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Original article

The relationship between intermittent limit cycles and postural instability associated with Parkinson's disease

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Abstract

Background: Many disease-specific factors such as muscular weakness, increased muscle stiffness, varying postural strategies, and changes in postural reflexes have been shown to lead to postural instability and fall risk in people with Parkinson's disease (PD). Recently, analytical techniques, inspired by the dynamical systems perspective on movement control and coordination, have been used to examine the mechanisms underlying the dynamics of postural declines and the emergence of postural instabilities in people with PD.
Methods: A wavelet-based technique was used to identify limit cycle oscillations (LCOs) in the anterior–posterior (AP) postural sway of people with mild PD ($n = 10$) compared to age-matched controls ($n = 10$). Participants stood on a foam and on a rigid surface while completing a dual task (speaking).
Results: There was no significant difference in the root mean square of center of pressure between groups. Three out of 10 participants with PD demonstrated LCOs on the foam surface, while none in the control group demonstrated LCOs. An inverted pendulum model of bipedal stance was used to demonstrate that LCOs occur due to disease-specific changes associated with PD: time-delay and neuromuscular feedback gain.
Conclusion: Overall, the LCO analysis and mathematical model appear to capture the subtle postural instabilities associated with mild PD. In addition, these findings provide insights into the mechanisms that lead to the emergence of unstable posture in patients with PD.

Keywords: Balance; Limit cycle; Parkinson's disease; Posture; Wavelets

1. Introduction

Parkinson's disease (PD) is a progressive, neurodegenerative disorder which compromises both motor and cognitive performance. Difficulty maintaining upright stance, a common motor symptom, appears to manifest early in PD[1] and increases in severity as the disease progresses. Although estimates vary across studies, it is generally accepted that between 50% and 70% of individuals with PD have fallen at least once.[2–5] Many of these individuals suffer debilitating injuries from their fall, drastically reducing their mobility, ability to perform daily activities, and overall quality of life.

1.1. Postural instabilities that occur with PD

Many factors such as muscular weakness, changes in the short- and long-loop postural reflexes, varying postural reactions to perturbation, and reduced anticipatory postural responses have been associated with postural instability and increased fall risk in people with PD.[6] Changes in postural stability associated with aging and disease are often assessed using the center of pressure (CoP) trajectory that is captured while an individual stands on a force plate. The CoP is the point location of the vertical ground reaction force vector. Declines in postural stability associated with PD have been observed in both the magnitude- and time-dependent dynamics of postural

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sway (assessed using the CoP trajectory). In regard to the magnitude of sway, it is consistently reported that, under a variety of manipulations such as standing with eyes open versus eyes closed or standing with an altered base of support, people with PD exhibit more postural sway than neurologically-intact individuals. The typical interpretation of this finding is that the increased sway is indicative of a decrease in balance stability.[7,8]

There are limitations when interpreting postural stability using only sway magnitude data. First, the implicit assumption that less sway is indicative of greater stability may not always be correct since some degree of extraneous body movement contributes to postural flexibility.[9] In contrast, adopting a rigid posture may hinder an individual's ability to respond to possible threats to balance.[10] For example, when balance is perturbed an individual cannot respond or recover as well without some flexibility and natural sway. Second, basic assessments of sway magnitude do not provide information describing the dynamics of CoP movement. It is important to note that the CoP is a collective variable that captures movement of all of the body's degrees of freedom. The underlying temporal evolution of movements in a variety of body segments provides information regarding how the body integrates multiple degrees of freedom into the completion of various tasks.[9] This temporal structure cannot be seen when assessing sway by taking spatial measures such as an average. Measures that examine the structure of postural sway provide valuable information regarding disease-related changes in the flexibility and adaptability of the postural system.

