Gait Characterizations in Parkinson's Disease

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Dedicatoria

A mi madre Nidia Ricaurte, gestora de todos los logros que he logrado en mi vida, por apoyarme incondicionalmente durante este y todos los procesos que he emprendido. A todas las personas (familia, amigos, conocidos) que me han apoyado en este proceso de consolidar mi proyecto de vida. A la vida, por enseñarme durante estos años que uno tiene la capacidad de transformar las cosas más inverosímiles en realidades que transforman, sin dejar de insistir, de persistir, de resistir y de nunca desistir de mis objetivos y de mis sueños.

“Marcher en ligne droite, on ne peut pas aller très loin.”
“Caminando en línea recta, no se puede ir muy lejos.”

Antoine de Saint-Exupéry.

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Resumen

Caracterizaciones de la marcha en la enfermedad de Parkinson

La enfermedad de Parkinson (EP) es una enfermedad neurodegenerativa que afecta el sistema de control motor encargado de los movimientos voluntarios del cuerpo humano y las funciones cognitivas. EP es la segunda enfermedad neurodegenerativa más común despues de la enfermedad de Alzhaimer con una población mundial aproximada de 6 millones y con un estimado de 18 millones de personas para el año 2040. Se caracteriza por la muerte de las neuronas dopaminérgicas en un area conocida como substancia nigra *pars compacta*, que afecta directamente la función de los ganglios basales, afectando el sistema de control motor. Las principales manifestaciones motoras que se presentan debido a EP son bradicinesia, hipocinesia, alteración del equilibrio y de la marcha. Ademas, la EP afecta la capacidad de aprendizaje movimientos y de tareas repetitivas. Debido a las limitaciones funcionales de los movimientos que se presentan durante la progresión de la enfermedad, se han diseñado tratamientos invasivos (quirúrgicos) y no invasivos (medicamentos) para mejorar la calidad de vida de los pacientes. Los trastornos motores en la EP muestran una alta variabilidad interindividual que desafía las estrategias actuales basadas en la observación en el entorno clínico para determinar la evolución real de la enfermedad y monitorear la respuesta a la terapia. Diferentes investigaciones han intentado analizar cuantitativamente los patrones de marcha por métodos lineales enfrentando varias limitaciones debido a la naturaleza no estacionaria de los patrones de marcha. Sin embargo, esa variabilidad contiene patrones ocultos que no son fácilmente cuantificables en una rutina clinica por su alta complejidad. Debido a que el patrón de marcha podría abordarse como un sistema caótico determinista, es posible asociar a individuos sanos con un alto comportamiento caótico (complejidad) y las anormalidades de la marcha presentes en pacientes con EP, se puede asociar con uno menor (menor complejidad). En el presente trabajo se desarrolló en dos partes. La primera parte consistió en la caracterización no lineal de la marcha de la EP mediante un análisis caótico determinista que representa la dinámica temporal de la marcha con un conjunto mínimo de parámetros. Específicamente, se obtuvieron parámetros retardo (*delay*) y dimensión embebida para reconstruir el espacio de fase y sus coeficientes característicos, a saber,exponente Lyapunov, dimensión de correlación y entropía aproximada. Se encontraron diferencias estadísticas ($p < 0,05$, prueba de Mann-Whitney) para el exponente de Lyapunov y la entropía aproximada al describir los patrones de marcha de los grupos control y EP. La segunda parte de este trabajo tuvo como objetivo representar de forma no lineal la cinemática de las extremidades inferiores, destacando las diferencias entre los estadíos de la EP. Para ello, se incluyó *pose estimation* basado en aprendizaje profundo para obtener los puntos de referencia del cuerpo y sus series temporales y, posteriormente, construir el espacio de fase basado en sus

derivadas. Luego se calculó el mayor exponente de Lyapunov, la dimensión de correlación y la entropía aproximada, dando como resultado diferencias estadísticamente significativas (Prueba de rango Kruskal-Wallis, $p < 0{,}05$), particularmente entre los controles sanos y las etapas 3, la etapa más avanzada, y al comparar el estadio 1 frente al estadio 3. Estos hallazgos brindan información sobre cómo los patrones complejos pueden estar relacionados con la progresión de la enfermedad en la EP y pueden implementarse fácilmente utilizando dispositivos de video RGB asequibles.

Palabras clave: Enfermedad de Parkinson, Caos, Exponente de Lyapunov, Sistema Dinámico, Marcha, Control Motor.

Abstract

Gait characterizations in Parkinson's disease

Parkinson's disease (PD) is a neurodegenerative disease that affects the motor control system responsible for the voluntary movements of the human body and cognitive functions. PD is the second most common neurodegenerative disease after Alzheimer's disease with a world population of approximately 6 million and an estimated 18 million people by 2040. It is characterized by the death of dopaminergic neurons in an area known as *substantia nigra pars compacta*, which directly affects the function of the basal ganglia, affecting the motor control system. Motor manifestations include bradykinesia, hypokinesia, balance and gait disturbance. In addition, PD affects the ability to learn movements and repetitive tasks. Due to the functional limitations of movements that occur during the progression of the disease, invasive (surgical) and non-invasive (medication) treatments have been designed to improve the quality of life of patients. Motor disorders in PD show high inter-individual variability that challenges current observation-based strategies in the clinical setting to determine the current course of the disease and monitor response to therapy. Several researchers have attempted to quantitatively analyze gait patterns by linear methods, facing several limitations due to the non-stationary nature of gait patterns. However, this variability contains hidden patterns that are not easily quantifiable in a clinical routine and are highly complex. Because of the gait pattern could be approached as a deterministic chaotic system, it is possible to associate healthy individuals with high chaotic behavior and the gait abnormalities present in PD patients can be associated with decreased chaotic behavior. This work is developed in two parts. The first part consisted in making a non-linear characterization of the PD gait by means of a deterministic chaotic analysis that represents the temporal gait dynamics with a minimum set of parameters. Specifically, embedding and delay dimension parameters were obtained to reconstruct the phase space and its characteristic coefficients, namely Lyapunov, correlation dimension, and approximate entropy. Statistical differences ($p < 0{,}05$, Mann-Whitney test) were found for the Lyapunov exponent and the approximate entropy when describing two gait patterns, that is, the control and PD groups. The second part of this work aimed to represent the kinematics of the lower extremities in a non-linear way, highlighting the differences between the stages of PD. For this, a widely used deep learning framework was implemented to obtain the reference points of the body and its time series and subsequently build the phase space based on the first-order derivatives. The largest Lyapunov exponent, correlation dimension, and approximate entropy were then calculated, resulting in statistically significant differences (Kruskal-Wallis rank test, $p < 0{,}05$), particularly between the healthy controls and stage 3, the most advanced stage, and compare stage 1 versus stage 3. These findings provide insight into how complex patterns may be related to disease progression in PD and can be easily implemented using imaging devices like RGB

video capture. **Keywords: Parkinson's disease, Chaos, Lyapunov exponent, Dynamical system, Gait, Motor control**.

Content

Abbreviations

Abbreviation	Meaning
PD	Parkinson's disease
WHO	World Health Organization
AD	Alzheimer's Disease
MS	Multiple Sclerosis
HY	Hoehn and Yahr scale
PET	Positron Emission Tomography
REM	Rapid Eye Movement
$SNpc$	Substancia-Nigra Pars compacta
BG	Basal Ganglia
τ	Time delay
ε_d	Embedding dimension
HUN	Hospital Universitario Nacional de Colombia
CNS	Central Nervous System
PNS	Peripheral Nervous System
CPG	Central Pattern Generator
CoM	Center of mass
MLR	Locomotor mesencephalic region
$UPDRS$	Unified Parkinson's Disease Rating scale
$CIM@LAB$	Imaging and Medical Applications Laboratory
$COCO$	Common Objects in Context
$MPII$	Human Pose Dataset
$PAFs$	Part Affinity Fields

Abbreviation	Methods
MI	Mutual Information
AMI	Average Mutual Information
FNN	False Nearest Neighbors
LLE	Largest Lyapunov exponent
$CorDim$	Correlation dimension
$ApEn$	Approximate entropy

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1 Introduction

1.1. Parkinson's disease

Parkinson's disease (PD) is a neurodegenerative disorder that affects the motor control system and non-motor functions associated with cognitive alterations [1]. After Alzheimer's disease (AD), PD is the second most common neurodegenerative disorder worldwide, with a affected population of 6 million and an estimation determinates that it will be an increase of 18 million in 2040 [2][3]. Alterations due to this disease include diminished quality of life of people in elderly age, increasing risk of falls and injuries. Although the manifestations of the disease are not visible earlier, the disease progression is well-defined by the cardinal features such as bradykinesia or slowness movement, rigidity, rest tremor, and postural instability [4]. In 1817, James Parkinson's work "An essay on the Shaking Palsy", was the first in describing this neurological syndrome [5]. Subsequent works were carried out based on separating the disease from other neurological conditions such as Multiple Sclerosis (MS) which has similar features. Despite to the clinical efforts for discovering therapeutics targets and minimize the disability, the mortality in PD has increased during the last two decades in populations among 70 to 85 years, with a mean life from to first diagnosis of 15.3 years [6][7]. Due to the disability caused by the disease, the economic burden increases significantly because the cost of diagnosis and treatment in the health system and the high mortality rate compared to the general population[8]. For this reason, research groups worldwide seek to design clinical trials, surgical and pharmacological treatments to counteract PD effects. Therefore, they seek to improve the accuracy of the diagnosis and the disease monitoring [9]. To the date, the Hoehn and Yahr scale (HY) is globally used to assess the PD progression, which is divided into 5 stages (table **1-1**), from mild involvement (stage 1) to severe involvement (stage 5) [10].

Hoehn and Yahr scale	Modified Hoehn and Yahr scale
1: Only unilateral involvement, usually with minimal or no functional disability.	1.0: Unilateral involvement only. 1.5: Unilateral and axial involvement
2: Bilateral or midline involvement without impairment of balance.	2.0: Bilateral involvement without impairment of balance. 2.5: Mild bilateral disease with recovery on pull test.
3: Bilateral disease: mild to moderate disability with impaired postural reflexes; physically independent.	3.0: Mild to moderate bilateral disease; some postural instability; physically independent.
4: Severely disabling disease; still able to walk or stand unassisted.	4.0: Severe disability; still able to walk or stand unassisted.
5: Confinement to bed or wheelchair unless aided.	5.0: Wheelchair bound or bedridden unless aided.

Table 1-1: Hoehn and Yahr Scale. Take from Movement Disorders: A Video Atlas 2021 Springer

However, PD diagnosis and monitoring is challenging since it can be confused with other pathologies that affect the motor control system. In this context, bio-markers have been developed for the early detection of PD disease such as positron emission tomography (PET) to detect the accumulation of α-synuclein protein levels in cerebrospinal fluid, cloud computing to assess voice disorders (dysphonia), phase alterations in Rapid Eye Movement (REM) [11][12][13]. Furthermore, gait and balance as biomarkers are valuable because they can be correlated with disease progression, are not expensive, non-invasive and reliable [14]. Gait and motor profile in PD is outlined below.

1.2. Gait and motor impairments

PD motor impairment is due to the loss dopaminergic neurons in the *Substantia-Nigra Pars compacta (SNpc)* located in the Basal Ganglia (BG) [15]. The most common symptoms are bradykinesia, rigidity, rest tremor, postural instability and gait disturbances [1][16]. Particularly, gait is a repetitive sequence of movements of all limbs, characterized by semi-periodic movements which requires complex interactions among the neuromuscular, tendon, and osteoarticular systems [17][18]. Usually, human gait is described in terms of cycles, a period between successive heel strikes of the same foot [19][20][21]. This cycle are divided in two phases: the stance phase that represents the 60 % - 62 % of entire cycle when the both limbs are in contact on the ground, and the swing phase which ranges from 38 % - 40 % when one limb are lifted off the ground and the other limb are in contact with the ground (figure **1-1**) [19][20][22].

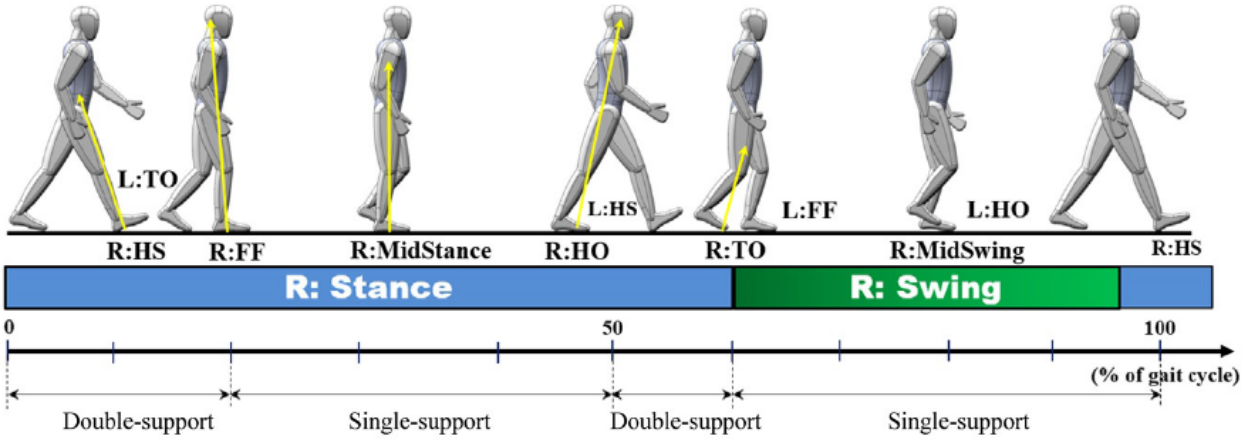

Figure 1-1: Phases of the gait cycle. Take from: A Review of Computational Musculoskeletal Analysis of Human Lower Extremities A. Alamdari, V.N. Krovi, in Human Modelling for Bio-Inspired Robotics, 2017.

Physical variables such as stride length, cadence, swing time, kinetics and kinematics features are usually obtained to describe the gait mechanics and the disability progression in PD. Typically, gait parameters are assumed to be normally distributed (e.g. identically and independently distributed) being the average and deviation the usual report. It has shown that these parameters may be correlated with the impairment in voluntary motor control becoming in disease's hallmarks [23][24]. However, meaningful clinical questions remain unsolved since gait complexity is reduced to a set of uncorrelated observations. In fact, human gait exhibits complex fluctuations that hides essential control mechanisms that are not easy quantifiable in a traditional linear analysis [18][25]. In contrast, the gait motor control is a dynamic complex system showing where different subsystems (sensory, cortical, sub-cortical, medulary and musculoskeletal) are interacting. A review of this system is summarized as follows

Gait motor control

Gait control is composed of motor commands generated and executed by the central nervous system (CNS) and the peripheral nervous system (PNS). This system is highly adaptable when an individual learn a new movement as the nervous system is damaged as well [26][27]. There are multiple conceptual frameworks to explain how these movements are learned, generated and optimized. However, the first approach to the PD monitoring relies on how functional movements are produced being the *motor control* they key concept. A simple motor control model consists of sensory input, central processing and the output. Motor output is constructed by matching sensory inputs namely, proprioceptive, vestibular and visual, to the internal representation of the body and retrieve a learned pattern (central

processing) composed of sequential muscle activation and a kinetic chain. Once the central processing select the most suitable motion sequence, motor commands are sent through of spinal cord to motor cells or α-motor neurons and toward the muscles by PNS [26][27][28]. This information processing is carried out by sensory and primary motor cortex, pre-motor cortex, supplementary motor area, cerebellum nucelus , the Thalamus, and basal ganglia. Particularly, basal ganglia (BG) generate positive feedback on the thalamus, brain cortex and the brain stem avoiding rigidity and hypokinesia, the default manifestation without this regulation.

