

**École polytechnique de Louvain**

**Simulation of the stride-to-stride variability  
of patients with Parkinson's disease and  
prediction of the impact of a robotic  
assistance**

Author: **Clémence VANDAMME**  
Supervisors: **Frédéric CREVECOEUR, Renaud RONSSE**  
Readers: **Virginie OTLET, Olivier WHITE**  
Academic year 2020–2021  
Master [120] in Biomedical Engineering



# Abstract

Parkinson's disease is the second widespread neurodegenerative disease. Gait disorders are one of the most critical symptom, as it impacts the mobility, and thus the autonomy of the patient. Specifically, the stride-to-stride variability increases and the long range autocorrelations exhibited in healthy gait pattern are reduced. Consequently, gait is unstable and the risk of falling increases. Robot-assisted gait training has shown interesting effects on the gait of these patients. Through the development of a gait model, we predict the potential benefits of an active pelvic orthosis, not yet tested on Parkinson's disease patients.

The model, based on optimal control, brings a novel insight on the origins of the long range autocorrelations in healthy gait. These would be due to a poor control on the stride duration and on the stride length, with still a tight control on the velocity. Furthermore, the model adapted to Parkinson's disease suggests that the decline in persistence observed in this population is due to a compensatory strategy set to reduce the variability. Finally, the orthosis is embedded in the model as a low-pass filter on the stride signals. With a suitable level of assistance, the results of the simulations indicate that patients recover a healthy gait pattern when using the orthosis. The results also highlight the importance of the adaptation of the patient to the orthosis. In conclusion, the predicted results give encouraging perspectives for the rehabilitation of patients with Parkinson's disease.

# Acknowledgements

First and foremost, I would like to thank my supervisors Professor Crevecoeur and Professor Ronsse for their support. Their advice, their availability and the sharing of their expertise have been valuable in the elaboration of this master thesis.

I also would like to thank Virginie Otlet for sharing her knowledge and experience and for her regular feedback.

I finally address my special thanks to my family and my friends for their support and valuable encouragements.

# List of Abbreviations

|                |                                |
|----------------|--------------------------------|
| <b>AOs</b>     | Adaptive Oscillators           |
| <b>APO</b>     | Active Pelvic Orthosis         |
| <b>BG</b>      | Basal Ganglia                  |
| <b>CNS</b>     | Central Nervous System         |
| <b>CPG</b>     | Central Pattern Generator      |
| <b>DFA</b>     | Detrended Fluctuation Analysis |
| <b>fBm</b>     | fractional Brownian motion     |
| <b>GEM</b>     | Goal Equivalent Manifold       |
| <b>H&amp;Y</b> | Hoehn & Yahr                   |
| <b>LQG</b>     | Linear Quadratic Gaussian      |
| <b>LRA</b>     | Long Range Autocorrelation     |
| <b>M1</b>      | Primary Motor Cortex           |
| <b>PD</b>      | Parkinson's Disease            |
| <b>POP</b>     | Preferred Operating Point      |
| <b>PSD</b>     | Power Spectrum Density         |
| <b>PWS</b>     | Preferred Walking Speed        |
| <b>RRA</b>     | Rescaled Range Analysis        |
| <b>SMA</b>     | Supplementary Motor Area       |

# Contents

|                                                                                                    |            |
|----------------------------------------------------------------------------------------------------|------------|
| <b>Abstract</b>                                                                                    | <b>iii</b> |
| <b>Aknowledgements</b>                                                                             | <b>iv</b>  |
| <b>List of Abbreviations</b>                                                                       | <b>v</b>   |
| <b>1 Introduction</b>                                                                              | <b>1</b>   |
| <b>2 Clinical consideration</b>                                                                    | <b>3</b>   |
| 2.1 Parkinson's disease . . . . .                                                                  | 3          |
| 2.1.1 Pathophysiology . . . . .                                                                    | 3          |
| 2.1.2 Symptoms . . . . .                                                                           | 5          |
| 2.1.3 Diagnosis: rating scales . . . . .                                                           | 6          |
| 2.1.4 Treatments . . . . .                                                                         | 7          |
| <b>3 Mathematical framework</b>                                                                    | <b>8</b>   |
| 3.1 LRA: Definition and properties . . . . .                                                       | 8          |
| 3.2 Methods to assess LRA in time series . . . . .                                                 | 9          |
| 3.2.1 Power spectrum analysis . . . . .                                                            | 9          |
| 3.2.2 Random walk analysis: RRA and DFA . . . . .                                                  | 10         |
| 3.2.3 Integrated method . . . . .                                                                  | 11         |
| 3.3 Performance analysis of methods used to assess LRA exponents . . . . .                         | 12         |
| 3.3.1 Evolution of the accuracy as a function of the series length . . . . .                       | 12         |
| 3.3.2 Evolution of the accuracy of the estimates as a function of the<br>true $\alpha/H$ . . . . . | 14         |
| 3.3.3 Discussion . . . . .                                                                         | 15         |
| <b>4 State of the art</b>                                                                          | <b>16</b>  |
| 4.1 Characteristics of healthy and parkinsonian gait . . . . .                                     | 16         |
| 4.2 Models . . . . .                                                                               | 17         |
| 4.2.1 CPG-based models . . . . .                                                                   | 17         |
| 4.2.2 Modelling of the basal ganglia loop . . . . .                                                | 18         |
| 4.2.3 Mechanical approach . . . . .                                                                | 18         |
| 4.2.4 Model based on optimal control . . . . .                                                     | 19         |

|          |                                                      |           |
|----------|------------------------------------------------------|-----------|
| <b>5</b> | <b>Material and methods</b>                          | <b>20</b> |
| 5.1      | Healthy gait . . . . .                               | 20        |
| 5.1.1    | Data . . . . .                                       | 20        |
| 5.1.2    | Model . . . . .                                      | 20        |
| 5.2      | Gait altered by Parkinson’s disease . . . . .        | 22        |
| 5.2.1    | Data . . . . .                                       | 23        |
| 5.2.2    | Model . . . . .                                      | 24        |
| 5.3      | Robot-assisted gait . . . . .                        | 25        |
| 5.3.1    | APO . . . . .                                        | 25        |
| 5.3.2    | Model . . . . .                                      | 26        |
| 5.4      | Block Diagram . . . . .                              | 27        |
| <b>6</b> | <b>Results</b>                                       | <b>29</b> |
| 6.1      | Healthy gait . . . . .                               | 29        |
| 6.1.1    | Comparison with human experimental data . . . . .    | 29        |
| 6.1.2    | Impact of the weights of the cost function . . . . . | 30        |
| 6.2      | Gait altered by Parkinson’s disease . . . . .        | 32        |
| 6.2.1    | Data analysis . . . . .                              | 32        |
| 6.2.2    | Model parameters fitting . . . . .                   | 33        |
| 6.3      | Robot-assisted gait . . . . .                        | 34        |
| <b>7</b> | <b>Discussion</b>                                    | <b>37</b> |
| 7.1      | Healthy gait . . . . .                               | 37        |
| 7.1.1    | Model interpretation . . . . .                       | 37        |
| 7.1.2    | Model limitations . . . . .                          | 37        |
| 7.2      | Gait altered by Parkinson’s disease . . . . .        | 38        |
| 7.2.1    | Data limitation . . . . .                            | 38        |
| 7.2.2    | Model interpretation . . . . .                       | 38        |
| 7.3      | Robot-assisted gait . . . . .                        | 40        |
| <b>8</b> | <b>Conclusion</b>                                    | <b>41</b> |
|          | <b>References</b>                                    | <b>42</b> |

# Chapter 1

## Introduction

Today, it is estimated that Parkinson's disease (PD) affects about 1% of the population over the age of 70 [1]. Given the ageing of the population, the prevalence is expected to increase in the coming years. This disease is an important cause of disability in the elderly.

Among the symptoms, a particular emphasis is given to gait disorders. PD patients walk slower, with smaller steps [2]. But more importantly, the pattern of gait variability is very different from healthy walking. Indeed, at constant speed, the series of inter-stride durations exhibit long range autocorrelations (LRA) [3]. This statistical persistence, marker of healthy gait, is reduced in PD patients. When gait disorders become serious, risk of falling increases. It is essential to avoid falls for their physical but also psychological consequences. Indeed, beyond the physical injury (for example, fracture), falls lead to a fear of falling, and therefore a decrease in activities. In general, falls lead to a loss of autonomy, muscle weakness, social isolation and dependence. Since regular physical activity is essential to control the progression of the disease, immobilization following a fall can have serious consequences on PD patients [4].

Progress in robotic assistance opens up new opportunities for patient rehabilitation, and could prevent these falls from occurring. We will investigate on the effect of an Active Pelvic Orthosis (APO), initially designed for transfemoral amputee. It is a light-weight, wearable exoskeleton, which provides assistance at the hip level to smooth the gait signal, while allowing the user to steer the movement [5].

Through modelling, this thesis aims to bring a novel insight on the origins of the LRA in healthy gait variability. For this purpose, we will draw on a model proposed in 2010 by Jonathan Dingwell and colleagues [6]. Then, this model will be adapted to gait altered by PD. Again, the interpretation of the model will enrich our understanding of the mechanisms that regulate walking in PD patients. Finally, a last objective is the determination of the potential benefits of the APO on the gait disorders. In particular, the question is whether patients can recover healthy gait patterns with the orthosis, and under which conditions.

To meet these objectives, we will first provide a detailed description of the Parkinson's disease. We will address the pathophysiology, the resulting symptoms, the current treatments and some scales to evaluate the disease's stage. Next, the mathematical foundations of LRA will be presented. In the same chapter, we will outline some methods to evaluate the presence of autocorrelations in a time series and discuss their performances. In Chapter 4, we will review current gait models, based on the present knowledge of gait characteristics in different populations. We will then present the model and its adaptations. We will be able to analyze the results of the simulations and validate them on experimental data. Finally, we will discuss the interpretation of the model and its limitations.

# Chapter 2

## Clinical consideration

### 2.1 Parkinson's disease

Parkinson's disease (PD) is a neurodegenerative disease that affects over 10 million people worldwide today [7]. This prevalence makes it the second wide-spread neurodegenerative disease, just after the Alzheimer's disease. Most people are diagnosed between 45 and 70 years old. In fact, more than 1 in 100 people over the age of 70 have PD [1, 8].

PD patients suffer from various motor disorders: resting tremor, decreasing amplitude of movement and movement slowing, gait disorders, etc. Physiologically, the main cause of these symptoms is the degeneration of dopaminergic neurons in the basal ganglia (BG), provoking less excitation of the cortex from BG [9].

Causes of this progressive destruction are not well known. However, genetic factors may be involved, as well as environmental factors (higher incidence in rural regions, use of pesticides, presence of heavy metals, etc.). Also, repeating head traumas (among boxers for example) is a risk factor [1].

#### 2.1.1 Pathophysiology

To better understand PD, here is a partial description of the structure of BG, its connections with the rest of the brain and some of its roles [10]. BG are composed of five substructures: the caudate nucleus, the putamen, the globus pallidus (internal and external parts, respectively GPi and GPe), the substantia nigra (pars compacta and pars reticula, SNpc and SNpr) and the subthalamic nucleus (STN). The caudate nucleus and the putamen form together the striatum (Str), the structure which receives the inputs of the BG. The striatum receives glutamatergic excitatory projections from the cortex and dopaminergic projections from the substantia nigra. All the interactions between these different parts are depicted in Figure 2.1.

The first main pathway is the corticostriatal pathway. When the striatum's neurons are activated by the cortex, they inhibit in turn the globus pallidus through GABAer-

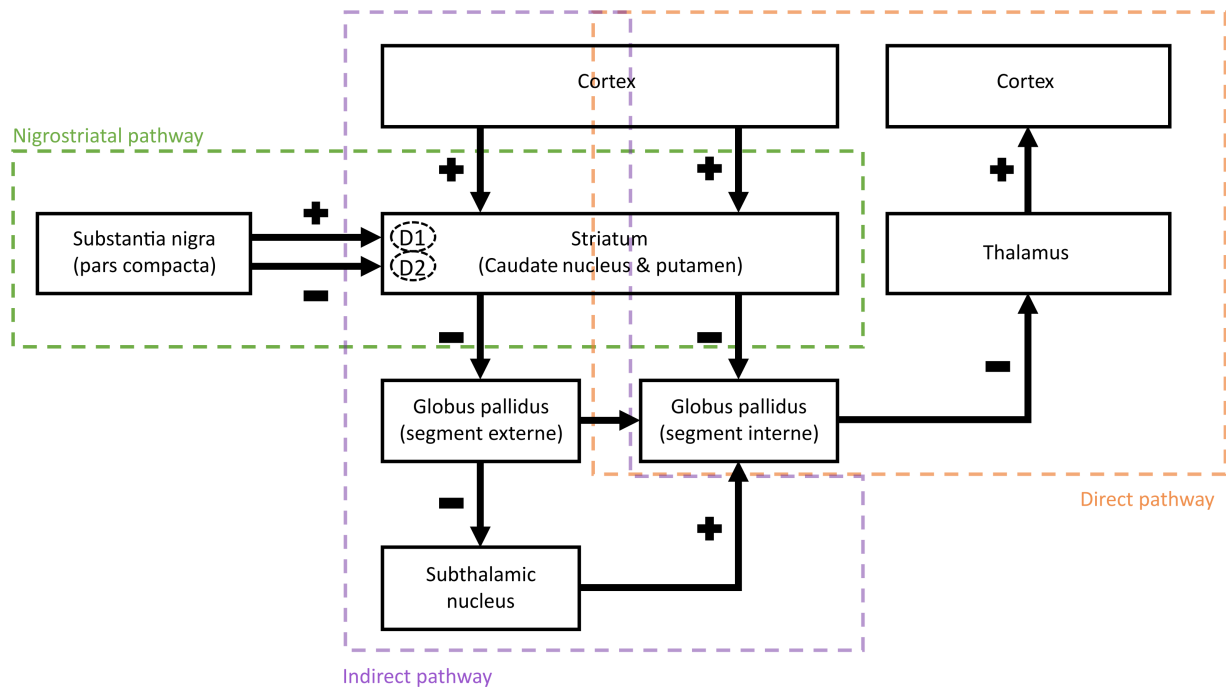


Figure 2.1: Diagram of the interactions within BG and towards the rest of the brain. Excitatory (resp. inhibitory) projections are represented by "+" (resp. "-"). Adapted from [10].

