

Gait rehabilitation with an active pelvis orthosis for patients with Parkinson's disease: model-based predictions and assessment of an adaptive framework

Ph.D. thesis presented by

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*Je veux me souvenir de mon papa poule, mon papa blagueur,
mon papa cuistot, mon papa bricoleur.
Je veux me souvenir de ta fierté pendant ma remise de diplôme,
encore plus grande quand tu as appris le sujet de ma thèse.
Tu es la motivation derrière tout ce travail,
sans toi tout cela aurait eu beaucoup moins de sens.*

Abstract

Parkinson's disease is a severe neurodegenerative disorder that affects sensorimotor control, leading to various gait impairments, such as decreased gait speed, stride length, and cadence. These impairments increase the risk of falling and significantly impact the daily lives of affected people. Additionally, they have a decreased level of long-range autocorrelations in series of stride durations, which is a subtle property of gait motor control characterizing natural gait variability. In this context, it is essential to develop innovative therapies that can compensate or mitigate these impairments. Wearable robots – such as active pelvis orthosis – have the potential to be part of this emerging therapeutic toolbox, since they can be used in daily life contexts. In this thesis, we assessed the effects of a walking assistance method relying on adaptive oscillators and delivered by an active pelvis orthosis. This framework is appealing in the context of walking assistance since it naturally adapts to the user's gait features.

In this thesis, we first developed model-based predictions about the loss of long-range autocorrelations in the gait of patients with Parkinson's disease, and then we explored the potential of restoring these autocorrelations through the use of the proposed framework relying on oscillator-based walking assistance. This first step demonstrated that this type of assistance has the potential to improve gait variability in patients.

Secondly, we examined the impact of this adaptive assistance, which intrinsically tends to normalize the gait pattern, on the level of long-range autocorrelations during walking experiments with healthy subjects. Indeed, many studies have demonstrated in the past that this long-range autocorrelation metric is impacted by external constraints, such as a treadmill or

a metronome, or by pathologies, such as Parkinson's or Huntington's diseases. Ten healthy participants, aged between 56 and 77 years, performed four overground walking sessions, wearing the orthosis with different assistive parameters. The results indicated that the adaptive assistance provided by this device can enhance gait metrics typically affected by aging, such as the hip range of motion, walking speed, stride length and duration, without impacting natural gait variability represented by the level of long-range autocorrelations in series of stride durations. These findings hold significant potential for gait rehabilitation in patients with Parkinson's disease, since the gait metrics that are improved by the walking assistance are precisely those that are affected by this disease.

In the last part of this thesis, we investigated the influence of the same wearable active pelvis orthosis on the gait of patients with Parkinson's disease. Eight patients with low to moderate disease progression (Hoehn and Yahr stages 1–2.5) performed overground gait training three times per week for four consecutive weeks, assisted by this device. The same metrics examined during the experiments with healthy individuals were assessed before, directly after, and one month after training. The results indicated improvements in hip range of motion, gait speed, stride length, and duration after training, which were maintained one month after its end. Regarding the level of long-range autocorrelations, the population's behavior was standardized towards a value closer to that of healthy individuals after training, but with no retention after one month.

This thesis therefore opens the door to the use of oscillator-based walking assistance, adapting in real time to the user's gait kinematics. It also highlights the importance of considering a gait metric characterizing the proper functioning of the locomotor system, i.e., the level of long-range autocorrelations in series of stride durations, throughout the whole rehabilitation pathway.

Résumé

La maladie de Parkinson est un trouble neurodégénératif sévère qui affecte le contrôle sensorimoteur, entraînant divers troubles de la marche, tels qu'une diminution de la vitesse, de la longueur des pas et de la cadence. Ces déficiences augmentent le risque de chutes et ont un impact significatif sur la vie quotidienne des individus concernés. De plus, ceux-ci présentent un niveau réduit d'autocorrélations à long terme dans leurs séries de durées de pas, une propriété subtile du contrôle moteur de la marche qui caractérise la variabilité naturelle de celle-ci. Dans ce contexte, il est essentiel de développer des thérapies innovantes qui peuvent compenser ou atténuer ces déficiences. Les robots portables, tels qu'une orthèse pelvienne active, ont le potentiel de faire partie de cet ensemble d'outils thérapeutiques émergents, car ils peuvent être utilisés dans la vie quotidienne. Dans cette thèse, nous avons évalué les effets d'une méthode d'assistance à la marche reposant sur des oscillateurs adaptatifs et délivrée par une orthèse pelvienne active. Cette approche est attrayante pour assister la marche car elle s'adapte naturellement aux caractéristiques de la marche de l'utilisateur.

Durant cette thèse, nous avons d'abord élaboré des prédictions basées sur un modèle concernant la perte d'autocorrélations à long terme dans la marche des patients atteints de la maladie de Parkinson, puis nous avons exploré le potentiel de restauration de ces autocorrélations grâce à l'utilisation d'une assistance à la marche basée sur des oscillateurs. Cette première étape a permis de démontrer que ce type d'assistance a le potentiel d'améliorer la variabilité de la marche chez ces patients.

Ensuite, nous avons examiné l'impact de cette assistance adaptative, qui tend intrinsèquement à normaliser le schéma de la marche, sur le niveau d'autocorrélations à long terme lors d'expériences de marche avec

des sujets sains. En effet, de nombreuses études ont démontré dans le passé que ce niveau d'autocorrélations à long terme est influencé par des contraintes externes, telles qu'un tapis roulant ou un métronome, ou par des pathologies, telles que la maladie de Parkinson ou de Huntington. Dix participants en bonne santé, âgés de 56 à 77 ans, ont effectué quatre séances de marche sur sol plat, en portant l'orthèse réglée avec différents paramètres d'assistance. Les résultats ont indiqué que l'assistance adaptative fournie par ce dispositif peut améliorer les mesures de la marche généralement affectées par le vieillissement, tels que l'amplitude du mouvement de la hanche, la vitesse de marche, la longueur et la durée des pas, sans affecter la variabilité naturelle de la marche représentée par le niveau d'autocorrélations à long terme dans les séries de durées de pas. Ces résultats offrent un potentiel significatif pour la rééducation de la marche chez les patients atteints de la maladie de Parkinson, puisque les mesures de la marche améliorées par l'assistance sont justement celles affectées par cette maladie.

Dans la dernière partie de cette thèse, nous avons étudié l'influence de cette même orthèse sur la marche des patients atteints de la maladie de Parkinson. Huit patients présentant une progression de la maladie faible à modérée (stades de Hoehn et Yahr 1–2.5) ont effectué des séances d'entraînement à la marche sur sol plat trois fois par semaine pendant quatre semaines consécutives, assistés par ce dispositif. Les mêmes mesures examinées lors des expériences avec des personnes en bonne santé ont été évaluées avant, immédiatement après et un mois après l'entraînement. Les résultats ont indiqué des améliorations de l'amplitude du mouvement de la hanche, de la vitesse de marche, de la longueur et de la durée des pas après l'entraînement, maintenues un mois après la fin de celui-ci. En ce qui concerne le niveau d'autocorrélations à long terme, le comportement des patients s'est rapproché de celui des personnes en bonne santé après l'entraînement, mais sans rétention un mois après.

Cette thèse ouvre donc la voie à l'utilisation d'une assistance à la marche basée sur des oscillateurs, qui s'adapte en temps réel à la cinématique de la marche de l'utilisateur. Elle met également en évidence l'importance de prendre en compte une mesure de la marche qui caractérise le bon fonctionnement du système locomoteur, à savoir le niveau d'autocorrélations à long terme dans les séries de durées de pas, tout au long du parcours de rééducation.

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List of abbreviations

ABC	Activities-specific Balance Confidence
AFA	Adaptive Fractal Analysis
APO	Active Pelvis Orthosis
CPGs	Central Pattern Generators
DFA	Detrended Fluctuation Analysis
fBm	fractional Brownian motion
fGn	fractional Gaussian noise
FOG	Freezing Of Gait
H&Y	Hoehn and Yahr
IMU	Inertial Measurement Unit
LRA	Long-Range Autocorrelations
MDS-UPDRS	MDS-Unified Parkinson's Disease Rating Scale
Mini-BESTest	Mini Balance Evaluation Systems Test
MMSE	Mini-Mental State Examination
PSD	Power Spectral Density
ROM	Range Of Motion
RRA	Rescaled Range Analysis
SCPG	Super Central Pattern Generator

1

Introduction

IN a growing and graying population, Parkinson's disease has become the fastest rising neurodegenerative disease [Ou et al., 2021]. Indeed, the number of people affected by this disease worldwide has risen from 2.5 million in 1990 [Dorsey et al., 2018] to 8.5 million in 2019 [Ou et al., 2021]. This leads to a growing economic burden for the healthcare system, society and patients. For example, it was estimated in 2016 in Luxembourg that a patient with Parkinson's disease costs on average €22,673 more per year to the national healthcare payer than a person of the same age without this disease [Schmitz et al., 2022]. This includes costs related to long-term care (e.g., institutionalized care, day care, at home care, ...), hospital stays, medication and medical devices, clinicians, specialist services (e.g., speech therapists, physiotherapists, opticians, ...), nurses, and laboratory tests.

Among the many disorders encountered by patients, those affecting their gait greatly impact their quality of life: they have a slower gait speed, shorter stride length and decreased cadence as compared to age-matched healthy individuals [Zanardi et al., 2021], which are associated with future falls [Creaby and Cole, 2018]. Indeed, the risk of falling is twice as likely in patients with Parkinson's disease as in age-matched healthy individuals [Kalilani et al., 2016]. This leads to a fear of falling, which induces patients to decrease their physical activities, and thus impacts their independence and therefore their quality of life [Bloem et al., 2001]. Consequences

of falls, such as fractures, also further increase the economic burden on the healthcare system [Pressley et al., 2003]. It is therefore important to consider gait rehabilitation in the treatment of patients with Parkinson's disease. In this framework, robot-assisted gait trainings are of particular interest, since they already showed interesting improvements in some gait parameters in patients with Parkinson's disease [Alwardat et al., 2018].

In this context, the objective of this thesis is to develop a gait rehabilitation protocol assisted by a wearable active pelvis orthosis for patients with Parkinson's disease, and to study its effect on several gait metrics. In particular, this thesis focuses on a metric characterizing natural gait variability, i.e., the level of long-range autocorrelations (LRA) in series of stride durations. This term refers to the fact that the current stride duration is influenced by those that happened several minutes ago [Bollens et al., 2013]. In particular, a certain level of LRA is present in series of healthy individuals, and deviations from this level can be used to identify a constrained or pathological gait.

This introductory chapter first describes the pathology and symptoms of Parkinson's disease, followed by existing treatments. Then, studies about the use of robot-assisted gait training with patients are reviewed. Finally, the thesis organization and research questions are developed.

1.1 Parkinson's disease

1.1.1 Pathophysiology and symptoms

In Parkinson's disease, the dopaminergic neurons in the substantia nigra pars compacta gradually disappear. This loss affects the proper functioning of the basal ganglia system, which plays a role in motor control, for example in the automatic execution of learned movements or in motor learning [Marsden and Obeso, 1994]. The nuclei composing this system are involved in the direct and indirect basal ganglia pathways (Figure 1.1). These two circuits work together to facilitate or inhibit motor activity respectively. In both pathways, cortical signals enter the striatum, flow through the output nuclei (the internal globus pallidus and the substantia nigra pars reticulata), then back to the cortex via the thalamus. The difference between both pathways occurs between the striatum and the output nuclei. In the direct circuit, as the name suggests, the signal passes from one

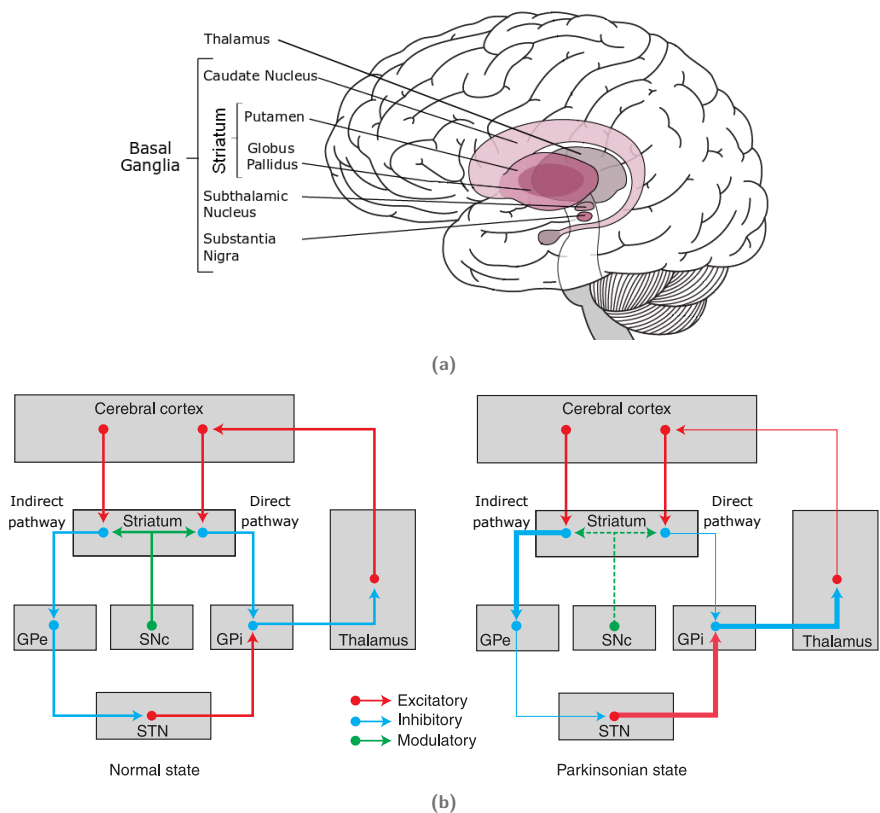


Figure 1.1 (a) Nuclei involved in the basal ganglia pathways (adapted from Merck & Co., Inc., Rahway, NJ, USA, 2023), and (b) schematic representation of the basal ganglia direct and indirect pathways (adapted from [Lanciego et al., 2012]), involving interactions between basal ganglia nuclei and other brain areas (i.e., the thalamus and motor cortex). The imbalance between the degrees of activation of the projections is represented by the arrows' thickness. Inhibitory (resp. excitatory) projections, represented in blue (resp. in red), obstruct (resp. stimulate) the activity of the nucleus on which they project. Modulatory projections, represented in green, regulate the activation of both pathways. SNc is the substantia nigra pars compacta, GPe/i the external and internal globus pallidus respectively, and STN the subthalamic nucleus.

to the other directly. Conversely, in the indirect circuit, the signal projects from the striatum to the external globus pallidus, then to the subthalamic nucleus, before reaching the output nuclei. By observing the projections between these different nuclei in Figure 1.1, the direct pathway has the effect of activating the motor cortex by inhibiting the internal globus pallidus. On the other hand, in the indirect pathway, this nucleus inhibits the activity of the thalamus, which therefore does not activate the motor

cortex. The proper functioning of these two circuits is due to the presence of dopamine in the striatum, coming from the substantia nigra pars compacta. The decrease of striatal dopamine due to the loss of neurons in Parkinson's disease has the effect of activating more the indirect circuit than the direct one. This imbalance between the basal ganglia pathways decreases the activation of the cortex, associated with movement initiation, resulting in bradykinesia [Lanciego et al., 2012].

Because of this neuronal loss, patients with Parkinson's disease encounter a wide range of motor and non-motor symptoms. Motor disorders are mainly caused by the loss of dopaminergic neurons in the substantia nigra pars compacta, while non-motor symptoms are thought to be caused by cell loss in other neuronal regions [Kouli et al., 2018]. The cardinal (i.e., prominent) motor symptoms are poverty of spontaneous movements (hypokinesia), slowness of voluntary movements (bradykinesia), rigidity, tremor and postural instability appearing in later stages. Other motor symptoms are for example postural abnormalities (forward or lateral bending of the trunk) and a hypokinetic gait, characterized by the gait disorders mentioned above [Balestrino and Schapira, 2019, Lanciego et al., 2012]. Moreover, some patients may experience freezing of gait (FOG), i.e., sudden and brief episodes where the patient cannot make a step forward despite the intention to walk [Nutt et al., 2011]. In addition, patients also encounter non-motor symptoms, such as for example loss of smell, excessive saliva production, sleep disorders, fatigue, depression, and cognitive disturbances [Balestrino and Schapira, 2019, Kouli et al., 2018].

As this neuronal loss is gradual, the symptoms of the disease evolve over time. Disease evolution can be staged through the Hoehn and Yahr (H&Y) scale according to the motor function level (Figure 1.2). The stages evolve from unilateral (stage 1) to bilateral disorder (stage 2), then to postural instability (stage 3), to loss of physical independence (stage 4), to finally being in a wheelchair or bedridden (stage 5). In the modified H&Y scale, stages 1.5 and 2.5 were added to account for intermediate states of the disease [Goetz et al., 2004].

1.1.2 Treatments

Existing pharmacotherapies act on three main axes. The first one is to restore the level of dopamine in the striatum by taking levodopa which is

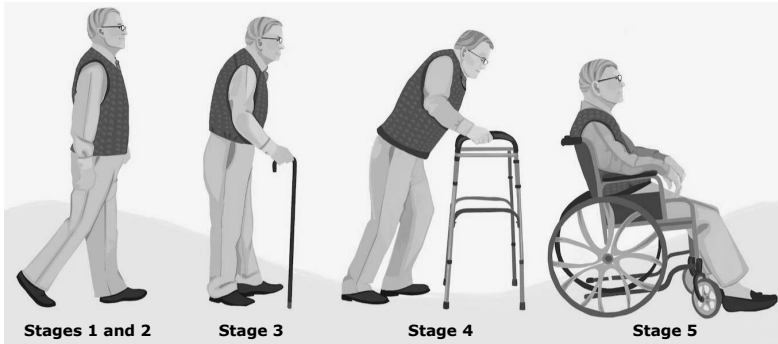


Figure 1.2 Illustration of the five stages of the Hoehn and Yahr scale characterizing Parkinson's disease (adapted from Dotdash Media, Inc., 2023).

converted to dopamine in the substantia nigra. The second one is to stimulate the dopamine receptors in the striatum with dopamine agonists, in order to activate the direct basal ganglia pathway. The last one is to prevent the degradation of dopamine by inhibiting the action of brain enzymes responsible for this degradation. Unfortunately, the effects of these drugs decrease as the disease progresses and add side effects to the symptoms of Parkinson's disease [Balestrino and Schapira, 2019, Zahoor et al., 2018].

Levodopa in particular can cause disabling side effects, especially in more advanced stages. Higher doses can induce dyskinesia, i.e., involuntary movements [Zahoor et al., 2018], by acting in the opposite way to parkinsonism on the basal ganglia pathways [Lanciego et al., 2012], therefore increasing the activation of the motor cortex (Figure 1.1). Levodopa can also induce on-off fluctuations, meaning that the effects of the medication wear off quickly in more advanced stages. During the "on" state, motor symptoms are relatively well-controlled, while the "off" state is characterized by severe motor symptoms, vanishing only with the next dose of levodopa [Zahoor et al., 2018].

For patients whose symptoms no longer respond effectively to medication, device-aided therapies can also be used. Levodopa can be administered directly and continuously into the intestine in gel form via a pump. There exist two gels with different compositions, i.e., Duodopa or Lecigimon [Armstrong and Okun, 2020, Nyholm and Jost, 2022]. This device allows to better control motor symptoms. Patients can also be implanted

with Deep Brain Stimulation electrodes, which sends electrical pulses either to the subthalamic nucleus, the internal globus pallidus or the thalamus [Balestrino and Schapira, 2019]. This stimulation also allows to better control motor symptoms, and to reduce medication.

However, current treatments only relieve motor symptoms of Parkinson's disease. Nowadays, treatments able to cure this disease are under active research. Since it is a neurodegenerative disease, two possible solutions exist: either re-injecting neurons when the patient is already advanced in the disease, or preventing this neurodegeneration if it can be diagnosed before the onset of neuronal loss. In response to the first solution, research is underway on stem cells [Rodríguez-Pallares et al., 2023], which has shown promising results but still requires more research. On the other hand, the second strategy raises two challenges: to be able to diagnose Parkinson's disease before the first motor symptoms appear and to find the correct neuroprotective treatment [Salamon et al., 2019]. The first challenge is addressed for instance by the Belgian product neuroCluesTM (P³Lab, Louvain-la-Neuve, Belgium, <https://neuroclues.com/>), based on eye movements examination and still under development. Regarding the second challenge, many drugs are currently being tested, targeting different mechanisms responsible for the neurodegeneration, as listed in a recent review paper [Sola et al., 2022].

Until such treatments are available, other solutions must be put in place to alleviate patients' symptoms which do not respond well to existing pharmacotherapy. In that case, a multidisciplinary approach is often adopted. In particular, physical therapy can help patients to improve their motor functions, such as gait and balance [Bloem et al., 2021, Osborne et al., 2022]. There exist many kinds of therapies, reviewed in detail in the following guideline [Osborne et al., 2022]. The most recommended are aerobic exercises, resistance training, balance training, external cueing, and gait training.

1.2 Robot-assisted gait training

Besides the conventional methods of gait training such as treadmill or overground walking, the past decade has seen the emergence of a growing number of studies on the rehabilitative effects of robot-assisted gait training on the gait of patients with Parkinson's disease. This framework has

become attractive because it enables patients to perform a large amount of gait cycle repetitions while reducing physical burden for the therapists [Marchal-Crespo and Riener, 2018]. This section reviews what has been done in the past for patients with Parkinson's disease and summarizes the main information about each study in Tables 1.1 to 1.3. It is partly inspired by the work carried out as part of the master thesis of M. Colasse and J. Vanderhaeghen [Colasse and Vanderhaeghen, 2023]. The reader is invited to consult their work to learn more about the general use of a robotic gait assistance in patients with Parkinson's disease.

The following studies can be differentiated by their purpose: several investigated the effects on the general physical state of the patient (e.g., spatiotemporal gait metrics, motor symptoms, mobility and/or balance; Table 1.1), others compared the effects of robot-assisted gait training with existing therapies (Table 1.2), while others analyzed the effects on FOG patients (Table 1.3).

Three types of robotic devices were used in these studies. On the one hand, there are end-effector devices (Figure 1.3a), which guide the movement of the lower-limbs through footplates [Molteni et al., 2018]. Among those used in robot-assisted gait training for patients with Parkinson's disease were the Gait Trainer GT1 (Reha-Stim, Berlin, Germany), the G-EO SystemTM (Reha Technology, Olten, Switzerland), and the Morning Walk (Curexo, Seoul, South Korea). These devices use predefined feet trajectories with adjustable step length to adapt to each patient [Picelli et al., 2012a, Sale et al., 2013, Choi et al., 2020]. On the other hand, there are treadmill exoskeletons (Figure 1.3b), which guide each lower-limbs joint along a preprogrammed trajectory [Molteni et al., 2018]. In this category, the Lokomat[®] (Hocoma, Zurich, Switzerland) was mostly used, and a few studies investigated the Walkbot_STM (P&S Mechanics Co., LTD., Seoul, South Korea). These first two types of devices are fixed and can only be used in a controlled environment, since they depend either on footplates or on a treadmill. This allows them to provide body weight support to patients. In most of the studies considered in this section, the gait speed was progressively increased while the body weight support was reduced as the training sessions progressed.

More recently, wearable orthoses (Figure 1.3c) have begun to emerge in robot-assisted gait training of patients with Parkinson's disease.

1 | Introduction

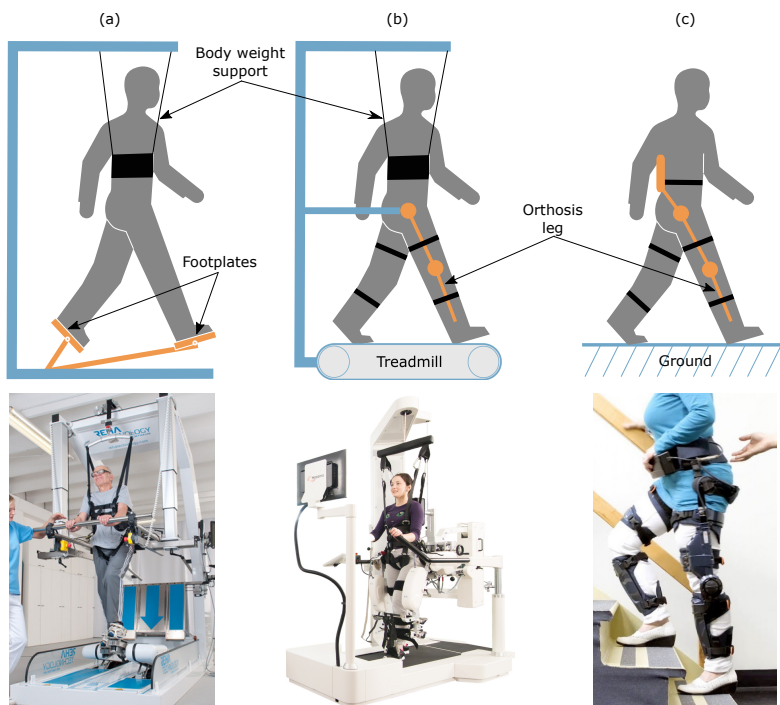


Figure 1.3 Schematic representation of the different kinds of robotic devices used in gait rehabilitation in patients with Parkinson's disease, with (a) an end-effector device, illustrated by the G-EO SystemTM (MossRehab, 2023), (b) a treadmill exoskeleton, illustrated by the Lokomat[®] (Arseus Medical Group, 2023), and (c) a wearable orthosis, illustrated by the Keeogo RehabTM (Neurophysio Rehabilitation, 2023). In the upper figures, the fixed parts are represented in blue, and the mobile parts in orange.

There is the SMA (Honda R&D, Tokyo, Japan), which assists the hip flexion-extension movements in order to increase the walk ratio (i.e., step length/cadence) [Buesing et al., 2015]. Another study used a wearable knee orthosis, the Keeogo RehabTM (B-Temia, Quebec, Canada), providing a complementary assistive torque to the user's knees during specific phases of the gait cycle [McLeod et al., 2017, McGibbon et al., 2018]. Finally, a study using the hip-knee-ankle exoskeleton EksoGTTM (Ekso Bionics, California, USA) is currently carried out on patients with Parkinson's disease [Romanato et al., 2022]. This exoskeleton provides an adjustable amount of assistance to move the legs according to a predefined gait pattern [Ramanujam et al., 2018].

Four articles have already reviewed most of these studies, with different focuses [Smania et al., 2013, Alwardat et al., 2018, Alwardat and Etoom, 2019, Picelli et al., 2021]. A. Picelli and colleagues [Picelli et al., 2021] highlighted that the robot-assisted gait trainings involved mainly a total of 10 to 20 sessions spread over 4 to 5 weeks, and lasting 20 to 45 min. A first conclusion from these reviews is that the majority of these studies showed an improvement in gait speed, stride length, motor symptoms, and balance functions, maintained up to six months after training [Smania et al., 2013, Alwardat et al., 2018, Picelli et al., 2021]. A second conclusion is that robot-assisted gait training has proved more effective than conventional physiotherapy, but equivalent to treadmill or balance training [Picelli et al., 2021]. Finally, six of these studies analyzed the effect of robot-assisted gait training on FOG episodes, whose severity and frequency were decreased in all of them [Alwardat and Etoom, 2019].

Some hypotheses on how these therapies influence these gait metrics have been put forward. Firstly, it could act as an external rhythmic cue on which patients can focus, thus compensating for the defective internal rhythm of the basal ganglia. Secondly, the repetition of gait-like movements might enhance the activation of automatic spinal control of locomotion. Finally, robot-assisted gait training also induces an increased physical activity, therefore strengthening the lower-limb muscles of patients as well as their cardiovascular status [Smania et al., 2013, Picelli et al., 2021].

In addition to the effects on the physical state of patients, some studies have also looked at other aspects. C. Fundarò and colleagues [Fundarò et al., 2018] examined the psychosocial impact of a gait rehabilitation training with the Lokomat®. Their findings revealed that the therapy was generally well accepted by the majority of patients, meaning that they were not disoriented or afraid when using it, irrespective of their age or level of mobility. On the other hand, the study of H. Kim and coworkers [Kim et al., 2023] investigated the changes induced by a robot-assisted gait training on brain structures. They showed that this training led to changes in white matter areas, likely reflecting improved gait automaticity and therefore a reduced cognitive effort during walking.

Table 1.1 Overview of studies on robot-assisted gait training in patients with Parkinson's disease analyzing the effects on the general physical state and capabilities of patients.

<i>Source</i>	<i>Device</i>	<i>Patients (H&Y)</i>	<i>Sessions</i>	<i>Follow-up eval?</i>	<i>Results</i>
[Paker et al., 2013]	Lokomat [®]	10 (1–3)	20 min, 2x/week for 5 weeks	6 weeks after	Gait speed and mobility ↗, and motor symptoms ↘, maintained at follow-up; quality of life ↗.
[Nardo et al., 2014]	Lokomat [®]	9 DBS* (–)	45 min, daily for 5 weeks	No	Gait speed, cadence, stride length and ankle ROM ↗; motor symptoms ↘; no effect on the hip and knee kinematics.
[Galli et al., 2016b]	G-EO System [™]	23 (–)	45 min, 5x/week for 4 weeks	No	Gait speed, cadence and stride length ↗; motor symptoms ↘.
[Fundarò et al., 2018]	Lokomat [®]	10 (–)	30 min, 3x/week for 4 weeks	No	Motor independence in activities of daily living ↗.
[Choi et al., 2020]	Morning Walk	8 (–)	30 min, 5x/week, 24 sessions	No	Ambulation ability ↗; no effect on lower-limb muscles strength.
[Yun et al., 2021]	Walkbot_S [™]	11 (2.5–3)	45 min, 3x/week for 4 weeks	4 weeks after	Gait speed ↗; balance ↗ and maintained at follow-up; no effect on gait automaticity.