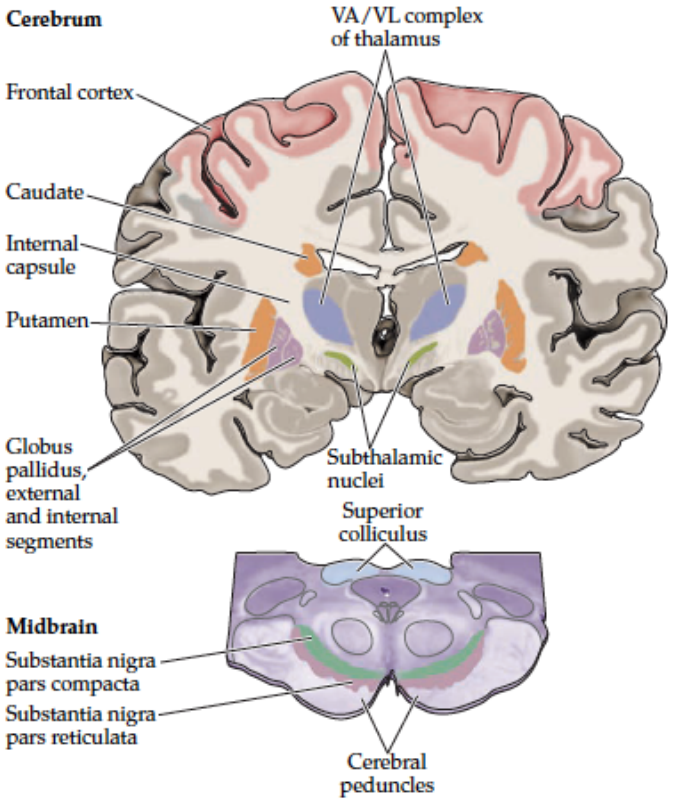

Figure 1-2: Motor components of the basal ganglia . Take from: Neuroscience.Purves D, Augustine GJ, Fitzpatrick D, Hall W, LaMantia AS, White L. Oxford University sixth edition.

Briefly BG is composed by "several nuclei namely putamen, subthalamic nuclei, caudate nucleus, globus pallidus, substancia nigra (dopaminergic cells)"[26] determining which motor plan should be execute at any time by positive feedback upon the motor cortex and brain stem nuclei (figure **1-2**) [28]. In addition, other dopamine-dirven neural networks within the CNS knows as central pattern generator (CPG) and locomotor mesencephalic region (MLR) produce cyclic and oscillatory flexor/extensor patterns outputs associated to normal movements, even in sensory absence [26][27]. In summary muscular commands results of merged

BG, CPG, MLR and motor cortex. Despite their oscillatory activation and the periodic-like behaviour of the gait, motor commands and motor output (kinematics) are variable due to sensory feedback, sensory noise and motor network redundancy [28]. Surprisingly, therefore, the variability of movements is a sign of normalcy, but a stereotypical behavior is a sign of dysfunction [26][27]. The variability may increase when the CNS or PNS are damaged and the control movement is impaired. For clinicians, this way of assessment would represent an unique opportunity to differentiate the cause of the problem through motion analysis. From this point of view, characterizing human gait as a complex a dynamical system may unveil meaningful patterns with prognostics and predictive value in PD.

Dynamical system

For a long time, several researches have studied the variability of human movement to assess motor performance in everyday tasks. In a first approach this variability has been assumed as system noise and modeled by linear models (additive or multiplicative) [29][30]. Linear system relies on the causality, superimposition (linear combination of the inputs) and time invariance assumptions. Similarly, normal distribution of the output are commonly accepted. Thus, linear analysis provides a description of the magnitude of variability by a statistical moment (e.g. median, deviation) referred to normal distribution. A major limitation for applying linear analysis upon gait patterns relies on ignoring the interdependence among gait cycles and the non-linearities herein observed. In fact, the variability of the apparently "noisy behaviour" results of non-linear interactions that may provide relevant information regarding the complex systems and motor networks [29][30]. Hence, nonlinear analysis may provides a way to observe the impaired state of the motor control system and associate it to the variability of the motor output i.e. joint kinematics [29][30]. In fact, nonlinear dynamics have been found in complex physical and biological signal, associated to human movements, brain and heart activity [29][30]. For this reason, researchers have performed gait analysis using nonlinear dynamical systems theory (fractals, nonlinear systems, **chaos**) to describe the biomechanics and human motion of the gait [25][31]. This phenomenon could be studied by as non-stationary process in the time domain as the evolution of its state-space from a set of initial conditions as a dynamical system [29][30]. Being so, complex fluctuations can be described as a set of continuous or discrete functions, which are solved using differential equations or different numerical methods. [1]

1.3. Chaotic behavior of gait

Gait is by nature a non-stationary dynamic system due to the presence of complex fluctuations in human locomotion, observed from time series. In the nature of the human gait, these time series are apparently random, noisy, unpredictable and furthermore, it hides re-

[1] Analysis nonlinear dynamical systems (Chaos theory) will be discussed in the next section.

levant information about the system. However, the irregular fluctuations that appear in the gait dynamics are not a stochastic system, since they can be determined and described by the temporal evolution of the system, since parameters and initial conditions [25][32][33]. Therefore, deterministic dynamical systems can describe these functions using differential equations or numerical methods for continuous or discrete cases respectively, which have nonlinear characteristics. The nonlinear systems can be studied through the chaos theory since it belongs to a subset of this area [29]. Chaos theory emerges due to interaction of simple nonlinear components and is defined as "aperiodic bounded dynamics of a deterministic system with sensitive dependence on initial conditions" [25][34]. However, it should be noted that all chaotic systems are nonlinear, but not all systems are chaotic [29][35]. The normal gait has a high complexity characterized by chaotic behaviour that can be associated with healthy subjects, and gait's abnormalities in PD has decreased its chaotic nature associated to fluctuations random and periodic [29][32][33].

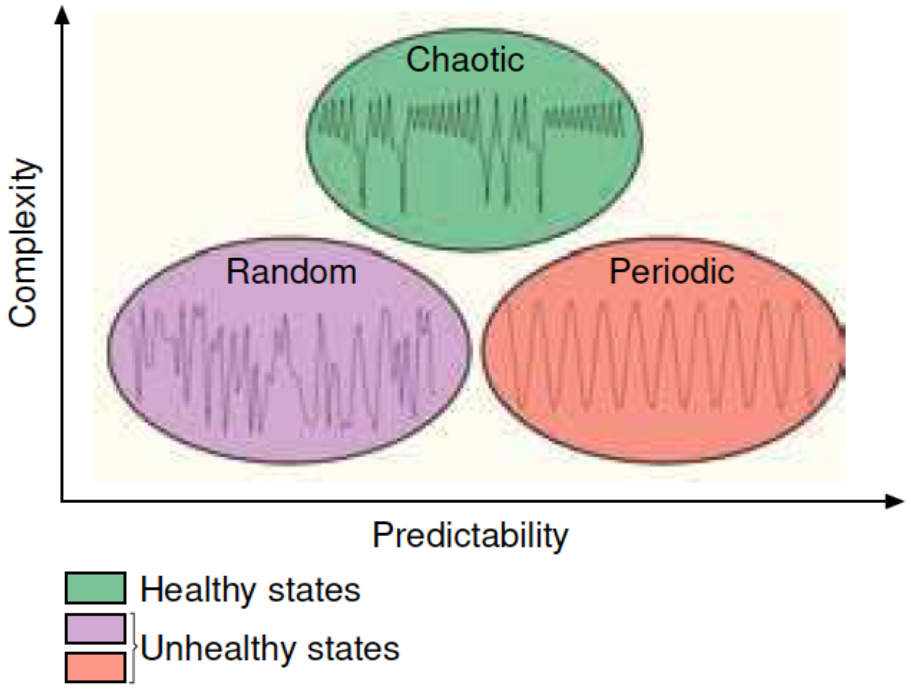

Figure 1-3: Theoretical model of complexity as it relates to health. Take from: Complexity and Human Gait L.M. Decker a, F. Cignetti a and N. Stergiou.Rev Andal Med Deporte. 2010;3(1):2-12

The predictability in a chaotic system lies between the periodic system which has high predictability and the noisy or random system which has low predictability (figure **1-3**). Therefore, complex fluctuations obtained from gait time series, may help to understand the level of complexity impairment given in PD progression [29][33]. For this reason, researchers

have developed techniques to analyze and quantify complex fluctuations that are present in nonlinear time series [25][33].

1.4. Chaotic quantification of the gait

The complex fluctuations are present in gait dynamical and they are associated to chaotic behaviour that can describe the disease progression in their different stages. For this, it is necessary make reconstructions of the system dynamics represented by state space or phase space in order to characterize the reconstruction dynamics [25].

1.4.1. Phase space

As mentioned above, the nature of gait implies chaotic behavior because of very complex fluctuations in gait dynamics. The gait is apparently random (figure **1-4**), but actually it is deterministic in the **phase space**. This type of representation provides alternative solutions when the differential equations are impossible to solve.

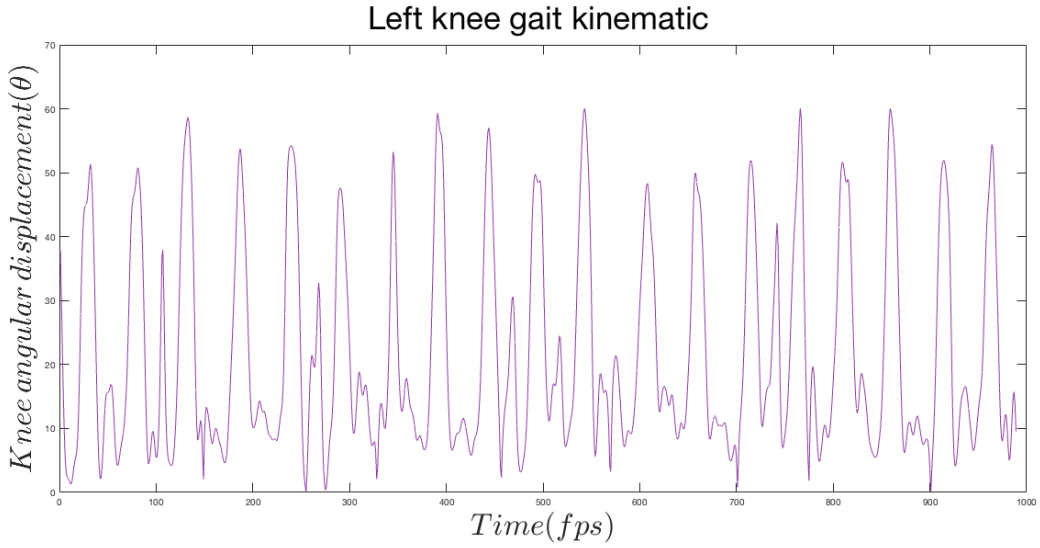

Figure 1-4: Left knee kinematic gait time series, apparently random and noisy.

A state-space is a representation of the dynamic systems, where the coordinates represents the values of a specific point of the state of the system [30][33]. These states values, can be defined a curve (phase trajectory) that representing the time evolution of the system into the phase space, where the trajectory converge in a subspace of low-dimensional called attractor (figure **1-5**) [33][36][37]. In the gait case, the attractor can gives information of asymptotic behaviour of the kinematic temporal evolution, joints and so on [33]. Therefore, a phase space is a representation of relations not visible in the original domain.

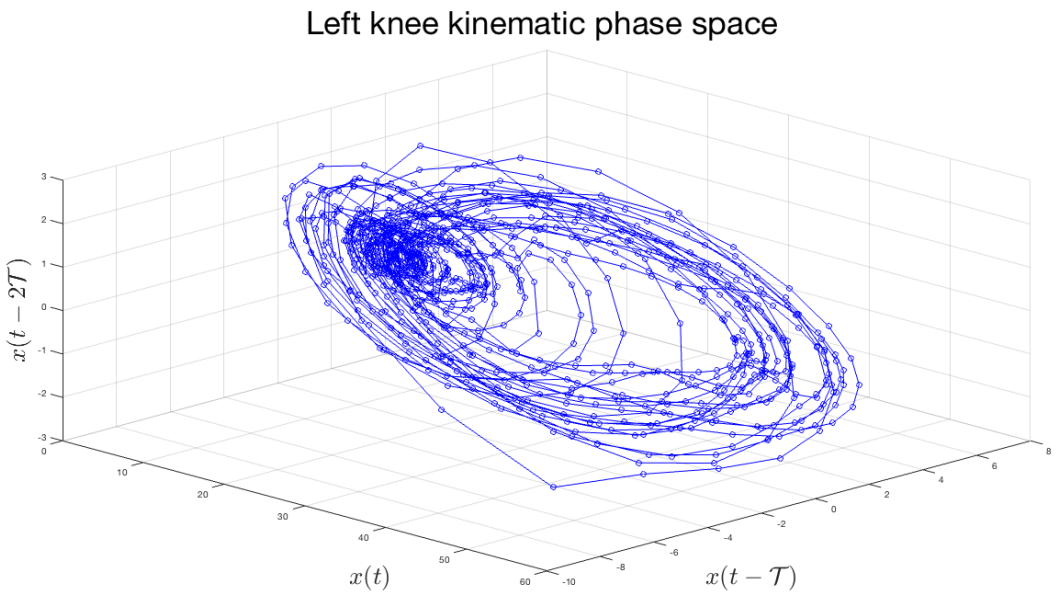

Figure 1-5: Phase space reconstruction. Representation of the time evolution of dynamical system by left knee. The trayectory into phase space converge in a subspace called attractor.

Takens' theorem is used to phase space reconstruction from two parameters: time delay (τ) and embedding dimension (ε_d) [38], where a system's phase space could be described by a single variable, $x(t)$ and its delayed versions $x(t-\tau)$, when the whole set of equations is unknown [38][39]. Let a time series:

$$x(t) = (x_1, x_2 \ldots, x_N) \tag{1-1}$$

and its parameter time delay τ, the phase space shows the correlations between time series original $x(t)$ and their displacement version

$$x(t-\tau) = (x_{1+\tau}, \ldots, x_{N+\tau}) \tag{1-2}$$

According to Takens' theorem, phase space reconstructions can be performed with any time delay (figure **1-6**). However, if the delay τ values $x(t)$ and $x(t-\tau)$ are small, the system does not show appreciable changes in the state and the information obtained will be little [25][39]. If the delay τ values are large, the values of each state will be almost independent, so the system loses information about its dynamics [25]. Therefore, it is necessary to find a suitable delay value that will not cause problems in the reconstruction of the dynamics.

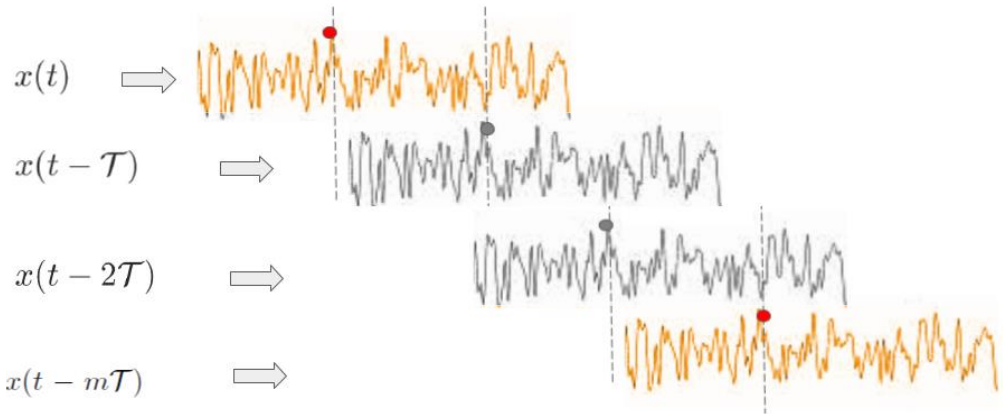

Figure 1-6: Time delay (τ). Original time series $x(t)$ and its delayed version $x(t-\tau)$ by τ factor.