Measures of entropy have been an increasingly popular technique to assess the structure of postural sway.[11] Entropy measures essentially provide information regarding the complexity of the time series. Higher values of entropy indicate the signal is more complex, while lower values indicate the signal is more regular or periodic in nature. In general, more complex sway has been interpreted to mean that more of the body's degrees of freedom are being used to maintain stance (a less rigid posture is being adopted) and is therefore considered to be a signature of a healthy postural system. People with PD typically (but not always) exhibit more regular CoP signals compared to typically aging adults.[12] For example, Maurer et al.[12] found an abnormally large 1 Hz oscillatory sway pattern in people with PD. More oscillatory (sinusoidal) and deterministic patterns of sway suggest that postural complexity may be reduced in individuals with PD. This interpretation is consistent with the loss of complexity hypothesis proposed by Lipsitz and Goldberger.[13] According to this hypothesis, physiological systems degrade with disease, resulting in less complex biophysical signals; whereas under healthy conditions, the biophysical signals that emerge from the interconnected physiological systems of the body naturally have a rich and complex structure. As mentioned above, in the case of PD, more oscillatory sway dynamics could indicate postural rigidity.

Non-linear signal measures such as entropy have proven to be a valuable tool to assess the underlying dynamics of postural control. These tools have helped redefine the understanding of movement variability and how this variability relates to the adaptability and flexibility of the postural system. However, these measures cannot capture the underlying mechanism associated with increased oscillatory patterns. Mathematical models of posture (described below) are needed to understand how sway behavior is affected by neurophysiological factors such as neuromuscular feedback gain, time-delay, muscle stiffness, and muscle damping. In this paper, we build upon previous dynamical systems postural research with a newer wavelet-based technique to capture limit cycle oscillations (LCOs) in the postural sway of people with PD. LCOs are self-sustained, periodic motions which arise in many systems with time-delayed feedback.[14–24] In the postural domain, LCOs have been suggested to exist in mathematical models of individuals who experience increases in sensory delays and feedback gains.[25–29]

There are several advantages to assessing LCOs in patients with neurological disease. First, unlike measurements such as root mean square (RMS) or entropy, LCOs can be used to directly interpret the emergence of postural instability. For example, as discussed above, directly interpreting postural stability using more traditional linear and non-linear methods can be challenging. However, using mathematical models, previous research has shown that LCOs are a marker of dynamic instability of upright posture.[25–29] These models ultimately help us interpret experimental data by identifying the mechanisms that lead to potentially unstable postural behaviors such as LCOs. Second, because tremor in people with PD can often be intermittent and change as a function of various states such as anxiety or task demand, using measures such as wavelets that can capture transient changes in the dynamics of postural sway may better assess the emergence of postural instability.

Declines in postural control associated with PD have been well documented to occur even in people who were recently diagnosed. In the first chapter of the 1817 book *An Essay on the Shaking Palsy*, Dr. James Parkinson[30] states that soon after subtle symptoms are found in the control of the hand and arm, postural symptoms begin to manifest. According to Parkinson, "After a few more months, the patient is found to be less strict than usual in preserving an upright posture, this being most observable whilst walking, but sometimes whilst sitting or standing" (p. 4).[30] The postural changes observed by Dr. Parkinson, and commonly observed by neurologists today, are very salient as the disease progresses. More recently, studies are beginning to examine whether slight postural changes can be observed during the relatively long prodromal phase of the disease. Maetzler and colleagues[31,32] have documented that changes in postural control were, upon reflection by the patient, one of the subtle symptoms they noticed before being diagnosed. Additionally, Maetzler and colleagues[32] found that, when placed in challenging body orientations, postural changes are observed in people at risk of developing PD. Interestingly, the postural changes observed in these at-risk people appear to be related more to the smoothness rather than the magnitude of movement. Thus, measures which examine the time-dependent dynamics of posture, like the LCO measure described here, may be better able to capture the early postural changes in people with PD, and may ultimately provide an opportunity to develop early clinical markers for PD.

