Developing measures of postural rigidity from quiet stance on an electronic platform

by

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1 Neurological background

Parkinson's disease (PD) is a common and disabling neurodegenerative disorder affecting millions of people worldwide. Recent positron-emission tomography (PET) studies have shown a loss of over 90% of dopamine in the posterior putamen (basal ganglia) in the brain already at the time of first clinical symptom manifestation. This indicates the presence of a long pre-clinical period of the disease, estimated at more than 6 to 10 years; cf. Hoehn and Yahr stage I PD (1967). We are currently witnessing a time of scientific optimism where new treatments, such as neuroimmunophillins and stem cell transplantation, are emerging that have the potential to reverse the natural history of this otherwise progressive disorder. These treatments are likely more effective when given early in the course of the disease rather than late. Therefore, identification of early or pre-clinical disease has become crucial to select patients for these novel therapies. Early identification of disease requires a sensitive and cost-effective screening method that can be applied to a large number of persons.

When standing quietly, the center-of-pressure (COP) beneath the feet moves in a stochastic manner. Based on the mathematical models of posture control described in this paper, quantitative postural stiffness measures are computed from the autocovariance function obtained from these trajectories. Preliminary data indicate that electronic platform balance testing is able to objectively distinguish parkinsonian imbalance from normal controls on the basis of a total body stiffness factor. We have also data that a subgroup of otherwise normal volunteers, especially elderly, have increased total body

stiffness showing striking overlap with the parkinsonian pattern yet in the absence of clinical symptoms of parkinsonism. It appears likely that this subgroup of apparently normal persons may be at risk of having or developing PD. The relevance of this study consists in the validation of an easy, quick and inexpensive screening method to detect preclinical PD in at-risk persons, such as family members of patients with PD. It will allow selection of novel neurorestorative therapy aimed to prevent or reverse the illness before symptom manifestation. Validation of the electronic platform efficiency is done with the much more costly PET scans; Gunn et al. (1998).

Preliminary results also show significant correlations between the postural stiffness measures and individual ratings of rigidity, bradykinesia, posture impairment, gait and leg agility as rated by the Universal Parkinson Disease Rating Scale (UPDRS) in patients with PD; Fahn et al. (1987). These data provide evidence that a higher intrinsic muscle stiffness factor may contribute to the specific parkinsonian symptoms; Bohnen (1998). From a clinical standpoint, this suggests that the COP-based postural stiffness measure increases with increased severity of the respective motor system disabilities associated with PD. We trust that some of the measures derived from the COP trajectory analyses will improve or superceed the existing subjective evaluations currently used by UPDRS.

2 A measure of rigidity

Chow and Collins (1995) proposed a mechanical model of posture control from which an analytical form for the autocorrelation function of the COP motion was derived. Later, a stiffness measure was derived from this model (Lauk et al., 1999). Here, we outline the calculations. To simplify the problem, we consider only motion in the $y-z$ plane. We suppose the body can be modeled by a flexible rod. 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

$$\beta\frac{\partial^2}{\partial t^2}y(z,t)+\frac{\partial}{\partial t}y(z,t)=\nu\frac{\partial^2}{\partial z^2}y(z,t)-\alpha y(z,t)+\eta(z,t). \tag{1}$$

This equation describes the motion of an infinitely long rod or polymer that is elastically pinned to a single location and driven stochastically. Parameters β and α^{-1} have dimensions of time and ν has a dimension of length squared divided by time. The stochastic force is assumed to have statistics $E(\eta(t))=0$ and $E(\eta(z',t')\eta(z,t))=2D\delta(t-t')\delta(z-z')$, with E denoting expectation.

¿From dimensional analysis, we find that α and β are related to the stiffness of the rod through the relation $\nu\sim(\alpha/\beta)L^2$, 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. 1999).