*DBS stands for patients implanted with Deep Brain Stimulation.

Table 1.2 Overview of studies on robot-assisted gait training in patients with Parkinson's disease comparing its effects with existing therapies.

Source	Device	Patients (H&Y)	Sessions	Follow-up eval?	Results	Comparison*
[Picelli et al., 2012a]	GT1	41 (2.5–3)	45 min, 3x/week for 4 weeks	4 weeks after	Gait speed, cadence, stride length, and walking endurance ↗, and fatigue and motor symptoms ↘, maintained at follow-up.	RAGT > PT
[Carda et al., 2012]	Lokomat®	30 (1–3)	30 min, 3x/week for 4 weeks	6 months after	Walking endurance and gait speed ↗, maintained at follow-up.	RAGT = TT
[Picelli et al., 2012b]	GT1	34 (3–4)	40 min, 3x/week for 4 weeks	4 weeks after	Balance functions and gait speed ↗, and balance confidence and motor symptoms ↘.	RAGT > PT
[Sale et al., 2013]	G-EO System™	20 (2.5–3.5)	40 min, 5x/week for 4 weeks	No	Gait speed and stride length ↗.	RAGT > TT
[Picelli et al., 2013]	GT1	60 (3)	45 min, 3x/week for 4 weeks	3 months after	Gait speed, stride length and walking endurance ↗, maintained at follow-up.	RAGT=TT > PT
[Galli et al., 2016a]	G-EO System™	50 (1.5–3)	45 min, 5x/week for 4 weeks	No	Gait speed, cadence and step length ↗.	RAGT > TT

*RAGT stands for robot-assisted gait training, PT for physiotherapy, and TT for treadmill training.

Table 1.2 Overview of studies on robot-assisted gait training in patients with Parkinson's disease comparing its effects with existing therapies (part II).

Source	Device	Patients (H&Y)	Sessions	Follow-up eval?	Results	Comparison*
[Furnari et al., 2017]	Lokomat [®]	38 (2–2.5)	30 min, 6x/week for 4 weeks	3 months after	Motor symptoms ↘, maintained at follow-up.	RAGT = OT
[Fundarò et al., 2019]	Lokomat [®]	20 (2–3)	30 min, 5x/week for 4 weeks; RAGT + virtual reality	No	Motor symptoms ↘.	RAGT < OT
[Kim et al., 2022]	Walkbot_S [™]	40 (2.5–3)	45 min, 3x/week for 4 weeks	4 weeks after	Dual-task gait speed and balance ↗; motor symptoms ↘.	RAGT = TT
[Gryfe et al., 2022]	Keeogo Rehab [™]	41 (1–4)	60 min, 2x/week for 8 weeks; PT* exercises with or without the robot	No	Walking endurance and cognitive functions ↗.	RAGT > PT
[Kawashima et al., 2022]	SMA	12 (2–4)	30 min, 10x over 3 months	No	Walking endurance ↗; motor symptoms and metabolic cost of walking ↘.	RAGT > OT
[Kim et al., 2023]	Walkbot_S [™]	31 (2.5–3)	45 min, 3x/week for 4 weeks	No	Gait speed and automaticity ↗, associated with changes in brain's white matter.	RAGT = TT

*RAGT stands for robot-assisted gait training, PT for physiotherapy, TT for treadmill training, and OT for overground gait training.

Table 1.3 Overview of studies on robot-assisted gait training in patients with Parkinson's disease experiencing freezing of gait episodes.

Source	Device	Patients (H&Y)	Sessions	Follow-up eval?	Results
[Lo et al., 2010]	Lokomat [®]	5 (–)	30 min, 2x/week for 5 weeks	No	FOG severity and frequency, and metabolic cost of walking ↓; gait speed, stride length and quality of life ↑.
[Ustinova et al., 2011]	Lokomat [®]	1 (3)	25–42 min, 3x/week for 2 weeks	15 weeks after	FOG frequency and motor symptoms ↓; gait speed, cadence and stride length ↑, maintained at follow-up.
[Barbe et al., 2012]	Lokomat [®]	3 (1.5–4)	30 min, 10–12x	6 weeks after	FOG severity and frequency ↓; gait speed and stride length ↑; no effect on motor symptoms.
[Pilleri et al., 2015]	GT1	18 (3–4)	30 min, 5x/week for 3 weeks	No	FOG severity and fear of falling ↓; gait speed, balance functions and quality of life ↑; no effect on motor symptoms.
[Andrenelli et al., 2018]	G-EO System [™]	9 (–)	3x/week for 4 weeks	No	FOG frequency and duration ↓; gait speed, walking endurance, step rhythm and balance functions ↑
[Capecci et al., 2019]	G-EO System [™]	96 (2–4)	45 min, 5x/week for 4 weeks; comparison with TT	No	FOG frequency and severity and motor symptoms ↓; gait speed, walking endurance and quality of life ↑; better improvements in RAGT than in TT*.

*RAGT stands for robot-assisted gait training, and TT for treadmill training.

1.3 Thesis objectives and structure

This thesis is organized around the key thread of investigating the presence of LRA in gait, particularly in the context of Parkinson's disease. The theory behind this concept is developed in **Chapter 2**, discussing its fundamental principles, exploring how its level in series of stride durations can be modified, and developing the theories about its origin in gait.

In Section 1.2, it was shown that robot-assisted gait training seems promising for these patients. However, currently used devices have certain limitations, listed in **Chapter 3**. To address these, we decided to use a wearable active pelvis orthosis that adapts in real-time to the user's gait kinematics. This device's design and functioning are detailed in the same chapter.

Then, this thesis is articulated around three successive modules, covered in Chapters 4 to 6. **Chapter 4** presents the predictive model that was implemented during the COVID-19 pandemic – i.e., when it was not possible to start a new experimental campaign, neither with patients nor with healthy participants – to investigate the impact of the oscillator-based walking assistance on the presence of LRA in inter-stride time series of patients with Parkinson's disease. These simulations provide predictions about the effects of the different tunable assistive parameters, which are useful for the following experiments.

As developed in Chapter 2, the level of LRA in series of stride durations can be modified when the gait is constrained, e.g., with a treadmill or a metronome. As delivering walking assistance can also be considered equivalent as adding a constraint to walking, **Chapter 5** aims to analyze the effects of a compliant walking assistance on the gait of healthy subjects, and to compare the effects of different assistive parameters on gait. This raises the following research questions:

Is the level of LRA in series of stride durations of healthy subjects impacted by an oscillator-based walking assistance?

What are the effects of increasing the assistance oscillator memory and phase lead on gait?

Thereafter, **Chapter 6** investigates the effects of a four-week training

program assisted by this wearable orthosis on several gait parameters, including the level of LRA in series of stride durations, in patients with Parkinson's disease. Indeed, as explained in Chapter 2, those patients have a decreased level of LRA as compared to healthy individuals. This chapter aims to answer the following research questions:

Does a gait training assisted by a wearable compliant pelvis orthosis improve gait of patients with Parkinson's disease?

Does this training increase the level of LRA in series of stride durations of these patients?

Finally, **Chapter 7** provides a general discussion and perspectives on this research, by summarizing the original findings of this work and answering the questions raised in this section. This chapter also outlines potential future directions for gait rehabilitation or assistance in patients with Parkinson's disease, identifying possible improvements in the design of the orthosis used in this work, and in the control system employed.

1.4 List of publications

- V. Otlet and R. Ronsse, "Predicting the effects of oscillator-based assistance on stride-to-stride variability of Parkinsonian walkers," 2022 International Conference on Robotics and Automation (ICRA), Philadelphia, PA, USA, 2022, pp. 8083–8089, doi: 10.1109/ICRA46639.2022.9811822.
- C. Vandamme, V. Otlet, R. Ronsse and F. Crevecoeur, "Model of Gait Control in Parkinson's Disease and Prediction of Robotic Assistance," in IEEE Transactions on Neural Systems and Rehabilitation Engineering, vol. 31, pp. 1374–1383, 2023, doi: 10.1109/TNSRE.2023.3245286.
- V. Otlet and R. Ronsse, "Adaptive walking assistance does not impact long-range stride-to-stride autocorrelations in healthy people," Journal of Neurophysiology, vol. 130(2), pp. 417–426, 2023, doi:10.1152/jn.00181.2023.
- V. Otlet, C. Vandamme, T. Warlop, F. Crevecoeur and R. Ronsse, "Effects of overground gait training assisted by a wearable exoskeleton in patients with Parkinson's disease," Journal of NeuroEngineering and Rehabilitation, vol. 20, 2023, doi:0.1186/s12984-023-01280-y.

2

Long-range autocorrelations

ALL human movements contain intrinsic variability, defined as the natural fluctuations observed in motor performance when a task is repeated. Indeed, repeating the same movement twice yields non-identical actions, because each repetition of a movement engages unique neural and motor patterns [Stergiou and Decker, 2011]. These variations can be studied from different angles. On the one hand, their magnitude around a central point can be measured, using linear statistics such as the standard deviation or the coefficient of variation. On the other hand, their structure or organization in a time series can be explored, using non-linear statistics. Indeed, although initially attributed to noise, these variations were found to have a particular temporal structure in several physiological signals, as they display *long-range autocorrelations* (LRA). It means that there is a persistent statistical dependence in the time series, as the current value is influenced by a large number of previous ones [Delignières and Marmelat, 2013]. Interestingly, this property has been found in a vast amount of physiological signals from different human systems – such as in gait [Hausdorff et al., 1995], heartbeat [Peng et al., 1995], neural activities [Linkenkaer-Hansen et al., 2001], breathing [Peng et al., 2002], and finger tapping [Delignières et al., 2004]. In this work, we are particularly interested in assessing the level of LRA in series containing successive stride durations, defined as the time between two consecutive heel strikes of the same foot. The presence of LRA in these

series captures that the duration of the current stride statistically depends on all those that happened in the past, i.e., from a few seconds to several minutes ago [Bollens et al., 2013].

This chapter presents the mathematical foundations of the concept of LRA, with its definition and properties. It then develops several methods used to assess the level of LRA in series of stride durations. Interestingly, different behaviors can influence the level of LRA in the series of stride durations, whether macroscopic or pathological. These influences are described in the fourth part of this chapter. Finally, in consideration of these different behaviors, some hypotheses regarding the origin of the presence of LRA in series of stride durations are depicted in the last part of this chapter.

2.1 Definition

To illustrate the concept of LRA concretely, consider the fractal object shown on (Figure 2.1a). This particular object possesses the key property of self-similarity, i.e., it is composed of an infinitely repeating pattern across several geometric scales [Ducharme and van Emmerik, 2018]. Similarly, this property can also be of statistical nature, and is found in fractal temporal processes (Figure 2.1b). In that case, smaller time scales of the time series resemble the whole time series [Ducharme and van Emmerik, 2018]. In such processes, each value within the signal is correlated to all the preceding values, and the signal therefore possesses long-range autocorrelations.

In mathematical terms, this property of temporal fractal processes is expressed by an autocorrelation function following a power-law distribution [Ducharme and van Emmerik, 2018]. Consider a discrete centered (zero mean) time series x_t^c of length N with constant variance. This series is stationary, i.e., it does not contain any significant trend. If this process possesses a memory of the previous values, its autocorrelation function, defined as the covariance of two samples separated by a number of samples k , follows the relationship [Rangarajan and Ding, 2000, Crevecoeur et al., 2010]:

$$C(k) = E(x_t^c, x_{t+k}^c) \sim k^{-\gamma} \quad (2.1)$$

Where $E(\cdot)$ is the expected value of the argument. The process memory is defined as the sum of $C(k)$ when $k \rightarrow \infty$. For a process with finite mem-

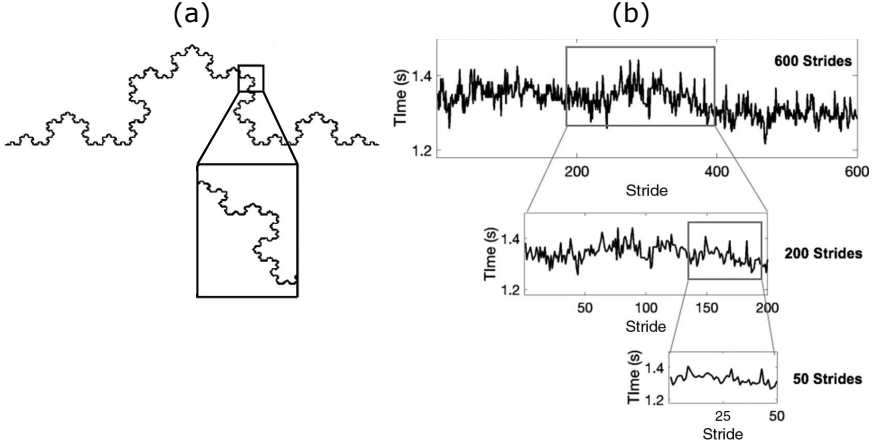


Figure 2.1 Examples of self-similarity property of (a) a geometric fractal object, and of (b) an inter-stride time series, adapted from [Ducharme and van Emmerik, 2018].

ory, i.e., when $\gamma > 1$, this sum converges to a finite value, indicating that the process is influenced by a limited number of preceding values. On the other hand, when $0 < \gamma \leq 1$, the process memory is infinite, i.e., the autocorrelation function decays very slowly for high values of k and tends to zero when $k \rightarrow \infty$. In this case, the process is said to possess long-term memory, because the value of x_t^c is statistically correlated with a large number of preceding values, with decreasing impact as these values become more temporally distant. This is illustrated in Figure 2.2 for values of $\gamma = [0.1, 0.3, 1.0]$. It can be observed that for lower values of γ , the persistence of the process is stronger and the series is more predictable [Marmelat and Delignières, 2011], since the correlation with past values on the current one remains significant over longer time spans. In contrast, a random process such as white noise has no memory, and its covariance function is therefore equal to the variance of x_t^c when $k = 0$, and to zero otherwise.

2.2 Properties

The monofractal model has been introduced in 1968 by B. Mandelbrot and J. Van Ness in order to describe and understand the properties of temporal fractal processes [Mandelbrot and Ness, 1968]. According to this model, two families of long-memory processes exist. The first one, known as *fractional Brownian motion* (fBm), consists of non-stationary processes, charac-

2 | Long-range autocorrelations

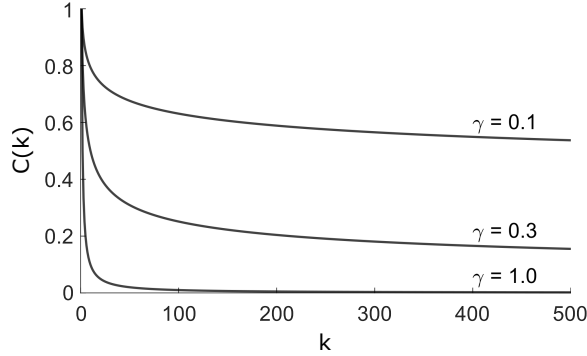


Figure 2.2 Examples of autocorrelation functions of long-memory processes, with different values of γ .

terized by variations in mean and/or variance over time. These variations can indicate the presence of trends within the processes. On the other hand, the second family, called *fractional Gaussian noise* (fGn), comprises stationary processes, that have constant expected mean and variance over time. These two families are intrinsically related: fGn can be obtained by differencing a fBm, while a fBm can be obtained by integrating a fGn. In other words, fGn represents the series of increments within a fBm, highlighting their interconnected nature [Marmelat et al., 2012].

The successive increments of fBm processes exhibit correlations over time, which are characterized by the Hurst exponent H . This exponent is related to the one of the autocorrelation function in Equation (2.1) by the relationship $\gamma = 2H - 2$ [Crevecoeur et al., 2010]. When H falls between 0 and 0.5, the process demonstrates anti-persistence, meaning that positive increments are more likely to be followed by negative increments, and vice versa. Conversely, for H values between 0.5 and 1, the process displays persistence, with positive (resp. negative) increments being more likely to be followed by positive (resp. negative) increments. When H is equal to 0.5, the process corresponds to the standard Brownian motion, which is the result of integrating white noise. As each fBm process is associated with a specific fGn process, they both share the same Hurst exponent H [Marmelat et al., 2012, Roume et al., 2019]. Examples of these two families of signals for several values of H can be seen in Figure 2.3.

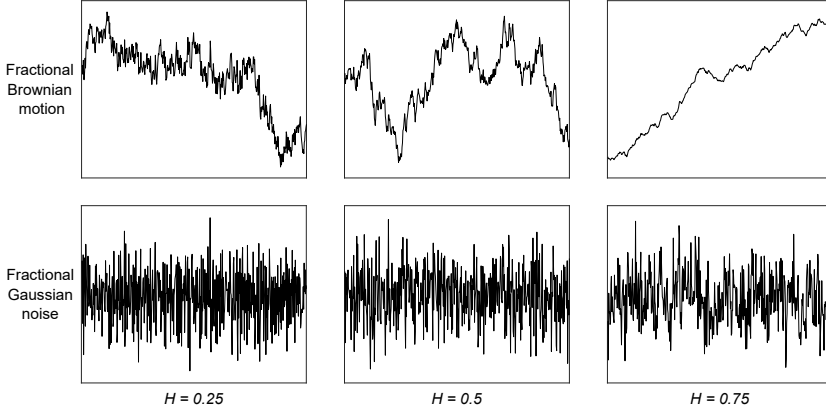


Figure 2.3 Examples of simulated fractal time series for different values of the Hurst exponent. The upper row represents fractional Brownian motions, and the lower row fractional Gaussian noises.

These processes have two important properties. A fBm process, denoted as x , exhibits the diffusion property, where its variance increases with time at a rate determined by the Hurst exponent [Roume et al., 2019]:

$$\text{Var}(x) \propto \Delta t^{2H} \quad (2.2)$$

where Δt is the time interval over which the variance is computed. Moreover, the power spectrum, i.e., the squared amplitude, of these processes is given by [Roume et al., 2019]:

$$S(f) \propto \frac{1}{f^\beta} \quad (2.3)$$

with $\beta = 2H - 1$ for fGn processes (with $-1 < \beta < 1$) and $\beta = 2H + 1$ for fBm processes (with $1 < \beta < 3$).

2.3 Assessment methods

The two properties of fBm and fGn processes given by Equations (2.2) and (2.3) serve as the foundation for various assessment methods used to characterize the nature and strength of the correlations present in these processes and described in this section. For all these methods, consider the time series x_t of length N . It is first centered by subtracting its mean value, i.e., $x_t^c = x_t - \bar{x}$.

In order to illustrate these methods, data from the experiments of Chapter 5 have been used. The panels pictured in Figure 2.5 correspond to a representative series of stride durations from the third subject.

2.3.1 Power Spectral Density (PSD) analysis

This method exploits the frequency property of fGn and fBm processes, i.e., Equation (2.3). As the power spectral density scales as $S(f) \sim 1/f^\beta$, it consists in plotting the power spectral density against the frequencies in a bi-logarithmic scale [Crevecœur et al., 2010]. The power spectral density is computed by $S(f) = |X(f)|^2$, with $X(f)$ the Fourier transform of the signal x_t^c . The slope of the regression line then gives an estimate of the spectral exponent β and is shown in Figure 2.5(b):

$$\log S(f) \sim -\beta \log f \quad (2.4)$$

An improved version of this algorithm, called the $\text{lowPSD}_{\text{we}}$ [Eke et al., 2000, Roume et al., 2019], provides a more reliable estimate of the spectral exponent β . This method adds two pre-processing steps to what is explained above. In the first one, a parabolic window W_t is applied to the signal, in order to decrease the emphasis on the data at its ends [Faugere, 1985]. Therefore, each value of the time series is multiplied by the following function [Roume et al., 2019]:

$$W_t = 1 - \left(\frac{2t}{N+1} - 1 \right)^2 \quad (2.5)$$

and $t = 1, 2, \dots, N$. Then, end-matching is performed on the resulting time series x_t^w by subtracting the line connecting the first and last points of the series, i.e., by removing to each value of the series the following function [Roume et al., 2019]:

$$l_t = \frac{(x_1^w - x_N^w)(t-1)}{N-1} + x_N^w \quad (2.6)$$

The power spectral density is then computed on the modified series $x^{w,l}$ and the fitting in the bilogarithmic plot excludes high-frequency power estimates, i.e., frequencies higher than $1/8$ of the maximal frequency [Roume et al., 2019].

2.3.2 Rescaled Range Analysis (RRA)

This method exploits the diffusion property of a fBm process, i.e., Equation (2.2). The time series is first integrated [Almurad and Delignières, 2016]:

$$y_i = \sum_{t=1}^i x_t^c \quad \text{for } i = 1, 2, \dots, N \quad (2.7)$$

This integrated time series is then divided into m non-overlapping intervals of length n , named y_s with $s = 1, \dots, m$. The $N - mn$ last data points of the series are discarded for the next steps. Thereafter, the trend y_s^{tr} in each interval is computed, by fitting a least squares first-order model to the data. The series is then detrended by subtracting these trends to the intervals.

Then, the range of each interval is computed as:

$$R_s = \max[y_{1,s} - y_{1,s}^{tr}, \dots, y_{n,s} - y_{n,s}^{tr}] - \min[y_{1,s} - y_{1,s}^{tr}, \dots, y_{n,s} - y_{n,s}^{tr}] \quad (2.8)$$

and normalized by the standard deviation of the corresponding interval of the original time series $\sigma(x_s)$:

$$\left(\frac{R}{S}\right)_s = \frac{R_s}{\sigma(x_s)} \quad (2.9)$$

for $s = 1, 2, \dots, m$. This rescaled range is then averaged over all the intervals of length n in order to obtain $\left(\frac{R}{S}\right)_n$. These steps are repeated for several interval's lengths, in general $n = 10, \dots, N/2$ [Crevecœur et al., 2010, Almurad and Delignières, 2016, Warlop et al., 2017].

Finally, this rescaled range scales as $\left(\frac{R}{S}\right)_n \sim n^H$. Therefore, the slope of the regression line in the bi-logarithmic space, i.e., the diffusion plot, gives an estimate of the Hurst exponent H and is shown in Figure 2.5(c):

$$\log \left(\frac{R}{S}\right)_n \sim H \log n \quad (2.10)$$

2.3.3 Detrended Fluctuation Analysis (DFA)

This method also exploits the diffusion property. However, it has the advantage, compared to RRA, of being indifferently applicable to both sta-

tionary (fGn) and non-stationary (fBm) time series, without having to know in advance to which family the series belongs [Roume et al., 2019]. It starts the same way as RRA, but instead of calculating the ranges of each interval as in Equation (2.9), the magnitude of fluctuations around the mean for a given interval length n is computed by:

$$F_n = \sqrt{\frac{1}{N} \sum_{s=1}^N [y_s - y_s^{tr}]^2} \quad (2.11)$$

As for RRA, this computation is repeated for several interval's lengths, in general $n = 10, \dots, N/2$ [Crevecoeur et al., 2010, Almurad and Delignières, 2016, Warlop et al., 2017].

The fluctuation function scales as $F_n \sim n^\alpha$. Again, the slope of the regression line in the diffusion plot allows to determine the DFA's exponent α and is shown in Figure 2.5(d):

$$\log F_n \sim \alpha \log n \quad (2.12)$$

with $\alpha = H$ for fGn series (with $0 < \alpha < 1$), and $\alpha = H + 1$ for fBm series (with $1 < \alpha < 2$).

However, the logarithmic transformations used to obtain the fractal exponent have two main drawbacks, observable on Figure 2.5(d). The first one is the increase in the density of points with the interval length, which gives more weight to long intervals in the computation of the slope. The second issue is that, in the region of longer intervals, the diffusion plot presents more irregularities around the linear trend. This is because there are fewer intervals over which to calculate the fluctuation function when the intervals are longer. This causes a larger uncertainty in this region, which carries nevertheless most of the weight in the regression [Almurad and Delignières, 2016].

To solve these two issues, Z. Almurad and D. Delignières [Almurad and Delignières, 2016] proposed an improvement of this algorithm, called the *evenly spaced averaged DFA*. The first step is to select an evenly spaced interval length vector n on a logarithmic scale, and then to average the points falling within each interval. In mathematical terms, the $\log(n)$ vector is divided into k bins:

$$bin_i = \left[\log_{10}(n_{min}) + \frac{i-1}{k} \log_{10} \left(\frac{n_{max}}{n_{min}} \right) ; \right. \\ \left. \log_{10}(n_{min}) + \frac{i}{k} \log_{10} \left(\frac{n_{max}}{n_{min}} \right) \right] \quad (2.13)$$

for $i = 1, 2, \dots, k$, and with $n_{min} = 10$ and $n_{max} = N/2$ the minimum and maximum interval lengths respectively. A value of $k = 18$ is generally chosen, although J. Liddy and J. Haddad [Liddy and Haddad, 2018] showed that the exponent's estimation is globally not impacted by the choice of this value. Then, the average time scale $\bar{n}$ and fluctuations $\bar{F}_n$ are computed within each of these bins, resulting in k points on the diffusion plot, on which a better linear model is fitted, as shown in Figure 2.5(e). This improvement can also be implemented with the RRA method.

2.3.4 Adaptive Fractal Analysis (AFA)

The implementation of this method is similar to that of DFA. However, the estimate of the fractal exponent provided by this method is more accurate than with DFA, but it is still not perfect. Indeed, although it better handles non-stationary time series and is more robust when using relatively short time series [Hollman et al., 2022], these factors still influence the accuracy of the fractal exponent estimation.

The time series is first divided into m intervals of length n overlapping by $p + 1$ points, with $p = (n - 1)/2$. Instead of making a linear fit on each of these intervals as in DFA, K th-order quadratic polynomials are fitted to these intervals and pasted together to obtain a globally smooth trend signal, as illustrated in Figure 2.4. In [Tung et al., 2011], the authors identified that values of $K = 2$ or $K = 3$ provide sufficient fitting to the points. In this work, second-order quadratic polynomials are used. The fit of the overlapping regions between two adjacent intervals is obtained by taking a weighted combination of the two adjacent fits [Riley et al., 2012], i.e.:

$$y^{(c)}(l) = w_1 y^{(i)}(l + p) + w_2 y^{(i+1)}(l) \quad \text{with } l = 1, 2, \dots, p + 1 \quad (2.14)$$

where $y^{(i)}$ and $y^{(i+1)}$ are the fitted polynomials for the i th and $(i + 1)$ th intervals respectively [Tung et al., 2011]. The weights are defined by $w_1 = 1 - \frac{l-1}{p}$ and $w_2 = \frac{l-1}{p}$, which means that they linearly decrease with

the distance between the l point and the center of the interval [Riley et al., 2012].

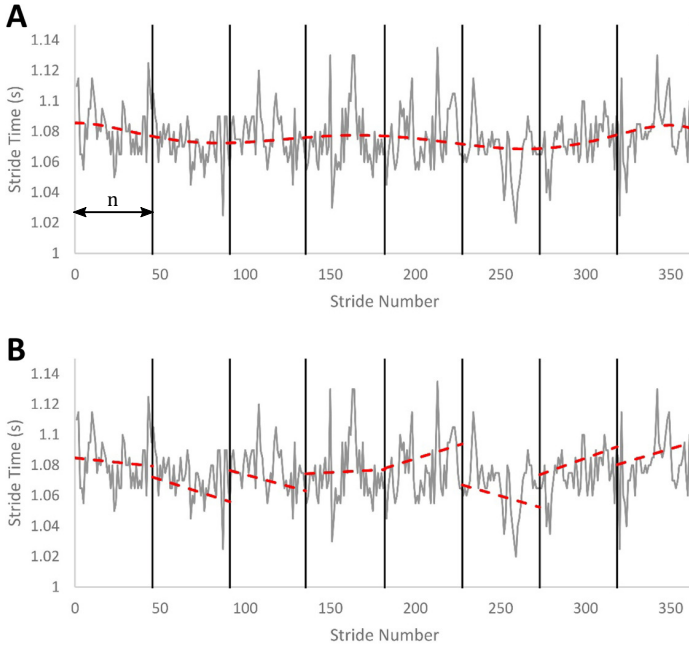


Figure 2.4 Illustration of the trends (dotted red line) fitted to the time series (gray) in the (A) adaptive fractal analysis (AFA) and (B) detrended fluctuation analysis (DFA) methods for a particular interval size $n < 50$, adapted from [Hollman et al., 2022].

Thereafter, as with DFA, the fluctuations around the mean are computed with Equation (2.11), by subtracting the global smooth trend to the original signal. These steps are repeated for several interval's length n , ranging from 5 to the first power of 2 smaller than $N/2$ by steps of 2. This range was determined in this work as the most appropriate to handle non-stationary time series. The evenly spaced averaged algorithm is then applied, by dividing the range of $\log(n)$ into a series of intervals of equal length with a step size of 0.5 and averaging the points falling within each interval. Finally, the fractal exponent α is obtained with Equation (2.12). The diffusion plot of this method is shown in Figure 2.5(f).

