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A new *route* to non invasive diagnosis in neurodegenerative diseases?

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Abstract

We propose a simple dynamical system to interpret the gait time series from patients affected by three neurodegenerative diseases: Parkinson, Huntington and Amyotrophic Lateral Sclerosis. The model is shown to reproduce the main aspects of the experimental time series. Within this scenario, quantitative differences in specific indicators are detected thus opening up the perspective for innovative, non invasive, diagnosis procedures from direct measurements of gait dynamics.

Keywords: Time series; Dynamical systems; Neurodegenerative disease

Walking is a voluntary process, but stride-to-stride regulation of gait is controlled by the nervous system in a largely automatic fashion [8,9]. Disruption of any portion of the neural networks involved in motor control can cause a person to produce uncoordinated and poorly controlled movements. Hence, detection of anomalies in the walking process can reveal underlying neurodegenerative disorders and eventually result in innovative and non invasive diagnostic protocols.

A neurodegenerative disease is caused by the deterioration of neurons. Changes in these cells cause them to function abnormally, eventually bringing about their death. Several experiments carried out by independent research units have, in various settings, measured gait time series from healthy subjects and patients affected by neurodegenerative pathologies such as Parkinson (PD), Huntington (HD) and Amyotrophic Lateral Sclerosis (ALS) [1,5]. Statistical tools have often been employed to extract quantitative indicators aiming at characterizing the degree of the disease [3–5].

In this paper we introduce an alternative approach by developing a simple dynamical model to interpret experimental gait measurements. Although very simple, this model is shown to capture the important features of gait time series, therefore providing a successful interpretative framework to develop innovative diagnostic strategies.

More specifically, we postulate the existence of a self-regulatory mechanism that stabilizes walking. Healthy subjects posses an "internal clock" which governs gait dynamics by inducing a sequence of equally spaced steps, as a result of an effective synchronization process. A respectively longer step is generally followed by a shorter one, and vice versa, to approach the mean ideal value. This natural tendency is here described as the effect of a linear control term. Furthermore, we hypothesize the presence of a stochastic noise competing with the ideal mechanisms above. Phenomenologically, this perturbative term is introduced to account for transient impediment of motility due to local neuromuscular failures. Punctual loss of ability in controlling the muscles along neuromuscular pathways can also occur in healthy individuals, the interaction with the surrounding environment being one possible source of disturbance. The above qualitative picture is translated into the following mathematical model:

$$x_{n+1} = x_n + k(l_0 - x_n) + \sigma_r R_n, \tag{1}$$

where x_n denotes the stride-to-stride interval at nth step. Here, the *control parameter* k and *average* stride-to-stride length l_0 are

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positive quantities.[1] R_n is a randomly distributed *Gaussian* variable with zero mean and variance equal to one; σ_r is a positive parameter that controls the amplitude of the stochastic component. Larger values of σ_r would point to an inherent failure of the neuromuscular architecture, possibly associated to the progression of an existing neurodegenerative pathology.

We choose to work in the so called *phase-space* by introducing the finite difference of stride-to-stride interval as an effective measure of the velocity, namely $v_n = x_{n+1} - x_n$ at nth step, and label with σ_x^2 and σ_v^2 the variances, respectively, associated to the distributions of the x_n and v_n. Assuming x_n and R_n to be independent variables, one can straightforwardly show that:

$$\frac{\sigma_v^2}{\sigma_x^2} = 2k, \qquad \sigma_r^2 = (2-k)k\sigma_x^2. \tag{2}$$

A prove is provided in the annexed supplemental material. Note that these relations hold true for infinitely long time series. Dedicated numerical simulations have been performed to assess their validity in our regime of long, but finite, experimental series.

The phase-plane portrait displays a characteristic shape of a rotated ellipse (see top left panel of Fig. 1). The inclination of the ellipse with respect to the horizontal axis increases with k, the larger σ_r the wider the ellipse. Clearly, one can always find a reference frame where the ellipse assumes a canonical form, with its major axis lying in the horizontal direction. Principal Component Analysis (PCA) [6] allows to express the rotation angle ϕ as a function of k by means of the relation

$$\tan 2\phi = \frac{2k}{2k-1}. \tag{3}$$

The latter is found to be independent of the noise σ_r. Further, note that the apparent singularity at $k = 0.5$ is due to the fact that for this value, σ_x and σ_v are equal and hence ϕ is not univocally defined.

Based on the above theoretical picture, we propose a new strategy to address the analysis of the experimental gait time series. Data are obtained from the Physiobank database [1] and have already been discussed in a series of preceding publications [3,4]. Three pathologies are here investigated: PD, HD and ALS.[2] Healthy patients (CTRL) represent a natural control and provide the reference case to measure the progression of the illness.