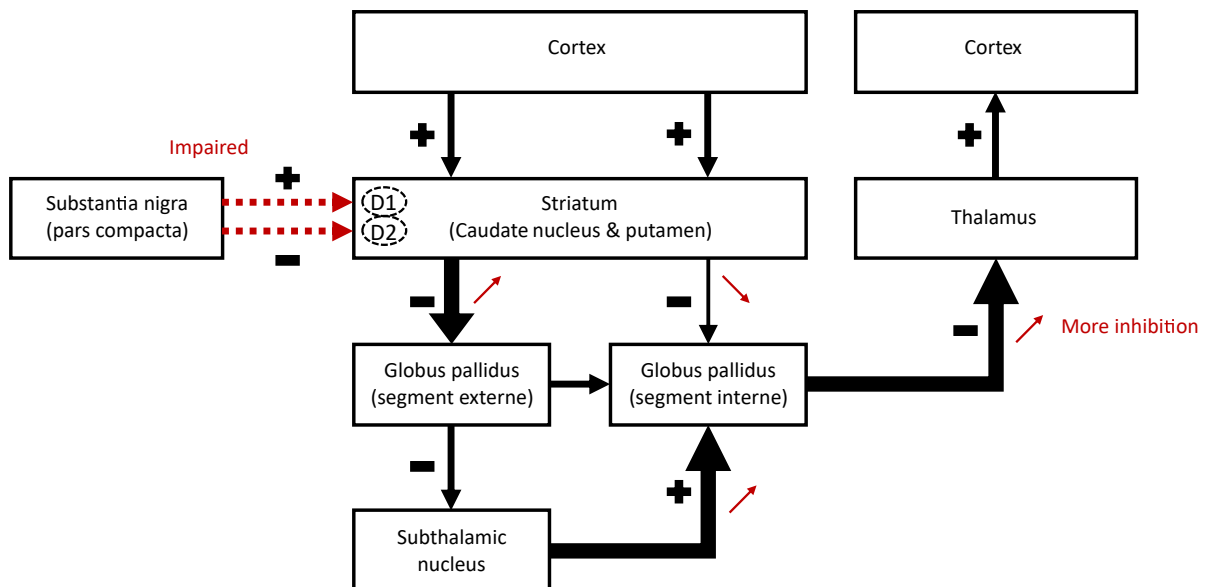


Figure 2.2: Consequences on the neuronal interactions in BG due to the degeneration of the substantia nigra in PD. Adapted from [10]

gic projections. At rest, the globus pallidus constantly inhibits the thalamus, which has excitatory projections towards the supplementary motor area (SMA). Within this pathway, we can distinguish the direct and the indirect pathway:

1. The direct loop is simple: the striatum projects on the *internal* segment of the globus pallidus. The consequence is the interruption or at least the reduction of the inhibition on the thalamus and therefore the excitation of the cortex.
2. The indirect loop passes through more intermediate neurons: the striatum projects on the *external* segment of the globus pallidus, which has projections on the subthalamic nucleus. This latter provokes activity in the internal segment of the globus pallidus and consequently more inhibition of the thalamus.

In a nutshell, the direct loop facilitates the cortex activity while the indirect loop reduces this activity. The balance between these two paths must be finely tuned. In the striatum, two types of neurons are at the origin of these two pathways: the neurons with dopaminergic receptors of type D1 (facilitated by dopamine) and those of type D2 (inhibited by dopamine).

The balance between the direct and the indirect pathway is regulated by the nigrostriatal pathway. The substantia nigra has dopaminergic projections on the striatum, facilitating on the one hand the direct pathway (by stimulation of D1 receptors) and on the other hand, inhibiting the indirect loop (by stimulation of D2 receptors). The net effect is therefore excitatory on the cortex, first by the diminution of the activity of the globus pallidus and consequently, by a bigger excitation of the thalamus.

Since PD consists in the progressive destruction of dopaminergic fibers to the striatum, the balance between the direct and indirect pathway is disrupted and it results in a lower stimulation of the motor cortex. As seen in Figure 2.2 the direct pathway is less facilitated and the indirect pathway is less inhibited.

Due to its connections to the SMA and the primary motor cortex, the BG is involved in motor preparation and motor control. It is thought that BG is responsible for the regulation of motion's quality: timing, speed and acceleration, and regulation of muscle tone [2].

### 2.1.2 Symptoms

As detailed in section 2.1.1, the projections between BG and the motor cortex (M1 and SMA) are disrupted in PD. Symptoms appear when 50% to 70% of dopaminergic neurons are destroyed. Before this point, the brain compensates the loss by plasticity processes. At the end of the disease, the loss of dopaminergic neurons reaches 90% [11].

It results in several movement impairments, such as movement slowing or reduced amplitude (bradykinesia); or at the extreme, no movement at all (akinesia) [12]. Motor preparation is also critical for PD patients. Reaction times are usually increased and the execution of complex and automatic movements requires more attention from the patients. For this reason, they often experience difficulties to execute two

tasks simultaneously [9]. PD patients also suffer from resting tremor, which tends to disappear during voluntary movements, muscle rigidity, abnormal rhythmicity and postural instability [8].

These symptoms are reflected in gait by reduced velocity, shorter stride length, asymmetry between the legs, impaired balance and lack of automaticity. Overall gait is unstable, leading to an increasing risk of falling. Like most symptoms of PD, gait disturbance is progressive with the stage of the disease [9].

### 2.1.3 Diagnosis: rating scales

Several indicators exist to assess the progress of the disease. One of the most used is the Hoehn & Yahr (H&Y) scale. It owes its name to its authors, Melvin Yahr and Margaret Hoehn and has been published initially in 1967 [13]. This qualitative scale describes five stages of the disease, from 1 to 5. In the modified H&Y scale, three stages has been added: 0, 1.5 and 2.5 [14]. An overview of this scale is presented in Table 2.1.

| H&Y | Symptoms                                                                                                                             |
|-----|--------------------------------------------------------------------------------------------------------------------------------------|
| 0   | No sign                                                                                                                              |
| 1   | Unilateral symptoms, of minimal severity<br>Tremor, bradykinesia, rigidity of one arm/leg<br>No functional impairment                |
| 1.5 | Unilateral symptoms, involving neck and spine                                                                                        |
| 2   | Bilateral symptoms, of minimal severity<br>No balance impairment<br>Potential speech abnormalities and muscle stiffness in the trunk |
| 2.5 | Mild symptoms on both sides                                                                                                          |
| 3   | Balance impairment, falls become common<br>Mild to moderate bilateral symptoms<br>No assistance needed for daily life activities     |
| 4   | Severe disability<br>Assistance needed for some daily life activities<br>Ability to walk unassisted despite difficulties             |
| 5   | Wheelchair essential to move around                                                                                                  |

Table 2.1: Description of all stages of the H&Y scale

While the H&Y score focuses on motor performances, the Unified Parkinson’s Disease Rating Scale (UPDRS) also includes other aspects, such as intellectual functions, mood, sleep disturbance, daily activities, etc. This scale was introduced in 1987 and recently updated by the Movement Disorder Society (MDS) [15]. Disabilities are

grouped in four sections and individually assessed by a score from 0 to 4, from no problem to severe problem. The total score indicates the severity of the disease, 199 being the maximum score.

More specific tests are also used to assess particular aspects of PD. For example, the BESTest assesses balance performance [16].

#### **2.1.4 Treatments**

Due to the variety of disorders affecting patients, treatments must be adapted to each individual case. It is however important to note that we cannot heal from PD, we can only mitigate symptoms. As soon as the treatment is interrupted, symptoms come back [7].

The most common therapy is pharmacologic. Drugs aim to increase dopamine concentration through dopamine precursor (Levodopa) or to mimic its effect (DA agonists, catechol-*O*-methyltransferase (COMT) inhibitors, and monoamine oxidase (MAO) inhibitors) [17]. Medication generally helps to reduce tremor and muscle rigidity, and to improve speed and coordination of movements. When the disease progresses, medications can be combined. Unfortunately, it quickly becomes insufficient.

Some patients may undergo surgery. Among the different alternatives, one consists in the removal of a part of the globus pallidus (inhibiting the thalamus). However, due to potential serious and irreversible side effects, it is currently almost no longer practiced [18]. A tube can also be inserted in the intestine tube to deliver continuously L-dopa. This treatment requires the patients to be connected to a pump, significantly limiting daily activities. For this reason, this treatment is only administered to patients in the severe stages of the disease [18]. Deep brain stimulation is also an option. A neurostimulator is implanted under the collarbone and connected to electrodes, placed to stimulate subthalamic nucleus or the internal part of the globus pallidus [1].

Complementary treatments are often needed, such as exercises or physical therapy. These therapies apply to specific movements. For example, gait disorders can be reduced using auditory or visual cues, split-belt treadmill can reduce gait asymmetry, etc [8]. Exercises can be guided by a robotic assistance to recover smooth and healthy movements and trajectories.

# Chapter 3

## Mathematical framework

The correlation structure of time series is a key parameter to characterize human gait. Healthy gait exhibits LRA, but it tends to disappear with age and some pathologies like PD. This chapter provides the mathematical foundations of LRA, its definition, properties and the methods used to assess whether a stochastic process is a long memory process or not.

### 3.1 LRA: Definition and properties

We consider a stationary time series  $f(n) = x_n$ , of mean  $\mu = 0$  and constant variance  $\sigma^2$ . The autocorrelation function  $C(\tau)$  of such stochastic process is defined as:

$$C(\tau) = Cov(x_n, x_{n+\tau}) \quad (3.1)$$

In other words,  $C(\tau)$  corresponds to the covariance between two samples spaced by a time  $\tau$ . The time series  $f(n)$  is said to be a long memory or a long correlated process if its autocorrelation function scales in a power-law fashion:

$$C(\tau) \sim \tau^{-\beta} \quad (3.2)$$

with  $0 < \beta < 1$  [19]. This theoretical function is depicted in Figure 3.1 for  $\beta = [0.2, 0.5, 0.8]$ . We observe an asymptotic behaviour: the function decays extremely slowly for high values of  $\tau$  and tends to 0 when  $\tau = \infty$ . Consequently, one property of the autocorrelation function of long memory process is that its sum over the infinite diverges [19]. Moreover, we observe that for lower values of  $\beta$ , the decline is slower. We say that the persistence of the process is stronger.

In practice, in a long-range correlated process, the value of  $x_n$  statistically depends on a large number of previous values, with a decreasing strength when these values are more distant in time. In contrast, in a short range autocorrelated processes,  $x_n$  only depends on a relatively small number of values (for example, if  $\beta > 1$ ).

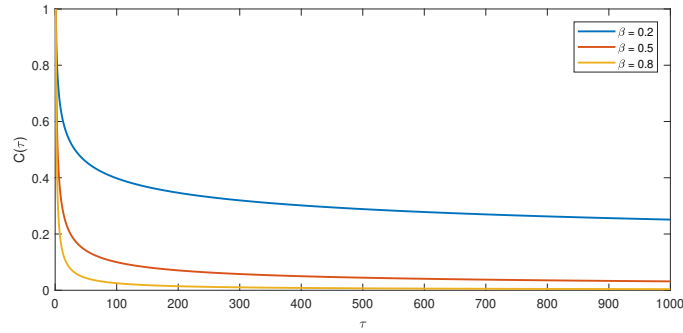


Figure 3.1: Autocorrelation function of a long memory process, with different values of  $\beta$

## 3.2 Methods to assess LRA in time series

When we have a time series to analyze, we do not know its autocorrelation function. In LRA, since the autocorrelation function is defined between 0 and infinity, it is particularly challenging to determine  $\beta$  from finite time series. Therefore, two indicators are used to assess whether a time series is a long memory process: the spectral exponent, denoted  $\alpha$ , and the Hurst exponent,  $H$ . Several methods exist to evaluate one or the other. However, due to the asymptotic behaviour of LRA, these methods are susceptible to produce inaccurate results. It is advised to use sufficiently long series to get the best result possible (Section 3.3.1). An integrated method is useful to check the consistency of the results (Section 3.2.3).

### 3.2.1 Power spectrum analysis

On the first hand, the spectral exponent is directly related to the spectrum of the time series. The Wiener-Kintchine theorem states that the power spectrum density (PSD) of a time series is the Fourier transform of its autocorrelation function [20]. Consequently, in LRA, the PSD of  $f(n)$  is:

$$P(k) \sim k^{-\alpha} \quad (3.3)$$

for small  $k$  and with  $\alpha = 1 - \beta$  [19]. It means that LRA present small fluctuations in high frequencies and high fluctuations in lower frequencies. Therefore, a rapid analysis of the PSD of the time serie provides  $\alpha$ . In the plane  $\log(PSD)$  versus  $\log(freq)$ ,  $-\alpha$  is the slope of the linear regression. This is illustrated in Figure 3.2. For LRA,  $\alpha$  ranges from 0 (white noise) to 1 (high persistence). This method is quick and computationally cheap but presents some disadvantages. The computation of the power spectrum density requires the choice of a particular window. The smoothing of the spectrum will be different according to the chosen window, which can alter the result  $\alpha$  [19].

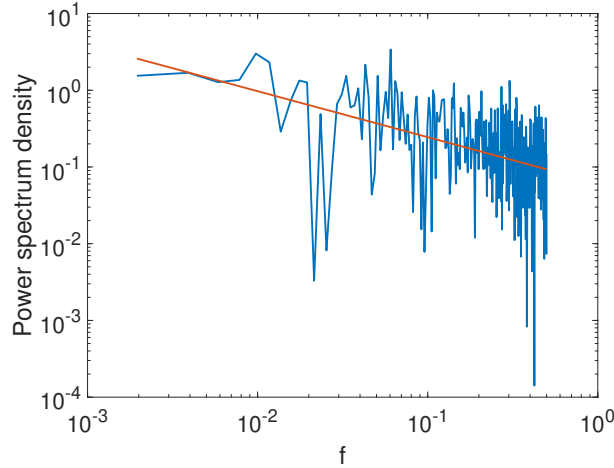


Figure 3.2: Power spectrum density of long memory process (blue) and linear regression (red) of slope  $-\alpha = -0.59$

### 3.2.2 Random walk analysis: RRA and DFA

On the second hand, random walk analysis can be used to find the Hurst exponent. A time series can be converted to a random walk using partial sum:  $R_n = x_1 + x_2 + \dots + x_n$ . Then, the mean square displacement is characterized by the Hurst exponent [21]:

$$\langle R_n^2 \rangle \sim n^{2H} \quad (3.4)$$

In this context, we will consider the Rescaled Range Analysis (RRA) and the Detrended Fluctuation Analysis (DFA).

The DFA has been introduced by Peng et al. [22] in 1994. We consider a time series of length  $N$ . The first step of this method is the partial sum computation to get the random walk profile. Then, this profile is divided into  $N_s = \frac{N}{s}$  non overlapping intervals of size  $s$ . The size of the interval typically ranges from 4 to  $\frac{N}{4}$  and are not necessarily a multiple of  $N$ . Therefore, at the end of the profile, a short part of the random walk will remain in most cases and will not be used. For each interval, the linear trend is removed and the standard deviation  $Q$  is computed. Then,  $Q$  is averaged over all the intervals of same size  $s$ . This operation is repeated for different sizes of interval.

The diffusion plot is the graphical representation of  $\log(Q)$  versus  $\log(s)$ . We observe that the mean standard deviation  $Q$  scales with  $s$  as a power law:

$$Q(s) \sim s^H \quad (3.5)$$

with  $H$  the Hurst exponent, equal to  $\frac{2-\beta}{2}$ . The Hurst exponent correspond to the slope of a regression line drawn in the diffusion plot, as illustrated in Figure 3.3a.

When  $H > \frac{1}{2}$ , the time series presents positive LRA. As  $H$  gets closer to  $\frac{1}{2}$ , the process becomes more random, while values close to 1 indicates a stronger persistence. Below  $\frac{1}{2}$ , the series is said to be anticorrelated, or negatively correlated.