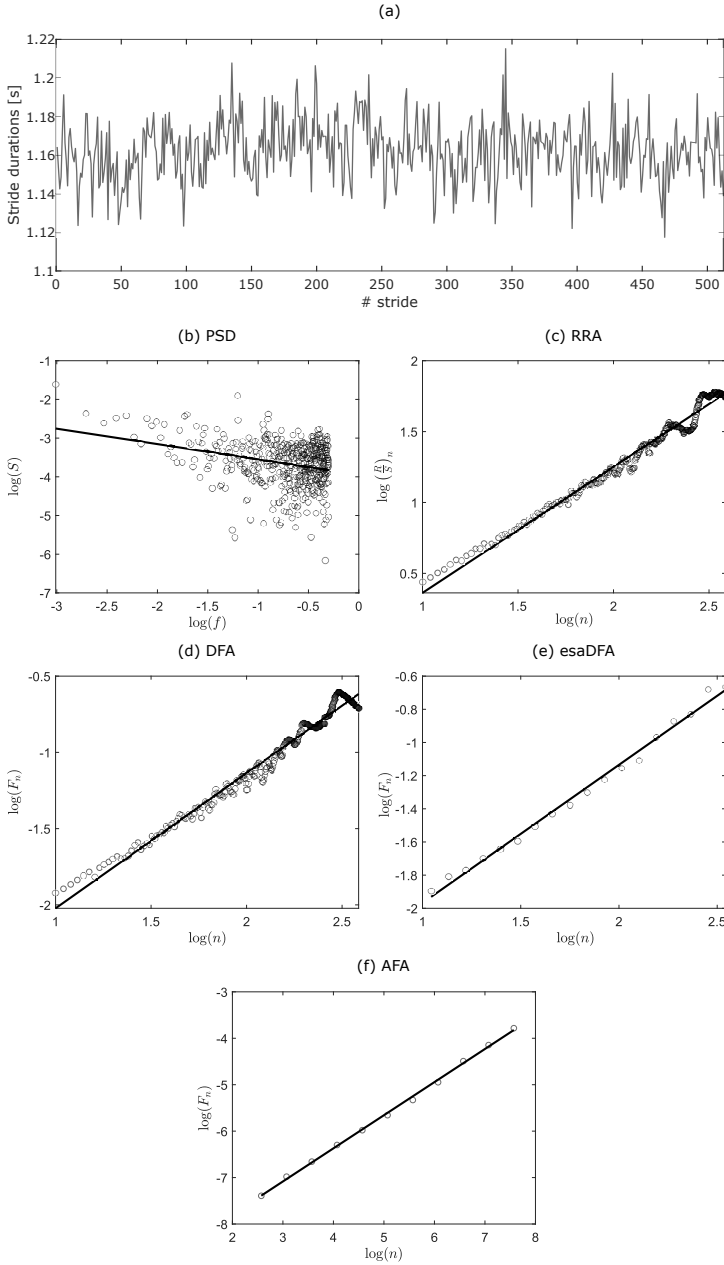


Figure 2.5 (a) Example of an inter-stride intervals time series of a healthy subject; bi-logarithmic plots of (b) the power spectral density analysis (Section 2.3.1), (c) the rescaled range analysis (Section 2.3.2), (d) the simple and (e) evenly spaced averaged detrended fluctuation analysis (Section 2.3.3), and (f) the adaptive fractal analysis (Section 2.3.4).

2.3.5 Interpretation of the fractal exponents

In Table 2.1, the value intervals of the different fractal exponents are given, according to their application field (fGn or fBm) and correlation properties. At the border between noises and movements is the ideal case of pink or $1/f$ noise, i.e., a process with a power spectral density inversely proportional to the frequency of the signal. This table is useful for interpreting fractal exponent values in the following chapters.

Table 2.1 Value intervals that can take the different fractal exponents; β is the spectral exponent, H the Hurst exponent, and α the DFA/AFA exponent, adapted from [Roume, 2019].

	fGn (stationary)			1/f noise	fBm (non-stationary)		
	Anti-persistent	White noise	Persistent		Anti-persistent	Brownian motion	Persistent
β	$-1 < \beta < 0$	0	$0 < \beta < 1$	1	$1 < \beta < 2$	2	$2 < \beta < 3$
H	$0 < H < \frac{1}{2}$	$\frac{1}{2}$	$\frac{1}{2} < H < 1$	1	$0 < H < \frac{1}{2}$	$\frac{1}{2}$	$\frac{1}{2} < H < 1$
α	$0 < \alpha < \frac{1}{2}$	$\frac{1}{2}$	$\frac{1}{2} < \alpha < 1$	1	$1 < \alpha < \frac{3}{2}$	$\frac{3}{2}$	$\frac{3}{2} < \alpha < 2$

When it comes to selecting the right method, it is worth comparing the pros and cons of each of them. One of the advantages of the method based on the power spectral density over all the others described in this section is its low computational cost. Nevertheless, in [Roume et al., 2019], the authors identified that it tends to overestimate the fractal exponent in non-stationary time series. However, when dealing with data of subjects, there is a greater risk of observing non-stationarities, e.g., due to a change in speed or cadence. Regarding temporal methods, given that the Hurst exponent, obtained through RRA, cannot distinguish between stationary and non-stationary time series [Roume et al., 2019], DFA and AFA are preferred, and in particular the evenly-spaced averaged version of the DFA, which refines the precision of the fractal exponent estimate (Figure 2.5). Moreover, the obtained series of stride durations can be quite short, especially in the case of patients with Parkinson’s disease who have more difficulty in walking during a long period of time. Therefore, AFA is more appropriate for assessing the fractal exponent of the series obtained during the experiments of this work [Hollman et al., 2022].

The methods explained in the previous sections represent only a fraction of the existing methods for assessing the level of LRA in time series, and are those explored during this thesis. There are actually many more, such as the Higuchi's fractal dimension [Phinyomark et al., 2020] or the ARFIMA(0, d ,0) modeling [Roume et al., 2019]. At present, there is no consensus on which method to use or how to set their parameters. We opted for the AFA method for the reasons explained above, without claiming that it is the best method, because it is the one that, to the best of our knowledge, best meets our needs and satisfies our constraints.

2.4 Influence on the level of LRA in gait

Several studies have demonstrated that LRA-related metrics can capture different macroscopic behaviors, such as free vs. constrained walking (with a treadmill or a metronome), or pathological behaviors. This section presents a non-exhaustive summary of these studies and of the influence of these behaviors on the level of LRA in series of stride durations.

2.4.1 Constrained walking

The level of LRA in series of stride intervals of healthy young adults was determined by [Hausdorff et al., 1996] to be $\alpha = 0.90 \pm 0.04$. In the same paper, authors showed that this "healthy" level was decreased to $\alpha = 0.50$ (corresponding to white noise) when walking to the pace of a metronome. This result was further explored in a study by P. Terrier and colleagues [Terrier et al., 2005], indicating that the level of LRA in series of step frequencies decreased under 0.50, indicating that the series became anti-persistent and not just random ($\alpha = 0.50$) as in [Hausdorff et al., 1996]. The authors explained it by the inability of the subjects to synchronize with the metronome rhythm, thus resulting in a continual shifting of the stride-interval duration around the pace of the metronome. When re-analyzing the data from [Hausdorff et al., 1996], they observed that this was also the case for some subjects of this study. Moreover, the authors showed that only the series of step frequencies were impacted, and not the series of step length or walking speed. They hypothesized that in free walking, the supraspinal networks apply a loose control on step generation. On the other hand, during metronomic walking, these networks integrate sensory feedback and correct the step frequency to follow the metronome rhythm,

therefore inducing less variations around the mean step frequency. Because this series is determined by the metronome rhythm and not by previous frequency values, there is no dependency between consecutive steps, resulting in a decreased LRA level.

A subsequent study of P. Terrier and colleagues [Terrier and Dériaz, 2011] showed that treadmill walking also significantly decreases the LRA level in series of healthy subjects, compared to overground walking. They explained this effect in the same way as the one of metronomic walking, but this time the constraint is on the speed and not on walking pace. The same result was obtained by [Hollman et al., 2016]. However, other studies have concluded that treadmill walking has no impact on the level of LRA in series of stride durations of healthy individuals [Chang et al., 2009, Bollens et al., 2010, Warlop et al., 2018, Hollman et al., 2020].

Finally, this "healthy" level has also been shown to be impacted by gait speed [Hausdorff et al., 1996], since it was slightly higher in slower and faster speeds than in normal speed. Nevertheless, another study [Bollens et al., 2012] showed that gait speed has no impact on the LRA level in series of stride durations. However, this last study was performed on a treadmill, whose effect on the LRA level is not clearly identified.

The details of each of these studies and the values of the fractal exponents are given in Table 2.2.

2.4.2 Pathology

J. Hausdorff and colleagues [Hausdorff et al., 2000] investigated the impact of neurodegenerative diseases on the level of LRA in series of stride durations. They compared three diseases: Huntington's disease, Parkinson's disease, and amyotrophic lateral sclerosis. Huntington's disease shares many symptoms with Parkinson's disease, since they both involve basal ganglia disorder [Hausdorff et al., 1997]. This disease is caused by an inherited genetic mutation, and is mainly characterized by unwanted involuntary movements [Roos, 2010]. On the other hand, amyotrophic lateral sclerosis affects the motor neurons, causing several motor symptoms such as abnormal walking [Hausdorff et al., 2000]. J. Hausdorff and colleagues showed that, compared to 16 healthy control subjects ($\alpha = 0.91 \pm 0.05$), the level of LRA in series of stride durations was decreased in 20 patients

Table 2.2 Overview of studies on the effect of constrained walking on the LRA level of series of stride durations of healthy subjects. Fractal exponents in constrained walking followed by [†] are not significantly different from the baseline.

Source	Assessment method	Duration	Baseline fractal exponent	Constrained fractal exponent
			Silent	Metronome
[Hausdorff et al., 1996]	DFA	30-60 min	0.90 ± 0.04	0.50
[Terrier et al., 2005]	DFA	30 min	0.71 ± 0.09	0.21 ± 0.05
			Overground	Treadmill
[Chang et al., 2009]	DFA	15 min	0.83 ± 0.06	$0.82 \pm 0.08^{\dagger}$
[Bollens et al., 2010]	RRA	15 min	0.79 ± 0.09	$0.79 \pm 0.12^{\dagger}$
[Terrier and Dériaz, 2011]	DFA	10 min	0.81 ± 0.09	0.72 ± 0.13
[Hollman et al., 2016]	AFA	6 min	0.81 ± 0.09	0.73 ± 0.09
[Warlop et al., 2018]	DFA	10 min	0.78 ± 0.07	$0.82 \pm 0.12^{\dagger}$
[Hollman et al., 2020]	AFA	6 min	0.78 ± 0.09	$0.77 \pm 0.12^{\dagger}$
			Normal speed	Slower/faster speed
[Hausdorff et al., 1996]	DFA; overground walking	60 min	0.90 ± 0.04	0.98 ± 0.07 (slower) 0.97 ± 0.05 (faster)
[Bollens et al., 2012]	RRA; treadmill walking	15-30 min	~ 0.77	$\sim 0.80^{\dagger}$ (slower) $\sim 0.77^{\dagger}$ (faster)

with Huntington's disease ($\alpha = 0.60 \pm 0.04$), in 15 patients with Parkinson's disease ($\alpha = 0.82 \pm 0.06$), and in 11 patients with amyotrophic lateral sclerosis ($\alpha = 0.74 \pm 0.07$), evaluated by applying DFA on series of 5-min walking [Hausdorff et al., 2000].

Regarding the impact of age on the LRA level in gait, results do not converge. A first study from J. Hausdorff and colleagues [Hausdorff et al., 1997] showed a decreased level of LRA in the 6-min walking time series of 10 healthy elderly compared to 22 young adults, i.e., $\alpha = 0.68 \pm 0.14$ compared to $\alpha = 0.87 \pm 0.15$ obtained with DFA. On the contrary, a study of

B. Bollens and coworkers [Bollens et al., 2012] revealed that this level was not influenced by age. Indeed, the level of LRA, obtained through RRA on time series of 15 min of walking on a treadmill, was 0.79 for the elderly subjects, and 0.81 for the young adults.

Nevertheless, this metric could be used to distinguish elderly people with walking impairments from those without. A study from T. Herman and colleagues [Herman et al., 2005] showed that the LRA level of 25 older adults affected by higher-level gait disorders with no known cause was decreased compared to the one of 28 aged-matched subjects, i.e., $\alpha = 0.75 \pm 0.18$ compared to $\alpha = 0.88 \pm 0.22$, assessed using DFA on series of 2-min walking. Moreover, this particular metric was the only one to distinguish fallers from non-fallers among older people with gait disorders, all other metrics (i.e., fear of falling, balance, lower extremity strength, gait speed, stride length, and standard deviation and coefficient of variation of series of stride durations) being similar between both groups. Indeed, it was lower in the elderly with gait disorders prone to falls than in those who were not, i.e., $\alpha \approx 0.65$ compared to $\alpha \approx 0.86$.

A study of Z. Almurad and colleagues [Almurad et al., 2018] analyzed the effects of walking arm-in-arm with a healthy young individual on the level of LRA in series of stride durations of older individuals. Compared with their initial level, i.e., $\alpha \approx 0.82$, subjects were able to synchronize their LRA level with that of the young individual, i.e., $\alpha \approx 0.95$, by walking arm-in-arm. Moreover, this level was maintained when subjects walked alone after a four-week training period. The LRA levels were assessed by applying evenly-spaced averaged DFA on series of 15-min walking. These results could be interesting for gait rehabilitation in patients with neurological diseases.

Regarding Parkinson's disease in particular, a study of R. Bartsch and coworkers [Bartsch et al., 2007] showed that the LRA level of patients was lower than in those recently diagnosed and not yet taking medication, i.e., $\alpha \approx 0.77$ compared to $\alpha \approx 0.82$. The fact that the LRA level is correlated with the stage of the disease was subsequently confirmed in [Warlop et al., 2016]. The authors showed that when the patient had a poorer level of balance, a pronounced disease severity, and strong motor symptoms, their LRA level was lower, meaning that their walking pattern was more random. Therefore, they proposed to use this metric as a marker of gait in-

stability in patients with Parkinson's disease, in combination with other metrics such as the coefficient of variation of stride durations, and questionnaires assessing fear of falling and postural stability. Nevertheless, considering the LRA level as a marker of gait instability must be done with caution [Stergiou and Decker, 2011]. Indeed, this depends on the meaning given to the presence of LRA in a physiological system: if we consider it to reflect the system's flexibility and adaptability to internal or external disturbances (see Section 2.5), the level of LRA can indeed be considered as reflecting the stability of the system, but this remains to be proven.

Considering again the study by T. Herman and colleagues [Herman et al., 2005] showing that the level of LRA in gait is decreased in people with gait disorders, and even more in those with a greater risk of falling, it is reasonable to envisage that improving this level, in addition with more conventional gait metrics, could also improve gait disorders and the tendency to fall in patients with Parkinson's disease. To this end, it is interesting to study which walking conditions impact, either negatively or positively, this level in patients' gait, in order to subsequently determine an effective therapy for this disease. The various conditions studied in the past are detailed in Table 2.3. Firstly, as in healthy subjects, synchronizing their cadence with the rhythm of a metronome reduces this level [Dotov et al., 2017, Lheureux et al., 2020b]. On the other hand, if the rhythmic auditory stimulation contains autocorrelated variability, the results do not converge. Indeed, it was shown that the LRA level was either maintained [Dotov et al., 2017], increased [Marmelat et al., 2020] or decreased [Lheureux et al., 2020b] compared to the baseline level, i.e., without auditory stimulation. Nevertheless, according to the authors of the latter study, their results are similar to those of [Dotov et al., 2017] since the fractal exponent with the autocorrelated auditory stimulation is maintained within the values usually encountered in healthy individuals, as calculated in [Warlop et al., 2017]. They also explained that [Marmelat et al., 2020] used as auditory stimulation a music with a salient rhythm containing autocorrelations, whereas their study and the one of [Dotov et al., 2017] used a metronome with an autocorrelated rhythm. Music would thus give patients more freedom, unlike the metronome, which provides a more rigid framework. An autocorrelated metronome might therefore not improve the level of LRA in patients, but it does not decrease it neither compared to an isochronous metronome. A second experimental condition impacting the level of LRA in gait is nordic walking. Indeed, it has been

demonstrated to increase the LRA level to that of age-matched healthy subjects, by utilizing increased arm-swing as a self-paced rhythmic external cue [Warlop et al., 2017]. Lastly, treadmill walking has been found to increase the LRA level of patients in comparison to overground walking, by also acting as a rhythmic external cue [Warlop et al., 2018, Hollman et al., 2020, Lheureux et al., 2020a]. Nevertheless, adding immersive virtual reality to treadmill walking would bring this level down to that of overground walking [Lheureux et al., 2020a]. Finally, to the best of our knowledge, there is no study about the effects of treatments currently used to alleviate the symptoms of Parkinson's disease on the level of LRA in patients' gait. There are, however, two studies showing a reduction in stride time variability, measured via the coefficient of variation, with levodopa [Schaafsma et al., 2003] and Deep Brain Stimulation [Hausdorff et al., 2009].

2.5 Theories about the origin of the presence of LRA

The exact physiological origin of LRA in gait is still largely debated in the literature. This section presents an overview of the main existing theories, but does not claim to provide an exhaustive list.

In the light of the changes observed in the level of LRA in gait induced by the behaviors explained in the previous section, J. Hausdorff [Hausdorff, 2007] postulated that supra-spinal neural control mechanisms are involved in the generation of LRA. This theory is based on the decrease in LRA levels in certain diseases affecting the central nervous system – such as Huntington's and Parkinson's diseases, and amyotrophic lateral sclerosis –, while it is intact in a disease degrading the peripheral nervous system, such as peripheral neuropathy [Gates and Dingwell, 2007]. Moreover, the decrease in this level during metronomic walking also supports this postulate, since it shares the same biomechanics and feedback systems as free walking.

One hypothesis proposed by J. Hausdorff is that central pattern generators (CPGs) play a role in the generation of LRA during gait. Indeed, these are intraspinal neural networks considered to be involved in many rhythmic movements, including locomotion [Hausdorff, 2007]. This theory has been implemented in a model proposed by B. West and N. Scafetta [West and Scafetta, 2003], and described in details in Chapter 4. This model also highlights the redundancy property of a complex system, using in particu-

Table 2.3 Overview of studies on the effect of several walking conditions on the LRA level of series of stride durations of patients with Parkinson's disease. The fractal exponent in the experimental condition followed by [†] is not significantly different from the baseline.

Source	Assessment method	Duration	Baseline fractal exponent	Experimental fractal exponent
			Silent	Metronome
[Dotov et al., 2017]	DFA	3 min	0.70 ± 0.18	0.58 ± 0.20
[Lheureux et al., 2020b]	esaDFA*	15 min	0.76 ± 0.09	0.44 ± 0.09
			Silent	Autocorrelated RAS**
[Dotov et al., 2017]	DFA	3 min	0.70 ± 0.18	$0.69 \pm 0.15^{\dagger}$
[Marmelat et al., 2020]	esaDFA*	15 min	0.76 ± 0.11	0.89 ± 0.07
[Lheureux et al., 2020b]	esaDFA*	15 min	0.76 ± 0.09	0.66 ± 0.09
			Free walking	Nordic walking
[Warlop et al., 2017]	RRA	12 min	0.70 ± 0.05	0.77 ± 0.08
			Overground	Treadmill
[Warlop et al., 2018]	DFA	10 min	0.66 ± 0.17	0.89 ± 0.14
[Hollman et al., 2020]	AFA	6 min	0.77 ± 0.20	0.91 ± 0.19
[Lheureux et al., 2020a]	esaDFA*	10-15 min	0.77 ± 0.07	0.85 ± 0.07
			Treadmill	Treadmill + iVR***
[Lheureux et al., 2020a]	esaDFA*	10-15 min	0.85 ± 0.07	0.76 ± 0.09

*Evenly-spaced averaged DFA; **rhythmic auditory stimulation; ***immersive virtual reality.

lar redundancy among neuronal pathways. Indeed, the locomotor system is composed of a huge amount of neuronal pathways carrying motor commands to numerous muscles exerting torques about joints with multiple degrees of freedom to perform a movement [Neilson, 1993], while integrating various sensory feedbacks [Hausdorff et al., 1995]. The complexity of the locomotor system arises from the coordination of these multiple components and subsystems acting at different time scales [Delignières and Marmelat, 2012, Delignières and Marmelat, 2013]. This complexity

also makes the locomotor system more robust, because of the redundancy among the combinations of neuronal pathways, muscles and joints to perform the same task [Delignières and Marmelat, 2013]. The system can therefore more easily compensate for injuries, and adapt to disturbances, whether external or internal. Indeed, humans need to continuously adapt every step in response to incoming proprioceptive feedbacks, corresponding for example to minor variations in the walking surface or to the inherent noise in the neuromuscular system [Terrier and Dériaz, 2011]. According to the theory of optimal movement variability [Stergiou and Decker, 2011], assessing the level of LRA in physiological signals could therefore be used to establish or confirm some clinical assessments. Indeed, this theory suggests that there is an optimal level of variability corresponding to a healthy state, reflecting the adaptability of the control system. Any deviation from this level, either in the direction of randomness or over-regularity, indicates the decrease or the loss of the system's adaptability to perturbations and corresponds to an unhealthy state.

Echoing this concept of redundancy, a complementary perspective to this statement is given by the framework proposed by [Dingwell et al., 2010], further studied by our team in [Vandamme et al., 2023], and briefly described in Chapter 4. In contrast to the model of B. West and N. Scafetta, this framework is not based on the redundancy among different neuronal pathways, but among different gait features. Indeed, it builds upon the postulate that there exist an infinite number of manners to modulate a step, by varying some features such as speed, step length or duration. In this context, humans are able to adapt their walking features from stride to stride, while adopting minimum intervention strategies to regulate them, in order to achieve a specific walking goal while enhancing task performance. Such a goal could be for example maintaining a constant walking speed in the case of treadmill walking [Dingwell et al., 2010, Dingwell et al., 2018], or a constant gait cycle timing in the case of walking with a metronome [Dingwell et al., 2010], or a constant step width during over-ground walking [Render et al., 2021]. The model of [Dingwell et al., 2010] managed to reproduce LRA in these various conditions with state model of low dimension.

On the other hand, another model proposes a purely biomechanical explanation for the presence of LRA in gait. It consists of a pendular model of gait, to which a push-off force is applied that varies from step to step due

to sensory and motor noises, regulated by a proportional feedback controller [Gates et al., 2007]. This model successfully reproduced the presence of LRA in inter-stride intervals time series of healthy adults, as well as conditions where this level was reduced. It suggests the involvement of simple mechanical and neurophysiological mechanisms (e.g., spinal reflexes), rather than more complex supra-spinal ones, in the generation of LRA in gait.

To conclude, nowadays, theories about the origin of the presence of LRA in gait do not converge. Most believe it to be neuronal, a few purely biomechanical. Although many experimental results point to a neuronal origin, it cannot be excluded that the origin could be a combination of both. If we assume that LRA originate in the central nervous system, we can consider that having a good level of LRA in gait would reflect the proper functioning of the locomotor system. Indeed, it would indicate that this system is redundant, and therefore flexible and adaptable to external or internal disturbances.

3

Wearable active pelvis orthosis

THE devices used until now for robot-assisted gait training in patients with Parkinson's disease and detailed in Section 1.2 present some disadvantages. To begin with, first generation devices, such as end-effector devices and treadmill exoskeletons, have the disadvantage of not being portable. They are therefore limited to rehabilitation therapies in non-ecological environments, i.e., either a treadmill or the end-effector's footplates. Wearable devices emerging recently in the rehabilitation of patients with Parkinson's disease offer the possibility to study their effects outside a treadmill, which has been shown to have an influence on gait in general [Shi et al., 2019]. In particular, it influences natural gait variability, assessed through the level of LRA, as outlined in Chapter 2. The use of a portable device in an ecological environment is therefore useful when studying such a metric. In addition, the portability of such devices also allows to use them for assistance, since they open the perspective to be worn in everyday life, at least for the most affected patients.

On top of this, most of the devices presented in Section 1.2 repeatedly apply a nominal gait pattern with high intensity to the patient [Yun et al., 2021]. Therefore, it does not encourage them to actively participate in the movement, since the device does it for them. Moreover, because it ap-

plies a stereotyped and constant gait pattern, this type of robot does not allow the patient to recover a healthy inter-stride variability. In contrast, more compliant robots, allowing users to choose their own gait kinematics, can increase the benefits of such therapies for patients, as was shown with other pathologies [Hogan et al., 2006, Vallery et al., 2008].

For all these reasons, we decided to use a wearable active pelvis orthosis (APO) relying on adaptive oscillators to provide a compliant assistance to the user. It offers the advantage of smoothing the movement of the user's hips, while adapting to their natural gait variations, since it leaves the user with the ability to steer the orthosis and to choose the main gait features [Leconte and Ronsse, 2016, Martini et al., 2019]. This orthosis assists the hip flexion and extension movements of individuals with mild gait impairments [Sanz-Morère et al., 2021]. The version used for this work is the fully portable version of the prototype described in [Giovacchini et al., 2015], which weighs approximately 6 kg.

3.1 Mechatronic structure

A brief description of the mechatronic design of the orthosis is given here (Figure 3.1). For further details, the reader is referred to [Giovacchini et al., 2015, Martini et al., 2020].

This APO is composed of a backpack housing the control electronics and battery. Two actuation units, one for each hip, are attached to the backpack using aluminium plates. The human and robot hip flexion-extension rotation axes have to be aligned in the sagittal plane [Giovacchini et al., 2015], which is done by a screw mechanism on the aluminium plates. The backpack interfaced with the user's trunk via an orthotic shell, designed to put most of the weight of the orthosis on the iliac crests [Martini et al., 2020]. The actuation units employ a series elastic actuator architecture, which includes a DC motor, a reduction stage based on harmonic gearing, and a custom torsional spring [Martini et al., 2020]. They also comprise two absolute encoders to estimate the user hips angle and to measure the spring deformation, in order to compute the output torque [Martini et al., 2020]. Each of the actuation units can deliver a peak torque of 16 Nm over a flexion-extension range of motion between -40° and 120° . The assistive torque is transferred from the actuation units to the hip joints through rigid links connected to the posterior part of the user's thighs by means of thigh



Figure 3.1 The Active Pelvis Orthosis developed in the framework of the CYBERLEGs and CYBERLEGsPlusPlus research projects, now brought to a commercial product by the company IUVO (Pisa, Italy, www.iuvo.company).

cuffs and adjustable straps [Martini et al., 2020, Sanz-Morère et al., 2021]. These links are also equipped with passive rotational degrees of freedom for hips abduction-adduction movements [Giovacchini et al., 2015].

3.2 Oscillator-based assistance

The controller of this orthosis employs an algorithm determining the assistive torque to be injected, and which requires no prior knowledge about the gait dynamics [Giovacchini et al., 2015]. The first step of this algorithm is to estimate the gait phase using a pool of adaptive oscillators. These are a set of non-linear differential equations capable of synchronizing with an input quasi-periodic signal, e.g., the hip angular profile during gait, and of providing an estimate of this signal in real time, i.e., without delay, corresponding to a filtered version of the input signal [Righetti et al., 2006, Buchli et al., 2008, Righetti et al., 2009]. They are able to do so by tracking the signal periodicity characteristics, such as the amplitude, frequency and lead phase [Giovacchini et al., 2015]. Thanks to a phase error learning module described in details in [Yan et al., 2016], a continuous phase variable can be obtained, resetting to 0 % of the gait cycle whenever a relevant biomechan-

ical event is detected, here the maximum hip flexion angle [Martini et al., 2020, Sanz-Morère et al., 2021].

The APO can be operated in *transparent mode*, where it does not provide assistance to the user, and in *assistive mode*, where the assistance can be computed following two different strategies. The first one is the *virtual stiffness assistive strategy*, which is used in this work. Using a set of adaptive oscillators coupled to a non-linear kernel filter, an estimate of the hip joint angle $\hat{x}(\varphi)$ can be obtained at each gait phase φ , as well as a prediction of its future value at a phase $\varphi + \Delta\varphi$ [Ronsse et al., 2011a]. In this strategy, the assistive torque is proportional to the difference between the predicted and the current estimated hip joint angles. This way, the user's hips are smoothly drawn towards their future position using an attractive virtual stiffness field [Giovacchini et al., 2015]. The assistive torque is therefore computed as follows [Ronsse et al., 2011a, Giovacchini et al., 2015, d'Elia et al., 2017]:

$$T = k(\hat{x}(\varphi + \Delta\varphi) - \hat{x}(\varphi)) \quad (3.1)$$

with k the tunable virtual stiffness [Nm/rad] which determines the magnitude of the assistance, φ the gait phase estimated by the oscillators [% of gait cycle], and $\Delta\varphi$ a tunable phase lead [% of gait cycle] determining how far in advance the signal of the hip is predicted. The real-time estimate of the hip angle signal $\hat{x}$ [rad] is obtained through n adaptive oscillators decomposing the input signal into n harmonics, as a kind of real-time Fourier decomposition, as illustrated on Figure 3.2. Each oscillator learns the features of one of the harmonic i , including the fundamental frequency ω , the phase φ_i , and the amplitude a_i , as described hereunder [Yan et al., 2016, Ronsse et al., 2011a]:

$$\dot{\varphi}_i(t) = \omega(t) \cdot i + \nu_\varphi \frac{F(t)}{\sum_{i=1}^n a_i(t)} \cos(\varphi_i(t)) \quad (3.2)$$

$$\dot{\omega}(t) = \nu_\omega \frac{F(t)}{\sum_{i=1}^n a_i(t)} \cos(\varphi_1(t)) \quad (3.3)$$

$$\dot{a}_i(t) = \eta F(t) \sin(\varphi_i(t)) \quad (3.4)$$

$$\dot{a}_0 = \eta F(t) \quad (3.5)$$

with a_0 a unique offset component.

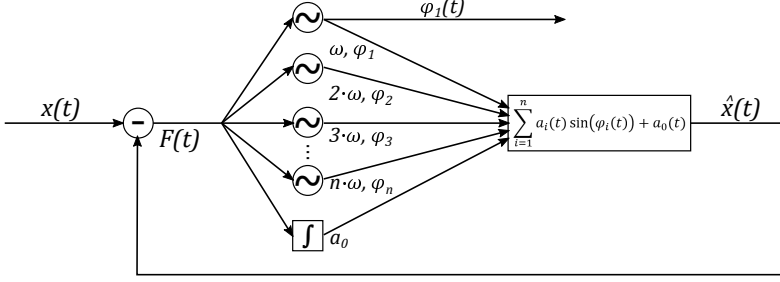


Figure 3.2 Block diagram of the adaptive oscillator's dynamic system. The input signal $x(t)$ is decomposed into n harmonics. Each oscillator learns the features of one of the harmonics, i.e., the fundamental frequency ω , the phase φ_i and the amplitude a_i . The error between the estimated signal $\hat{x}(t)$ and the measured one $x(t)$ drives the evolution of the dynamic system, adapted from [Yan et al., 2016].