1.2. Mathematical models of posture in people with PD

As mentioned above, mathematical models can provide a window into the mechanisms underlying the control of balance in people with PD and insights into disease-related changes in the dynamics of postural sway. Previous models have demonstrated that increases in sensory feedback processing delays are likely to be responsible for generating the (4–6 Hz) Parkinsonian tremor. For example, Stein and Oğuztöreli[33] showed that increases in feedback gain and time-delay in the long loop reflexes can cause oscillations in the extremities. Applying these findings to postural control, excessive time-delays and larger than normal feedback gains in the neuromuscular pathways governing upright stance may ultimately be responsible for the postural instability and may be one of the causes leading to falls in people with PD.[34]

Recent mathematical models have examined how destabilizing postural dynamics emerge from disease-related changes in the neuromuscular system.[25–29] These models show that LCOs typically occur when time-delays are increased beyond a critical threshold, leading to instability of a static position. Thus, the presence of LCOs in postural sway indicates the system is deviating from a stable upright equilibrium. It is important to note that current models typically only assess anterior–posterior sway. The future development of medial–lateral models may provide insights into the medial–lateral instability associated with PD. Chagdes et al.[29,35,36] experimentally confirmed the presence of LCOs as predicted by the aforementioned models. Specifically, they demonstrated that LCOs are a signature of postural instability in two different clinical populations: people with multiple sclerosis and people with concussion, suggesting LCOs are found in a variety of neurological disorders that are speculated to have longer neuromuscular time-delays.[37–39]

1.3. Bifurcation analysis

One major benefit of non-linear bio-mathematical models is that they can identify the different postural states of the system such as upright equilibrium, leaning posture, and LCOs, and provide a valuable opportunity to examine the factors that lead to bifurcations, or transitions, between various postural states. For example, Chagdes et al.[29] found that the limit cycle behaviors in concussed athletes and people with multiple sclerosis were intermittent. Specifically, within a single trial, there were epochs when LCOs were present and epochs when they were absent. We posited that the intermittent nature of the LCOs resulted from the individual bifurcating between different postural states (an upright equilibrium point attractor and a limit cycle attractor). These postural states can be examined by constructing stability diagrams (further described below) that visualize the underlying parameters (i.e., passive stiffness, passive damping, neuromuscular feedback gain, and time-delay) that influence the stability of upright stance.[29]

A bifurcation such as the one described above is a signature property of non-linear dynamical systems, including human motor control.[40] A bifurcation is a transition between two states that occurs when a parameter (referred to as a control parameter) is scaled. Several human neuromuscular systems display bifurcations. For example, if a person starts oscillating his or her index fingers in an anti-phase manner, an abrupt bifurcation occurs to in-phase movement as movement frequency (the control parameter) increases.[40] Other examples include bifurcations from walking to running as gait speed increases,[41] upright human balance,[25–29] heartbeat,[42] human brain,[43] physiological control,[15] biological oscillators,[44,45] traffic,[18] and predator–prey models.[19–21]

Examining bifurcations between states is a common mathematical technique used in the study of many dynamical systems[46–48] but has not been commonly examined in a postural context. The stability of a system describes how small perturbations around the system's equilibrium positions will behave and if, in time, the system will return to the equilibrium position. A bifurcation can also describe how smooth changes in a system's control parameters elicit behavioral changes in the system's topology and sudden changes in the stability of equilibria.[46–48] By investigating bifurcations inherent in a bio-mathematical model of human posture, one can understand how changes to control parameters that typically occur with disease can result in sudden changes in postural dynamics.

Two common bifurcations that have been identified in models of upright balance in the anterior–posterior direction are the pitchfork and the Hopf bifurcations.[25,26,28,29] A pitchfork bifurcation occurs when a single equilibrium changes stability and two additional equilibria appear symmetrically around the original equilibrium point.[46–48] This bifurcation is said to be supercritical if the single equilibrium changes from stable to unstable and the two appearing equilibria are stable; if the opposite is true, it is considered subcritical. A Hopf bifurcation occurs when a single equilibrium changes stability and a limit cycle emerges around the equilibrium point.[46–48] The bifurcation is said to be supercritical if a stable limit cycle emerges around an unstable equilibrium point; otherwise it is considered subcritical when the opposite is true.

