

A double closed loop to enhance the quality of life of Parkinson's Disease patients: REMPARK system

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Abstract. This paper presents REMPARK system, a novel approach to deal with Parkinson's Disease (PD). REMPARK system comprises two closed loops of actuation onto PD. The first loop consists in a wearable system that, based on a belt-worn movement sensor, detects movement alterations that activate an auditory cueing system controlled by a smartphone in order to improve patient's gait. The belt-worn sensor analyzes patient's movement through real-time learning algorithms that were developed on the basis of a database previously collected from 93 PD patients. The second loop consists in disease management based on the data collected during long periods and that enables neurologists to tailor medication of their PD patients and follow the disease evolution. REMPARK system is going to be tested in 40 PD patients in Spain, Ireland, Italy and Israel. This paper describes the approach followed to obtain this system, its components, functionalities and trials in which the system will be validated.

Keywords. Parkinson's Disease, Wearable System, Disease Management

Introduction

Parkinson's disease (PD) is the second most common neurodegenerative disease after Alzheimer's disease. PD is a progressive neurological condition, resulting from the degeneration of dopamine-producing neurons in the substantia nigra, which is located within the basal ganglia circuit, deep in the lower region of the brain. According to the World Health Organization, 5.2 million people suffer PD in the World [1]. Mortality is

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two to five times higher among affected people than among age-matched controls [2]. Given that PD is mainly suffered by elderly people, and that this population group is growing PD is becoming a first magnitude public health problem [3], due to the associated reduced capacity for self-care and quality of life (QoL).

Given the degeneration in the substantia nigra that PD provokes, patients suffer a lack of dopamine, which is one of the neurotransmitters involved in the control of movement. The symptoms of PD can be broadly classified into motor symptoms and non-motor symptoms. Motor symptoms (MS) include rigidity, tremor, bradykinesia (slow movement), postural alterations, tendency to fall, reduced gait speed, reduced step length, and episodes called freezing of gait (FoG) [7], which consists of a blockade of the motor activity, resulting in a sudden inability to start or continue walking, as if glued to the spot [4]. Non-motor symptoms (NMS) may include dementia, depression, anxiety, sleep initiation and sleep maintenance disturbances, urinary problems, sexual disturbances, olfactory dysfunction and fatigue [5][6].

Currently, there are two main approaches that are being researched in order to deal with PD symptoms: continuous [10][11] and discontinuous monitoring [8][9]. Both approaches aim to meet two goals: on the one hand, both monitoring types might have the purpose of providing richer information to neurologists and, on the other hand, they expect to lead to some specific actuations (listed later on) in order to increase the QoL of PD patients.

Continuous monitoring devices consist in unobtrusive inertial sensors capable of continuously monitoring patients during daily life activities. These devices typically comprise inertial sensors (accelerometers, gyroscopes and magnetometers). Many examples exist in the literature, such as wrist sensors to monitor tremor [8], ankle sensors to monitor FoG and gait parameters [11] or waist sensors to monitor gait [10]. On the other hand, discontinuous monitoring devices require the patient to perform specific activities and, consequently, they are able to provide a snapshot of the current patient status at isolated times. For instance, *Kinesia* system is a device that requires the patient to perform specific motor exercises [12] similarly to the system presented by Patel et al. [8]. It should be noted that, although MS can be monitored either continuously or discontinuously, NMS are capable of being monitored only discontinuously since questionnaires and direct observation are the unique tools available to determine the current non-motor status of PD patients [13]. In this sense, it has been recently developed a specific questionnaire that quantifies their assessment in PD, which is called Non-Motor Symptoms Scale (NMSS), although other standard scales quantifies both NMS and MS such as Movement Disorder Society-Unified Parkinson's Disease Rating Scale (MDS-UPDRS) [13].

