ELECTRONIC PLATFORM MEASURES OF BALANCE IMPAIRMENT IN PARKINSONIANS AND FIRST DEGREE RELATIVES

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Abstract: Several measures of balance obtained from quiet stance on an electronic platform are described. These measures were found to discriminate patients with Parkinson disease (PD) from normal control subjects. First degree relatives of patients with PD show greater variability on these measures. A primary goal is to develop sensitive measures that would be capable of identifying impaired balance in early stages of non-clinical PD.

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1. A Description of Causes and Conditions Present in Parkinson Disease

Parkinson disease (PD) is a clinical syndrome consisting of a variable combination of symptoms of tremor, rigidity, postural imbalance and bradykinesia.
The clinical features of PD result from degeneration of dopaminergic cells in the substantia nigra pars compacta and the ventral tegmental area, accompanied by the formation of Lewy bodies (Hughes [12], Hughes et al [13]). The greater the neuronal loss in the substantia nigra, the lower the concentration of dopamine in the projection areas to the striatum, limbic regions, and frontal cortex in the brain. Langston and Koller noted that PD can be viewed as a disease having two phases. The first phase is a preclinical period that covers the period from disease inception to the time when the disease becomes symptomatic (Langston and Koller, [15]). The second phase represents the symptomatic period, where the classical symptoms of PD such as bradykinesia, tremor and rigidity occur. Before the appearance of the classic Parkinsonian signs and symptoms, there may be a prodromal stage, where signs and symptoms occur but do not specifically indicate PD (Horstink and Morrish, [11]). For example, analysis of video footage of the famous English footballer Ray Kennedy revealed subtle motor aberrations 8 years before a clinical diagnosis of PD could be made (Lees, [18]). The clinical diagnosis of PD is most difficult early in the disease when the signs and symptoms are subtle (Koller and Montgomery, [14]).

Montgomery et al (see [21]), using a test battery evaluating motor function, found that 22.5% of first degree relatives of patients with PD had abnormal test scores compared to 9% of normal control subjects of the general population. None of the subjects who had an abnormal test score had neurological signs or symptoms of PD. The increased frequency of abnormal test results in first degree relatives of patients with PD may represent a genetic or shared environmental factor in the pathogenesis of PD (or a combination of both).

The causes of PD are being unraveled and rational neuroprotective therapy is close to reality (Marsden and Olanow, [19]). Neuroprotective therapies are likely more effective when given early in the course of the disease rather than late. Therefore, identification of very early disease has become crucial to select subjects for treatments that may have the potential of secondary prevention of PD. A biomarker, to be useful in screening large populations to identify preclinical disease, should be inexpensive, easily administered, and sufficiently sensitive and specific to avoid unacceptable false negatives or positives (Tetrud, [24]). Measures of dopamine nerve terminal integrity with positron emission tomography (PET) have allowed preclinical disease to be detected in relatives of patients with PD (Brooks, [3]). However, PET imaging is very expensive and not suitable for mass screening of at risk subjects.

In this paper we focus on the development of measures of postural stiffness and motor dysfunction by making use of a Kistler electronic platform. There
is preliminary evidence that some of these measures are significantly correlated with descriptive clinical assessments, such as those used in the Universal Parkinson Disease Rating Scale (UPDRS), particularly the Motor Sub-scale (Lauk et al [16]). The platform measures are more objective measures than those offered by the UPDRS. They are inexpensive and can be easily done in a doctor office. It would be particularly promising if these platform measure prove to be good covariates of the amount of dopamine in the brain as measured by a PET scan. This would provide an inexpensive means of correctly assessing the status of PD in preclinical cases. At this time we only have evidence that some of the platform measures are highly correlated with the scores on the peg board tests. These scores are, on the other hand, known to correlate well with the amount of dopamine in the brain. We hope to produce direct evidence of such correlation by carrying out PET and platform readings on patients.