All these variables converge to the corresponding ones of the measured input $x(t)$ by using as teaching signal the error between the measured and estimated inputs: $F(t) = x(t) - \hat{x}(t)$ [Righetti et al., 2006]. The learning speeds are obtained with the following equations [Ronsse et al., 2013]:

$$\eta = \frac{2}{\tau} [1/s]; \quad \nu_\omega = \frac{20}{\tau^2} [\text{rad/s}^2]; \quad \nu_\varphi = \sqrt{24.2\nu_\omega} [\text{rad/s}] \quad (3.6)$$

where η is the amplitude gain, ν_ω is the frequency gain, ν_φ is the phase gain, and τ is a time constant determining the time for the oscillators to learn and to adapt to changes in the input signal features. It is equivalent to the time required for the system to reach approximately 63 % of its stationary value, in response to a change in its inputs.

The input signal is then estimated by a frequency summation of the extracted variables [Yan et al., 2016, Ronsse et al., 2011a]:

$$\hat{x}(\varphi) = \sum_{i=1}^n a_i \sin(\varphi_i) + a_0 \quad (3.7)$$

The second assistive strategy that can be adopted with the orthosis is the *feed-forward assistive strategy*. In this strategy, the torque profile is a function of the gait phase estimated by the adaptive oscillators and is computed as a sum of two Gaussian functions, one for hip flexion and the other for hip extension [Martini et al., 2020, Sanz-Morère et al., 2021]. This strategy is not detailed here as it is not used in this work.

3.3 Results of previous studies

Several studies involved the use of the APO since the first prototype described in [Giovacchini et al., 2013]. The first study testing the effects of the orthosis on gait was performed on one elderly subject using the virtual stiffness assistive strategy [Parri et al., 2014]. The authors showed no difference between the transparent and active modes in the hips range of motion (ROM), range of velocity and shape of the angle profile. Another study tested the same strategy with five healthy subjects on a treadmill and showed that the step length and cadence were not impacted by the assistance, but that the ROM of the hips and knees increased when increasing the assistance provided by the APO [d'Elia et al., 2017].

More recent studies analyzed the effects of the feed-forward assistive strategy. A first one studied the effect of a four-week treadmill gait training on 20 elderly subjects divided into an APO group and a control group [Martini et al., 2019]. The authors showed a decrease in the metabolic cost of transport after the training for the APO group and not for the control group, as well as an increased peak hip flexion angle during the training while wearing the APO. A subsequent study on seven healthy subjects and two transfemoral amputees showed a significant decrease in the metabolic cost of transport for the amputees, but not for the healthy subjects [Martini et al., 2020]. Finally, the effects of a four-week overground gait training on seven transfemoral amputees were also analyzed [Sanz-Morère et al., 2021]. The authors showed an increased gait speed and more symmetrical gait patterns after training.

The APO was also used for balance recovery after slippages in a study involving eight elderly people and two transfemoral amputees [Monaco et al., 2017]. This study showed that the orthosis can identify a loss of balance following an unexpected slipping-like perturbation delivered by a split-belt treadmill, and that it applied compensating torques at the hips to help restore balance.

On top of this, a bio-inspired control strategy is still under development, based on the principle of motor primitives to generate the desired hip joint torque profiles. It has already been validated in healthy subjects during overground walking [Ruiz Garate et al., 2016], ascending and descending stairs [Ruiz Garate et al., 2017], walking on positive and neg-

ative slopes [Laloyaux et al., 2022], as well as for the symmetrization of gait [Laloyaux et al., 2023]. Finally, a new gait phase estimator based on discrete wavelet transform was validated in eight healthy subjects and three transfemoral amputees [Livolsi et al., 2022]. This algorithm is proposed to replace the gait phase estimation based on adaptive oscillators currently used in the APO. It is capable of identifying gait events such as heel strike and toe off, which are more biomechanically relevant gait events than the maximum hip flexion angle currently used to reset the gait phase variable to 0 % of the gait cycle.

3.4 Implications for this work

In the framework of this thesis, the virtual stiffness assistive strategy of the APO is used. This strategy employs three tunable parameters: the virtual stiffness k , the phase lead $\Delta\varphi$, and the oscillator memory τ . In the subsequent chapter, the effects of several values of the virtual stiffness and the oscillator memory on the level of LRA in series of stride durations in patients with Parkinson's disease are investigated using model-based simulations. In the experiments with healthy subjects (Chapter 5), the value of the virtual stiffness is this time dependent on the subject's weight. On the other hand, several conditions involving two values of the phase lead and of the oscillator memory are tested, in order to identify the optimal parameter values for the experiments on patients with Parkinson's disease (Chapter 6).

4

Model-based predictions

The content of Sections 4.1 to 4.3 is adapted from:



V. Otlet and R. Ronsse, "Predicting the effects of oscillator-based assistance on stride-to-stride variability of Parkinsonian walkers," 2022 IEEE International Conference on Robotics and Automation (ICRA), 2022, pp. 8083–8089, doi: 10.1109/ICRA46639.2022.9811822.

and Section 4.4 is a summary of:



C. Vandamme, V. Otlet, R. Ronsse and F. Crevecoeur, "Model of gait control in Parkinson's disease and prediction of robotic assistance," IEEE Transactions on Neural Systems and Rehabilitation Engineering, 31:1374–1383, 2023, doi: 10.1109/TNSRE.2023.3245286.

THE goal of this chapter is to develop a set of model-based predictions about the deterioration of LRA in people affected by Parkinson's disease, and how this can be partially restored by an assistive method mediated by a compliant orthosis. As introduced in Chapter 2, several models for simulating series of stride durations containing LRA

exist [West and Scafetta, 2003, Gates et al., 2007, Dingwell et al., 2010, Sarbaz et al., 2011]. Our team has worked in parallel on the adaptation of two models in particular, the *super central pattern generator model* [West and Scafetta, 2003] and the *optimal control model* [Dingwell et al., 2010]. The first one is described in more details in this thesis, while the second was developed by another PhD student, namely Clémence Vandamme, as part of her master thesis [Vandamme, 2021], and subsequently published in [Vandamme et al., 2023]. This second model is summarized in Section 4.4.

The super central pattern generator (SCPG) model relies on the hypothesis that locomotion is regulated by CPGs. It has evolved over the last few decades to model the series of stride durations with particular fractal properties obtained under several walking conditions. J. Hausdorff and coworkers first developed a correlated CPG model [Hausdorff et al., 1995], composed of a chain of stride frequencies occurring with different probabilities, and producing series of stride durations containing LRA. Y. Ashkenazy and colleagues further extended this model to describe changes in fractal properties of these time series with maturation [Ashkenazy et al., 2002], i.e., the development of neural connections from childhood to adulthood, by making the chain of stride frequencies short-range correlated. In these first two versions, biological variability was modeled by noise added to the output of each node in the chain [Scafetta et al., 2009]. In the final version of the model, B. West and N. Scafetta added a nonlinear oscillator to account for this biological variability [West and Scafetta, 2003]. This new version allows to reproduce the fractal properties of gait under several conditions, i.e., at slow, normal and fast speeds, and while following the rhythm of a metronome. It must be noted that the architecture of this model should not be considered as a reflection of real anatomical structures. However, it can be considered to capture the global properties of the locomotor system [Delignières and Marmelat, 2013].

4.1 Methods

4.1.1 Model

In this section, we first detail the SCPG model according to the formalism described in [West and Scafetta, 2003, Delignières and Torre, 2009] in order to generate inter-stride intervals time series containing LRA with similar properties as healthy human walkers (Figure 4.1a). Then, the effect of the

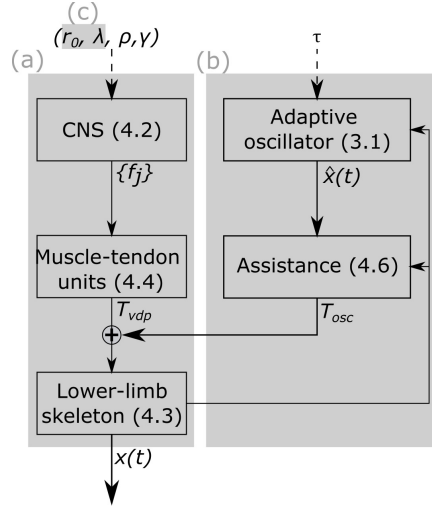


Figure 4.1 Block diagram of (a) the SCPG model and body coupled to (b) an oscillator-based assistance. The parameters (c) are those to be adapted from healthy values to take into account the impact of Parkinson’s disease. Model parameters are indicated by dashed lines. Numerical labels between brackets refer to the corresponding equations in the text.

orthosis is added to the model, by adding the equations of an adaptive oscillator (Figure 4.1b). Finally, the model parameters are adapted to match the characteristics of real inter-stride time series of patients with Parkinson’s disease (Figure 4.1c).

Super central pattern generator model

This model is composed of two parts. The first one represents the correlated firing activity of the central nervous system. It is modeled through a Markov chain (Figure 4.2), whose nodes X_i can be seen as alternative neuronal pathways successively activated to perform a specific task [Delignières and Marmelat, 2013]. As described by Equation (4.1), these pathways are exponentially correlated, because neighboring pathways share common components [Delignières and Marmelat, 2013]. This Markov chain is thus modeled by [West and Scafetta, 2003, Delignières and Torre, 2009]:

$$X_i = \exp(-1/r_0)X_{i-1} + \varepsilon_i \quad (4.1)$$

with r_0 the short-range spatial correlation size, and ε a zero-centered discrete Gaussian process of variance λ^2 [Delignières and Torre, 2009].

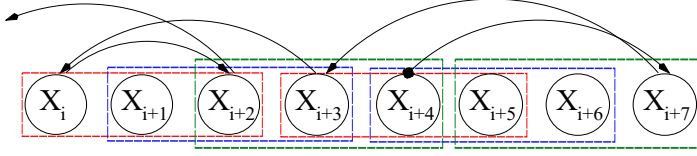


Figure 4.2 Illustration of the Markov chain characterizing the CPG, adapted from [Ashkenazy et al., 2002]. The neural pathways X_i are short-range correlated, forming superimposed zones (dashed colored boxes) of size $r_0 = 3$ in this example, centered around each pathway. Arrows indicate the jumps of the random walker.

From this short-range correlated series $\{X_i\}$, a new long-range correlated one $\{X_j\}$ is obtained by following the jumps of a random walker along this chain. The jump size follows a Gaussian distribution of width ρ , i.e., $\sim \mathcal{N}(0, \sigma^2)$ with $\sigma = \rho / (2\sqrt{2 \ln(2)})$.

Each of these pathways X_j produces a particular stride frequency, resulting in a long-range correlated time series of virtual frequencies [West and Scafetta, 2003, Delignières and Torre, 2009]:

$$f_j = f_0 + \gamma X_j \quad (4.2)$$

where f_0 is the driver frequency, i.e., the average frequency of the series, and γ a constant.

The second part of this model captures a dynamical model of the lower-limb biomechanics. Indeed, the actual stride frequencies are not exactly equal to the output of the central nervous system, but are constrained by the biomechanical motor control system [Scafetta et al., 2009]. This is modeled with a forced van der Pol oscillator. This type of nonlinear oscillator generates stable oscillations, or limit cycles, mimicking the quasi-periodic gait dynamics [Scafetta et al., 2009]. Therefore, the time series $\{f_j\}$ of the previous part is taken as input to this nonlinear oscillator, such that the j^{th} cycle of the oscillator is initiated with an intrinsic frequency f_j . The system composed of Equations (4.3) and (4.4) forms a van der Pol oscillator, as described in [West and Scafetta, 2003, Delignières and Torre, 2009]:

$$\ddot{x} = T_{vdp} \quad (4.3)$$

$$T_{vdp} = \sin(2\pi f_0 t) - x^2 \dot{x} + \dot{x} - (2\pi f_j)^2 x \quad (4.4)$$

where $x(t)$ is the hip angular position and $\dot{x}(t)$ and $\ddot{x}(t)$ represent its two first time-derivatives, i.e., angular velocity and acceleration of the hip. This oscillator is driven by a periodic force, characterized by a nominal frequency f_0 , that is equal to the average of the frequency series of Equation (4.2).

Finally, the simulated inter-stride intervals time series is given by the actual period of the successive cycles of $x(t)$, obtained by solving this second-order differential equation using a four-stage Runge-Kutta integrator [West and Scafetta, 2003]. By convention, these cycles are delimited by the zero-crossings of the signal $x(t)$ when it is decreasing.

Walking assistance

In this work, we assume that the walking assistance is delivered by an adaptive oscillator, described in Chapter 3. This mathematical tool provides an estimate of the hip angular trajectory $\hat{x}(t)$, according to Equation (3.7), with the assumption for this model that $n = 1$. It is important to note that the whole dynamics of the adaptive oscillator can be tuned by a single parameter, namely τ , that governs the learning rate of the adaptive oscillator's state variables, as shown in Equation (3.6).

The assistance provided by the device is taken into account by adding a supplementary term to the van der Pol oscillator, i.e., Equation (4.3):

$$\ddot{x} = T_{vdp} + T_{osc} \quad (4.5)$$

Here, we consider that the device provides an assistive torque T_{osc} that is proportional to the difference between the estimate $\hat{x}(\varphi + \Delta\varphi)$ and the actual signal $x(\varphi)$ of the hip position. Two cases are considered for the simulation of the device's assistive torque: $\Delta\varphi = 0$ or $\Delta\varphi > 0$. The first case is similar to what [Leconte and Ronsse, 2016] did for the upper-limb. Indeed, the authors showed that delivering this assistance helps in smoothing the movement but with no injection of mechanical work, on average. The second case models a situation closer to those of the experiments in Chapters 5 and 6, with the phase lead at default device's setting, i.e., $\Delta\varphi = 0.628$ [rad]. In this second case, it is thus expected that the device would inject energy to the user, and the assistive torque is therefore given by:

$$T_{osc} = -k(x(\varphi) - \hat{x}(\varphi + \Delta\varphi)) \quad (4.6)$$

with the constant k determining the level of assistance. Note that it has no unit corresponding to real biomechanics, but it can be considered equivalent to a virtual stiffness since it relates a torque to a position. Therefore, in the following, a.u. stands for arbitrary unit.

In order to estimate the contribution of this extra assistance torque in the whole dynamics of the model, we compute δ_{osc} as the ratio between the peak torque provided by the assistance over the peak total torque, i.e.:

$$\delta_{osc} = \frac{\max_{cycle} |T_{osc}|}{\max_{cycle} |T_{vdp} + T_{osc}|} \cdot 100 [\%] \quad (4.7)$$

Selection of parameter values

In order to simulate time series corresponding to patients with Parkinson's disease, some parameters of the model have to be adapted compared to the values reported in [West and Scafetta, 2003, Delignières and Torre, 2009] for healthy people. Neurodegenerative disorders like Parkinson's disease can be interpreted in this model as a decrease in the correlation between neural centers, characterized by r_0 [West and Scafetta, 2003]. To match the decreased presence of LRA in real time series of patients (obtained from [Warlop et al., 2016]), this parameter is decreased to $r_0 = 6$ compared to the value for a healthy subject, i.e., $r_0 = 25$. To take into account the increased standard deviation of those time series, λ is set to 0.8, and finally, $f_0 = 1/1.07$ [Hz] since the mean stride durations of patients is equal to 1.07 s, as obtained from real time series of [Warlop et al., 2016]. The other parameters of the model are left at the same values as in [West and Scafetta, 2003, Delignières and Torre, 2009], i.e., $\gamma = 0.02$ and $\rho = 25$.

In this work, we would like to predict the effect of the oscillator-based assistance for several magnitudes of assistance k and several learning time constants τ of the oscillator. For the case with $\Delta\varphi = 0$, we explore 30 combinations, i.e., $k = 2, 4, \dots, 20$ [a.u.] and $\tau = 0.5, 4, 10$ [s]. For the case with $\Delta\varphi > 0$, we explore only a subset of these 30 combinations, i.e., the four combinations corresponding to $k = 10$ and 20 [a.u.] and $\tau = 4$ and 10 [s]. One hundred series of frequencies $\{f_j\}$ containing 1024 points

each are simulated in Matlab version R2019a for each pair of assistance parameters (k, τ) .

4.1.2 Statistical analysis

From the series of stride durations, two metrics were obtained and analyzed for each combination (k, τ) : the standard deviation σ and the level of LRA α . The latter was obtained through the evenly spaced-averaged DFA described in Chapter 2, with $n = 10, \dots, N/2$.

Model-based predictions regarding the effect of oscillator-based assistance as a function of the assistance level k and the adaptive oscillator's learning rate τ required the design of some statistics, using linear mixed-effects models. In order to take into account the bi-linearity of the data shown in Figure 4.4 when $\Delta\varphi = 0$, we fitted a bi-linear model to the data, given by:

$$\begin{aligned} H_{i,k,\tau} = & \beta_0 + \beta_1 k + \beta_2 k \mathbb{1}_{\tau=4} + \beta_3 k \mathbb{1}_{\tau=10} \\ & + \beta_4 \max(k - 4, 0) + \beta_5 \max(k - 4, 0) \mathbb{1}_{\tau=4} \\ & + \beta_6 \max(k - 4, 0) \mathbb{1}_{\tau=10} + \varepsilon_{i,k,\tau} \end{aligned} \quad (4.8)$$

for $i = 1, 2, \dots, 100$ and $k = 0, 2, \dots, 20$. In this equation, H is the answer variable, i.e., the α exponent or the standard deviation of the inter-stride intervals time series, β_0 is the ordinate at the origin for $k = 0$, $\mathbb{1}_{\tau=t}$ is the indicator function, i.e., it is equal to 1 if $\tau = t$ and to 0 if $\tau \neq t$, and $\varepsilon_{i,k,\tau} \sim \mathcal{N}(0, \sigma_\varepsilon^2)$ is the error term. A first line is fitted for each τ to the data between $k = 0$ and $k = 4$, and is characterized by the slope β_1 for $\tau = 0.5$, β_2 for $\tau = 4$, and β_3 for $\tau = 10$. Then a second line is fitted to the data between $k = 4$ and $k = 20$, and is characterized by the slope β_4 for $\tau = 0.5$, β_5 for $\tau = 4$, and β_6 for $\tau = 10$.

For the case where $\Delta\varphi > 0$, as there are fewer experimental conditions that were generated, it cannot be concluded that there is bi-linearity in the data. The equation of the linear mixed-effects model is therefore given by:

$$H_{i,k,\tau} = \gamma_0 + \gamma_1 k + \gamma_2 k \mathbb{1}_{\tau=10} + \varepsilon_{i,k,\tau} \quad (4.9)$$

with γ_0 the ordinate at the origin for $k = 0$, γ_1 the slope for $\tau = 4$, and γ_2 the one for $\tau = 10$.

Then, a general linear hypothesis test was applied on this model, using a contrast matrix allowing to compare all the conditions to the baseline with no assistance, i.e., $k = 0$. The p -values are also adjusted for multiple comparisons using the Benjamini and Hochberg correction [Benjamini and Hochberg, 1995]. These tests were performed in R version 3.6.2.

4.2 Results

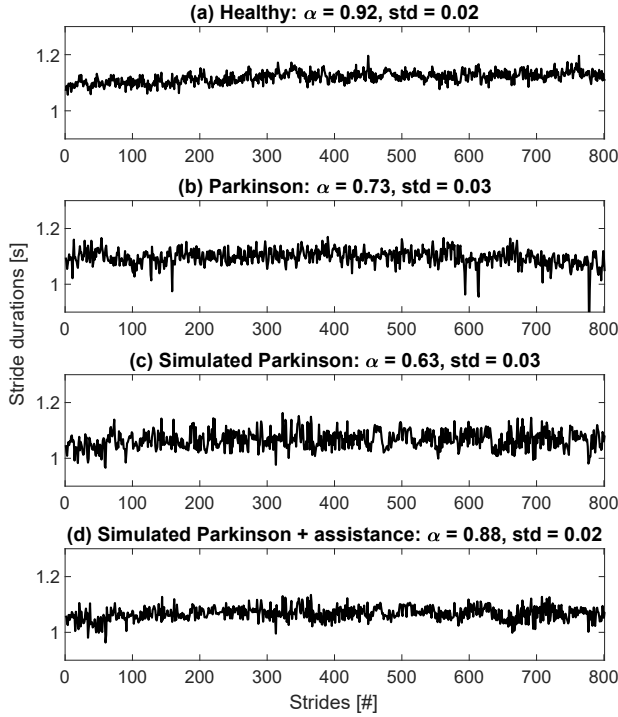


Figure 4.3 Comparison between a real inter-stride intervals time series of (a) a healthy subject, from [Hausdorff et al., 1996] and retrieved from PhysioNet, and of (b) a patient with Parkinson's disease, from [Warlop et al., 2016], (c) a simulated time series of a patient, and (d) the same simulated time series but with the assistance based on an adaptive oscillator, with $k = 16$, $\tau = 10$ and $\Delta\varphi = 0$; α is the fractal exponent and "std" stands for standard deviation.

Typical real time series of a healthy walker and of a patient with Parkinson's disease are shown in Figure 4.3, as well as a simulated time series of a patient, with and without the walking assistance based on an adaptive oscillator, with $\Delta\varphi = 0$. Two metrics are computed for each of them: the

α exponent and the standard deviation. While these metrics are originally lower and higher than those of the healthy time series respectively, it can be observed that the metrics of the simulated Parkinsonian time series become closer to those of the healthy one thanks to the simulated walking assistance.

Figure 4.4 shows the same metrics computed for the simulated time series for different values of k and τ . In particular, it highlights an increase in α exponent and a decrease in standard deviation of the time series when k and τ increase, regardless of the value of the phase lead $\Delta\varphi$. It also shows that for $\tau = 10$ and $k = 12$, the α exponent is close to the one of healthy walkers when $\Delta\varphi = 0$. For higher values of k , this metric is higher than 1, meaning that the time series is non-stationary, and that no conclusion can be drawn about its persistence. On the other hand, standard deviation of the time series becomes closer to the healthy level, but never reaches it.

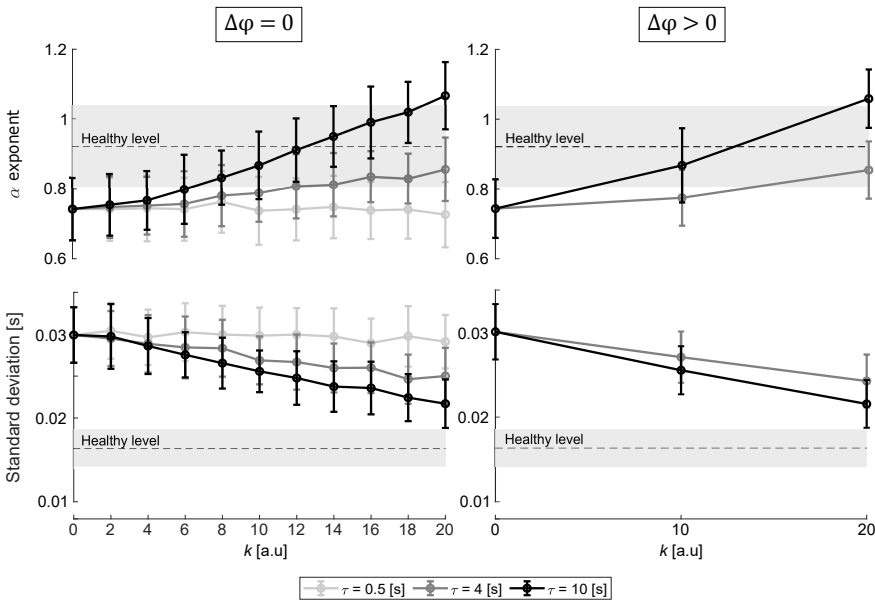


Figure 4.4 Evolution of the fractal exponent (above) and the standard deviation (below) of the simulated inter-stride intervals time series of patients with Parkinson's disease for several assistance levels, with a zero (left) or a positive phase lead (right), compared to the value of healthy walkers (means indicated by dashed lines, standard deviations indicated by shaded areas) obtained from [Hausdorff et al., 1996] and retrieved from PhysioNet. The case where no assistance is applied corresponds to $k = 0$.

With regard to the standard deviation, when $\Delta\varphi = 0$, statistical results show that for $\tau = 0.5$, slightly significant differences ($p < 0.05$) were observed between assistance conditions with $k = 16, 18, 20$ and baseline. Highly significant differences ($p < 0.001$) were observed for $\tau = 4$ and $\tau = 10$ for all k . The same observations apply when the phase lead is positive.

Concerning the α exponent, when $\Delta\varphi = 0$, statistics show that for $\tau = 0.5$, no significant difference was observed between all assistance parameter pairs and baseline, while highly significant differences ($p < 0.001$) were observed for $\tau = 4$ and $k \geq 8$, and for $\tau = 10$ and $k \geq 6$. These findings also hold when the phase lead is positive, for both values of k and τ tested in that case.

Finally, the contribution of the torque provided by the walking assistance as a fraction of the peak total torque is provided in Figure 4.5. It shows that the torque contribution of the simulated adaptive oscillator increases with k and τ , but stays below 10 % for the values we tested for $\Delta\varphi = 0$. On the other hand, when the phase lead is positive, the torque provided by the assistance is greater as expected, contributing to around 18 to 32 % of the peak total torque.

The effect of the orthosis was also simulated on the series of stride durations of healthy individuals. The model parameter values set for this case and the figures showing the results are included in the Appendix A.

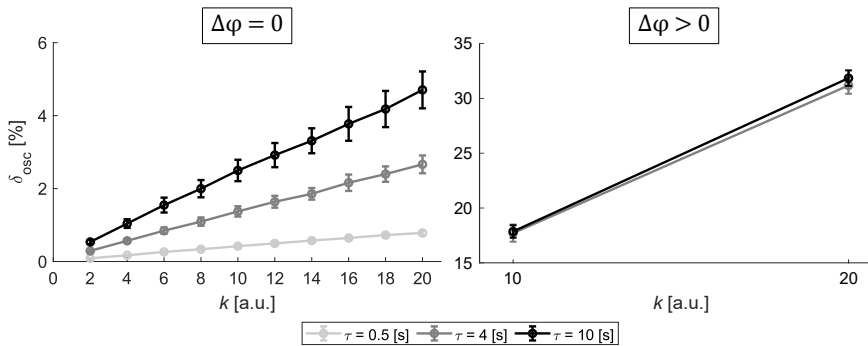


Figure 4.5 Ratio δ_{osc} between the peak torque provided by the oscillator-based assistance and the peak total torque of the model, with a zero (left) or a positive phase lead (right).

4.3 Discussion

In this study, we aimed at predicting the effects of a walking assistance based on adaptive oscillators on the level of LRA in inter-stride intervals time series of patients with Parkinson's disease. These simulations showed that for some values of τ , great improvements can be observed for a sufficient level of assistance. We can highlight two main points from this analysis: the more k and τ increase, the more the presence of LRA in the time series increases (α exponent), and the more the variability of the time series decreases (standard deviation), regardless of whether the phase lead is zero or positive.

Previous articles [Ronsse et al., 2013, Ronsse et al., 2011b] have shown that adaptive oscillators act as a low-pass filter on the input signal. With a higher level of assistance, the oscillator-based assistance filters more frequency fluctuations, and thus contributes to the decrease of the time series variability. As the time series becomes less random, the presence of LRA is increased. This particular effect of filtering out the high frequencies is visible in Figure 4.3, by comparing panels (c) and (d). On the other hand, the time constant τ characterizes the time it takes to the adaptive oscillator to learn and synchronize with the input signal. Therefore, higher values of τ means that the adaptive oscillator has a longer memory, and thus forces the gait to resemble previous cycles, leading to less variability in the series.

The only difference between the case where the phase lead is zero and the case where it is positive is the maximal torque provided by the oscillator-based assistance. When $\Delta\varphi = 0$, it was one order of magnitude smaller than the torque produced by the simulated lower limbs. Nevertheless, this assistance had a significant dynamic effect on time series metrics. This is in agreement with [Leconte et al., 2019], which showed that this type of assistance had significant benefits on the harmonic content of upper-limb movement of post-stroke patients, while injecting no mechanical work on average. These results highlight that letting the patient steering their movement without injecting too much mechanical work remains beneficial for them. On the other hand, when $\Delta\varphi > 0$, the torque provided by the assistance is much higher. This result raises an interesting model-based prediction about this controller, namely that it allows to independently control the level of assistance by energy injection (controlled by the phase lead $\Delta\varphi$) and the impact on the level of LRA and variability in the time series

(through the parameters k and τ). This prediction will be put to test in the experimental part of the present thesis, in Chapters 5 and 6.

These simulations naturally lead to some assumptions and questions about the results we could obtain during actual experiments with patients with Parkinson's disease, who would receive this assistance with the APO described in Chapter 3. The model predicts better results for an oscillator-based assistance with a longer memory, i.e., about 10 cycles. Until now, studies that have been done with this type of walking assistance used adaptive oscillators capable of learning quickly, i.e., about four cycles, in order to avoid preventing the user's ability to change the features of their movement. Therefore, we can ask ourselves if by using a greater learning time constant, the user will retain enough freedom to steer their movement, i.e., to change cadence or amplitude. In addition, the virtual stiffness k of this model must be interpreted carefully. Indeed, this value can be increased arbitrarily in this model, giving eventually rise to a normalization of the computed metrics. Nevertheless, in reality, there are physical limits to this value in order to keep the level of assistance below safety margins, so as neither harming the user nor damaging the robot. Therefore, the predictions of the model regarding the presence of LRA in the time series will probably be influenced by this limit imposed on k . Nevertheless, the model shows that the applied torque remains less than 10 % of the torque produced by the lower limbs, which is within the physical limits of the actual device.