To understand how slow changes in neuromuscular feedback gain and time-delay lead to instabilities, we used the DDE-BIFTOOL MATLAB package[49] to investigate the bifurcation in a mathematical model of upright stance. We adapted the single degree-of-freedom inverted pendulum model proposed by Chagdes et al.[29] Within this model, we assume that the passive control parameters were held constant with stiffness (K) assumed to be 75% of K^{cr} and damping (C) assumed to be 10% of K^{cr}, where K^{cr} is equal to the product of the individual's body mass, height to center of mass, and acceleration due to gravity, consistent with prior works.[25,29,50–52] Within the model, we allow neuromuscular feedback gain (K_a) and time-delay (τ) to vary to investigate how PD affects upright posture. These specific parameters were chosen to vary as it is well known that postural control parameters such as stiffness and time-delay change with the progression of PD.[53,54]

Examining the stability regions can help explain bifurcations between postural states (Fig. 1). Specifically, this bifurcation analysis demonstrates that upright posture can be destabilized by two different types of instabilities. The first instability occurs when neuromuscular feedback gain is decreased beyond a

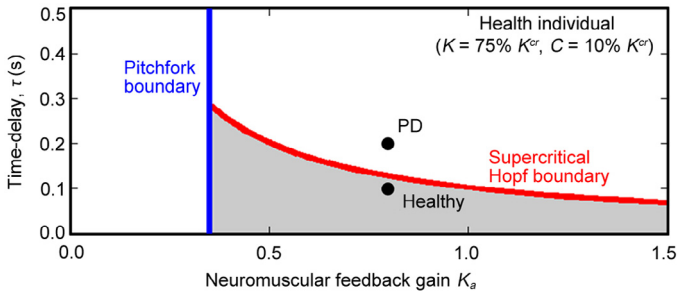

Fig. 1. Upright equilibrium stability regions of a mathematical model of posture as a function of neuromuscular feedback gain (K_a) and time-delay (τ). The stable region (gray) and unstable regions (white) are bounded by a supercritical pitchfork bifurcation (blue line) and a supercritical Hopf bifurcation (red line). Indicated on the figures is the hypothetical region where a healthy person and a person with Parkinson's disease (PD) would operate.

critical threshold causing the system to cross a supercritical pitchfork bifurcation (Fig. 1). When the supercritical pitchfork bifurcation is crossed, the upright equilibrium position loses stability and two stable leaning equilibrium positions appear symmetrically around the upright position. In this region, any perturbation around the upright position will be attracted by one of the two offset equilibria, eventually leading to a leaning posture. The other instability occurs when the combination of neuromuscular feedback gain and time-delay increases and the system crosses a supercritical Hopf bifurcation (Fig. 1). In this region, all perturbation around the upright posture will be attracted by the limit cycle eventually leading to LCOs in postural sway. It is important to note that when neuromuscular parameters are such that the system lies near the bifurcation boundary, small changes in parameters could lead to large postural differences. Furthermore, near the boundary, parametric noise can cause the system to slowly move between the regions of stable upright posture and LCOs, leading to intermittent LCOs. It is well known that postural control parameters such as stiffness and time-delay change with the progression of PD.[53,54] We believe that these parameter changes associated with PD will lead the limit cycle instability predicted by the mathematical model. One major advantage of interpreting LCOs in conjunction with a bio-mathematical model is that the mechanisms underlying bifurcations between stable and unstable postures can be revealed. Although traditional measures of postural sway have been assessed extensively in people with PD, evidence of LCOs will provide new and complementary information regarding the underlying mechanisms of instability. Thus we examined if intermittent LCOs are observed in individuals with PD. The likelihood of finding LCOs was increased by having the participants stand on a foam surface (greater postural challenge). The foam surface compromises the sensory information from the plantar foot surface and provides an unstable surface. Since cognitive tasks alter the structure and magnitude of the postural sway time series,[55] an easy communication task was implemented across all conditions to control for cognitive load while standing. We hypothesize that only people with PD will demonstrate LCOs, and LCOs will be more prevalent with increased postural challenge due to foam surface.