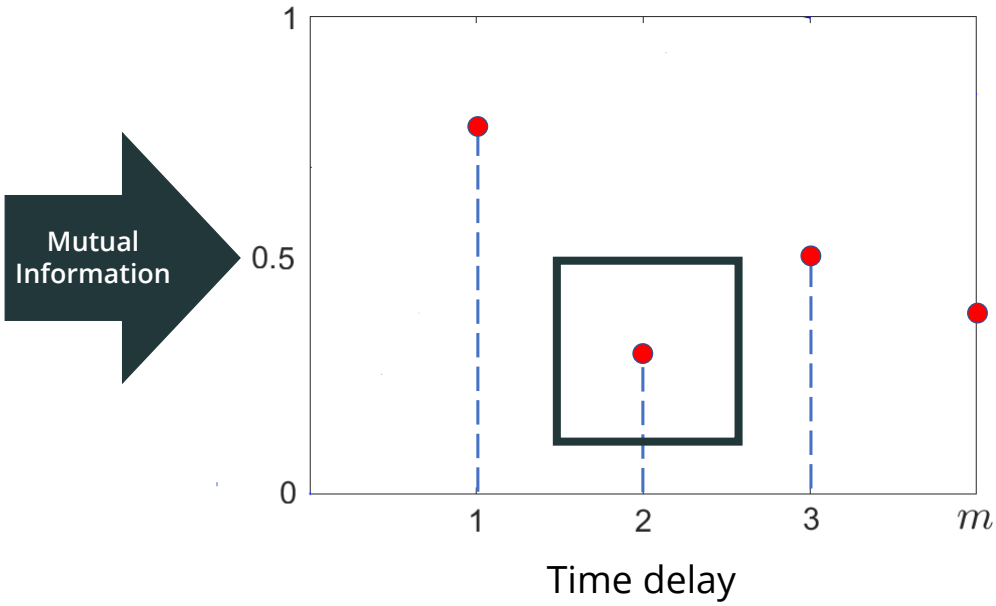

Figure 1-7: First local minimum of the Average Mutual Information (AMI) between $x(t)$ and its delayed versions $x(t-\tau)$.

For this, it is calculated the dependence as the mutual information (MI) $I(x(t), x(t-\tau))$ that is auto-correlated between $x(t)$ and $x(t-\tau)$ by τ factor. To find the best time delay value, choose the first local minimum of the Average Mutual Information (AMI) [40] between $x(t)$

and its delayed versions (figure **1-7**), which are associated to the delay τ, and it is estimated as follows [39][41]:

$$\tau = \underset{\tau}{\operatorname{argmin}} \sum_{i=1}^{N} p\left(x_i, x_{i+\tau}\right) log_2 \left(\frac{p\left(x_i, x_{i+\tau}\right)}{p\left(x_i\right) p\left(x_{i+\tau}\right)} \right) \tag{1-3}$$

"In practice the AMI function may not have a local minimum, but may, e.g., be a monotonically decreasing function of τ. Consequently other criteria have been developed, such as the lowest value of τ for which the AMI function drops below the value 1/e or 0"[41].

Once obtained time delay, it is calculated the smallest number of trajectories not crossing each other into the phase space or called embedding dimension (ε_d), using False Nearest Neighbors (FNN) method. This means that the embedding dimension is the minimum number of variables required to form a phase state from times series [29]. Let us defined [25][29][41]:

$$Y_\tau(t) = \left(x_t, x_{t+\tau}, \ldots, x_{t+(d-1)\tau}\right) \tag{1-4}$$

$$Y_\tau(t)^* = \left(x_t^*, x_{t+\tau}^*, \ldots, x_{t+(d-1)\tau}^*\right) \tag{1-5}$$

where $Y_\tau(t)$ is a point d-dimensional and $Y_\tau(t)^*$ is a point nearest neighbor into phase space. Let a:

$$R^2(d) = || \, Y_\tau(t) - Y_\tau(t)^* \, ||_2^2 \tag{1-6}$$

and r a threshold for pair FNN points $Y_\tau(t)$ and $Y_\tau(t)^*$

$$\sqrt{\frac{R^2(d+1) - R^2(d)}{R^2(d)}} > r \tag{1-7}$$

Therefore, the embedding dimension ε_d is equivalent to the smallest value d, when calculating the distances between the points d and $d+1$ dimensions (figures **1-8** and **1-9**). If the value of r is greater than a threshold, the "neighbor" is considered a false neighbor [29][30].

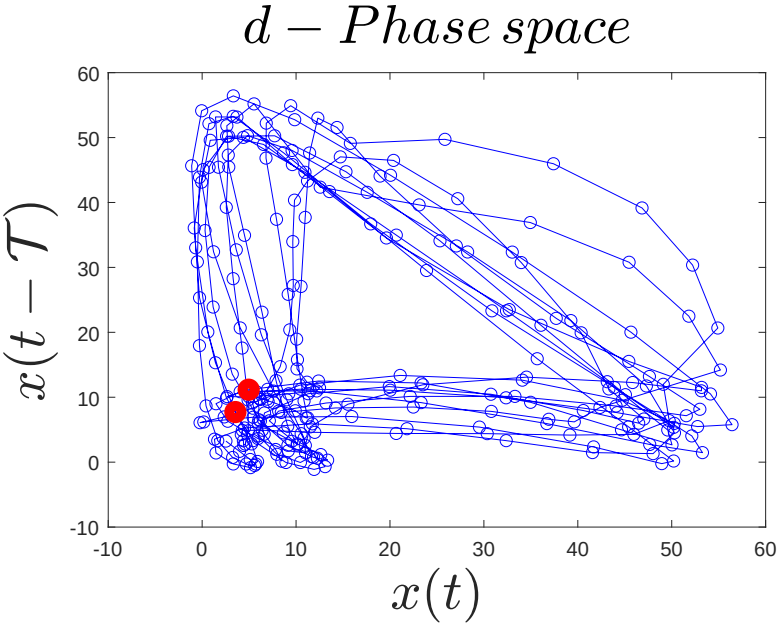

Figure 1-8: The points (red) are apparently look like neighbors in a dimension d.

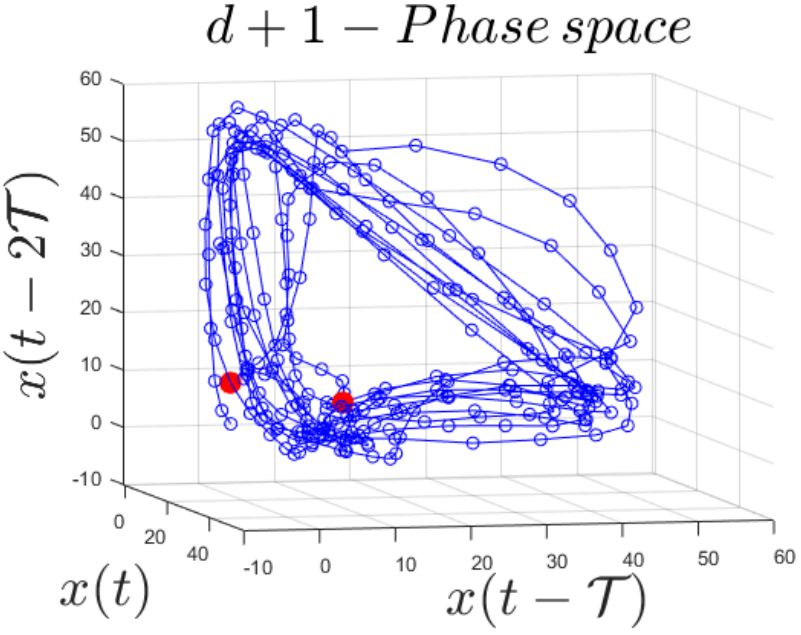

Figure 1-9: The points (red) in the highest dimension $d+1$, shows that one of the points is a false neighbor.

Although the delay time and embedding dimension are found, this parameters to phase space reconstruction can produce inaccurate values. The calculation for time delay can be affected by noisy, because if the sampling frequency of the time series is too high to obtain more data, the points are strongly correlated and is possible that first minimal local of MI are not found [29][30]. In the case of the embedding dimension, the noise increases the percentage of false neighbors, which increases the number of dimensions mistakenly [29][30]. Alternatively, due to the inaccuracy of the calculated values for the time delay and the embedding dimension, the phase space reconstruction can be done calculating the first order derivatives as velocity $\frac{dx}{dt}$ and acceleration $\frac{d^2x}{dt^2}$ provide a description more accurate of these relationship fundamentals. It is known as the differential phase space or differential embedding:

$$x(t_i) \rightarrow \left\{ (t_i), \frac{dx}{dt}(t_i), ..., \frac{d^{m-1}x}{dt^{m-1}}(t_i) \right\}, \tag{1-8}$$

where $x(t_i)$ is i-th term of the time series and m the derivative order [42][43]. Once the phase space is constructed, the level of complexity that present the attractor due to the behaviour chaotic in the gait, it can be used as nonlinear tools to describe the dynamical system. Chaos descriptors as Largest Lyapunov exponents (LLE), Correlation dimension (CorDim) and Approximate entropy (ApEn) , can describe the loss information, the sensitivity to the initial conditions and system's complexity.

1.4.2. Chaos descriptors

Largest Lyapunov exponent

A way to measure the level of complexity of dynamical system into phase space (for this case chaotic behaviour) is Largest Lyapunov exponent. LLE characterizes the rate of separation of infinitesimally nearby the trajectories, where they can converge or diverge (figure **1-10**). Two points of the trajectories $Y(t)$ and $Y(t)^*$ are choose randomly as initials conditions within the phase space and then, Euclidean distance is calculated, as [29][30][40]:

$$D(t) = || \, Y(t) - Y(t)^* \, ||_1 \tag{1-9}$$

The distance $D(t)$ can be expressed as a function of t and λ as follows:

$$|| \, Y(t) - Y(t)^* \, ||_1 \simeq Ce^{\lambda t} \tag{1-10}$$

$$\ln(\, || \, Y(t) - Y(t)^* \, ||_1) \simeq \ln C + \lambda t \tag{1-11}$$

where λ is the Lyapunov exponent.

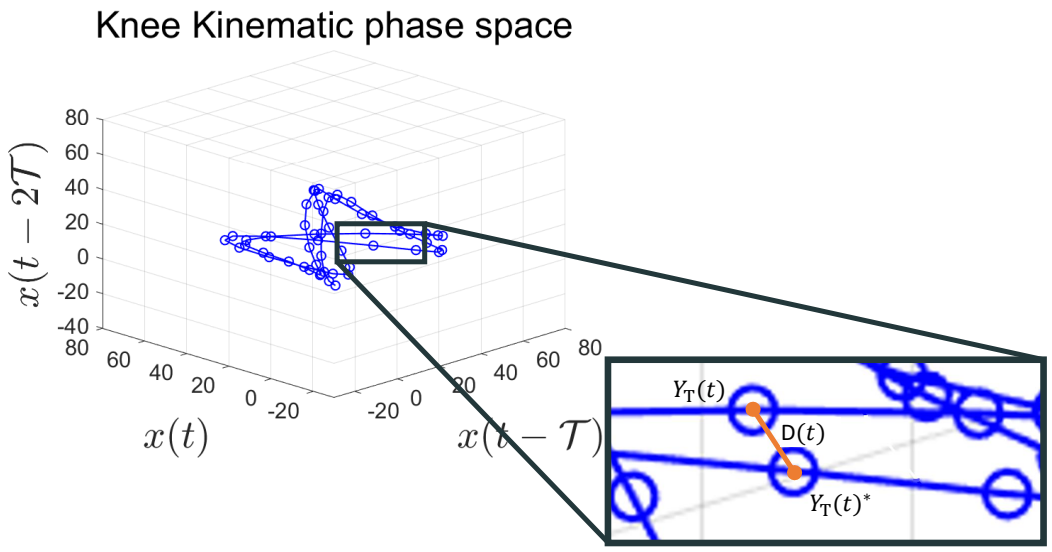

Figure 1-10: Knee kinematic trajectories into phase space. Two trajectories experience exponential separation.

Then, the largest Lyapunov exponent is then calculated using the slope of the least-squared line (figure **1-11**) defined by $ln(D(t))$ vs t^{-1} as follows:

$$\lambda = \frac{1}{t} \langle \ln(\mid\mid Y(t) - Y(t)^* \mid\mid_1) \rangle \tag{1-12}$$

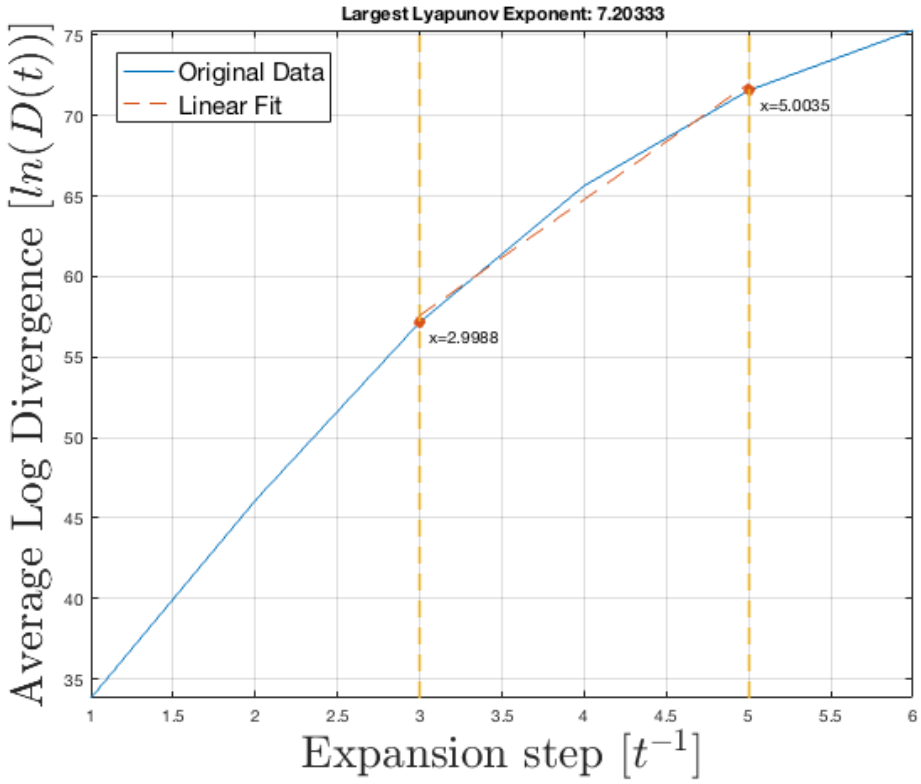

Figure 1-11: LLE is determined by calculating the slope of the plot (red linear fit) of the average divergence versus expansion step on a log–log plot.

Type of motion	Lyapunov exponent
stable fixed point	$\lambda < 0$
stable limit cycle	$\lambda = 0$
chaos	$0 < \lambda < \infty$
noise	$\lambda = \infty$

Table 1-2: Possible types of motion and the corresponding Lyapunov exponents. Take from Kantz, Holger, and Thomas Schreiber. Nonlinear time series analysis. Vol. 7. pag 68. Cambridge university press, 2004.

If $\lambda > 0$, the trajectories have an exponential divergence, i.e, chaos. However, this separation of the trajectories cannot separate further that the diameter of attractor [29][30][44]. If $\lambda < 0$, trajectories quickly exponentially converge to a stable fixed point [29][30]. If $\lambda = 0$, there is no convergence or divergence of the trajectories, because the trajectories only move away or toward each other more slowly than exponentially (table **1-2**). This appears in a set of movements with a limit of cycles and it is known as marginally stable [29][30].

Correlation dimension

Correlation dimension (CorDim) estimates the probability that two points $Y_i(t)$ and $Y_j(t)^*$ in the phase space are close after a distance threshold is set, where $Y_i(t)$ and $Y_j(t)^*$ are patterns of the kinematic data [29][45]. To calculate the correlation sum $C(\alpha)$, it is calculated a function of different values of α for N points of vector time series into m-dimensional sphere (figure **1-12**), and it is counted the number of points of attractor into the sphere as follows [29][33]:

$$C(\alpha) = \frac{1}{N(N-1)} \sum_{i,j=1, i \neq j}^{N} \Theta(\alpha - \|Y_i(t) - Y_j(t)^*\|) \tag{1-13}$$

$$\Theta = \begin{cases} 0 & if \quad \alpha - \|Y_i(t) - Y_j(t)^*\| < 0 \\ 1 & if \quad \alpha - \|Y_i(t) - Y_j(t)^*\| \geq 0 \end{cases} \tag{1-14}$$

where $C(\alpha)$ is the correlation sum for each α, over all points on attractor and Θ is the Heaviside step function [29][30][33].