Finally, the interpretation of the parameters of the SCPG model points out a potential explanation about the origin of the loss of LRA in patients with Parkinson's disease. To adapt the model in order to account for the decrease in the level of LRA in series of stride durations, we had to decrease r_0 , i.e., the correlation size between neural centers of a CPG. Indeed, the loss of dopaminergic neurons occurring in Parkinson's disease leads to a less correlated motor control system, modeled here through the Markov chain [Scafetta et al., 2009]. This decrease in the level of LRA could also have been associated to an increase in the amplitude of the driving force of the van der Pol oscillator, as those patients pay more attention to their gait [West and Scafetta, 2003].

Nevertheless, this model has some limitations. Firstly, it is a simplified model of the central nervous system, the leg biomechanics, as well as the

robot. It models the loss of dopaminergic neurons by a decreased correlation between neural centers, but Parkinson's disease is much more than that. For instance, this model does not take into account the alteration of the basal ganglia pathways leading to an inhibition of the motor neurons of the cortex. Secondly, it does not account for the weight of the robot, which can influence the way the user walks, by modifying the body morphology and the associated biomechanics, or by accelerating fatigue. Finally, it incorporates a model about the robot adaptation to the subject, but not the other way around. Note moreover that the statistics developed to compare the different pairs of assistance parameters with the unassisted condition were not strictly necessary. Instead, we could have just computed the effect size, since these are data that we generated, with a variability that we fixed.

In conclusion, this study predicts an improvement of the presence of LRA in the inter-stride intervals time series of patients with Parkinson's disease receiving an oscillator-based walking assistance with a large memory, i.e., about 10 cycles.

4.4 Alternative model

In parallel to the work on the SCPG model, our team also worked on adapting the model of [Dingwell et al., 2010], called the *optimal control model*, in the same way as above. This work was the subject of C. Vandamme's master thesis [Vandamme, 2021], and was subsequently published in [Vandamme et al., 2023]. The reader is referred to this paper for a detailed description of this model. This section rather proposes an overview of how this model works, and an interpretation of the changes made to it in order to take account of the effects of Parkinson's disease on the level of LRA in walking, as well as the influence of the oscillator-based walking assistance on it.

In this model, the strides are characterized by their length L and duration T , from which the speed is derived by $S = L/T$. These stride features are updated iteratively using the following equation [Vandamme et al., 2023]:

$$x_{n+1} = x_n + u(x_n) + N_n u(x_n) + \eta_n \quad (4.10)$$

where x_n is composed of the features of the previous stride (T_n, L_n) , $u(x_n)$ is a motor command, and $N_n u(x_n) + \eta_n$ are motor and perceptual noises

[Vandamme, 2021]. The motor command is governed by a controller, which regulates the variability in stride features caused by internal and external sources of noise, aligning them with a specific gait goal, e.g., maintaining a constant gait velocity. However, achieving this goal encompasses an infinite number of combinations of stride durations and lengths. These combinations constitute a straight line in the plane formed by these two features, called the *goal equivalent manifold*. Along this redundant dimension, one pair of stride duration and length is naturally preferred by each individual, called the *preferred operating point* [Vandamme et al., 2023], as illustrated in Figure 4.6. Because of neuromuscular noise [Dingwell et al., 2010], human beings cannot maintain the features corresponding to this point at all strides. Instead, deviations are allowed along the goal equivalent manifold, while maintaining control to stay close to the preferred operating point and to respect the gait goal [Vandamme et al., 2023]. These deviations result in the presence of LRA in series of stride durations of healthy individuals.

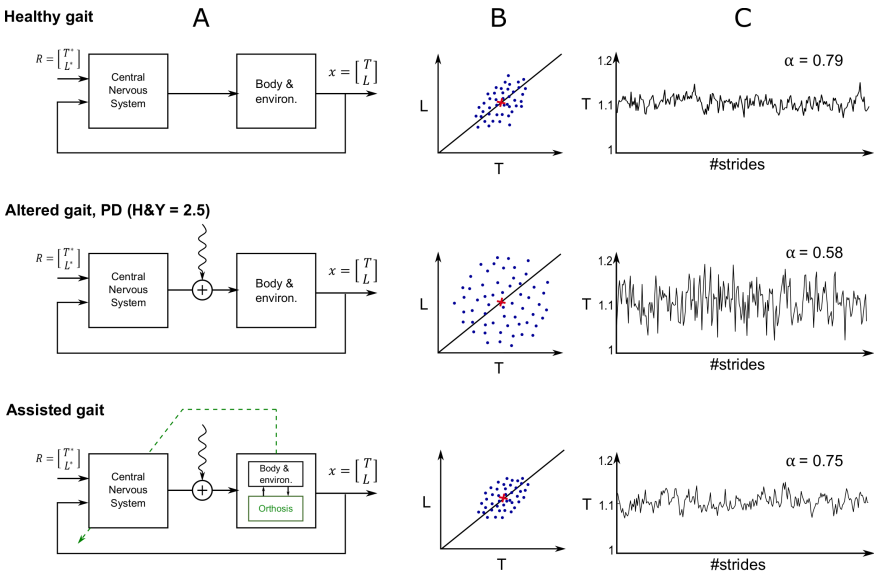


Figure 4.6 (A) Block diagrams of the model, (B) simulated stride distributions around the goal equivalent manifold (black straight line) and the preferred operating point (red cross), and (C) examples of simulated series of stride durations and their corresponding fractal exponent α obtained with AFA, for, from top to bottom, healthy gait, gait altered by Parkinson's disease, and gait altered by Parkinson's disease and assisted by an oscillator-based walking assistance, adapted from [Vandamme et al., 2023].

To reflect the increased variability and the decreased level of LRA in series of stride durations of patients with Parkinson's disease, the noise level and the penalty to stay close to the preferred operating point are both increased. This suggests that patients adopt a different control strategy than healthy individuals. Indeed, in order to compensate for the higher inter-stride variability encountered by patients, they regulate more strictly their gait features around the preferred operating point. This results in a more random time series, and therefore in a reduced level of LRA [Vandamme et al., 2023]. This hypothesis is in line with the fact that patients focus more on their walking than healthy individuals [Baker et al., 2008], in order to bypass the defective basal ganglia pathways, normally enabling automatic movements.

Regarding the addition of the walking assistance using adaptive oscillators in the model, this kind of assistance has been shown to have a net effect on the input signal comparable to a low-pass filter [Ronsse et al., 2011b]. It has therefore been added as such in the present model. As the walking assistance continuously interacts with the user's body dynamics, it has a direct impact on the generation of the next stride, as shown by [Vandamme et al., 2023]:

$$x_{n+1} = x_n + u(x_n) + N_n u(x_n) + \eta_n - \lambda(x_{n+1} - x_n) \quad (4.11)$$

where the low-pass filter effect has been added to Equation (4.10), with λ characterizing the level of assistance of the orthosis. By adjusting the level of assistance λ so that the variability in series of stride durations of patients matches that of healthy individuals (Figure 4.7A), the LRA level is also increased compared to the patients' initial value. Two cases have been considered here: one where patients adapt to the assistance, and one where they do not. These two cases generate a different degree of increase in the level of LRA, as shown in Figure 4.7B. However, it can be assumed that patients actually adapt at least partially to the assistance, based on previous research on adaptation to split-belt treadmill [Roemmich et al., 2014]. In that case, the impact of the assistance on the LRA level would be between the results obtained with full adaptation and those obtained in the absence of adaptation [Vandamme et al., 2023].

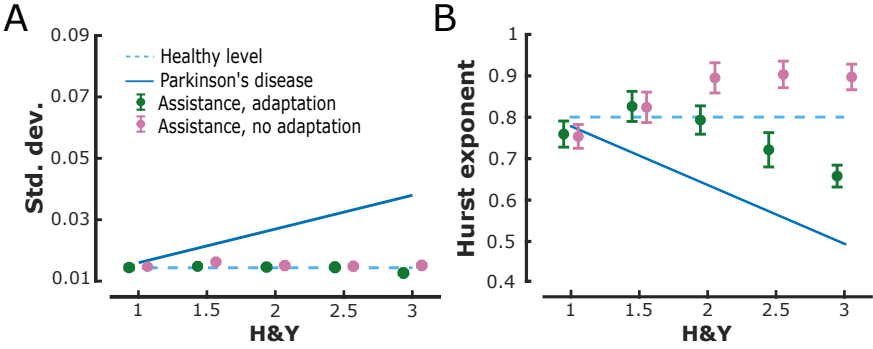


Figure 4.7 Simulation of the effect of an oscillator-based walking assistance on (A) the standard deviation and (B) the level of LRA in series of stride durations of patients with Parkinson's disease for several H&Y stages, with (green) and without (pink) adaptation to the assistance; comparison with the LRA level of healthy individuals (light blue dashed line), and of patients without the assistance (blue), adapted from [Vandamme et al., 2023].

4.5 Comparison of both models

We described in this chapter two different models, both with a different level of complexity and grounded on different hypotheses to explain the origin of the presence of LRA in gait. The SCPG model suggests that it originates from the coordinated activity of interconnected neural circuits, i.e., the CPGs, which generate rhythmic patterns of muscle activation and movement. On the other hand, the optimal control model proposes that the presence of LRA in gait originates from the fact that variability in stride lengths and durations is allowed, while simultaneously applying strong control to deviations from the gait goal, e.g., maintaining a constant speed. Nevertheless, despite the fact that these two models differ in their implementation, they are both based on the principle of redundancy. As a reminder, this concept refers to the fact that there exist several ways of achieving the same task of performing a stride. Indeed, in the case of the SCPG model, there are different neural pathways capable of generating a stride around a specific stride frequency, while in the case of the optimal control model, there are different combinations of stride length and duration to achieve the same speed. Moreover, these two models propose a similar explanation for the origin of the decrease in LRA in patients with Parkinson's disease, i.e., the increased attentional cost associated with walking. Indeed, even if this is not the option chosen in this work, the decrease in the level of LRA in the SCPG model can also be induced by

increasing the amplitude of the driving force of the van der Pol oscillator, which could be interpreted as a greater attentional cost from patients to their walk.

Finally, although these two models address different aspects of the walking assistance, their results point in the same direction. Indeed, they both show that the level of LRA in series of stride durations of patients with Parkinson's disease is increased with an assistance based on the use of adaptive oscillators. This hypothesis is tested in the experiments described in the following chapters.

Nevertheless, a number of factors cast doubt on the relevance of the SCPG model. Indeed, it lacks physiological relevance in the way it interprets the origin of the presence of LRA in the locomotor system and models Parkinson's disease. Moreover, capturing the lower-limb biomechanics with a van der Pol oscillator raises some concerns, since there is no evidence that leg biomechanics is governed either by a frequency-dependent stiffness or by a position-dependent viscosity, i.e., the terms $(2\pi f_j)^2 x$ and $-x^2 \dot{x}$ in Equation 4.4 respectively. Another major limitation of this model is that it does not take into account the user's adaptation to the assistance, suggesting that the increase in the level of LRA is purely due to the adaptive oscillators. On the contrary, the optimal control model stands out for its simplicity. It is more promising in terms of predictive capability, as it requires fewer parameters to be tuned by hand. However, the way Parkinson's disease is modeled does not accurately reflect the disease either, i.e., the loss of dopaminergic neurons affecting basal ganglia pathways. Indeed, this model is rather phenomenological, and models the effects of the disease on the variability present in the patient's series of stride durations.

5

Experiments on healthy aging subjects

The content of this chapter is adapted from:



V. Otlet and R. Ronsse, "Adaptive walking assistance does not impact long-range stride-to-stride autocorrelations in healthy people," *Journal of Neurophysiology*, vol. 130(2), pp. 417–426, 2023, doi:10.1152/jn.00181.2023.

MANY studies have demonstrated in the past that the level of LRA in series of stride durations is impacted by external constraints or by pathologies, as reviewed in Chapter 2. The aim of the present study is to analyze the impact of delivering an oscillator-based walking assistance through a wearable active pelvis orthosis on the level of LRA in series of stride durations of a healthy aging population, i.e., people over 55. This age range was chosen with a perspective of using this group as a control one for experiments with patients with Parkinson's disease, that has been identified as developing between the ages of 55 and 65 [Rizek et al., 2016]. Delivering walking assistance can be considered equivalent as adding a constraint to walking, like a treadmill or a metronome, since it

intrinsically tends to assist the gait pattern. However, in the perspective of being used in rehabilitation with pathological populations such as people with Parkinson's disease, who already have a level of LRA below the one of a healthy population, it is relevant to provide robotic assistance that does not amplify this trend, or better, that could mitigate it. Indeed, the results of the modeling studies presented in Chapter 4 predicted that this assistance framework could have a positive effect on the level of LRA, at least for people with pathological levels [Otlet and Ronsse, 2022, Vandamme et al., 2023]. In that respect, we hypothesize that the adaptive assistance provided by the orthosis used in this study will not lower the LRA level as a metronome or treadmill would do. Indeed, the assistance algorithm has been specifically designed to keep the wearer in control of their main gait features. The experiments in this study are conducted in a semi-ecological environment, i.e., overground instead of on a treadmill, in order to isolate the effects of gait constrained by our walking assistance.

5.1 Materials and methods

5.1.1 Participants

A total of ten healthy participants aged between 56 and 77 years (mean 63.10, SD 6.12 years, 6 females) participated in this study. Exclusion criteria were the inability to walk independently or less than 20 consecutive minutes, and the presence of any neurological disease or other medical condition that could directly affect gait. This study was conducted at the Mounier Sports Center (Brussels, Belgium), and under the approval of the local ethical committee (Comité d'Éthique Hospitalo-Facultaire des Cliniques universitaires Saint-Luc, EudraCT n. 2019-002048-26), in compliance with the declaration of Helsinki. Participants provided written consent prior to data collection and were left free to leave the study at any moment.

5.1.2 Procedures

Subjects were asked to walk while wearing the APO in transparent mode and under three different assistive conditions. For each condition, subjects were asked to walk freely at their comfortable speed in a sports hall during 15 min. They had to follow a rectangular path of 7×12 m with rounded corners, so that the gait is as steady as possible throughout the acquisition, for LRA assessment purposes. The walking session was performed in a quiet environment so as to keep the attentional cost of walking as low as

possible [Warlop et al., 2016]. After a period where subjects can adapt their gait to the device's assistance, the acquisition started and speed steadiness was verified by timing the time taken by the subject to complete each lap, and delivering qualitative instructions to adapt walking speed if needed.

5.1.3 Hip kinematics and kinetics

As described in Section 3.1, the orthosis itself provides some signals, i.e., the hip flexion-extension angle and the injected torque. In the present chapter, only data from the right leg were analyzed, since inter-stride intervals time series were obtained only from that side.

The torque injected was first normalized by the weight of each subject. Then, hip angle and torque signals were divided into individual gait cycles using the maximum hip extension angle as separation event between cycles. The hip angle was also time-differentiated and then used to compute the power exerted by the orthosis over each cycle, i.e., $P = Tdx/dt$, with P the power [W/kg], T the injected torque [Nm/kg], and x the hip angular position [rad]. Finally, the energy injected to the hip by the orthosis was obtained by integrating this power over each gait cycle. The hip ROM and the energy injected to the hip were computed for each gait cycle, then averaged over all cycles. In addition, the occurrence time of the maximum hip flexion angle and of the maximum torque injected at the hip during the gait cycle were computed as the time difference between the beginning of a cycle and the following maximum in the angle or torque signal respectively, normalized by the duration of the corresponding cycle.

5.1.4 Stride intervals computation

The sagittal shank angular velocity was recorded at a sample rate of 500 Hz using an inertial measurement unit (IMU; NGIMU, x-io Technologies, Bristol, UK), which includes a 200 Hz antialiasing low-pass filter on the gyroscope signals. It was fixed just above the right lateral malleolus using a Velcro strap, with its x -axis oriented in the direction of walking.

A zero crossings detection algorithm was used in order to obtain inter-stride time series, i.e., the time between two consecutive heel strikes of the same foot. The negative-going zero crossing occurring just after the maxima in the sagittal shank angular velocity indicates the end of a swing phase [Hundza et al., 2014], corresponding to heel strike events (Figure 5.1).

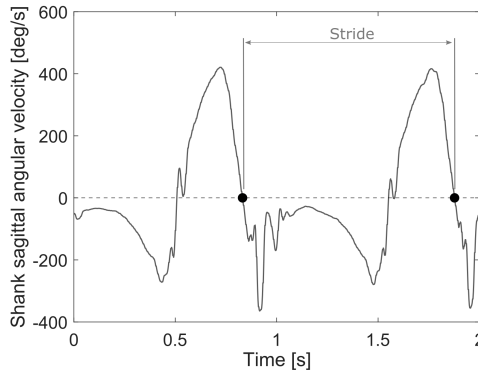


Figure 5.1 Detection of zero crossings with negative slope corresponding to the end of the swing phase. The duration of a given stride is taken as the time interval between two consecutive crossings.

The maxima of the signal were first identified. Then, the first sign change occurring after each of these maxima was detected. Finally, a linear interpolation was performed between both adjacent points to obtain the most accurate zero crossing detection. When all these events were detected, the inter-stride time series was obtained by differentiating the series of these time-stamped events. For the following analyses, the first and last 30 steps of each recording were discarded, in order to analyze steady-state behavior only. The series of stride durations contained at least 512 points, which is a typical requirement for LRA assessment [Warlop et al., 2017].

5.1.5 Spatiotemporal data

From the inter-stride intervals time series, the mean stride duration was computed. Walking speed per lap was computed by dividing the lap distance (38 m) by the time taken by subjects to walk through each of them. Finally, the mean stride length over the whole trial was obtained by taking the product between the mean stride duration and the mean walking speed. These last two metrics were then normalized by dividing by the leg length of each subject.

Moreover, the level of LRA, characterized by the fractal exponent α , was extracted from the series of stride durations. It was computed with

AFA described in Chapter 2, with the subsequences' length n ranging from 5 to the first power of 2 smaller than $N/2$ by steps of two.

5.1.6 Experimental conditions

The torque provided by the APO in this study is obtained following Equation (3.1) in Chapter 3. This assistance can be adjusted using three parameters. The first one is the virtual stiffness k [Nm/rad], which determines the magnitude of the assistance. It was adjusted as a function of the weight of the subject, i.e., so that the peak torque at the hips was equal to 0.1 Nm/kg for each condition described hereunder, corresponding to a comfortable and safe level of assistance as reported in [d'Elia et al., 2017]. The second one is the phase lead $\Delta\varphi$ [%], determining how far in advance the signal of the hip is predicted for computing the injected torque. Finally, the third parameter is the learning time constant τ [s] of the adaptive oscillators, characterizing the time it takes to the oscillators to adapt to changes in gait features.

A total of four conditions were tested:

- (o) Transparent mode, where the orthosis applied no torque;
 - (i) Baseline condition: $\tau = 4$ s and $\Delta\varphi = 1$ %;
 - (ii) Increased oscillator memory: $\tau = 10$ s and $\Delta\varphi = 1$ %;
 - (iii) Increased phase lead: $\tau = 4$ s and $\Delta\varphi = 10$ %.

The transparent mode was selected as the control setting to ensure that the device's weight does not affect the analysis of the presence of LRA in series of stride durations, thereby making the conditions comparable. A value of $\tau = 4$ s corresponds to the basic setting of the device, while a value of $\tau = 10$ s was chosen in order to challenge the results of a previous modeling study [Otlet and Ronsse, 2022] described in Chapter 4, predicting that increasing the oscillator memory increases the level of LRA in time series. A value of $\Delta\varphi = 1$ % is the smallest possible value to have assistance provided, while a value of $\Delta\varphi = 10$ % corresponds to the basic setting of the device.

Conditions were randomized for each participant, and they were blinded to the three assistance conditions. Two conditions were tested each day over two days, to avoid fatigue effects. The minimum break between

the two conditions of the same day was five minutes, and could be increased upon request from the participant. All subjects completed all the conditions.

5.1.7 Statistical analysis

Data were processed with Matlab version R2019a, and statistical tests were performed in R version 3.6.2.

Conditions (o) and (i) were compared with each other and with the conditions (ii) and (iii), in terms of each metric presented above. Linear mixed-effects models were fitted to the different studied metrics. These include fixed effects, which model average trends of the metric for each experimental condition, and random effects, which model the extent to which these trends vary across participants [Brown, 2021]. The linear mixed-effects model equation is given by:

$$Y_i = \gamma_0 + I_i + bX_i + \epsilon_i \quad (5.1)$$

with Y_i the gait metric for the i th subject, γ_0 a general intercept, I_i a random intercept for each subject, X_i the experimental condition number and b its regression coefficient, and ϵ_i the residuals. An analysis of variance was then performed on these models, using a Kenward-Roger's approximation to degrees of freedom [Kenward and Roger, 1997]. If the p -value of this test was lower than 0.05, Tukey's tests for multiple pairwise comparisons were performed, using the Benjamini-Hochberg correction [Benjamini and Hochberg, 1995].

The variances of the α exponent in the four conditions were also compared with a Levene's test [Levene, 1960], in order to determine whether there is a normalizing effect on subjects' behavior with the assistance of the device. If significant, this test was followed by pairwise Levene's tests, and a Benjamini-Hochberg correction was applied on the resulting p -values.

For graphical representation of all these metrics, inter-subject variability is represented through the standard error of the mean, computed as the standard deviation divided by the square root of the number of subjects. Only the inter-subject variability of the α exponent is represented by the standard deviation, since this parameter is compared across the different conditions.

5.2 Results

On average, subjects took 675.30 strides (SD 68.19) in condition (o), 674 strides (SD 99.51) in condition (i), 688 strides (SD 62.94) in condition (ii), and 718.80 strides (SD 66.22) in condition (iii).

Kinematics profiles are shown in Figure 5.2 for a representative subject (left column) and averaged across all subjects (right column). As expected, it can be observed that the torque in transparent mode, and therefore also the power injected at the hip, are close to zero. For the assistive modes, the maximum torque applied to the hips was approximately equal to 6 Nm for the representative subject, as their weight is about 60 kg. It can also be observed that the amplitude of the hip joint angle is larger in the three assistive modes than in the transparent mode. Finally, it can be noted that the maximum flexion angle in condition (iii) is slightly shifted in time compared to both other assistive conditions, and this also shifts the peak torque applied to the hip.

As expected, the statistical tests showed that the mean energy injected during a cycle was higher for the three assistive conditions, i.e., 7.74 J/kg (SD 2.06), 7.96 J/kg (SD 2.52) and 7.25 J/kg (SD 1.64) respectively, than in the transparent mode, i.e., 0.14 J/kg (SD 0.06) ($p < 0.001$). The time occurrence of the maximum hip flexion angle (Figure 5.3a) was smaller in condition (ii) compared to the transparent mode, i.e., 30.04 (SD 2.36) versus 31.58 (SD 1.46) % of gait cycle ($p < 0.01$), and larger in condition (iii) than in (i), i.e., 32.55 (SD 1.47) versus 30.51 (SD 2.06) % of gait cycle ($p < 0.001$). The time occurrence of the maximum torque injected at the hip (Figure 5.3b) was smaller in condition (iii) than in (i), i.e., 15.27 (SD 1.47) versus 19.02 (SD 2.06) % of gait cycle ($p < 0.001$). Concerning the hip ROM (Figure 5.3c), the statistical tests revealed that its mean value over cycles was significantly higher in conditions (i) and (ii) than in the transparent mode, i.e., 54.45° (SD 6.52) and 54.92° (SD 7.22) respectively versus 48.35° (SD 2.86) ($p < 0.001$). On the other hand, it was significantly lower in condition (iii) than in (i), i.e., 48.64° (SD 5.65) versus 54.45° (SD 6.52) ($p < 0.01$). Regarding the spatiotemporal gait metrics (Figure 5.3d-f), the statistical tests indicated an increase in gait speed and stride length between the conditions (i) and (iii) and the transparent mode, i.e., 1.20 L/s (SD 0.16) and 1.21 L/s (SD 0.14) respectively versus 1.10 L/s (SD 0.14) ($p < 0.05$) for speed, and 1.40 L (SD 0.16) and 1.39 L (SD 0.14) respectively versus 1.34 L (SD

5 | Experiments on healthy aging subjects

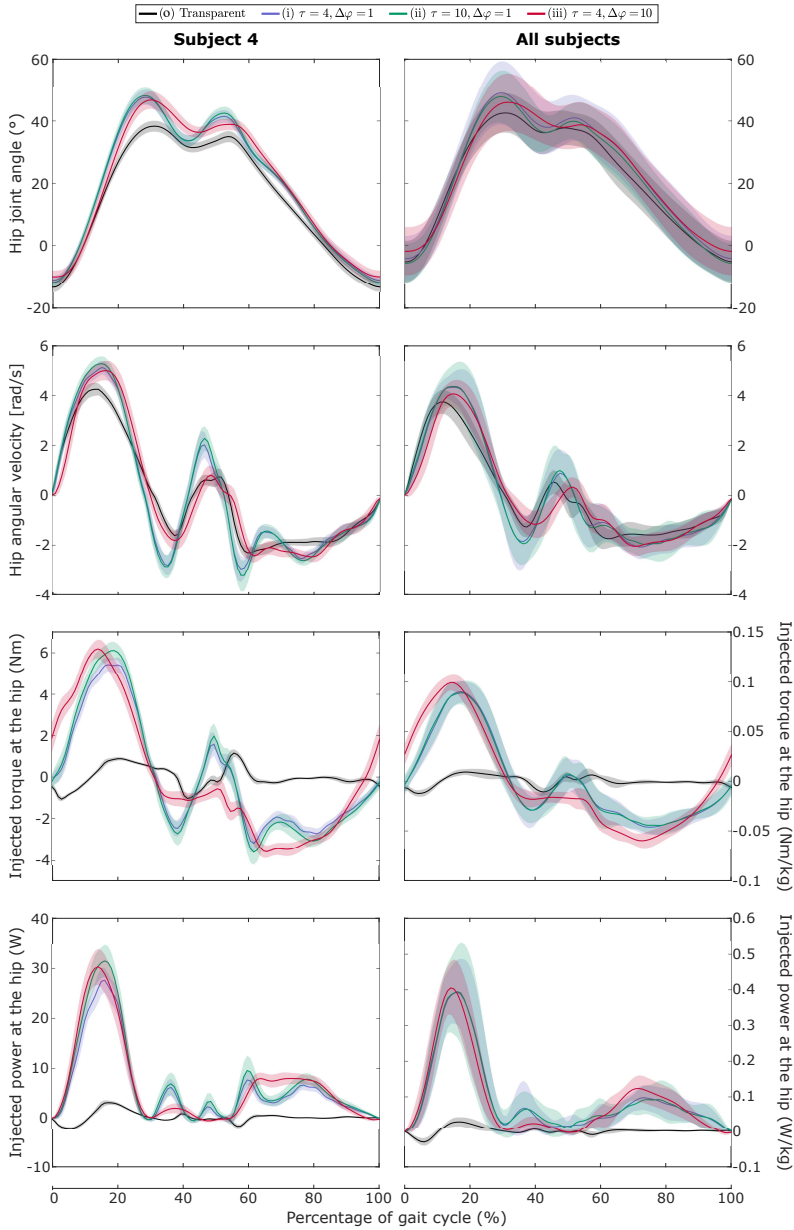


Figure 5.2 Top to bottom: angular position and velocity of the right hip, delivered torque and power for subject 4 (left) and all subjects (right) in transparent mode and in the three different assistive conditions. Signals were time-normalized over the gait cycle. Solid lines represent the mean and the shaded areas represent the standard deviation over all gait cycles (left) or across subjects (right).

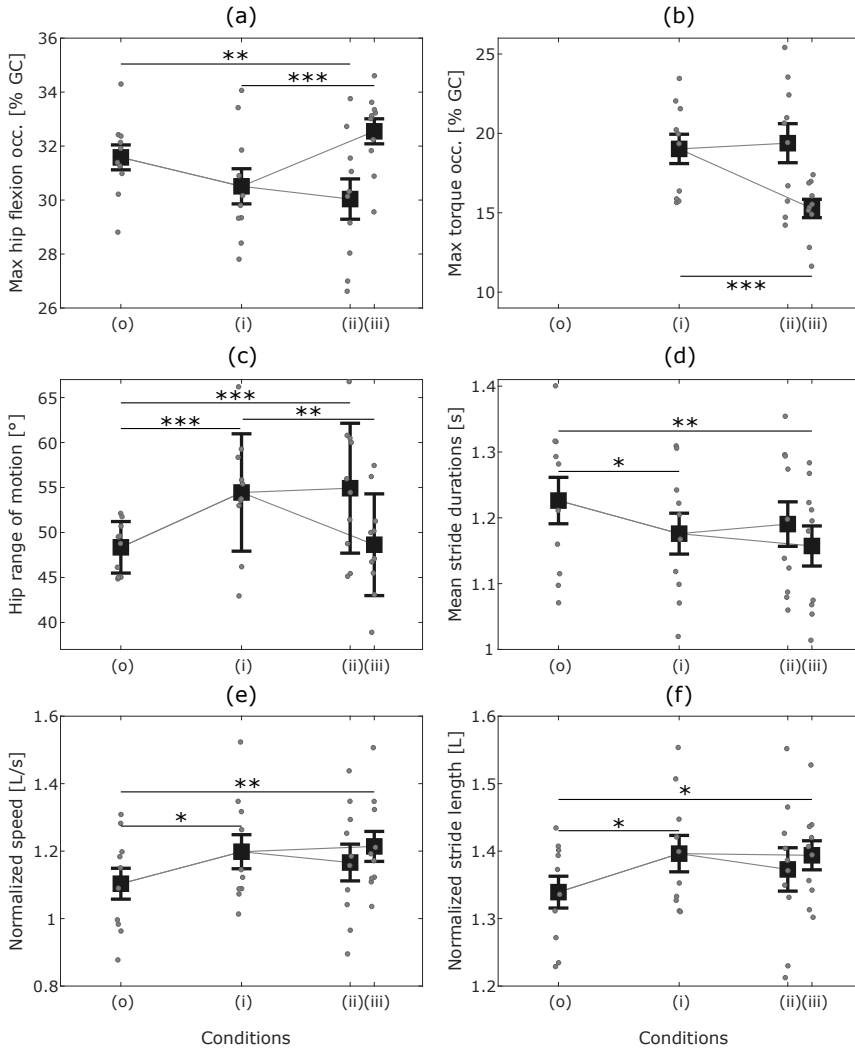


Figure 5.3 (a) Maximum hip flexion time occurrence and (b) maximum torque injected at the right hip in percentage of the gait cycle (GC), (c) right hip range of motion, (d) mean stride duration, (e) normalized gait speed, and (f) normalized stride length, as a function of the experimental conditions, i.e., (o) transparent mode, (i) $\tau = 4$ s and $\Delta\varphi = 1$ %, (ii) $\tau = 10$ s and $\Delta\varphi = 1$ %, and (iii) $\tau = 4$ s and $\Delta\varphi = 10$ %. Squares represent the mean across participants and whiskers indicate standard error of the mean. Each point corresponds to individual data of one participant in each condition. Significance levels: *** $p < 0.001$, ** $p < 0.01$, * $p < 0.05$.

