

# Increased Instability of Heartbeat Dynamics in Parkinson's Disease

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## Abstract

*Parkinson's disease (PD) has been reported to involve postganglionic sympathetic failure and, in 25% of patients, autonomic failure. In this work we investigate autonomic dynamics in PD using a novel methodology able to provide instantaneous estimates of the Lyapunov spectrum within a point process framework.*

*Physiological signals were recorded from 10 healthy subjects and 9 cognitively preserved PD patients. We computed conventional heart rate variability (HRV) features as well as the full Lyapunov spectrum over 600s recordings at rest, and tested for significant group effects using a general linear model taking into account age and gender as nuisance covariates. Additionally, the discriminatory power of all features was tested by training a Support Vector Machine (SVM) classifier combined with recursive feature elimination (RFE) with a variable number of target features.*

*The first and second Lyapunov exponents were significantly higher ( $p < 0.05$ ) in PD patients vs. controls. No other HRV measure differed significantly between groups. The best classification performance (75% sensitivity, 80% specificity, area under ROC curve 0.8) was attained when instructing RFE to retain 2 features, where the algorithm selected the first and second Lyapunov exponents.*

*Our results suggest that autonomic control in PD entails a preponderance of nonlinear, more unstable heartbeat dynamics with respect to controls. This could point to possible autonomic dysfunction which cannot be detected by conventional HRV measures.*

## 1. Introduction

Symptoms of cardiovascular dysautonomia are a

common occurrence in Parkinson's disease (PD) [1]. This finding is in agreement with the results of pathological studies, which have demonstrated how the degenerative process in PD largely involves subcortical, brainstem and medullary autonomic centres as well as post-ganglionic sympathetic fibers [2-4]. While cardiovascular dysautonomia has traditionally been associated with the late stages of PD, it has recently become evident that it can occur throughout the disease, and that its onset can even precede the appearance of motor symptoms [1, 4, 5].

Dysautonomic symptoms may have a significant impact on daily activities and quality of life and lead to an increased morbidity and mortality in PD [6]. In this context, early recognition and treatment of cardiovascular autonomic failure is mandatory in PD, and measures of dysautonomia could play a potential role as sensitive biomarkers of disease.

Recently, measures of heart rate variability (HRV) have been employed to non-invasively explore autonomic alterations in PD by evaluating the modulatory effects of autonomic system on sinus node activity [7, 8]. Also, an increase in complexity of systolic arterial pressure (SAP), measured through the mean squared prediction error (MSPE) of autoregressive models, was found in PD patients [9]. The aim of this paper was to explore how a novel approach for quantifying instantaneous complexity within a point-process framework can contribute to providing additional, dynamic biomarkers for early differential diagnosis of PD.

## 2. Methods

### 2.1. Experimental protocol

Physiological signals (ECG, Plethysmography, Respiration) were recorded from 10 healthy subjects (HS, 5 males, 5 females, age 53.1 +/- 15.4 years, mean +/- s.d)

and 9 cognitively preserved PD patients (6 males, 3 females, age 64.9 +/- 7.2 years, mean +/- s.d). Subjects were placed horizontally in a supine position and remained at rest during the whole recording (600s). During the acquisition, all subjects were instructed not to talk and maintained relaxed spontaneous breathing. Peak detection and correction of ectopic beats was performed with an automatic technique previously described in [10]. All participants gave written informed consent to participating in the study, which was approved by the local ethics committee.

## 2.2. The point process model

Assuming history dependence, the probability distribution of the waiting time  $t - u_j$  until the next R-wave event  $u_{i-j}$  follows an inverse Gaussian model [11]:

$$f(t | \mathbf{H}_t, \xi(t)) = \left[ \frac{\xi_0(t)}{2\pi(t - u_{\hat{N}(t)})^3} \right]^{\frac{1}{2}} \times \exp \left\{ -\frac{1}{2} \frac{\xi_0(t)[t - u_{N(t)} - \mu_{RR}(t, \mathbf{H}_t, \xi(t))]^2}{\mu_{RR}(t, \mathbf{H}_t, \xi(t))^2 (t - u_{\hat{N}(t)})} \right\}$$

with the instantaneous mean RR defined as:

$$\begin{aligned} \mu_{RR}(t, \mathbf{H}_t, \xi(t)) = & RR_{\hat{N}(t)-1} + \gamma_0(t) + \sum_{i=1}^p \gamma_1(i, t) \Delta RR_i \\ & + \sum_{i=1}^q \sum_{j=1}^q \gamma_2(i, j, t) \Delta RR_i \Delta RR_j \\ & + \sum_{i=1}^r \sum_{j=1}^r \sum_{k=1}^r \gamma_3(i, j, k, t) \Delta RR_i \Delta RR_j \Delta RR_k + \delta(t) \end{aligned}$$

where  $\hat{N}(t) = \max\{k : u_k < t\}$  is a left continuous function denoting the index of the previous R-wave event occurred before time  $t$ ,  $\mathbf{H}_t = (u_j, RR_j, RR_{j-1}, \dots)$  is the history of events,  $\Delta RR_i = (RR_{\hat{N}(t)-i} - RR_{\hat{N}(t)-i-1})$ ,  $\xi(t) = [\xi_0(t), \gamma_0(t), \dots, \gamma_3(r, r, r, t)]$  is the parameter vector, and  $\delta(t)$  are independent, identically distributed Gaussian random variables. The choice of a third order nonlinear autoregressive (NAR) system retains an important part of the non-linearity of the system and provides robustness against the presence of measurement noise in the data [11].