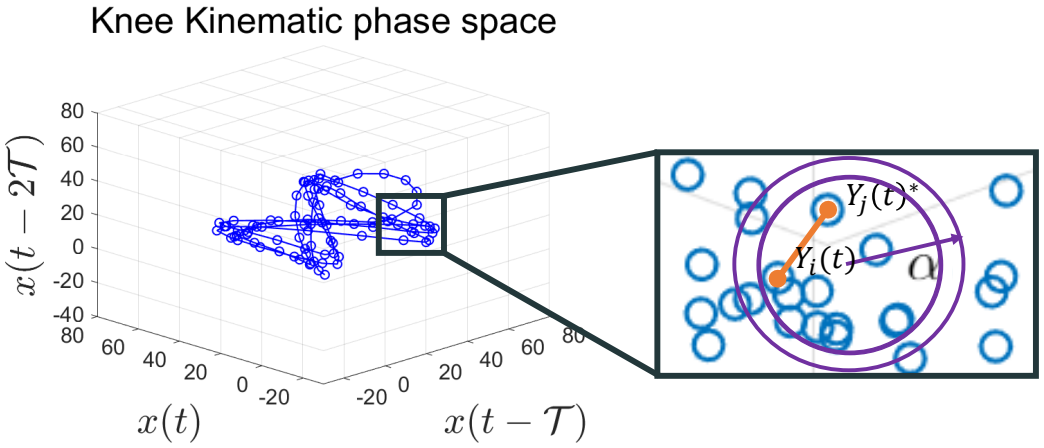

Figure 1-12: A point choosing circumscribed by multiple circles of radius α, where the number of points is counted within these circles.

The correlation dimension is calculated finding the slope of a $\log - \log$ between the correlation sum against the α values (figure **1-13**) [29][30][45].

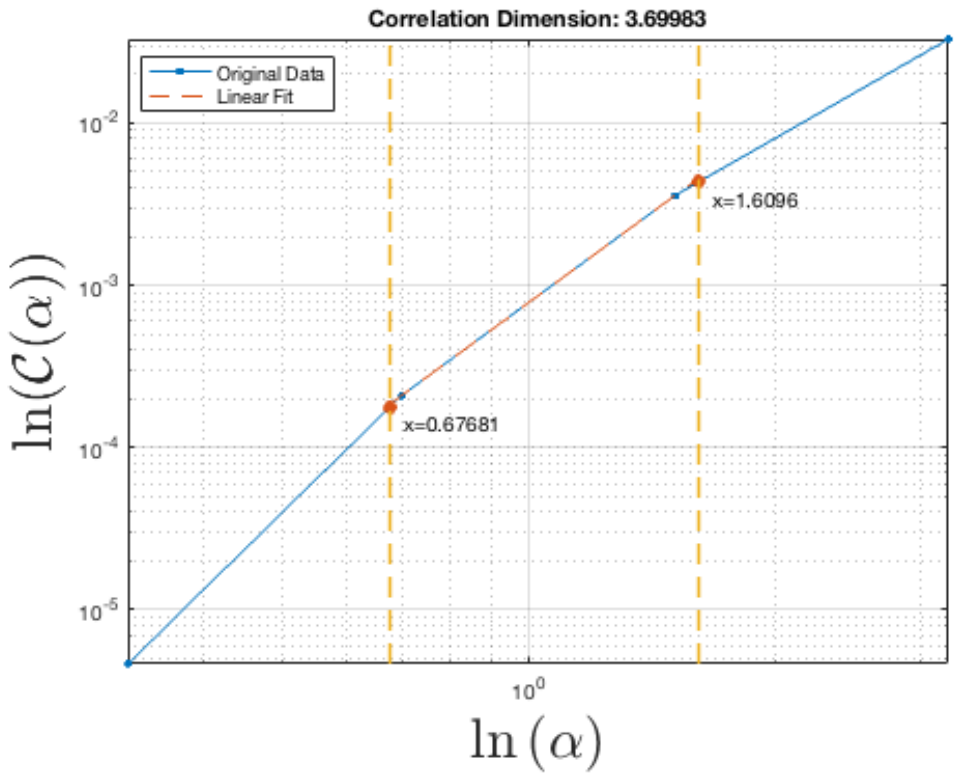

Figure 1-13: Correlation dimension is determined by calculating the slope of the plot (red linear fit) of the correlation sum versus α on a log–log plot.

Approximate entropy

Approximate entropy estimates probability observation patterns are not similar [30][46]. ApEn takes points of the time series of length $N = x_1, x_2, ..., x_N$ and is divided into shorts vectors of length ε_d, where ε_d is a pattern window (figure **1-14**). Once is divided the length in shorts vectors, it is counted how many vectors are similar to each other. For example, to determine whether two vectors are similar respect to a pattern window defined, it is compared each element of the first vector with the corresponding element in the second vector [29][30]. Therefore, if the differences are below the radius $r = \| Y(i) - Y(j)^* \|_1$ of the entire time series, with $Y_i(t)$ and $Y(j)^*$ points into phase space, can be considered as similar."If the r value is too small, then the counts are thrown off because similar data points are not seen as similar. If r is too large, then details of the system dynamics are lost"[29]. This process is repeated, but now with pattern window of length $\varepsilon_d + 1$ [29]. The indicator function, N_i is computed as:

$$N_i = \sum_{i,j=1,i\neq j}^{N} 1(\|Y_i(t) - Y_j(t))\|_1 < 0{,}2 * var(x(t))) \tag{1-15}$$

where $(\|Y_i(t) - Y_j(t))\|_1$ is not higher than 0,2 times the variance of the time series $x(t)$ [47].

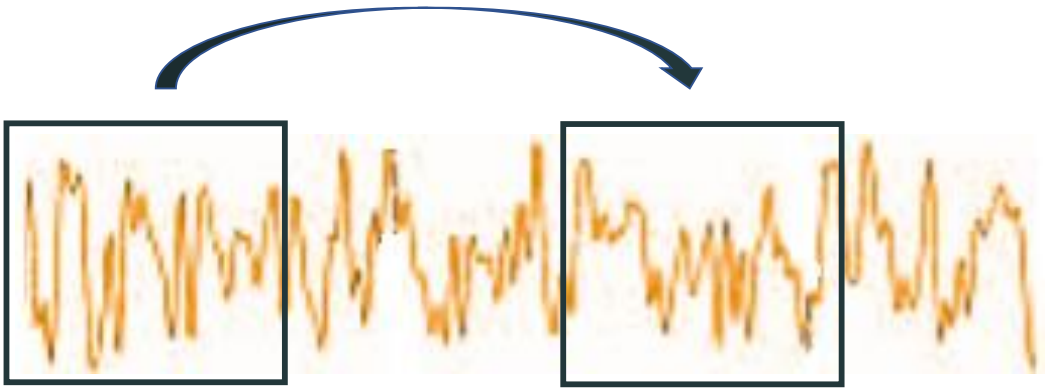

Figure 1-14: Time series of length N, where its compare the similarity between two sections of N by a pattern window ε_d.

Finally, approximate entropy is estimated by the difference between $\phi^{\varepsilon_d} - \phi^{\varepsilon_d+1}$ (Eqn.3-9)

$$\phi^{\varepsilon_d} = \frac{1}{N - \varepsilon_d + 1} \sum_{i=1}^{N} log(N_i) \tag{1-16}$$

$$Ent_{Approx} = \phi^{\varepsilon_d} - \phi^{\varepsilon_d+1} \tag{1-17}$$

where ϕ^{ε_d} and ϕ^{ε_d+1} are the functions to compare the different counts for each length ε_d and $\varepsilon_d + 1$. If $\phi^{\varepsilon_d} - \phi^{\varepsilon_d+1}$ value is approximately zero, the time series is repeatable (for example the sin function). However, if $\phi^{\varepsilon_d} - \phi^{\varepsilon_d+1}$ is positive when the time series are apparently randomness.

1.5. Contribution

The main contribution of this study is a novel characterization of the Parkinson disease by non-linearly representing of the temporal gait dynamics in a phase space which allow make objective measurements of the disease progression. This work used two ways to explore the differences among the different disease stages:

- The presented method captures the non-linear structure of gait and serves to discriminate between Parkinson's and healthy patterns by manually tracking of the main joints of the lower limbs. The method starts by reconstructing a phase space from the gait data and a chaotic analysis estimates delay and embedding dimension parameters from which main gait descriptors are obtained.

- The method was applies a deep learning framework to track body joints in a 2D video and the resultant time series are stored to find differences among the disease stages. Since the human gait is a semi-periodic and mechanically constrained to a dynamic system, position, velocity and acceleration describe the system and configure a phase space. This phase plane is constructed by computing the first and second order derivatives of the kinematics times series.

The advantage of characterizing the progression of Parkinson's disease from gait dynamics is that this method could be used as an alternative tool for clinicians to help assess the level of motor control impairment caused by the disease. This method is easy to implement and interpret, at low cost.

2 Article No. 1

Characterizing the gait dynamic by estimating Lyapunov exponents on gait kinematic trajectories in Parkinson's Disease

Presented on the 15th International Seminar on Medical Information Processing and Analysis SIPAIM 2019, Medellin Colombia, November 2019

Observation of Gait patterns is the available evaluation in clinical routine of the motor manifestations in Parkinson's Disease (PD). Lately, different investigations have attempted to quantitatively analyze gait patterns by linear methods facing several limitations since the non-stationary nature of the gait patterns. This study presents a non-linear characterization of the Parkinson's disease gait by a deterministic chaotic analysis which represents the temporal gait dynamics with a minimum set of parameters. Specifically, delay and embedding dimension parameters were obtained for reconstructing the phase space and its characteristic coefficients, namely Lyapunov, correlation dimension, and approximate entropy. Statistical differences ($p < 0{,}05$, Mann-Whitney test) were found for the Lyapunov exponent and the approximated entropy when describing two gait patterns, i.e., control and PD groups.

2.1. Introduction

Parkinson's disease (PD) is the second most common neurodegenerative disorder after Alzheimer's disease increasing the social and economic burden in societies with a high aging rate [48]. Its anatomopathological process involves the progressive loss of dopaminergic neurons of the mesencephalic black substance pars compacta (SNpc), as well as the presence of intracellular inclusions called Lewy bodies [49]. PD is clinically characterized by akinesia or slowness of movement, rest tremor and rigidity [49], including gait disturbances. Slow and shuffling gait with shortened stride length are thus, the main hallmarks of parkisonian gait maintaining normal cadence in most of the cases [50]. In this context, gait analyses and functional scores have been used as a part of routine clinical test for the assessment of the motor performance [32] and the disease progression such as 2 minute walk test, up-and-go

test, 180-degree U-turn test, and the The Unified Parkinson's Disease Rating scale (UPDRS) [51][52]. However, many studies have suggested that the course of PD is not linear being the rate of deterioration highly variable and faster in the early phase of the disease, specially in PD patients with gait abnormalities [52][53]. Hence, different studies have been aimed to quantitatively analyze the PD, including in most of the cases, linear analysis models on gait times series. These models have several limitations for capturing the non-stationary of the gait. Because linear methods are based on superposition principle, they assume that small changes in the gait cycles result in small long-term effects on gait pattern [30]. Thus, several quantitative gait assessments in PD do not take into account the non-linear dynamic of the gait patterns reducing its analysis to descriptive statistics. In contrast, some studies have highlighted the chaotic behaviour of the gait time series as a marker the normal and abnormal movement [32][54]. The term chaos herein used, describes an apparently unpredictable behaviour whose long-term evolution can be determined by its phase space reconstruction, given a particular set of initial conditions [55]. In this sense, gait pattern must be understood like a chaotic process whose states are determined by non linear descriptors [54][56]. Previous research has shown this chaotic dynamic on different biomedical signals such as motion records including gait and eye movement [57][58], using several characteristic coefficients such as largest Lyapunov exponent, correlation dimension and approximate entropy [57]. Although some research have been conducted on chaotic gait analysis in PD gait patterns [32], the results have not been extended to clinical setting, since most of them included small population and few gait data. In this sense, exploratory studies are required for an accurate quantitative characterization of PD gait.

The main contribution of this study is a characterization of the PD patterns by a deterministic chaotic analysis of the kinematic gait times series. Unlike other gait analyses, the method herein presented captures the non linear structure of the gait and serves to discriminate Parkinson and healthy patterns. The method starts by reconstructing a phase space from the gait data and a chaotic analysis estimates delay and embedding dimension parameters from which main gait descriptors are obtained, namely the largest Lyapunov exponent, correlation dimension and approximate entropy.

2.2. Methods

2.2.1. Data set

This exploratory analysis was conducted in a video database from CIM@LAB (Computer Imaging and Medical Applications Laboratory) at the Universidad Nacional de Colombia. Database included 14 subjects, distributed in 7 PD patients and 7 control subjects recruited by free consent and under ethical approval of a certificated committee. They showed a low fall risk during balance and functional performance screening. Each subject, freely walking under uncontrolled conditions, was recorded by a single lateral camera at 24 and 60 frames

per second. Subjects were asked to maintain 5 meters walkway during 1 minute, completing between 25-30 gait cycles at their normal walking speed. Body-Attached marker protocol was implemented according to the industry standard 'plug-in-gait full body' marker set[59].

Group	Male	Female	Age: years (mean± std)	Height: meters (mean± std)
Control	4	3	60.85±9.59	1.68±0.09
Stage 2	2	2	53±10.29	1.6±0.09
Stage 3	2	1	67.33±2.08	1.53±0.05

Table 2-1: Participants

Lower limb kinematic data (hip and knee) were extracted from body marker references using Kinovea. Once the time series were obtained, right and left limbs were separately analyzed by the chaos descriptors taking into account each frequency sample of the video.

2.2.2. Chaotic gait approximation

Chaos may be though of as an apparently random dynamics of a set of observations in the time domain, which actually follow deterministic patterns that are made evident when the phase space is constructed. In such space, trajectories determinedly evolve towards a particular subspace or attractor of the system [55]. This kind of processes has been identified in several biomedical signals like electroencephalogram or arterial blood flow patterns by computing their Lyapunov exponent and correlation dimension [57][60][61][62]. Likewise, gait has been reported to follow sort of chaotic rules in both young and healthy elder people, interestingly a phenomenon characterized using a unique parameter, i.e., the Lyapunov exponent [57][63][64]. In consequence, it turns appealing to get a gait characterization with a single descriptor. Specifically, kinematic time series $x(t)$ were herein analyzed in the phase space $\mathcal{X}_t^{\phi}(\tau, \varepsilon_d)$, using the above-mentioned chaos descriptors and PD motor alterations were characterized.

2.2.3. Construction of the phase space: time delay and the embedding dimension

A phase space should represent fundamental relations between system variables. Takens theorem [38] claims that a system phase space could be described by a single variable, $x(t)$ and its delayed versions $x(t-\tau)$, when the whole set of equations is unknown. For an N-dimension time series $x(t) = (x_1, \ldots, x_N)$, and its delay parameter τ, the phase space $\mathcal{X}_t^{\phi}$ represents the correlations between $x(t)$ and the time-delayed versions $x(t-\tau) = (x_{1+\tau}, \ldots, x_{N+\tau})$ of x. The first local minimum of the Mean Mutual Information [40] between $x(t)$ and its delayed

versions, is associated to the delay $\mathcal{T}$, estimated as follows:

$$\mathcal{T} = \underset{\tau}{\operatorname{argmin}} \sum_{i=1}^{N} p\left(x_i, x_{i+\tau}\right) log_2 \left(\frac{p\left(x_i, x_{i+\tau}\right)}{p\left(x_i\right) p\left(x_{i+\tau}\right)} \right) \tag{2-1}$$

A number of delayed time series may be then determined by multiples of the $\mathcal{T}$ parameter, $x(t-m\mathcal{T})$, being m a non negative integer value. The smallest number of delayed-time series required to reconstruct the phase space $\mathcal{X}_t^{\phi}$, including the original time series $x(t)$, is known as the embedding dimension ϵ_d, herein determined by the False Nearest Neighbors (FNN) [65]. Let us define $Y_{\mathcal{T}}(t) = \left(x_t, x_{t+\mathcal{T}}, \ldots, x_{t+(d-1)\mathcal{T}}\right)$ a point within the d-dimensional phase space and $Y_{\mathcal{T}}(t)^* = \left(x_t^*, x_{t+\mathcal{T}}^*, \ldots, x_{t+(d-1)\mathcal{T}}^*\right)$ its nearest neighbor, $R^2(d) = || \, Y_{\mathcal{T}}(t) - Y_{\mathcal{T}}(t)^* \, ||_2^2$ and the regularizer value r of the pair of FNN points a lower bound as:

$$\sqrt{\frac{R^2(d+1) - R^2(d)}{R^2(d)}} > r \tag{2-2}$$

Hence, the embedding dimension ε_d is equivalent to the smallest d value that generates a minimal number of FNN points in the phase space. Once the phase space is constructed, three main statistical invariants can be introduced to analyze the chaos properties, such as the Lyapunov exponent and the entropy and attractor dimension measurements. Those descriptors have been useful for assessing the sensitivity to the initial conditions, the information loss and the system complexity respectively [55].