2. Postural Motor System Dynamic Modeling

The link between postural stability and PD has been probed by many researchers in the past (Bloem et al [2], Horak et al [10]). These studies have been in both static (quiet standing) and dynamic (response to perturbations) conditions. The dynamic experiments are often difficult to perform and yield conflicting results. Studies of static posturography focus on subjective perceptions of balance stability and descriptive statistical measures of the center-of-pressure (COP) motion as measured by an electronic platform, such as the length and area of the sway path. However, these studies have also produced contradictory results, with some reporting a decrease in postural sway in PD patients and others reporting an increase (Horak et al [10], Schieppati and Nardone, [23]). For the majority of these studies, descriptive statistics were obtained, but no attempt was made to produce a model.

Descriptive statistics of COP motion do not provide the resolution required for accurately discriminating healthy subjects from PD afflicted individuals. This is because descriptive or summary statistics neglect the dynamical aspects of the COP trajectories. This neglect was first noted by Collins and De Luca (1993) who proposed that autocorrelation functions of the COP motion would contain more information (Collins and De Luca, [6]). They subsequently showed that this measure was reliable in discriminating age related changes between healthy subjects and PD patients (Collins and De Luca, [7], Mitchell et al [20]). Subsequently, Chow and Collins (1995) developed a mechanical model that describes the COP motion during quiet stance (Chow and Collins, [4]).
This model provides a direct connection between the dynamics of COP motion and the underlying physiology of postural motor control. This was followed by work that showed that static and dynamic postural control were related (Lauk et al [17]).

Here we extend the dynamic modeling of the COP motion with data driven stochastic analysis. The Kistler electronic platform is registering the COP position beneath the feet of a quietly standing individual at 50 observations per second. The platform data are recorded as a time series curve in the $xy$-plane. Our two approaches are based on the autocovariance, and the related autocorrelation function, of the within-subject high frequency recordings of the mediolateral coordinate of the time series provided by the COP trajectory. In this paper we discuss the time domain analysis. We investigate the mediolateral projection of the COP data, since it was found that mediolateral instability is an important factor of balance impairment in the elderly, cf. Mitchell et al in [20]. The autocovariance function is:

$$a(t) = \sum (y_{i+1} - \mu)(y_i - \mu),$$

where the $y_i$ are the mediolateral $y$-coordinates of the COP trajectory and $\mu$ is the mean of the process.

Chow and Collins in [4] proposed a mechanical model of posture control from which an analytical form for the autocorrelation function of the COP motion was obtained. Later, a stiffness measure was derived from this model (Lauk et al [16]). The dynamic model that we adopt assumes that the body during quiet standing can be represented by a flexible string (polymer) with stiffness and damping (Lauk et al [16]). In addition, the model predicts the analytical form of the time-dependent correlations of COP displacements, from which a set of physiologically relevant parameters can be extracted. We also insisted that it should relate to functions of the human postural control system. From this biomechanical model, a “body stiffness” parameter $k$ was derived (Lauk et al [16]). We assume the body is close to being upright and that the combination of the destabilizing effects of gravity and the stabilizing effects of the imperfect control system are captured by a simple stochastic forcing term. This hypothesis is based on the observation that the dynamics of the COP obey a correlated random walk. We represent the COP motion as a single point on the rod. The resulting equation is

$$\beta \frac{\partial^2}{\partial t^2} y(z, t) + \frac{\partial}{\partial t} y(z, t) = \nu \frac{\partial^2}{\partial z^2} y(z, t) - \alpha y(z, t) + \eta(z, t).$$

In this equation $y(z, t)$ denotes the coordinate of the COP in the mediolateral direction. The equation describes the motion of an infinitely long rod or
polymer that is elastically pinned to a single location and driven stochastically. Parameters $\beta$ and $\alpha^{-1}$ have dimensions of time and $\nu$ has a dimension of length squared divided by time. The stochastic force is $\eta$. From dimensional analysis, we find that $\alpha$ and $\beta$ are related to the stiffness of the rod through the relation $\nu \sim \alpha/\beta^2 L^2$, where $L$ is the length of the original rod, from which we obtain a parameter we call the normalized stiffness $k = \alpha/\beta$ (Lauk et al [16]).