2. Methods

2.1. Subjects

Ten individuals with PD (5 females; age range 55–77 years, mean 65.3 years) and 10 age-matched healthy controls (5 females; age range 60–78 years, mean 67.1 years) (Table 1) served as participants. There were no significant differences in age between the groups ($F = 0.30$, $p = 0.59$). Both groups had similar levels of education (PD: 18.1 ± 2.3 years; control: 17.6 ± 2.8 years; mean ± SD), were native speakers of English, and reported normal hearing at the time of participation. Exclusionary criteria included: no respiratory or neurological diseases other than PD, no acute or chronic orthopedic injury, no smoking in the past 5 years, and no head, neck, or chest surgery. All participants had to score within the normal limits in the composite severity rating of the Cognitive-Linguistic Quick Test[56] to be included in the study. Approval for this study was granted by the Purdue University Institutional Review Board and all participants gave written consent. The Cognitive-Linguistic Quick Test was used instead of the Mini Mental State Examination because it is more sensitive to subtle cognitive changes than the Mini Mental State Examination.[57] Participants

Table 1
Participant demographics and characteristics of individuals with Parkinson's disease (PD) and healthy older adults.

Code	Sex	Control		PD			
		Age (year)	Fall history	Age (year)	Fall history	Time since diagnosis (year)	Medication
1	Female	60	No	55	Yes	6	1, 3, 12
2	Female	78	No	77	No	3	None
3	Female	64	Yes	63	No	7	4, 5, 10, 11, 13, 15
4	Female	64	No	61	Yes	7	6, 7, 8, 14
5	Female	70	No	70	Yes	2	2, 12
6	Male	66	Yes	64	Yes	10	14
7	Male	60	Yes	60	No	6	2, 3, 9, 10, 14
8	Male	63	No	61	No	2	1, 6
9	Male	75	No	71	Yes	9	12
10	Male	71	No	71	Yes	6	12, 6

Note: Medication Key 1, amantadine; 2, amitriptyline; 3, azilect; 4, baclofen; 5, Coenzyme Q10; 6, mirapex; 7, oxazepam; 8, paroxetine; 9, primidone; 10, requip; 11, selegiline; 12, sinemet; 13, sinemet carbidopa levodopa; 14, stalevo; 15, wellburtrin.

with PD were tested within 1–3 h of taking their PD-related medications.[58] The diagnosis of PD was made or confirmed by each participant's neurologist. All participants had Hoehn and Yahr scale scores of I–II,[59] indicating mild motor impairment. The neurologists who see most of our participants did not routinely take Unified Parkinson's Disease Rating Scale (UPDRS) measures; thus these scores were not obtained. Fall history was assessed by asking the participants if they had fallen in the past year.

2.2. Procedure

In order to minimize participant fatigue, each individual participated in two sessions within a 2-week span. Both sessions were identical, except for the surface on which the participant stood. For one session, the participant stood directly on a force platform (AMTI, Watertown, MA, USA; stable condition); for the other session, the participant stood on a 3-inch (7.6 cm) thick foam Airex® Balance pad (Schweiter Technologies AG, Horgen, Switzerland), which was placed directly on the force platform (foam condition). The pad was made of closed cell foam that compressed but did not settle during the session. The foam condition was designed to challenge balance.[60] The order of surface conditions was counterbalanced across participants.

During the experimental task, the participants stood facing a computer screen that was approximately 7 feet (2.1 m) away, with their eyes open and feet shoulder width apart. Participants were instructed to stand comfortably. Participants viewed one of three possible photographs and heard a female talker produce one of a set of sentences describing the photograph. After hearing each sentence, the participants repeated it aloud. This process was repeated 12 times with different sentences while CoP data were collected. Each subject performed this task one time, which lasted at least 100 s. To prevent fatigue, the participants took a 5-min seated rest break in the middle of the trials. The same procedure was used when the participants returned for their second testing session with the exception that they stood on the other surface (i.e., rigid or foam).

The sentence repetition task was utilized as part of a larger study and also served to standardize the cognitive demands of the standing task. Standardizing the cognitive task was important given that previous research has indicated that engaging in a cognitive task alters the structure and magnitude of the postural sway time series.[55] Thus, requiring an individual to just stand can be problematic because there is no way to control what the individual participant is thinking. By employing a communication task that is the same across conditions and participants, the cognitive load and any small postural movements caused by speech production were controlled.