2.2.4. Largest Lyapunov exponent

Largest Lyapunov exponent(λ) characterizes the separation of infinitesimally nearby trajectories in the $\mathcal{X}_t^{\phi}(\mathcal{T}, \epsilon_d)$ phase space. Once the delay parameter $\mathcal{T}$ and the embedding dimension ε_d are estimated, the exponential separation rate between d-dimensional points can be expressed as $D(t) = || \, Y_{\mathcal{T}}(t) - Y_{\mathcal{T}}(t)^* \, ||_1$. This can also be expressed as a function of t and λ as $D(t) = Ce^{\lambda t}$ (Eqn. 3-2 and Eqn. 3-3), as follows [40]:

$$|| \, Y_{\mathcal{T}}(t) - Y_{\mathcal{T}}(t)^* \, ||_1 \simeq Ce^{\lambda t} \tag{2-3}$$

$$\ln(\, || \, Y_T(t) - Y_T(t)^* \, ||_1) \simeq \ln C + \lambda t \tag{2-4}$$

The largest Lyapunov exponent is then calculated using the slope of the least-squares line defined by $ln(D(t))$ vs t^{-1} as follows:

$$\lambda = \frac{1}{t} \left\langle \ln(\, || \, Y_T(t) - Y_T(t)^* \, ||_1) \right\rangle \tag{2-5}$$

If $\lambda > 0$, the system is defined as chaotic [44]. Conversely, when $\lambda < 0$ the system converges to a fixed point in the phase space. Thus, Rosenstein algorithm [40] has been the most used implementation for this computation, providing a robust calculus for short and noisy time series.

2.2.5. Correlation dimension and approximate entropy

Correlation dimension estimates the probability that two points $Y_i(t)$ and $Y_j(t)^*$ in the phase space are close after a distance threshold is set. In contrast, approximate entropy is the likelihood that observation patterns are not similar [30][46]. These two descriptors were estimated for the same $\mathcal{X}_t^{\phi}(\tau, \varepsilon_d)$ phase space. A mathematical description was included in the Appendix 3.5. Chaos descriptors, in sections 3.2.6, 3.2.7, were calculated in MATLAB 2018b (Mathworks, Natick, Massachusetts, USA).

2.2.6. Statistical analysis

Since the current data showed a non-normal distribution, Mann-Whitney statistical test (MW) was used to evaluate statistical differences under a significance level of $p < 0{,}05$, in order to differentiate the Control and Parkinson group.

2.3. Results

A main aim of the present investigation was to characterize the gait with a minimum number of parameters, searching basically a sparse interpretation of the gait kinematic temporal series for each of the herein explored groups: Control and PD. Fig. **3-4** shows the reconstructed phase space from one participant of each experimental group, with associated delay ($\mathcal{T} = 10$ and embedded dimension $\varepsilon_d = 3$) for the control subject, while the PD patient had ($\mathcal{T} = 7$ and $\varepsilon_d = 3$). The found values for these parameters reflect actual differences of gait patterns in these two conditions. Since Parkinson's disease is characterized by reduced movements (hipokinesia), its attractor showed a smaller value when comparing with the control subject. As observed, the cycles defined by these two conditions follow very different patterns for both the hip and the knee, indicating this complex dynamics could be summarized. These qualitative differences were also tested by extending the analysis to quantitative chaos descriptors aforementioned in section 3.2.6. Mean and dispersion values of chaos descriptors for hip kinematics are presented in Tab. **2-2**, and statistically significant differences were found between groups for both Lyapunov exponent and approximate entropy. Higher Lyapunov exponent values were found in healthy, evidencing the higher variability in the gait pattern of control subjects. Likewise, Tab. **2-3** shows similar results for knee kinematic data, being the Lyapunov exponent in control group higher than PD. Statistical differences were again found. Previous investigations have reported chaotic patterns associated with healthy

central nervous systems [32], in agreement with our current results. In contrast, correlation dimension was not different in both groups.

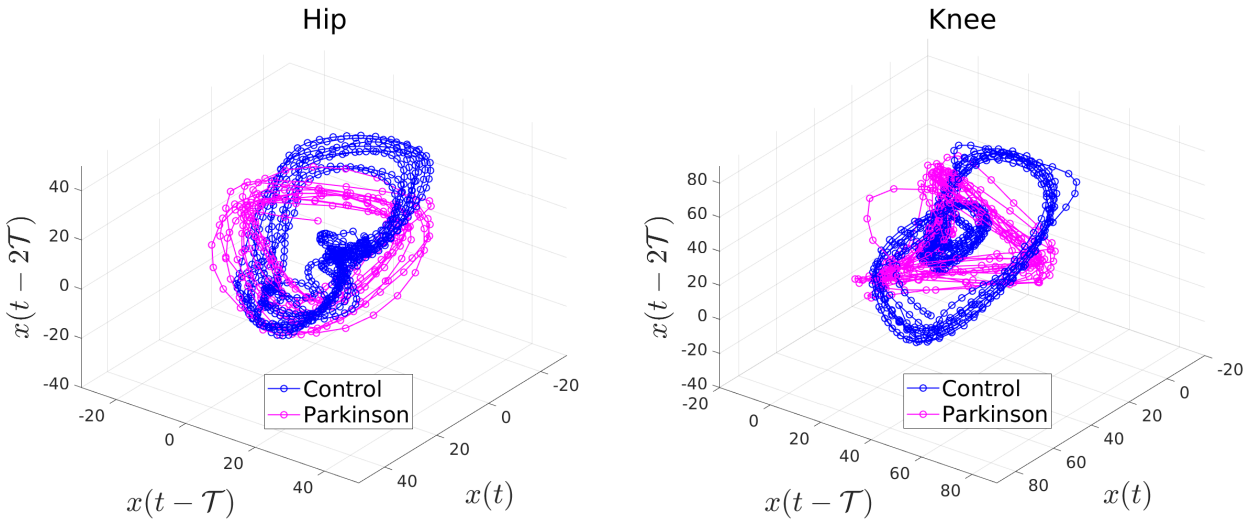

Figure 2-1: Right lower limb

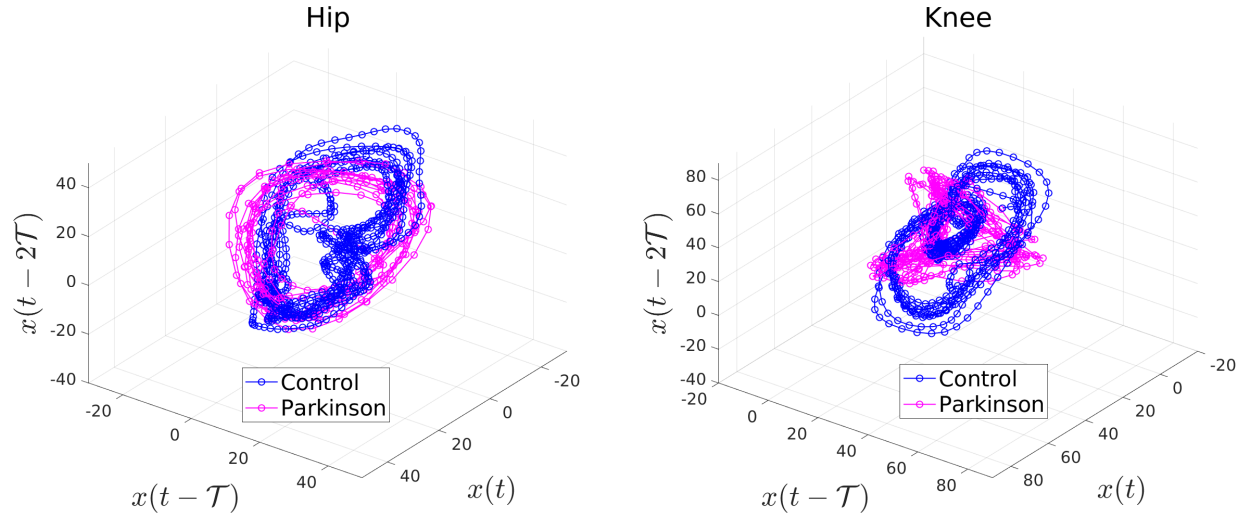

Figure 2-2: Left lower limb

Figure 2-3: Qualitative results: Typical phase space reconstruction for a PD subject and a control subject from kinematic time series: right (1a) and left (1b) sides. For each, the phase parameters were: Parkinson ($\mathcal{T} = 7, \varepsilon_d = 3$) and Control subjects ($\mathcal{T} = 10, \varepsilon_d = 3$).

		Largest Lyapunov exponents			Approximate entropy			Correlation dimension		
		mean	*SD*	*p*	*mean*	*SD*	*p*	*mean*	*SD*	*p*
Hip (L)	***Control***	11.88	1.58	$< 0{,}01$	0.55	0.07	$< 0{,}01$	2.63	1.08	0.62
	PD	4.6	0.81		0.31	0.1		2.51	0.63	
Hip (R)	***Control***	10.52	2.39	$< 0{,}01$	0.59	0.06	$< 0{,}01$	3.15	0.27	0.53
	PD	5.13	1.03		0.3	0.09		3.42	0.84	

Table 2-2: Hip kinematic analysis in left(L) and right(R) limbs.

		Largest Lyapunov exponents			Approximate entropy			Correlation dimension		
		mean	*SD*	*p*	*mean*	*SD*	*p*	*mean*	*SD*	*p*
Knee (L)	***Control***	12.37	2.43	$< 0{,}01$	0.58	0.1	$< 0{,}01$	2.58	0.33	0.53
	PD	4.78	1.94		0.39	0.15		2.66	0.52	
Knee (R)	***Control***	12.18	2.21	$< 0{,}01$	0.59	0.06	$0{,}053^{*}$	2.26	0.72	0.71
	PD	5.28	1.40		0.29	0.09		2.68	0.85	

Table 2-3: Knee kinematic analysis in left(L) and right(R) limbs.(*) indicates marginal significance.

2.4. Discussion

The deterioration of the neuronal structures yielded by movement disorders are complex showing different chaotic patterns [50][66]. Different studies have been done to quantify the chaotic disturbances that occur in gait. Kinematic time series may be chosen as input for state space reconstruction [63]. Likewise, the chaotic nature of the motor output has been also addressed by a physiologically model of stride interval of the gait [32]. This model indicated that stride interval is chaotic in healthy subject, but this chaotic nature changed towards a stochastic behaviour in PD states [32]. Furthermore, there are evidences show that fractal behaviour is seen in gait of healthy participants but it is reduced in PD gait [50]. Our purpose, was to calculate the chaos descriptors on gait kinematic temporal series (hip and knee). We also found a higher chaotic behaviour in PD in agreement with previous research [67]. However, there are several limitation in the current work, since the small sample and the short time series.

2.5. Conclusions

A novel gait characterization of parkinsonian gait patterns was presented. Phase space reconstruction from kinematic patterns qualitatively highlighted the chaotic gait patterns in both groups. Furthermore, the largest Lyapunov exponent and the approximated entropy can be used as descriptors of the motor impairment for differentiating PD and healthy gait. Whether the current methodology is able to accurately describe or predict the PD progression, must be tested in future research. Finally, this kind of biomarkers is easily interpretable and integrable with medical practices, improving the current predominance of observational motor assessments.

2.6. Appendix - Math definitions

2.6.1. Correlation dimension

Correlation dimension estimates the probability that two points $Y_i(t)$ and $Y_j(t)^*$ within the phase space are close according to a distance threshold α. First, the correlation sum $C(\alpha)$ is calculated as a function of α for N points in $\mathcal{X}_t^{\phi}(\tau, \varepsilon_d)$ as follows [45]:

$$C(\alpha) = \frac{1}{N(N-1)} \sum_{i,j=1, i \neq j}^{N} \Theta(\alpha - \|Y_i(t) - Y_j(t)^*\|) \tag{2-6}$$

$$\Theta = \begin{cases} 0 & if \quad \alpha - \|Y_i(t) - Y_j(t)^*\| < 0 \\ 1 & if \quad \alpha - \|Y_i(t) - Y_j(t)^*\| \geq 0 \end{cases} \tag{2-7}$$

Where Θ (Eqn. 3-6) is the Heaviside step function. Thus, the slope of the $log(C(\alpha))$ vs $log(\alpha)$ determines the correlation dimension value, a quantity directly proportional to the level of chaos in the system and to the space occupied by the trajectories into $\mathcal{X}_t^{\phi}(\tau, \varepsilon_d)$ [45][68].

2.6.2. Approximate entropy

Approximate entropy reflects the likelihood that observation patterns are not similar [30][46]. First, it was estimated the number of points $Y_j(t)$ of the above-mentioned phase space of N points and ε_d dimensions, with a distance respect to a $Y_i(t)$ point, $|| \, Y(i) - Y(j)^* \, ||_1$, is not higher than 0,2 times the variance of the original time series $x(t)$ [47]. This value is denoted as N_i. Being **1** the indicator function, N_i is computed as:

$$N_i = \sum_{i,j=1, i \neq j}^{N} 1(\|Y_i(t) - Y_j(t))\|_1 < 0{,}2 * var(x(t)) \tag{2-8}$$

An ϕ^{ε_d} parameter is then calculated as the sum of the logarithms for all N_i values, divided in $N - \varepsilon_d + 1$ (Eqn. 3-8). The same computation for a $\mathcal{X}_t^{\phi}(\tau, \varepsilon_d + 1)$ phase space is repeated. Finally, approximate entropy is estimated by the difference between $\phi^{\varepsilon_d} - \phi^{\varepsilon_d+1}$ (Eqn.3-9)

$$\phi^{\varepsilon_d} = \frac{1}{N - \varepsilon_d + 1} \sum_{i=1}^{N} log(N_i) \tag{2-9}$$

$$Ent_{Approx} = \phi^{\varepsilon_d} - \phi^{\varepsilon_d+1} \tag{2-10}$$

3 Article No. 2

Characterizing Parkinson's disease from gait dynamics using chaos descriptors

As presented on the 17th International Seminar on Medical Information Processing and Analysis SIPAIM 2021, Campinas Brasil, November 2021.

Motor disorders in Parkinson's Disease (PD) show high inter-individual variability which challenges the current observational-based strategies in the clinical setting to determine the actual disease evolution and monitoring the therapy response. In spite the recent development of the motion capture technology, it is still hardly transferable to the routine exam and the non-linear disease patterns are poorly explored. Because gait pattern could be approached as deterministic chaotic system, this work aimed to non-linearly represent lower limb kinematic standing out the differences among PD stages. For doing so, a widely used deep learning framework was implemented for obtaining the body landmarks and their temporal series and thereafter, construing the phase space based on the first order derivatives. Largest Lyapunov exponent, correlation dimension and approximate entropy were then computed resulting in statistically significant differences (Kruskal-Wallis rank test, $p < 0{,}05$), particularly between healthy controls and stages 3, the most advanced stage, and comparing stage 1 face to stage 3. These findings provide insights on how the complex patterns may be related with the disease progression in PD and easily implemented using affordable video devices.

