated to a normal cycle of clinical ambulatory tuning: the patient goes to the physician (or vice versa) and the new parameters are reprogrammed into the device, until a new mapping is required, repeating this cycle (cDBS). cDBS remains an effective treatment but innovations that help the patients are still possible. Automatic *reprogramming* is one of the possibilities (Bronstein et al., 2011b), (Yu & Neimat, 2008), (Kupsch et al., 2011) particularly after DBS surgery, when patients face a fragile stabilization period, implying poor compliance and increased risk. While the technology to implement real-time changes of DBS parameters is a relatively simple and well-established, this Is not true for the assessment methodology to monitor the condition of the PD patient to obtain a feasible control variable, and all the methods proposed have some advantages but also present some reliability issues and implementation drawbacks. Another approach, supported in this thesis, is to use various assessment methods to create a more complete and reliable report of the motor condition of the patient: developing a patient-centered reporting system that follows the patient in everyday life and daily activities: the output of this system could be used not only as a control variable for a closed-loop system but as a patient-centered daily diagnostic support to the physician.

This type of system fits in well a complete telemonitoring paradigm, which does not only involve the automatic treatment feedback but also the possibility of a constant monitoring of the patient, even real-time responsive (e.g. emergency calls and on demand physician advice or a day-by-day diagnostic diary report freely accessible by the clinician and caregiver).

2.2 Main objective

This work aims to design and implement a system able to remotely monitor PD patients implanted with DBS systems in order to provide effective symptom evaluation. The results will:

(1) support research for new DBS therapies (Point of Care Research):

(a) *compare quantitative assessments of the various methodologies;*

(b) integrate heterogeneous data;

***(2)* Support patient's management through:**

(a) Caregiver support;

(b) Decision support system (DSS) for physicians

2.3 Specific objectives

To achieve the main objectives, the specific objectives targeted in this work are:

i. *Is it possible to implement a system for quantitative assessment of symptoms?*
ii. *Is it possible to integrate the quantitative assessment with other neurophysiological variables that can be detected through new DBS systems (LFP)?*
iii. *Is it possible to implement a support application for patients/caregivers able to have bidirectional communication with institutional or research systems?*

The validation has been performed throughout the achievement of the objectives by using a controlled experiment (Arlotti et al, 2018). The experiment was conducted on PD patients immediately after the implantation of DBS electrodes. In this "acute" setting we both tested the integration of quantitative assessment variables with neurophysiological data (LFPs), and the implementation of the mobile health application. Even though this validation has been done in a controlled hospital environment, the results we obtained allowed evaluating the system and the methodology. However, the system requires, in the next future, a more focused testing procedure with the patients in their home environment to further verify usability and robustness in longitudinal studies.

3 Objective I: Implement a system for quantitative assessment of symptoms

3.1 Introduction

This objective was achieved by testing the use of a wearable acquisition system composed by a single tri-axial wrist accelerometer to estimate the patient motor conditions and implementing a mobile app that store the sensor data and administers an e-diary to the patient in a small scale scenario(see 3.1.1). More specifically we tested whether using commercially available components, easy to wear (such as a smartband) and a smartphone application it is possible to track the patient's activity and bradykinesia. The following scenario was the starting point: a patient with daily fluctuating symptoms needs to be constantly monitored. The patient could be assisted by a caregiver and is free to move in his/her environment carry on his/her daily living activities during waking hours. A wearable sensor is applied to the patient, specifically an accelerometer smartband and a mobile device to collect self-reported data from the patient and to act as a hub to the remote system. A cloud service connects the mobile device with the remote system, where clinicians and researchers could access the patient data remotely.
Defining the scenario allowed us to define the requirements for both the sensors and the mobile application.

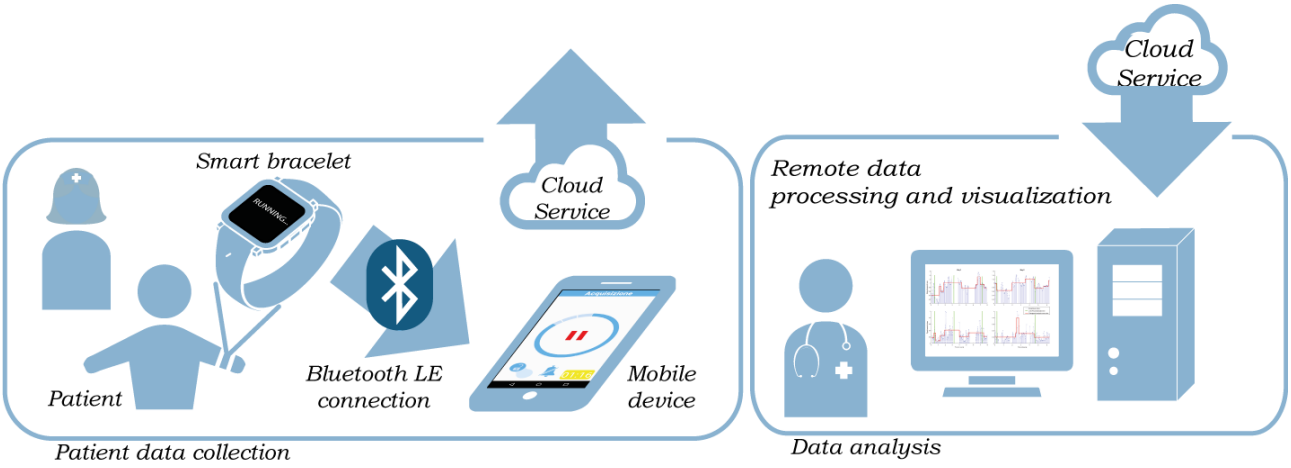


Figure 12: Prototypal system architecture.

3.1.1 Requirements definition

The system must work for at least one session (8 hours) without recharging the batteries during daily living activities. The system must be tailored to physically challenged patients, sometimes with impaired cognitive capabilities and without technological literacy.

The minimum requirements:

1. The system must work for at least 8 hours without recharging;

2. The system must be tested without interruptions during the daily living of the patient, in a near-ecological environment (the patient is still in a "controlled" hospital);
3. The patient-side-system must be operated nearly entirely by the patients, with little or no help from caregivers or relatives.

Additional requirement includes:

1. Easy to use interactive mobile systems, big screen and easy front-end graphical user interfaces;
2. Low-to-medium cost devices, with a particular regard of consumer-grade multipurpose equipment;
3. High modularity to adapt to different wearables, different mobile devices and different studies.

In this first phase the objective is to implement a system for quantitative assessment of symptoms. Steering from a classical tremor sensing algorithm, used in many studies (Ossig et al., 2016), (Bot et al., 2016), (Parra et al., 2013), the study tested two algorithm to assess bradykinesia for akinetic patients through 4 to 8 hours' trials using the accelerometric data from the wrist. To test the additional requirement number 2 the study tested two different wristband devices, a consumer-grade available multipurpose smartwatch: the Pebble Time and a dedicated research smartband, the ShimmerSensing device. For the smartphone 2 different budget-grade phone were tested: Motorola Moto X Play smartphone, a more performing device with a relatively big screen (5.5" (140 mm) 1080 × 1920 pixel (403 ppi) IPS LCD) and a high capacity battery (3630 mAh Li-Po) and a Huawei Nova Young, with smaller screen and less capabilities.

The steps for objective I are:

1) Verify if the devices chosen satisfy the minimum requirements 1,2 and 3;
   Devices used:
   a) Pebble Time smartwatch;
   b) ShimmerSensing IMU smartband;
   c) Moto X Play smartphone;
   d) Huawei Nova Young smartphone;
2) Develop a smartphone app to:
   a) Acquire the smartband data;
   b) Acquire patient e-diaries;
3) Test 2 different algorithm to assess dyskinesia with akinetic post-surgery DBS patients hospitalized;
4) Test patient e-diary acquisition with the same patients.

Due to requirement 3 this study choses the Android OS as smartphone based app, the language used is android native.

3.2 Methods

3.2.1 Experimental hardware setup

IMU are inexpensive, small and reliable sensors. When dealing with movement, these devices can be used during daily living activities in an ecological environment, embedded in bracelet, anklet or belts. These sensors don't offer a clear postural picture as a combinations of static room motion analysis setup like a multi camera acquisition system.
An automated accelerometric analysis on the movement of the patient does not require patient training, nor berate the patient with recurring tasks with the sole exception on wear the sensor during the activities of the day. Due to the particular nature of our study subjects, the hospitalized post-surgery DBS patients, a wrist worn accelerometric sensor was chosen; this due to the fact that the patient tends to stay bedridden, with only sporadic short walks, so only the arms are relatively unconstrained during the day. Wrist worn accelerometric sensor are well tolerated even after a period of prolonged wearing by the patients in hospital and at home or homecare environment, so they tend to not berate the patient (Fisher, Hammerla, Rochester, Andras, & Walker, 2016).

3.2.2 Pebble Time Watch

Figure 13: Pebble Time Smartwatch with accelerometer sensor reference.

Pebble Time is a programmable smartwatch running a proprietary operative system (OS) called Pebble Operative System, version 3.0. The Pebble time CPU is a one core Cortex M4, with 96 kB of RAM, 32 kB dedicated to the apps, with 24 kB for the app developers to use and 8 kB dedicated to the real-time scheduling supported by Pebble OS. The device has 2 MB of internal storage memory. The IMU sensor is a Bosch BMI160, the specific of this device are reported in Table 6, the Pebble OS supports only the accelerometer tri-axial sensor even if the chip includes the gyroscope. The accelerometer sampling supported by Pebble OS reach 100 samples/s or less.

Bosch BMI160

Parameter	**Technical data**
Digital resolution	Accelerometer (A): 16 bit Gyroscope (G): 16bit
Measurement ranges (programmable)	(A): ± 2 g, ± 4 g, ± 8 g, ± 16 g (G): ± 125°/s, ± 250°/s, ± 500°/s, ± 1000°/s, ± 2000°/s
Sensitivity (calibrated)	(A): ±2g: 16384LSB/g ±4g: 8192LSB/g ±8g: 4096LSB/g ±16g: 2048LSB/g (G): ±125°/s: 262.4 LSB/°/s ±250°/s: 131.2 LSB/°/s ±500°/s: 65.6 LSB/°/s

	±1000°/s: 32.8 LSB/°/s ±2000°/s: 16.4 LSB/°/s		
Zero-g offset (typ., over life-time)	(A): ±40mg (G): ± 10°/s		
Noise density (typ.)	(A): 180 (G): 0.008 °/s/√Hz		µg/√Hz
Bandwidths (programmable)	1600 Hz … 25/32 Hz		

Table 6: Pebble Time Sensor specifications (Sensortec, 2015)

The smartwatch support the development of custom C-based app that can even run as a background service, compiled by an online dedicated site ("Pebble Developers," 2018).

The device has a 64-color 1.25" e-paper color display with 144x168", 192 ppi resolution and 4 buttons, while it is not a big screen, especially for older people, the e-paper technology is low power and, being paper-like, relatively not influenced by bright light condition. Paired to the buttons it could be used to perform simple interactions. The device has a little vibrating motor to leave haptic feedback, used mainly for notifications and remainders.

This kind of smartwatch, due to the limited storage memory, are meant to be used always paired to the smartphone through a Bluetooth 4.0 connection; the wrist device act as a quick access frontend and accelerometric data provider, and the mobile device provides a connected hub feeding messages, notifications, remainders and other computationally intensive services, like analyzing the sensor output of the smartwatch. The proprietary mobile phone app that act as a service to communicate with the smartwatch, after the initial installation and pairing does not require further interaction. The Android edition supports intent and queued messages, making it possible to interact with other apps, for this framework a custom Android native app was developed and described in Section 3.2.6, exploiting this interaction.

Pebble Time smartwatch custom app (PebbleTestBench):

This app was developed through CloudPebble, a C IDE and compiler working online via browser (it was used Google Chrome, http://cloudpebble.net, 2016). When activated Figure 14.C through the central button it acquires 100 samples every seconds of tri-axial accelerometric data, until deactivated Figure 14.B via the same button. During its acquisition cycle it sends through Bluetooth 4.0 packets of 5 rows of tri-axial time-stamped data (16 bit, 3 axis, 5 rows: 240 bit plus a 64 bit timestamp: 304 bit every 5 seconds, a mean of ~61 bit/s of useful data). This system is power heavy on the smartwatch side

due to the 100 samples/s acquisition and the continuous Bluetooth interaction, even so, repeated tests showed that it can easily sustain 8 to 10 hours of continuous data acquisition if recharged correctly. The criticality, not due to power issues as anticipated, was with data loss: the high computational load of acquiring, storing and sending the tri-axial information coupled with a multipurpose real time OS (RTOS) was sometime too much for the device. This issue was addressed resampling the data at 80 samples/s.

Figure 14: Pebble Time custom accelerometric acquisition app. On the left, A: OS menu selection; Center, B: App frontend before acquisition start; on the right, C: acquisition running.

3.2.3 ShimmerSensing IMU/EMG

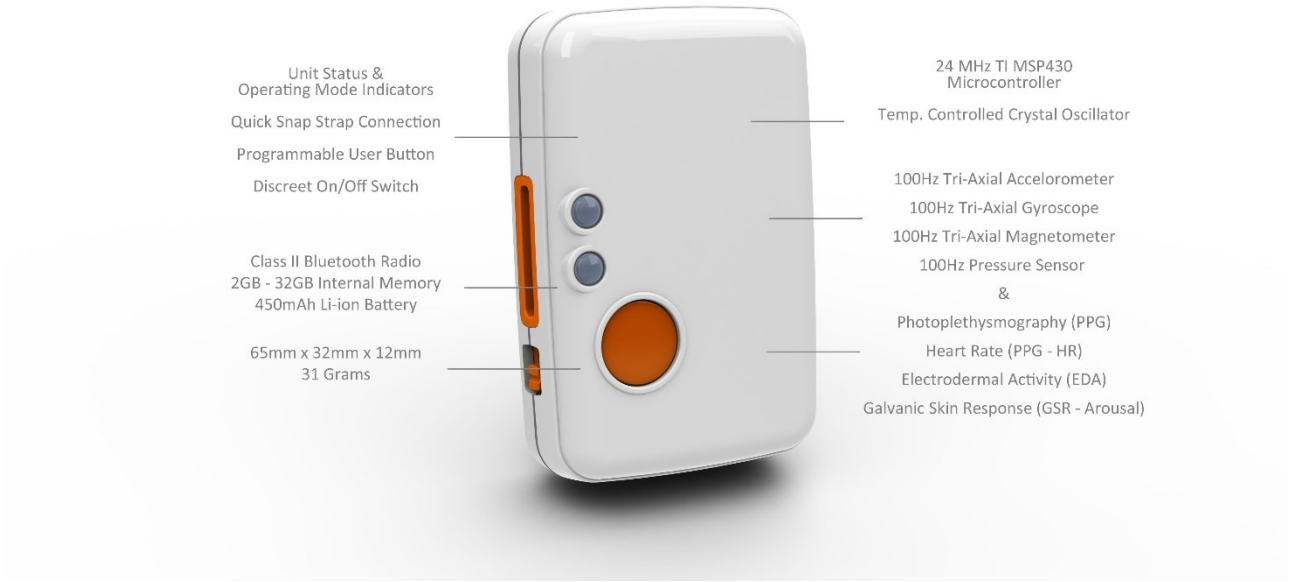


Figure 15: On the top: ShimmerSensing bracelet with technical characteristic; bottom: reference frame for the sensors.

The second smartband is a research-grade (even if with a relatively affordable price but with limited synchronization capabilities) device. The device is equipped with a 24 MHz MSP430 CPU with 16 kB of RAM and 256 kB of internal storage, it also has a large storage internal expansion capabilities (it has an internal microSD slot) and a JTAG debugging mode with a specific connector, giving the researcher the means to reprogram the internal firmware.

The sensors included on the device are 1 IMU (wide range accelerometer and magnetometer), a low noise accelerometer, a gyroscope and a pressure sensor (not used and not reported in Table 7).

STMicro LSM303DLHC – Wide range Accelerometer

Parameter	**Technical data**
Digital resolution	Accelerometer (A): 16 bit Magnetometer (M): 16 bit
Measurement ranges (programmable)	(A): ± 2 g, ± 4 g, ± 8 g, ± 16 g (M): ± 1.3, ± 1.9, ±2.5, ± 4.0, ± 4.7, ± 5.6, ± 8.1 Ga
Sensitivity (calibrated)	(A) 1000 LSB/g at ± 2g (M) 1100 LSB/Ga at ± 1.3
Noise density (typ.)	(A): 27.5 mm/s (M) 0.0081 normalized local flux
Operating current	110 μA

Kionix KXRB8-2042 Low noise Accelerometer

Parameter	**Technical data**

Digital resolution	Accelerometer (A): 16 bit
Measurement ranges (programmable)	(A): ± 2 g
Sensitivity (calibrated)	600 ±18 mV/g
Noise density (typ.)	(A): 5.09 mm/s
Operating current	500 μA

Invensense MPU9150 Gyroscope

Parameter	**Technical data**
Digital resolution	Gyroscope (G): 16 bit
Measurement ranges (programmable)	(G): ± 250, ± 500, ± 1000, ± 2000 dps
Sensitivity (calibrated)	(G): 131 LSB/dps at ± 250
Noise density (typ.)	(G): 0.0481 dps
Operating current	3.5 mA

Table 7: ShimmerSensing sensors specifications, ("Shimmer3 Spec Sheet V.1.6," n.d.)

All corioli force gyroscopes, the common commercial sensor technology, consume considerably more power than accelerometers and magnetometers: in Shimmer IMU they are built in a different chip to be deactivated to save battery.

The device could acquire data at 218 samples/s, reprogrammable for other sampling frequency too. Initial testing revealed that even with 200 samples/s for all the sensor activated and streaming the data via Bluetooth they could last 8 hours, provided they have been fully charged.

3.2.4 Smartphones

The two smartphones (Figure 16) technical specs are compared in Table 8.

Figure 16: Smartphones used, on the left Motorola Moto X Play, on the right Huawei Nova Young.

	MOTO X PLAY	**NOVA YOUNG**
Manufacturer	Motorola Mobility	Huawei
Series	Motorola Moto	Nova Young
Form factor	Slate	Slate
Dimensions	148 mm x 75 mm x 10.9 mm	143.8 mm x 72 mm x 8.35 mm
Weight	169 g (6.0 oz)	150 g
Operating system	Original: Android 5.1.1 "Lollipop" Current: Android 6.0.1 "Marshmallow" (For Droid Maxx 2) Android 7.1.1 Nougat (For Moto X Play)	Android 6.0 "Marshmallow" with Emotion UI 4.1
System on chip	Qualcomm Snapdragon 615	Cortex-A53 MediaTek MT6737T
CPU	1.7 GHz 64-bit Octa-core	1.4 GHz Quad Core
GPU	Adreno 405	Mali-T720MP2
Memory	2 GB LPDDR3 RAM	2 GB LPDDR3 RAM
Storage	16 GB	16 GB
Removable storage	microSD up to 128 GB	Micro SD up to 128 GB
Battery	3630 mAh	3000 mAh
Display	5.5" 1080 × 1920 pixel (403 ppi) IPS LCD	5" 720 x 1280 pixel (294 ppi) IPS LCD

Table 8: Smartphones comparison from official manufacturer sites (https://www.motorola.it/products/moto-x-play consulted on November 2018, https://consumer.huawei.com/it/phones/nova-young/specs/ consulted on November 2018).