For parameter estimation, a local maximum likelihood method [12] using a sliding window of duration  $W$  is used to estimate the unknown time-varying parameter set. After parameter estimation, conventional HRV features

(total spectral power, low frequency power (0.04-0.15 Hz, LF), high frequency power (0.15 – 0.45 Hz, HF), RR interval variability) can be estimated in an instantaneous manner from the first order regression terms [12, 13].

## 2.3. Instantaneous Lyapunov exponents

The NAR model can be rewritten in an M-dimensional state space canonical representation:

$$r_n^{(k)} = \begin{cases} r_{n-1}^{(k+1)} & \text{if } k < M \\ F(r_{n-1}^{(M)}, r_{n-1}^{(M-1)}, \dots, r_{n-1}^{(2)}, r_{n-1}^{(1)}) & \text{if } k = M \end{cases}$$

where  $F(\dots)$  directly arises from the above. By evaluating the Jacobian  $\mathbf{J}(n)$  over the time series, the Lyapunov exponents (LEs) can be determined using the QR decomposition:

$$[\mathbf{J}(n)] \mathbf{Q}_{(n-1)} = \mathbf{Q}_{(n)} \mathbf{R}_{(n)}$$

This decomposition is unique except in the case of zero diagonal elements. Then the LEs are given by

$$\lambda_i = \frac{1}{\tau H} \sum_{j=0}^{N-1} \ln R_{(j)ii}$$

where  $H$  is the available number of matrices within the local likelihood window  $W$  (90 s in this paper), and sampling time step  $\tau$  (0.05 s in this paper) (see [14] for further details). The estimation of the LEs is performed at each time  $t$  from the corresponding time-varying vector of parameters. This provides us with a time-varying vector,  $\lambda_i(t)$ , able to track the Lyapunov spectrum in continuous time. We set forth the first and second instantaneous LEs as  $\lambda_1(t)$  and  $\lambda_2(t)$ .

## 2.4. Statistical analysis and classification

Between-group analysis (HS vs. PD) was carried out using single general linear models (GLMs) which treated conventional HRV features as well as all  $\lambda_i$  as the dependent variable, group as a categorical predictor and age and gender as continuous and categorical covariates of no interest, respectively. Additionally, the discriminatory power of all features (i.e.  $\lambda_i$ ) was tested by training a Support Vector Machine (SVM) classifier (linear kernel and complexity parameter = 0.001) through sequential minimal optimization (SMO). Feature selection was performed using recursive feature elimination (RFE), which employs an SVM classifier to

evaluate the usefulness of a feature [15], and was carried out 21 times imposing a different number of features to be retained (from 1 to 21 – this last case is equivalent to directly feeding all features to the SVM). Performance was quantified through the area under the ROC curve (AUC). Sensitivity and specificity were also recorded. Feature selection and classification were carried out using WEKA software package (version 3.6.8) [16].

### 3. Results

Figure 1 shows representative results (mean RR, RR variability, first and second Lyapunov exponents) in one HS and one PD patient. In between-group GLM analysis, the first (LE1, Figure 2) and second (LE2, Figure 3) Lyapunov exponents were significantly ( $p < 0.05$ ) higher in PD vs. HS (LE1:  $0.108 \pm 0.105$  vs.  $-0.012 \pm 0.055$ ; LE2:  $-0.115 \pm 0.042$  vs.  $0.167 \pm 0.038$ , mean  $\pm$  s.d.). No other HRV measure differed significantly between groups.