RRA is based on the same principle. The metric  $Q$  is no longer the standard deviation of the interval, but the range of this interval divided by the standard deviation [23].

RRA and DFA present the advantage to be less sensitive to imperfect measurements. Indeed, the noise level is reduced when the time series are converted into random walk. Moreover, they are more reliable to distinguish trends caused by external effects from LRA, since the intervals are systematically detrended [21]. However, of these two methods, only the DFA can be used on non-stationary series [24].

### Evenly-spaced DFA

In order to increase the accuracy of the DFA, evenly spacing should be adopted. The method is similar to the classic DFA but differs in the choice of the interval's sizes. While the classic method uses integers between a minimum and a maximum length, the evenly spaced DFA selects values of  $s$  that are linearly spaced in the diffusion plot [25].

In practice, a minimum ( $s_{min}$ ) and maximum ( $s_{max}$ ) interval length should be determined, as well as the number of length  $k$ . Then:

$$\begin{aligned} s_1 &= s_{min} \\ s_i &= s_{i-1} * 10^{\frac{\log_{10}(s_{max}) - \log_{10}(s_{min})}{k-1}} \end{aligned} \quad (3.6)$$

The difference between the classic DFA and the evenly spaced DFA is illustrated in Figure 3.3. Both methods are executed on the same sequence of length  $N = 1024$  with a minimum interval length of 4 and maximum  $\frac{N}{4}$ . For the evenly-spaced DFA, we chose  $k = 50$ . The expected  $H$  is 0.75. The evenly spaced DFA is closer to the results, with an estimated  $H = 0.7532$ , versus  $H = 0.7273$  found with the traditional method. This difference is explained by a disproportionate weighting of the larger timescale  $s$  in non-uniform spacing. This region is over-represented in the diffusion plot and affects the regression computation.

### 3.2.3 Integrated method

An integrated method, suggested by Rangarajan and Ding [19], allows to detect possible mistakes in the assessment of the correlation exponent. Two methods should be used, the spectral analysis and either DFA or RRA. Then, if the estimates are correct, the spectral exponent and the Hurst exponent should be consistent with equation 3.7. This equation will rarely be satisfied, due to the asymptotic behaviour of LRA. Therefore a difference  $d = |H - \frac{1+\alpha}{2}| < 0.1$  is tolerated [19, 16]. This integrated method is more robust to relatively short sequences (up to 512 points).

$$H = \frac{2 - \beta}{2} = \frac{1 + \alpha}{2} \quad (3.7)$$

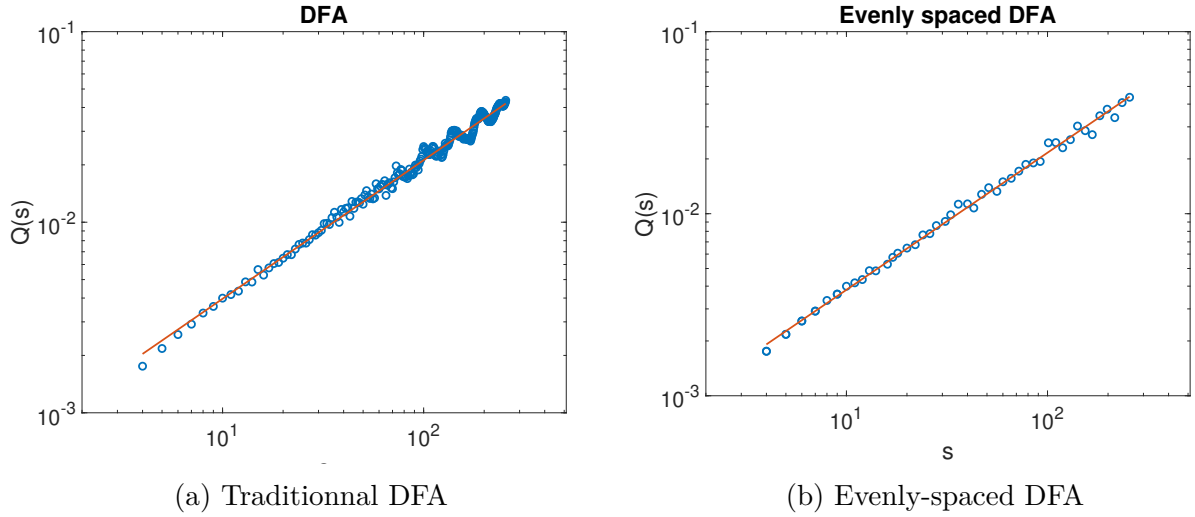


Figure 3.3: Comparison between a) the traditional DFA and b) the evenly-spaced DFA on the same time series

### 3.3 Performance analysis of methods used to assess LRA exponents

#### 3.3.1 Evolution of the accuracy as a function of the series length

For all methods described above, the length of the process under analysis is a key factor in determining the accuracy (and therefore the reliability) of the result. This section aims at analyzing the evolution of the accuracy of these methods for different series lengths.

Two methods have been used to generate long memory processes characterized by a Hurst exponent of 0.8, or equivalently  $\alpha = 0.6$ . The first method, the spectral synthesis, uses the spectrum property of LRA of Equation 3.3. The method is described in [19]. The second one generates a fractional Brownian motion (fBm) through a method described by Rambaldi et al. [26]. With each of these two methods, we generated 500 series of 128, 256, 512, 1024 and 2048 points (100 series of each length). Then, we computed the Hurst exponent of each series with the spectral analysis, RRA, DFA and evenly-spaced DFA. Finally, we calculated the mean and standard deviation of the results obtained on series of the same length, generated with the same method and evaluated with the same methods. In Figure 3.4 each point is the average Hurst exponent found across 100 time series. Figure 3.5 represents the standard deviation of these results.

From Figure 3.5, we clearly observe that the variability of the results decreases when the sequences are longer in all cases. This supports the idea that using longer series allow to get more reliable estimates of the correlation structure of these series. Biases, highlighted by Figure 3.4, tends also to be reduced in longer series, especially when

using RRA. We also observe that estimation methods perform better when series were generated by the method belonging to the same domain: the spectral analysis results are more accurate when the series have been generated by spectral synthesis and DFA have better performance with fBm. This was already observed by Roume et al. [27]. These graphs also confirm that evenly-spacing reduces the bias of DFA.

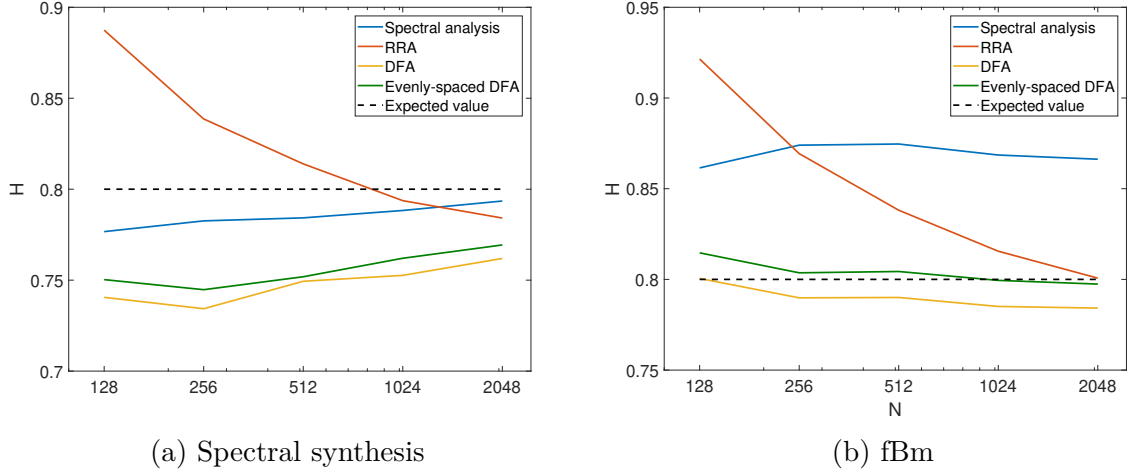


Figure 3.4: Mean Hurst exponent obtained for different series length  $N$ , with spectral analysis (blue), RRA (red), DFA (yellow) and evenly-spaced DFA (green). For each  $N$ , 100 series have been generated based on a) spectrum synthesis and b) fBm theory. The expected value (dashed line) is  $H = 0.8$ .

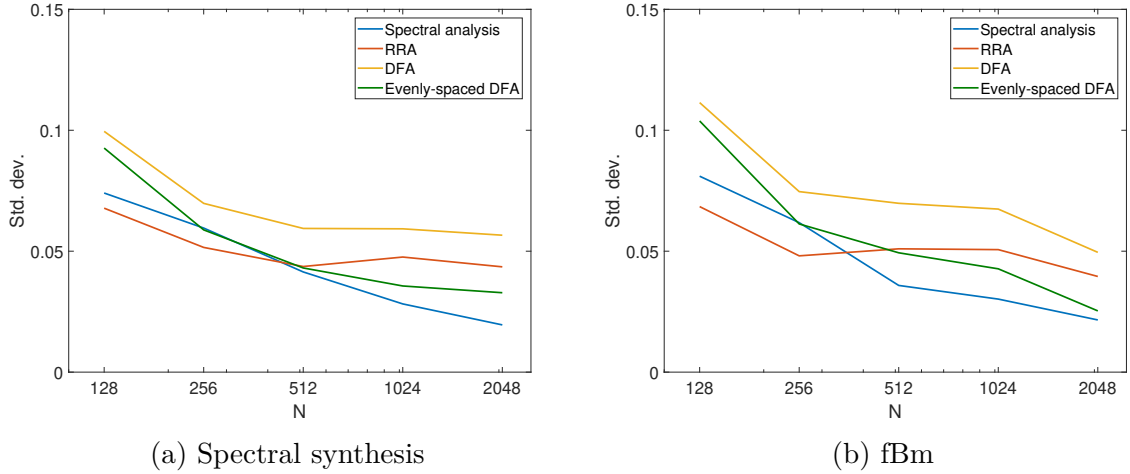


Figure 3.5: Evolution of Hurst exponent variability as a function of the length of the time series for different assessment methods: spectral analysis (blue), RRA (red), DFA (yellow) and evenly-spaced DFA (green).

### 3.3.2 Evolution of the accuracy of the estimates as a function of the true $\alpha/H$

Borders values ( $\alpha = 0$  or  $1$ ,  $H = 0.5$  or  $1$ ) are also subjects to some inaccuracies. In this section, we analyse the performances of all the methods of correlation structure assessment for different strengths of persistence. In Figure 3.6,  $H$  (resp.  $\alpha$ ) has been discretized from  $0.5$  (resp.  $0$ ) to  $1$  by step of  $0.5$  (resp.  $1$ ). For each value of  $H$  or  $\alpha$ , 100 time series have been generated with spectral synthesis or through fBm theory. Then, these series have been analyzed with spectral analysis, RRA, DFA or evenly-spaced DFA. Each sub-panel is referred to one different pair of analysis method and generation method. The average result over the 100 of each true  $H$  value is represented on the Figure 3.6.

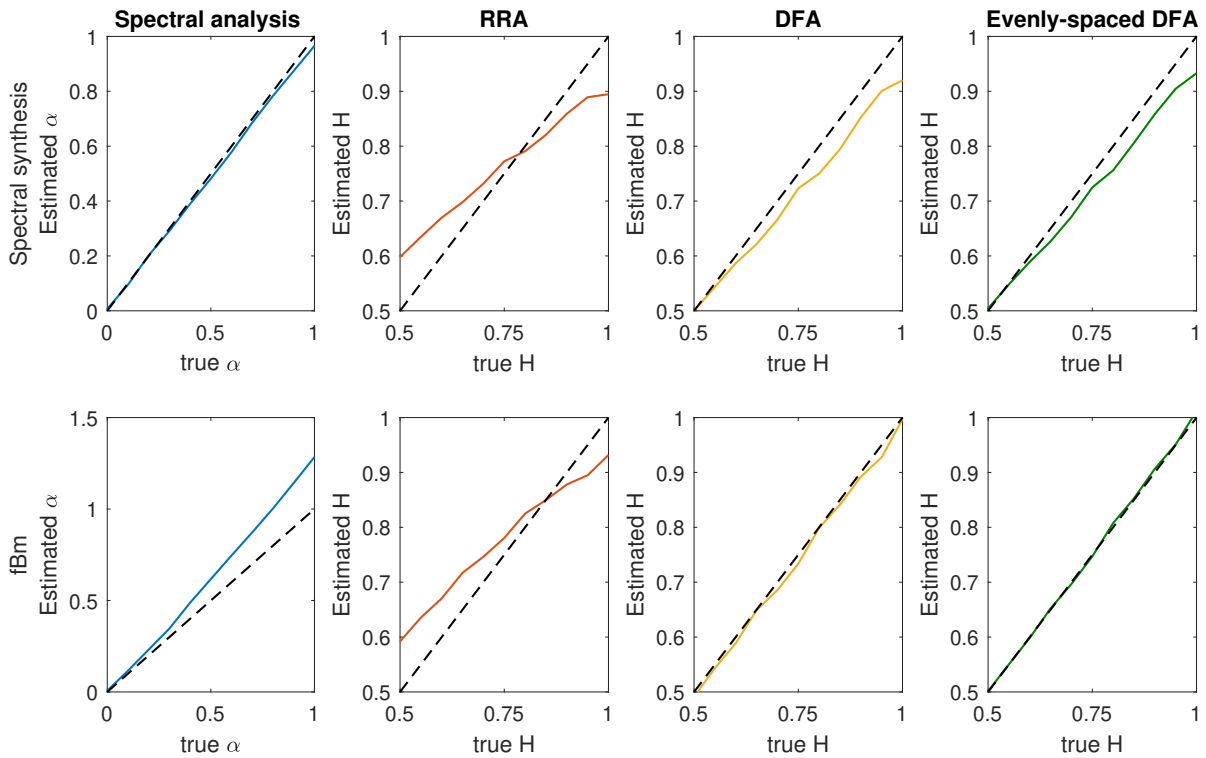


Figure 3.6: Evolution of the accuracy of LRA assessment methods as a function of the expected LRA exponent. Long range autocorrelated processes have been generated either by spectral synthesis (first row) or fBm (second row) and assessed through spectral analysis (blue), RRA (red), DFA (yellow) and evenly-spaced DFA (green).

Again, it appears clearly that spectral analysis is more biased for series generated on the basis of fBm theory, series on which DFA is more performant. Furthermore, spectral analysis is more reliable when the persistence is weaker, but gets defective for values of  $\alpha$  close to 1. In contrast, DFA tends to under-estimates the persistence for strong autorrelation, but gets high precision for more random processes. On the other hand, RRA presents biases at both sides of the interval. It should be noted, however, that generation methods may be at the origin of the biases.

### 3.3.3 Discussion

For all simulation performed later in this work, we will generate series of 1024 strides. Above this length, the accuracy is no longer significantly improved, compared to the computation costs that arise from it. However, concerning experimental data, the constraints linked to their collection does not allow us to have series of such length. In particular, most PD patients are not able to walk 1024 consecutive strides. Consequently, series of 256 or 512 strides will be analysed.