The derivative of the autocovariance can be found from this mechanical model explicitly and is given by the formula

$$\frac{d}{dt} a(t) = \frac{e^{-t/2\beta}}{2\sqrt{\nu\beta}} J_0 \left( \frac{\sqrt{4\alpha\beta - 1}}{2\beta} t \right),$$

for $t > 0$, where $J_0$ is the zeroth-order Bessel function (Chow and Collins, [4], Chow et al [5], Lauk et al [17]).

Preliminary data from Boston University have shown that the COP-based postural stiffness measure $k$ increases with more severe Parkinsonian motor symptoms and correlates with UPDRS motor scores in PD patients, see Table 1 (Lauk et al [16]). These data indicate that this parameter not only measures stiffness but also bradykinesia and other motor impairments in PD. We extend this analysis with data from the University of Pittsburgh, and show that the discrimination between populations is particularly effective when the average residual to a smoothed version of the data and the rebound measures are used.

### Table 1: Correlation coefficients between UPDRS measures and the postural stiffness measure $k$

<table>
<thead>
<tr>
<th>Clinical measure</th>
<th>Kendall $\tau$ correlation coefficients</th>
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<tbody>
<tr>
<td>Rigidity</td>
<td>0.48 ($P &lt; 0.006$)</td>
</tr>
<tr>
<td>Bradykinesia</td>
<td>0.46 ($P &lt; 0.008$)</td>
</tr>
<tr>
<td>Posture</td>
<td>0.60 ($P &lt; 0.0005$)</td>
</tr>
<tr>
<td>Leg agility</td>
<td>0.52 ($P &lt; 0.003$)</td>
</tr>
<tr>
<td>UPDRS motor score</td>
<td>0.49 ($P &lt; 0.005$)</td>
</tr>
</tbody>
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3. Data Driven Stochastic Analysis

We first discuss some visual features of the processed data that prove useful in pinpointing qualitative differences between the three populations under study.
Using the above-mentioned autocovariance and autocorrelation functions we found several marked differences between PD patients and normal control subjects enabling us to identify three significant traits of the autocorrelation curve (ac-curve, for short) on which measures of balance impairment are based. Typical Parkinsonian curves for the five readings of a single PD patient are displayed at left in Figure 1A. A 95% confidence band on the estimate of the autocorrelation curve, based on the five curves, appears next to it in Figure 1A. For comparative purposes we display the corresponding features in a normal control in Figure 1B.

As can be seen from the figures, the Parkinsonian curves are generally characterized by a precipitous initial drop, followed by rebounding efforts. By contrast, normal controls tend to exhibit gradual, essentially straight line, decay.

First degree relatives of patients with PD have greater variability indicating heterogeneity in this group. As can be seen from Figure 2, first degree relatives demonstrate increased rebound efforts to maintain balance when compared to normal control subjects. A patient with subcortical ischemic disease ("lower body" or "vascular" parkinsonism) demonstrated a more severe pattern of postural impairment with rapid crossing time and decreased rebound efforts (Figure 2D).

We developed and aim to utilize five numerical measures based on postural motor system modeling to characterize and quantify Parkinsonian motor dysfunction. Among the first degree relatives of patients with PD we isolated two who show striking overlap with the Parkinsonian pattern of the autocorrelation curves in the absence of clinical parkinsonism. This finding and the observed
increased heterogeneity in our group of first degree relatives of patients with PD led to the hypothesis that this subgroup of apparently normal persons may be at risk of developing PD.

4. The Average Residual Measure

Three populations were studied: Parkinsonians, first degree relatives of patients with PD, and normal controls. Several measures were used to study the differences between the three groups. Thus far it seems that the statistics that best discriminate between the three groups are found in the residuals of the COP trajectories. The autocovariance of the trajectories was discussed in the previous section. The dynamical measure highlights some differences between the three populations. A purely statistical analysis of the residuals in the $x$-coordinate of the trajectory, obtained after smoothing the series over two-second intervals, yields an even better separation between the groups. It is consistent with the dynamical measure but the statistics have a much stronger level of significance.