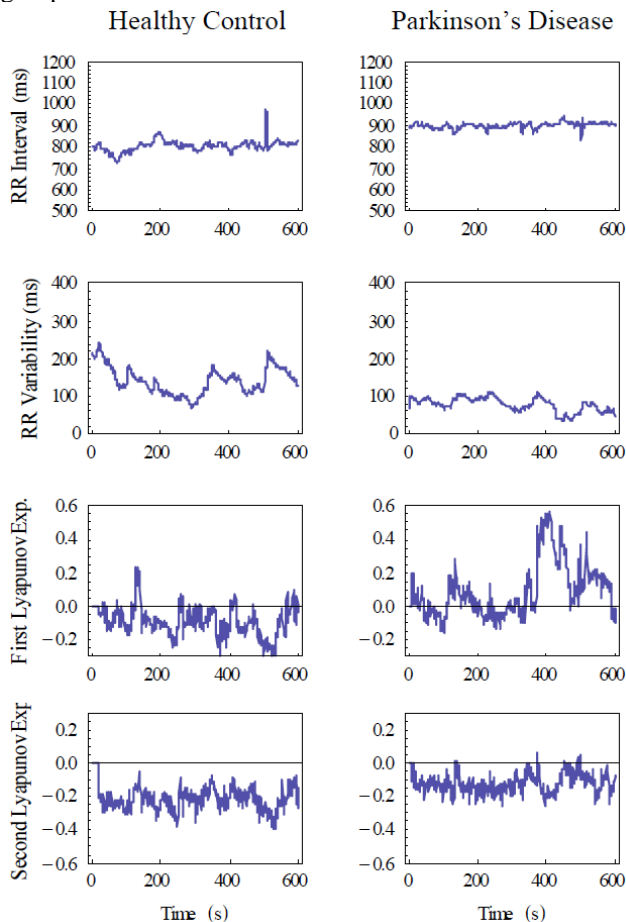


Figure 1. Representative results for one HC (left) and one PD patient (right). While both subjects display similar RR interval series (first pane) and similar RR variability (second pane), PD patients showed significantly higher average first and second Lyapunov exponents.

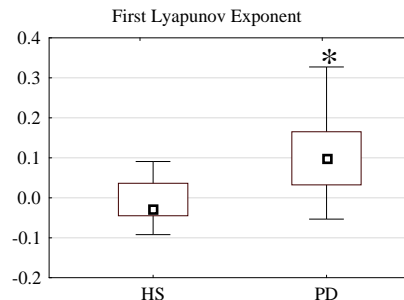


Figure 2. Average first Lyapunov exponent in healthy subjects (HS) and PD patients (PD). The latter was seen to be significantly higher ( $*p < 0.05$ , GLM accounting for age and gender as nuisance covariates).

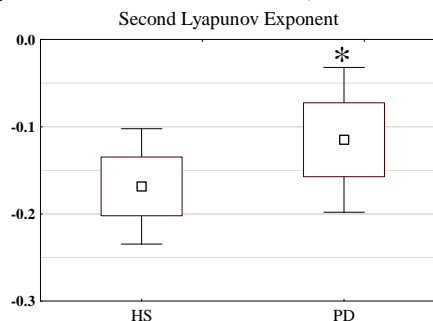


Figure 3. Average second Lyapunov exponent in healthy subjects (HS) and PD patients (PD). The latter was seen to be significantly higher ( $*p < 0.05$ , GLM accounting for age and gender as nuisance covariates).

The area under ROC curve of the RFE-SVM while varying number of features to be retained is shown in Fig. 4. The highest AUC was observed for the SVM fed with 2 features (which were  $\lambda_1$  and  $\lambda_2$ ) and resulted in classification with 75% sensitivity and 80% specificity (area under ROC curve 0.8).

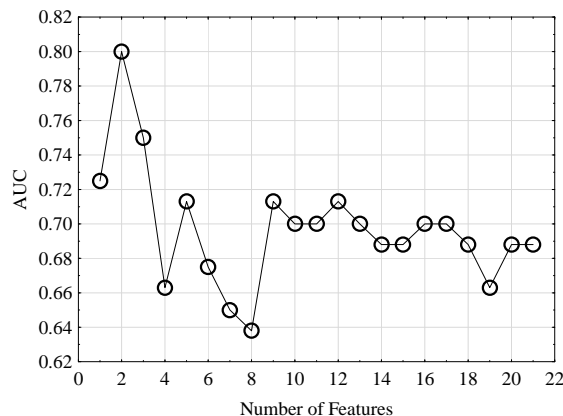


Figure 4. Area under the ROC curve (AUC) as a function of the number of features to be retained in RFE. The 2 features retained in the case which yielded the highest AUC were  $\lambda_1$  and  $\lambda_2$ .

## 4. Discussion and conclusion

In PD, autonomic system disturbances (dysautonomia) reflect neurodegenerative processes which reach beyond the nigrostriatal dopaminergic system, and follow a largely independent pathological progression when compared to dopaminergic symptoms. As a consequence, dysautonomia can appear in all stages of PD and its study can provide independent information which could aid in the differential diagnosis (DD) of parkinsonisms such as multiple systems atrophy (MSA) and progressive supranuclear palsy (PSP) or even in the stratification of PD subtypes.

Our results suggest that autonomic control in PD entails a preponderance of nonlinear, less stable heartbeat dynamics with respect to controls. This could point to possible autonomic dysfunction which cannot be detected by conventional HRV measures, and which could be exploited as potential biomarker in the DD of parkinsonisms and related disorders.

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