Monitoring of PD symptoms aims to improve patients' QoL by actuating onto the disease. In this sense, different actuation paradigms can be found in the literature. First, it was recently tested the automatic regulation of the dosage administered by an infusion pump according to patient's status, which was estimated by a waist sensor [14], similarly to current closed-loop approaches for diabetes. Second, since FoG episodes are mostly overcome by means of audio cues, an Auditory Cueing System (ACS), which consists of a small wireless earphone, was employed to provide these audio cues when FoG episodes were detected [11]. Finally, a closed-loop actuation consists in neurologists adjusting the medication regimen of patients according to the information provided by monitoring devices.

This paper describes the REMPARK system, which is the first system that unites monitoring of both MS and NMS in PD as well as different actuation approaches. More

concretely, REMPARK includes FoG and gait disturbances correction through audio cues and enables neurologists to adjust the medication regimen. Moreover, the REMPARK system has been also validated to control other actuators such as haptic cueing devices and apomorphine infusion pumps. This system is composed of two main components: a wearable system with FoG actuation capabilities and a cloud-based service that enables neurologists, patients and caregivers to follow the disease evolution and communicate among them. This wearable system contains a belt-worn sensor that continuously monitors patients' movement. This device analyzes in real-time the signals provided by the sensor based on personalized machine learning algorithms that were developed from a database of labeled signals obtained from 93 PD patients [15]. REMPARK system has been recently developed and is going to be tested with 40 patients stemming from Spain, Italy, Ireland and Israel.

The remainder of the paper is described as follows. First, the wearable system is described and, second, the cloud-based service is detailed. Then, the previously collected REMPARK database that enabled the development of movement disorder detection algorithms is presented. Next, the tests that will guide the validation of REMPARK system in 40 PD patients are presented and, finally, conclusions are presented.

1. REMPARK wearable system

REMPARK wearable system aims to monitor PD patients both continuously and discontinuously. It is composed of three devices: a movement sensor that continuously monitors MS and determines their presence in real-time, a headset capable of providing audio cues to PD patients in order to overcome FoG or improve their gait and, finally, a smartphone that discontinuously monitors both MS and NMS of patients, controls the audio cueing based on movement sensor information and sends the gathered information to the cloud-based service. Figure 1 depicts the structure of the wearable system.

REMPARK wearable system not only provides a way of monitoring motor and non-motor fluctuations of PD patients, but also enables them to deal with FoG since the combination of its three elements helps to prevent and overcome FoG episodes. Thus, REMPARK wearable system can be also seen as a closed-loop system.

The following subsections describe the complete REMPARK system according to each one of their components.

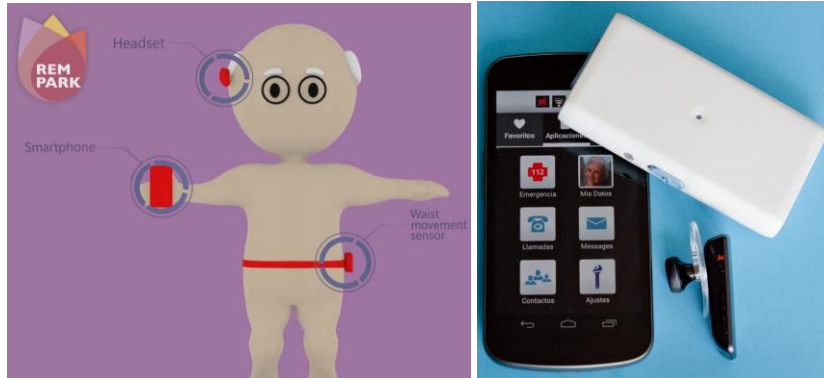


Figure 1. REMPARK wearable system.

1.1. Movement sensor

REMPARK movement sensor [16] is worn inside a hypoallergenic neoprene belt in order to locate it near the iliac crest. This sensor is capable of determining in real-time and at minute-basis the presence of bradykinesia, dyskinesia, FoG and falls. Moreover, it provides information on energy expenditure, cadence and if the patient has fallen at minute-level as well. This movement sensor has a Bluetooth connection by which shares the information with the smartphone.