Consider the spatiotemporal autocorrelation function $S(z-z',t-t')=E(y(z,t)y(z',t'))$. The autocorrelation function desired is given by $S(z_0,\tau)$ where z_0 is an arbitrary point

on the polymer and without loss of generality we can choose $z_0 = 0$. We solve (1) using Fourier-Laplace transform methods. In transformed space the correlation function is given by

$$\hat{S}(k,\omega) = E(|\hat{y}(k,\omega)|^2) = \frac{2D}{|-\beta\omega^2 - i\omega + \alpha + \nu k^2|^2}. \tag{2}$$

The Green's function is given by

$$\hat{G}(k,\omega) = \frac{1}{-\beta\omega^2 - i\omega + \alpha + \nu k^2}. \tag{3}$$

From (2) and (3), we find that

$$\mathrm{Im}\,\hat{G}(k,\omega) = \frac{i\omega}{2D}\hat{S}(k,\omega).$$

In the time domain, this implies

$$G(z,t) = -\frac{1}{2D}\frac{dS(z,t)}{dt}, \qquad t > 0.$$

The autocorrelation is $S(0,t) = \langle y(0,t)y(0,0)\rangle$. Inverse Fourier transforming the Green's function gives in the time domain (Chow and Collins, 1995)

$$G(0,t) = \frac{e^{-t/2\beta}}{2\sqrt{\nu\beta}}\, J_0\left(\frac{\sqrt{4\alpha\beta - 1}}{2\beta}\, t\right), \tag{4}$$

where $J_0(x)$ is the zeroth-order Bessel function. For $4\alpha\beta < 1$, J_0 is replaced by the zeroth-order modified Bessel function I_0.

3 Computational aspects of model validation

From the COP trajectory of a patient, obtained as a sequence of 50 readings per second for a total of 120 seconds, we aim to estimate the parameters α and β, and subsequently the measure of stiffness as α/β. The $y-$component of the COP trajectory, viewed as a time series, allows immediate computation of the autocovariance $A(t)$. We use lags of up to 20 seconds, since after that $A(t)$ flattens out to zero. Its numerical derivative, $\frac{d}{dt}A(t)$ is an estimate of the theoretical expression written in (4). We aim to find those values of α and β in (4) which give the best (nonlinear) fit to the data ecapsulated in $\frac{d}{dt}A(t)$. Though estimation of derivatives is notoriously unstable, ability to collect data at high frequency, coupled with suitable smoothing, allows us to produce reliable estimates. Bessel functions, when viewed as power series, become quickly numerially unstable. Using a Levenberg-Marquardt algorithm (Press et al., 1992), we obtain the best estimates for α and β. In this case, the errors for the parameters of the fitted functions can be obtained from the covariance matrix of the fit (Press et al., 1992). The numerical optimization routines are written in *C* and *Splus*.

4 Statistical modelling of other autocorrelation invariants

In addition to the stiffness measure, several other invariants of the autocovariance function can be derived from the electronic platform testing. These invariants would then all be used to classify the state of PD in a subject and study correlations with measures obtained from the UPDRS scales. Data suggests that the following features of the covariance curve as particularly informative: (1) *The waiting time until the autocorrelation curve hits zero for the first time.* All indications are that the distributions of this variable are different for PD and non-PD subjects. This variable encapsulates well the overall degree of balance that a subject possesses. The analysis uses survival analysis techniques. A related measure is the area under the autocorrelation curve from the trigger point to the first time the autocorrelation hits zero. (2) *The rate of decay of the autocorrelation function.* PD patients show a faster rate of decay than normal controls, though they also seem to rebound more. (3) *The changes in concavity of the autocovariance.* PD patients rebound more in order to regain balance. Such motion is reflected in the autocovariance as critical points, that is, as local extrema or points of inflection. Details of the specific findings shall appear elsewhere.

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RESUME

Center of pressure electronic platform testing is proposed as an affordable early diagnostic tool for persons at risk of Parkinson's disease. Stiffness measures based on statistical concepts are used in such a diagnosis.