2.3. Data processing

Ground reaction forces and moments as well as audio signals of participant speech were sampled at 12,600 Hz. Ground reaction forces and moments were used to calculate the CoP time series in the anterior–posterior direction.[61] To calculate the CoP when standing on foam, one needs to take into account the additional torque generated as a result of the foam vertical displacement. This offset calculation is as follows:

$$CoP_{AP} = \frac{M_{ML} - F_{AP} d_z}{F_z} \tag{1}$$

where CoP_{AP} represents the CoP in the anterior-posterior direction, M_{ML} represents the moment about the medio-lateral direction, F_{AP} represents the force in the anterior-posterior direction, F_z represents the force in the vertical direction, and d_z represents the vertical offset of the foam ($d_z = 7.3$ cm in this study). The data were then down sampled to a frequency of 49.2 Hz. Each set of time series data were truncated to 90 s. The spatial magnitude of postural sway was examined by calculating the RMS,

$$X_{RMS} = \sqrt{\left(\sum_{n=1}^{N} |x_n|^2\right) \Big/ N} \tag{2}$$

of each CoP time series in the anterior–posterior direction for both CoP position and CoP velocity.

LCOs were identified using a continuous wavelet transform. A wavelet transform decomposes a signal into a series of wavelet basis functions at different timescales.[62] The wavelet basis function can be chosen to best fit the typical fluctuations of the signal and can detect the structure of a signal over various timescales. The continuous wavelet transform converts a signal $x(t)$ into a wavelet coefficient $T(a,b)$ at each timescale

$$t_a = \frac{a}{f_c f_{sampling}} \tag{3}$$

and time instant b in a two-dimensional space (a,b) where f_c is the center frequency of the wavelet basis function and $f_{sampling}$ is the sampling frequency. Each wavelet coefficient, representing the measurement of the correlation of the signal to the wavelet basis function, is calculated by convoluting the signal $x(t)$ with the complex conjugate of the wavelet basis function $\psi^*_{a,b}$ at various scales and translations,[62]

$$T(a,b) = \int_{-\infty}^{\infty} x(t)\psi^*_{a,b}(t)\mathrm{d}t \tag{4}$$

Compared to various dynamical systems measures used to examine signals at various timescales such as the detracted fluctuation analysis, the continuous wavelet analysis is not affected by the duration of the trial.[62] We adopt the wavelet method for identifying LCOs using a similar method as Chagdes et al.[29] Specifically, LCOs are identified as instances in a signal where large amplitude oscillations are present at a dominant timescale, about 2–4 s as predicted by the mathematical model. This is accomplished by first decomposing the signal using the continuous wavelet transform (Fig. 2A and B). Then, an amplitude criterion is applied by ignoring all wavelet coefficients below $T^{cr} = 110$ mm-s (Fig. 2C and D), which corresponds to a CoP oscillation of 10 mm at a frequency of 0.25 Hz. The frequency of 0.25 Hz was chosen to match the predicted LCOs of the mathematical model.[29] Last, the method searches for a repeating and alternating series of maxima and minima wavelet coefficients that repeat more than twice consecutively ($n > 2$). The repeating