3.1. Introduction

Parkinson's disease (PD) is a neurodegenerative disorder typically characterized by akinesia or slowness of the movement, rest tremor, rigidity, and gait disturbances [69][70], due to the loss of dopaminergic cells in the substantia nigra and a subsequent basal ganglia dysfunction [71]. Currently, the monitoring of the disease progression relies on observational-based screening as the the Parkinson's disease rating scale (UPDRS) and the neurologist expertise.

Nevertheless, the evolution motor disorder in PD are highly variable among patients being the actual disease status commonly underestimated by the clinical exam [24]. Particularly, gait disturbances are hardly quantified in clinical settings since these involve complex multi-level interactions between the neuromuscular and musculoskeletal systems leading to reduced step length and joint of motion and increased inter-limb asymmetries [72]. Moreover, main spatio-temporal gait variables i.e, stride interval, step length and cadence, are commonly reported as an average value in places where sophisticated devices for motion capture are available. In this context, a previous research has found cadence, stride and stance duration as the most discriminating gait variables between the early PD stage and unaffected subjects using a marker-based tracking strategy [73]. However, gait dynamics is characterized by an apparently irregular or chaotic behaviour that hides essential or deterministic patterns not easily quantifiable by the average and similar statistics [18], which suggest that non linear approaches are needed. Particularly, double pendulum models have provided the first insights about the chaotic behaviour of the gait, a phenomenon that may be associated to the dynamics of the neuromuscular subsystem [33]. Consequently, non-linear dynamics has been explored to distinguish between PD and healthy patterns when the gait times series are mapped to the phase space [39] (a previous study of ours) and clustered using Gaussian mixture models [74]. However, what extent these approaches may capture patterns associated with PD progression has not been sufficiently explored. Summarizing, a gait based staging and monitoring in PD urgently demand of robust data representation and reliable metrics reducing the current dependency on expensive equipment.

A main contribution of this study is a novel characterization of the Parkinson disease by non linearly representing the temporal gait dynamics in a phase space which facilitates objective measurements of the disease progression. Briefly, the method applies a deep learning framework to track body joints in a 2D video and the resultant time series are stored for later analysis. Since the human gait is a semi-periodic and mechanically constrained dynamic system, position, velocity and acceleration describe the system and configure a phase space. This phase plane is constructed by computing the first and second order derivatives of the kinematics times series. As the gait dynamic is chaotic and non-linear by nature, largest Lyapunov exponents (LLE), the correlation dimension (CorDim), and the approximate entropy (ApEn) were calculated to characterize abnormal spatio-temporal patterns in a set of patients with different degrees of the disease. This article is organized as follows: first the whole framework is explained, followed of the description of the experimental set up. Finally, qualitative and quantitative results are presented ending up with discussion and some conclusions.

3.2. Methods

As gait abnormalities are not easily quantifiable for PD stages in clinical scenarios, spatiotemporal patterns are computed in gait cycles using video recordings. Firstly, body landmarks

were first tracked for a set of gait recordings using a deep learning strategy [75]. Velocity and acceleration were then calculated from the resulting kinematics times series and used as dimensions of a phase space. Finally, the respective non-linear descriptors of the system are obtained for comparing disease stages.

3.2.1. Data set

This analysis was conducted with the CIM@LAB (Computer Imaging and Medical Applications Laboratory) video database at the National University of Colombia, constituted by 18 PD patients and 20 control subjects, enrolled under ethical approval of a certified committee. PD patients were categorized based on UPDRS scale being this applied by trained personal. Each participant walked at normal speed along a 4-meter walkway during two minutes, completing between 25 to 30 gait cycles. Motion in lateral view was recorded by a single RGB camera at 24 in some patients and 60 frames per second in the remaining data set, being the resulting videos up-sampled and down-sampled respectively to 50 frames per second using single interpolation and random sub-sampling.

Group	*Male*	*Female*	*Age: years(mean±std)*	*Height: meters(mean±std)*
Control	11	9	60.95 ± 8.22	1.65 ± 0.008
Stage 1	5	1	61.35 ± 8.93	1.63 ± 0.09
Stage 2	2	1	63.2 ± 10.88	1.61 ± 0.12
Stage 3	5	4	61.06 ± 9.23	1.63 ± 0.09

Table 3-1: Participants

3.2.2. Body landmarks detection

Openpose is a widely used deep learning framework that detects a set of body landmarks [75], trained with annotated databases of common daily activities, i.e., the common Objects in Context (COCO) and Human Pose Dataset (MPII) [76][77]. This network is composed of 7 convolutional layers applied in two stages estimating both, a vector field that encodes limb orientation, the Part Affinity Fields (PAFs), and the body parts as a confidence map, resulting in a set of 25 keypoint candidates. As the keypoint candidates must be associated to specific body segments, the network aligns the estimated PAFs with a model of body segments [75], and each of the body landmarks is labeled and retrieved as shown in figure **3-1**.

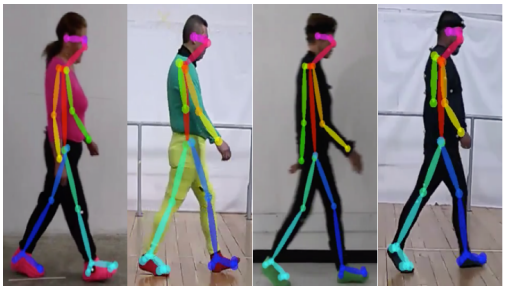

Figure 3-1: Openpose landmarks. Showing from left to right: control subject, PD stage 1, PD stage 2 and PD stage 3. Key points are retrieved as 2D coordinates in the image domain

3.2.3. Pre-processing and kinematic reconstruction

Since lower limbs are prone to self-occlusion when applying a single lateral view of the gait, their respective keypoints may be missed for certain parts of the gait cycle. Therefore, the miss-located coordinates were manually detected and linearly interpolated using an open source tool with a MATLAB interface [78]. Afterwards, angles with respect to the vertical of the hip, knee and ankle were calculated at each time point, using 3 consecutive key points given by $\arctan(\theta)$, and producing the time series of the joint motion [17]. Since the keypoint estimation is also prone to small oscillations (jitter [79]), a Savitzky-Golay smoothing, a 2-order polynomial least-squares fitting, was applied to a sliding window of 15 samples [80]. Resulting times series were characterized using a deterministic chaotic approach

3.2.4. Chaotic gait approximation

Chaotic systems have been widely observed in several biomedical signals like electroencephalogram or arterial blood flow [57][60][61][62]. Human gait shows a chaotic dynamics that involves complex and non-linear interactions between neuromuscular and musculoskeletal systems. Usually, chaos is associated with a unpredictable dynamics. While a chaotic system is highly dependent on the initial conditions, its behaviour is deterministic and bounded in the phase space [29]. This essential feature of the human motion have been found disrupted in PD gait which may be associated to the motor network impairment [18][32]. Therefore, this kind of non-linear approach could be highly sensitive to the disease progression as neuron and network damage progresses. Since gait is a quasi-periodic pattern and is subject to mechanical and physiological constraints, the solution of the associated equations can be bounded to a compact space or attractor. A previous research has demonstrated that non-linear descriptors can be properly implemented even in a extremely short data set (e.g. 200 samples) when the right parameters are chosen and considering that it is difficult to acquire large time series from human walking [81]. Furthermore, a chaotic approximation captures complex behavior using few coefficients that typically describe the phase space trajectories

as it will be herein demonstrated.

3.2.5. Construction of the phase space

A phase space is a representation of relations not visible in the original domain. The phase space is usually determined by the local minimal of the Mutual information between time-delayed versions of the original kinematic times series and the smallest number of dimensions for reconstructing an attractor with not crossing trajectories [65]. Nevertheless, this method depends on the delay computation which may be quite inaccurate for many time series [42]. Alternatively, the first order derivatives $\frac{dx}{dt}$ such as velocity and acceleration $\frac{d^2x}{dt^2}$ provide an equivalent and more accurate description of such fundamental relationships, an approximation known as the differential phase space or differential embedding as follows [42][43]:

$$x(t_i) \rightarrow \left\{ (t_i), \frac{dx}{dt}(t_i), ..., \frac{d^{m-1}x}{dt^{m-1}}(t_i) \right\}. \tag{3-1}$$

$x(t_i)$ is i-th term of the time series and m the derivative order. Once the phase space is constructed, the trajectories form regular but no identical loops known as attractor, a hallmark of the non-linear dynamics. A comprehensive description of this phenomenon is provided by several descriptors like Lyapunov exponent, Correlation Dimension and Approximate entropy which are further explained below.

3.2.6. Largest Lyapunov exponent

The level of complexity is measured by the rate of convergence or divergence of nearby trajectories within the attractor. One way of measuring this is by using Lyapunov exponent (λ), a description of the infinitesimal separation among nearby trajectories in the phase space, read as $D(t) = || \ Y(t) - Y(t)^* \ ||_1$, where $Y(t)$ and $Y(t)^*$ are points on trajectories inside the phase space. This can also be expressed as a function of t and λ as $D(t) = Ce^{\lambda t}$ (Eqn. 3-2 and Eqn. 3-3), as follows[40]:

$$|| \ Y(t) - Y(t)^* \ ||_1 \simeq Ce^{\lambda t} \tag{3-2}$$

$$\ln(\ || \ Y(t) - Y(t)^* \ ||_1) \simeq \ln C + \lambda t \tag{3-3}$$

The largest Lyapunov exponent is then calculated using the slope of the least-squared line defined by $ln(D(t))$ vs t^{-1} as follows:

$$\lambda = \frac{1}{t} \langle \ln(\ || \ Y(t) - Y(t)^* \ ||_1) \rangle \tag{3-4}$$

Typically, this computation provides and a set of coefficients known as the Lyapunov exponent spectrum. Obtained attractor related to the solution of a set of nonlinear differential equation is defined as chaotic if presents at least one positive Lyapunov exponent $\lambda > 0$ [44][29]. If $\lambda < 0$, the trajectories will have exponentially fast convergence [29]. If $\lambda = 0$, there is neither convergence nor divergence of the trajectories [29].

3.2.7. Correlation dimension and approximate entropy

Correlation dimension (CorDim) estimates the probability that two points $Y_i(t)$ and $Y_j(t)^*$ in the phase space are close after a distance threshold is set. In contrast, approximate entropy (ApEn) is the probability observation patterns are not similar [30][46]. Chaos descriptors, in sections 3.2.6, 3.2.7, were calculated in MATLAB 2020a (Mathworks, Natick, Massachusetts, USA).

3.2.8. Statistical analysis

Since the computed descriptors showed non-normal distribution and several disease stages are simultaneously compared, multi variable non-parametric statistical test (Kruskal-Wallis which relies on the ranks of the data and the chi-square (χ^2) statistic) and *pos-hoc* analysis was applied to evaluate statistical differences between control and Parkinson groups under a significance level of $p < 0{,}05$.

3.3. Results

A non linear characterization of the lower limb gait kinematic in PD was performed by a quantitative measure of the disease stages. Globally, λ parameter was set greater than zero in all groups (figure **3-4** and **3-7**) and the phase space trajectories formed distinguishable and non overlapping attractor, which suggests the chaotic nature of the phenomenon [44]. In spite of this observation is extremely difficult, under the current experimental conditions, to be completely sure that the widespread assumptions related to chaotic dynamics are being fulfilled e.g. to guarantee infinitesimal perturbations between time points at the fixed frequency sampling. Moreover, it is so difficult to state that every trial of a patient's gait comes from a deterministic model in which an actual chaotic attractor is observed since neuromuscular control may introduce additional non-linearity as opposed to a simply mechanical model. Therefore, current results must be carefully interpreted.

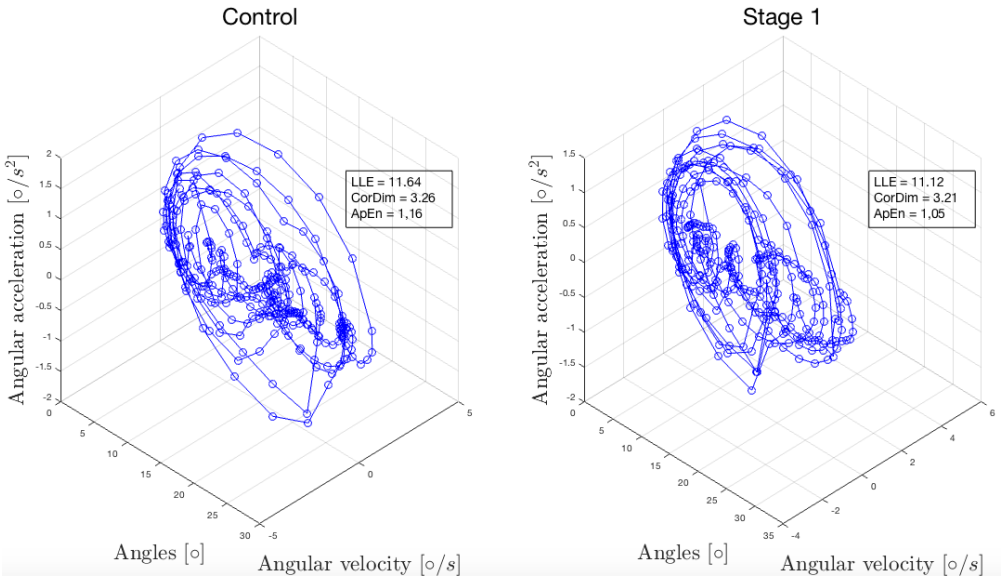

Figure 3-2: Right Hip

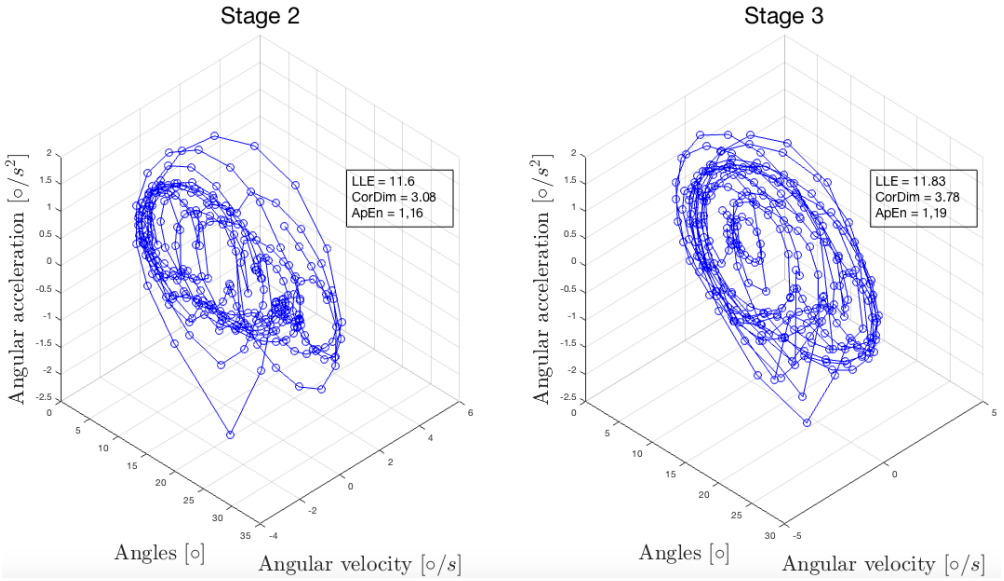

Figure 3-3: Right Hip

Figure 3-4: Typical phase space reconstruction for different disease stages from hip kinematic time series.