The waist device is composed of three triaxial inertial sensors (accelerometer, gyroscope and magnetometer), a microcontroller (dsPIC33F), a Bluetooth communication module and a memory unit. The microcontroller samples data at 200 Hz. It also includes a Real-Time Clock/Calendar module that was calibrated against both Network Time Protocol (NTP) servers and frequency meters. A temperature correction by using an internal sensor is applied, obtaining a deviation lower than 40 ms. in a 48-h period. Its dimensions are 77 x 37 x 21 mm and its weight, with the battery, is 78 g.

This movement sensor determines the presence of bradykinesia, dyskinesia and FoG based on real-time machine learning approaches. These approaches employ, mainly, frequency features and 2nd order statistics as the input for Support Vector Machines [10]. The algorithms were developed based on a database of signals that were gathered by the same movement sensor device and that were labeled by clinicians. Section 3 describes in detail this database, in which 93 PD patients participated.

1.2. Auditory Cueing System

The ACS employed in REMPARK system enables patients to overcome FoG and improve their gait. It consists of a wireless earphone that employs Bluetooth to communicate with the smartphone, which centralizes REMPARK's wearable system.

The auditory cueing is activated by the system as soon as FoG or bradykinesia are detected by the movement sensor. The provided cueing is composed of repetitive sounds that help patients regain their normal gait cadence [11]. Thus, once a patient has continued walking without bradykinesia or has stopped walking, the cueing is

discontinued. The rhythm and volume of the cues provided by the ACS can be configured through the smartphone.

The ACS can be any commercial Bluetooth headset with, at least, Bluetooth version 2.1 and A2DP profile.

1.3. Smartphone

The smartphone has different roles within REMPARK's wearable system. First, it is the node in which the communications are centralized, since both movement sensor and ACS communicate with it. This way, it is also responsible of sending the collected data to the cloud-service so that they are available to clinicians. Second, it is in charge of controlling the ACS based on the current symptoms, as it has been previously described. Third, the smartphone offers patients a wide range of services to assist them in their activities of daily life through applications such as: medication manager, medication reminders, agenda or easy visualization of symptoms detected by the system. Finally, it performs a discontinuous monitoring of MS and NMS as it is explained below. The smartphone employed in REMPARK is a Samsung Galaxy Nexus.

The discontinued monitoring performed by the smartphone provides a snapshot of patients' status on a given instant. This snapshot is capable of providing information on both MS and NMS. On the one hand, the smartphone offers the patient specific games in which the motor state is analyzed. Two different tests are offered:

- Tap Prompt: A mole appears on the screen in different positions and the user is asked to tap the appearing mole as soon as possible.
- Touch a Button Repeatedly Prompt: The user is asked to press a button repeatedly for a predefined number of times in order to fill a container.

On the other hand, the smartphone offers the possibility of filling in questionnaires or scales that enable clinicians to know the state of the patients. These scales can be answered by the same patient or by a caregiver. Finally, the smartphone also provides other tests that evaluate patients' NMS, such as the backwards Corsi Prompt, in which a number of blocks are highlighted in sequence and then the user is asked to touch the squares that had previously been highlighted in a backwards sequence.

2. Disease management

REMPARK system comprises a second closed-loop that consists in the disease management, in which neurologists and caregivers are involved. Figure 2 depicts this second closed-loop system.

Disease management gathers the information provided by the REMPARK wearable system. This information represents the long-term evolution of MS and NMS. This way, this information can be used by neurologists to provide suitable rehabilitation to their patients or tailor their medication regime.

This second closed-loop of actuation is composed of different parts. Data sent by REMPARK wearable system is collected in REMPARK server. With this server, a so-called rule engine analyzes and enriches the information sent by the REMPARK wearable system. Then, this information is presented to patients, caregivers and clinicians through the so-called Disease Management Application (DMA). Finally, the

DMA also enables neurologists to manage the disease by making appointments with patients or even change the medication regime. The following sections describe the different parts of the disease management loop.