Specifically, we register the COP motion of a subject for two minutes at 50 readings per second, we repeat the process 5 times on the same subject. On each person we therefore have 5 COP time series, and we focus on the $x$-coordinate of the 5 series only. Data on each individual consists, therefore, of 5 time series of the $x$-coordinates of the COP motion [In a few cases data was missing or was misrecorded due to operator or machine error, in such cases we have fewer than
Table 2:

<table>
<thead>
<tr>
<th>Number of Subjects</th>
<th>Average Squared Residual (ASR)</th>
<th>Standard Deviation of ASR</th>
</tr>
</thead>
<tbody>
<tr>
<td>Parkinsonians</td>
<td>26</td>
<td>14.93</td>
</tr>
<tr>
<td>Normal controls</td>
<td>14</td>
<td>3.68</td>
</tr>
</tbody>
</table>

5 series per individual. Each series is smoothed over intervals of 2 seconds, that is, we average 100 consecutive readings across the series, the residual vector is, by definition, the difference between the original series and the smoothed series. We view the smoother series as a trend. The trend cannot be modeled formally in any traditional sense, since two series on the same individual can look very dissimilar in terms of trend. But the residuals show significant consistency, if the smoothing is done over the same time length. It is these residuals that we are taking interest in.

One of the simplest statistics is the average squared residual, i.e., the squared norm of the residual vector divided by its length. We summarize the results on the average residuals in Table 2. The subjects selected were of comparable age, across the groups. Inspection of the data shows that the variance in the average residual visibly varies from subject to subject, a formal test rejects the hypothesis of equality of variances (the p-value is 0). This makes computation of confidence intervals for differences in the average residuals between groups a bit nonstandard. Even the most conservative approach (using always the larger estimate of the variance among two groups) yields the result that the Parkinsonians have, on average, the average residual significantly greater than each of the other two groups (p-values of 0 in both cases, using a Gaussian test).

Nonparametric tests offer similar conclusions. A Wilcoxon rank test finds that the median of the Parkinsonian average residual is significantly different from the other two groups, but the blood relatives and normal controls do not have median average residuals that are significantly different. These comparisons were also performed after taking away a smoothed trend over time intervals of five seconds, rather than two, and the results did not show any dramatic qualitative change.

Table 3 below displays summary information on the correlation of the average residual with some clinical UPDR scores. For purposes of comparison we focus on the same variables used in Table 1 for the stiffness measure. As in the case of the stiffness measure, foot agility shows the highest correlation, with bradykinesia and UPDRS motor both at 58%.
Clinical measure & Spearman correlation coefficient \\
--- & --- \\
Rigidity & 0.58 \((P < 0.0009)\) \\
Bradykinesia & 0.55 \((P < 0.0010)\) \\
Posture & 0.63 \((P < 0.0001)\) \\
Foot agility (right) & 0.52 \((P < 0.0002)\) \\
Foot agility (left) & 0.68 \((P < 0.0000)\) \\
UPDRS motor score & 0.58 \((P < 0.0006)\) \\

Table 3: Spearman correlations between UPDRS measures and the average squared residual

5. The Rate of Decay of the Autocovariance

The family of derivatives written in (3) does not appear to have antiderivatives that can easily be expressed in closed analytical form. The data in general, and Figure 1 in particular, indicate differences in the rate of decay of the autocovariance between the Parkinsonians and normal controls. In order to study these rates we fitted a simple exponential decay function. More complicated models were tried, but they offered no substantial gains to the qualitative understanding of the decay rates. Over a time interval of 30 seconds we fit the exponential family

\[ a(t) = ae^{-bt}. \]

The parameter \( a \) is simply the variance of the time series of the mediolateral COP coordinate (which we call mediolateral noise), while \( b \) is the rate of decay. We used the Splus Statistical Package to fit this model to the data. The fit yields the least squares estimates of the rate and intercept. For a given subject we then obtain an estimate of the variance from the (at most 5) repeated platform readings. The variances are dependent upon the individual. From this point on the analysis parallels the one described in Section 4.