Also, in the rest of this work, we will systematically use the evenly-spaced DFA for the Hurst exponent assessment, due to the strong evidence of the performance of this method, shown both in the previous sections and in the literature [25, 28].

# Chapter 4

## State of the art

### 4.1 Characteristics of healthy and parkinsonian gait

Gait is a complex mechanism involving several neural structures such as the motor cortex, the cerebellum and basal ganglia. It also requires the integration of sensorial feedback from visual, vestibular and peripheral receptors [29]. The complex coordination of these structures is not yet fully understood. Therefore, models continue to evolve to best simulate the characteristics of healthy walking and to adapt to other populations, such as the elderly or patients with neurologic impairments.

In particular, we are interested in the small fluctuations present in the gait pattern under stationary conditions. It was initially assumed that those subtle fluctuations were pure random noise. However, Hausdorff and colleagues have shown that those fluctuations exhibit long range autocorrelations, extending over hundreds of strides [3]. Among different studies, those LRA have been quantified with a Hurst exponent of 0.76 [3], 0.88 [30], 0.9 [29], 0.79 [31, 32] and 0.78 [6].

According to the walking speed, the persistence of stride series follows a U-shaped function, with the minimum at the preferred walking speed (PWS). The stronger persistence for higher and lower velocities reflects a loss of adaptivity and stability. The PWS is determined by biomechanical constraints, the selected velocity minimizes energy consumption. When one moves away from its PWS, he is subject to a "biological stress", reducing its adaptive capabilities [33].

At contrary, reduced persistence is observed in elderly and in people suffering from neurodegenerative disease, like PD and Huntington disease [34]. Concerning PD, the degree of impairment is correlated with the loss of persistence [16]. It must also be noted that the variability is increased, unlike the elderly for those the variability remains unchanged. The lack of persistence is associated with instability, people fail to optimally regulate their gait. Therefore, they are more likely to fall.

We conclude that the level of correlation in gait variability is a key element. Deviations from an optimal level in either direction are a marker of lower adaptive

capabilities [35]. On the one hand, stronger correlations suggest a sub-correction of gait. These are due for example to non-optimal velocities, leading to less degree of freedom for strides corrections. On the other hand, weaker correlations indicate over-correction of gait and are associated with poor health. Due to impaired control, people do not exploit the redundancy of walking enough and therefore spend too much energy in strides corrections.

There is a growing clinical interest of LRA indicators. Currently, the clinical diagnosis is based on the means and standard deviations of the velocity and of the stride durations. Since LRA change significantly with age and disease, this indicator could contribute to the development of an accurate and reliable diagnosis [36]. Moreover, this index help to discriminate fallers from non-fallers, while other measurements do not [37].

## 4.2 Models

Our understanding of the origins of LRA in gait is still limited. Through the interpretation of gait models, one could identify the causes of this pattern. In particular, whether LRA are of biomechanical or neuronal origin is still an open question.

### 4.2.1 CPG-based models

A popular model is the SCPG, the Super Central Patter Generator. CPG are neural networks that are thought to be responsible for the generation of rhythmic movements, due to their oscillatory activity. To end up with the SCPG, CPG-based models have evolved a lot in the last decades, in parallel with the new findings about gait. The basic building block of this model is a simple oscillator, which produces a periodic output. A first attempt to generate strides series with LRA is the *noisy CPG*, described in [3]. The frequency of the oscillator switches randomly at each strides, i.e. a gaussian noise is added to the mean frequency. However, the *noisy CPG* fails to reproduce the correlation structure of human gait. In the same paper, Haudorff et al., present a successful alternative: *the correlated CPG model*. Again, the frequency of the oscillator fluctuates, but according to some rules. Only certain transitions from one frequency to another are allowed, and with a certain probability. This model generates series characterised by a Hurst exponent of 0.75. Nevertheless, the *correlated CPG model* does not address the question of gait altered by age or by diseases.

This issue is solved by the *Neural hopping model*, published in 2001 by Hausdorff and Ashkenazy [34]. The model can be seen as a random walk on a chain of different neural centers, each of them characterized by a different frequency  $f_i$  (Figure 4.1). A step of the random walk from one mode to another represents the "hopping". Frequencies  $f_i$  follow a Gaussian distribution and have short-range correlations. At each stride, there is a jump from one center to another: the jump size follows a Gaussian distribution of width  $C$ . This parameter varies according to the populations:

for stronger persistence of the series,  $C$  is bigger, allowing larger jumps and therefore a wider exploration of the chain. Finally, a low amplitude noise is added to the frequency of the chosen neural center.

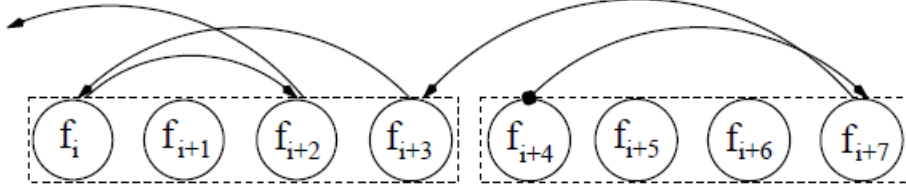


Figure 4.1: Illustration of the neural hopping model. Sequence of four transitions. The frequencies  $f_i$  have short range correlations and the jump size follows a gaussian distribution. [34]

At last, the *SCPG* is presented by West and Scafetta [38]. It is composed of a similar stochastic correlated CPG to that of the *neural hopping model*, coupled to non-linear oscillators. The most important difference is the absence of Gaussian noise at the output of each node. Instead, the series of frequencies generated by the random walk feed a forced Van der Pol oscillator, whose output models the motion of the lower limb. Moreover, West and Scafetta modelled the change of velocity by modifying the strength of correlation among the neural centers.

## 4.2.2 Modelling of the basal ganglia loop

As the basal ganglia degenerations are linked to gait impairments, another modelling approach focuses on the basal ganglia loop. Those models are based on the knowledge of the BG structure and projections (both internal and external). Artificial neural networks directly mimic the neural structure of BG. One layer represents one population of neurons (one substructure of BG). The number of neurons in each layer and the projections between layers are as close as possible to the real structure of BG. Those models are convenient to simulate the changes that arise in PD. Indeed, the decreased dopamine level can be modelled on acting on the connections between neurons [39]. However, those models are not directly linked with gait.

Models of the basal ganglia has also been refined in the last decades. For example, it has been recently discovered that the external globus pallidus was not homogeneous [40]. Such a discovery allows to refine the model by adding new projections and new sub-populations of neurons.

## 4.2.3 Mechanical approach

While the neural origin of LRA seems widely accepted, some argue that the correlation structure might be of biomechanical origins. In their paper published in

2007, Gates et al. [41] presented a pure mechanical model able to reproduce the persistence observed in both healthy subjects and PD patients. They adapted a simple passive walking model [42] composed of two legs connected by a friction-less hip joint. The system weight is represented by two point masses located at the feet and one at the hip. An impulse push-off gives at each step the necessary energy to maintain the movement. This force, applied to the trailing foot, varies from step to step to include motor and sensory noise. Moreover, it is regulated by a proportional feedback controller. By modifying noise levels and feedback gains, a large range of correlation structures were obtained.

The major flaw of this method is the lack of interpretability: it is difficult to translate the model parameters into physiological characteristics. Moreover, there is no unique solution to model gait degradation (for example in PD patients), which suggests different explanations of the changes in the LRA structure.

Although this model reproduces successfully different gait pattern, one cannot deny the supra-spinal influence on the correlation structure. For example, gait becomes more uncorrelated when guided with a metronome [34]. As the low motor neurons, actuators and feedback are the same as in free walking, supra-spinal control is critical in the deterioration of the LRA. Therefore, one can infer that LRA generation could not be only of biomechanical origin.

#### **4.2.4 Model based on optimal control**

In 2010, Dingwell et al. proposed a discrete model based on optimal control [6]. Thanks to a higher level of abstraction, this paper suggests a simple interpretation of the origins of LRA in gait. We will detail this model in the next section and extend it to model the parkinsonian condition, with and without robotic assistance.

# Chapter 5

## Material and methods

### 5.1 Healthy gait

This section introduces the model developed to reproduce the properties of the human gait variability. This model is adapted from a controller proposed by Dingwell et al. (2010) [6]. They simulated series of 512 strides and validated it on healthy subjects walking on a treadmill. The first objective was to reproduce the results of this paper, then to extend it to sequences of 1024 strides.

#### 5.1.1 Data

The experimental data used to validate the model are those collected by Dingwell, available in open access on *Dryad*. The dataset is composed of 34 strides sequences. The experiment involved 17 healthy young adults. Each participant were asked to walk on a treadmill for 5 minutes at a self-selected speed. Each one completed two trials with a 2 minutes break in between. Series length ranges from 248 to 309 strides.

#### 5.1.2 Model

The model is described by a discrete system. Each stride is characterized by two variables, the stride duration and the stride length. Those variables are computed by iteration by the following system:

$$\mathbf{x}_{n+1} = \mathbf{x}_n + G(I + N)\mathbf{u}(\mathbf{x}_n) + \eta \quad (5.1)$$

where  $\mathbf{x}_n$  is the state vector containing  $T_n$ , the stride period and  $L_n$ , the stride length;  $G$  is a diagonal gain matrix;  $I$  is the identity matrix to which  $N$ , a diagonal noise matrix is added. The term  $N\mathbf{u}(\mathbf{x}_n)$  is therefore a command-dependant noise. Finally,  $\eta$  is an additional noise vector. The first (resp. second) non-zero term of  $N$  and the first (resp. second) term of  $\eta$  follow a zero-mean Gaussian distribution of variance  $\sigma_1$  (resp.  $\sigma_2$ ). The index  $n$  indicates the stride number.

This system can be interpreted as follows: each stride ( $x_{n+1}$ ) is equal to the previous stride ( $x_n$ ), to which motor noise ( $N\mathbf{u}(\mathbf{x}_n)$ ) and perceptual noise ( $\eta$ ) are added. A

correction is applied through the command  $\mathbf{u}(\mathbf{x}_n)$  to meet the walker's goal.

The objectives of the walker are represented by the cost function and the command is computed to minimize this cost function. In the context of treadmill walking, the only constraint is to stay on the treadmill. In order to meet this constraint, it is assumed that subjects aim to maintain a constant velocity, equal to that of the treadmill ( $v$ ). Mathematically, it means that the following equation holds at each step.

$$L_n - vT_n = 0 \quad (5.2)$$

This objective function leaves room for some variability as several pairs  $[T, L]$  lead to the same velocity. In the T-L plane, all these pairs form a straight line, called the Goal Equivalent Manifold (GEM). However, a specific pair  $[T^*, L^*]$  is naturally chosen by subjects as the Preferred Operating Point (POP). This pair is determined by the minimization of energy consumption and depends on biomechanical characteristics such as length of the legs and inertia. A control is therefore applied to stay close to this point. Considering the objective on the velocity and on the POP, the cost function is given by:

$$C = \alpha e^2 + \beta p^2 + \gamma u_1^2 + \delta u_2^2 \quad (5.3)$$

The first term penalizes the error on the velocity, with  $e^2 = (L - vT)^2$ . The second term concerns the distance from the POP, with  $p^2 = (T - T^*)^2 + (L - L^*)^2$ . The third and fourth terms penalize the command,  $u_1$  (resp.  $u_2$ ) being relative to the correction applied to  $T$  (resp.  $L$ ).

Finding the optimal command is a classic linear-quadratic-gaussian (LQG) control problem. The system described in Equation 5.1 is linear and corrupted by Gaussian noises and the cost function is quadratic. The LQG framework provides an output, namely the command, optimal in the sense that it minimizes the expected value of a quadratic cost criterion.

We consider this system to be fully observable, i.e. at each step the exact state is known and not estimated from noisy information. In that case, as developed by Todorov [43], the system described in Equation 5.4 has as optimal solution the command in Equation 5.5.

$$\begin{aligned} \mathbf{x}_{n+1} &= A\mathbf{x}_n + B\mathbf{u}_n + \epsilon_n C\mathbf{u}_n + \eta \\ \text{Cost per step} &= x_n^T Q_n x_n + u_n^T R u_n \end{aligned} \quad (5.4)$$

$$\begin{aligned} u_n &= -K_n x_n \\ K_n &= (R + B^T S_{n+1} B + C^T S_{n+1} C)^{-1} B^T S_{n+1} A \\ S_n &= Q_n + A^T S_{n+1} (A - B K_n); \quad S_N = Q_N \end{aligned} \quad (5.5)$$

As the system here is time-invariant, the feedback gain  $K_n$  is constant and found by solving Equation 5.6 [44].

$$\begin{aligned} K &= (R + B^T S B + C^T S C)^{-1} B^T S A \\ S &= Q + A^T S A - (A^T S B)(R + B^T S B + C^T S C)^{-1} B^T S A \end{aligned} \quad (5.6)$$

The main difference with the paper of Dingwell (2010) concerns the command computation. While the model introduced above aims at finding the optimal command, the model of Dingwell relies on a sub-optimal command to over-correct the velocity error. Indeed, the command is first computed with  $G$  (Equation 5.1) equal to the identity matrix. Then, a gain ( $G = 1.24I$ ) is applied to this command to compute next states.

Table 5.1 presents a summary of the parameters used for the simulations. In addition, the initial state is set to the target state.

| Parameter         | Dingwell's model                                                                                                                                | Adapted model                                     |
|-------------------|-------------------------------------------------------------------------------------------------------------------------------------------------|---------------------------------------------------|
| G                 | $\begin{bmatrix} 1 & 0 \\ 0 & 1 \end{bmatrix}$ for command computation<br>$\begin{bmatrix} 1.24 & 0 \\ 0 & 1.24 \end{bmatrix}$ for state update | $\begin{bmatrix} 1 & 0 \\ 0 & 1 \end{bmatrix}$    |
| $\sigma_1$        | 0.01                                                                                                                                            | 0.01                                              |
| $\sigma_2$        | 0.017                                                                                                                                           | 0.017                                             |
| $\alpha$          | 10                                                                                                                                              | 30                                                |
| $\beta$           | 2.79                                                                                                                                            | 1                                                 |
| $\gamma = \delta$ | 10                                                                                                                                              | 10                                                |
| $v$               | $1.21 \left[ \frac{\text{m}}{\text{sec}} \right]$                                                                                               | $1.21 \left[ \frac{\text{m}}{\text{sec}} \right]$ |
| $T^*$             | $1.105 \text{ [sec]}$                                                                                                                           | $1.105 \text{ [sec]}$                             |
| $L^*$             | $vT^* \text{ [m]}$                                                                                                                              | $vT^* \text{ [m]}$                                |

Table 5.1: Values of the parameters of the models for a healthy subject

Each model will be used to generate 20 series of 1024 strides. Each simulation generates a stride duration series  $T[n]$ , a stride length series  $L[n]$  and velocity series  $S[n]$ . The mean, the standard deviation and the Hurst exponent of each series is computed. Those variables are then averaged over the 20 simulations and compared to experimental results.

## 5.2 Gait altered by Parkinson's disease

Gait degradation is a critical symptom of Parkinson's disease since it is linked to an increasing risk of falling. This section focuses on the walk pattern of subjects with

PD: what is different compared to healthy subjects, and the physiological reasons of these differences.