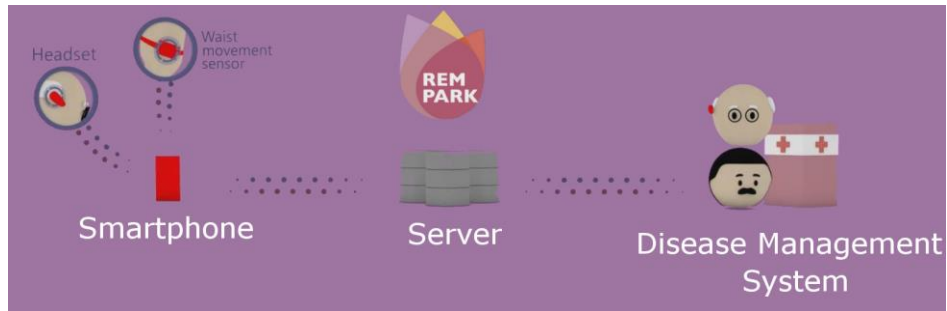


Figure 2. REMPARK disease management.

2.1. Server database and Rule Engine

REMPARK's central server collects all the information available from REMPARK wearable system. It is permanently updated so doctors are able to follow the evolution of the patients' disease.

Data collected in the server is processed through an intelligent data treatment at this second level based on a rule engine. This rule engine provides clinicians and patients a global overview of the patient situation, thus enabling them to translate the immediate information provided by the wearable system to the middle/long term scope.

REMPARK central server consists of a standard database with different interface capabilities to communicate with the rest of the system elements. The rule engine consists in a service deployed in the same central server that enriches the information contained in it.

2.2. Disease Management Application (DMA) - Monitoring and actuation

DMA is a web application that not only presents the information collected in the central server in a suitable way to clinicians, caregivers and patients but also enables them to manage the disease by monitoring the evolution of MS and NMS, making appointments and by changing or informing about treatment plans.

Consequently, the DMA has different interfaces depending on the role of a person within the disease management. Moreover, DMA interacts with the Electronic Health Record, so that information about the symptoms can be inserted in it by REMPARK system or, on the other hand, clinicians may improve treatment by knowing co-morbidity related information.

DMA is able to graphically present the information contained in the central server. For instance, it can graphically depict the presence of dyskinesia, bradykinesia or FoG along a day. Moreover, DMA enables clinicians to define deviation range from normal values and, when this deviation is given, the system pops up an alert on the clinicians interface and, in some cases, it presents protocols to overcome the situation. This way, thanks to data gathering and the rule engine, the DMA is also capable of providing decision support mechanism to the doctors, suggesting clinical actions. Finally, the

DMA has the ability to ask patients to fill in a clinical assessment questionnaire by the smartphone.

Finally, it should be noted that this solution is adequate for most PD population since it can be used at different settings of drug delivery through, for instance, pump or oral treatments. Thus, this second closed-loop of the REMPARK system is useful for different treatments and, consequently, at different stages of the disease progression.

3. REMPARK database for movement disorders detection

As it has been previously mentioned, REMPARK project has developed a database of signals and relevant clinical data from 93 PD patients in Israel, Italy, Ireland and Spain. This database led to the final REMPARK system that has been previously described and, moreover, enabled obtaining the movement disorder detection algorithms that monitor ON/OFF motor fluctuations and the detection of dyskinesia, bradykinesia and FoG symptoms. This section describes the data collected in this database.

Data collection took place at patient's home and lasted 4 to 8 hours, thus providing remarkable information on daily life environment of patients. Moreover, data collection was divided into two kinds of tests:

- Short controlled tests during which patients were asked to perform certain activities so that specific motor symptoms, false positives, UPDRS scale values, gait speed and step/stride length were obtained. These tests were closely controlled so that an accurate gold-standard was obtained
- Free activity monitoring of the patient so that natural symptoms and activities were recorded. This monitoring lasted for hours and the gold-standard used in these tests was not required to be as accurate as in the previous case.

The two types of experiments took place in alternation and were performed in each motor state. Thus, when the patient was in the OFF phase, the specific controlled tests for the OFF symptoms were conducted and the remaining OFF state time was used for monitoring their free and natural activity. Similarly, when the patient entered the ON phase, some short tests for capturing ON symptoms were performed and the remaining time was devoted to monitoring the free natural activity.