As stated before, these two smartphones were chosen to represent a medium-budget and low-budget system to validate the framework from an economic savvy perspective, with small screens, long

computational times and relatively small battery capabilities.

3.2.5 Experimental protocol

We enrolled 13 hospitalized PD patients four days after the surgery for STN DBS electrode implantation in the Neurosurgery Unit at Fondazione IRCCS Ca'Granda Ospedale Maggiore Policlinico in Milan from March 2016 to January 2017 without experiencing any surgical complication. The study was approved by the institutional review board and conformed with the Declaration of Helsinki (ClinicalTrials.gov identifier: NCT02154724), and all patients provided written informed consent to the experimental procedures.

The recording session varies from 4 to 8 hours on two days (Session 1: day 5 and Session 2: day 6 after the surgery), in total we recorded 20 sessions. The patients, at the beginning of day 5 and day 6, were left without therapy to assess a baseline OFF state, then, after the bracelet was worn, their therapy was resumed (L-DOPA and DBS) regularly. After that, the patient wore an adaptive LFP based DBS external prototype (aDBS, explained in 1.3.4) in a pouch and the wrist sensor, they were given the smartphone and they initiated the acquisition session aided by a caregiver. On the Day 5, the external prototype was set only in "recording" mode (i.e., no stimulation delivered, LFP recordings on). On Day 6, the external prototype delivered beta power-driven unilateral aDBS on the selected side and, at the same time, recorded and stored LFPs. Both experimental sessions begun after 12 hours of medication withdrawal. Each experimental session lasted from 4 to 8 hours (aDBS stimulation and recording lasted 7 to 8 hours), during which the patient underwent the following assessments performed by an experienced neurologist:

1- Baseline assessment: after 12 hours medication withdrawal, Unified Parkinson's Disease Rating Scale, part III, motor part (UPDRS III), and Unified Dyskinesias Rating Scale (UDysRS), part 3 and 4;

2- Peak dose/Med ON 1: when the first administration of the patient's usual morning medication was effective (about 45-60 minutes after medication intake depending on patient's response), UPDRS III and UDysRS, part 3 and 4.

3- End Dose/Med OFF 1: at the end of the effect of the first administration of the patient's usual morning medication, UPDRS III and UDysRS, part 3 and 4.

4- Peak dose/Med ON 2: when the usual second levodopa dose was effective (about 45-60 minutes after medication intake), UPDRS III and UDysRS, part 3 and 4.

5- End dose/Med OFF 2: at the end of the usual second levodopa dose, UPDRS III and UDysRS, part 3 and 4.

Before the experimental sessions all the real time clocks in the wearable and the mobile device are automatically set using the internet time of the server "time.windows.com".
At the beginning of the experimental session, the patient, aided by the caregiver, is asked to wear the wrist sensor, (the Pebble Time is placed on the wrist as shown in Figure 17, the Shimmer device is placed on the wrist with the connect port opposite to the hand) and being in close proximity to the mobile device during daily living activities. Every time the remainder alarm goes off, the patient access the smartphone and answer the e-diary multiple choice questionnaire.

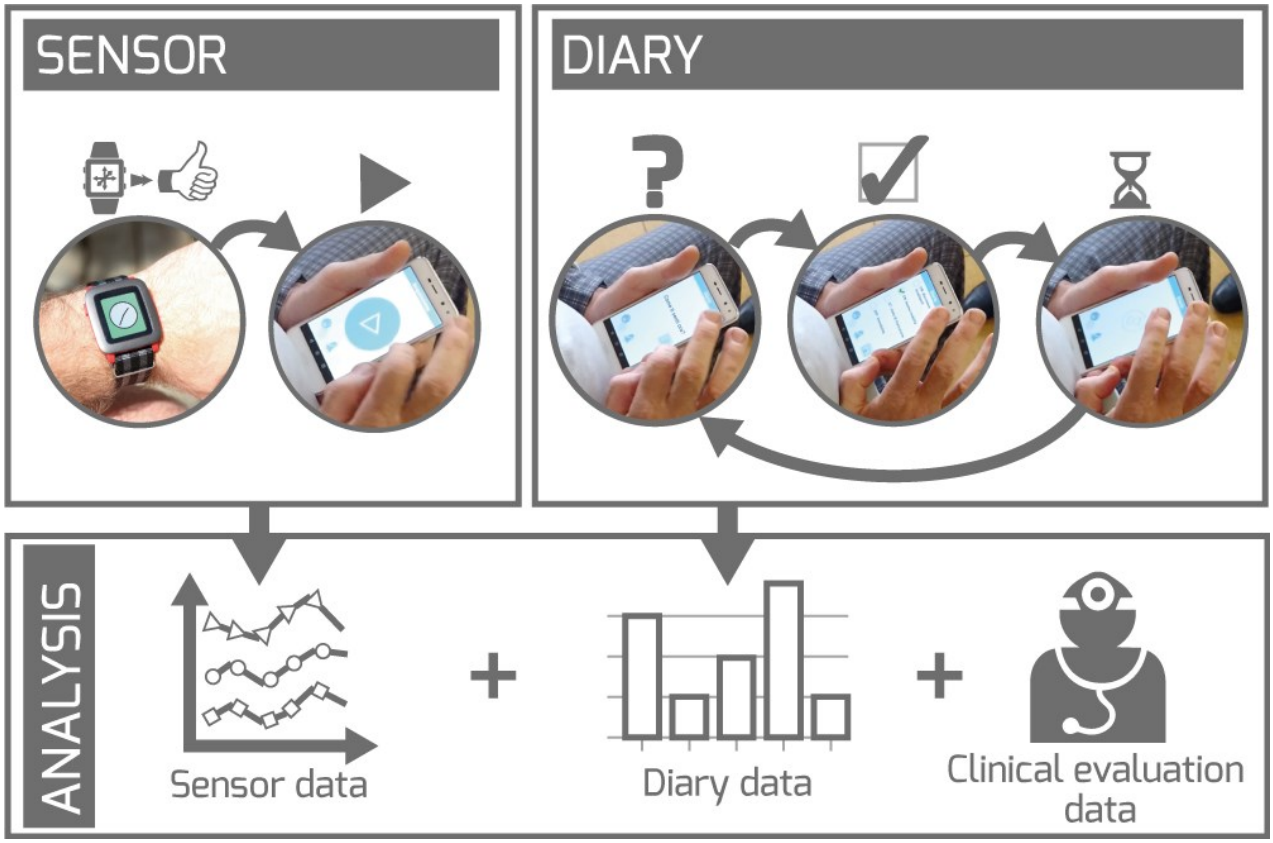


Figure 17: the experimental setup framework, wearable sensor acquisition and diary administration.

Every 30 minutes the e-diary was filled in, two question items, translated in Italian were presented:

"Come ti senti ora" (how do you feel?)
"ON: Discinesie invalidanti" (ON: invalidating dyskinesia)
"ON: Buona mobilità" (ON: good mobility)
"TS: stato di transizione" (TS: transition state)

“OFF: Immobilità” (OFF: Immobility)

And

“Quale è stata la tua attività principale nell’ultima mezz’ora?”

What was your main activity in the last half-hour?

“Camminare” - Walking

“Conversazione” - Talking

“Pasto” - Meal

“Relax” - Relax

“Dormire” - Sleeping

“Altro” - Other

Patients did not receive a standardized training to the question, but only a brief explanation by the caregiver.

Between assessments, the patient was free to move and to carry out his/her normal activities (e.g., walking, eating, watching TV, sleeping), while the aDBS external prototype was comfortably placed in a pouch.

The Caregiver aided the patient with the starting of the session, he/she stopped the session if any adverse or unexpected event occurred, and, at the end, he/she exported the data to the local memory repository, and sent it to the researcher remote database. A patient could take all the tasks of the caregiver role by him/her self but due to the harsh test condition (post-surgical DBS patients with late stage PD), these tasks were delegated to the caregivers.

The physician did not interact directly with the system in this preliminary stage, but he/she only evaluated the patient (aided by standardized clinical indexes, e.g. UPDRS). The Researcher, at the end, downloaded the data and performed the analyses.

The Researcher created a new database repository for each session, configured the session length (e.g. 8 hours, and the diary administration intervals (e.g. 30 minutes).

At the end of the session data was downloaded and analyzed by the researcher and a clinician asked the patients if the smartwatch was uncomfortable during the day (“Il braccialetto le ha dato fastidio durante la giornata?” options: “No” or “Sì” (“Yes”, in Italian), if the answer was “Sì”, please explain why).

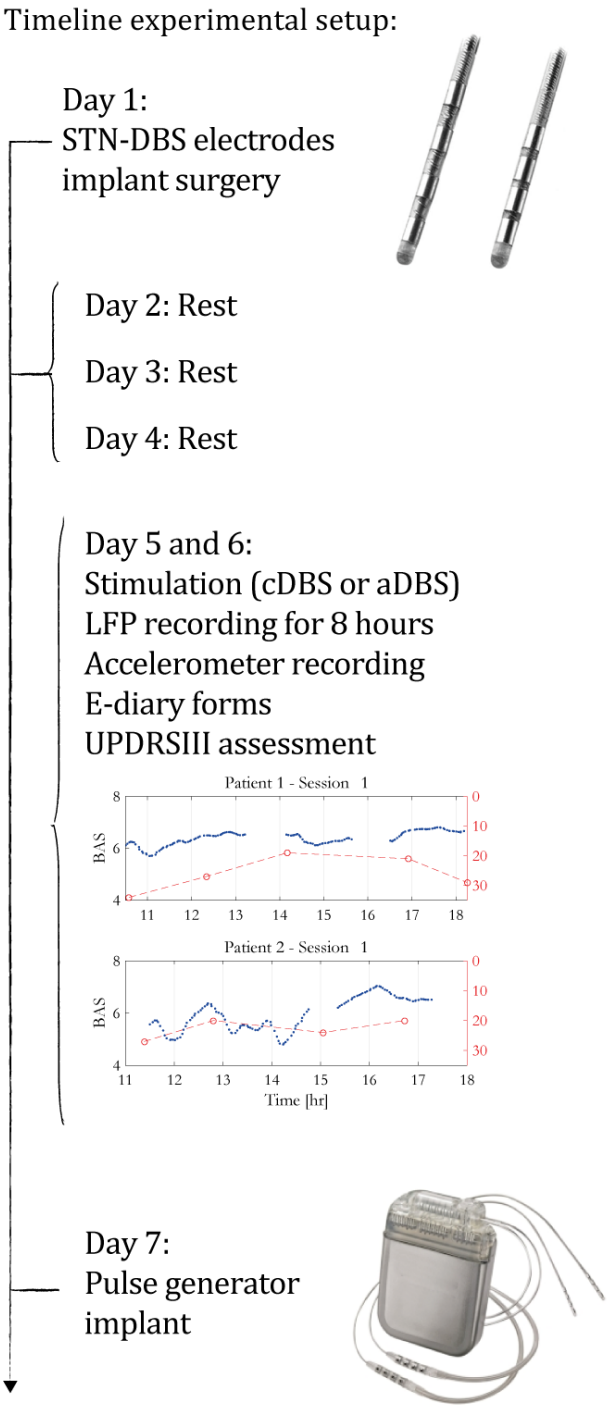


Figure 18: Timeline of the experimental protocol.

3.2.6 The patient app

The patient app (PAT) was developed with a patient-centered approach in mind, the users are statistically: old (>50 years) with motor and non-motor disabilities, the basic requirement were:

1. Visible and easy to interact user interface: big character font and big responsive interfaces (simple timer sliders, and big buttons);
2. Separation of concerns: 1 view access only 1 function;
3. Lock/unlock slide to keep the interaction to only voluntary movements;
4. Disaster recovery: even if the app is forcefully terminated, the data acquisition will continue, or, at least, the data already acquired will not be lost.
5. Modular: the architecture of the app must be easily adaptable to various wearables and multiple e-diaries choice.

3.2.7 The User Interface

To implement the User Interface (UI) with these requirements 3 main actors were found:

1. The patient;
2. The caregiver: he/she helps the patient with the device;
3. The researcher: he/she configures the app and respond to different emergency scenario (in case of misuse or malfunction stops the acquisition).

Figure 19: USE-CASE diagram for the UI of the app.

The user-interface was developed after some mock-up testing with hospitalized patients (Figure 19) and clinicians. It has three main pages, accessible with the slide left or right motion, using the Android Fragment navigation pattern. Accelerometer acquisition page, Diary acquisition page and the main menu page.

The app supports two languages, English and Italian, based on the local settings on the phone (in this study the settings were Italian, due to the nationality of the patients).

In Figure 20 the main UI is shown, a layer over the three pages shows the button used to silence the alarms (1) and the lock/unlock slide (2). Every page has a title, white on blue at the top, with the translated name of the page ("Acquisizione" for acquisition page, "Menù Principale" for main menu page and "Diario" for the diary page). The app has two entry points, clicking the app icon the user is presented with the acquisition page, also if an app notification is clicked the app opens with the diary page.

App configuration:

Sliding to the left main menu page is possible to configure the app.

Every new patient has a dedicated database, the researcher creates a new one when he/she access the "NUOVO" button on the main menu.

The app timers, accessible by the "TIMER" button in the main menu, may be regulated at the beginning

of every session, setting the session length and the interval between the administration of the patient e-diary (e.g. session of 8 hours and 0 minutes and diary interval of 00 hours and 30 minutes, this at total of means 16 diary administrations), after these operations, the system is ready to start.

Acquiring the IMU data:

Sliding to the center page, if the bracelet is correctly paired to the smartphone (this app works with Pebble Time and ShimmerSensing devices, using different backend class discussed in 3.2.8) it is possible to press the main "PLAY" button, if it is pressed for at least 2 seconds, the mobile phone vibrate and the acquisition will start. The acquisition page will show the count-down completion graphic (Figure 20.A), a count-down numeric timer on the bottom right (Figure 20.B) and the red pause button in the center. If pressed, the red pause button will start a scaling out animation, if the finger pressure will remain on the button the animation will end and the acquisition will stop, returning to Figure 20.A.

Diary page:

Every time the diary interval configured in the first step is reached, an alarm will sound and vibrate (if the volume of the phone and the vibration is on) and the diary page with a questionnaire item question is automatically shown. After deactivating the alarm with the silence button the patient could press the (Figure 20.A.2) button to proceed to the answer, right now only multiple choices answer are supported. Chosen the answer it is possible to proceed to the next item, or, if it was the last item it is possible to send to the database the outcome. After this operation a wait page is shown (Figure 22.C) until the next interval is reached. Questionnaires do not stack up, it is not possible to answer a questionnaire after its time interval has passed and another entry has taken its place.

Sending and exporting the data:

At the end of the acquisition session the caregiver, or a skilled patient, could access the main menu and export the database, saving it in a comma separated value text file into the smartphone local storage or directly send it via internet to the database system, in the latter case the database is exported and then sent.

The USE-CASE for the patient is limited to the acquisition page and the diary page; the main menu, even if accessible by all, is mainly used by caregivers and researchers, to limit the involuntary access to the sensitive operations (main menu buttons and the start/stop acquisition command) the lock/unlock slide was created, it activates or deactivates all the functions expect silence the alarms and the diary page (Figure 20.A). Visible locks as shown as a further remainder of this function.

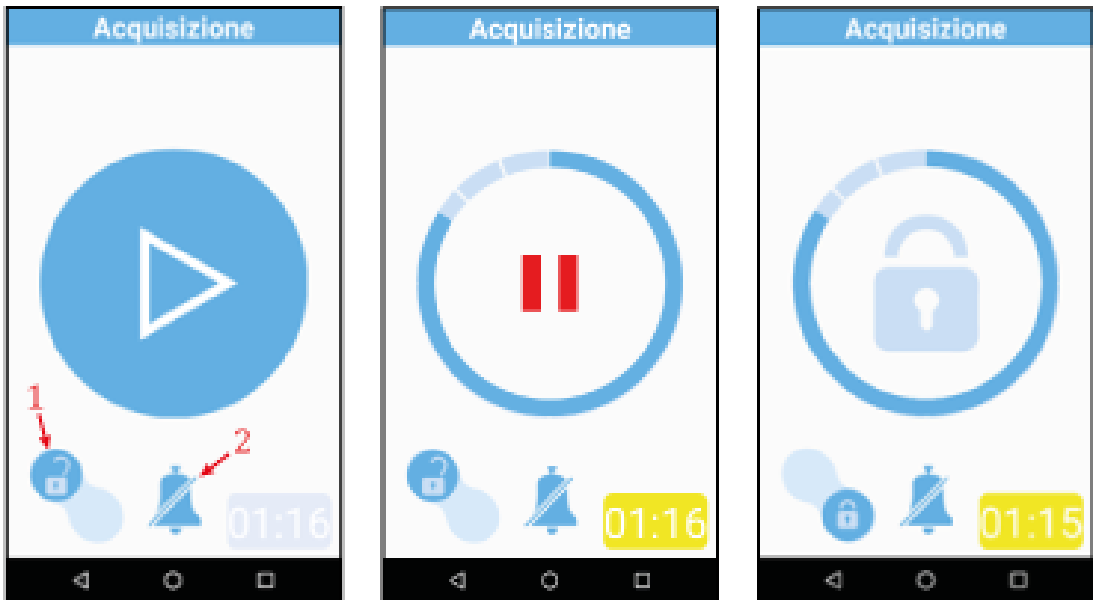


Figure 20: App accelerometric acquisition interface. A (left), start, 1: locking slide, 2: alarm stop button; B (center), acquisition started; C (right), acquisition started with locked interface.

Figure 21: App main menu. A (left), normal mode; B (right), Debug mode with locked interface.

Figure 22: App e-diary interface. A (left), question; B (center), answers; C (right), waiting for the next iteration of the e-diary.

3.2.8 The backend

The app backend is divided in three main packages:

Diary:

This package contains three main classes, the interface and its implementation DiaryAlarm are dedicated to implement the various sound or haptic (vibration) remainders. The DiaryParser class is tasked to read the Extensible Markup Language file (.XML) present in the resources of the app with the patient diary information and create the various Pages (object of the class Page) that forms the e-diary questionnaire visualized by the DiaryFragment.

```
<?xml version="1.0" encoding="utf-8"?>
<study name='pd-39' lang='it' >
    <page title='diary' type='question'>
        Come ti senti ora?
    </page>
    <page title='diary' type='radiogroup'>
        <radiogroup>
            <radiobutton>
                ON: discinesie invalidanti
            </radiobutton>
            <radiobutton>
                ON: buona mobilità
            </radiobutton>
            <radiobutton>
                ST: stato di transizione
```

```
            </radiobutton>
            <radiobutton>
                OFF: immobilità
            </radiobutton>
        </radiogroup>
    </page>
</study>
```

Figure 23: xml file example for the e-diary template.

