Nonlinear DDE Analysis of Repetitive Hand Movements in Parkinson's Disease

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Abstract Time series analysis with nonlinear delay differential equations (DDEs) [1, 3, 2] is a very powerful tool since it reveals spectral as well as topological properties of the underlying dynamical system and is robust against noise. Here we apply nonlinear DDEs to examine the nature of the spatiotemporal distortions in repetitive finger tapping movements of mild to moderate Parkinson's disease (PD) patients on and off their dopamine replacement therapy and of age-matched controls.
Using DDE analysis, there was a nearly complete separation of the data of all three groups: PD patients were classified separately from control subjects, and PD patients on and off medication were clearly distinguished. The non-linear phase coupling terms were particular important in being able to separate groups. There was an increased degree of multiplicity of frequencies in the temporal patterns when going from control to PD on medication to PD off medication. This analysis was then compared with clinical scores provided by physicians, the UPDRS (United Parkinson's Disease Rating Scale) scores. The values of the nonlinear term of the DDE shows good correlation to this clinical scores.
We conclude that such measures may provide a more objective and precise measure of the spatiotemporal disruption of rhythmic movements in PD, and the reversal of these deficits by pharmacological (or surgical) therapies.

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1 Parkinson's disease

The temporal structure of hand movements in Parkinson's disease (PD) is known to be impaired [4], but the nature of these temporal distortions remains unexplored. Likewise it is unknown how dopamine replacement therapy modulates these temporal abnormalities. To address this issue, we used non-linear time series analysis to examine the nature of the spatiotemporal distortions in repetitive finger tapping movements in PD patients on versus off dopaminergic medications.

6 mild to moderate PD patients were tested on and off their dopaminergic medications and compared to 6 age-matched controls. The clinical state of the PD subjects at the time of testing was rated using UPDRS.

Subjects were asked to tap their right index finger and thumb together making large rapid movements for 10 seconds. Three repetitions of the tapping movements were made while subjects had their eyes open. A 12 camera PhaseSpace 3D motion monitoring system (PhaseSpace, Inc.) was used in the newly developed Motion Capture Lab of the Temporal Dynamics of Learning Center at UCSD to record the positions of infra-red markers attached to the subject's index fingertip, thumb, and back of the hand. Data were sampled at 120 Hz.

2 DDE Analysis

A **DDE** is an equation, that relates the velocity of a data point to previous data points of the signal, i.e. $\dot{x} = f(x_{\tau_1}, x_{\tau_2}, ...)$ where $x_\tau = x(t-\tau)$. Here we use DDEs to model the temporal evolution in the embedding [5] space. The simplest linear DDE is $\dot{x} = ax_\tau$. If $x(t)$ is a harmonic signal with one frequency, $x(t) = \cos(ft)$, then $\tau = \frac{\pi}{2f}$ and $a = -f$. Therefore $\dot{x} = ax_\tau$ can be used to determine distinguishing frequencies (delays) for different signal classes. The simplest non-linear DDE $\dot{x} = ax_{\tau_1}x_{\tau_2}$ has one non-linear term that is only non-zero for phase couplings.

For three signal classes a DDE $\dot{x} = a_1x_{\tau_1} + a_2x_{\tau_2} + a_3x_{\tau_3} + a_4x_{\tau_1}x_{\tau_2} + a_5x_{\tau_1}x_{\tau_3} + a_6x_{\tau_2}x_{\tau_3}$ with three delays corresponding to three distinguishing frequencies of the three different conditions (control, PD on and off medication) can be used. The non-linear terms in this equation correspond then to the phase couplings between these characteristic frequencies. This equation has six coefficients a_j, $j = 1,2,\ldots,6$ and since we want to use this coefficients as features for our further analysis, a reduction to a lower dimensional feature space would be preferable. For this reason we split above mentioned DDE into three DDEs, each of them reading as

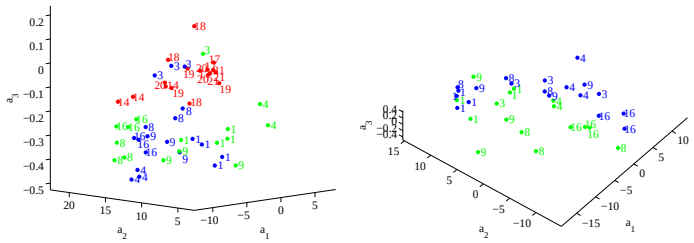
$$\dot{x} = a_1x_{\tau_1} + a_2x_{\tau_2} + a_3x_{\tau_1}x_{\tau_2}\,. \tag{1}$$

The feature space for each of these equations is three-dimensional and can be viewed easily. Each equation allows distinguishing between each pair of the three classes.