Data collected in this database comprise:

- Relevant clinical data. It consists of UPDRS values obtained in each motor state, socio-demographic data and the presence of symptoms among the population.
- Labeled inertial signals. These signals were acquired based on two inertial sensors: one in the wrist for assessing tremor and one in the waist near the Iliac Crest for detecting the rest of symptoms. The wrist device contains a triaxial accelerometer, a microcontroller and a communications unit. Its microcontroller acquired samples at 80 Hz and sent them to the waist sensor using a Bluetooth (BT) 2.1 link.

Once the inertial signals were collected, typically a day after the experimentation, the signals corresponding to the short tests were labeled by clinicians according to the video recording taken during the tests. This way, since signals and videos were previously synchronized, signals were labeled according to the severity of each signal. Table 1 summarizes the amount of signals collected in the database according to different symptoms.

Supervised learning algorithms were then employed to exploit them and the final algorithms were implemented in real-time within the movement sensor belonging to the REMPARK wearable system.

Table 1. Summary of labeled inertial signals in REMPARK database.

Symptom	Amount of signals (h)	Amount of signals in ON state (h)	Amount of signals in intermediate state (h)	Amount of signals in OFF state (h)
Bradykinesia	45.2	2.9	5.6	36.8
Dyskinesia	68.1	48.2	12.2	7.7
Tremor	51.4	15.1	12.4	23.9
FoG	4.8	0.9	0.7	3.2
Total	360.4	170.3	73.5	116.6

4. REMPARK system validation

A validation of the described system will be performed by 40 PD patients from Italy, Israel, Spain and Ireland. A specific clinical study has been designed in order to study the performance and reliability of the REMPARK system under real conditions and to study the validity of the ON/OFF motor phase detection by the system. Moreover, the following secondary objectives have been set:

1. To study the validity of questionnaires and tests administered via the smartphone in detecting ON/OFF states
2. To investigate the validity of inventories administered via the smartphone to assess non-motor Parkinson's disease symptoms
3. To study the efficacy of an auditory cueing system, activated by an algorithm, in improving FoG.
4. To assess both usability and user's satisfaction referring to the REMPARK system application under real daily living conditions
5. To study the validity of the fall detection algorithm of the REMPARK system.
6. To verify the safety of the REMPARK system in individuals with PD.

The reference population for this study is formed by Parkinson's patients with moderate to severe disease and motor symptoms including ON/OFF phases, FOG or dyskinesia (Hoehn & Yahr scale value greater than 2 in ON phases and lower than 5 in OFF phases).

The validation will take place along 5 days. The first one will be employed to adjust the system to the patient, enabling detection algorithms to be personalized to each patient. The rest of the 4 days patients will be wearing and using REMPARK system under real conditions.

For comparison purposes, patients will note down the exact time of every motor change they feel in a diary. In addition they will record their motor phase hourly in the ON-OFF diary. This way, the accuracy of the motor state detection performed by REMPARK system will be measured.

5. Conclusions

This paper describes REMPARK system, which aims to increase QoL of PD patients and is composed of two closed-loop levels. The first one comprises a wearable system that enables disease management based on actuation against gait disturbances through audio cueing. The second closed-loop consists in a disease management that actuates on the mid-to-long term and that involves patients, caregivers and clinicians.

REMPARK system enables the monitoring of MS and NMS at the same time. On the one hand, movement sensor and smartphone are in charge of establishing the motor state of PD patients, the former in a continuous way and the latter in specific instants given the interaction needed with the patient. On the other hand, the smartphone provides NMS monitoring through the questionnaires presented to patients.

REMPARK system was developed by exploiting a database previously collected from 93 PD patients at their natural environment. This database provided 360 hours of inertial signals that were labeled by clinicians, which led to reliable movement disorder detection algorithms that are included in the movement sensor worn at waist.

In the following months the validation of REMPARK system will start. It will be tested in Italy, Ireland, Spain and Israel by 40 PD patients during 4 days.

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