The hierarchical structure is:

<study name='name_of_the_study' lang='international_code'> : This encapsulate all the pages of the e-diary, it has an attribute "name" to identify the study and an attribute "lang" to identify the language in which is written using international codes (e.g. 'it' for Italian, 'eng' for English).

<page title='diary' type='radiogroup'>: this tag identify every single page of the diary, in the order that are visualized by the diary fragment. The attribute "title" identify the page and the attribute "type" classify the page as a 'question', only the written question of the e-diary or an answering methodology as the type 'radiogroup', the only supported class for now; it means a multiple selection answer like shown in Figure 21.B. The question items and the possible answers are not limited, it is possible to do multiple question questionnaires, concatenating multiple pages tag.

Database:

The database package includes two classes used to create and instantiate a new SQLite local (resides in the local memory of the app) database: AccelerometerDatabaseContract and AccelerometerDbHelper, and a class to export the database class in a text file with comma separated values (".csv"), it also handles the communication with the remote system.

Core:

In this package reside the AcquisitionService class that creates a background service with an adapter to the wearable interface (AccelData, if it's Pebble Time it only instantiate a broadcast listener to the accelerometric data from the other Pebble Time proprietary app, if it's ShimmerSensing it implements all the acquisition drivers directly in the app code). This package also manage the SQLLite database transaction (it encapsulates rows of accelerometer data in batch transactions queries to the database management system to ease the memory writing load) and stores with the PATConfigBaseImplementation all the initialization parameters (it is task to parse and implement the right configuration xml file). Globals class is static global variable class, used sparingly mainly for debug purposes.

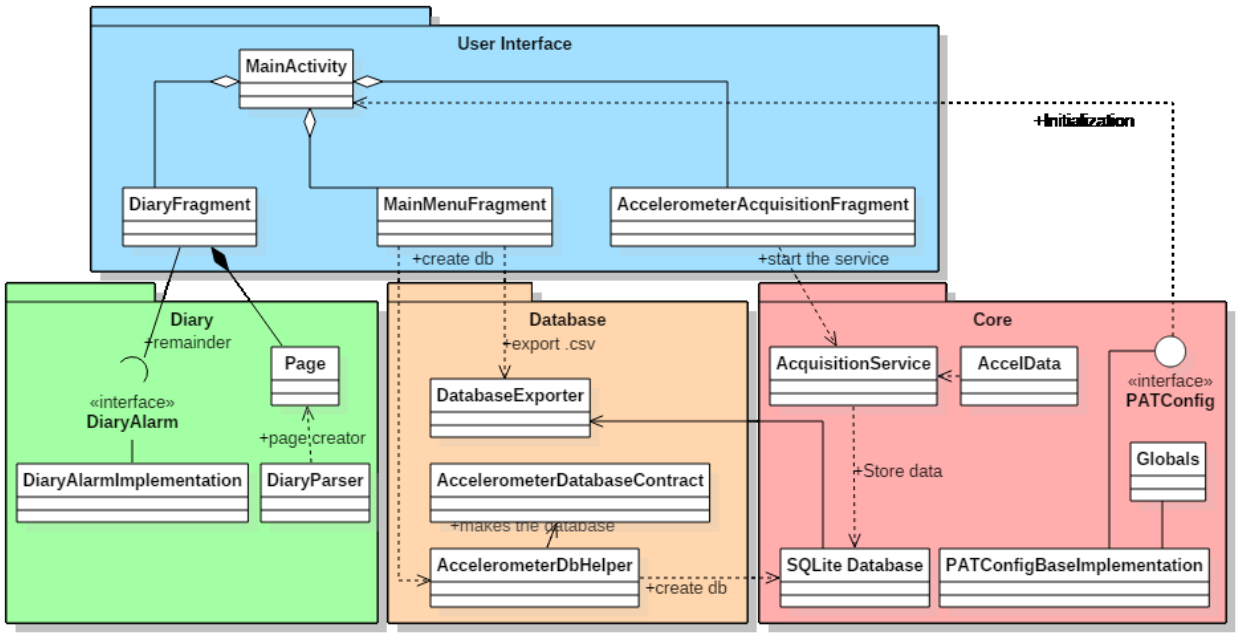


Figure 24: Class diagram of the App with the 4 packages: UI, Diary, Database and Core.

3.3 Data analysis

3.3.1 The Bradykinesia Accelerometric Score (BAS) algorithm:

The first algorithm tested is based on a FDA approved and patented research (US20110098608A1, 2011) adapted to be used with the Pebble Time smartwatch riddled with data loss. The algorithm was tested on 5 patients (4 sessions). As stated before, the patient was clinically assessed using the Unified Parkinson's Disease Rating Scale (UPDRS) part III, motor part that was correlated with the bradykinesia status obtained through the wearable equipment.

The algorithm calculates the Bradykinesia Accelerometric Scores (BAS) in data bins of 4 minutes. The BAS is lower when the patient is bradykinetic. The scores were further analyzed using a mean and variance changepoint analysis (Killick & Eckley, 2014) with a binary segmentation algorithm and a bayesian information criterion as penalty. The change-points and the mean values between 28 minutes (7 bins) of the BAS scores were then compared with the medical clinical evaluation (UPDRS part III, UPDRSIII), the L-DOPA administration time and the patient diary.

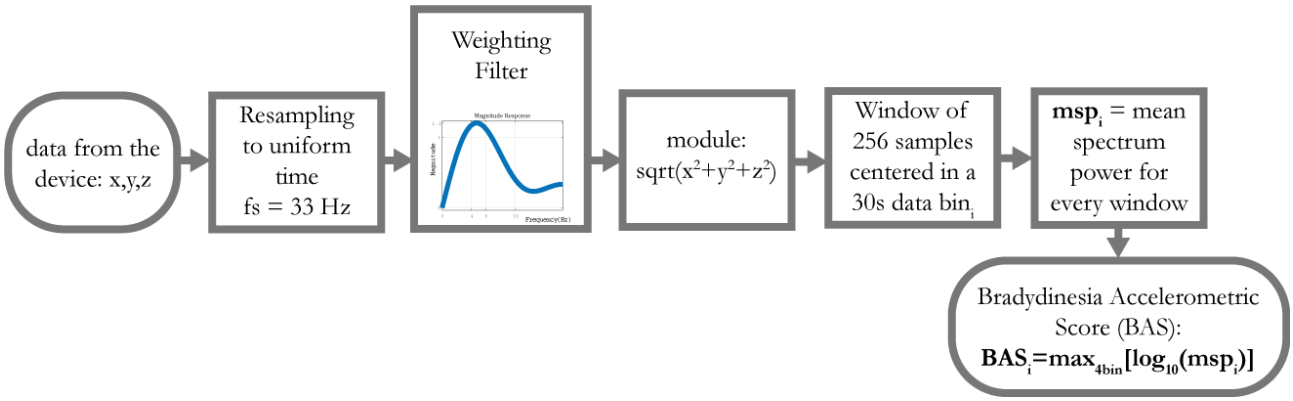


Figure 25: BAS algorithm chain.

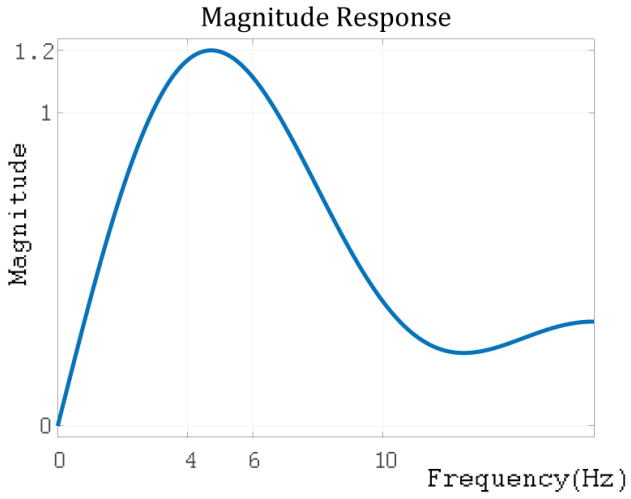


Figure 26: Impulsive filter response of the band-pass filter.

In Figure 25 the BAS algorithm is shown. Tri-axial data are taken, resampled at 33 Hz, then a pass band filter is applied. The particular impulse response of the filter is engineered to weight more the frequency around 4 Hz to 5 Hz, and linearly diminish the weight of the higher and lower frequencies (Figure 26, please note that the magnitude is not logarithmic). Then a module is applied and the data are divided in 30s bins. Around the maximum of these bins, a square window of 256 samples is placed centered with the maximum at the 128° sample. Then, the mean of the spectrum in these windows is calculated. The BAS is the maximum of the base 10 logarithm of these windows. The rationale behind this algorithm is the following: if a patient is bradykinetic, his/her maximum wrist acceleration during multiple bins will be consistently lower than the maximum acceleration during normal ON state bins: BAS value reflects this consistency. Since bradykinesia means the incapability to make fast movements, if in a sufficiently large time-frame (2 to 10 minutes) no such fast movements (and fast accelerations) are found, the BAS score is low, implying bradykinesia.

3.3.2 The Bradykinesia Index (BradIndex) algorithm:

This is a novel data analysis algorithm, developed for this study. It takes into account the repeated voluntary movement that the patient performs during the day (reading a book, using the smartphone, walking, eating, drinking, gesticulating when talking etc.) and compare similar repeated movements to quantitatively estimate the motor condition (e.g. turn the pages of a book it will be less swift and more time consuming in an OFF-bradykinesia related state).

The tri-axial accelerometric signal is taken as a module $A_{mod\,i} = \sqrt{(x_i^2 + y_i^2 + z_i^2)}$. A bandpass FIR filter is then applied in the band of 0.3 Hz and 8 Hz to remove the gravitational force and the high frequency not correlated with voluntary movement. After this operation, a narrow band-filter centered at 2 Hz is applied and the signal is fractioned in bins of 256 samples, divided by a hamming window overlapped at 128 samples. The sum of the signal in these bins is inserted in a time series and a peak detection algorithm is used to assess the notable spikes of this spectrum; this is done in order to isolate the voluntary movement within the session and to assess a possible candidate to be a recurring movement. A windowing of algorithm centered on these peaks is then applied to the original module signal (after the band-pass filter of 0.3 to 8 Hz), the window size is 600 samples (6 seconds). An autocorrelation function is applied and with another peak detection algorithm is detected the first local maximum after the absolute maximum; this is done to do isolate the recurring signal and to calculate their periods, every window that does not have a significant peak (both in amplitude and time-wise) is discarded. In the next phase the signal candidates are resampled according to the fastest peak detected, to discard some time related information to the signal, retaining only their shape; this is done to take into account the hypothesis that

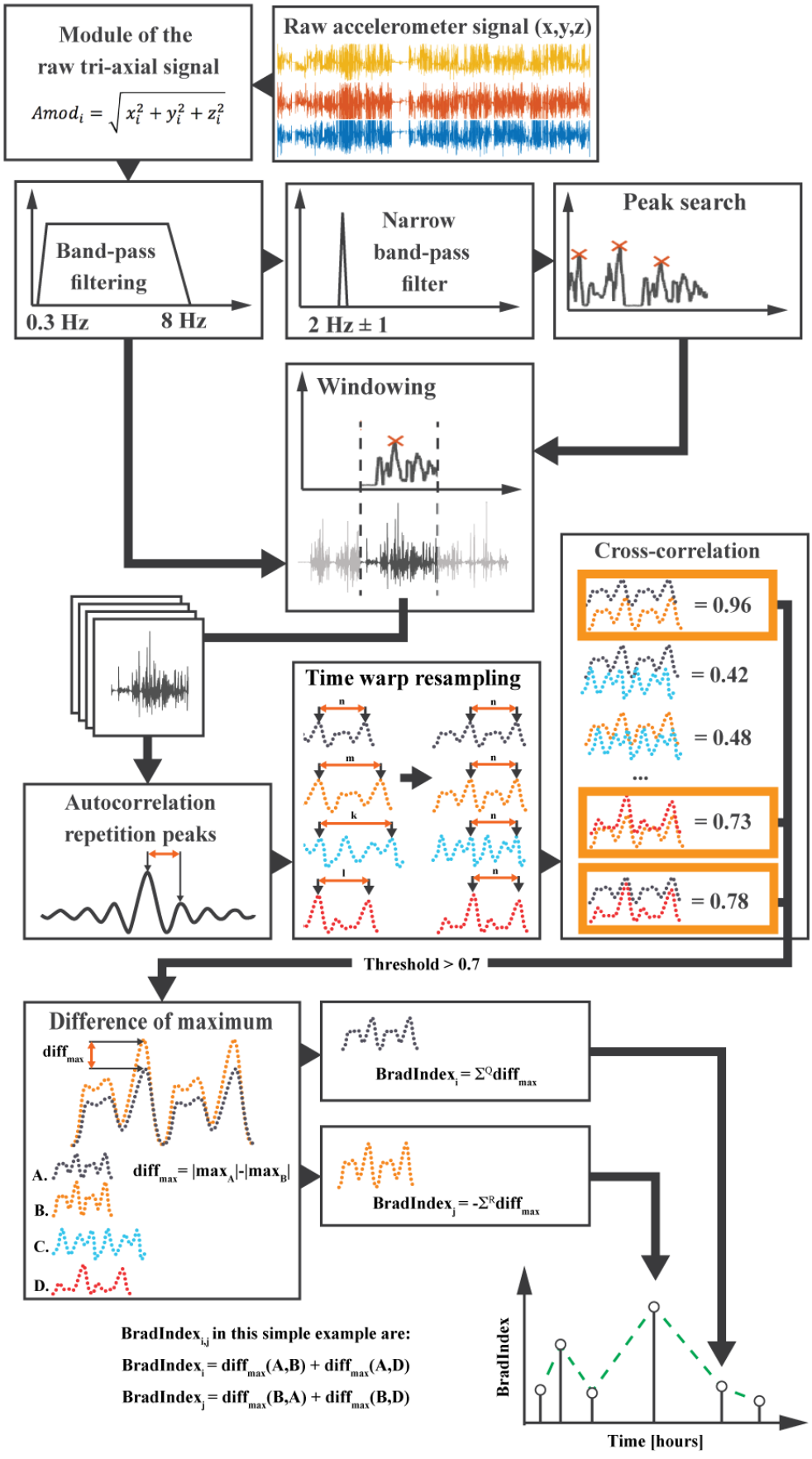


Figure 27: BradIndex algorithm chain.

the same repeated movement can show the same wave type through the day, but not the same frequency related to the motor status of the patient. In the last phase a cross-correlation is performed cycling the first signal window with all the other candidates, if the maximum correlation between two signals is above a threshold (>0.7, from 0 to 1) the difference of the maximum of the signal module is calculated, this measure is then added to the results of the other pairs above the threshold ($BradIndex_i$). The temporal maximum is preferred between the spectral density maximum for the hypothesis that a fast and not encumbered movement is done in one swift motion, instead of a slow protracted movement that accumulates energy with time. After this operation, every BradIndex is placed in a session timeline where the initial 2 Hz peak was detected and a moving average of 6 elements smooths the resulting BradIndex graph.

3.4 Results

3.4.1 Accelerometric analysis

In total, of the 13 patients, 2 were dropped (1 caused by data loss, 1 caused by a defective wristband strap). The wrist worn accelerometer sensors used were the Shimmer3 ECG/EMG (it also contains an inertial measurement unit, IMU) and the Pebble Watch Time smartwatch. The first was used for 5 patients, the latter for the initial 4 patients. Both these devices acquire tri-axial accelerometric data at 100 samples/s. In total were recorded 16 sessions, 3 were dropped in day 6 due to varying clinical schedule. 6 Patients have used the Motorola Moto X Play smartphone and 5 the Huawei Nova Young smartphone.

3.4.2 BAS algorithm results

Due to the data loss caused by the Pebble Time connection for the BAS algorithm every data time-series was resampled uniformly at 80 samples/s (even the ShimmerSensing wrist data, without measurable data loss). The Pebble Time, not having a capable on-device data storage, presented an additional data loss when the patient wander off from the smartphone due to scheduled exams or forgetfulness, an example of the BAS score with the missing data points are visible in Figure 28.
A changepoint analysis described in section 3.3.1 was then performed and the significative mean values extracted to be correlated with the UPDRSIII scores, the results were 0.541 ($p<0.004$, Pearson).

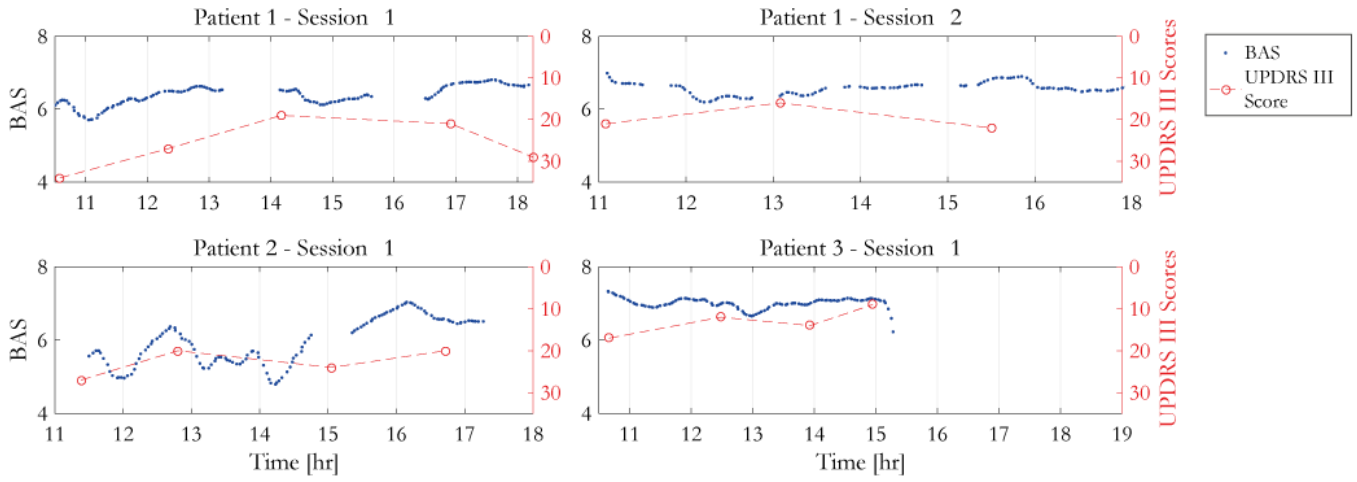


Figure 28: BAS and UPDRSIII for three patients and four sessions.
In blue the calculated BAS, in red, with the inverted y axis, the UPDRSIII scores.