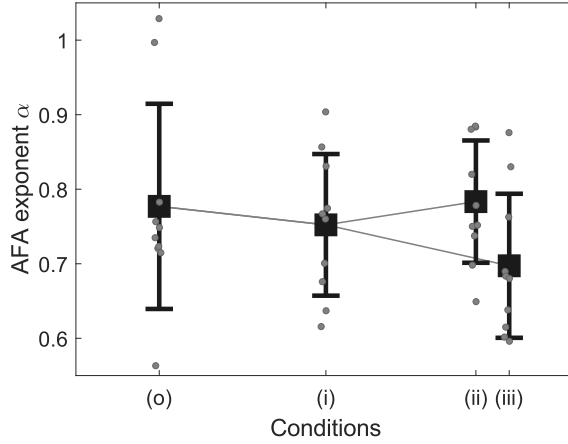


Figure 5.4 AFA exponent α , reflecting the level of LRA, as a function of the experimental conditions, i.e., (o) transparent mode, (i) $\tau = 4$ s and $\Delta\varphi = 1$ %, (ii) $\tau = 10$ s and $\Delta\varphi = 1$ %, and (iii) $\tau = 4$ s and $\Delta\varphi = 10$ %. Squares represent the mean across participants and whiskers indicate standard deviation across participants. Each point corresponds to individual data of one participant in each condition. No pairwise comparison was significant.

0.14) ($p < 0.05$) for stride length. Moreover, a decrease in stride duration was observed between the same conditions and the transparent mode, i.e., 1.18 s (SD 0.10) and 1.16 s (SD 0.10) respectively versus 1.23 s (SD 0.11) ($p < 0.01$).

Finally, concerning the level of LRA in the inter-stride time series (Figure 5.4), indicated by the α exponent, no significant differences were found between conditions, either with respect to means or standard deviations, with values of 0.78 (SD 0.14) in condition (o), 0.75 (SD 0.10) in condition (i), 0.78 (SD 0.08) in condition (ii), and 0.70 (SD 0.10) in condition (iii). The p -values were 0.11 for the analysis of variance test, and 0.78 for the Levene's test. We carried out a similar analysis with another LRA assessment method, i.e., the adapted version of the Power Spectral Density analysis $\text{low PSD}_{\text{we}}$ described in Chapter 2, and this did not yield significant results either.

5.3 Discussion

This section discusses the main results reported previously, and interpret them as a function of the different experimental conditions.

Our results confirm that the orthosis provided energy in the three assistive conditions compared to the transparent mode. No distinction is made between conditions, because the virtual stiffness k was tuned for each individual condition in order to reach a similar peak torque, and because the velocity profile did not significantly change across conditions.

This injected energy induced a change in the behavior of the user. Indeed, the hip ROM, walking speed and stride length were significantly increased between condition (i) and the transparent mode, accompanied by a decrease in stride duration. The change in hip kinematics could be explained by the assistance compensating for the loss of hip muscles force due to aging. Indeed, previous results established that the lower-limb maximum muscle force and power decrease by 8 % per decade between the ages of 25 and 75 [Grimmer et al., 2019]. More precisely, a decrease of 22 % in the maximum isometric torque of hip flexor muscle for people aged around 75, compared to healthy young adults, has previously been reported [Dean et al., 2004]. The energy injected by the device might thus have helped users to retrieve a larger hip ROM during walking. It might also have helped users to increase their cadence – observed via the decreased stride duration – and their stride length. Both of these changes are known strategies for increasing walking speed [Picelli et al., 2012a].

Moreover, two other assistive conditions have been tested, focusing on the potential influence of key parameters in the oscillator-based framework, namely its memory τ and its phase lead $\Delta\phi$. Different changes can be observed in the previously mentioned gait metrics depending on which assistive parameter was increased. In condition (ii), increasing the oscillator memory mitigated the effect of the assistance on the spatiotemporal gait metrics, i.e., stride duration, gait speed, and stride length. This is possibly due to the fact that with a larger memory, the device is less compliant with kinematic changes across steps, leaving the user with less authority over these gait metrics. Nevertheless, this interpretation should be taken with caution, since there is no significant difference between this condition and the transparent (o) or baseline conditions (i); while the latter two are significantly different. On the other hand, condition (iii) showed that increasing the phase lead mitigated the effects on the hip ROM. Indeed, it can be observed in Figure 5.3 that although the maximum flexion angle for all subjects is higher than in the transparent mode, the extension angle

is smaller, thus giving rise to no significant increase in ROM. This can be explained by the different assistive pattern observed in this condition compared to condition (i), since the maximum hip flexion angle occurred later in the gait cycle, and the maximum torque was injected earlier.

The study by N. d’Elia and colleagues [d’Elia et al., 2017] is a good benchmark to ours, since they used the same APO and the same oscillator-based assistance framework than in our study, with the same assistive parameters as in our condition (iii). Their experiments involved five healthy young adults, who walked on a treadmill at three different speeds and under five different conditions, i.e., without the APO, in transparent mode, and in three assistive modes with increasing assistance level k (peak torque at the hips ≤ 0.14 Nm/kg). They showed that the assistance had no effect on step length and cadence, and that the hip ROM increased when wearing the device in transparent and assistive modes compared to without the APO. These results are thus not entirely consistent with ours, especially concerning the spatiotemporal gait metrics. A key difference between both protocols is that the one of N. d’Elia and colleagues was performed on a treadmill, thus imposing the walking speed and de facto inducing kinematic constraints. In our case, participants performed overground walking. They were thus free to adapt all features of their gait to the provided assistance, and even to walk at different forward speeds between conditions.

In contrast, previous studies reporting the effects of an overground training program with wearable hip orthoses have shown similar results to ours with respect to spatiotemporal gait metrics. A first example is the study of C. Sanz-Morère and colleagues [Sanz-Morère et al., 2021], which analyzed the effect of the second assistive strategy of the APO, i.e., the feed-forward assistive strategy as described in Chapter 3, and tested on transfemoral amputees. These authors reported an increase in gait speed and in gait symmetry after a four-week training program with the device. Another device also using adaptive oscillators for gait phase estimation, namely the Gait Enhancing and Motivating System (GEMS, Samsung Electronics Co., Suwon, South Korea), also led to increased gait speed, cadence and stride length in people with hemiparetic stroke, after 10 training sessions, half of them performed on a treadmill [Lee et al., 2019]. Finally, a study with the Stride Management Assist (SMA[®], Honda R&D, Tokyo, Japan) [Buesing et al., 2015], adapting the provided torque according to a

target walk ratio (step length/cadence), showed that a six to eight week training program led to increased gait speed, cadence, step time and stride length with post-stroke people.

A limitation of our experiment highlighted by these previous studies is the lack of investigation of the effect of assistance on the metabolic cost of walking, although this is a key parameter capturing walking rehabilitation in the elderly. Nevertheless, the study of C. Sanz-Morère and colleagues [Sanz-Morère et al., 2021] using the same APO showed that, with a level of peak torque similar to the one provided in our three assistive conditions, the energy cost of transport was decreased, measured through a portable gas analyzer. This remains to be verified in our protocol.

As opposed to the spatiotemporal gait metrics, no assistive condition had a significant effect on the level of LRA in series of stride durations. Our participants had good baseline mobility and therefore a level of LRA corresponding to healthy people of the same age [Hausdorff et al., 1998, Bollens et al., 2012]. Some studies have hypothesized that a decrease in LRA in inter-stride time series would indicate a more random temporal organization of this series, and thus would be a marker of gait instability, in particular in elderly [Herman et al., 2005] or patients with Parkinson's disease [Warlop et al., 2016]. LRA-related metrics have therefore been proposed as a valuable clinical tool for assessing mobility and gauging the effectiveness of therapeutic interventions [Terrier and Dériaz, 2011], associated with other metrics such as the coefficient of variation of stride durations, and questionnaires assessing fear of falling and postural stability [Warlop et al., 2016]. The present study showed that with an assistance based on adaptive oscillators, the capacity to display levels of LRA observed during unconstrained walking is preserved in healthy aging people. Regardless of whether LRA reflects a complex organization of physiological subsystems [Delignières and Marmelat, 2012, Delignières and Marmelat, 2013], or the trace of a goal-equivalent manifold control [Dingwell et al., 2010], our results show that this natural dynamics is not affected by the assistance we tested. It also determined the influence of the different parameters of the assistance on some gait metrics. These observations are important in the perspective of using this orthosis and this assistive framework for the rehabilitation of pathological populations such as patients with Parkinson's disease. Indeed, several studies have shown that the LRA level of these patients is deteriorated [Hausdorff et al., 1998]. Moreover, it has been shown

that the gait of these patients is characterized by a slower walking speed, a lower cadence, as well as shorter strides, which makes them more prone to fall [Creaby and Cole, 2018]. These metrics are precisely among those improved by the assistance method tested in the present study, as shown on healthy aging people. In addition, a three-month overground training program with the SMA[®] orthosis on patients with Parkinson's disease [Kawashima et al., 2022] showed an increased exercise endurance and walking speed, as well as improvements in motor symptoms of this disease. Obtaining similar results with our approach would therefore offer great perspectives for people suffering from locomotion disorders induced by a neurodegenerative disease.

There are a number of limitations that need to be addressed regarding the current study. Firstly, it was conducted as an open-label uncontrolled trial, which can induce observer and reporting biases. Secondly, the sample size of our study was relatively small, reducing the power of the study. Finally, as the hip angle was given by the orthosis, the results about the hip ROM should be taken with caution since there can be a relative movement between the subject's hip and the orthotic one, because the mechanical impedance between the device and the user's legs is not infinite, but strongly constrained by the soft tissues surrounding the skeletal bones.

In conclusion, an oscillator-based wearable walking assistance can improve several gait metrics in healthy aging people, such as hip ROM, stride duration, gait speed, and stride length, by adequately selecting the assistive parameters. Moreover, this assistance does not deteriorate the level of LRA present in series of stride durations of these people. This results is of interest for the field of locomotion, since it is uncommon to observe that external constraints do not alter the level of LRA in series of stride durations. Besides, combining these two features is appealing for the development of a rehabilitation device for people having a decreased level of LRA, as it is the case with some neurodegenerative diseases.

5.4 Complementary discussion

This section contains supplementary discussion points that are not included in the corresponding publication. The results of this study can be compared with those obtained from simulated series of stride durations of healthy individuals, obtained with the SCPG model described in Chapter 4

and which can be found in the Appendix A. To this end, in addition to the results already obtained in the present study, we compare the standard deviations of the series of stride durations between the four conditions, in the same way as explained in Section 5.1.7. With values of 0.024 (SD 0.014) in condition (o), 0.018 (SD 0.005) in condition (i), 0.019 (SD 0.008) in condition (ii), and 0.018 (SD 0.006), no significant difference was found with the analysis of variance test. The absence of significant difference between the four conditions for this metric and the α exponent is not in line with the results obtained with the model. Indeed, it showed an increase in the α exponent for higher values of the oscillator memory τ and of the assistance level k , while the standard deviation in the series of stride durations was decreased.

Several aspects could explain these discrepancies between predicted and actual results, considering the differences between these experiments and the model. Firstly, the level of assistance provided by the device was set according to the subject's weight in the experiments. In contrast, in the model, it was one of the parameters whose influence on the α exponent and the variability in the series of stride durations was studied, meaning that its value was not fixed but varied over a wide range. There is no direct relationship between the level of assistance k of the model and that of the actual device, making it difficult to say at what value of k the experiments are located in Figure A.1, and therefore what results can be expected. Secondly, the adaptation of the subjects to the assistance is not considered in this model. This could have mitigated the increase in the α exponent, as it is the case in the optimal control model when this adaptation is taken into account (Figure 4.7). Finally, an important factor also not modeled is the weight of the device, which is around 6 kg. Indeed, it was reported that the level of LRA in series of stride lengths and durations was reduced when walking with a weight of 25 % or 45 % of body weight [Krajewski et al., 2020]. Considering all these differences, it is plausible that the increase in the α exponent and the decrease in standard deviation of series of stride durations observed with the model have been mitigated by the level of assistance, the adaptation of subjects to the assistance, and the weight of the device, although this represents on average only 8.74 % (SD 1.63) of the subjects' body weight.

After these experiments, a pilot test was carried out with a patient with Parkinson's disease. This test showed that for phase lead values below

10 %, the torque assistance provided by the device was less smooth (Figure 5.5), which caused disturbances for the patient and could potentially lead to a fall. On the other hand, the oscillator memory value τ did not seem to influence the assistance provided. Finally, the patient rapidly reported fatigue caused by the weight of the device. These observations led to the following choices concerning the clinical investigation with patients: the phase lead is systematically set to $\Delta\varphi = 10\%$, and subjects are requested to walk for 8 min to obtain at least 256 strides, instead of 15 min.

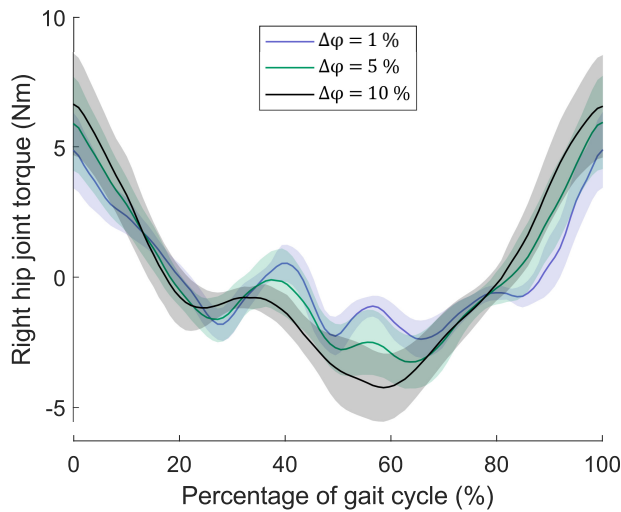


Figure 5.5 Torque profiles injected to the right hip of a patient with Parkinson's disease during a pilot test, for several values of the phase lead $\Delta\varphi$.

6

Experiments on patients with Parkinson's disease

The content of this chapter is adapted from:



V. Otlet, C. Vandamme, T. Warlop, F. Crevecoeur, and R. Ronsse, "Effects of overground gait training assisted by a wearable exoskeleton in patients with Parkinson's disease," *Journal of NeuroEngineering and Rehabilitation*, vol. 20, 2023, doi:0.1186/s12984-023-01280-y.

THE positive effects of the APO on some gait metrics in healthy aging people having been demonstrated, as well as the absence of any negative effect on the level of LRA in series of stride durations, the final stage of this thesis is to test this assistance on patients with Parkinson's disease. This study is the first to investigate the effect of an assistance based on adaptive oscillators, adapting in real time to the user's gait kinematics, on patients with Parkinson's disease after overground gait training. This allows to measure the impact of this assistance in a semi-ecological condition, and to leverage this condition to assess a gait metric affected by this disease, i.e., the level of LRA in series of stride durations.

6.1 Materials and methods

6.1.1 Participants

Eight patients with Parkinson's disease participated in this study. They were recruited according to the following inclusion criteria: positive diagnosis according to the UK Brain Bank Criteria, modified H&Y scale between 1 and 3, a minimum of 24/30 on the Mini-Mental State Examination (MMSE), and no contraindication to physical exercising. Medication was stable for the four weeks preceding the study, and was maintained throughout the study. One participant was treated with Deep Brain Stimulation. The study took place at the Mounier Sports Center (Brussels, Belgium) between February 2022, the date of first inclusion, and November 2022, the date of last follow-up visit. It received the approval of the local ethical committee (Comité d'Ethique Hospitalo-Facultaire des Cliniques universitaires Saint-Luc, EudraCT n. 2019-002048-26), and was performed in compliance with the declaration of Helsinki. Participants provided written consent prior to data collection and were left free to leave the study at any moment. Clinical characteristics and anthropometrics data of patients are displayed in Table 6.1.

Table 6.1 Characteristics of the study population; H&Y stands for the Hoehn and Yahr scale, and * for the patient implanted with Deep Brain Stimulation.

ID	Age	Gender	Weight (kg)	H&Y	Most affected side
1	76	M	83	2	Left
2*	67	M	79.5	2.5	Right
3	69	M	70.5	2.5	Left
4	73	F	53.5	1	Left
5	57	M	93	2	Right
6	76	M	83.5	2	Right
7	72	M	83	2	Left
8	75	M	79.5	2	Left

6.1.2 Procedure

For each patient, the entire protocol lasted eight weeks. It began with a first evaluation session (T_0), consisting in evaluating their motor disorders through the MDS-Unified Parkinson's Disease Rating Scale (MDS-UPDRS) part III score, also allowing the identification of the side most affected by the disease for each patient, and their cognitive state through the MMSE, both assessed by a neurologist. Then, the balance functions were evaluated using the Balance Evaluation Systems Test (Mini-BESTest), assessed by a physiotherapist. Moreover, patients were asked to walk at their comfortable speed in a sports hall, following a rectangular path of $7\text{ m} \times 12\text{ m}$ with rounded corners in order to have the most steady gait for LRA assessment. The walking session was performed in a quiet environment so as not to increase the attentional cost of walking [Warlop et al., 2016]. Patients performed several laps during 8 min. Speed steadiness was verified by timing the time taken by the subject to complete each lap, and delivering qualitative instructions to adapt walking speed if needed. During this walking session, patients wore a motion capture system (MVN Awinda, Xsens, Enschede, Pays-Bas) composed of eight IMUs, allowing to reconstruct the movement of their hips during walking, as explained in Section 6.1.4. They also wore two IMUs (NGIMU, x-io Technologies, Bristol, UK), placed just above the external malleolus of both ankles, with their x -axis oriented in the direction of walking. These were used to obtain the sagittal shank angular velocities for calculating series of stride durations, as explained in Section 6.1.3. Finally, patients were asked to complete a questionnaire at home about their confidence in performing daily activities without losing balance, assessed through the Activities-specific Balance Confidence (ABC) scale.

Thereafter began an intervention phase, consisting of three training sessions a week during four weeks, similar to what has already been done in previous studies as summarized in [Picelli et al., 2021]. During these 12 sessions, patients walked with the APO during 5 to 8 min, after a period where they can adapt their gait to the device's assistance. In this study, the virtual stiffness k of the assistance, introduced in Equation 3.1 in Chapter 3, was adjusted according to the weight of the subject, i.e., so that the peak torque delivered at the hip was equal to 0.1 Nm/kg , corresponding to a comfortable and safe level of assistance as reported in [d'Elia et al., 2017]. This value was determined during the first training session, and

then maintained constant throughout the following sessions. The phase lead $\Delta\phi$ determining how far in advance the signal of the hip is predicted for computing the injected torque was set to 10 % of gait cycle. Finally, the oscillator memory τ alternated between two values from one session to the next, i.e., $\tau = 4$ s and $\tau = 10$ s, which is discussed in Section 6.4.

This intervention phase was followed by a second evaluation session (T1), taking place one or two day(s) after the last training session. During this session, the same clinical tests as during the first evaluation session were performed, with the exception of the MMSE. This evaluation session was repeated after a four-week wash-out period (T2).

Moreover, patients were asked to complete an ease-of-use and satisfaction questionnaire at T1, whose questions are listed in Appendix B, along with the results.

6.1.3 Stride intervals computation

The series of stride durations were obtained in the same manner as described in Chapter 5. Patients walked between 5 and 8 min for each session, depending on their daily physical condition, fatigue, and their gait speed. The first and last 10 strides of the series were discarded, in order to restrict our analysis to steady-state behavior only, with the objective to keep as many strides as possible, with a minimum of 256 as recommended in [Warlop et al., 2017] for LRA assessment. Only data from the most affected side were analyzed. However, due to connection issues between the IMUs and the computer, some trials displayed gaps in the recorded data. This happened in three of the 24 evaluation sessions. In that case, data from the least affected side were used.

6.1.4 Gait metrics

Regarding the evaluation sessions, several gait metrics have been computed to study the effect of training on the patient behavior. On the first hand, some spatiotemporal gait metrics were computed. The walking speed per lap was computed by dividing the lap distance (38 m) by the recorded time taken by subjects to walk through each of them. The mean stride duration over each lap was obtained from the inter-stride time series, divided into laps thanks to the average measured time to make a lap. Finally, the average stride length per lap was obtained by taking

the product between the stride duration and the walking speed per lap. The stride length and the walking speed were then normalized by the leg length of each subject.

On top of this, the hip motion was reconstructed from the motion capture system signals. The accelerometer and magnetometer signals from each IMUs of the system, recorded at a sample rate of 100 Hz, were used to determine the orientation and position of each IMU relative to that of the pelvis. From these, the movement of each lower-limb segment was obtained and used to derive the hip angle signals, which were low-pass filtered at a cutoff frequency of 18 Hz. Finally, the flexion-extension hip range of motion (ROM) was computed as the difference between the highest and the lowest value of this signal over a gait cycle. As for the series of stride durations, only data from the most affected side were analyzed. Data from two acquisitions could not be reconstructed correctly (subjects #3 in T1 and #6 in T2) and were thus withdrew from the analyses.

Finally, the level of LRA in series of stride durations, characterized by the fractal exponent α , was also obtained. It was computed with AFA as described in Chapter 2, with the subsequences' length n ranging from 5 to the first power of 2 smaller than $N/2$ by steps of two.

6.1.5 Level of assistance

Since the assistive method based on adaptive oscillators constantly adapts to the patient behavior, it is not possible to predict how much mechanical energy will be delivered to the patient during each training session. Therefore, this becomes a metric of interest to be investigated. The orthosis behavior during training sessions was quantified through signals acquired by onboard sensors at 100 Hz, i.e., the hip flexion-extension angle and the injected torque, as explained in Chapter 3. The hip flexion-extension angle was time-differentiated to obtain the angular velocity. The torque injected was first normalized by the weight of each subject, then divided into gait cycles using the maximum hip extension angle as separation between cycles. It was then used to compute the energy injected to the hip per cycle [J/kg]:

$$E = \int_{cycle} T \dot{x} dt \quad (6.1)$$

with T the injected torque [Nm/kg], and $\dot{x}$ the hip angular velocity [rad/s]. The maximal torque injected at the hip per gait cycle was also analyzed.

6.1.6 Statistical analysis

Data were processed with Matlab R2019a, and statistical tests were performed in R version 4.2.2. Statistics were performed on the spatiotemporal gait metrics (one data point per lap), on the hip ROM (one data point per gait cycle), and on the clinical scores (one data point per evaluation session). The three evaluation sessions were compared to each other via linear mixed-effects models fitted to the different studied metrics [Brown, 2021], whose ability to take into account variations in trends according to the subject is particularly interesting in the case of patients with Parkinson's disease, which are very heterogeneous [Dotov et al., 2017]. The linear mixed-effects models equation is given by:

$$Y_{i,j} = \gamma_0 + I_i + bX_{i,j} + \epsilon_{i,j} \quad (6.2)$$

with $Y_{i,j}$ the gait metric for the i th subject and the j th repetition (lap or cycle), γ_0 a general intercept, I_i a random intercept for each subject, $X_{i,j}$ the evaluation session number and b its regression coefficient, and $\epsilon_{i,j}$ the residuals. An analysis of variance was then performed on these models, using a Kenward-Roger's approximation to degrees of freedom [Kenward and Roger, 1997]. If the p -value of this test was lower than 0.05, Tukey's tests for multiple pairwise comparisons were performed, using the Benjamini-Hochberg correction [Benjamini and Hochberg, 1995]. The variances of these three sessions were also compared with a Levene's test [Levene, 1960]. If significant, this test was followed by pairwise Levene's tests, and a Benjamini-Hochberg correction was applied on the resulting p -values.

Linear mixed-effects models were also used to assess whether the evolution of maximal injected torque and injected energy through trainings was significant or not, using the same equation as (6.2) with $X_{i,j}$ being the training sessions.

For graphical representation, the relative change in spatiotemporal gait metrics and ROM was computed by taking the difference between the values in T1 or T2 and T0, divided by the value in T0 and converted in percent-

age. For these metrics, inter-subject variability is represented through the standard error of the mean, computed as the standard deviation divided by the square root of the number of subjects.

6.2 Results

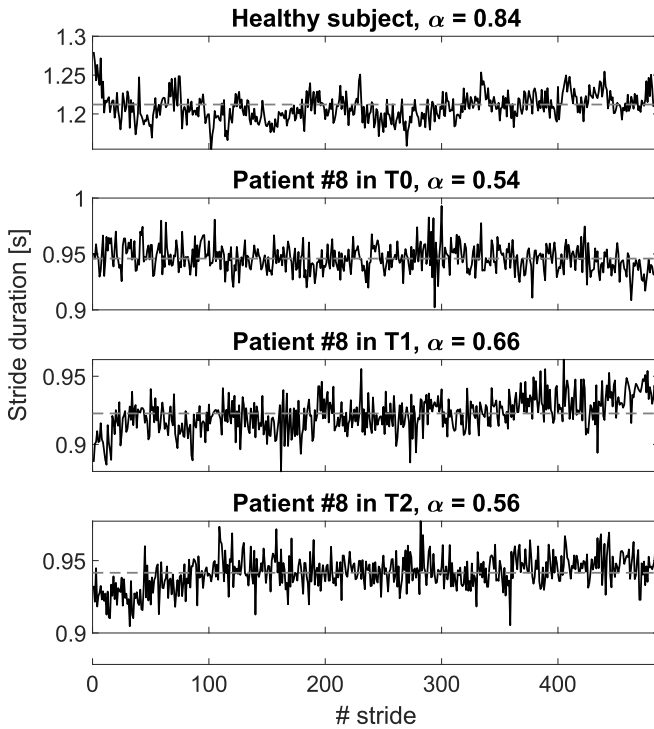


Figure 6.1 From top to bottom: series of stride durations of a healthy 62-year-old subject freely walking overground during a pilot test, and patient #8 in T0, T1 and T2. The gray dashed lines indicate the mean stride durations, and α is the fractal exponent.

Series of stride durations of a healthy adult acquired during a pilot test and of a representative patient with Parkinson's disease in T0 and T1 are shown in Figure 6.1. As expected, the LRA level, i.e., α exponent, is lower in the patient than in the healthy adult. It can also be noted that the mean stride duration of the patient is decreased between T0 and T1. Figure 6.2 reports the hip angle profile of a representative patient. It can be observed that the ROM is larger in T1 and T2 than in T0.

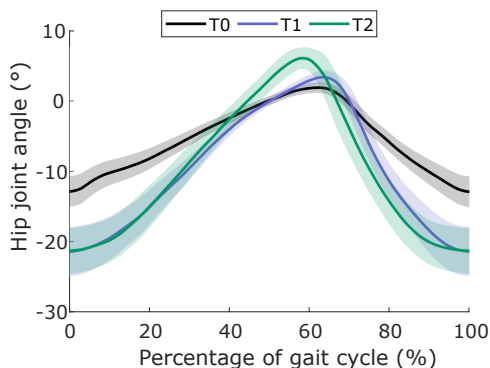


Figure 6.2 Left hip angle profile for patient #1 in the three evaluation sessions. Signals were time-normalized over the gait cycle. Solid lines represent the mean and shaded areas represent the standard deviation over all gait cycles.

These representative trends were further assessed at the population level by running statistical tests. Assessment of spatiotemporal gait metrics (Figure 6.3a-c) indicate an increase in gait speed and stride length and a decrease in stride duration between T0 and T1 ($p < 0.001$) and T0 and T2 ($p < 0.001$). The hip ROM (Figure 6.3d) also increased from T0 to T1 ($p < 0.001$) and to T2 ($p < 0.001$).

In contrast, no significant difference was found in the mean level of LRA in the inter-stride time series, indicated by the α exponent, between evaluation sessions (Figure 6.4). However, the inter-subject variance in LRA exponent during T1 was significantly lower than in T0 ($p < 0.01$) and in T2 ($p < 0.05$). Concerning the individual evolution of this α exponent between T0 and T1, five subjects with lower initial LRA levels had a mean increase of 16 % (#2, #3, #5, #6, #8), while the three others had a mean decrease of 8 % (#1, #4, #7), as shown in Figure 6.4.

Regarding the behavior of the orthosis during the training sessions (Figure 6.5), the maximal torque and energy injected at the hip significantly decreased across training sessions ($p < 0.001$ for both metrics).