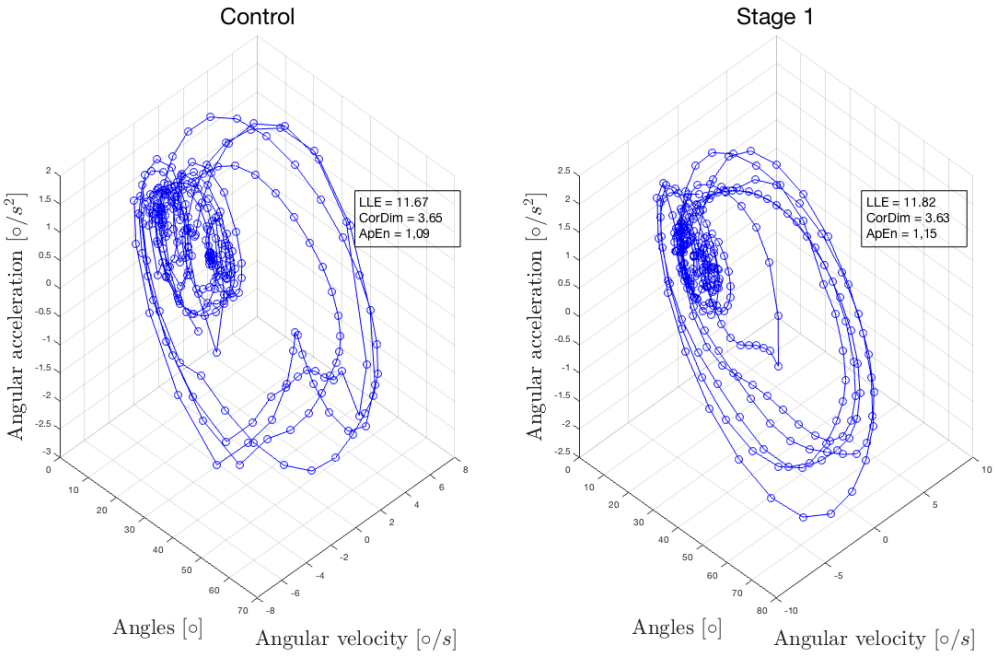

Figure 3-5: Right Knee

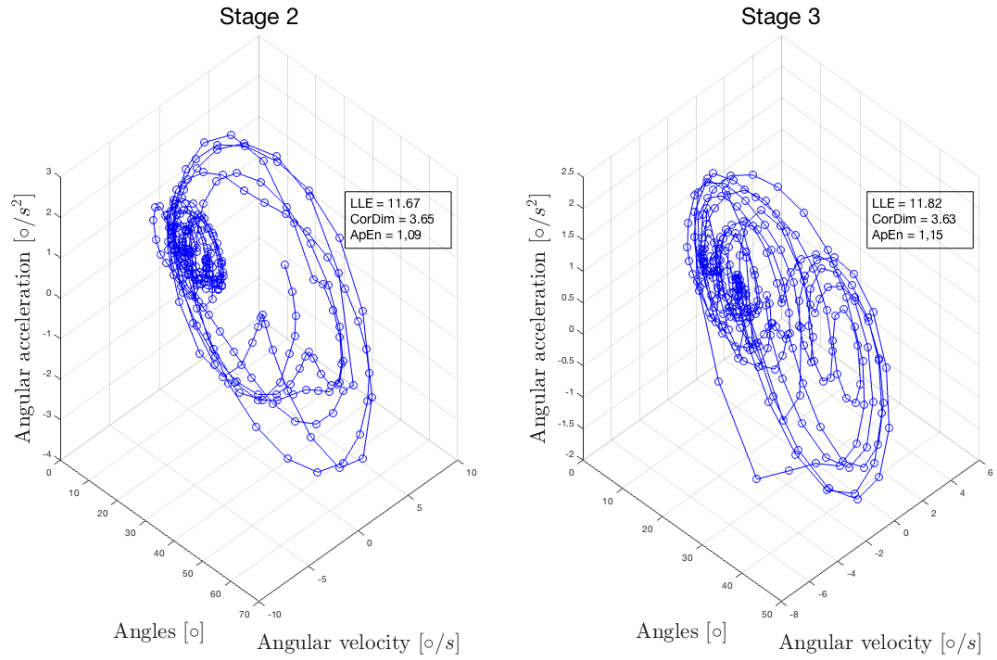

Figure 3-6: Right Knee

Figure 3-7: Typical phase space reconstruction for different disease stages from knee kinematic time series.

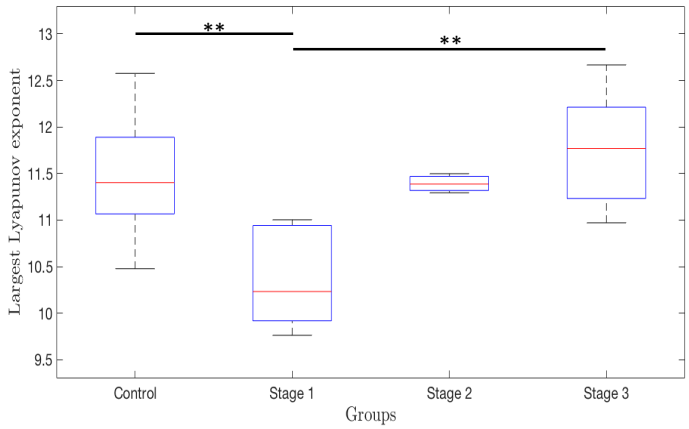

Figure 3-8: Left Hip

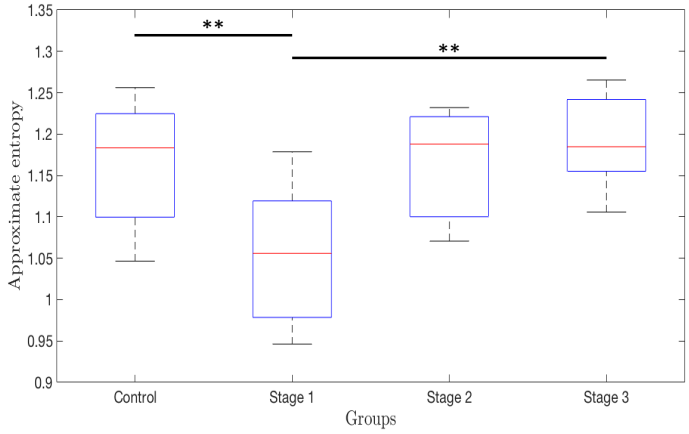

Figure 3-9: Right Hip

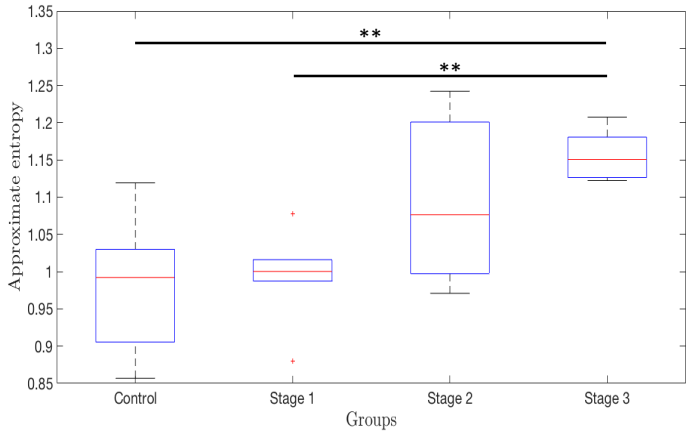

Figure 3-10: Right Knee

Figure 3-11: Statistically significant differences are signed as ** after *pos hoc* analysis is performed

Statistical test results were summarized only presenting the chaos descriptors that showed significant differences among PD stages.
Qualitatively, the phase space derived from hip kinematics showed a characteristic ellipsoidal attractor with no single path, consistent with its quasi-periodic motion and the joint mechanical restrictions. Consequently, these trajectories look similar among groups as shown in figures **3-2** and **3-3**, where some differences can be observed in the average λ and ApEn. Multi-class statistical test showed that λ and ApEn coefficients comes from different distributions (figure **3-8** and **3-9** with χ^2 probability of 0,002 and 0,03 respectively) being the difference for the stage 3 when compared to stage 1 statistically significant in the *post-hoc* contrast. However, no differences were found w.r.t. states 2 and 3. These results suggest hip mechanisms are affected in most advanced stages since the clinical stages 2 and 3 are similarly compromised.
As in the hip joint, mapping knee kinematic temporal series to the phase space results in a well-defined attractor where a small loop of trajectories in the upper-left are circumscribed within a larger loop, suggesting two mechanically constrained phases of the knee joint during gait cycle (figure **3-5** and **3-6**). Similarly, λ coefficient was greater than zero in all cases for the knee data. Unlike hip dynamics, knee patterns appear quite different in stage 3 (figure **3-6** at left). Nevertheless, observation showed significant differences for *ApEn* among PD stages (χ^2 probability of 0,002). *Pos-hoc* contrast confirmed statistical differences between control group and stage 3, and between stage 1 and stage 3, which are reasonable observations from a clinical point of view (figure **3-10**). As in the hip characterization, no differences between stage 1 and control group. Therefore, knee dynamics is mainly affected in the last stages of PD. Summarizing the current results, lower limb dynamics was characterized by a chaotic pattern in all PD groups and healthy controls, being the last stages the ones exhibiting large coefficients while no findings were observed in early stages.

3.4. Conclusions

This work aimed to characterize PD stages by non linearly representing the gait dynamics, using a deep learning-based pose estimation framework. Chaotic patterns were bilaterally found in the phase space derived from the lower limb kinematics in PD and control, highlighting the gait hidden and deterministic dynamics. As the three non-linear parameters namely, λ, ApEn and CorDim were found to be higher in the last stages of disease and similar to healthy controls in the first stage, this representation of the gait data might distinguish complex patterns associated with the disease progression, a desirable tool for monitoring the actual disease status and the therapy response. Since chaotic system assumptions may not be fully met in the current experimental conditions, results must be carefully interpreted. Alternatively, deviations from a periodic behaviour could be addressed as a more general stochastic process to overcome some of these limitations. Finally, being the current methodology cost affordable an easily implementable, it could be tested in a large cohort of PD

patients for establishing the gait pattern as robust PD biomarker.

3.5. Appendix-Math definitions

3.5.1. Correlation dimension

Correlation dimension estimates the probability two points $Y_i(t)$ and $Y_j(t)^*$ within the phase space are close according to a distance threshold α. First, the correlation sum $C(\alpha)$ is calculated as a function of α for N points in the phase space as follows [45]:

$$C(\alpha) = \frac{1}{N(N-1)} \sum_{i,j=1,i\neq j}^{N} \Theta(\alpha - \|Y_i(t) - Y_j(t)^*\|) \tag{3-5}$$

$$\Theta = \begin{cases} 0 & if \quad \alpha - \|Y_i(t) - Y_j(t)^*\| < 0 \\ 1 & if \quad \alpha - \|Y_i(t) - Y_j(t)^*\| \geq 0 \end{cases} \tag{3-6}$$

Where Θ (Eqn. 3-6) is the Heaviside step function. Thus, the slope of the $log(C(\alpha))$ vs $log(\alpha)$ determines the correlation dimension value, a quantity directly proportional to the level of chaos in the system and to the space occupied by the trajectories into phase space.

3.5.2. Approximate entropy

Approximate entropy estimates probability observation patterns are not similar[30][46]. First, it was estimated the number of points $Y_j(t)$ of the above-mentioned phase space of N points and ε_d dimensions, with a distance respect to a $Y_i(t)$ point, $||\ Y(i) - Y(j)^*\ ||_1$, is not higher than 0,2 times the variance of the time series $x(t)$ [47]. This value is denoted as N_i. Being **1** the indicator function, N_i is computed as:

$$N_i = \sum_{i,j=1,i\neq j}^{N} 1(\|Y_i(t) - Y_j(t))\|_1 < 0{,}2 * var(x(t))) \tag{3-7}$$

An ϕ^{ε_d} parameter is then calculated as the sum of the logarithms for all N_i values, divided in $N - \varepsilon_d + 1$ (Eqn. 3-8). The same computation for a phase space is repeated. Finally, approximate entropy is estimated by the difference between $\phi^{\varepsilon_d} - \phi^{\varepsilon_d+1}$ (Eqn.3-9)

$$\phi^{\varepsilon_d} = \frac{1}{N - \varepsilon_d + 1} \sum_{i=1}^{N} log(N_i) \tag{3-8}$$

$$Ent_{Approx} = \phi^{\varepsilon_d} - \phi^{\varepsilon_d+1} \tag{3-9}$$

4 Conclusions

This work presented a novel strategy to characterize Parkinson's disease using nonlinear representation of temporal gait dynamics in a phase space that facilitates the objective measurements of disease progression. The information about gait abnormalities was extracted from kinematic time series of gait cycles using video recordings. The method takes advantage of spatial and temporal relationships that allows characterized gait patterns dynamics and associate them to disease's progression. Finally, the strategy was able to distinguish differences among some stages of the disease.

In this thesis, a novel strategy to extract kinematic time series was used with a deep learning-based pose estimation framework. The phase space reconstruction was essential to represent the hidden patterns inside the deterministic dynamics of the gait, allows find the chaotic nature of the gait using the chaos descriptors as LLE, CorDim and ApEn. Despite the high variability and the complex fluctuations of kinematic time series, initially, it was possible quantify and to find differences between healthy subjects and patients with PD and then find differences among some stages of the disease but, since chaotic system assumptions may not be fully met in the current experimental conditions, results must be carefully interpreted. Finally, being the current methodology cost affordable an easily implementable, it could be tested in a large cohort of patients with PD.

In addition, although the pose estimation frame tracking used to assess lower limbs kinematic gait patterns is acceptable, the upper limbs kinematic time series tracking needs improvement, due to tracking errors of each limb joint. The important reason is because by having the tracking information of the upper and lower limbs, the gait balance could be characterized when the dynamic movement of coupled angles between the left shoulder and the right hip or between the right shoulder and the hip is analyzed. Also, the dynamics of the CoM could be characterized because it is potentially a biomarker that gives relevant information about of disease progression.

Although gait dynamics were characterized from kinematic time series of healthy subjects and patients with PD, it is important to make capture video in the frontal plane since lateral movements are associated with trunk stability during a gait cycle and these could provide information about how the balance is disturbed and how the CoM moves whereas the disease progresses. Therefore, the additional information extracted by frontal plane video capture

could complement the information obtained with sagittal plane video capture and it could make a reconstruction model to characterize the kinematic gait dynamic and the CoM in 3D. As the number of video captures of patients with PD is limited, it is recommended to increase the number of videos to expand the current database, it is even suggested to create a public database managed by the ethics committee, with identity protection of participants to reproduce the results obtained in this work or to obtain new results.

References

[1] G. DeMaagd and A. Philip, "Parkinson's disease and its management: part 1: disease entity, risk factors, pathophysiology, clinical presentation, and diagnosis," *Pharmacy and therapeutics*, vol. 40, no. 8, p. 504, 2015.

[2] K. McFarthing, G. Rafaloff, M. A. Baptista, R. K. Wyse, and S. R. Stott, "Parkinson's disease drug therapies in the clinical trial pipeline: 2021 update," *Journal of Parkinson's Disease*, vol. 11, no. 3, p. 891, 2021.

[3] E. Dorsey, T. Sherer, M. S. Okun, and B. R. Bloem, "The emerging evidence of the parkinson pandemic," *Journal of Parkinson's disease*, vol. 8, no. s1, pp. S3–S8, 2018.

[4] C. Váradi, "Clinical features of parkinson's disease: the evolution of critical symptoms," *Biology*, vol. 9, no. 5, p. 103, 2020.

[5] C. G. Goetz, "The history of parkinson's disease: early clinical descriptions and neurological therapies," *Cold Spring Harbor perspectives in medicine*, vol. 1, no. 1, p. a008862, 2011.

[6] P. C. Poortvliet, A. Gluch, P. A. Silburn, and G. D. Mellick, "The queensland parkinson's project: an overview of 20 years of mortality from parkinson's disease," *Journal of Movement Disorders*, vol. 14, no. 1, p. 34, 2021.

[7] S. Rong, G. Xu, B. Liu, Y. Sun, L. G. Snetselaar, R. B. Wallace, B. Li, J. Liao, and W. Bao, "Trends in mortality from parkinson disease in the united states, 1999–2019," *Neurology*, vol. 97, no. 20, pp. e1986–e1993, 2021.

[8] F. Yang, A. L. Johansson, N. L. Pedersen, F. Fang, M. Gatz, and K. Wirdefeldt, "Socioeconomic status in relation to parkinson's disease risk and mortality: A population-based prospective study," *Medicine*, vol. 95, no. 30, 2016.