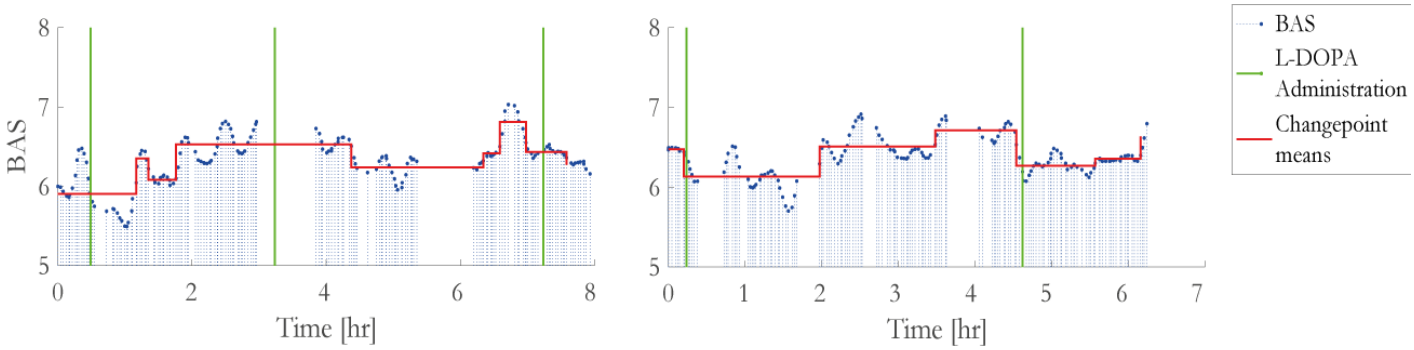


Figure 29: Changepoint means, in red, and L-DOPA administration time in green. BAS scores in blue.

3.4.3 BradIndex algorithm results

After the first algorithm steps some adjustment were made, a threshold was applied to the autocorrelation phase setting, it was chosen the 1/10 of the window size (60 samples) to be the minimum time where a repetition can occur, if some peaks are found inside that time frame they will be discarded and the next minimum exceeding the time limit is taken, all the other not discarded signals were resampled to match this time-frame. An example in Figure 30 shows the comparison of two pairs of correlating (maximum cross-correlation > 0.7) signals, after the time adapting resample. The arrows show the maximum used to calculate the $diff_{max}$.

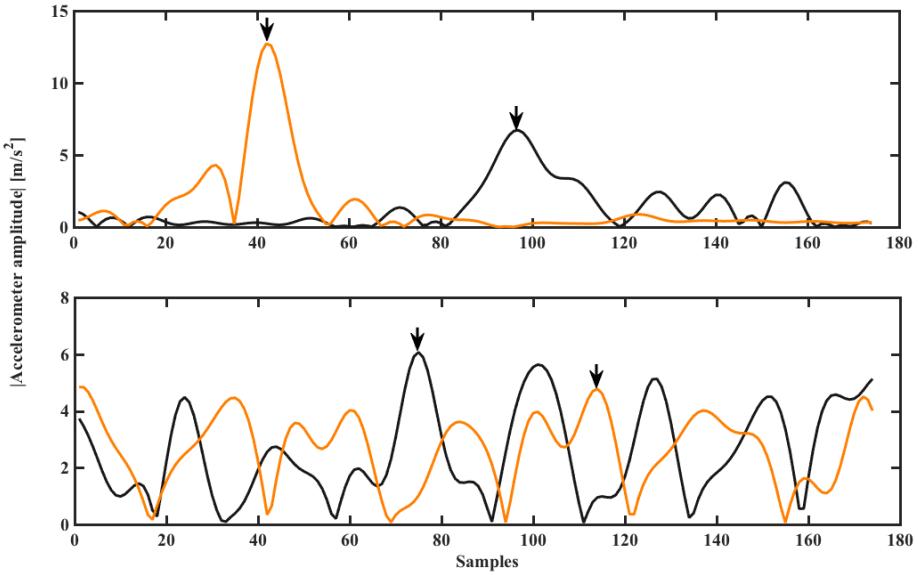


Figure 30: two data windows modules compared in the BradIndex algorithm. The arrows point at the maximum.

The BradIndex evaluated by the algorithm is shown in Figure 31, a moving average of 6 samples was applied at the end of the algorithm to smooth the transition; this was done to take into account the heterogeneity of all possible movement. After the smoothing the signals was compared to the UPDRSIII relative variation during the day; the maximum value of the Session is 100% and the lowest is 0%.The correlation between the two estimates (UPDRSIII variation and BradIndex) was calculated using Pearson correlation, evaluating only the nearest (time-wise) BradIndex to the UPDRSIII value, the resulting correlation is -0.500 0 ($p < 0.0005$, Figure 4), the correlation on Session 1 is -0.573 ($p < 0.0005$) and Session 2 is -0.400 ($p < 0.005$). The inverse correlation is due to the fact that the BradIndex estimates movement capabilities, so it is proportionally inverse to the UPDRSIII value, were the highest numbers are related to severe symptoms.

To further the analysis, we have correlated the absolute UPDRSIII values (not normalized), as expected the results are not statistically correlated: -0.200 ($p < 0.13$, Pearson).

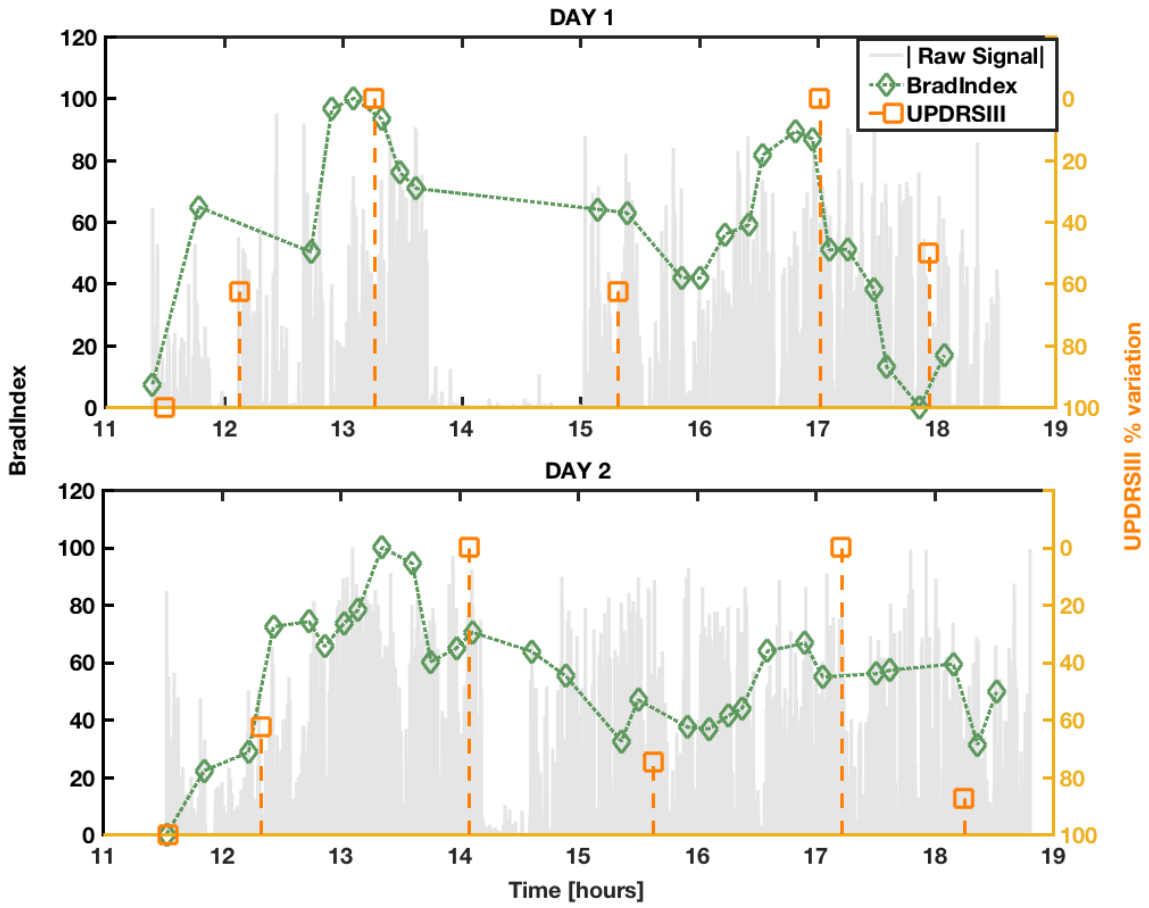


Figure 31: BradIndex results and UPDRSIII comparison of two session of one patient. |Raw signal| means the module of the three-axis accelerometric values.

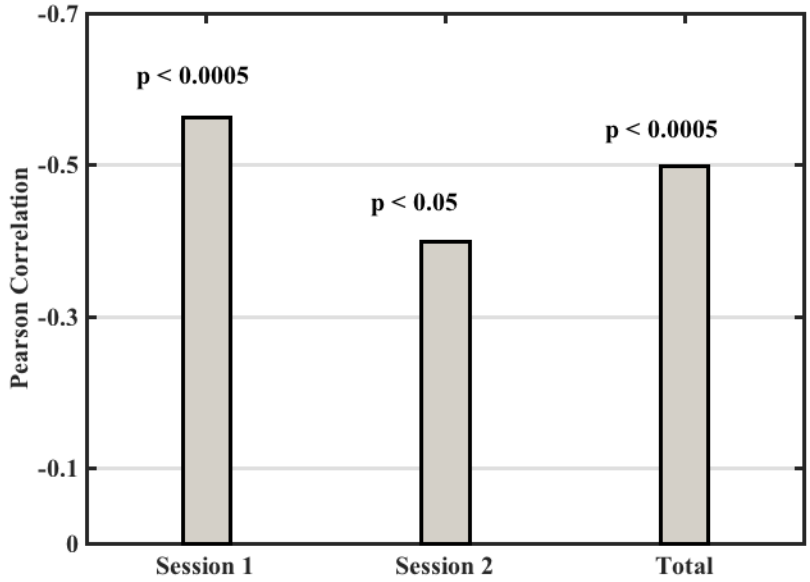


Figure 32: correlation values of the two sessions, in total -0.500, p<0.0005, Pearson.

3.4.4 Diary analysis

We analyzed the first recording session diaries of the four patients correlated with the normalized UPDRSIII scores screened in their relative time frame. A total of 21 paired data (UPDRSIII scores and Diary entries) were assessed. There were no "ON with Dyskinesia" state reported by the patients.
The diary answers were categorically sorted in a ranked order following Table 9:

Question Item (Italian)	Question Item (English)	Rank score
"ON: Discinesie invalidanti"	ON with invalidating dyskinesia	4
"ON: Buona mobilità"	ON	3
"TS: stato di transizione"	TS: transition state	2
"OFF: Immobilità"	OFF	1

Table 9: ranking order of the question items for self-reported motor condition.

This score was correlated with the UPDRSIII evaluation at the corresponding time frame.
The resulting value was significative (-0. 7416, $p < 0.0005$, Pearson) with the BradIndex accelerometric index (0.6042, $p < 0.05$, Pearson).
Figure 33 shows the means of the normalized UDPRSIII for all patient's states and the relative statistical error. There are significant differences between "OFF state" and both "transition" and "ON" states ($p < 0.05$, Wilcoxon). Conversely, there was no difference between the transition state and ON state.

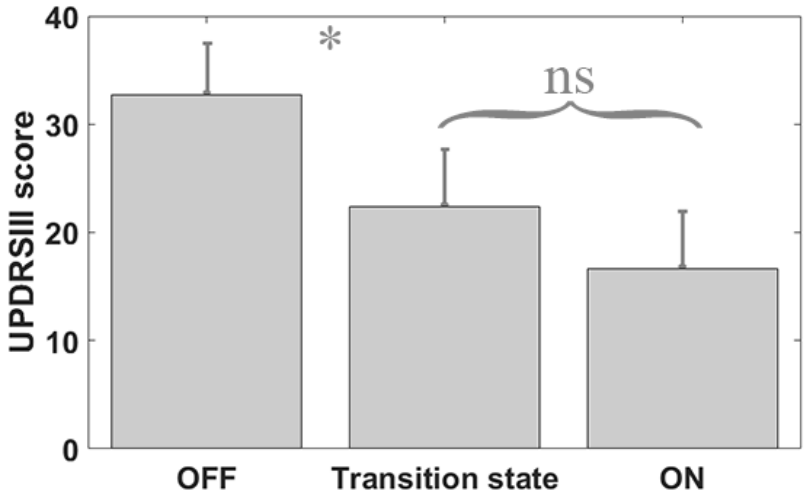


Figure 33: Normalized UDRSIII scores means for all the patient divided by self-reported state.
**: OFF and Transition State differences are significant (p < 0.05, Wilcoxon)*
but ns: Transition State and ON are not.

Diary activity data was not analyzed in this chapter, but in the next will be used extensively.

3.4.5 Patient tolerance of the devices and compliance

The final question "was the smartwatch uncomfortable during the day?" was always answered with a

“No”, regarding the smartwatch type (Pebble Time or ShimmerSensing). The smartphone App tolerance and usability was not assessed through patient questionnaire but the final e-diary data was used to gain a perspective on the compliance, in total all the expected 140 diary recordings were received by the system. Of them, 117 were filled-in whereas 23 arrived with null values, of these 23, 20 where filled by a single patient, it is worthy to notice that some of the Caregivers (family members mostly) aided the filling of the patient questionnaire even if instructed to not do that, answering for the patients, but it was not possible, with our resources, to monitor this behavior.

4 Objective II: Integrate the quantitative assessment with other neurophysiological variables that can be detected through new DBS systems.

The framework illustrated in this thesis was included in a STN-LFP adaptive DBS experimental protocol, illustrated in 3.2.5. In this chapter an integration between STN-LFP recordings, accelerometric data, self-reported data, and clinical assessments is analyzed and validated.

The aDBS device and methodology were already validated in a 2 hour study (Rosa et al., 2017), and at the time that this study was made there were no other studies with longer time frame. This experimental protocol terminated in January 2017 and after that, in 2018, a research paper comparing aDBS efficacy versus only L-DOPA intake in a time frame of 8 hours (Arlotti et al., 2018).

The device adapt the stimulation parameters using the synchronous presynaptic and postsynaptic activity of LFP recorded through the electrodes delivering the stimulation in a beta band oscillation (between 11 Hz to 35), modulated by L-DOPA administration, movement preparation and execution, motor planning and the electrical stimulation of DBS. In section 1.3.4 is shown how the LFP are accepted motor status predictor for PD, using this control variable the aDBS device tested linearly modulates the stimulation voltage according to the LFP power in the beta band, adapting moment-by-moment the electrical output of the stimulation following the patient status. The effect of this stimulation it was proven to be more effective, controlling L-DOPA induced dyskinesias (Rosa et al., 2017) and, using a different device that only activate or deactivate the stimulation sensing a threshold of the LFP, it was proven to improve motor scores (Little et al., 2013).

4.1 Methods

The LFP recording and aDBS experimental setup consist in a calibration phase, where it was used a normal biomedical amplifier and Analog to Digital Converter to a PC and the recording phase, where the aDBS is used to only record the LFP chosen from the calibration phase and, at the end, the stimulation phase, where the aDBS device record the LFP and adapt its parameters accordingly.

4.1.1 aDBS External prototype and LFP recording

The device used was fully describe in another study (Arlotti, Rossi, Rosa, Marceglia, & Priori, 2016) and used in the previous clinical study (Rosa et al., 2017) approved by the Italian Ministry of Health. The device, of which the technical specification were left to the previous study based on the research of (L. Rossi et al., 2007), is external but portable (dimensions: 12 cm x 7 cm x 2.5 cm, weight: 150g) and can be placed in a pouch mounted on a belt worn by the patient.

The calibration phase is useful to adapt the aDBS settings to the LFP beta band power of every patients, to do so the calibration session was performed at rest at the beginning of day 5. The signal was recorded directly from the electrodes of the patient sensing the various contacts pairs, first from the hemisphere

contralateral to that of the disease onset and the from the ipsilateral hemisphere. The technical specification could be found in the supplementary material of (Arlotti et al., 2018). The oscillatory activity was analyzed with the power spectral density (PSD) in the frequency domain calculating the intrinsic background noise (neural and specific acquiring device), if there is a peak in the beta band exceeding this threshold, the summed PSD of the peak and a band of ±2 Hz around it is used as a linear control variable. If there are more than one beta peaks, the more significant one is chosen. The hemisphere and the related contact pair with the most significant beta peak for recording is selected, and the DBS stimulation is administered by the contact between the two.

After this operation the DBS settings were chosen: an experienced neurologist assessed the patient to define the therapeutic window (Sara Marceglia et al., 2010): the threshold for the clinical effect (upper limb rigidity improvement on the side contralateral to stimulation by at least 60% without side effects), and the upper threshold for the side effects ensuring that the maximum stimulation voltage delivered remains between this window. When this window is chosen, the patient put on the smartband (instructed by the researcher or caregiver) and starts the accelerometric acquisition via the smartphone app.

In Day 5, after the calibration phase, the device was in recording-only mode, registering continuously the beta power data in the personalized band defined for each patient, and stored them for further download and analysis.

In Day 6, the device was programmed to a standard 130 Hz stimulation with a 60 μs pulse, the amplitude linearly changes following the LFP PSD, according to beta power recorded, between 0 V and the effective stimulation amplitude (threshold for clinical effects increased by 10-20%, according to the length of the therapeutic window) calculated for each patient. The device also recorded and stored the stimulation amplitude delivered throughout the whole session. In addition, the device recorded and stored continuous beta power data (with the same configuration as in Day 1) that were used for the analysis. The aDBS is switched off after the session, leaving the patient with only the pharmacological therapy. When the aDBS is switched off, the accelerometric acquisition is stopped, the database exported and sent and the wrist band in taken from the patient.

4.2 Integrating aDBS LFP recordings, accelerometric data, e-diaries and clinical assessments

To make sense of all of these data a clear time-frame synchronized between all the devices must be instantiated.

The beta power recorded has a data point every 1 second, the UPDRSIII assessment, the levodopa administration and the session start was taken using GSM synchronized smartphones with a sensibility of ±1 minute. Considering the time interval of ±10 minutes around an UPDRSIII assessment the time precision of ±1 minute is regarded, for this study, as acceptable.

Beta Power percentage change was calculated from the baseline with this formula:

$BetaPower\% = (BetaPower_t - BetaPower_{baseline})/BetaPower_{baseline}$

where t is the time point during the experimental session (Peak dose 1, End dose 1, Peak dose 2, End dose 2) and baseline is the first morning assessment after 12 hours overnight medication washout.

The stimulation voltage, following betapower%, was also collected throughout the entire session on Day 6. To allow comparisons the normalized stimulation voltage was calculated as percentage of the maximum voltage delivered to the patient in the session:

$StimVolt\% = ((StimVolt_{max} - StimVolt)/ StimVolt_{max})*100$.

4.2.1 The new accelerometer algorithm: "Activity Index"

The BAS and BradIndex shown in the last chapter have some drawbacks: they were made to follow only bradykinesia and, especially the second one, act in a hourly time frame where the LFP are considered every 10 minutes. A new index was proposed, not to follow a particular symptom but to follow the movement of the patient, an active patient means a high score, an inactive patient a low score.