Finally, the ABC score was significantly higher in T1 and T2 compared to T0 ($p < 0.05$), with a mean score of 35.63 (SD 9.64; maximum possible is 45) in T0, 37.88 (SD 8.01) in T1 and 38.25 (SD 7.15) in T2. In contrast, no significant difference was found in the other clinical measures, i.e., neither

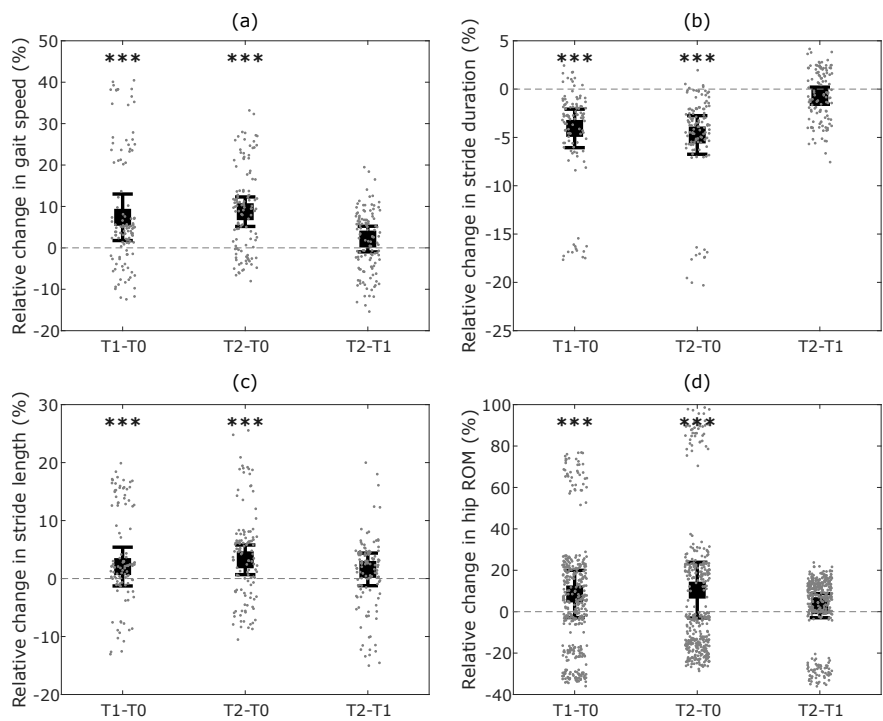


Figure 6.3 Relative changes in (a) normalized gait speed, (b) stride duration, (c) normalized stride length per lap, and (d) hip ROM per gait cycle, for the three pairwise differences between the three evaluation sessions. Each point corresponds to individual data of a given participant in a given lap or gait cycle. Squares represent the mean across participants and whiskers indicate standard error of the mean. Significance level: *** $p < 0.001$.

in the MDS-UPDRS part III score, even when divided into its Postural Instability and Gait Difficulty and rigidity subscores, nor in the Mini-BESTest score.

The absolute values of the spatiotemporal gait metrics, the hip ROM, and the clinical measures are given in Table 6.2 for each subject in the three evaluation sessions. The values meeting the minimal clinically important improvement from T0, i.e., the smallest improvement recognized as important by clinicians [Horváth et al., 2015], are also highlighted. This value is only available for certain metrics used in this study for patients with Parkinson’s disease. Firstly, the threshold for the gait speed is an increase of 0.06 m/s [Hass et al., 2014], and four patients over the eight met it in T1 and T2. Secondly, the threshold for the MDS-UPDRS part III score is a

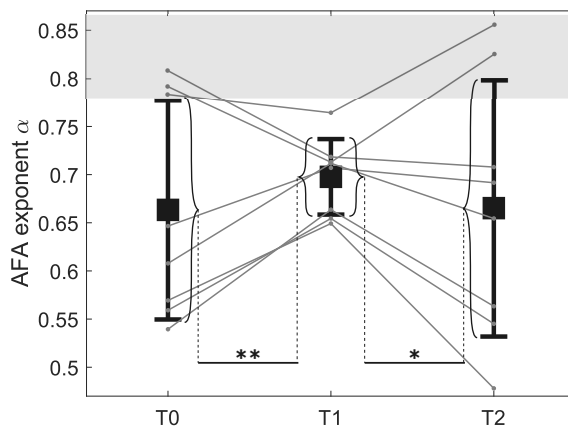


Figure 6.4 LRA level, characterized by the α exponent, for the three evaluation sessions. Each gray bar correspond to the data from one patient. Squares represent the mean across participants and whiskers indicate standard deviation across participants. The shaded area corresponds to values of healthy walkers obtained by applying AFA on 10 series of 1024 points from [Hausdorff et al., 1996]. Brackets indicate significant differences between standard deviation. Significance levels: ** $p < 0.01$, * $p < 0.05$.

decrease of 3.25 points [Horváth et al., 2015], and only one patient in T1 and two in T2 met it. Finally, the threshold for the Mini-BESTest score is an increase of 4 points [Godi et al., 2020], and only one patient met it in T1.

6.3 Discussion

Numerous studies have shown the beneficial effects of robot-assisted gait training for improving spatiotemporal gait metrics in patients with Parkinson's disease. They particularly showed an increase in gait speed, stride length and cadence [Lo et al., 2010, Ustinova et al., 2011, Carda et al., 2012, Barbe et al., 2012, Paker et al., 2013, Nardo et al., 2014, Picelli et al., 2012a, Sale et al., 2013, Picelli et al., 2013, Galli et al., 2016a, Andrenelli et al., 2018, Capecci et al., 2019]. These three metrics are connected since the increase in gait speed can be enhanced by increasing cadence, stride length, or both [Picelli et al., 2012a]. These results are in accordance with those of the present study showing an increase in gait speed, stride length and cadence – equivalent to the observed decrease in stride duration –, and we further showed that these positive outcomes are maintained one month after the end of the training. Several reasons have been proposed by previous papers to explain these positive evolutions after training with robotic de-

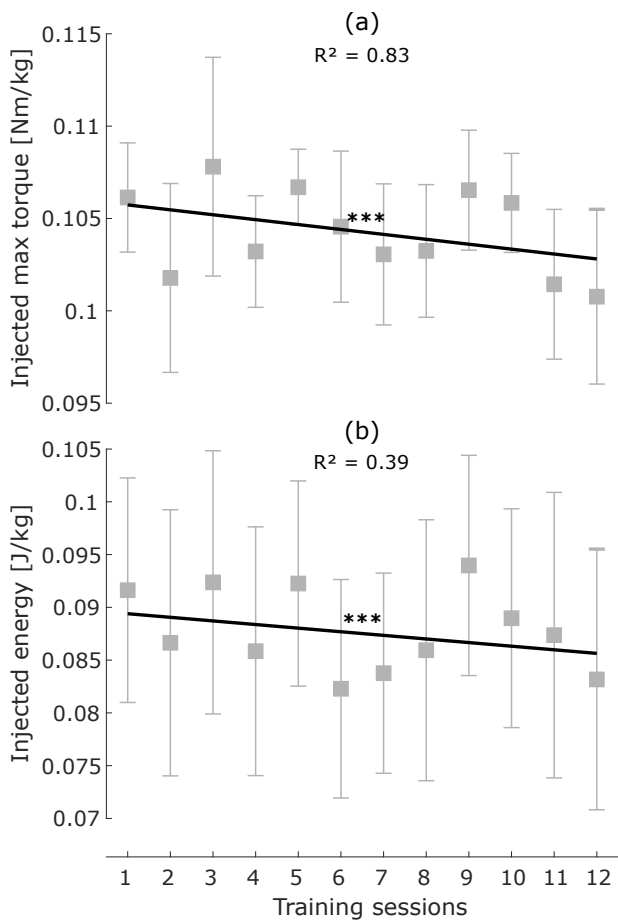


Figure 6.5 Evolution of the injected (a) maximal torque and (b) energy at the hip during training sessions. Squares represent the mean across participants, whiskers indicate standard error of the mean, and R^2 is the coefficient of determination of the regression. Significance level: *** $p < 0.001$.

Table 6.2 Absolute values of outcome measures for each subject in T0|T1|T2. The values for the three clinical tests/questionnaires are given in points.

ID	Speed [m/s]	Stride duration [s]	Stride length [m]	Hip ROM [°]	MDS-UPDRS III	Mini-BESTest	ABC scale
1	0.73 0.65 0.76	1.29 1.30 1.29	0.94 0.85 0.98	15.51 25.94 29.04	29 17* 24*	19 24* 22	23 29 28
2	1.23 1.31* 1.28	1.01 0.97 0.99	1.24 1.27 1.27	38.57 26.53 29.99	22 31 19	21 23 24	22 23 28
3	1.33 1.65* 1.65*	1.06 0.99 1.00	1.41 1.63 1.65	49.15 NA 59.37	13 11 13	25 21 23	42 42 43
4	1.29 1.21 1.26	1.01 1.00 0.97	1.30 1.21 1.22	52.14 50.58 50.55	13 10 8*	25 26 28	44 45 45
5	1.59 1.65* 1.76*	0.97 0.95 0.93	1.54 1.57 1.64	36.12 38.17 43.70	11 12 11	28 27 26	40 42 43
6	1.11 1.13 1.23*	1.16 1.16 1.11	1.29 1.31 1.37	41.10 50.91 NA	21 20 21	28 26 28	45 45 45
7	0.77 1.06* 0.95*	1.43 1.20 1.18	1.10 1.27 1.12	40.85 32.89 35.21	27 27 24	24 25 26	28 36 35
8	1.31 1.35 1.28	0.95 0.92 0.94	1.24 1.24 1.20	31.34 36.62 26.01	33 31 34	27 25 25	41 41 39

*Meeting the minimal clinically important improvement in performance from T0.

vices. First, P. Sale and colleagues [Sale et al., 2013] suggested that these improvements were due to the intense repetition of a stereotyped gait pattern, which induced somatosensory cueing and stimulation. K. Ustinova and coworkers [Ustinova et al., 2011] also stated that improvements of these spatiotemporal gait metrics were due to the use of the treadmill, being necessary with the Lokomat exoskeleton, building upon results from other studies using a treadmill alone. Nevertheless, the present study tends to show that it is possible to obtain equivalent results after overground gait training with a compliant orthosis that does not follow a stereotyped gait pattern. We rather explained these improvements in gait parameters by the increased ROM, which, to the best of our knowledge, has never been reported in previous studies on patients with Parkinson's disease. This increase could be due to the assistance provided by the robot that compensates for a disease-induced hip flexor muscle weakness [Skinner et al., 2019]. Observing this result is facilitated by the semi-ecological environment used in our study, since the patients' hips kinematics were constrained neither by the environment nor by the provided assistance. We hypothesize that this larger hip ROM helped patients to increase their cadence and stride length, and therefore their gait speed. Interestingly, these changes in gait occurred even if the maximal injected torque was moderate (about 0.1 Nm/kg, i.e., about 17 % of what a healthy hip delivers during overground walking [Winter, 1983]), and this torque moreover decreased along training sessions. These improvements are very important in preventing falls for patients with Parkinson's disease. Indeed, a decrease in these gait metrics is considered as a marker of a higher risk of falling [Creaby and Cole, 2018]. An important caveat to this discussion is that similar results could have been observed after an equivalent amount of exercising without the robot. This was not addressed in this study, since no control group was included. Nevertheless, several studies involving control groups performing conventional physiotherapy (i.e., joints mobilization, conventional overground gait training, muscle stretching, ...) with the same intensity as a robot-assisted group reported larger effects with the latter as compared to the former group [Picelli et al., 2012a, Picelli et al., 2012b, Picelli et al., 2013]. It is also interesting to mention that some patients spontaneously reported that being assisted by a robot helped them and increased their motivation. Indeed, some patients arrived at the training session very tired, and the robotic assistance encouraged them to carry on with the session until the end.

Regarding the clinical metrics, only the balance confidence (ABC scale) decreased after training, and this result was maintained after one month post-training. This result was also reported in previous articles [Picelli et al., 2012b, Pilleri et al., 2015], and was associated with an improvement in balance functions. Similar improvements in balance were not identified in our results through the Mini-BESTest. Since the ABC scale is a subjective one, this result shows that patients felt an improvement in their self-perceived balance confidence after this robot-assisted gait training, although this was not confirmed by a measured improvement in their postural control assessed with the Mini-BESTest score. This can be explained by the fact that both studies reporting increased balance functions involved patients in more advanced stages (H&Y 2.5–4), thus having more pronounced postural instability than the patients of the present study. Another potential explanation for the lack of improvement in balance in this study is the absence of body weight support, in contrast to previous studies reporting an improvement in this parameter. With body weight support, it was hypothesized that patients can better regulate weight shifting during walking [Picelli et al., 2012b, Yun et al., 2021]. On the other hand, the scale rating the motor symptoms did not improve either. This is probably because training with the orthosis was only intended to impact the patients' gait, and not other motor aspects of the disease assessed by the MDS-UPDRS part III scale, such as rigidity, bradykinesia, or tremor [Pilleri et al., 2015].

Finally, the level of LRA in series of stride durations of patients with Parkinson's disease was 0.66 (SD 0.11) before training (Figure 6.4), which is lower than the one of healthy walkers, i.e., 0.82 (SD 0.04) as computed by applying AFA on 10 series of 1024 strides from [Hausdorff et al., 1996]. Having a decreased LRA level in series of stride durations indicates a more random temporal organization of the series, which is thought to be a marker of gait instability in pathological populations [Warlop et al., 2016]. However, in the present study, the level of LRA of patients did not significantly increase after the training sessions; although individual data were more clustered around a value of α exponent closer to the one of healthy individuals. Indeed, the five subjects who displayed the lowest level of LRA before training (T0) increased it during the second evaluation session (T1). In contrast, this level slightly decreased or remained constant for the three participants who had a high level before training. These levels returned to, or exceeded, their initial values in T2, indicating that there was

no training retention effect after one month. The models described in [Olet and Ronsse, 2022, Vandamme et al., 2023] predicted that the level of LRA in series of stride durations is increased when the subject is assisted by the device. The present results suggest that a training with the device standardized this level in patients with Parkinson's disease, by increasing it for those who had a lower initial one. Further investigations should be conducted to assess the potential rehabilitative effect of this observation, and the causes and consequences of the fact that it is not retained in the longer term.

We did not find a relationship between the increase in the level of LRA in some patients and other metrics assessed in this study. In particular, no correlation has been found between the α exponent and the H&Y score, reflecting the level of disease progression. This may be because this study mostly included patients with a moderate disease stage (H&Y 2–2.5), and is therefore not capturing the whole spectrum of gait impairments encountered in patients with Parkinson's disease. Experiments should be conducted on a wider range of stages and on a larger number of patients to identify if a specific stage of the disease would better respond to this therapy. Moreover, this difference across patients' response to robot-assisted gait training can have other origins than motor functions as assessed by the H&Y scale. Indeed, because of the heterogeneity of Parkinson's disease, every patient is not impacted in the same way by the disease. There is a large variability in symptoms and disease progression across individuals. This is due for example to genetic factors causing patients to respond differently to the same drug [Titova and Chaudhuri, 2017], or to a more active lifestyle slowing down the disease progression [Miller et al., 2019]. All these differences have led clinicians to create different sub-groups of patients, based on age of onset, motor phenotype, nonmotor symptoms and genetic mutations. This heterogeneity of the disease further emphasizes the importance of personalized treatment for each patient [Ryden and Lewis, 2019]. The present study suggests that robot-assisted gait training might lead to different effects regarding LRA as a function of the patient profile. Further investigations should be conducted to establish if this is connected to genetic or behavioral markers.

Despite the small sample size of the present study, these experiments were able to highlight interesting results for patients with Parkinson's disease. A larger and more diversified sample (in terms of H&Y stage and

gender diversity) could help to show an improvement in the level of LRA in series of stride durations of these patients. Moreover, a longer training period, or incorporating this device into weekly physiotherapy sessions, might also induce an improvement in this metric, and potentially longer-term retention after training.

In conclusion, this study showed that an adaptive walking assistance delivered by a wearable robot does improve several gait metrics in patients with Parkinson's disease, such as gait speed, stride duration and length, and hip ROM. It also opened new research avenues for assessing the effects of such assistance on the level of LRA in series of stride durations, in order to identify which patient profile might benefit the most of this assistance, especially regarding this particular motor control metric.

6.4 Complementary discussion

This section reports complementary discussion points that have not been included in the corresponding submitted manuscript. As a starting point, Figure 6.6 shows the evolution of the various metrics characterizing patients' behavior over the course of training sessions. For the spatiotemporal metrics, this evolution is consistent with the improvement observed between evaluation sessions. Regarding hip ROM, since it was not measured with the same equipment during evaluation and training sessions, we are reluctant to compare this metric quantitatively between both types of sessions. However, the evolution over the training sessions is significant, corresponding to an improvement in hip ROM, as indicated by the statistical test comparing the evaluation sessions. Lastly, only the evolution of the LRA level was not significant. It does, however, indicate a decrease in this level over the course of trainings, whereas the level at T0 is closer to that of healthy subjects. This would suggest an after-effect induced by the training sessions, i.e., that the device would induce an adaptation in one direction during the training sessions that would be followed by a deviation in the other direction once the robot is removed in T1 [Della-Maggiore et al., 2014]. This should however require further analyses to be properly interpreted.

An additional point of discussion is the effect of the oscillator memory τ on the gait metrics. During the experiments of the present chapter, this parameter alternated between two values from one session to the next, i.e.,

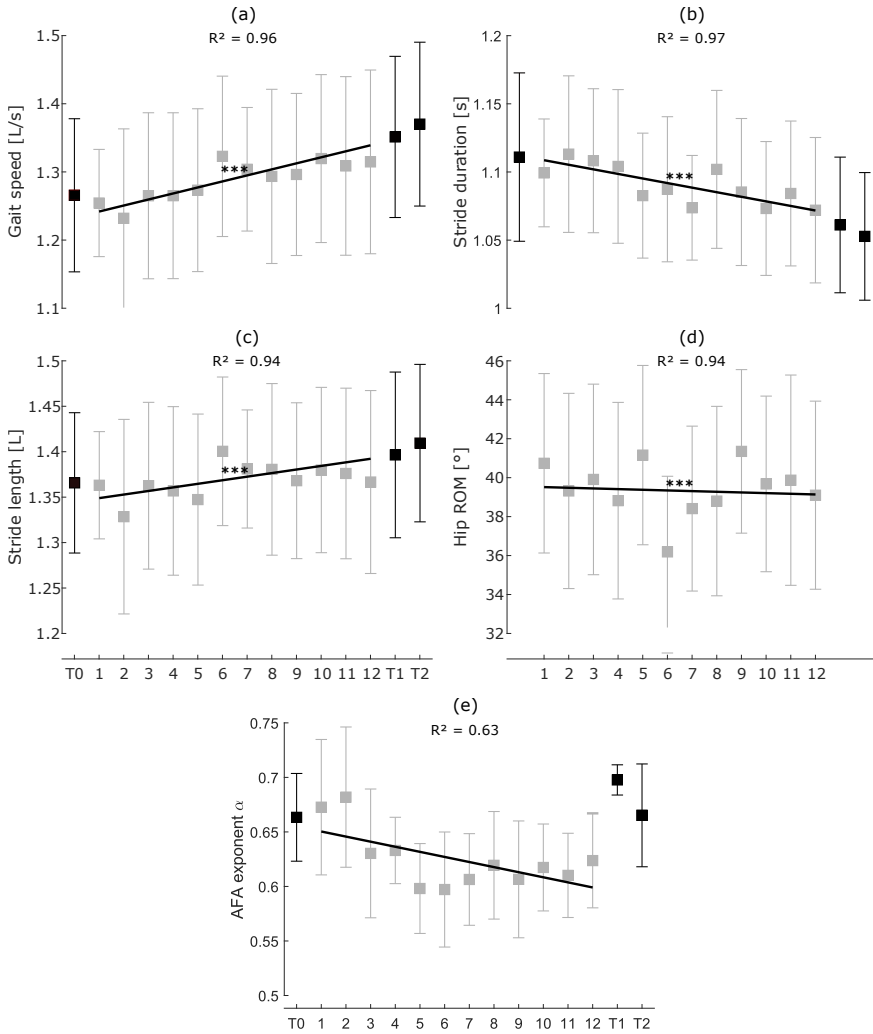


Figure 6.6 Evolution of (a) gait speed, (b) stride duration, (c) stride length, (d) hip ROM, and (e) LRA level during training sessions in gray, and during the three evaluation sessions in black. Squares represent the mean across participants, whiskers indicate standard error of the mean, and R^2 is the coefficient of determination of the regression. Note the evaluation sessions were not included for the hip ROM since different measuring equipment was used between evaluation and training sessions. Significance level: *** $p < 0.001$.

$\tau = 4$ s and $\tau = 10$ s. These values were selected in order to challenge the results obtained with the model described in Chapter 4. Indeed, they showed that for the same level of assistance k , the fractal exponent α was higher with $\tau = 10$ s than with $\tau = 4$ s, and the standard deviation of the series of stride durations was lower, although not statistically tested. Alternating between these two values also enables to determine whether the conclusions drawn from the experiments with healthy subjects of Chapter 5 are also applicable to patients with Parkinson's disease. Indeed, they showed that using the assistance with these two values of τ produced different results for the spatiotemporal gait metrics.

The following linear mixed-effects model is used to fit two lines on each measured metric, one line for each value of τ :

$$Y_{i,j} = \gamma_0 + I_i + b_1 X_{i,j} + b_2 Z_{i,j} + b_3 X_{i,j} Z_{i,j} + \epsilon_{i,j} \quad (6.3)$$

with $Y_{i,j}$ the gait metric for the i th subject and the j th repetition (lap or cycle), γ_0 a general intercept, I_i a random intercept for each subject, $X_{i,j}$ the training session number and b_1 its regression coefficient, $Z_{i,j}$ the value of τ corresponding to the training session and b_2 its regression coefficient, $b_3 X_{i,j} Z_{i,j}$ the interaction between the training session number and the value of τ , and $\epsilon_{i,j}$ the residuals. The standard deviation of the series of stride durations was also analyzed, in addition to the metrics described earlier in this chapter. For a different effect to be observed between the two values of τ on the gait metrics, the slope of these two lines must be significantly different. The results of this test show that the two values of τ have no different effect on any of the metrics analyzed (all $p > 0.05$).

The model presented in Chapter 4 showed an increase in the fractal exponent for higher values of τ and of the assistance level k , while the standard deviation of the series of stride durations was decreased. Although the results of the present analysis do not support the model's results, it is consistent with those obtained during experiments on healthy subjects, which showed no difference across the four conditions for these two metrics. Several aspects could explain these discrepancies between the results obtained with the model and those obtained in the present analysis, which are the same as those highlighted for the study on healthy subjects (see Section 5.4). As a reminder, these differences concern (1) the level of assistance of the model and that of the robot, which are not directly comparable; (2)

the patient adaptation to the assistance, which is not taken into account in the model; (3) the weight of the robot, which is not included in the model, and which represents on average 7.88 % (SD 1.47) of the patients' body weight. All these differences could have mitigated the increase in the α exponent and the decrease in the standard deviation of series of stride durations observed with the model.

Regarding the spatiotemporal gait metrics and the hip ROM, the results of the present analysis should be compared with caution with those obtained during experiments with healthy subjects. The results of Chapter 5 showed that the assistance with $\tau = 4$ s and $\Delta\varphi = 1$ % improved all these metrics, but that increasing the oscillator memory τ mitigated the effect of the assistance on the spatiotemporal gait metrics, while it made no difference to the hip ROM. However, as there was no significant difference between the condition where $\tau = 4$ s and the one where $\tau = 10$ s, both with $\Delta\varphi = 1$ %, it cannot be concluded from these experiments that there was a difference between these two values in terms of their effects on the spatiotemporal gait metrics. Moreover, the condition where $\tau = 10$ s and $\Delta\varphi = 10$ %, corresponding to what was applied in the present experiments, was not tested during the ones with healthy subjects. An increased value of the phase lead could compensate for the effect of a longer memory of the adaptive oscillators, and could thus improve the spatiotemporal gait metrics.

In conclusion, increasing the oscillator memory, as suggested by the results obtained with the model described in Chapter 4, does not appear to be relevant. Indeed, patients reported no difference in sensation during the training sessions, which is reflected by the results of the present analysis. Nevertheless, the protocol used here was probably not optimal for comparing the effects of these two values of τ . Indeed, by alternating between them, the different effects they cause, if any, are probably influenced by the previous session, when the other value was used. In order to be able to interpret the different effects of these two values of τ on gait, it would have been better to divide the subjects into two groups, one receiving an assistance with $\tau = 4$ s, and the other with $\tau = 10$ s.

7

General discussion and perspectives

THIS concluding chapter discusses the results obtained during this thesis and adopts a forward-looking perspective on their potential future repercussions in gait rehabilitation. It begins by summarizing the main contributions of this work, as well as providing an answer to the research questions raised in the introduction. Then, future directions offered by this work with regard to the use of the orthosis and LRA assessment in a clinical perspective are discussed. Finally, the implementation of an assist-as-needed control on the orthosis is explored.

7.1 Original contributions

As detailed in Chapter 2, the level of LRA in gait, characterizing its natural variability, is reduced in patients with Parkinson's disease compared to healthy individuals [Hausdorff et al., 2000]. Many authors emphasize that this feature of gait characterizes the proper functioning of the locomotor system [Hausdorff, 2007]. Therefore, several therapies have been explored to increase this level in patients. However, to our knowledge, the effect of a wearable orthosis on this metric has never been studied.

The first step in this work was to simulate the effect that an oscillator-based walking assistance could have on the variability present in the series of stride durations of patients with Parkinson's disease, assessed by the level of LRA and the standard deviation of the time series, as described in Chapter 4. This first part showed that this variability could be improved for certain memory values of the adaptive oscillator constituting the assistance, as well as certain assistance magnitudes, to reach the level of healthy individuals.

However, these simulations do not take into account many factors, such as the weight of the device, the physical condition of the user, the limits imposed on the assistance to remain comfortable and safe to use, among others. As numerous studies have shown that constraining gait, e.g., with a treadmill or a metronome, could influence the level of LRA in series of stride durations [Hausdorff et al., 1996, Terrier et al., 2005, Terrier and Dériaz, 2011, Warlop et al., 2018, Hollman et al., 2020], it is important to investigate whether constraining gait with an oscillator-based walking assistance, adapting to the user's gait kinematics, has the same effects, in the perspective of using it with patients with Parkinson's disease. This leads to answer the following question:

Is the level of LRA in series of stride durations of healthy subjects impacted by an oscillator-based walking assistance?

We have shown, through experiments described in Chapter 5, involving 10 subjects aged between 56 and 77 and under three different assistance conditions, that this metric is not impacted by compliant assistance-constrained walking. From this point of view, it could be used safely in patients with Parkinson's disease.

These experiments on healthy subjects also enabled to compare the effects of two parameters of the oscillator-based assistance. The first one is the oscillator memory τ , characterizing the time taken by the adaptive oscillators to adapt to changes in gait features, and taking the values $\tau = 4$ s and $\tau = 10$ s. The second one is the phase lead $\Delta\varphi$, determining how far in advance the signal of the hip is predicted for computing the injected torque, and taking the values $\Delta\varphi = 1$ % and $\Delta\varphi = 10$ % of the gait cycle. This brings us to answer to the following question:

What are the effects of increasing the assistance oscillator memory and phase lead on gait?

An improvement in gait metrics was observed for the condition where $\tau = 4$ s and $\Delta\varphi = 1$ %, i.e., hip ROM, gait speed, stride length and cadence were significantly increased, compared to the transparent mode. When the phase lead $\Delta\varphi$ was increased, the hip ROM improvement was mitigated, while an increase in the oscillator memory τ led to a similar mitigation in the other three metrics. It can therefore be assumed that the condition giving the best results is the one with the smallest values for these two assistive parameters. However, during a pilot test on a patient with Parkinson's disease, a phase lead value of 1 % resulted in an assistive torque presenting more variability than with 10 %, which was considered to be unsafe since it could destabilize patients.

With these observations in mind, a study involving eight patients with Parkinson's disease was carried out, as described in Chapter 6. They were required to walk while wearing the orthosis during a four-week training period, at a frequency of three sessions per week. The gait metrics were assessed before the training, just after, and one month after its end. This allowed to investigate the rehabilitative effect of the orthosis, i.e., the learning of a new behavior without the device. This study allows to answer the following question:

Does a gait training assisted by a wearable compliant pelvis orthosis improve gait of patients with Parkinson's disease?

Experiments with healthy subjects demonstrated the assistive effects of the orthosis on the spatiotemporal gait metrics and the hip ROM, since these were measured while the subjects were wearing the orthosis. In experiments with patients, these metrics were measured without the robot, before and after a training period with its assistance. The same improvements as in healthy subjects were observed, i.e., an increase in hip ROM, gait speed, stride length and cadence, revealing this time the rehabilitative effects of a training with the orthosis. Indeed, these improvements were not only observed immediately after training, but were also maintained one month after its end. Nevertheless, the minimal clinically important difference has not been established in the literature for all these metrics in patients with Parkinson's disease with a H&Y score between 1 and 3. As a reminder, this is the smallest improvement recognized as important by clinicians [Horváth et al., 2015]. Observing a statistical improvement in these metrics is a first step, but it is better if it is clinically relevant. Unfortunately, the results of the satisfaction questionnaire (Appendix B) indicate

that the majority of patients did not perceive any improvement in their performance over the course of the training sessions, but this is a subjective assessment.

The same study also provides insight into the following question:

Does this training increase the level of LRA in series of stride durations of these patients?