To address these questions, experimental data will be first analysed to quantify these changes at different stages of the disease. Then, the model developed for healthy subjects will be adapted to best fit PD condition.

### 5.2.1 Data

The data that were analyzed and subsequently used to build the model were collected by Warlop et al. for a paper published in 2016 [16]. This study includes 20 patients with PD asked to walk overground for 10 minutes at a self-selected speed. For each patient, stride durations were extracted for series of at least 512 strides. In addition, the data provides the state of the disease of each patient, assessed through the H&Y score. Table 5.2 shows the distribution of subjects as a function of the H&Y score.

| H&Y | # subjects |
|-----|------------|
| 1   | 3          |
| 1.5 | 3          |
| 2   | 5          |
| 2.5 | 6          |
| 3   | 3          |

Table 5.2: Distribution of subjects according to the H&Y score

We are interested in the evolution of the standard deviation and the correlation exponent of the strides interval series as a function of the disease progression. We already know from the literature that the variability is increased with PD and that the persistence gets weaker. To quantify those change, the standard deviation and the Hurst exponent of the inter-stride duration series of each subject are computed. Then those values are plotted against the H&Y score of the patient. A linear regression is drawn to fit these points in order to outline the evolution of those variables according to the disease's stage. The model will then be adapted to fit the values given by this regression. Moreover, the correlation between those variables and the disease's stage is assessed through the Spearman's coefficient.

In the article of Warlop [16], the Hurst exponents were computed using evenly spaced DFA with overlapping intervals. In contrast, we used here non-overlapping intervals, as described in section 3.2.2, for the sake of consistency with the rest of the analysis. We can therefore expect slightly different results.

## 5.2.2 Model

The parameters of the model must be adjusted to fit the values given by the regression found with the experimental data.

We expect a higher level of variability and a lower degree of persistence (Chapter 4). Therefore, at first, to reflect the increased variability, noise is added to the system. In practice, we simply amplify by a factor  $\xi$  the additive noise  $\eta$ :

$$\mathbf{x}_{n+1} = \mathbf{x}_n + G(I + N)\mathbf{u}(\mathbf{x}_n) + \xi\eta \quad (5.7)$$

We are able to quantify, or at least approximate, the variability increase of stride duration sequences ( $T$ ) for each stage of the disease thanks to experimental data. However, we have no information concerning the variability of stride length series ( $L$ ). Therefore, it is assumed that both variables evolve the same way with the disease. Then, both components of the noise will be amplified by the same factor. If the variability of stride duration increases, it is likely that variability of stride length increases too. The origins of this supplementary noise will be discussed in Chapter 7.

Next, the decline in persistence is handled through the modification of the control gains. Indeed, it is discussed in [6] that stronger control over a variable leads to less error persistence. This principle is applied to Parkinson's condition:  $\beta$ , weighting the error over  $T^*$  and  $L^*$ , is increased to reduce the persistence of both  $T$  and  $L$  series. Again, as we have no experimental data of  $L$  series, it is assumed that its persistence evolves in a similar way to that of the  $T$  series.

It must be noted that increasing the variability in the system has also a slight effect on the persistence and increasing the control through  $\beta$  reduces the variability. We must therefore consider the parameters conjointly rather than independently.

The regressions drawn among the experimental data will indicate the values to approach for each H&Y score. In order to select the best parameters for each stage of the disease, several combinations of values of  $\beta$  and  $\xi$  have been systematically tested. The multiplicative factor  $\xi$  has been discretized from 1 to 4 by step of 0.1 and  $\beta$  has been discretized from 1 to 10 (by step of 0.1 from 1 to 5, then by step of 1). For each pair of parameters, 100 sequences of 1024 strides have been generated. The mean standard deviation ( $std$ ) of the stride duration series and their mean Hurst exponent ( $H$ ) have been compared with the reference values ( $std^*$  and  $H^*$ ). The selected parameters are those minimizing the error as expressed in the following equation:

$$\xi, \beta = \underset{\xi, \beta}{\operatorname{argmin}} \left[ \left( \frac{std - std^*}{std^*} \right)^2 + \left( \frac{H - H^*}{H^*} \right)^2 \right] \quad (5.8)$$

## 5.3 Robot-assisted gait

The robot-assisted gait training has shown interesting effects on the gait of PD patients and might be used for rehabilitation purposes [45]. This section introduces the APO, a device initially designed for transfemoral amputees and which has never been tested on PD patients. Through the integration of the APO in the gait model, we could predict its impact on patients and potentially support its benefits.

### 5.3.1 APO

The devices currently used for robot-assisted gait training have some disadvantages: they do not allow walking in an ecological environment, they steer the movement of the patient’s legs, and they do not encourage the patient to actively participate in the task, since they provide them with a strong assistance. The APO described in details in Giovacchini et al. [5], addresses these drawbacks. It is a light-weight, wearable exoskeleton which provides active assistance for the hip flexion-extension movement. The control of the orthosis is designed to provide an “assistance-as-needed” to the patient. It means that the patient participates actively to the movement, the effort is promoted. Furthermore, there is no predefined trajectories, the robot adapts to the user’s intentions in real time. To fulfill these requirements, the control is based on an algorithm presented by Ronsse et al [46], which relies on the use of adaptive oscillators (AOs).

AOs are a mathematical tool introduced by Righetti et al [47], capable to learn the frequency, amplitude and offset of a periodic quasi-sinusoidal input signal, in this case the hip position, in dedicated state variables. It can therefore anticipate the evolution of these state variables in real-time. When the main features of the input signal slowly change, it produces an error signal computed as the difference between the estimated state and the actual state. From this error signal, the oscillator learns the new signal characteristics, and synchronizes its output. AOs act like a low-pass filter to smooth the input signal [48].

In gait, the input signal (lower-limb position) is periodical but no longer sinusoidal. Since the signal is periodic, we can derive an estimate from its Fourier decomposition. Several oscillators must be put in parallel, such as each one of them learns one frequency component of the signal [46].

In the APO, the assistance torque is computed thanks to an inverse model[46]. The future value of the hip position is estimated through the AOs. Then, the inverse model is used to compute the expected torque of the hip, part of which will be supplied by the robot[5]. This fraction characterized the robot stiffness. The more the robot participates in the movement, the stiffer it is.

A major advantage of this method is that it only requires to measure the joint position to get the user’s intention, unlike methods based on the EMG. Moreover, no reference trajectory needs to be specified. The only a-priori knowledge embedded

to the controller is the assumption that lower-limb movement is periodic [48]. The APO adapts to the patient's will, while helping them to have a smoother walk .

### 5.3.2 Model

As the orthosis has a low-pass filter effect, it can be modelled as a :

$$\begin{aligned}
\mathbf{x}_{n+1} &= \mathbf{x}_n + (I + N)\mathbf{u}(\mathbf{x}_n) + \xi\eta - \lambda(\mathbf{x}_{n+1} - \mathbf{x}_n) \\
(1 + \lambda)\mathbf{x}_{n+1} &= (1 + \lambda)\mathbf{x}_n + (I + N)\mathbf{u}(\mathbf{x}_n) + \xi\eta \\
\mathbf{x}_{n+1} &= \mathbf{x}_n + (1 + \lambda)^{-1}((I + N)\mathbf{u}(\mathbf{x}_n) + \xi\eta) \\
\text{where } \lambda &= \begin{bmatrix} \lambda_1 & 0 \\ 0 & \lambda_2 \end{bmatrix}
\end{aligned} \tag{5.9}$$

The parameter  $\lambda$  represents the level of assistance of the orthosis, with  $\lambda_1$  the filter strength on the state variable  $T$  and  $\lambda_2$  on  $L$ . Higher values correspond to a higher degree of assistance.

For the first set of simulations, it is assumed that the patients adapt their control to the orthosis. It means that the motor command computation takes into account the filter and is optimal in the sense of the system described by Equation 5.9. For each H&Y score, the level of assistance required to recover healthy level of variability is computed. In other words, we search for the optimal  $\lambda$  so that the average variability of the  $T$  series is as close as possible to that of healthy subjects. For this purpose, 36 values of  $\lambda$  between 0 and 3.5 have been tested, with 20 strides simulation for each value. Then, when the optimal  $\lambda$ 's have been found, 20 series are simulated for each H&Y score with the corresponding  $\lambda$ . The mean Hurst exponents and the mean standard deviations across these simulations are extracted.

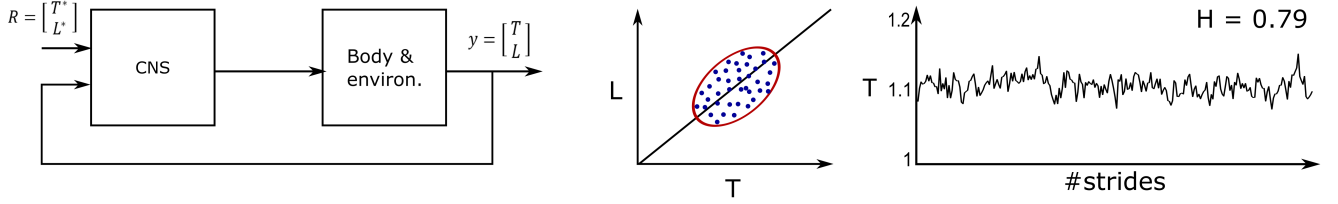
The same process is conducted in a second set of simulation. In that case, we consider that the patients do not adapt to the orthosis. Then, the command computation is based on the system described by Equation 5.7.

A second question is whether the filter is applied to both variables, only the stride length or only the stride frequency. We consider at first that the filter is applied to both  $T$  and  $L$ , with the same strength, i.e.  $\lambda_1 = \lambda_2 > 0$ . Next, we compare these results with those obtained when the APO acts only on the stride frequency, i.e.  $\lambda_1 > 0$  and  $\lambda_2 = 0$ ; or when it acts only on the stride length, i.e.  $\lambda_1 = 0$  and  $\lambda_2 > 0$ . For each scenario we simulate 20 series for each H&Y score, with the values of  $\lambda$  found under the assumption that the patients do adapt to the orthosis.

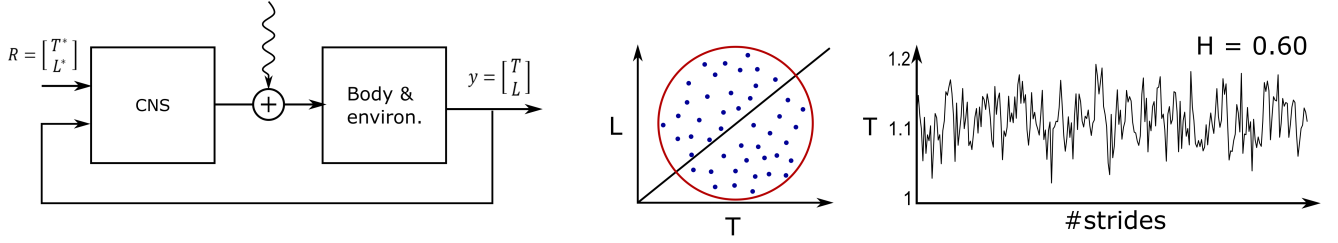
## 5.4 Block Diagram

Figure 5.1 provides a schematic presentation of the models in the cases of healthy gait, altered gait by PD and gait of patients assisted by the APO. To illustrate, the general stride distribution and an example of a series are provided.

### Healthy gait



### Altered gait, PD (H&Y = 2.5)



### Assisted gait

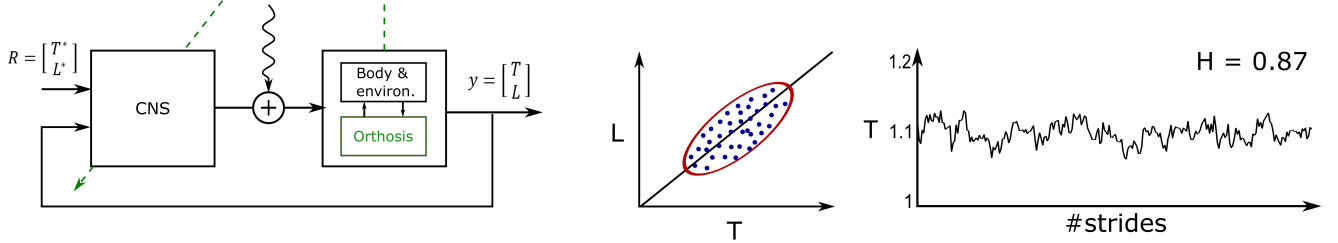


Figure 5.1

We first consider the case of healthy gait. The central nervous system (CNS) receives as input the target strides characteristics  $T^*$  and  $L^*$  that arise from the target speed. Moreover, the actual values of  $T$  and  $L$  are fed back to the CNS. Thanks to these information, this block computes the optimal command sent to the body, the second block. According to this command and to the system characterized by the body and by the possible external disturbances, the following stride is generated. This stride is sent back to the CNS and the loop start again.

In middle panel, we represented the schematic stride distribution. In healthy gait, the strides (blue dots) are distributed along the GEM (black line) and form an ellipse, whose center is the POP. Recall that the GEM is the line formed by the T-L pairs

with which the target speed is obtained. The control applied on the speed pushes the points close to the GEM; the control applied on the POP brings the points closer to the POP. Therefore, the elliptical shape in healthy gait is due to a high control to the velocity and a low control on the POP. This low control give rise to LRA in series of inter-stride duration like the one represented in the top right panel, with a Hurst exponent around 0.8.

In gait altered by PD, noise is added to the command that comes from the CNS to the body. It results in a greater dispersion of the strides in the T-L plane and in higher fluctuations in the stride series. Moreover, the control gain on the POP is increased, which gives a more circular shape to the distribution of strides. In the series shown in the middle left panel, the strides duration are more random, testifying a lower correlation exponent.

Finally, the robotic assistance acts directly on the body. The CNS is aware of the changes it makes and adapts the control. From Equation 5.9, it appears that the noise is reduced. Therefore, the strides distribution is less spread out. The command is impacted by the same factor. We see from the bottom right panel that the persistence is stronger than the one of the healthy gait ( $H = 0.87$  versus  $H = 0.79$ ). In the T-L plane, this is manifested by a narrower and longer elliptic distribution along the GEM.

# Chapter 6

## Results

### 6.1 Healthy gait

In this section, we will first compare the results of the simulations with the experimental data to validate our model. Next, we will analyse the effect of some parameters on these results.

#### 6.1.1 Comparison with human experimental data

The results of both models, compared to human data, are represented in Figure 6.1.