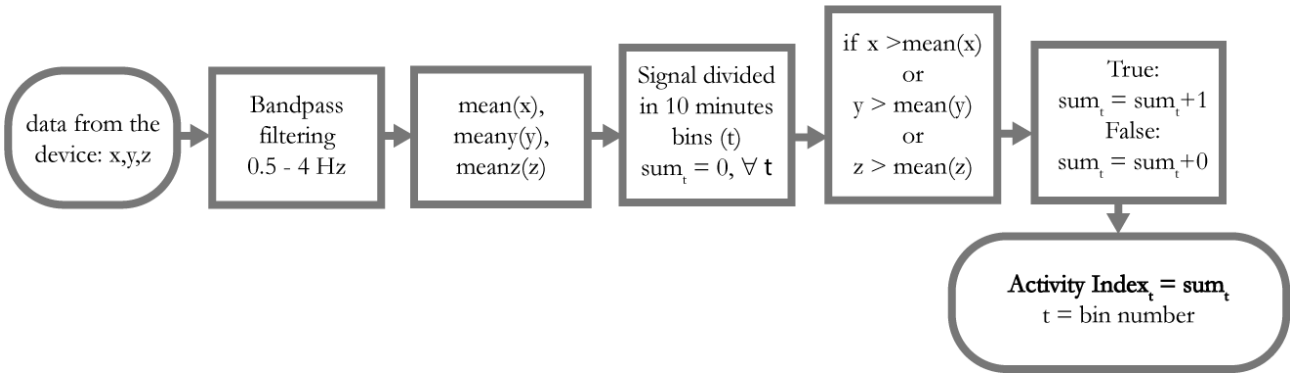


Figure 34: Activity Index algorithm chain.

To calculate this index (Figure 34), it was considered the accelerometer data in the band of 0.5 Hz to 4 Hz to eliminate the gravity effects (low frequencies) and the high frequencies not related to voluntary movement. After this filtering a mean of every accelerometer axis was determined and the data was divided in 10 minutes bins. Every sample within the bin was tested sample by sample to check if at least one of the three axis is superior to his mean (e.g. if x(ntT) > mean(X), x(ntT) single sample of axis x, of the t bin, with a T sampling frequency, n = 1 to N_t where N_t is the numerical size of the bin, and X vector of every sample of axis x), if it is a +1 is added to a counter of that bin (sum_t), if there are no values (x(ntT), y(ntT) or z(ntT)) superior to their means no value is added for that sample to the counter (sum_t). Every bin, at the end of the calculation, is a linear sum of the number of time samples that exceed their means (at least one of the axis). A 10 minutes bin, with 100 samples/s of triaxial accelerometric data, could have an activity index that ranges from 0 to 6000 (100 samples/s in 10 minutes are 6000 data points). The mean check was done to rule out rest tremor and the sum cut off to regard every significant activity without put too much weight into a sparse but intensive movement (like falling or sitting).

4.2.2 Diary assessment

The e-diary administrated to the patient was useful especially for the activity questionnaire (question item: “Quale è stata la tua attività principale nell’ultima mezz’ora?”), as the STN LFP beta band is also affected by voluntary movement, after an estimation of activity a categorization of that activity was also critical. The cross-check of the actual patient report activity with the quantitative measurement of wrist/body movement was also designed to rule out suspicious high activity reported by the patient not correlated with real movement, and to give a better time-wise estimate in the 30 minutes time frame. E.g.: the patient was sleeping or relaxing for 20 minutes and for 10 he/she was walking, if the patient reported outcome was “Walking” with this cross-source analysis is possible to estimate the real “Walking” time frame.

4.3 Results

The Figure 35 shows one session from 11 am to 6 pm of one patient, with all the aggregated data, at the top, the pictograms depict the self-reported e-diary of activities, described also by the labels (Talking, Sleeping, etc.), at the center the activity index graph, with data points every 10 minutes, it is important to notice the data loss, during the day, caused mainly by the patients wandering off from the smartwatch (this particular patient was a Pebble Time smartwatch user), the scaled y axis is the activity index described before. At the bottom the beta power % change values, with a negative y axis, due to the baseline assessment, taken where the patient was in medication washout so starting with a high beta peak value. At the bottom of the timeline there are the UPDRSIII evaluation time and the L-DOPA administration time. It is possible to notice in the relaxing window, how the self-reported outcome is plausible for the last half of the 30 minute frame, but the first half is more in line with the walking activity reported before.

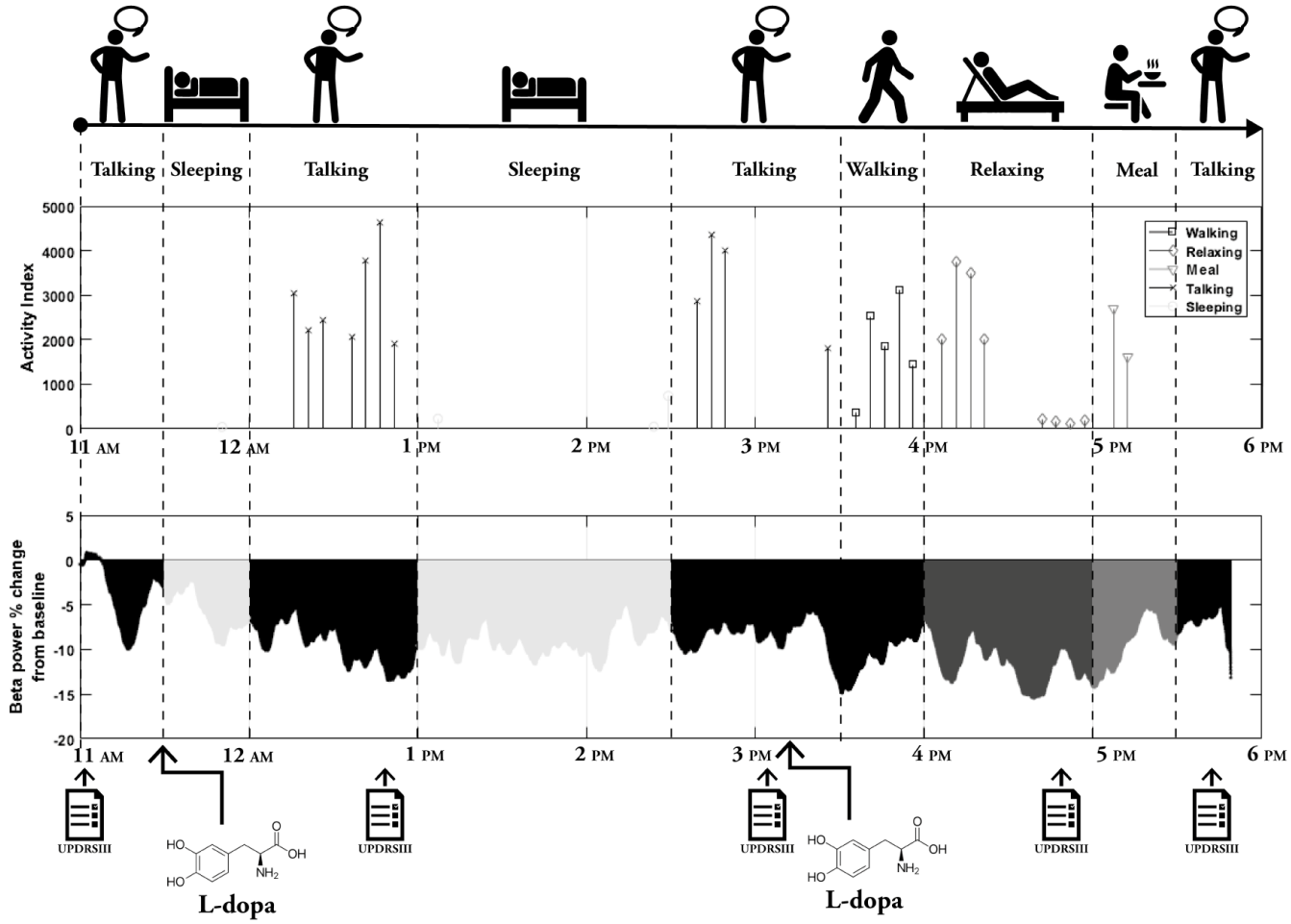


Figure 35: Activity self-reported e-diary (top), Activity Index (center) and LFP beta power % change (bottom) with UPDRSIII assessment and L-DOPA administration during a single session of a patient.

The study found that the beta power responded to levodopa administration, as expected, with an average decrease of 18.0% < 0.03 in peak dose compared to a 8.3% ±0.03 in end dose (p=0.009) with respect to baseline (Med OFF, Stim OFF after 12 hours levodopa withdrawal).

In addition, the beta power confirmed to correlate with the patient's clinical state as measured by the UPDRS III (Pearson's correlation coefficient = 0.477, p<0.001), and was specifically modulated during walking, with respect to talking and relaxing (beta power change from baseline during walking: -14%±4.212, talking:-11.2 %±2.724, and relaxing: -8.811%±2.418, one-way ANOVA p<0.0001). The self-reported outcomes that were not consistent with the activity data (Relaxing or Sleeping with a mean activity value superior to 2500) were not considered in the outcome.

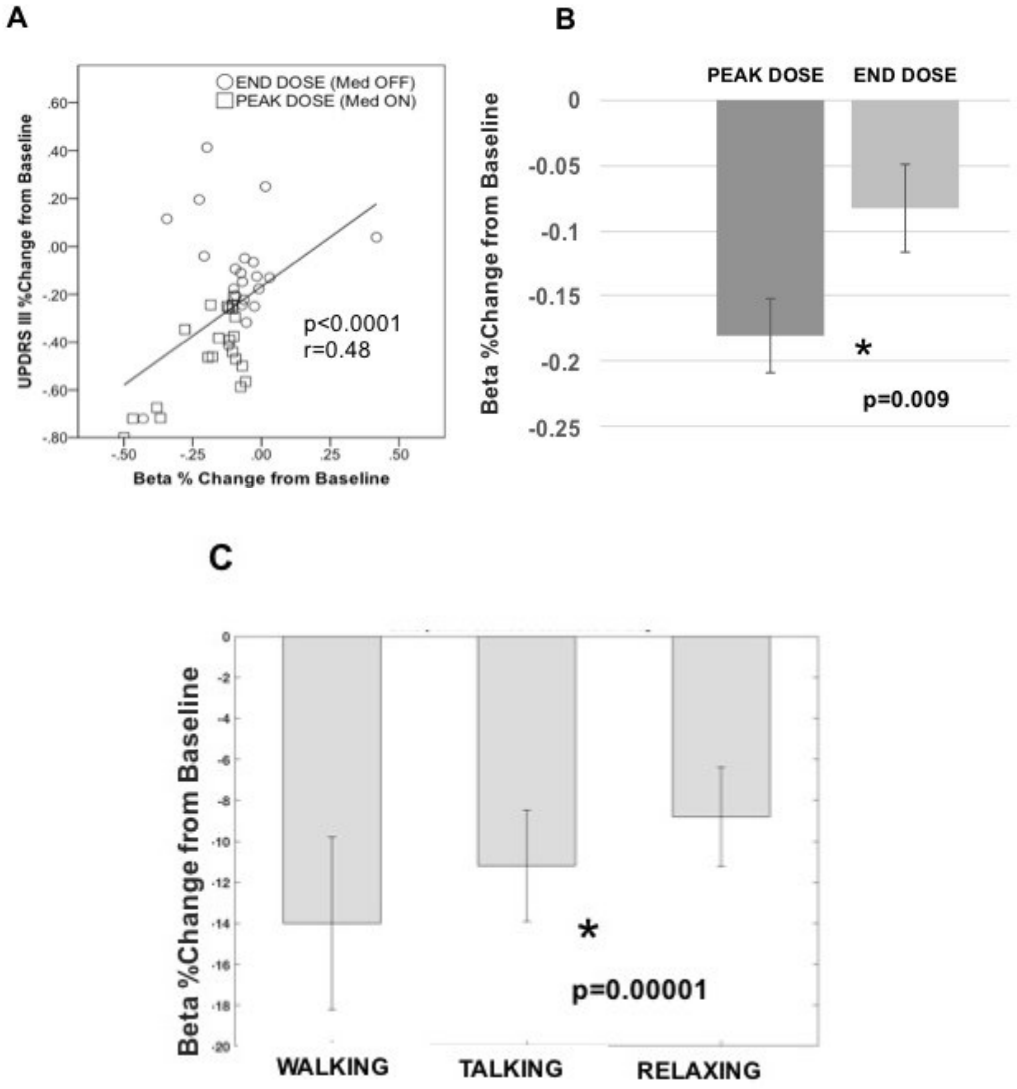


Figure 36: A: Correlation between UPDRSIII % change from the baseline and beta power % change from the baseline, Pearson; B: Beta change % power between peak dose and end dose, t test; C: Beta % change from the baseline between self-reported activities Walking, Talking, Relaxing, ANOVA.

5 Objective III: Implement a support application for patients/caregivers able to have bidirectional communication with institutional or research systems.

In this chapter the initial point of care data integration system prototype is expanded in a multi-centered perspective to implement a true bidirectional communication with institutional or research system with the patients/caregiver, giving a safe and reliable layered design of point of care data integration tailored for research.
As a preliminary assessment, to allow such widened perspective, the regulations for data privacy and management were analyzed in the context of the research.

5.1 Data: care and management

Patient data require to be handled with particular care. In a big data oriented world a collection of a multitude of health data taken from a large population is invaluable, but use this data and at the same time preserving the privacy and safety of the single patients is a delicate and complex task. Informed consent given by the patient is important but still the clinical data must be regarded with care. Regarding the use of the patient data, especially if this data will affect the patient, or future patients regarding research data, privacy and safety are not the only concern, reliability is also an important attribute, because this data will affect the health of people.

5.1.1 Privacy and safety of data in a multi-centered perspective

In the previous framework prototype we used simple local data not attributable to a single patients by using completely anonymous devices (smartphone where not connected to internet or cellular networks, no patient sensible data or demographics was recorded into the device, but only the minimum sensor and e-diary data, after stored in a safe local researcher repository was deleted from the device, session by session). Developing a connected and expanded system this approach is no feasible anymore, further steps must be made to ensure data privacy and safety to collect this research data.
Health Insurance Portability and Accountability (HIPAA) is a United States legislation that provides data privacy and security provisions for safeguarding medical information. The HIPAA Privacy rule calls "Protected Health Information" (PHI) the individually identifiable health information held or transmitted by a covered entity or its business associate, in any form or medium, whether electronic, on paper, or oral.
HIPAA identify the process of de-identification, by which data identifiers are removed from the health information, mitigates the privacy risks to individuals, and thereby supports the secondary use in large shared studies like comparative effectiveness studies, policy assessment, life science research and other.

De-identification is not an easy task, a simple name, date removal is often not enough to guaranteed a full de-identification, data aggregation could still identify people, like combining ambulatory visit timestamps within a limited population and gender/age specific disease reports. However, in recognition of the potential utility of health information even when it is not individually identifiable, HIPAA permits a covered entity to create information that is not individually identifiable by following the de-identification standard and implementation specifications.

The HIPAA Privacy Rule provides two de-identification methods: 1) a formal determination by a qualified expert; or 2) the removal of specified individual identifiers as well as absence of actual knowledge by the covered entity that the remaining information could be used alone or in combination with other information to identify the individual. In our system, to render the data most openly available, the second method is used.

5.1.1.1 The "Safe Harbor" method:

For the HIPAA removing the information in is a good way to provide the de-identification required

- *(A) Names*
- *(B) All geographic subdivisions smaller than a state, including street address, city, county, precinct, ZIP code, and their equivalent geocodes, except for the initial three digits of the ZIP code if, according to the current publicly available data from the Bureau of the Census:*
- *(C) All elements of dates (except year) for dates that are directly related to an individual, including birth date, admission date, discharge date, death date, and all ages over 89 and all elements of dates (including year) indicative of such age, except that such ages and elements may be aggregated into a single category of age 90 or older*
- *(D) Telephone numbers*
- *(L) Vehicle identifiers and serial numbers, including license plate numbers*
- *(E) Fax numbers*
- *(M) Device identifiers and serial numbers*
- *(F) Email addresses*
- *(N) Web Universal Resource Locators (URLs)*
- *(G) Social security numbers*
- *(O) Internet Protocol (IP) addresses*
- *(H) Medical record numbers*
- *(P) Biometric identifiers, including finger and voice prints*
- *(I) Health plan beneficiary numbers*
- *(Q) Full-face photographs and any comparable images*

- *(J) Account numbers*
- *(R) Any other unique identifying number, characteristic, or code, except as permitted by paragraph (c) of this section [Paragraph (c) is presented below in the section "Re-identification"]; and*
- *(K) Certificate/license numbers*

Table 10: HIPAA "Safe Harbor" de-identification items.

This list of identifiers, as stated before, does not totally guarantee a "Safe Harbor" because, the HIPAA states: "*The covered entity does not have actual knowledge that the information could be used alone or in combination with other information to identify an individual who is a subject of the information.*" ("Guidance on De-identification of Protected Health Information," 2012)
The data must be always reviewed to assess this issue.

Re-identification

True anonymization of data means that all the possibilities of re-identification are lost, but health data re-identification could be useful to the patient, so HIPAA has guidelines for this operation.
A unique code to the de-identified health information is the suggested way to permit re-identification by the covered entity, but disclosure of a code or otherwise de-identified information to be re-identified is also considered a disclosure of PHI. This means that the code association repository must be kept in a safe place within the boundaries of the covered entity. The HIPAA states that:

Implementation specifications: re-identification:

A covered entity may assign a code or other means of record identification to allow information de-identified under this section to be re-identified by the covered entity, provided that*:*

(1) Derivation. The code or other means of record identification is not derived from or related to information about the individual and is not otherwise capable of being translated so as to identify the individual*;*
(2) Security. The covered entity does not use or disclose the code or other means of record identification for any other purpose, and does not disclose the mechanism for re-identification.
- ("Guidance on De-identification of Protected Health Information," 2012)

5.1.2 The General Data Protection Regulation, GDPR

Regarding the privacy of patient data in the Europe Union (EU) GDPR was recently put into place to unify all the regulations within the union. The General Data Protection Regulation (GDPR, EU 2016/679)

is a regulation affecting data protection and privacy, it affects all the individuals within the EU, the European economic area and the exporting of personal data outside these boundaries.
The GDPR art. 4 recital 26 states clearly the difference between anonymization and pseudoanonyzation:

> *"The principles of data protection should apply to any information concerning an identified or identifiable natural person. Personal data which have undergone pseudonymisation, which could be attributed to a natural person by the use of additional information should be considered to be information on an identifiable natural person. To determine whether a natural person is identifiable, account should be taken of all the means reasonably likely to be used, such as singling out, either by the controller or by another person to identify the natural person directly or indirectly. To ascertain whether means are reasonably likely to be used to identify the natural person, account should be taken of all objective factors, such as the costs of and the amount of time required for identification, taking into consideration the available technology at the time of the processing and technological developments. The principles of data protection should therefore not apply to anonymous information, namely information which does not relate to an identified or identifiable natural person or to personal data rendered anonymous in such a manner that the data subject is not or no longer identifiable. This Regulation does not therefore concern the processing of such anonymous information, including for statistical or research purposes." - GDPR art. 4 recital 26*

Stating clearly that pseudoanonymized data with additional information could be used to identify a subject.
In art. 4 recital 34 is discussed the Personal Health data, in particular stating that a number or symbol could uniquely identify a natural person:

> *"Personal data concerning health should include all data pertaining to the health status of a data subject which reveal information relating to the past, current or future physical or mental health status of the data subject. This includes information about the natural person collected in the course of the registration for, or the provision of, health care services as referred to in Directive 2011/24/EU of the European Parliament and of the Council to that natural person; a number, symbol or particular assigned to a natural person to uniquely identify the natural person for health purposes; information derived from the testing or examination of a body part or bodily substance, including from genetic data and biological samples; and any information on, for example, a disease, disability, disease risk, medical history, clinical treatment or the physiological or biomedical state*

of the data subject independent of its source, for example from a physician or other health professional, a hospital, a medical device or an in vitro diagnostic test." - art. 4 recital 34

The system proposed must be patient-centered where the safety of data is relatively secure (within the boundaries of the organization where the data is collected, e.g. hospitals and clinics) and data-centered outside. Mitigation of these issues are further discussed in section 5.1.4.