Subjects were instructed to walk at their normal pace along a 77-m long hallway for 5 min. To measure the gait rhythm and the timing of the gait cycle, force-sensitive insoles [2] were placed in the subject's shoe. These inserts produce a measure of the force applied to the ground during ambulation. Elaborating this information, the stride time or duration of the gait cycle, i.e. the time from initial contact of one foot to subsequent contact of same foot, was determined for each stride.[3] The interested reader may find further details about the data collection protocol and the experimental apparatus in [1,3,4].

Note that the patients walk back and forth following a linear path. As the opposite turning points are approached, the walking differs significantly from the unconstrained, *free* gait dynamics. To avoid the artificial bias induced by this boundaries effect, we removed the points belonging to the experimental time series that were distant more than one standard deviation from the mean (*median filter*). A similar strategy was adopted in [3,4]. Phase-space portraits are plotted from the measured data and display the characteristic elliptic profile (top right panel in Fig. 1), already observed within our simplified theoretical scenario. This qualitative agreement motivates us to inspect quantitatively the analogies. For instance, one can geometrically estimate the angle ϕ_{exp} that measures the inclination of the experimental elliptic halo. Assuming Eq. (1) to model the dynamics, it is therefore possible to extract an estimate of the parameter k from each set of measured data, by inserting the value of ϕ_{exp} in Eq. (3) and solving for k. Moreover, one can evaluate the variances σ_x^2 and σ_v^2 from the experimental time series, these estimates being independent from the above measure of k. Surprisingly, the ratio σ_x^2/σ_v^2 scales linearly with k, the slope being 2 as predicted by the theory developed above. Importantly, this behaviour holds true both for healthy subjects and patients affected by PD, ALS and HD, as clearly demonstrated in Fig. 1. The excellent predictive adequacy of model (1) confirms the validity of our interpretative framework.[4]

Furthermore, we calculate σ_r using the estimates for σ_x and k. The values of k and σ_r relative to the same pathologies are averaged together and pictorially represented in Fig. 1 (bottom right), with the associated errors. Results indicate that both the linear control parameter and the noise amplitude are directly influenced by the type of disease, the pairs (k, σ_r) being localized in different portions of the parameters space. This conclusion is further strengthen by performing a dedicated t-test [7], whose results are enclosed in Table 1. The ranges relative to ALS and HD patients are completely disjointed from the one corresponding to the healthy subjects. This is a crucial observation that could possibly allow to define new, non invasive, diagnostic protocols for neurodegenerative disease.

In addition, we investigated possible dependencies of k on the age (years) of the patients and limited this analysis to the case of healthy and PD subjects. As concerns healthy individuals, the values of k and the age are apparently uncorrelated. On the contrary, for the PD, we found a positive correlation between k and the age of the patients. A simple linear regression returns a slope 0.007 ± 0.003, the correlation coefficient being

[1] Note that putting $\sigma_r = 0$ results in a fully deterministic model: if $0 < k < 2$, for all initial condition, x_n converges to l_0. In other words after a large enough number of steps, all stride-to-stride intervals are close together and close to l_0.

[2] All the Subjects were recruited from the Neurology Outpatient Huntington's Disease Clinic at Massachusetts General Hospital (MGH). The age ranges between 36 and 70 years old [3,4].

[3] Walking at constant speed, this amounts to access a direct measure of relative step extension.

[4] Stride-to-stride measurements of footfall contact times are acquired for about 300 s. In developing our investigations, we analyzed the records from 10 individuals affected by the ALS, 19 patients with HD, 11 subjects with PD and 14 healthy reference persons. After the median filter, the average number of elements constituting the time series is calculated for each of the above categories and read, respectively, 172 (ALS), 196 (HD), 213 (PD), 220 (CTRL).