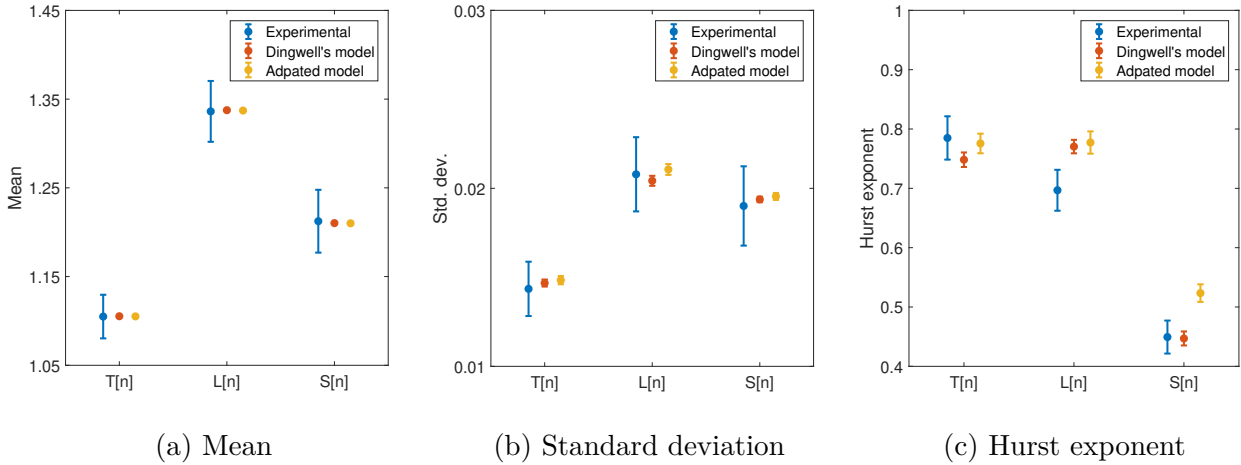


Figure 6.1: Comparison of a) the mean values, b) the standard deviations, and c) the Hurst exponent of the inter-stride duration  $T$ , length  $L$  and velocity  $S$ , between experiment data (in blue) and simulated data (in red). Dots represent the mean value across 20 simulations and the vertical bars represent the 95% confidence interval.

By construction, the means fit exactly their experimental corresponding data, since it is set as the goal function. The variability is also very similar to the human data for  $T$ ,  $L$  and  $S$  and for both models. Also, these ones succeed to reproduce a relatively strong persistence of  $T$  and  $L$  series.

However, experimental data suggest that velocity is slightly antipersistent ( $H < 0.5$ ). The model of Dingwell reproduces this behavior through the use of a sub-optimal command. On the other hand, with a high optimal control of the velocity (high  $\alpha$ ), this variable is no longer anti-persistent but is close to random noise.

### 6.1.2 Impact of the weights of the cost function

The control gain  $\alpha$  and  $\beta$  (Eq. 5.3) may have a significant impact on the results of the simulation. The effects on the variability and on the persistence are studied in this section. These parameters represent the relative importance of the error on the velocity and on the preferred point  $[T^*, L^*]$  respectively, balanced with the penalty given to a high corrective command. The higher the importance of the error, the stronger the control. Results of the analysis are presented in Figure 6.2.

The stride period and stride length sequences show similar evolution, regarding the magnitude of the variability and the statistical persistence (Figures 6.2a, 6.2c, 6.2b and 6.2d). The standard deviation and the persistence increase with lower values of  $\beta$  but the impact of  $\alpha$  is limited. Indeed,  $\beta$  weights the distance to the preferred point, regulating directly the length and the period of the stride. A high weight gives more penalty on this term and reduces the persistence of the error.

Concerning the velocity, the variability (Figure 6.2e) and the persistence (Figure 6.2f) are higher when both  $\alpha$  and  $\beta$  are small, i.e., when the control on both the velocity and the preferred point is low. When  $\alpha$  is large (yellow, purple and green lines), the impact of  $\beta$  is limited. Indeed, the velocity is already tightly regulated so the increasing regulation of  $T$  and  $L$  has no effect. However, when  $\alpha$  is lower, i.e. when the control on the velocity is weaker,  $\beta$  has a more crucial role. Through the regulation of  $T$  and  $L$ , the speed is also constraint. By approaching the preferred point, we also approach the target speed, since the speed is expressed as  $\frac{L}{T}$ .

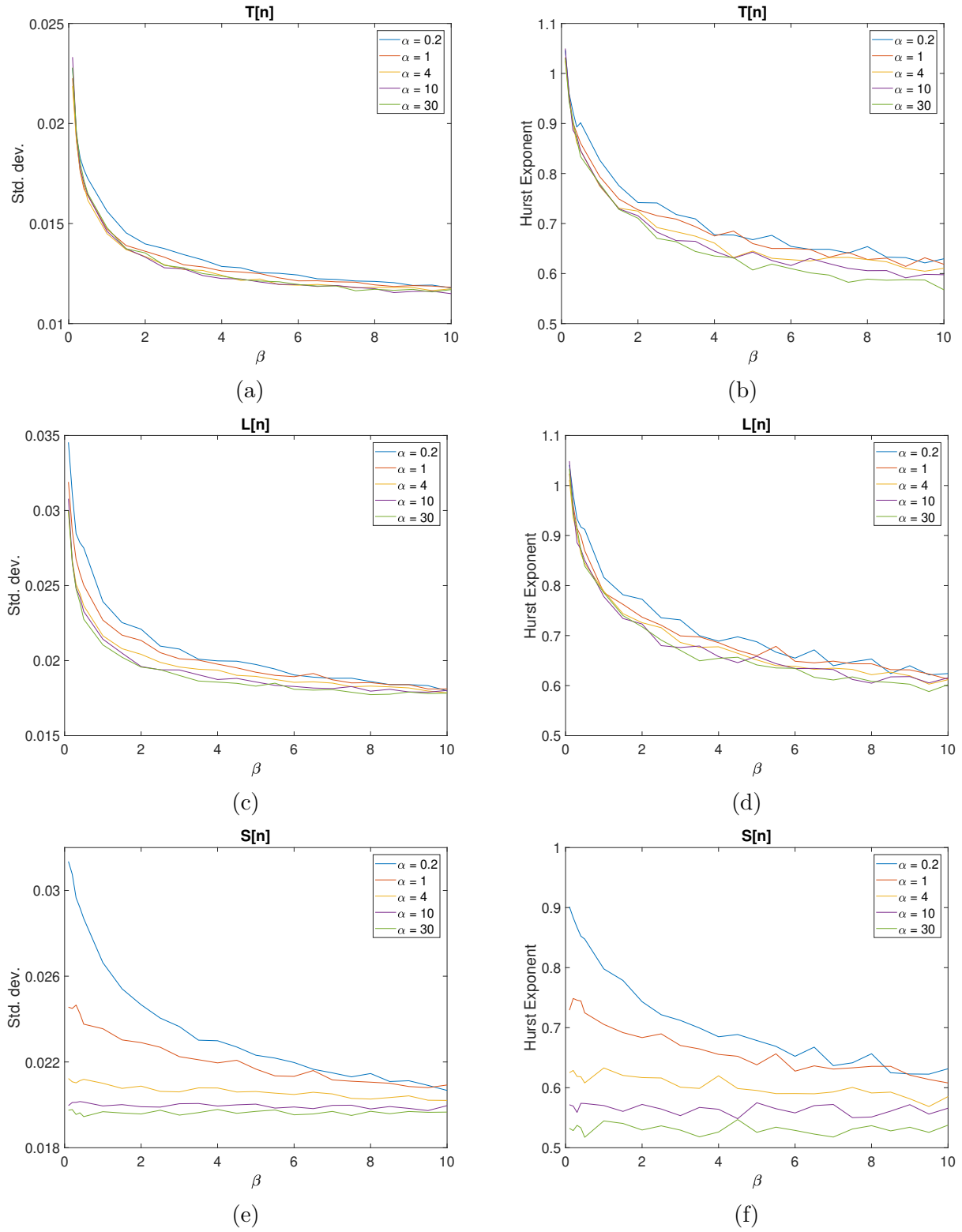


Figure 6.2: Evolution of (a,b) the stride period, (c-d) the stride length, and (e-f) the velocity as a function of beta. Each line correspond to a different value of alpha. For these simulations,  $\gamma = \delta = 10$ .

## 6.2 Gait altered by Parkinson's disease

### 6.2.1 Data analysis

The evolution of the strides characteristics is outline in Figure 6.3. Each point represents one subject. In Figure 6.3a (resp. Figure 6.3b), its x-position depends on the progress of the disease, while its y-position depends on the observed variability (resp. LRA exponent) in the inter-strides duration series. These results are approximate with the regression lines in red. First, it confirms that the variability increases and the persistence decreases in patients with PD, compared to control healthy subject. However, patients in the first stage of the H&Y scale exhibit gait characteristics similar to healthy patients.

Furthermore, the gait alterations are progressive. The variability is correlated with the H&Y score with a Spearman's coefficient of 0.50. Concerning the persistence, the coefficient is equal to  $-0.63$ . This latter is lower than the one found by Warlop. Those coefficient being relatively high, we can conclude that the disease stage is relevant to the variability of stride duration series and to the temporal organisation of this variability.

We also notice that gait is not significantly altered in patients at stage 1 of the disease, compared to healthy subjects. According to the linear regression, persistence is even stronger. Since we observe no notable difference, parameters for the population with this H&Y score will remain unchanged.

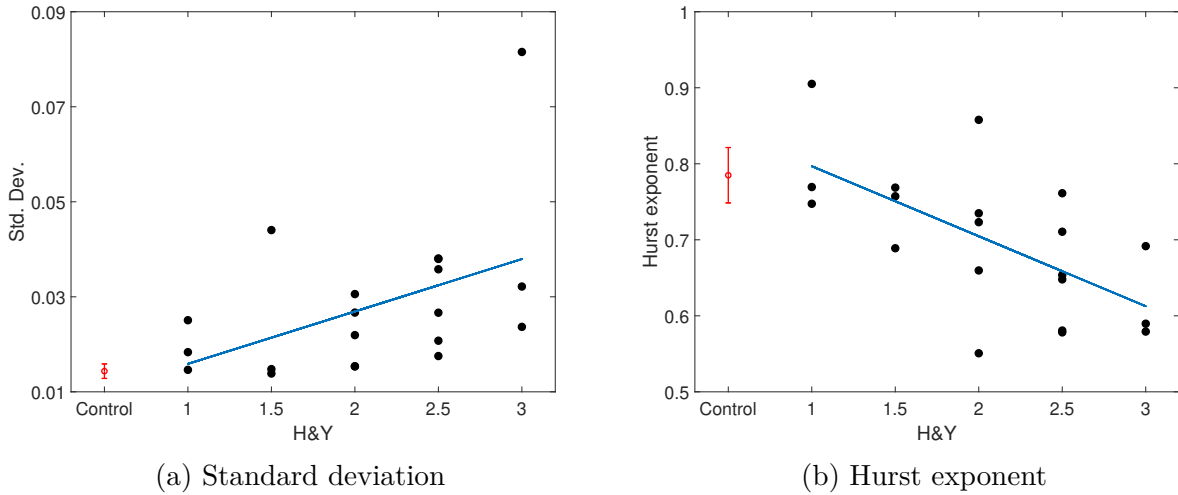


Figure 6.3: Evolution of a) the standard deviation and b) the Hurst exponent of the inter-stride duration with the Parkinson's disease stage assessed through the H&Y score.

## 6.2.2 Model parameters fitting

Next, we need to find the parameters so that the simulation results match the regressions drawn in Figure 6.3. From all the parameters tested in the optimization process, optimal parameters are summarized in Table 6.1, for each stage of the disease and for healthy subjects. Both  $\beta$  and  $\xi$  increase with the H&Y score.

| H&Y score | $\beta$ | $\xi$ |
|-----------|---------|-------|
| Control   | 1       | 1     |
| 1         | 1       | 1     |
| 1.5       | 1.2     | 1.5   |
| 2         | 1.85    | 2     |
| 2.5       | 3       | 2.5   |
| 3         | 6       | 3.2   |

Table 6.1: Model parameters in different stage of PD

As shown in Figure 6.4, these parameters produce stride sequences which, on average, meet the variability and persistence requirements. Stage 1 is the only exception, since we chose not to optimize the model parameters, due to the high similarity to healthy gait characteristics.

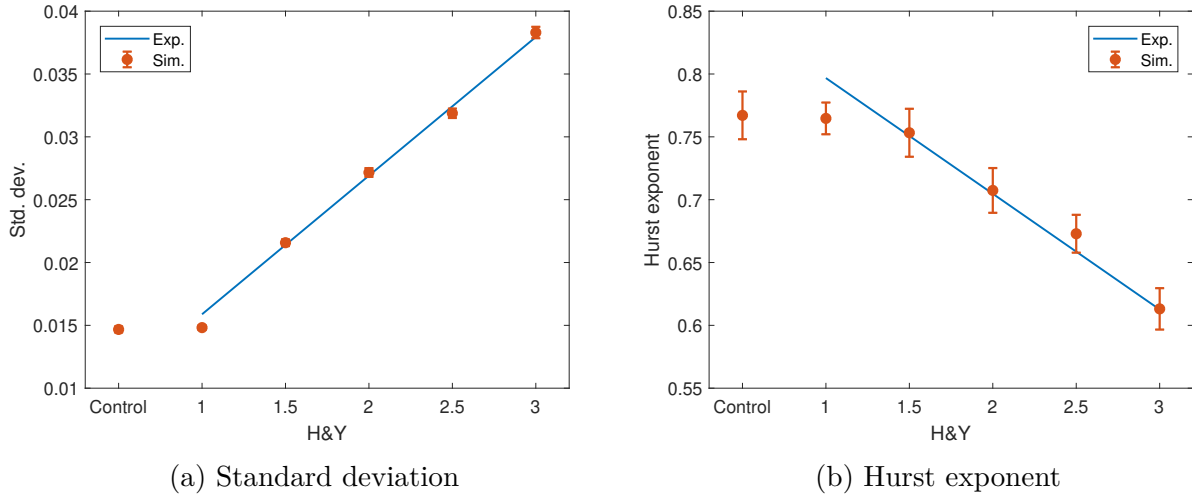


Figure 6.4: Simulation of inter-stride duration in patients with different stages of Parkinson's disease. Comparison of a) the standard deviation and b) the Hurst exponent of the simulated sequences (red dots) with with the regression line obtained through experimental data (in blue).

### 6.3 Robot-assisted gait

As stated in Section 5.3.2, the values of the parameter  $\lambda$ , representing the level of robotic assistance, have been selected according to a variability criteria. The optimal values are summarized in Table 6.2.