Clinical trials (and WebBioBank, WBB) already supports another key feature, in the GDPR, the "consent" regarding his/her data process and usage given by an individual have been strengthened resulting in the obligation for the companies to state clearly their conditions, in clinical experiments the subject must be informed clearly and directly of the trials, but, in a research contest is not always possible to state every application of the data so art. 4 recital 33 of the GDPR states:

"It is often not possible to fully identify the purpose of personal data processing for scientific research purposes at the time of data collection. Therefore, data subjects should be allowed to give their consent to certain areas of scientific research when in keeping with recognized ethical standards for scientific research. Data subjects should have the opportunity to give their consent only to certain areas of research or parts of research projects to the extent allowed by the intended purpose." - art. 4 recital 33

The institution of a (not always mandatory) Data Protection Officer (DPO), an individual tasked to internal record keeping, is also guaranteed in the form of a Principal Investigator or some more specialized role, this role, in our USE-CASE scenario is one of the Researchers.

There are also some key features of GDPR that are exceptions in our application:

GDPR states that the controller shall provide a copy of the personal data, free of charge and in an electronic format to the subject, providing the "right to access" (art. 15 recital 63). Another concern is the "right to be forgotten", where a subject could request the erasing of every data concerning him/her from every system affected.

5.1.3 WebBioBank: an anonymous data management tool

A system capable of multi-center study management that implements the HIPAA "Safe Harbor" rules and de-identify the patient was proposed in (E. Rossi, Rosa, Rossi, Priori, & Marceglia, 2014), even if with the introduction of the EU GPDR some updates may be occurred. The requirements of interest for this framework are:

1. A unique common template for data and biosignal collection shared between different centres will guarantee the availability of comparable data to clinicians, researchers, and biosignal analysis specialists, while signals and data should be locatable, supporting a faster and more cost-effective protocol.

2. Anonymous data processing and sharing between different centers ensuring patient's privacy also when involved in multi-center studies.

3. Users with different roles (Role-Based Access Control) will gain access according to their job function in the clinical center during each specific research protocol. User access must be controlled using authentication to avoid unauthorized access. Each user will only be authorized for access to the web-applications that implement their corresponding job tasks according to their assigned role.

WBB (www.webbiobank.com) is web-based, it integrates clinical data collection with signal management and processing. The system is based on the wHospital framework 7 that is a commercial EHR system used in several healthcare institutions and Regional implementations. WBB includes dedicated functionalities to support multicenter clinical studies and an adjunctive module for biosignal storage, management, and analysis. The system is accessed through a standard web browser, allowing users to perform various tasks for data management in an anonymous mode according to shared protocols, thus guaranteeing real time interaction between researchers and clinicians in different research centers. Clinicians can add patient's clinical information using shared clinical forms specific for the clinical study.

5.1.3.1 IDBAC

WBB implements a unique patients' IDs (IDBAC) to identify the subjects without displaying demographic information. The re-identification is possible using lists of demographic information pairing with the IDBAC linking the clinical information of the patient, these lists are stored within the local physical boundaries of the organization tasked to care about that data. E.g. hospital, clinics or ambulatories retain the pairing table lists between IDBAC and the internal primary key to identify the patients, where the clinical information, with only the IDBAC as primary key, is stored remotely in the WBB servers. The organizations in charge of their group of patients are called Operative Units (OU), and, having both the clinical data and the demographic data, it's given them the possibility to use the WBB as an local Electronic Health Records (EHR) repository, because the WBB, based on a EHR system used in hospitals, "wHospital" ("wHealth," 2018) provides a multi-role-based access control, providing authentication and authorization capabilities. This ensures that only authorized users within pre-defined roles, will gain access to their specific subset of data, and could perform only the operations of their role. The system also keeps track of the user activity, like timestamped logins and failed logins attempts, and all the data management operations done by the user. The strength of WBB is the possibility to go outside the boundaries of the single OU and provide de-identified clinical data to multi-center studies, accessible by researchers, in this case traditional EHR became "research" EHR (rEHR, Figure 37) and Case Report Forms (CRF).

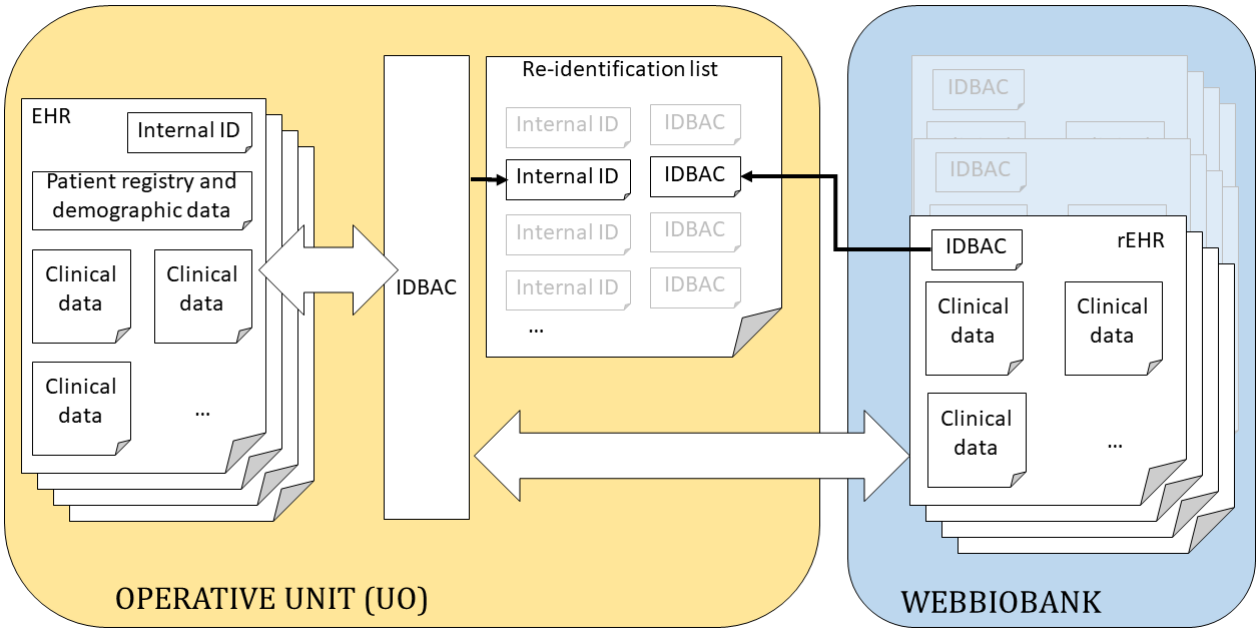


Figure 37: WBB IDBAC schema.

5.1.4 Data types

PHI data on the WBB may have different formats: biomedical signals with integrated patient health metadata, photos, videos, demographic data and user traceability. Table 11 shows the risks associated with the different kinds of data.

Data	Type	Risk	Risk mitigation
Biomedical signal	LFP recordings	Biometric identification	Criptography, signal segmentation and signal sanitization (Bonomi & Fan, 2018) (not yet implemented)
DBS electrodes metadata	Target (e.g. STN, thalamus), coordinates and stimulation contacts		
Patient health status metadata	Sperimental condition, ON-OFF state, pharmacological therapy, disease onset	Sensible data	Minimization of the data (e.g. L-DOPA equivalent dose, active molecule for other pathologies).
CRF	Diagnosis, clinical indexes	Sensible data	Anonymization
Demographic data	Age, gender…	Indirect identification	No temporal or geographic data metadata

Photo or videos	Clinical indexes evaluation tasks…	Identification of patient or physicians	Obscurization of the faces
UO	Name of the center where the patient is cured.	Geographical identification	"Safe-Harbor" de-identification.

Table 11: PHI data types risk and risk mitigation by WBB

5.2 Requirements definition

The clinical data delivers critical information and to be usable in scientific research not only must protect the patient privacy but also must be reliable.

5.2.1 ALCOA

The desirable features of clinical data are known as "ALCOA", meaning the data must be attributable, legible, contemporaneous, original and accurate.

A: Attributable, every piece of data or document and every modification, reviews or cancellation must be attributed to an author. The GDPR states, on art. 15 recital 64 that the controller (of data) should use all reasonable measures to verify the identity of a data subject who requests access, in particular in the context of online services and online identifiers. This means that the tracking the modification of a document must be tracked to a user, but also that this user must be a verified individual. FDA introduce the definition of Metadata Audit Trail: metadata is the "data about data", contextual information required to manage and understand data. E.g. measurement unit, like km, or meter, attached to values, provide contextual information about measurement, or fields like name and surname provides metadata about categorization. FDA regards metadata audit trail means as an electronic record that is ("Use of Electronic Records and Electronic Signatures in Clinical Investigations Under 21 CFR Part 11," 2017):

1. Secure, 2. Computer-generated and 3. Time-stamped.

This metadata computer records allows for timeline reconstruction of the all events relating to the creation, modification, or deletion of an electronic record. Using the FDA definition, an audit trail is a chronology of the "who, what, when and why" of a record.

Electronic audit trails are directly related to the attribute A of ALCOA, they guarantee the tracking creation, modification, or deletion of data (such as processing parameters and results) and the users that make those changes.

L: Legible, relates to data readability, data composed by ASCII text are preferable than raw binary data and file metadata must be human readable.

C: Contemporaneous means that reliable data must have a time-frame, and any change on the recording must be fully tracked via timestamp, also stating the reason for modification with mandatory time-stamped signature. Metadata audit trail is useful also to ensure this requirement.

O: Original means that the initial data recording must be accessible and kept safe. Further modification to this original data (or processes) must not erase the original.
FDA defines the concept of backup: for the FDA this term has two meaning, the first is used to refer to a true copy of the original. Data must be maintained securely throughout the records retention period. Data backup means that the file contain the data and metadata in the original format or at least in a format compatible with the original format. FDA clarify that the backup definition should not be confused with the second usage of these term, meaning "temporary backup" that may be created during normal computer use and temporarily maintained for disaster recover but fixed, safe and secure original, these temporary backup copies would not satisfy the requirement to maintain a backup file of data.
A: Accurate regards data reliability, meaning that the recorded information describe the conduct of the study without error. What or who generated that data? An unreliable device (e.g. the consumer grade Pebble Time Watch, or research-grade ShimmerSensing IMU) or an unreliable subject (e.g. a clinical assessment of an expert physician or a patient self-generated report).

5.3 Scenario: including the real multi-center implementation perspective

In section 3.1 a basic scenario for the simple initial setup was presented. In this section the scenario will be expanded to include a real multi-centered perspective, adding the elements to render the local research prototype a true remote system. In chapter 3 it was never specified where the exported databases at the end of each section were sent, nor how they were stored, and the clinical assessments storage methodology were never showed. These important features will be explained in this chapter.
The main actors of the expanded scenario are the same: Patient, Caregiver, Physicians and Researchers. The OUs: clinics, hospitals, homes or ambulatories generate the PHI data. In the various OU every clinical data recording are performed with the framework validated in chapter 3: the wearable device (WD), the mobile device (MD) and the app (APP); this will be defined as Patient System.
In a clinical research, to achieve the research objectives the Researcher must define the measures needed and the data collection process. As shown in chapter 3 the Patient, aided by the Caregiver, collects his/her self-reported outcomes and the signal from the wearables through the Patient System. The Patient System have not the capabilities to collect clinical data created by the Physicians. This information must be collected by another system, in this scenario the WBB has all the capabilities to create and modify clinical forms and provides a web based interface to enable Physicians in filling in these forms and store the results. Due to the large scale capabilities the data collection process is necessary a precise and interconnected workflow manager (e.g., it reminds the Physician to assess the patient, and the Patient/Caregiver to start the daily acquisition, etc.). This system, that effectively bridge the Patient System with the WBB, is called Workflow Manager (WFM).

The Researcher access primarily the WBB to analyzed data or create new clinical assessment forms and the WFM. In this scenario, WFM is used by the Researchers to access remotely the Patient System and change the configuration or tasks of the acquiring/e-diary session, enabling the Patient System to be used in ecological conditions like homecare without the physical supervision of the Researchers, just with a periodical network connection.

The Physicians access primarily the WFM to manage their workflow, and WBB to fill in the required clinical indexes. The Patient, aided by the Caregivers, access the Patient Systems.

The gateway outside the UO, where the patient-reported data, the clinical assessment and the recorded signals (both LFP and accelerometric data) will be a workflow manager (WFM) tasked to bridge and manage data sources between the storing system (WBB) and the various Patient Systems.

The remote data manager is the WBB, primarily tasked to safely store the clinical de-identified data, control access and trace data processes.

In Figure 38 is reported the new USE-CASE diagram, the Patient and Caregiver operations are the same shown in Chapter 3 with an added use case, the remainders and notification built in the smartphone app. The Physician access his workflow from the experiment from a browser web app within the WFM, the interface provides remainders, tasks list and clinical forms to fill up (e.g. UPDRSIII clinical index).

WFM not only instantiate the remainder tasks and the visualize the clinical forms but also is a tool for the Researcher to define the clinical protocol of all the experiment, this module configures the Patient System for multiple patients and manage the scheduling of every clinical task and assessment.

The Researcher, other than defining the experiment protocol through WFM, he/she also access the WebBioBank to retrieve and analyze data and to create new clinical forms that Physician can use.

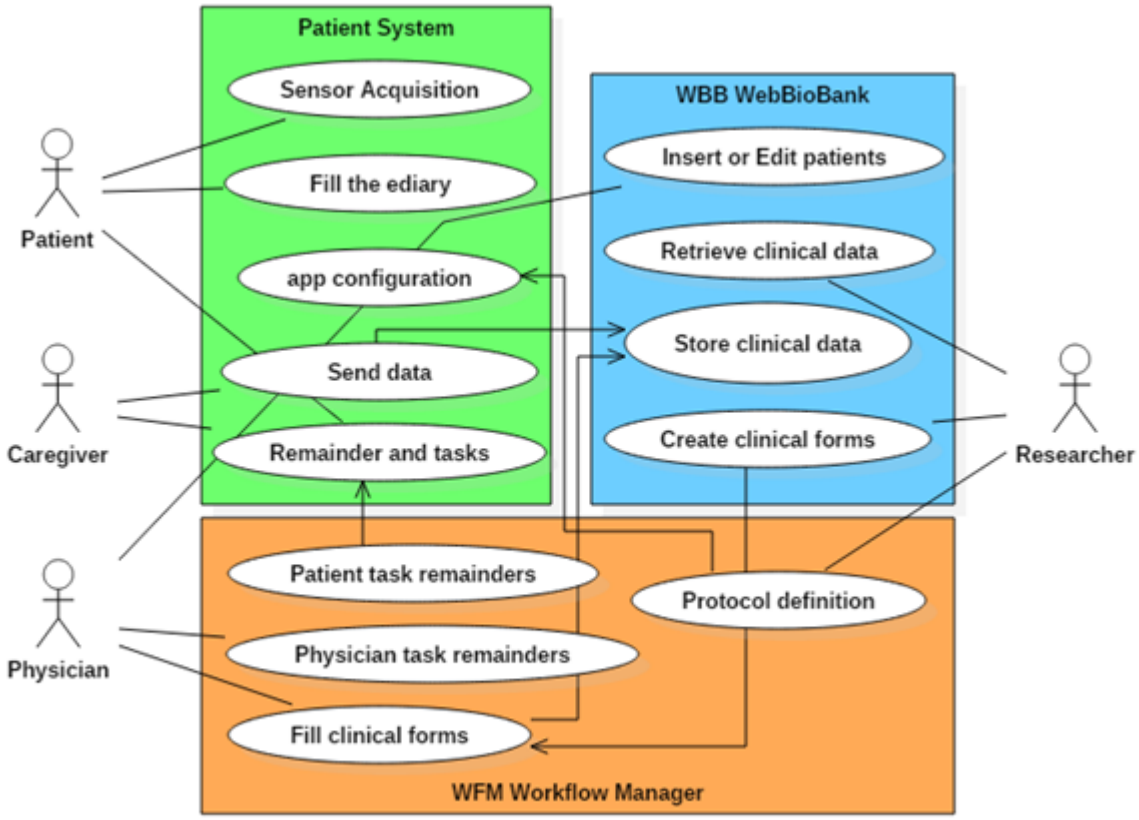


Figure 38: USE-CASE diagram for the expanded scenario.

5.4 Methods: experimental protocol

To validate the implementation, we used the same experiment described in 4.XXX

5.5 Results: Standards-based Architecture

This is a system created to a framework for research: scalability, modularity and interoperability are fundamental pillars of its creation. To implement such a system a standard based architecture is mandatory, based on the last iteration of the most used standards suggested by international guidelines.