[9] J. Jankovic and E. K. Tan, "Parkinson's disease: Etiopathogenesis and treatment," *Journal of Neurology, Neurosurgery & Psychiatry*, vol. 91, no. 8, pp. 795–808, 2020.

[10] P. Martinez-Martin, M. Skorvanek, J. M. Rojo-Abuin, Z. Gregova, G. T. Stebbins, C. G. Goetz, and Q. S. Group, "Validation study of the hoehn and yahr scale included in the mds-updrs," *Movement Disorders*, vol. 33, no. 4, pp. 651–652, 2018.

[11] N. I. of Health *et al.*, "Parkinson's disease: challenges, progress, and promise," 2009.

[12] K. A. Al Mamun, M. Alhussein, K. Sailunaz, and M. S. Islam, "Cloud based framework for parkinson's disease diagnosis and monitoring system for remote healthcare applications," *Future Generation Computer Systems*, vol. 66, pp. 36–47, 2017.

[13] A. Tekriwal, D. S. Kern, J. Tsai, N. F. Ince, J. Wu, J. A. Thompson, and A. Abosch, "Rem sleep behaviour disorder: prodromal and mechanistic insights for parkinson's disease," *Journal of Neurology, Neurosurgery & Psychiatry*, vol. 88, no. 5, pp. 445–451, 2017.

[14] M. Gerlach, W. Maetzler, K. Broich, H. Hampel, L. Rems, T. Reum, P. Riederer, A. Stöffler, J. Streffer, and D. Berg, "Biomarker candidates of neurodegeneration in parkinson's disease for the evaluation of disease-modifying therapeutics," *Journal of neural transmission*, vol. 119, no. 1, pp. 39–52, 2012.

[15] P. P. Michel, E. C. Hirsch, and S. Hunot, "Understanding dopaminergic cell death pathways in parkinson disease," *Neuron*, vol. 90, no. 4, pp. 675–691, 2016.

[16] A. Iarkov, G. Barreto, J. Grizzell, and V. Echeverria, "Strategies for the treatment of parkinson's disease: beyond dopamine. front. aging neurosci. 2020; 12: 4," 2020.

[17] D. A. Winter, *Biomechanics and motor control of human movement*. John Wiley & Sons, 2009.

[18] D. Grabli, C. Karachi, M.-L. Welter, B. Lau, E. C. Hirsch, M. Vidailhet, and C. François, "Normal and pathological gait: what we learn from parkinson's disease," *Journal of Neurology, Neurosurgery & Psychiatry*, vol. 83, no. 10, pp. 979–985, 2012.

[19] A. Alamdari and V. N. Krovi, "A review of computational musculoskeletal analysis of human lower extremities," *Human Modelling for Bio-Inspired Robotics*, pp. 37–73, 2017.

[20] L. M. Silva and N. Stergiou, "The basics of gait analysis," *Biomechanics and Gait Analysis*, vol. 164, p. 231, 2020.

[21] J. Kawalec, "Mechanical testing of foot and ankle implants," in *Mechanical Testing of Orthopaedic Implants*, pp. 231–253, Elsevier, 2017.

[22] C. Price, T. Schmeltzpfenning, C. J. Nester, and T. Brauner, "Foot and footwear biomechanics and gait," in *Handbook of Footwear Design and Manufacture*, pp. 79–103, Elsevier, 2021.

[23] C. W. Hess and M. Hallett, "The phenomenology of parkinson's disease," in *Seminars in neurology*, vol. 37, pp. 109–117, Thieme Medical Publishers, 2017.

[24] L. di Biase, A. Di Santo, M. L. Caminiti, A. De Liso, S. A. Shah, L. Ricci, and V. Di Lazzaro, "Gait analysis in parkinson's disease: An overview of the most accurate markers for diagnosis and symptoms monitoring," *Sensors*, vol. 20, no. 12, p. 3529, 2020.

[25] S. Iqbal, X. Zang, Y. Zhu, H. M. A. A. Saad, and J. Zhao, "Nonlinear time-series analysis of different human walking gaits," in *2015 IEEE International Conference on Electro/Information Technology (EIT)*, pp. 025–030, IEEE, 2015.

[26] R. T. Lazaro, S. G. Reina-Guerra, and M. Quiben, *Umphred's Neurological Rehabilitation-E-Book*. Elsevier Health Sciences, 2019.

[27] D. Umphred and C. Carlson, *Neurorehabilitation for the physical therapist assistant*. Slack Incorporated, 2006.

[28] D. F. Dale Purves, George J. Augustine, *Neuroscience*. Oxford University Press, 2018.

[29] N. Stergiou, *Nonlinear analysis for human movement variability*. CRC press, 2018.

[30] H. Kantz and T. Schreiber, *Nonlinear time series analysis*, vol. 7. Cambridge university press, 2004.

[31] R. E. van Emmerik, S. W. Ducharme, A. C. Amado, and J. Hamill, "Comparing dynamical systems concepts and techniques for biomechanical analysis," *Journal of Sport and Health Science*, vol. 5, no. 1, pp. 3–13, 2016.

[32] Y. Sarbaz, F. Towhidkhah, A. Jafari, and S. Gharibzadeh, "Do the chaotic features of gait change in parkinson's disease?," *Journal of theoretical biology*, vol. 307, pp. 160–167, 2012.

[33] L. M. Decker, F. Cignetti, and N. Stergiou, "Complexity and human gait," *Revista Andaluza de Medicina del Deporte*, vol. 3, no. 1, pp. 2–12, 2010.

[34] M. Galatzer-Levy, Robert, "Understanding nonlinear dynamics.: D. kaplan and l. glass. new york: Springer-verlag, 1995," *Psychoanalytic Quarterly*, vol. 66, pp. 737–737, 1997.

[35] R. C. Hilborn *et al.*, *Chaos and nonlinear dynamics: an introduction for scientists and engineers*. Oxford University Press on Demand, 2000.

[36] P. Berge, Y. Pomeau, and C. Vidal, "Order within chaos: towards a deterministic approach to turbulence," 1986.

[37] N. Stergiou, U. Buzzi, M. Kurz, and J. Heidel, "Nonlinear tools in human movement," *Innovative analyses of human movement*, pp. 63–90, 2004.

[38] F. Takens, "Detecting strange attractors in turbulence," in *Dynamical systems and turbulence, Warwick 1980*, pp. 366–381, Springer, 1981.

[39] D. Ricaurte, G. Pineda, and E. Romero, "Characterizing the gait dynamic by estimating lyapunov exponents on gait kinematic trajectories in parkinson's disease," in *15th International Symposium on Medical Information Processing and Analysis*, vol. 11330, p. 1133010, International Society for Optics and Photonics, 2020.

[40] M. T. Rosenstein, J. J. Collins, and C. J. De Luca, "A practical method for calculating largest lyapunov exponents from small data sets," *Physica D: Nonlinear Phenomena*, vol. 65, no. 1-2, pp. 117–134, 1993.

[41] S. Wallot and D. Mønster, "Calculation of average mutual information (ami) and false-nearest neighbors (fnn) for the estimation of embedding parameters of multidimensional time series in matlab," *Frontiers in psychology*, p. 1679, 2018.

[42] P. Xu, "Differential phase space reconstructed for chaotic time series," *Applied Mathematical Modelling*, vol. 33, no. 2, pp. 999–1013, 2009.

[43] J. Lekscha and R. V. Donner, "Phase space reconstruction for non-uniformly sampled noisy time series," *Chaos: An Interdisciplinary Journal of Nonlinear Science*, vol. 28, no. 8, p. 085702, 2018.

[44] A. Wolf, J. B. Swift, H. L. Swinney, and J. A. Vastano, "Determining lyapunov exponents from a time series," *Physica D: Nonlinear Phenomena*, vol. 16, no. 3, pp. 285–317, 1985.

[45] L. S. McCue and A. W. Troesch, "Use of lyapunov exponents to predict chaotic vessel motions," in *Contemporary Ideas on Ship Stability and Capsizing in Waves*, pp. 415–432, Springer, 2011.

[46] J. M. Hausdorff, C. Peng, Z. Ladin, J. Y. Wei, and A. L. Goldberger, "Is walking a random walk? evidence for long-range correlations in stride interval of human gait," *Journal of Applied Physiology*, vol. 78, no. 1, pp. 349–358, 1995.

[47] S. M. Pincus, "Approximate entropy as a measure of system complexity.," *Proceedings of the National Academy of Sciences*, vol. 88, no. 6, pp. 2297–2301, 1991.

[48] L. M. De Lau and M. M. Breteler, "Epidemiology of parkinson's disease," *The Lancet Neurology*, vol. 5, no. 6, pp. 525–535, 2006.

[49] R. Martínez-Fernández, C. Gasca-Salas, Á. Sánchez-Ferro, and J. Á. Obeso, "Actualización en la enfermedad de parkinson," *Revista Médica Clínica Las Condes*, vol. 27, no. 3, pp. 363–379, 2016.

[50] M. Ferrarin, L. Lopiano, M. Rizzone, M. Lanotte, B. Bergamasco, M. Recalcati, and A. Pedotti, "Quantitative analysis of gait in parkinson's disease: a pilot study on the

effects of bilateral sub-thalamic stimulation," *Gait & posture*, vol. 16, no. 2, pp. 135–148, 2002.

[51] J. 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*, vol. 19, no. 2, p. 026113, 2009.

[52] J. Jankovic, "Parkinson's disease: clinical features and diagnosis," *Journal of neurology, neurosurgery & psychiatry*, vol. 79, no. 4, pp. 368–376, 2008.

[53] J. B. Dingwell and L. C. Marin, "Kinematic variability and local dynamic stability of upper body motions when walking at different speeds," *Journal of biomechanics*, vol. 39, no. 3, pp. 444–452, 2006.

[54] V. S. Anishchenko, T. Vadivasova, and G. Strelkova, "Deterministic nonlinear systems," *A Short Course. Switzerland: Springer International Publishing*, vol. 294, 2014.

[55] L. Tang, H. Lv, F. Yang, and L. Yu, "Complexity testing techniques for time series data: A comprehensive literature review," *Chaos, Solitons & Fractals*, vol. 81, pp. 117–135, 2015.

[56] D. Lasagna, "Sensitivity analysis of chaotic systems using unstable periodic orbits," *SIAM Journal on Applied Dynamical Systems*, vol. 17, no. 1, pp. 547–580, 2018.

[57] S. Mehdizadeh, "The largest lyapunov exponent of gait in young and elderly individuals: a systematic review," *Gait & posture*, vol. 60, pp. 241–250, 2018.

[58] C. Aştefănoaei, E. Pretegiani, L. Optican, D. Creangă, and A. Rufa, "Eye movement recording and nonlinear dynamics analysis–the case of saccades," *Romanian journal of biophysics*, vol. 23, no. 1-2, p. 81, 2013.

[59] B. Galna, G. Barry, D. Jackson, D. Mhiripiri, P. Olivier, and L. Rochester, "Accuracy of the microsoft kinect sensor for measuring movement in people with parkinson's disease," *Gait & posture*, vol. 39, no. 4, pp. 1062–1068, 2014.

[60] E. D. Übeyli, "Lyapunov exponents/probabilistic neural networks for analysis of eeg signals," *Expert Systems with Applications*, vol. 37, no. 2, pp. 985 – 992, 2010.

[61] D. Yılmaz and N. F. Güler, "Analysis of the doppler signals using largest lyapunov exponent and correlation dimension in healthy and stenosed internal carotid artery patients," *Digital Signal Processing*, vol. 20, no. 2, pp. 401 – 409, 2010.

[62] K. Harezlak and P. Kasprowski, "Searching for chaos evidence in eye movement signals," *Entropy*, vol. 20, no. 1, p. 32, 2018.

[63] S. Bruijn, O. Meijer, P. Beek, and J. Van Dieën, "Assessing the stability of human locomotion: a review of current measures," *Journal of the Royal Society Interface*, vol. 10, no. 83, p. 20120999, 2013.

[64] S. M. Bruijn, D. J. Bregman, O. G. Meijer, P. J. Beek, and J. H. van Dieën, "Maximum lyapunov exponents as predictors of global gait stability: a modelling approach," *Medical engineering and physics*, vol. 34, no. 4, pp. 428–436, 2012.

[65] C. Rhodes and M. Morari, "The false nearest neighbors algorithm: An overview," *Computers & Chemical Engineering*, vol. 21, pp. S1149–S1154, 1997.

[66] Y. Sarbaz and H. Pourakbari, "A review of presented mathematical models in parkinson's disease: Black-and gray-box models," *Medical & biological engineering & computing*, vol. 54, no. 6, pp. 855–868, 2016.

[67] W. Caesarendra, B. Kosasih, K. Tieu, and C. A. Moodie, "An application of nonlinear feature extraction-a case study for low speed slewing bearing condition monitoring and prognosis," in *2013 IEEE/ASME International Conference on Advanced Intelligent Mechatronics*, pp. 1713–1718, IEEE, 2013.

[68] J. Theiler, "Efficient algorithm for estimating the correlation dimension from a set of discrete points," *Physical review A*, vol. 36, no. 9, p. 4456, 1987.

[69] F. Magrinelli, A. Picelli, P. Tocco, A. Federico, L. Roncari, N. Smania, G. Zanette, and S. Tamburin, "Pathophysiology of motor dysfunction in parkinson's disease as the rationale for drug treatment and rehabilitation. parkinsons dis. 2016," 2016.

[70] T. R. Mhyre, J. T. Boyd, and R. W. Hamill, "and kathleen a. maguire-zeiss," *Protein Aggregation and Fibrillogenesis in Cerebral and Systemic Amyloid Disease*, vol. 65, p. 389, 2012.

[71] P. Chand and I. Litvan, "Parkinson's disease," in *Encyclopedia of Gerontology (Second Edition)* (J. E. Birren, ed.), pp. 322–333, New York: Elsevier, second edition ed., 2007.

[72] J. Perry and J. Burnfield, "Gait analysis: normal and pathological function. slack," *Inc., Thorofare, NJ*, 1992.

[73] M. Pistacchi, M. Gioulis, F. Sanson, E. De Giovannini, G. Filippi, F. Rossetto, and S. Z. Marsala, "Gait analysis and clinical correlations in early parkinson's disease," *Functional neurology*, vol. 32, no. 1, p. 28, 2017.

[74] P. Pérez-Toro, J. Vásquez-Correa, T. Arias-Vergara, E. Nöth, and J. Orozco-Arroyave, "Nonlinear dynamics and poincaré sections to model gait impairments in different stages of parkinson's disease," *Nonlinear Dynamics*, vol. 100, pp. 3253–3276, 2020.

[75] Z. Cao, T. Simon, S.-E. Wei, and Y. Sheikh, "Realtime multi-person 2d pose estimation using part affinity fields," in *Proceedings of the IEEE conference on computer vision and pattern recognition*, pp. 7291–7299, 2017.

[76] T.-Y. Lin, M. Maire, S. Belongie, J. Hays, P. Perona, D. Ramanan, P. Dollár, and C. L. Zitnick, "Microsoft coco: Common objects in context," in *European conference on computer vision*, pp. 740–755, Springer, 2014.

[77] M. Andriluka, L. Pishchulin, P. Gehler, and B. Schiele, "2d human pose estimation: New benchmark and state of the art analysis," in *Proceedings of the IEEE Conference on computer Vision and Pattern Recognition*, pp. 3686–3693, 2014.

[78] J. Stenum, C. Rossi, and R. T. Roemmich, "Two-dimensional video-based analysis of human gait using pose estimation," *PLoS computational biology*, vol. 17, no. 4, p. e1008935, 2021.

[79] D. H. Wolaver and D. H. Wolaver, *Phase-locked loop circuit design*, vol. 1. Prentice Hall USA, 1991.

[80] R. W. Schafer, "What is a savitzky-golay filter?[lecture notes]," *IEEE Signal processing magazine*, vol. 28, no. 4, pp. 111–117, 2011.

[81] J. M. Yentes, N. Hunt, K. K. Schmid, J. P. Kaipust, D. McGrath, and N. Stergiou, "The appropriate use of approximate entropy and sample entropy with short data sets," *Annals of biomedical engineering*, vol. 41, no. 2, pp. 349–365, 2013.