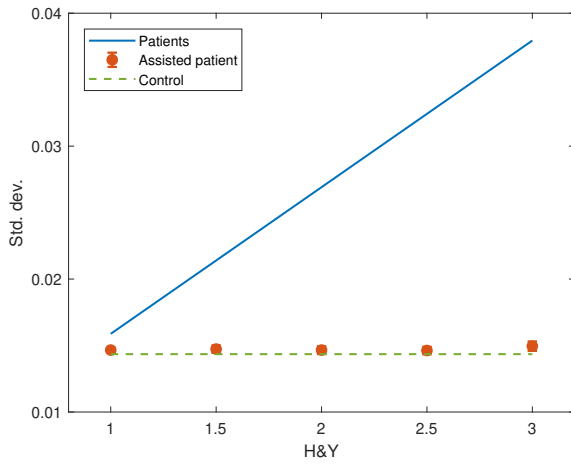
| <b>H&amp;Y</b> | $\lambda_{1,2}$<br><b>with adaptation</b> | $\lambda_{1,2}$<br><b>without adaptation</b> |
|----------------|-------------------------------------------|----------------------------------------------|
| 1              | 0                                         | 0                                            |
| 1.5            | 0.7                                       | 0.7                                          |
| 2              | 1.4                                       | 1.5                                          |
| 2.5            | 2                                         | 2.3                                          |
| 3              | 2.5                                       | 3.3                                          |

Table 6.2: Value of the APO parameter for different disease's stage, with and without the adaptation of the patient to the APO

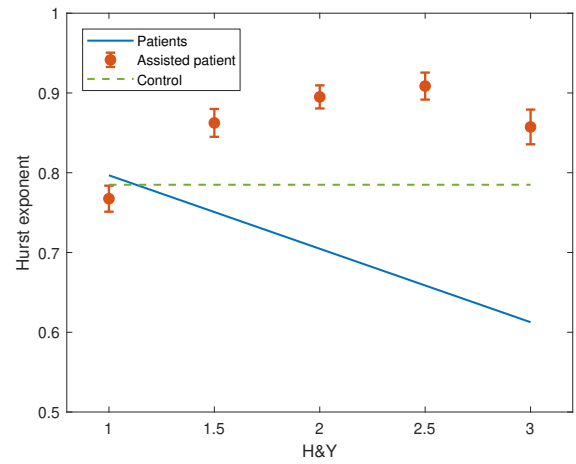
Two scenarios are under analysis, either the user adapts his motor control to the APO or he does not. In both case, as expected, the more the disease progresses (higher H&Y), the higher the level of assistance (higher  $\lambda$ ). We also observe that the level of assistance required to recover healthy levels of gait variability is higher if the patient does not adapt to the APO. Lastly, we stress that it is not necessary to provide assistance for patients at the first stage of PD ( $\lambda = 0$ ).

These values of  $\lambda$  produces strides series of mean standard deviations and mean Hurst exponent represented in Figure 6.5 (case 1: the patient adapts his control) and in Figure 6.6 (case 2: the patient does not adapt his control).

In both scenarios, the APO reduces gait variability and increases the Hurst exponent of stride duration series. The variability of assisted patients fits perfectly the one of healthy subjects. Since it was the only criteria for  $\lambda$  optimization, one could expect this result. In contrast, the levels of persistence go beyond the healthy levels, in particular when the patients do not adapts. In the most extreme case (no adaptation, H&Y = 3 ), the mean Hurst exponent is almost 1, the upper limit value of LRA.

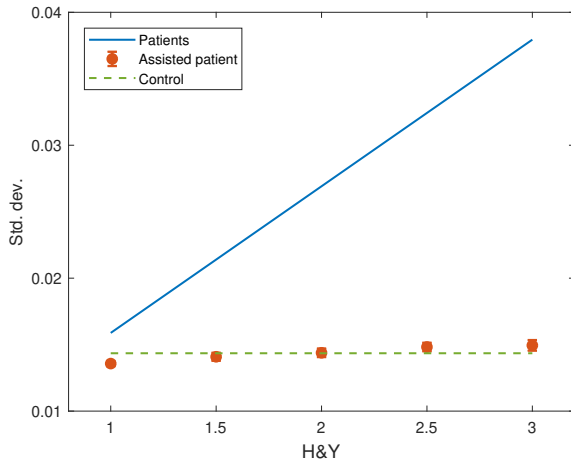


(a) Standard deviation

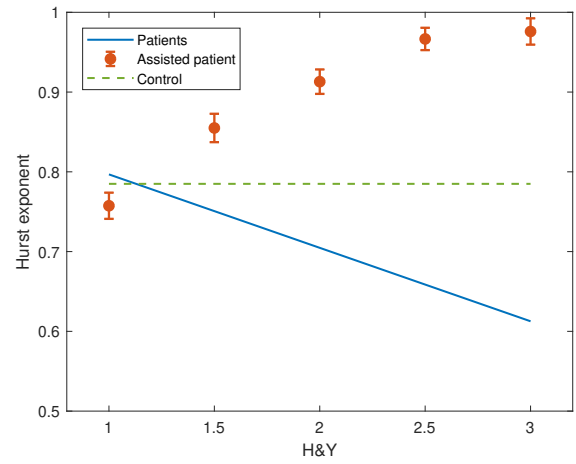


(b) Hurst exponent

Figure 6.5: Simulation of the effect of the APO on inter-stride duration series of patients, in case of patient adaptation to the orthosis. Comparison of a) the standard deviation and b) the Hurst exponent of the simulated data (red dots) to non-assisted patients (blue line) and healthy subjects (green line)



(a) Standard deviation



(b) Hurst exponent

Figure 6.6: Simulation of the effect of the APO on inter-stride duration series of patients, in case of no adaptation from the patient to the orthosis. Comparison of a) the standard deviation and b) the Hurst exponent of the simulated data (red dots) with non-assisted patients (blue line) and healthy subjects (green line)

Finally, Figure 6.7 presents the comparison of the Hurst exponents of the stride duration obtained with different variables impacted by the filter.

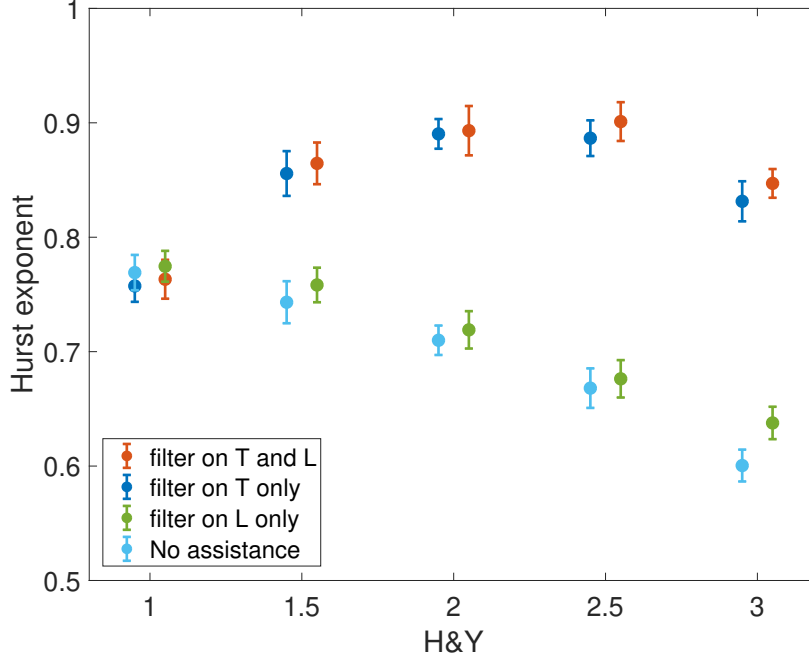


Figure 6.7: Comparison of the Hurst exponent of inter-stride duration sequences of patients with robotic assistance, in case the robot filters 1) both the stride duration and length (dark blue), 2) only the stride duration (red), 3) only the stride length (green) and 4) no robot assistance (light blue)

It appears that the persistence of the  $T$  series is not significantly increased when the APO only acts on the length of the strides, in comparison with a situation of non-assistance. The Hurst exponent of the stride duration series is only increased if the APO acts directly on the cadence, regardless of whether the APO acts on  $L$  or not. Still, there is a small decline if the APO only filters the stride duration.

# Chapter 7

## Discussion

### 7.1 Healthy gait

The model succeed to reproduce gait fluctuation, in terms of standard deviation and statistical persistence.

#### 7.1.1 Model interpretation

This model provides a simple interpretation. LRA in gait variability is simply due to a limited control on the stride durations and stride lengths. Errors on the POP are tolerated within a certain range, as long as the speed remains relatively constant. The correlation structure of one series depends on how important the errors are. If the cost of the correction is dominant compared to the benefit of having a no error, then the error will "persist". The command sent to correct the error will be low to balance the high control gain. Therefore, if we take a look at Equation 5.1, the stride will mainly depend on the previous one and trends will appear in the stride series. At contrary, if errors are highly penalized (like the velocity), they will be systematically corrected. In that case, the term  $\mathbf{x}_n + \mathbf{u}(\mathbf{x}_n)$  will be almost constant and the stride fluctuations are only due to noise.

This is confirmed by the results of the analysis done in section 6.1.2. We observed that, all variables included, when we increase the control gains  $\alpha$  or  $\beta$ , the persistence of the corresponding series is reduced.

#### 7.1.2 Model limitations

The simplicity of the model presents the advantage to provide a straight-forward interpretation. But as a consequence, this model has several limitations. First, only fluctuations around the mean behavior are modelled. It is assumed that the target speed is the PWS and remains constant during the whole walking session. In addition, no explanation is given for the choice of this speed. This assumption is valid for treadmill walking, as the velocity is set by the treadmill and does not change, but it is harder to apply to overground walking. Changes in velocity could have an

impact on the variability. It is known that the PWS is the velocity minimizing the variability in gait [33]. However, in our model, target velocity is decorrelated from the fluctuations regulation. Any change to this parameter will have no impact on the variability or the persistence in the stride series.

Next, the model is discrete. It is not intended to describe the full dynamics within each stride, rather the net effect on the inter-stride dynamics. While this model describes a discrete control, it is thought that humans have online control on gait. It is therefore difficult to establish a link between the model and physiological structures.

## 7.2 Gait altered by Parkinson’s disease

### 7.2.1 Data limitation

First of all, we question the reliability of the values taken as references to adjust the healthy model. These are taken from the regression plotted from the experimental data.

First, due to a methodological difference for the estimation of the Hurst exponent, those results are slightly different from those reported by Warlop [16]. While Warlop proceed to the DFA with overlapping intervals, we used non-overlapping intervals. In the literature, it is often specified to use non-overlapping intervals [22, 25, 21]. However, to our knowledge, no clear arguments has been reported to justify this choice, thus not excluding that both methods are valid.

Then, the use of the H&Y score could be misleading. This indicator is not directly related to gait. Moreover, it classifies patients in broad categories. Some patients could have the same H&Y score but relatively different gait characteristics.

Finally, we must keep in mind that this regression is constructed from the data of only 20 patients. For some H&Y score, only three strides series were available. Additional data could modify this regression and could even show a non-linear evolution. In this case, in the absence of a clear trend, the more obvious choice was the linear regression.

All these aspects lead us to question the reliability of the regression line that the model aimed to fit, but the quantitative values are not really the subject. These data allow us to sketch an evolution of the walking characteristics. This qualitative analysis is sufficient to draw some interesting conclusions about gait disorders in PD.

### 7.2.2 Model interpretation

Two main parameters change compared to the healthy gait model: the amplitude of noise in the system (through the factor  $\xi$ ) and the weight of the error over the POP in the cost function ( $\beta$ ). We will discuss in this section the possible physiologic origins of these changes.

In particular, the model does not explain why variability increases. Indeed, this element is modelled through an input value of the model, rather than a consequence of any change. A first hypothesis is to relate the variability increase to a reduced velocity. PD patients generally walk slower than healthy subjects. It is also known that healthy subjects naturally select the speed which minimizes the energetic cost, and therefore the variability. Consequently, one could argue that if patients walk slower for some reasons, they move away from their optimal speed and the variability increases. However, several studies reject this hypothesis and claim that velocity decline is not correlated to the variability increase or only partially [30, 49, 50]. For example, older people walk more slowly but such an increase in variability is not observed [51].

The reduced gait speed is actually a typical example of movement slowing (bradykinesia), a well known symptom of Parkinson’s disease. It is explained as a higher sensibility to energetic cost. For PD patients, fast and large movements are associated with higher energy expenditure than they really are. In fact, capacities are intact, patients are able to perform normal movement if they are asked to, but they will be less likely to do so if they have no specific instruction. In 2007, Mazzoni et al [12] showed that Parkinson’s patients need more trials to reach the required velocity, but once they do, they have the same accuracy as control subjects. Movement slowing does not compensate any loss of accuracy, but rather respond to energy criteria.

Physiologically, the increased variability might be due to the disruption of the connection between BG and the motor cortex [8]. The lack of dopamine to stimulate the striatum results in less excitation of the cortex. The connection is weakened and more unstable, producing more variable response. We would then consider a noisy command. In the literature, a longer motor preparation is observed in PD patients [52]. If they have the possibility to initiate a movement when they are ready, they will take more time than control subjects[12]. This delay is not possible while walking, as strides follow each other. If the motor preparation is not appropriate, motor command is not optimal and produce more variability. However, walking is an automatic behavior and should involve the cortex in a minimal way.

While the causes of the variability increase remain unclear, it is very likely that the persistence decrease results from a strategy to compensate the variability increase. Patients would pay more attention to regulate not only the velocity, but also stride duration and stride length. In the model, this is equivalent to increase the weight ( $\beta$ ) of the error over the POP in the cost function. Several elements support this hypothesis.

First, we observe a decrease in automaticity in patients. The movement, normally automatic, requires a conscious effort. Walking requires more attentional resources and involves higher neural structures [53]. Moreover, gait is highly impacted when patients have to execute another task while walking[54]. The attentional resources are recruited for this second task and gait must relies on the faulty BG.

Secondly, the use of temporal and spatial cues improve gait stability in PD patients [8, 51, 53]. Indeed, using a metronome to set stride frequency or using floor markers to set stride length help patients to reduce gait variability. It can be seen as an element that forces patients to take the compensatory strategy further.

### 7.3 Robot-assisted gait

The purpose of those simulation was to determine if the orthosis would help patients to recover a healthy gait and in what conditions.

First, the APO succeed in reducing the variability to recover levels similar to those of healthy subjects. However, the persistence of the stride durations series is higher than those of healthy subjects. This is particularly true for patients in advanced stages of the disease and under the hypothesis that patients do not adapt their control to the orthosis. It is however reasonable to assume that patients do adapt to the APO, considering that Parkinson's patients adapt successfully their gait to split-belt treadmill [55]. This adaptation is thought to be done within the first 50 strides [56]. However, this could take longer to the specific adaptation to the APO. Further researches would be needed to investigate on the time constant of the adaptation in order to adjust the orthosis rigidity to this time constant. The level of assistance would increase as the patient adapts to it.

It should also be noted that the reference value taken for healthy subject is derived from only 34 experimental stride series. As mentioned in chapter 4, different values have been reported in the literature. Those ranges from 0.76 to 0.9. Values in this range might be acceptable, but indicate an unstable gait beyond.

Next, the results indicate that the orthosis does not necessarily have to act on the stride length to recover healthy correlation structure of the strides duration. However, it would be probably necessary to enhance the stride length series. This stride state variable has not been extensively studied due to the absence of data. However, one might anticipate a similar behavior to the strides duration series. By the definition of AOs, it is clear that the APO smoothes the walking pace but we can also reasonably assume that the stride length are also low-pass filtered.

# Chapter 8

## Conclusion

Due to the population ageing, Parkinson's disease affects more and more people. Gait disorders experienced by these patients can be a significant handicap, as they increase the risk of falling and therefore lead to a loss of autonomy.

Gait is a complex mechanism, involving several neural structures. Locomotion is an automatic behavior, but its regulation is not fully understood. In particular, the stride-to-stride variability exhibits LRA, whose origin is unclear. Therefore, gait models have evolved a lot in the last decades, especially to reproduce the LRA of healthy gait and to adapt to other populations. While some models successfully reproduce different gait pattern, their interpretation might be difficult.