5.5.1 CDA-2 PHMR

The Clinical Document Architecture Release 2 (CDA-2) is a document markup standard developed by Health Level 7 (HL7) defines a document as having the following characteristics("HL7 Standards Product Brief - CDA® Release 2," 2018), similar to the ALCOA: 1. Persistence, 2 Stewardship, 3. Potential for authentication, 4. Context, 5. Wholeness and 6. Human readability. The purpose of this standard is the exchange between healthcare providers and patients. Its benefits, as stated by HL7, are supporting

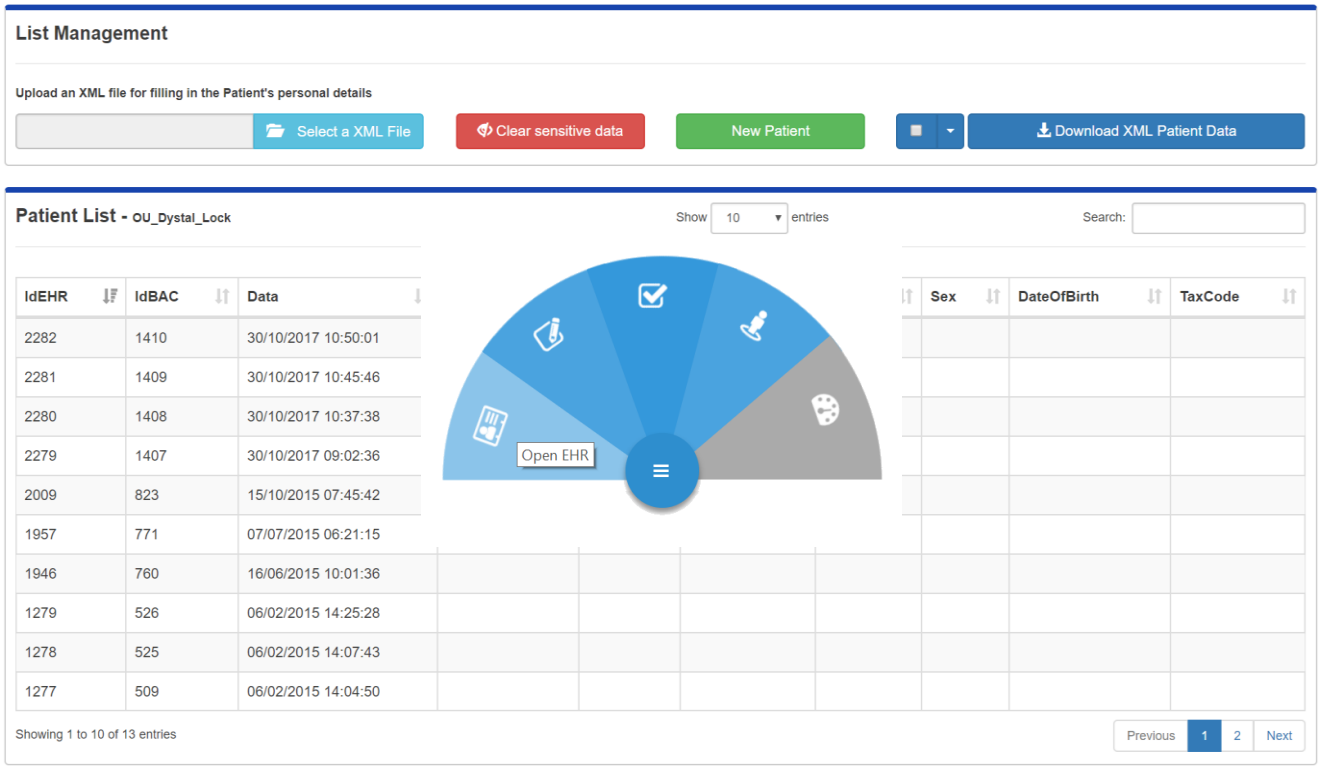
the exchange of clinical documents between those involved in the care of the patient, and the support of the re-use of clinical data for public health reporting, quality monitoring, patient safety and clinical trials. CDA operates within the concept of "incremental semantic interoperability"; it is left to the user to choose the complexity of the specifications, setting their level of compliance. The minimum CDA level is a small number of XML-encoded metadata fields (such as provider name, document type, etc.) and body. The body can contain common MIME type data, such as Microsoft Word files .doc, portable document formats (pdf) or images formats.

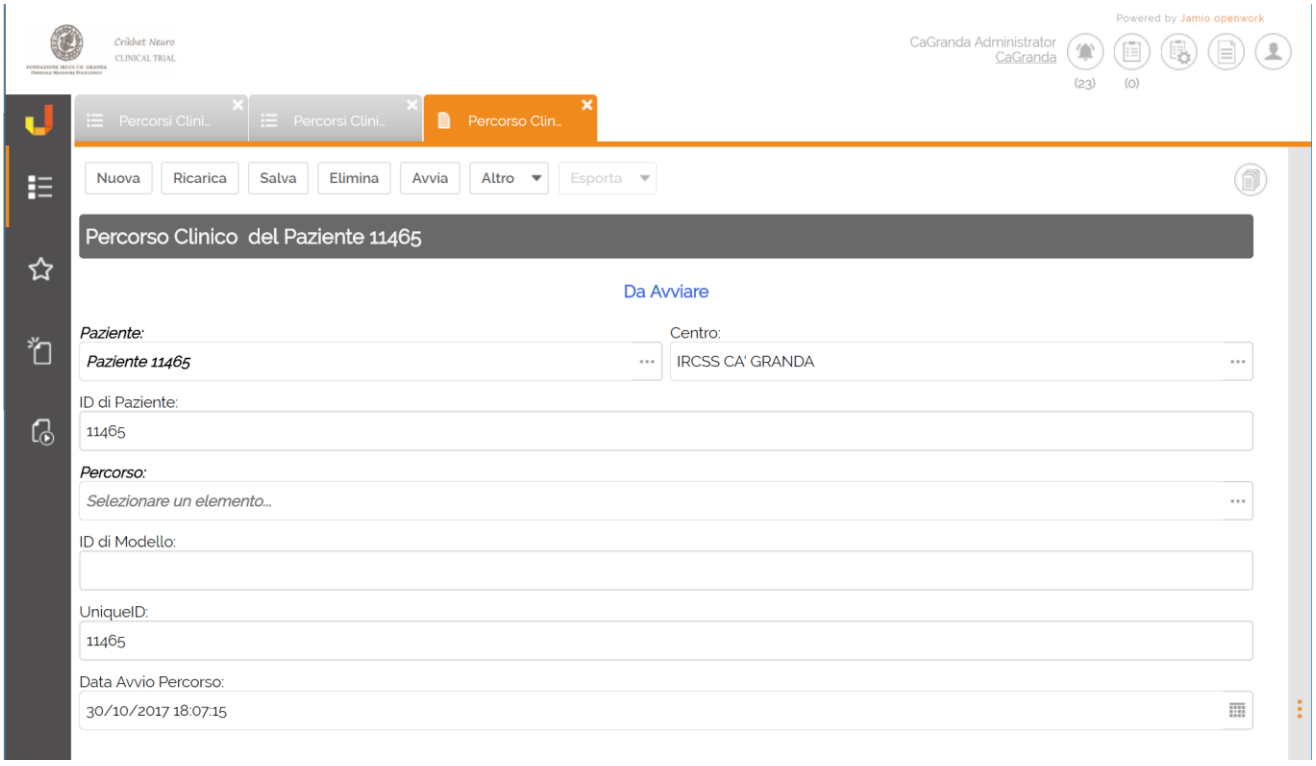
In a point of care prospective a CDA-2 reference format is the Personal Healthcare Monitoring Report (PHMR) born to exchange data of remotely monitored patients, such as vital signs or other health status data.

PHMR is a structured document reusing and enhancing the existing C-CDA (Consolidated CDA). As stated by the HL7 the benefit of PHMR are enabling the automated reporting of Personal Connected Healthcare Alliance (PCHA) and Personal Healthcare Monitoring (PHM) consumer devices. Fosters the development of automated acquiring interfaces in a network of data monitoring services and EHR systems and helping PHM data to be transferred to EHR. One of the strengths of PHMR is the attributability of the data, in our study this characteristic is useful but clashes with the anonymization requirements of a multicenter study. In (S. Marceglia, Fontelo, Rossi, & Ackerman, 2015) is described a modified implementation of the CDA-2 PHMR (CDAR2_IG_PHMRPTS_R1.1_DSTU_2010OCT). This implementation was called mPHMR to specifically address the exchange between the MD and the WFM ensuring anonymous communication and prevents the exchange of identification data through unsecure connections, as well as the maintenance of these data into unsafe environments.

5.6 System implementation

In Figure 39 is shown the patient list page of the WebBioBank, through there with an interactive fan menu item is possible to access their EHR and manage the patients through the WFM. In this example the role used to access the patient list is "Physician" and it is in the boundaries of the UO that manages the patient data, so IDEHR (the ID that links patients with the clinical data in the EHR system) and the precise dates when the patient was first inserted into the system. This was done to help the Physician to navigate the system, notice that the other information it still not shown and must be requested with the interface button, for privacy reasons. Selecting a single patient and the option to assign tasks and protocols through the fan tool the systems leaves the boundaries of the UO and goes remotely to the WFM system, where the patient is only identified by IDBAC and UO. In WFM is possible to assign the already defined experimental protocol to the patient, WFM knows which Physician follows that particular patients for the clinical assessment so the management workflow engine inside the WFM assign every task schedule for the patients (through the Patient Systems) and the Physicians (displayed by the WFM).


List Management
Upload an XML file for filling in the Patient's personal details
Select a XML File
Clear sensitive data
New Patient
Download XML Patient Data
Patient List - OU_Dystal_Lock
Show 10 entries
Search:
IdEHR
IdBAC
Data
Sex
DateOfBirth
TaxCode
2282 1410 30/10/2017 10:50:01
2281 1409 30/10/2017 10:45:46
2280 1408 30/10/2017 10:37:38
2279 1407 30/10/2017 09:02:36
2009 823 15/10/2015 07:45:42
1957 771 07/07/2015 06:21:15
1946 760 16/06/2015 10:01:36
1279 526 06/02/2015 14:25:28
1278 525 06/02/2015 14:07:43
1277 509 06/02/2015 14:04:50
Open EHR
Showing 1 to 10 of 13 entries
Previous
1
2
Next


Powered by Jamio openwork
CaGranda Administrator
CaGranda
(23)
(0)
Percorsi Clini..
Percorsi Clini..
Percorso Clin..
Nuova
Ricarica
Salva
Elimina
Avvia
Altro
Esporta
Percorso Clinico del Paziente 11465
Da Avviare
Paziente:
Paziente 11465
Centro:
IRCSS CA' GRANDA
ID di Paziente:
11465
Percorso:
Selezionare un elemento...
ID di Modello:
UniqueID:
11465
Data Avvio Percorso:
30/10/2017 18:07:15

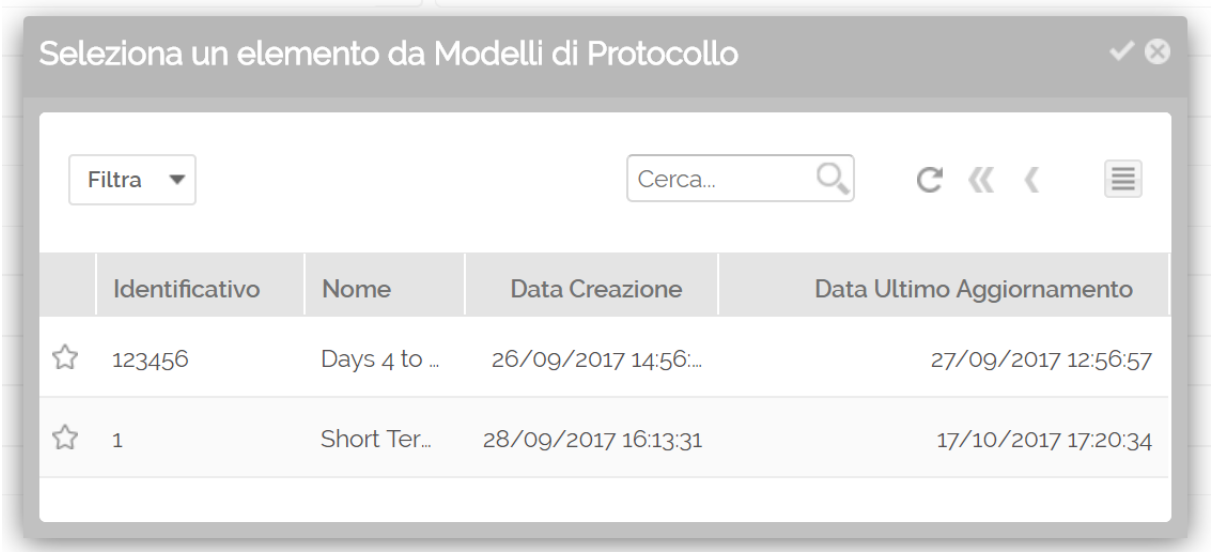


Figure 40: WFM screenshot, selecting protocols for different patients. At the top (A) the patient view, at the bottom (B) the protocol selection popup for that particular patient, also in Italian.

In Figure 41 is shown an example of clinical index form interface presented by the system to the Physician, connected to the various remainders and tasks fed by the WFM. It contains various type of fields: multi-choice, calendar, free strings and even simple calculators (e.g. dosage calculator). The different clinical forms are created by the Researcher, but the system is fully customizable, not only the various fields but also the layout in which they are presented. The layout could be created with the help of the end user (the Physician) to help him/her to fill the form in a more efficient and comfortable way. An incomplete form could be saved as draft and completed or modified later but when the Physician is satisfied by the document it could be electronically signed and stored. Even if draft modification are also traced by the system for a signed clinical form every subsequent change must be a revision, explicitly shown in the document history.

The web based interface could be used not only as a task and clinical form visualizer but it could also be used to give to the Physician instructions on how to perform these various tasks, like show the protocol procedures and updating them of possible adverse effect found during the experimental phase, even if in this initial version it doesn't implement a direct communication tool between Physician and Researcher.

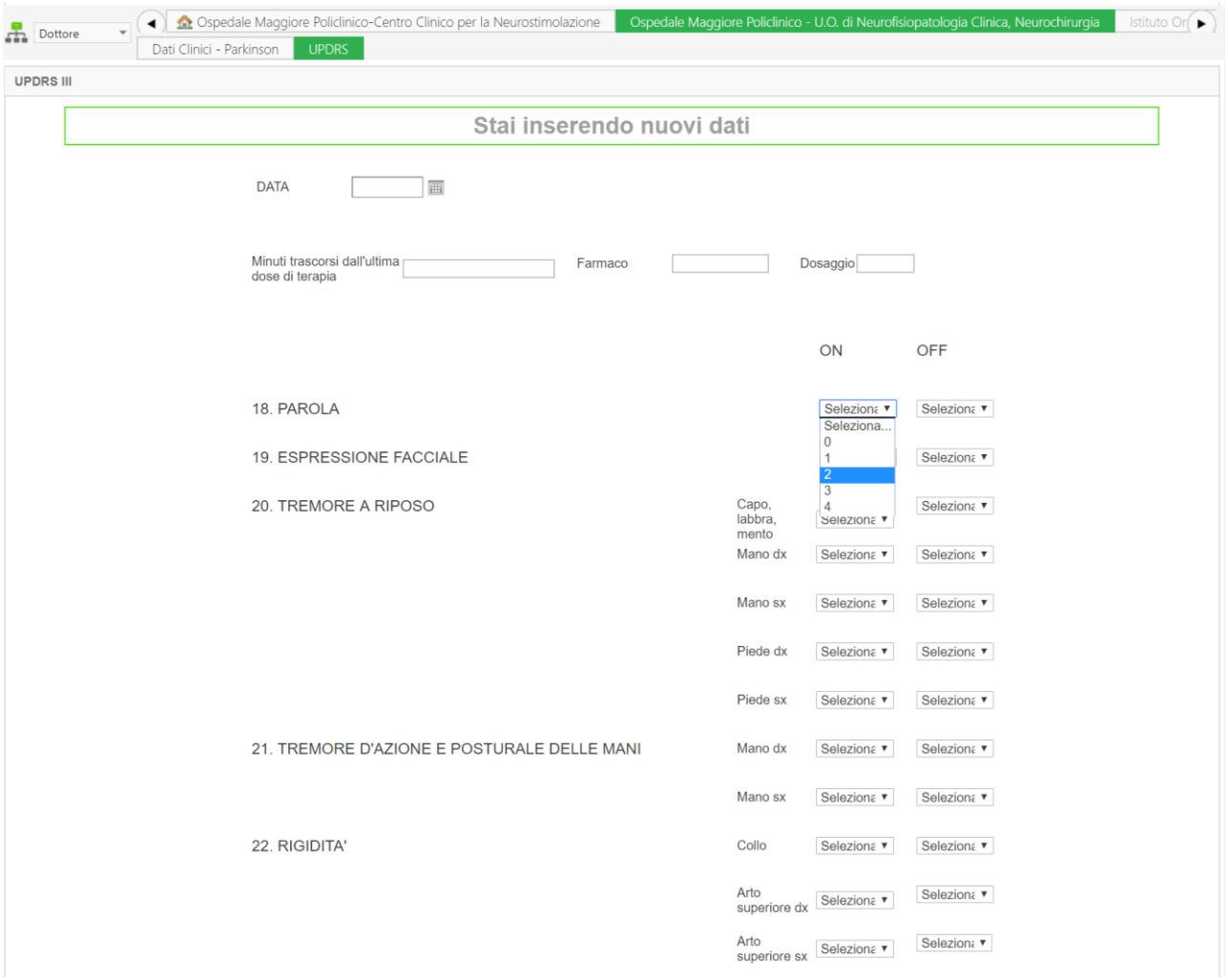


Figure 41: Clinical form (UPDRSIII) customizable interface accessible by Physician through WFM and WBB. In Italian.

Two web services were developed to support the communication and integration between the WBB and the WFM. The first one (wHvpc) is devoted to the integration of user roles and patients' IDs: it allows the verification of the privacy criteria for doctors/researchers who access the WFM to create or assign the patient's protocol and, once the doctor accesses to assign the study protocol, allows the exchange of patient's ID and contact information from WBB to WFM. Then, when the protocol has been assigned and the patient is registered in WFM, the WFM deletes contact information and keeps only the patient's ID. In this way, the synchronization between the two systems is guaranteed thus allowing attributability and integrity, and patient's contact information do not reside on WFM, thus allowing security and privacy. The second one (wHcda) is devoted to the exchange of CDA-2 standard documents between the WFM and the WBB. Once the WFM receives patient-generated data from the mobile application, it creates and encrypts the CDA-2 document according to the mPHMR template, and sends it to the WBB using the wHcda web service. Data reliability is therefore ensured by the use of standard documents that are accepted by the WBB platform and processed as clinical documents.

The Patient System App developed in chapter 3 is further expanded, creating another authenticated and authorization layer capable of interact with the exposed services of WFM and to visualize the notification and task of the workflow. The Patient System, even if protected by anonymizing the patient through the IDBAC, is intrinsically unsafe, because is mostly hand held by the same patient, gaining access to the device is possible to link the patient to the IDBAC, and IDBAC are easily accessible through the WFM. To mitigate this criticality WFM assigns another Unique ID to the Patient System as shown in Figure 40, this ID identify the App user, if someone wants to know the patient IDBAC it must have access to the lists inside the private WFM servers.

More specifically, the WFM stores the patient data into the correct rEHR on the WBB by calling the wHcda service passing the identification number of the patient (IDBAC). The patient data inside the database are anonymous for all users, and only the patient's doctor can re-identify them by means of a local registry. De-identification is guaranteed also by the WFM registration process that does not require patient's demographic information, but uses the contact information retrieved at the time of assignment that are then deleted when the patient is successfully registered. In addition, in the case WFM does not receive the patient-generated data on time, according to the protocol, it sends new requests, and then notifies the WBB of the deviation from the protocol, sending a specific CDA-2 with the indication of the deviation using the wHcda web service.