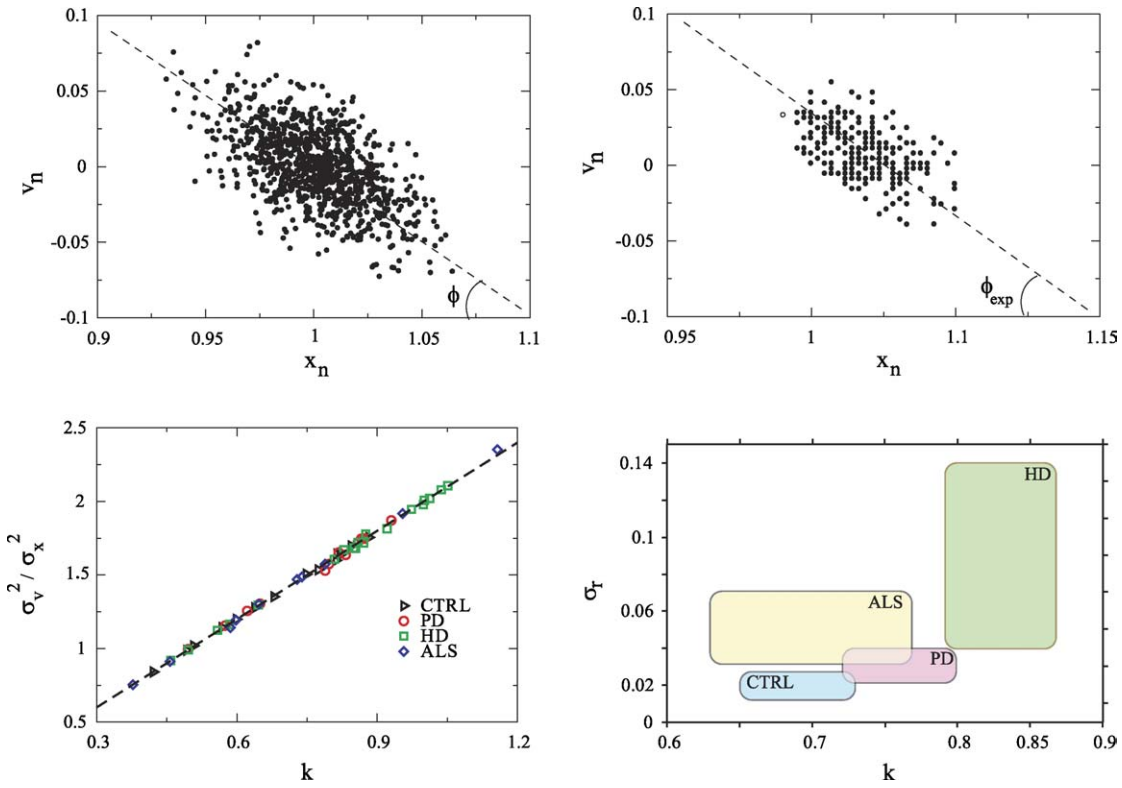

Fig. 1. Top left panel: phase space portrait as originated from (1). The plot refers to the parameters choice $l_0 = 1$, $k = 0.69$ and $\sigma_r = 0.02$. Top right panel: phase space portrait as obtained from the experimental time series. The data refers to a healthy individual. Bottom left: Plot of σ_x^2/σ_v^2 as function of k for healthy control individuals CTRL (triangles), patients affected by the PD (circles), HD patients (squares) and ALS subjects (diamonds). The dashed solid line refers to the analytical prediction. Bottom right: Graphical representation of the pair (k, σ_r). Rectangles are centered in correspondence of the mean values, the width being set according to the errors.

$r = 0.6$. Based on the above and assuming that the time since the onset of the disease is longer in older PD subjects, we can conclude that k increases with the progression of the disease. This scenario can be tested by representing the computed values of k against the so-called Hohn and Yahr score [1], a clinical measure of disease severity or duration (a higher score indicates more advanced functional impairment). As expected the quantities display a positive correlation and a linear fit gives a slope equal to 0.11 ± 0.03 ($r = 0.7$). Analogous conclusions hold true for σ_r. To validate these findings, we suggest to periodically repeat the experiments and monitor the time evolution of both k and σ_r.

Table 1
The average k (resp. σ_r) values from different samples are compared to determine whether the clustering tendency observed in the parameters' plane (k, σ_r) is experimentally relevant

	CTRL	HD	PD	ALS
CTRL	1	0.0009	0.004	0.0016
HD		1	0.024	0.025
PD			1	0.055
ALS				1

Assume as a working (null) hypothesis that the means are equal. A paired t-test [7] is performed and the estimated difference quantified in a p-value, i.e. the probability that measures the correctness of the initial ansatz. Small p-values cast doubt on the validity of the null hypothesis. In this analysis the averages relative to k and σ_r are treated as independent and therefore the probabilities multiplied. Results reported in the table strongly point to the statistical relevance of our analysis.

In this paper, we propose a simplified model to interpret and reproduce experimental stride-to-stride interval gait time series. Available data analyzed within our theoretical picture allow to draw preliminary conclusions. Quantitative differences in specific indicators were detected, thus allowing to distinguish, at various levels, healthy controls from patients affected by the neurodegenerative diseases considered here. It is here anticipated that a refined analysis could be carried out by accessing a larger amount of data, thus probably allowing one to gain deeper insight into the mechanisms outlined above. By enhancing current statistics, we could aim at translating this knowledge into efficient diagnostic procedures. Finally, we also stress that new experiments could be designed to better appreciate the complex interplay between ambulation process and neurodegenerative disease.

Appendix A. Supplementary data

Supplementary data associated with this article can be found, in the online version, at doi:10.1016/j.neulet.2005.10.065.

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