Moreover, we have highlighted the complexity of the analysis of LRA. The existing methods to assess quantitatively the presence and the strength of the persistence can produce biased results. To improve the accuracy, it is suggested to use sufficiently long time series, which is rarely possible in experimental conditions.

The development of a discrete model based on optimal control brought a novel insight on the origins of the LRA in healthy gait variability. The LRA would be simply due to a weak control on the strides duration and on the strides length. In contrast, the control on the velocity is tight and enables a steady gait.

Then, the adaptation of this model to PD patients suggested that the persistence decline observed in this population is due to a reinforced control strategy set up to reduce the increased variability. However, the origin of this additional variability remains unclear. Moreover, data are insufficient to draw any quantitative conclusions.

Finally, the simulations indicate that the APO could help patients to recover healthy gait patterns, provided that they take into account the orthosis in their motor control. By acting as a low-pass filter on gait variables, the APO reduces gait variability and positively acts on the statistical persistence of the strides series. Consequently, gait is more stable and the risk of falling should decrease. In the future, those promising predictions will have to be validated on subjects.

# Bibliography

- [1] Julie Duqué and Marcus Missal. Liepr1024: Fondements neurophysiologiques et neuropsychologiques de l'apprentissage et du contrôle moteur. Class lecture.
- [2] Yashar Sarbaz, Shahriar Gharibzadeh, Farzad Towhidkhah, Masood Banaie, and Ayyoob Jafari. A gray-box neural network model of parkinson's disease using gait signal. *Basic and Clinical Neuroscience*, 2(3):33–42, 2011.
- [3] Jeffrey M Hausdorff, CK Peng, ZVI Ladin, Jeanne Y Wei, and Ary L Goldberger. Is walking a random walk? evidence for long-range correlations in stride interval of human gait. *Journal of applied physiology*, 78(1):349–358, 1995.
- [4] Resilient innovation. Les chutes dans la maladie de parkinson. <https://www.walkbyresilient.com/post/chutes-maladie-parkinson>. Accessed: 2021-06-08.
- [5] Francesco Giovacchini, Federica Vannetti, Matteo Fantozzi, Marco Cempini, Mario Cortese, Andrea Parri, Tingfang Yan, Dirk Lefeber, and Nicola Vitiello. A light-weight active orthosis for hip movement assistance. *Robotics and Autonomous Systems*, 73:123–134, 2015.
- [6] Jonathan B Dingwell, Joby John, and Joseph P Cusumano. Do humans optimally exploit redundancy to control step variability in walking? *PLoS Comput Biol*, 6(7):e1000856, 2010.
- [7] Parkinson's foundation. Understanding parkinson's. <https://www.parkinson.org/understanding-parkinsons>. Accessed: 2021-05-15.
- [8] Meg E Morris. Movement disorders in people with parkinson disease: a model for physical therapy. *Physical therapy*, 80(6):578–597, 2000.
- [9] Yashar Sarbaz, Farzad Towhidkhah, Ayyoob Jafari, and Shahriar Gharibzadeh. Do the chaotic features of gait change in parkinson's disease? *Journal of theoretical biology*, 307:160–167, 2012.
- [10] Dale Purves et al. *Neurosciences*. De Boeck, 2005, 3rd edition.
- [11] Inserm. Comprendre la maladie de parkinson. <https://www.inserm.fr/information-en-sante/dossiers-information/parkinson-maladie>, 2015. Accessed: 2021-06-08.

- [12] Pietro Mazzoni, Anna Hristova, and John W Krakauer. Why don't we move faster? parkinson's disease, movement vigor, and implicit motivation. *Journal of neuroscience*, 27(27):7105–7116, 2007.
- [13] Margaret M Hoehn, Melvin D Yahr, et al. Parkinsonism: onset, progression, and mortality. *Neurology*, 50(2):318–318, 1998.
- [14] European Parkinson's Disease Association. About parkinson: Symptoms: rating scales. <https://www.epda.eu.com/about-parkinsons/symptoms/rating-scales/>, 2017. Accessed: 2021-05-15.
- [15] Christopher G Goetz, Barbara C Tilley, Stephanie R Shaftman, Glenn T Stebbins, Stanley Fahn, Pablo Martinez-Martin, Werner Poewe, Cristina Sampaio, Matthew B Stern, Richard Dodel, et al. Movement disorder society-sponsored revision of the unified parkinson's disease rating scale (mds-updrs): scale presentation and clinimetric testing results. *Movement disorders: official journal of the Movement Disorder Society*, 23(15):2129–2170, 2008.
- [16] Thibault Warlop, Christine Detrembleur, Benjamin Bollens, Gaetan Stoquart, Frederic Crevecoeur, Anne Jeanjean, and Thierry Lejeune. Temporal organization of stride duration variability as a marker of gait instability in parkinson's disease. *Journal of rehabilitation medicine*, 48(10):865–871, 2016.
- [17] Stewart A Factor. Current status of symptomatic medical therapy in parkinson's disease. *Neurotherapeutics*, 5(2):164–180, 2008.
- [18] Medtronic. Options de traitements pour la maladie de parkinson. <https://www.medtronic.com/fr-fr/patients/traitements-therapies/maladie-de-parkinson.html>, April 2018. Accessed: 2021-05-15.
- [19] Govindan Rangarajan and Mingzhou Ding. Integrated approach to the assessment of long range correlation in time series data. *Physical Review E*, 61(5):4991, 2000.
- [20] Athanasios Papoulis. *Probability, random variables and stochastic processes*. Macgraw Hill, 2002, 4th edition.
- [21] Jan W Kantelhardt, Eva Koscielny-Bunde, Henio HA Rego, Shlomo Havlin, and Armin Bunde. Detecting long-range correlations with detrended fluctuation analysis. *Physica A: Statistical Mechanics and its Applications*, 295(3-4):441–454, 2001.
- [22] C-K Peng, Sergey V Buldyrev, Shlomo Havlin, Michael Simons, H Eugene Stanley, and Ary L Goldberger. Mosaic organization of dna nucleotides. *Physical review e*, 49(2):1685, 1994.
- [23] Frédéric Crevecoeur, Benjamin Bollens, Christine Detrembleur, and TM Lejeune. Towards a “gold-standard” approach to address the presence of long-range auto-correlation in physiological time series. *Journal of neuroscience methods*, 192(1):163–172, 2010.

- [24] Didier Delignieres, Sofiane Ramdani, Loïc Lemoine, Kjerstin Torre, Marina Fortes, and Grégory Ninot. Fractal analyses for ‘short’ time series: a re-assessment of classical methods. *Journal of mathematical psychology*, 50(6):525–544, 2006.
- [25] Zainy MH Almurad and Didier Delignières. Evenly spacing in detrended fluctuation analysis. *Physica A: Statistical Mechanics and its Applications*, 451:63–69, 2016.
- [26] Sandro Rambaldi and Ombretta Pinazza. An accurate fractional brownian motion generator. *Physica A: Statistical Mechanics and its Applications*, 208(1):21–30, 1994.
- [27] Clément Roume, Samar Ezzina, Hubert Blain, and Didier Delignieres. Biases in the simulation and analysis of fractal processes. *Computational and mathematical methods in medicine*, 2019, 2019.
- [28] Joshua J Liddy and Jeffrey M Haddad. Evenly spaced detrended fluctuation analysis: Selecting the number of points for the diffusion plot. *Physica A: Statistical Mechanics and Its Applications*, 491:233–248, 2018.
- [29] Kimberlee Jordan, John H Challis, and Karl M Newell. Long range correlations in the stride interval of running. *Gait & posture*, 24(1):120–125, 2006.
- [30] Jeffrey M Hausdorff, Susan L Mitchell, Renee Firtion, Chung-Kang Peng, Merit E Cudkowicz, Jeanne Y Wei, and Ary L Goldberger. Altered fractal dynamics of gait: reduced stride-interval correlations with aging and huntington’s disease. *Journal of applied physiology*, 82(1):262–269, 1997.
- [31] Benjamin Bollens, Frédéric Crevecoeur, Virginie Nguyen, Christine Detrembleur, and Thierry Lejeune. Does human gait exhibit comparable and reproducible long-range autocorrelations on level ground and on treadmill? *Gait & posture*, 32(3):369–373, 2010.
- [32] Benjamin Bollens, Frédéric Crevecoeur, Christine Detrembleur, Thibault Warlop, and Thierry M Lejeune. Variability of human gait: effect of backward walking and dual-tasking on the presence of long-range autocorrelations. *Annals of biomedical engineering*, 42(4):742–750, 2014.
- [33] Kimberlee Jordan, John H Challis, and Karl M Newell. Walking speed influences on gait cycle variability. *Gait & posture*, 26(1):128–134, 2007.
- [34] Jeffrey M Hausdorff, Yosef Ashkenazy, Chang-K Peng, Plamen Ch Ivanov, H Eugene Stanley, and Ary L Goldberger. When human walking becomes random walking: fractal analysis and modeling of gait rhythm fluctuations. *Physica A: Statistical mechanics and its applications*, 302(1-4):138–147, 2001.
- [35] Nicholas Stergiou and Leslie M Decker. Human movement variability, nonlinear dynamics, and pathology: is there a connection? *Human movement science*, 30(5):869–888, 2011.

- [36] Frédéric Dierick, Charlotte Vandevoorde, Frédéric Chantaine, Olivier White, and Fabien Buisseret. Benefits of nonlinear analysis indices of walking stride interval in the evaluation of neurodegenerative diseases. *Human Movement Science*, 75:102741, 2021.
- [37] Jeffrey M Hausdorff. Gait variability: methods, modeling and meaning. *Journal of neuroengineering and rehabilitation*, 2(1):1–9, 2005.
- [38] Bruce J West and Nicola Scafetta. Nonlinear dynamical model of human gait. *Physical review E*, 67(5):051917, 2003.
- [39] Roderick Edwards, Anne Beuter, and Leon Glass. Parkinsonian tremor and simplification in network dynamics. *Bulletin of mathematical biology*, 61(1):157–177, 1999.
- [40] Jyotika Bahuguna, Tom Tetzlaff, Arvind Kumar, Jeanette Hellgren Kotaleski, and Abigail Morrison. Homologous basal ganglia network models in physiological and parkinsonian conditions. *Frontiers in computational neuroscience*, 11:79, 2017.
- [41] Deanna H Gates, Jimmy L Su, and Jonathan B Dingwell. Possible biomechanical origins of the long-range correlations in stride intervals of walking. *Physica A: Statistical Mechanics and its Applications*, 380:259–270, 2007.
- [42] Mariano Garcia, Anindya Chatterjee, Andy Ruina, and Michael Coleman. The simplest walking model: stability, complexity, and scaling. 1998.
- [43] Emanuel Todorov. Stochastic optimal control and estimation methods adapted to the noise characteristics of the sensorimotor system. *Neural computation*, 17(5):1084–1108, 2005.
- [44] Stanford University. Linear quadratic stochastic control with partial state observation. <https://web.stanford.edu/class/ee363/lectures/lqg.pdf>, Winter 2008-2009. Accessed: 2020-11-06.
- [45] Marianna Capecci, Sanaz Pournajaf, Daniele Galafate, Patrizio Sale, Domenica Le Pera, Michela Goffredo, Maria Francesca De Pandis, Elisa Andrenelli, Mauro Pennacchioni, Maria Gabriella Ceravolo, et al. Clinical effects of robot-assisted gait training and treadmill training for parkinson’s disease. a randomized controlled trial. *Annals of physical and rehabilitation medicine*, 62(5):303–312, 2019.
- [46] Renaud Ronsse, Tommaso Lenzi, Nicola Vitiello, Bram Koopman, Edwin Van Aseldonk, Stefano Marco Maria De Rossi, Jesse Van Den Kieboom, Herman Van Der Kooij, Maria Chiara Carrozza, and Auke Jan Ijspeert. Oscillator-based assistance of cyclical movements: model-based and model-free approaches. *Medical & biological engineering & computing*, 49(10):1173–1185, 2011.
- [47] Ludovic Righetti, Jonas Buchli, and Auke Jan Ijspeert. Dynamic hebbian learning in adaptive frequency oscillators. *Physica D: Nonlinear Phenomena*, 216(2):269–281, 2006.

- [48] Renaud Ronsse, Nicola Vitiello, Tommaso Lenzi, Jesse Van Den Kieboom, Maria Chiara Carrozza, and Auke Jan Ijspeert. Adaptive oscillators with human-in-the-loop: Proof of concept for assistance and rehabilitation. In *2010 3rd IEEE RAS & EMBS International Conference on Biomedical Robotics and Biomechatronics*, pages 668–674. IEEE, 2010.
- [49] Jeffrey M Hausdorff. Gait dynamics in parkinson’s disease: common and distinct behavior among stride length, gait variability, and fractal-like scaling. *Chaos: An Interdisciplinary Journal of Nonlinear Science*, 19(2):026113, 2009.
- [50] Mon S Bryant, Diana H Rintala, Jyhong G Hou, Ann L Charness, Angel L Fernandez, Robert L Collins, Jeff Baker, Eugene C Lai, and Elizabeth J Protas. Gait variability in parkinson’s disease: influence of walking speed and dopaminergic treatment. *Neurological research*, 33(9):959–964, 2011.
- [51] Silvi Frenkel-Toledo, Nir Giladi, Chava Peretz, Talia Herman, Leor Gruendlinger, and Jeffrey M Hausdorff. Effect of gait speed on gait rhythmicity in parkinson’s disease: variability of stride time and swing time respond differently. *Journal of neuroengineering and rehabilitation*, 2(1):1–7, 2005.
- [52] Pietro Mazzoni, Britne Shabbott, and Juan Camilo Cortés. Motor control abnormalities in parkinson’s disease. *Cold Spring Harbor perspectives in medicine*, 2(6):a009282, 2012.
- [53] Katherine Baker, Lynn Rochester, and Alice Nieuwboer. The effect of cues on gait variability—reducing the attentional cost of walking in people with parkinson’s disease. *Parkinsonism & related disorders*, 14(4):314–320, 2008.
- [54] Sue Lord, Katherine Baker, Alice Nieuwboer, David Burn, and Lynn Rochester. Gait variability in parkinson’s disease: an indicator of non-dopaminergic contributors to gait dysfunction? *Journal of neurology*, 258(4):566–572, 2011.
- [55] Ryan T Roemmich, Nawaz Hack, Umer Akbar, and Chris J Hass. Effects of dopaminergic therapy on locomotor adaptation and adaptive learning in persons with parkinson’s disease. *Behavioural brain research*, 268:31–39, 2014.
- [56] Farshid Mohammadi, Sjoerd M Bruijn, Griet Vervoort, Erwin E van Wegen, Gert Kwakkel, Sabine Verschueren, and Alice Nieuwboer. Motor switching and motor adaptation deficits contribute to freezing of gait in parkinson’s disease. *Neurorehabilitation and neural repair*, 29(2):132–142, 2015.

UNIVERSITÉ CATHOLIQUE DE LOUVAIN  
École polytechnique de Louvain

Rue Archimède, 1 bte L6.11.01, 1348 Louvain-la-Neuve, Belgique | [www.uclouvain.be/epl](http://www.uclouvain.be/epl)