For our analysis we first have to choose good delays. To do so, we use the simplest linear DDE, $\dot{x} = ax_\tau$ to find characteristic frequencies and therefore estimate

the mean coefficient a by using singular value decomposition for each data class as function of the delay. We then choose two delays for two classes to the two most distinguishing coefficients which are related as mentioned above to the most distinguishing frequencies. We get $\tau_1 = 5$ and $\tau_2 = 30$ to separate PD on or off medication from controls and $\tau_1 = 52$ and $\tau_2 = 115$ to separate PD on from PD off medication. Such a choice of the delays in a nonlinear DDE is expected to reveal different types of couplings for the different classes.

For our data analysis we use Eq. (1). The linear terms reflect, as mentioned above the dominant frequencies or dominant time scales and the non-linear terms the phase couplings or feedback. In Fig. 1 the features a_i, $i = 1,2,3$ of the three data sets are



(a) $\tau_1 = 5$, $\tau_2 = 30$ (b) $\tau_1 = 52$, $\tau_2 = 115$

Fig. 1 DDE feature space ($a_{1,2,3}$)

plotted in red (control), green (PD off medication), and blue (PD on medication). Subjects 1, 3, 4, 8, 9, and 16 are PD patients and subjects 14, 17, 18, 19, 20, and 21 are controls. For nearly all subjects there is perfect separation of controls vs. PD patients as can be seen in Fig. 1(a). Only subject 3 has features similar to those of the controls. This person suffers only very mild PD and the clinical score for finger movements is only 0.5 (on a scale from 0 to 4). The separation of PD patients on and off medication is also very good as shown in Fig. 1(b). The tables 1 were obtained by training a Support Vector Machine (SVM) on all except one group of either condition and testing on the left out groups. The numbers are the areas under the ROC curves on the distances from the hyperplane chosen by the SVM. In Tab. 1(a) the nearly perfect separation of controls from PD patients can be seen. Only subject 3 cannot be separated. In Tab. 1(b) the diagonal shows the excellent separation of PD on vs. PD off for each subject when the SVM was trained on all other subjects.

We further compared the values of the nonlinear coefficient a_3 to the clinical UPDRS score in Fig. 2. There is a good correlation of the nonlinear coefficient a_3 to the UDPRS score. Each subject shows a value of a_3 closer to the controls when on medication than when off medication.

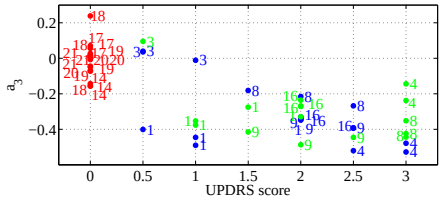


Fig. 2 a_3 vs. UPDRS score; $\tau_1 = 5$, $\tau_2 = 30$; the controls were not clinically rated, but added to the plot with a score of approximately 0 for comparison

Table 1 DDE-analysis: Area under the ROC curve for leave-one-subject-out cross-validation

(a) $\tau_1 = 5$, $\tau_2 = 30$; PD vs. controls

subject	14	17	18	19	20	21
1	100	100	100	96	100	100
3	0	0	67	0	0	0
4	100	100	100	100	100	100
8	100	100	100	100	100	100
9	100	100	100	100	100	100
16	100	100	100	100	100	100

(b) $\tau_1 = 52$, $\tau_2 = 115$; PD on vs. off med.

subject	1	3	4	8	9	16
1	**44**	100	83	67	50	17
3	25	**100**	100	67	100	0
4	0	100	**100**	67	83	0
8	83	100	100	**100**	100	100
9	67	89	78	67	**67**	56
16	0	100	100	67	100	**100**

3 Conclusion

We used nonlinear DDEs to investigate repetitive tapping movement data from Parkinson patients on and off medication and a control group. Our analysis resulted in good separation of PD versus controls as well as PD on from off medication. There was also a good correlation of our analysis to the UDPRS score.

These results are very promising and suggest the investigation of other movement types of PD patients which is planned in future work.

Acknowledgments

This work was supported in part by NIH grant # NS036449 and NSF grant # SBE-0542013 to UCSD.

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