There was no significant overall increase in the level of LRA in series of stride durations after training. When looking at patients' individual behavior, some of them had an initial LRA level in the range of that of healthy people, and our results showed that the intervention had no impact on this level, which corresponds to the results obtained in our experiments with healthy individuals. On the other hand, for patients whose initial level corresponded to what had previously been reported for Parkinson's population, an improvement was observed. Unfortunately, this effect was not maintained one month after the end of the training. The metrics obtained during this study were not sufficient to determine what differentiated the five patients with lower initial LRA levels from the other three. Further studies are needed to determine which patient profile would benefit from this oscillator-based walking assistance. A non-exhaustive list of factors that can influence patients' response to these therapies includes their activity level in daily life, the type of drug treatment they receive, their genetics, other health problems influencing physical condition, and the nature of motor symptoms (i.e., tremors, rigidity, etc.). These factors need to be taken into account when designing a future experimental protocol.

7.2 Potential applications for the orthosis

Given the positive results of a training with the orthosis on several gait metrics in patients with Parkinson's disease, there exist two future potential applications for it: either using it as a rehabilitation device during physiotherapy sessions, or as an assistive device in everyday life.

In the first case, the patient could walk with the device once or twice a week during their physiotherapy sessions. Since most of these sessions last between 30 minutes and 1 hour, this is feasible, as positive effects on patients' gait are already visible after training sessions lasting only 8 min. It remains to be confirmed that with one or two sessions a week only, the

orthosis would achieve the same improvements as those demonstrated in the experiments of Chapter 6. Other studies on other diseases, however, have shown that a robot-assisted gait training session once or twice a week can already have a positive effect on gait. Indeed, a case study involving a stroke patient reported that after one training session per week for two months with the HAL[®] exoskeleton (Cyberdyne Inc., Tsukuba, Japan), her speed, cadence and balance functions improved, and that these improvements were slightly reduced after a two-month follow-up period, but still higher than at baseline [Yoshimoto et al., 2016]. Another study involving 10 children with cerebral palsy receiving training with the Lokomat[®] twice a week for three months showed improvements in motor functions, particularly in walking, and in their quality of life [De Luca et al., 2022]. In view of these results, it is reasonable to assume that improvements in gait metrics of patients with Parkinson's disease will also be observed with these weekly or twice-weekly physiotherapy sessions assisted with the APO over the long term.

However, one point in particular remains to be improved if it is to be used in this perspective. Indeed, after discussions with physiotherapists, improving the system for adjusting the orthosis size to each patient is a crucial element in their opinion. They believe that taking 10 minutes of the session just to adjust the orthosis is impractical. With this in mind, a notched slide, in which each notch is secured by a wing screw, could be an alternative to explore for replacing the current perforated-plate and screw system. Finally, the physiotherapists need to be convinced of the benefits of this assistance compared with other, less expensive physiological therapies. This will require studies comparing two groups, one receiving a training with the orthosis, and the other a training with more conventional methods (e.g., classical physical exercises, treadmill training, external cueing, etc.).

Concerning the possibility of using this orthosis as an assistance in everyday life, a number of aspects still need to be improved. During discussions with patients, it frequently emerged that the weight of the orthosis and the tightness of its straps caused them discomfort. This observation is supported by the results of the ease-of-use questionnaire (Appendix B), which shows that around 57 % of patients were bothered by the weight of the orthosis, and around 71 % by the tightness of its straps. It was also observed during training that the lateral encumbrance of the ortho-

sis interfered with the arms' natural swing during gait, which is thought to be an important factor in maintaining or recovering stability and minimizing energy consumption during walking [Meyns et al., 2013, Hill and Nantel, 2019]. If we consider two of its competitors, Honda's Walking Assist weighs about 2.7 kg [Honda Motor Co., Ltd., nd], and Samsung's Gait Enhanced and Motivating System weighs about 2.1 kg [Jayaraman et al., 2022], and they both have a minimal general encumbrance (Figure 7.1). By comparison, the APO weighing about 6 kg, there is still room for design improvements, although it can deliver a peak torque greater than that of its competitors, i.e., 16 Nm versus 4 Nm for Honda's orthosis and 12 Nm for Samsung's. This device is not ready yet in its current version to be used to assist patients with Parkinson's disease in their daily activities.



(a) (The Institution of Engineering and Technology, 2023)



(b) (KED Global News Network, 2023)

Figure 7.1 Illustration of (a) the Walking Assist (Honda Motor Co., Ltd., Tokyo, Japan) and (b) the Gait Enhanced and Motivating System (Samsung Electronics Co., Suwon, South Korea) hip orthoses.

Finally, it should not be forgotten that the APO requires the patient to be able to walk on their own, since it assists walking but does not walk for the patient. It is therefore suitable for patients with H&Y stages 1 to 3. Nevertheless, the moment at which patients would benefit more from this assistance in their daily lives is when they lose their independence, i.e., at H&Y stages 4 and 5. It would therefore be interesting to explore the implementation of this assistance based on adaptive oscillators on an orthosis

providing body weight support, such as the hip-knee-ankle exoskeleton EksoGT™ (Ekso Bionics, California, USA, www.eksobionics.com), to help the most affected patients.

In conclusion, from my point of view, the APO has the potential to be used in rehabilitation for patients who can still walk on their own, with minor design modifications, to prevent gait deterioration. On the other hand, for patients at more advanced stages, for whom walking assistance could be useful in everyday life, it would be worth investigating the implementation of an assistance using adaptive oscillators in a device providing body weight support.

7.3 Long-range autocorrelations as clinical metric

As the key concept of this thesis, the assessment of the presence of LRA in series of stride durations also represented one of its greatest challenges. There exist a wide range of possibilities when it comes to evaluating LRA in gait, both in terms of the method to be used and the selection of its parameters values, and the literature does not converge towards a single option. We explored several methods in the course of this thesis, and we often encountered difficulties in setting the parameters of these methods, as modifying them usually leads in variations in the resulting fractal exponent. One problem caused by this wide range of possibilities is that results from one study to another using different methods or different parameters are difficult to compare. There is a strong need to unify these methods and to establish a procedure for determining their parameters depending on each dataset.

We eventually opted for the AFA method, which we believed was the most appropriate for our experimental data. We also studied several values for its parameters and opted for those giving the most plausible fractal exponents for our data, including non-stationary time series. Nevertheless, we do not claim that this is the best method or that better parameter tuning cannot be achieved.

The level of LRA in series of stride durations has been proposed in the literature as a marker of gait instability in the elderly [Herman et al., 2005] and in patients with Parkinson's disease [Warlop et al., 2016], in combination with other clinical metrics. This would enable the identification of in-

dividuals most at risk of falling, and to establish a rehabilitation program accordingly. In practice, however, this is an ambitious goal that raises a number of challenges. Firstly, this connection between gait instability and the presence of LRA in gait has yet to be proven. Establishing a correlation between these two elements would be a first step in this direction. For this purpose, the level of LRA in patients with Parkinson's disease with varying degrees of gait and balance disorders could be recorded, as well as the incidence of falls in the months or years following this first assessment. Secondly, unlike other more conventional gait metrics, this one requires series of at least 256 strides to produce a single value, which is not always possible for patients with gait disorders and which makes it complicated to implement in a clinical context. Finally, observing an improvement in a metric has limited significance if it is not felt by patients. This requires a clinical translation of this metric, by establishing the minimal clinically important improvement, which has not yet been done, as the presence of LRA in gait remains an abstract concept.

Finally, the presence of LRA has also been observed in other physiological signals produced by the locomotor system, such as in series of center of body mass accelerations [Abe et al., 2010], of stride lengths [Dingwell et al., 2010], of magnitudes of impact ground reaction forces [Winter and Challis, 2017], and of arm swings [Rincón et al., 2020]. If it can be established that these signals share the same fractal properties, during the same walking experiments and using the same LRA level assessment method, this would tend to prove that the presence of LRA is a central feature characterizing the functioning of the locomotor system. This would represent a major step forward in our understanding of this metric.

To conclude, this metric is not yet sufficiently mature or understood, and is still too capricious at this stage, to be used in clinical assessment. Nevertheless, it is an interesting metric to explore further in order to characterize the functioning of the locomotor system, and to include with the more standard metrics for assessing the effects of different treatments on gait.

7.4 Assist-as-needed control

When we designed the research agenda of the present thesis, a fourth and final part was supposed to be the implementation of an assist-as-needed control on the APO for patients with Parkinson's disease. However, because of the delay caused by the pandemic in carrying out the experiments of Chapters 5 and 6, research in this direction has been outsourced to two master theses [De Jaeger, 2022, Colasse and Vanderhaeghen, 2023].

Assist-as-needed control adapts the assistance provided by the device to the patient's current needs, e.g., their level of disability and effort made [Jamwal et al., 2020]. This could be achieved on the APO by adjusting the level of assistance k in real time according to the current user's needs. This concept is particularly relevant in the case of the freezing of gait (FOG) symptom, which is encountered by 50 % of patients with Parkinson's disease [Bernardes et al., 2022]. As a reminder, this symptom is characterized by sudden and brief episodes where the patient cannot make a step forward despite the intention to walk [Nutt et al., 2011]. The onset of this symptom fluctuates according to internal and external stimuli perceived by the patient. Indeed, many factors have been identified as triggering these episodes [Rahman et al., 2008, De Jaeger, 2022]: turning around, fatigue, being in a confined or narrow space (such as a corridor, between objects or in doorways), being in a crowd, walking over an irregular surface, stressful situations, etc. As these situations frequently occur in everyday life, this symptom has a major impact on patients' quality of life. Moreover, it is often resistant to pharmacological treatments [Bernardes et al., 2022]. Consequently, other tools have been developed to help patients overcome FOG episodes more quickly. Most of these tools are based on the principle of cueing, i.e., using an external stimulus that the patient can focus on, and has proven effective in reducing FOG episodes [Ginis et al., 2018]. This cueing has been incorporated into portable systems to be used in patients' everyday lives. For example, the GaitAssist [Mazilu et al., 2014] provides auditory cues via a smartphone, the Laser Cane [Buated et al., 2012] provides visual cues, and the system described in [Alvarado Cando et al., 2016] uses vibratory insoles as somatosensory cues. To the best of our knowledge, the use of a wearable orthosis with an assist-as-needed control has never been explored to alleviate this symptom. Indeed, using the APO to provide this assistance would allow to provide haptic external cueing, with the advantage of adapting to patients' gait kinematics in real

time thanks to the adaptive oscillators.

To enable the orthosis to adapt the assistance when the patient encounters a FOG episode, it is important to detect the onset of this episode reliably and in real time. Several detection methods have been developed over the years, which are summarized in [Colasse and Vanderhaeghen, 2023]. However, these methods are not yet sufficiently effective and need to be improved in order to reduce the detection of false positives and shorten the detection delay, in order to be used in an assist-as-needed control framework.

An interesting perspective would be to record patients' behavior in their everyday activities at home, and not just in a controlled environment. This would allow to determine what happens before and during an episode, which would certainly enable these detection methods to be improved. For this purpose, the use of IMUs has already been explored [Mancini et al., 2021, Denk et al., 2022]. Other monitoring tools offer attractive solutions, such as instrumented socks [Amitrano et al., 2020, Walha et al., 2021, Arpan et al., 2022] or reconstructing patients movements using radio waves [Kabelac et al., 2019, Liu et al., 2022]. Additionally, two Belgian companies offer home-based monitoring products that would be worth investigating for this purpose. MintT's sensors (Brussels, Belgium, www.mintt.care) use infrared light to reconstruct movement in order to detect falls in nursing homes. Byteflies (Antwerp, Belgium, www.byteflies.com) proposes sensors recording various physiological signals (i.e., heart rate, muscular activity, respiration, etc.) in addition to acceleration and angular velocity signals of body segments. These different monitoring tools offer the possibility of identifying what happens to the patient during FOG episodes, among a variety of potential behaviors measured using signals of different origins.

It may also be interesting to consider whether putting so much effort into developing a FOG episode detection algorithm is necessary. Indeed, it could be imagined that the patient presses a button on the orthosis when they feel an episode coming on, which would trigger a slight push from the device, serving as somatosensory cueing to get the patient out of this episode. In this case, the intensity and duration of this push should be determined according to each patient's sensitivity, so as not to disturb them and cause them to fall. Nevertheless, if the aim is simply to provide so-

matosensory cueing, it may be more interesting to consider systems that are less bulky than a wearable orthosis. As stress is a known trigger for FOG episodes, using a bulky wearable orthosis in everyday life might be counterproductive due to potential increased strangers' attention to the patient, that can stress them.

In conclusion, I believe it is not worth implementing an assist-as-needed control on a wearable orthosis for patients with Parkinson's disease for everyday use. In fact, a training program assisted by a robot can already improve FOG episodes, by reducing their severity and frequency, as summarized in [Alwardat and Etoom, 2019]. This is in line with the conclusion drawn in Section 7.2, proposing that the APO should be used for rehabilitation rather than assistance.



Simulations for healthy individuals

THE SCPG model, as described in Chapter 4, was also used to model series of stride durations of healthy individuals, which allowed to perform the same analyses as on patients with Parkinson's disease. The methods and results of these simulations are given in this Appendix.

1.1 Methods

The model parameters have been set to the following values: $r_0 = 25$, $\lambda = 0.3$, $f_0 = 1/1.1$, $\gamma = 0.02$ and $\rho = 25$.

Only the case with the positive phase lead, see Equation (4.6), has been simulated here, to get closer to the experiments in Chapter 5. One hundred series of 1024 strides each were simulated for each pair of assistance parameters, i.e., $k = 10$ and 20 [a.u.] and $\tau = 4$ and 10 [s]. The level of LRA α , obtained using the evenly spaced averaged DFA, and the standard deviation σ were compared between these different pairs of assistance parameters through the same statistical tests as described in Section 4.1.2, with Equation (4.9).

1.2 Results

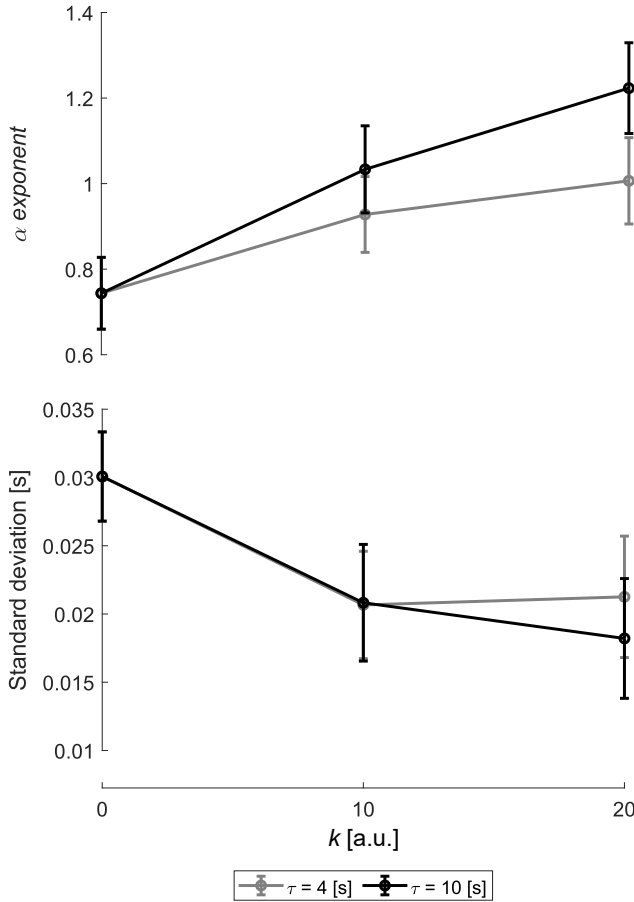


Figure A.1 Evolution of the α exponent (above) and the standard deviation (below) of the simulated inter-stride intervals time series of healthy walkers for several assistance levels. The case where no assistance is applied corresponds to $k = 0$. The level of LRA is given by the α exponent, and "std" stands for the standard deviation.

Figure A.1 shows the α exponent and standard deviation in stride durations for different values of k and τ . It can be observed that for $\tau = 10$, the α exponent is higher than 1 for both values of k , meaning that the series become non-stationary.

With regard to the standard deviation, highly significant differences

($p < 0.001$) were found for all pairs of assistive parameters (k, τ). The same results were observed for the α exponent.

Finally, the contribution of the torque provided by the walking assistance as a fraction of the peak total torque is provided in Figure A.2. It shows that the torque contribution of the simulated adaptive oscillator increases with k and τ from around 18 % to 33 %.

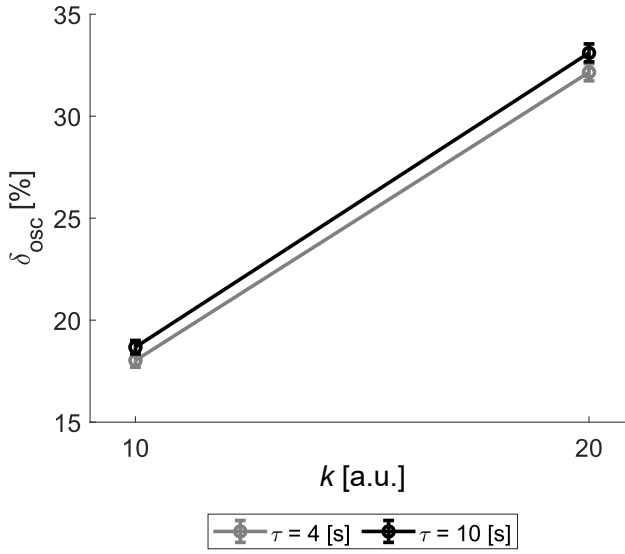


Figure A.2 Ratio δ_{osc} between the peak torque provided by the oscillator-based assistance and the peak total torque of the model, for simulations of healthy subjects.



Ease-of-use questionnaire

AS part of the experiments on patients with Parkinson's disease described in Chapter 6, they were asked to complete an ease-of-use and satisfaction questionnaire at the end of the training period (T1). This questionnaire allows to gather their feedback on the use of the device and potentially to identify some points to improve in the device design, which could be useful for the company producing it. The following questionnaire is adapted from the one proposed in [Kwon et al., 2020] in order to accommodate our device and experiments. In addition, some multiple-choice questions are added in order to quantify some of the feedback received during experiments with healthy subjects.

2.1 Questions

The questions of the questionnaire are transcribed below, with the original French version in italics. For all non-multiple-choice questions, patients were asked to answer using a Likert scale, ranging from "1 - strongly disagree" ("*pas du tout d'accord*") to "5 - strongly agree" ("*tout à fait d'accord*"). For the multiple-choice questions, patients could choose several of the options listed below the question.

Robot and experiment safety

Sécurité du robot et de l'expérience

- Were you able to wear the device easily?
Etait-ce facile de porter le dispositif ?
- Did you feel safe during the experiment?
Vous sentiez-vous en sécurité pendant l'expérience ?
- Did you have any pain or discomfort during or after using the device?
Avez-vous eu des douleurs ou gênes pendant ou après l'utilisation de l'appareil ?
 - ☐ No pain or discomfort.
Aucune douleur ou gêne.
 - ☐ Back pain.
Mal au dos.
 - ☐ Abnormal pressure point when wearing the robot.
Point de pression anormal lors du port du robot.
 - ☐ Legs pain.
Douleurs dans les jambes.
 - ☐ Delayed muscle pain (e.g., the next day).
Douleur musculaire différée (ex. : le lendemain).
- Did you feel you were at risk of hurting yourself by using the device?
Aviez-vous l'impression que vous risquiez de vous blesser en utilisant l'appareil ?

Effects of the robot

Effets du robot

- Did you feel a difference in the way you walked when you were wearing the robot compared to actual walking?
Avez-vous senti une différence dans votre manière de marcher lorsque vous portiez le robot par rapport à votre marche "normale" ?
 - ☐ No difference.
Aucune différence.
 - ☐ Push behind the thigh.
Poussée derrière la cuisse.
 - ☐ Longer steps.
Pas plus longs.
 - ☐ Shorter steps.
Pas plus courts.

- ☐ Feet lifted off the ground.
Pieds soulevés du sol.
- ☐ Feet dragging on the ground.
Pieds trainant au sol.
- ☐ Increased speed.
Vitesse augmentée.
- ☐ Decreased speed.
Vitesse diminuée.
- ☐ Sensation of pelvis tilting forward.
Sensation de bascule du bassin en avant.
- ☐ Sensation of pelvis tilting backwards.
Sensation de bascule du bassin en arrière.
- ☐ Forward-leaning walk.
Marche penchée vers l'avant.
- ☐ Backward-leaning walk.
Marche penchée vers l'arrière.
- ☐ Sensation of stronger assistance in the right leg.
Sensation d'assistance plus forte dans la jambe droite.
- ☐ Sensation of stronger assistance in the left leg.
Sensation d'assistance plus forte dans la jambe gauche.
- ☐ Sensation of having no control over my gait.
Sensation de n'avoir aucun contrôle sur ma marche.
- ☐ Sensation that the robot adapts smoothly to my gait.
Sensation d'adaptation fluide du robot à ma marche.
- Did you feel a difference in the way you walked after the experiment?
Avez-vous senti une différence dans votre manière de marcher après l'expérience ?
 - ☐ No difference.
Aucune différence.
 - ☐ The sensations that I mentioned in the previous question remained for a few minutes after the robot was removed.
Les sensations que j'ai indiquées à la question précédente sont restées pendant quelques minutes après le retrait du robot.
 - ☐ I felt lighter.
Je me sentais plus léger.

B | Ease-of-use questionnaire

- ☐ I found it harder to walk without the robot's assistance for a few minutes.
J'avais plus de mal à marcher sans l'assistance du robot pendant quelques minutes.

Use of the robot

Utilisation du robot

- Was it easy to adjust to using the device?
A-t-il été facile de s'adapter à l'utilisation du dispositif ?
- Were you overly tensed when using the device?
Étiez-vous excessivement tendu(e)/stressé(e) lors de l'utilisation de l'appareil ?
- Did you feel excessive muscle fatigue while using the device?
Avez-vous ressenti une fatigue musculaire excessive en utilisant le dispositif ?
- Did you feel out of breath when using the device?
Vous êtes-vous senti essoufflé(e) en utilisant le dispositif ?
- Did you see an improvement in your performance over the course of the training sessions?
Avez-vous vu une amélioration de vos performances au fur et à mesure des séances d'entraînement ?

Ergonomics

Ergonomie

- Was the device worn appropriately on your body?
Trouvez-vous que le dispositif s'adaptait correctement à votre corps ?
- Was it comfortable to wear the robot?
Était-ce confortable de porter le robot ?
- What did you find inconvenient about using the robot?
Qu'est-ce qui vous a gêné dans l'utilisation du robot ?
 - ☐ Nothing.
Rien.
 - ☐ Its weight.
Son poids.
 - ☐ The straps tightening.
Le serrage des sangles.

- ☐ Its width.
Sa largeur.
- ☐ Its rigidity.
Sa rigidité.
- ☐ The noise of the motor as you walk.
Le bruit du moteur lorsque vous marchiez.
- ☐ The noise of the robot's "cracking".
Le bruit lié aux "craquements" du robot.

Satisfaction

- Are you satisfied with our robot-assisted gait experiment?
Êtes-vous satisfait de l'expérience de marche avec le robot que nous vous avons proposée ?
- Would you like to work with this device during your physiotherapy sessions?
Pendant vos séances de kinésithérapie, aimeriez-vous travailler avec cet appareil ?
- Would you like to use this robot for your daily activities (such as walking outside) if the problematic points were modified (weight, straps, robot adjustments, etc.)?
Aimeriez-vous utiliser ce robot pour vos déplacements quotidiens (tels que des promenades) si les points problématiques étaient modifiés (poids, sangles, réglage du robot, ...) ?

2.2 Results

One patient did not fill in the questionnaire. Moreover, one patient told us after completing the questionnaire that he had difficulty interpreting the Likert scale. His responses to the related questions were therefore discarded, but those for the multiple-choice questions were retained. As a reminder, a score of 1 corresponds to the statement "Strongly disagree", and a score of 5 to "Strongly agree".

The results regarding the safety of the robot and the experiments are as follows:

- Four patients found it easy to wear the device (two with a score of 4, two with a score of 5), and two patients were neutral (score of 3).

B | Ease-of-use questionnaire

- All patients felt safe during the experiments (two with a score of 4, four with a score of 5).
- None of the patients thought they could be injured using the device (three with a score of 1, two with a score of 2, one with a score of 3).

Moreover, slightly more than half the patients experienced pain during the experiments, as shown on Figure B.1. However, the pain was not severe enough to force them to stop the experiments.

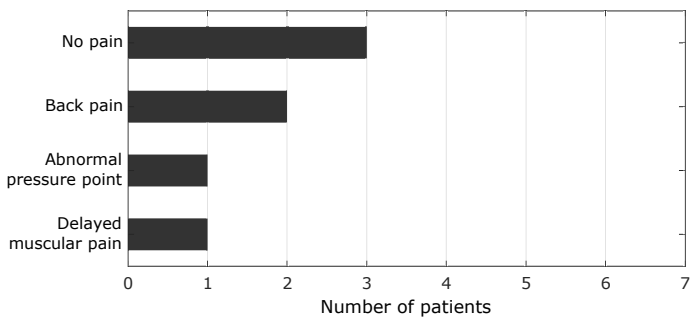


Figure B.1 Responses to the question "Did you have any pain or discomfort during or after using the device?".

Regarding the effects of the robot while wearing it, Figure B.2 summarizes the patients' impressions. Options not selected by any patient are not shown in the figure. Moreover, most patients (six) felt no difference in their gait after the experiment. One patient felt lighter when the device was removed.

The results regarding the use of the robot are as follows:

- All patients found it easy to adapt (two with a score of 4, four with a score of 5).
- Most patients were not feeling stressed during the experiment (two with a score of 1, two with a score of 2), but one felt the opposite (one with a score of 4), and one was neutral (score of 3).
- None of the patients felt a muscular fatigue during the experiment (two with a score of 1, three with a score of 2, one with a score of 3).
- None of the patients felt out of breath during the experiment (two with a score of 1, two with a score of 2, two with a score of 3).

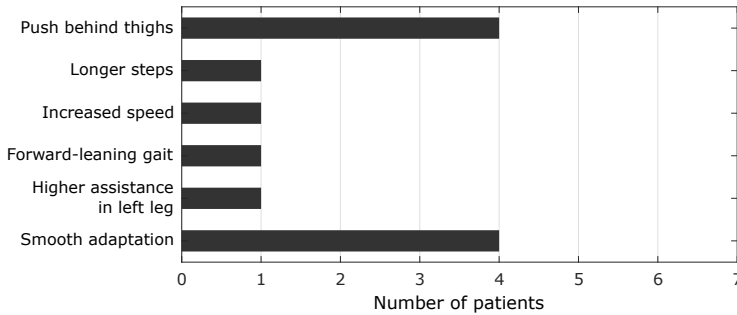


Figure B.2 Responses to the question "Did you feel a difference in the way you walked when you were wearing the robot compared to actual walking?".

- Most patients did not see an improvement in their performance over the course of the training sessions (three with a score of 1, two with a score of 2), but one did see it (score of 4).

Regarding the ergonomics of the device, Figure B.3 shows that the patients' responses were not unanimous regarding the robot's adaptability to their bodies, or the comfort of wearing it. Most patients kept the same score between these two questions, with the exception of one patient who felt the device fitted well to his body (with a score of 4), but was not comfortable to wear (with a score of 2). Figure B.4 reveals the aspects of the device that bothered patients.

Finally, all patients were satisfied with the experiment (one with a score of 4, four with a score of 5, and one with a score of 3). However, the responses are more disparate when it comes to using this device in the future:

- Two patients do not want to use this device during their physiotherapy session (one with a score of 1, one with a score of 2), three patients would like it (two with a score of 4, one with a score of 5), and one patient is neutral (score of 3).
- Four patients would not like to use this device in their daily activities (two with a score of 1, two with a score of 2), one patient would like it (score of 5), and one was neutral (score of 3).

B | Ease-of-use questionnaire

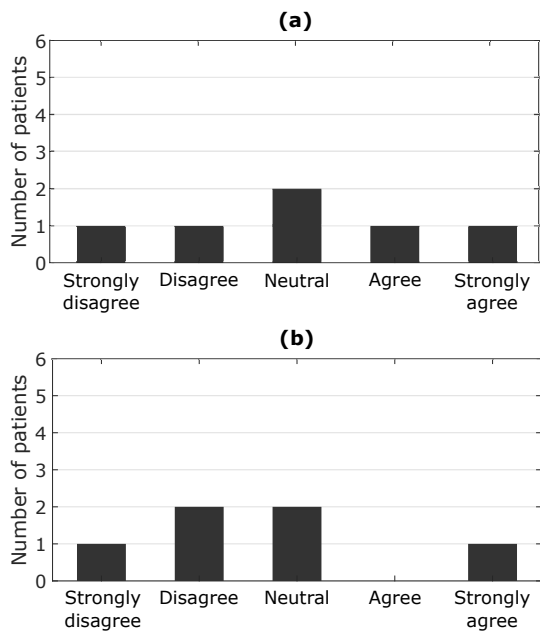


Figure B.3 Responses to the questions (a) "Was the device worn appropriately on your body?", and (b) "Was it comfortable to wear the robot?".

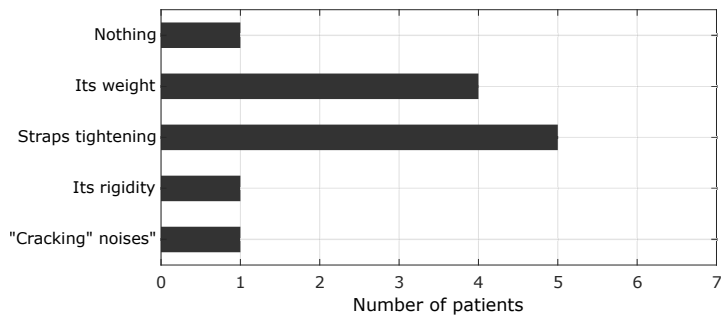


Figure B.4 Responses to the question "What did you find inconvenient about using the robot?".

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