When categorized by presence or absence of PD we obtain an average decay rate of 14.9 with a standard error of 1.3 for PD patients, and 8.6 with a standard error of 1.1 for normals, by standard error we always understand the standard deviation of the estimate of the parameter under discussion. A formal test for equality of the two population means rejects the hypothesis that the means are equal in favor of the alternative that the Parkinsonians have a significantly higher rate of decay of the autocovariane function, the \( p \)-value is 0.

With regard to the mediolateral noise \( a \) of the model, the Parkinsonians on average have mediolateral noise equal to 56.5 with a standard error of 7.6 while the normal controls register 17.5 with an standard error of 5.3. The conclu-
sion is that the Parkinsonians produce much greater noise in the mediolateral movement than normal subjects. An additional statistic, with potential clinical use, is the significant Spearman correlation of 0.51 that exists between the mediolateral noise and the number of falls that the subject experiences.

6. The Rebound Efforts

A measure of how much a person rebounds while trying to keep balance under quiet standing may be measured by the arc length of the autocovariance function per unit time. A long arc indicates significant rebounding efforts, whereas a short arc length is likely to be associated with autocovariance close to a straight line. The later, as in Figure 1, is easily associated with absence of balance impairment. Figure 3A illustrates an autocovariance curve associated with considerable rebounding efforts (a Parkinsonian subject), whereas Figure 3B depicts the curve of short arc length of a normal subject. We attempted to do a Fourier analysis in order to detect presence of cycles. Our experience has met with mixed success at best, since it appears that, in general, there are no clear cyclical effects. The rebounds, when present, have irregular structure with no evident periodicity. It appears that the arc length offers the best opportunity to numerically quantify this effect.

We computed the arc length by normalizing the two axes to a same average increment, then summed the square roots of the sum of squares of the differenced time and autocovariance series, it is the usual formula for arc length. The rebound measure (or arc length of the autocovariance function) has a significant Spearman correlations with all the clinical variables listed in Table 3, and of about the same magnitude (plus or minus 10%). It has a Spearman correlation of 49.3% with the number of falls. Not unexpectedly the rebound measure and the average residual are highly correlated. The rebound measure has, however, the advantage of not being dependent on any smoothing.

7. Developing a Predictive Model

Using the five platform measures constructed above and the UPDR clinical scores as input variables, we constructed a logistic model having three categories as output for a subject under study: normal, pre-Parkinsonian and Parkinsonian. This trinomial logistic model assigns probabilities (the sum of which is 1) that a subject falls in each of the three categories and classifies the person within the category that carries the highest probability as estimated from data.
The statistical packages S-plus and SPSS have been used to analyse the data. We only give here the resulting classification. It should be observed that the true state of nature is not known with regard to the relatives of Parkinsonians. Of the 26 Parkinsonians 6 were misclassified as normal. This misclassification is due to the fact that, though clinically known to have PD, the 6 subjects do not manifest balance problems. The model classified two out of the four relatives of Parkinsonians to be pre-Parkinsonian. This is consistent with other type of analyses of the data, as well as medical opinion based on clinical evaluation - though not on PET scans, and shows that the trinomial model seems reliable in this respect. Only one of the 10 normal subjects has been misclassified as Parkinsonian, although the true state of nature is not known in this case either.

8. Conclusions

Five measures of balance based on the center of pressure movement in the mediolateral direction were studied in this paper. The electronic platform studies produced at the University of Pittsburgh and the Veteran Administration Hospital in Pittsburgh show significant differences among the measures of balance in patients with PD and normal controls. It also identifies some first degree
relatives of PD patients that have platform measures in a critical range as potential carriers of preclinical PD. This points in the direction of using electronic platform data, which is inexpensive to obtain, as an early diagnostic tool for people with preclinical Parkinsonian symptoms. Studies that involve direct comparisons between platform measures and PET scan mappings of amounts of dopamine in the brain would be a natural next step in developing preventive diagnostics for people with preclinical PD.

References