The diary and the accelerometer data, as in the first implementation, is stored internally in the SQLite DBMS. When the device is synchronized with the WFM, an mPHMR document is generated, and the data is compressed and encoded in MIME format in an observation of the CDA-2 document (content-type: application/x-compressed, Content-Transfer-Encoding: BASE64) and all the diary data on another plain text observation of the same document. It is worthy of notice that the accelerometric raw data of a session of 8 hours, especially when encoded in BASE64, has high volume that significantly encumbers the network capabilities. A BAS algorithm was implemented into the local app (this algorithm is less computationally heavy of BradIndex) to greatly reducing data volume, this operation is against the "Original" requirement of ALCOA but it was regarded as a useful compromise in this validation.

If the mPHMR document is correctly stored and approved by the WFM, a positive feedback is sent back to the mobile device and the internal database is erased for security reason. This feedback and the other remainders are sent through a web-service exposed by the WFM. The use of standard CDA-2 documents between the App and the WFM ensures data integrity, attributability, and safety (in the CDA-2 the author is the patient, identified only by his/her ID). Also, the mobile app does not retrieve any clinical data, but deletes them when the WFM correctly receives the CDA-2 and validates the data

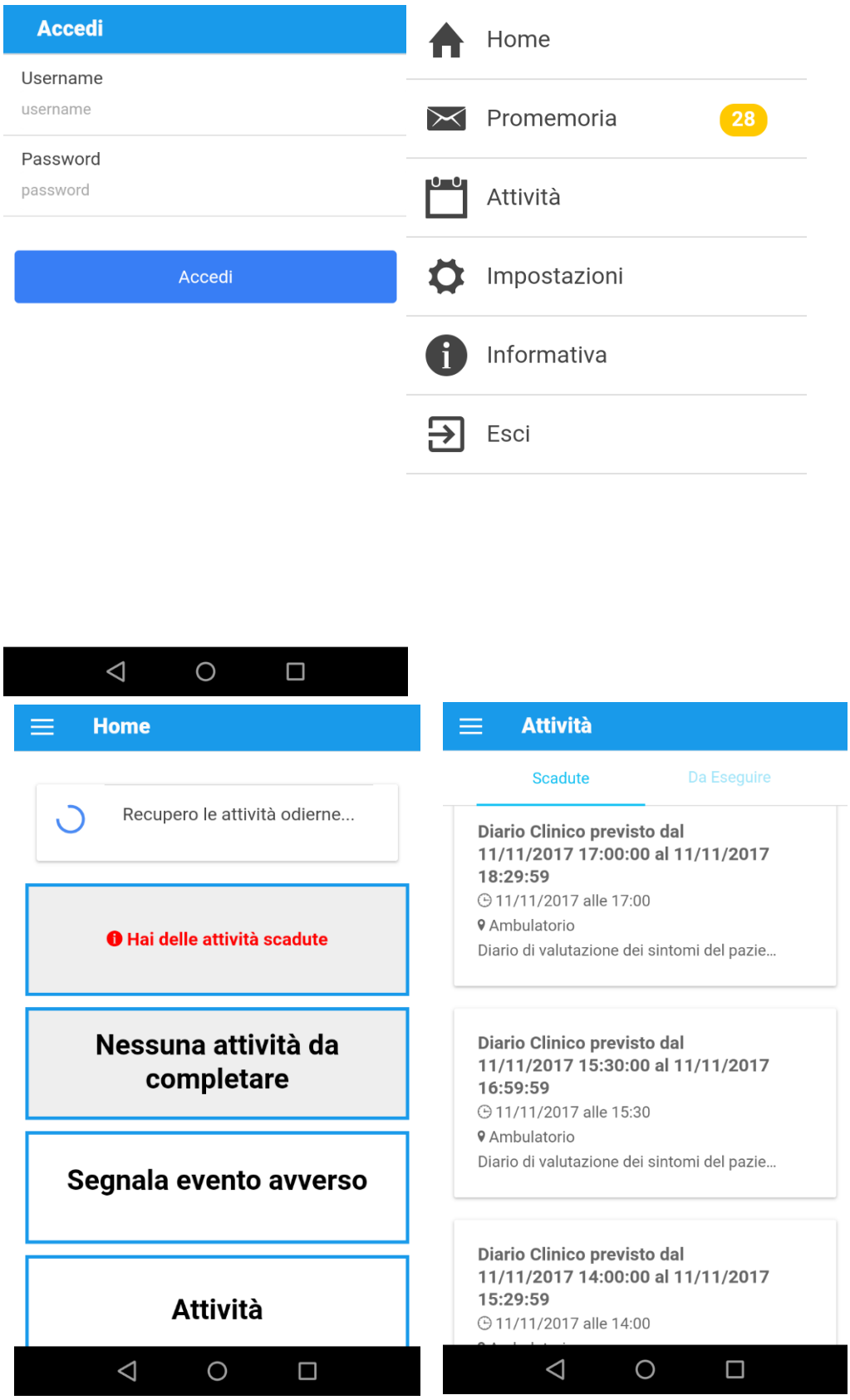


Figure 42: Top left (A), Patient System app login page; Top right (B), User main menu; Bottom left (C), activity with notifications; Bottom right (D): task list.

5.7 System validation

To validate this system a new user role, “inspector”, was created to test the audit functionalities. The patients, devices and methodologies are the same explained in section 3.2.5, the only difference was the data collection. In the first iteration the raw data was downloaded manually every session by the Researcher through the local storage of the app (the “Export Database” button) and in the second iteration the data was sent through WFM mPHMR documents using the “Send Database button”.
The researcher created 7 forms:

1. *Patient’s disease history;*

2. *DBS surgery details*
    a. *model of electrodes implanted;*
    b. *the target position;*
    c. *the intraoperative monitoring results (e.g. intraoperative electrodes impedance);*

3. *Details of the experimental setting*
    a. *L-DOPA equivalent dose administered to the patient;*
    b. *Neurophysiologic parameters retrieved to set the aDBS device;*

4. *Clinical assessment including the UPDRSIII (Figure 41) and the UDysRS scale;*

5. *View of patient-generated data.*

All the expected 140 diary recordings were received by the system. Of them, 117 were filled-in whereas 23 arrived with null values. This poor compliance was expected due to the fragile post-surgery conditions that DBS patients are, still the data collection were reasonable consistent with every patient except one. There were no errors in the data diary data transmission.
A total of 130 hours of accelerometer data were recorded. As stated before, the accelerometer data loss was due to a poor connection between the wearable device and the mobile app, especially for the Pebble Time smartwatch users.
The correlation (see section 3.3.1) between clinical assessments and patient-generated data was significant, thus suggesting that the measures obtained by the wearable device are reliable for assessment purposes, even though data are incomplete.
In this validation some use-case tests were performed, to finalize the system to be used in future studies and to provide a useful mHealth framework for the general research, the ALCOA requirements are checked in the results Table 13.

Use-Case: create a new de-identified clinical form.
Actors: Physician (P), WebBioBank/WFM System (WBB).
Description: A doctor fills a de-identified clinical form into the system.
Precondition: the Physician must be authenticated and authorized by the system, with the IDBAC list of the right OU opened.
Workflow steps: P: uploads the local xml to pair IDBACs to the local system patients; WBB: visualize the name, surname and date of birth from IDBAC found into the xml; P: selects the right IDBAC WBB: shows the patient page with all the forms and the acquisition data; P: clicks the form to fill; WBB: shows the right blank form; P: fills the form and clicks “save”; WBB: display the “sign” option; P: the doctor click the sign option, finalizing the form;
Extensions: 3a or 6a. D: selects the wrong IDBAC/Form; WBB: shows the wrong IDBAC/Form D: clicks on the “Go Back” button; WBB: return to step 1 (IDBAC de-identified); 9a. D: the doctor does not sign the document; WBB: shows the IDBAC list on step 1 and it displays +1 draft in the inbox;

Table 12: USE-CASE 1: Physician interaction with the WFM/WBB system.

Use Case: Caregiver/Patient use the app and smart bracelet to collect data and a researcher reads the results in WBB.
Actors: Patient/Caregiver (P), Researcher (R), System (WBB), smartphone app (APP), smart-bracelet (B).
Description: A Patient/Caregiver logs into the app, the patient wears the bracelet and starts the data acquisition (with the app "play" button).
Precondition: the Patient/Caregiver and the Doctor must be registered into the system.
Workflow: P: Logs into the app with the patient ID and password; APP: shows the "please, wear the bracelet" pop-up and the "play" button page; P: Wears the bracelets and press the "play" button; APP: starts the timer; B: starts the accelerometric acquisition and sends the data to the app via Bluetooth; APP: Every 30 minutes shows the diary page; P: compiles the diary and clicks the "completed" button; APP: write the data in the local database; APP: At the end of the timer count the app shows the initial "play" button page and sends the data to the WBB; B: stops the acquisition and the transmission; WBB: confirms the successful transmission of the data; R: logins in WBB with Doctor ID and password; WBB: shows the IDBAC lists; R: selects the IDBAC of the patient; WBB: shows the patient page with all the forms and the acquisition data; R: selects the last acquisition data; WBB: starts the download of the acquisition data and the diary data;
Extensions: 2a or 12a: APP or WBB: shows again the login page with an informative text ("wrong password/id"); return to step 1. 4a. B: the bracelet is not working or the smartphone Bluetooth is not on; APP: shows an informative popup, stops the timer; 11a. APP: cannot reach the WBB or the connection is not stable, APP shows a popup and retry to connect every 5 minutes; if successful continue to 12.

Table 13: USE-CASE 2, Caregiver/Patient use the app and smart bracelet to collect data and the Researcher reads the results in WBB.

Expected results for USE-CASE 1: Every System response (WBB) must be carried out correctly. No IDBAC with personal information must remain cached in the gridform except between steps 2 and 3. Every personal detail must be only retained on the local database file, no browser must retain this information; This data cannot leave the local machine. Signed form cannot be deleted or modified. Saved but not signed forms can be modified. All the data must be saved correctly.
Results for USE-CASE 1: 1. Every System step was fulfilled, to test this scenario we used UPDRSIII and UDysRS forms; 2a. the system was tested with Google Chrome (ver. 62.0.3202) and Internet Explorer 11 as browsers, no information were visualized on all the other steps except 2,3; 2b. Wireshark (ver. 2.0.3) was used to test the internet/WLAN traffic during this test, no personal data was exchanged outside the local machine; 3. it's not possible to modify or delete the form, also, the "save" and the "sign" operation are logged with the system timestamp (server-side) ALCOA ; 4. Saved forms can be modified but not deleted without Administrator's rights. ALCOA 5. Every forms was stored correctly. ALCOA

Expected results for USE-CASE 2: Every System response (APP, B, and WBB) must be visualized correctly. Limited data loss during the acquisition process; At least 8 hours acquisition session without recharging the smartphone or the bracelet; Downloaded data by the researcher must be in a known readable format (comma separated values or xls, Excel format);
Results USE-CASE 2: 1. Every System step was fulfilled correctly; 2. Some accelerometric data in particular timeframes were missing due to the distance of the mobile device from the patient caused by forgetfulness or special conditions (e.g. MRI or other exams). In normal operating condition, the data throughput is sufficient to guarantee more than 80 sample/seconds. ALCOA. 3. Pebble Time and the smartphone (Motorola Moto X Play and Huawei Nova Young) fully charged lasted more than 8 hours. 4. The data was downloaded and successfully analyzed (even with some accelerometric data loss due to devices). ALCOA.

Table 13: Results for USE-CASE 1 and USE-CASE 2. Every steps involving data process states if an ALCOA requirement is met, highlighting in black the corresponding letter. If a letter is red the requirement is not met.

6 Discussion

In this work a system for telemonitoring DBS patients was designed, implemented and tested in a real research environment. The first step of this validation, the patient-centered phase, confirms that the combination of two technologies, mobile e-diary and wearable monitoring, was a reliable tool to collect information relevant for tracking patient's activity and symptoms, and in the second phase, with the integration of the LFPs and neurological data, it suggests that a multi-data/multi-sensor system may improve the reliability of research outcomes and even diagnostic results.

1. *Effective Telemonitoring:*

The third phase of this work suggests that the system, expandable to broader applications, is able to integrate the clinical data acquisition, the personally collected health data, and, using a standard based architecture, able to ensure the fulfillment of the basic requirements for meaningful data exchange with institutional healthcare records ("HL7 Standards Product Brief - CDA® Release 2," 2018).

The patient reported outcomes collection tool developed by this study and especially the e-diary is regarded to as a desirable characteristic both in research and in patient health monitoring by the Movement Disorder Society ("PD Diary," 2018). The system could be used to implement the latest wearable technology, but also, due to the CDA-2 standard here adopted, it could be used to connect to various medical devices not limiting the data collection to personal area network systems.

The framework shows reliability in protecting the PHI and addressing the evolving regulations regarding this particular topic, ensuring privacy requirements that spans from the EU GDPR and other regulations to the US HIPAA guidelines, even if this is an initial test on the topic a fully updated validation test is possible in future, including patients as a direct digital data source.

In a communication-wise perspective, the proposed architecture is in agreement with the hypothesis that interoperability issues in health IT can be addressed by using web services (Koumaditis, Themistocleous, & Da Cunha, 2013). In fact, the system implements specific web services to ensure interoperability among the different systems (WebBioBank, WFM, and mHealth App) and to enable the communication among patients/caregiver, researchers, and physicians by using standards such as PHMR template compliant with RIM (CDA2) and dictionaries.

To address the serious issues on accuracy and reliability caused by the commercial nature of the personal devices, the low clinical knowledge of the patients and the lack of clinical supervision, we tested multiple and independent sources (i.e. accelerometric smartband and patient diary). This multiple data source gathering gives the physician a bigger and more reliable picture related to the same clinical outcome, even if created by less reliable means. The usability, even if not directly measured via questionnaire, was ensured by the actual e-diary data volume filled-in by the patients. The heterogeneity of data given by the use of multiple personal sources can also be used to extract useful information within the interaction of those data, e.g. the patient cognitive status (diaries) versus his/her motor

status (bracelet), or to further understand the issues that patients can have with the device. This approach gives a more patient-centered perspective without overlooking his/her real motor condition. Using a commercial smartband showed that not all devices are up to the task and it is critical to made a technology assessment of wearables. The smartphones specifications, instead, could be more lax and the standardization between budget grade models made them virtually interchangeable (notice that user satisfaction, on this topic, was not tested) but when further elaborations (e.g. BAS algorithm calculation) a more capable device, or directly cloud assistance, is required.

This study also highlighted that the ability of a wearable to collect data autonomously (the real criticality of all the Patient System) during the daily living of these especially fragile patients not used to keep the mobile phone close to them is one of the most important feature. Daily network data collection compliance (even with the aid of Caregivers) was high, but minute-by-minute compliance of a simple task like carry the smartphone, was not. This internal storage capability will be a major requirement in the future implementations of this framework.

The initial thesis work suffered from the same issues that it wants to address, i.e. the data integration within a single subject and single time frame. To gather the results, all the components must be simultaneously and synchronously working for every patient to gather significant results but the various data sources are all from systems in prototypal stage, starting from the patient App developed for untested, even if commercial, devices; the different implementations of the WBB, the development of the new WFM and the LFP aDBS recording device.

A lot of time was dedicated to gain the technological and methodological footing to make the initial study possible but the initial work is laying the foundation to make the system effective, modular and scalable.

2. Implications for aDBS development

In phase two of our experiment the patient generated data was integrated with the aDBS stimulator. The overall system provided useful data in one of the longest experiments with aDBS, with a freely moving patient. The clinical observations, paired to the accelerometric and e-diary data, showed that varying the DBS voltage linearly with beta rhythm, in conjunction with normal levodopa assumption, provides constant benefit for hours of unrestricted patient activity.

The analysis of daily of life activities like talking, sleeping, relaxing, was reported with the e-diary and the data from the smartband accelerometer. The combination of the two data sources in 30-minute windows provided useful indication of the predominance of a certain activity during this time frame, even if cannot track the probable co-occurrence of different activities during those time frames. To mitigate this limitation the beta power was studied in average during the 30-minute window. The framework can be further expanded using more sensors to further increase the time granularity and expanding the activity classes using a more quantitative approach. The framework was useful to assess how the beta-based aDBS can induce stable control of PD-related motor disturbances by adapting the

stimulation parameters, and how the beta power follows the other two reporting methodologies (accelerometer and e-diary).
The aDBS algorithm was able to adapt to all the patient beta modulations, which we assume were related to clinical motor fluctuations. The beta power reduction induced by levodopa produced a decrease in stimulation voltage, resulting in a lesser voltage impulse amplitude delivered to the patient.
Overall, this study framework is useful in the development of the new generation of implantable aDBS devices for treating PD.
The clinical findings reported by the neurologists were consistent with both the accelerometer/e-diary and the beta power LFPs reported by the external aDBS device.
The study provided also preliminary information on safety of both aDBS and the other wearable system, since no adverse events were observed due to device malfunction or the stimulation.

As stated in this chapter, future studies are needed to establish this system in a true ecological environment and with larger populations but our results suggest that an integration between patient-generated data and clinical data could be used to support research studies and opens the way in using personally collected data to improve or facilitate longitudinal research introducing a true holistic patient's personal assessment and a continuous monitoring.

6.1 Limitations and future research

In a normal USE-CASE the personally generated data do not come from a controlled environment (hospitalized patients) and not from a specifically developed app with multiple users. These are the limitation of the study presented in this thesis:

1. The sample size of patients involved was small:

The sample size of this thesis, comprised by Rigid-Akinetic post-surgery STN-LFP DBS PD patients, is limited. Further studies are being made with the now established framework.

2. The validation was performed in a controlled environment:

In this regard, a hospitalized patient is not in a true ecological environment, testing daily living activities in these conditions do not fully represent a patient at home or in a homecare environment.
In the next future a more focused testing procedure with the patients in their home environment must be carried out to verify the usability (with also dedicated questionnaires) and robustness in longitudinal studies.

3. The mHealth App was developed ad hoc:

The app was made for this study and the data exchange could be finely tailored to fit in the framework, also the Pebble Time Watch product is not on the market anymore and all the support was discontinued,

following the FitBit acquisition ("RIP Pebble," 2016) deprive the research of a pseudo open programmable system.

The data formats of the various consumer grade devices are mostly not open, even if big companies like Apple is following the HL7 standard based architecture mentality ("Accessing Health Records | Apple Developer Documentation," 2018). A migration to FHIR and implementation with Apple Research Kit ("ResearchKit and CareKit - Apple," 2018) and Android Research Stack framework ("ResearchStack," 2018) is the aim of future development.

4. Patient centered technology assessment:

A usability and electronic literacy questionnaire were not administered to not stress to much the patient in his/her particular condition, and it was not possible to really assess the user mobile phone opinion.

Cognitive patient condition was not assessed directly, even if the compliance was high the particular post-surgery status could not be representative of a more generalized condition.

As stated in point 1 a usability study in an ecological environment must be carried out to assess a true patient centered perspective.

6.2 Conclusions

Our results suggest that an integration between patient-generated data and clinical data for supporting research studies is possible. The mobile patient system was well tolerated and the compliance was high, combining the patient reported outcomes with wearable sensor measurement. This opens the way for using personally collected health data to improve or facilitate longitudinal research, introducing holistic patient's personal assessment and monitoring.

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