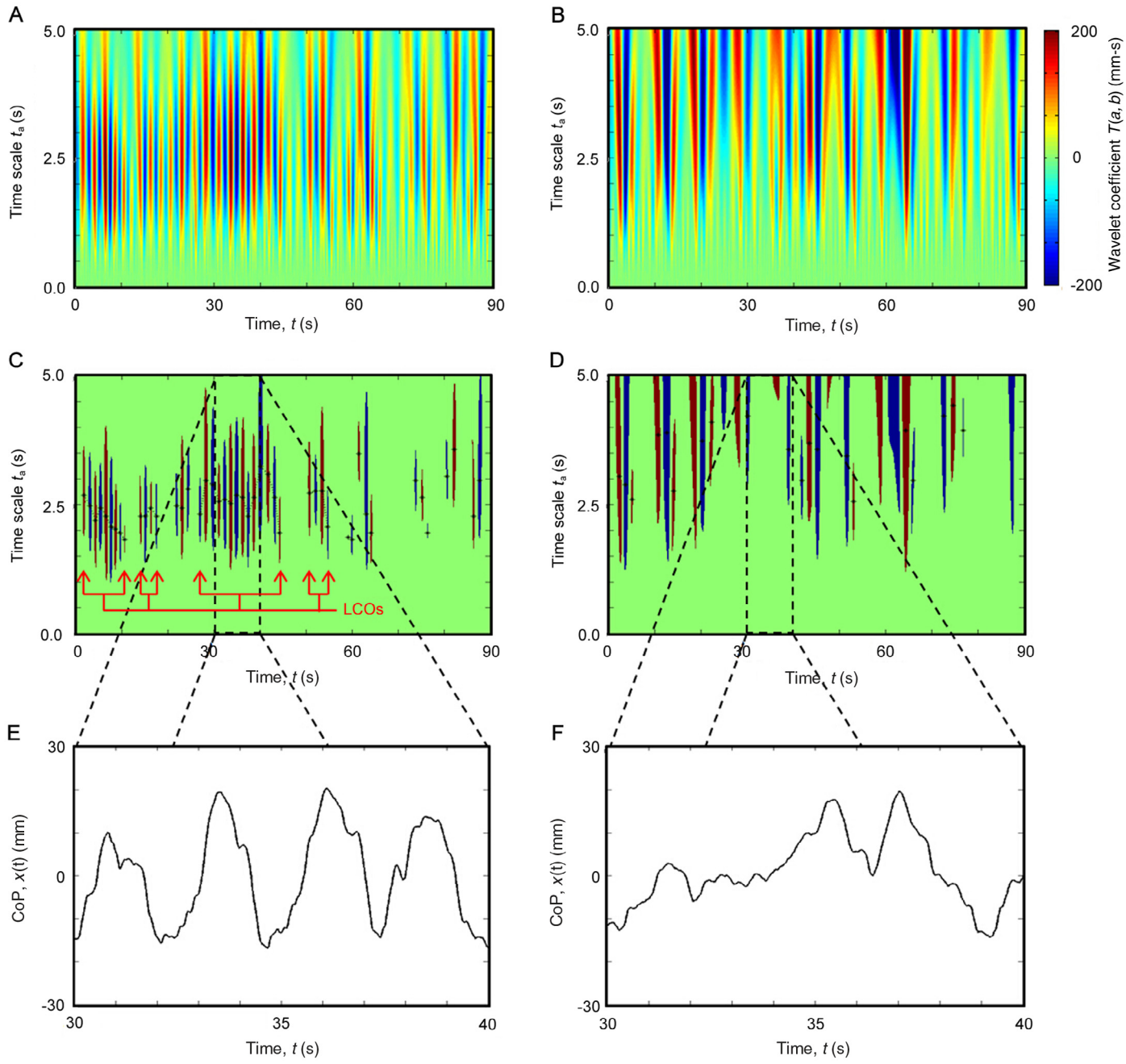

Fig. 2. Continuous wavelet transform (A, B), continuous wavelet transform with wavelet coefficient of at least magnitude 110 mm-s (C, D), and the corresponding center of pressure (CoP) time series (E, F), of an individual with Parkinson's disease (PD) showing intermittent limit cycle oscillations (LCOs) (left) and a control individual not showing intermittent LCOs (right) while standing on foam. The values of the wavelet coefficients are indicated by color where a positive coefficient (red) represents forward sway and a negative coefficient (blue) represents a backward sway.

and alternating series of maxima and minima wavelet coefficients are only identified if the timescale of oscillation between consecutive wavelet coefficients does not drift more than 1 s in time scale per 1 s ($m = 1$) and the time period between consecutive maxima or minima wavelet coefficients is within 10% of their average time scale of oscillation ($\chi = 10$). Fig. 2C and D shows this method applied to the CoP signals of an individual with PD and a healthy age-matched control individual. The data in Fig. 2C are an example of data where LCOs were identified in three regions, one of which can be seen in Fig. 2E.

Differences in RMS differences were assessed using a two-way repeated measures ANOVA. Group (PD *vs.* healthy) was a between-subject factor that was repeated within surface type (stable *vs.* foam).

3. Results

An exemplar time series while standing on foam from a person with PD and a healthy control participant is displayed in Fig. 3. The RMS of CoP position revealed a significant main

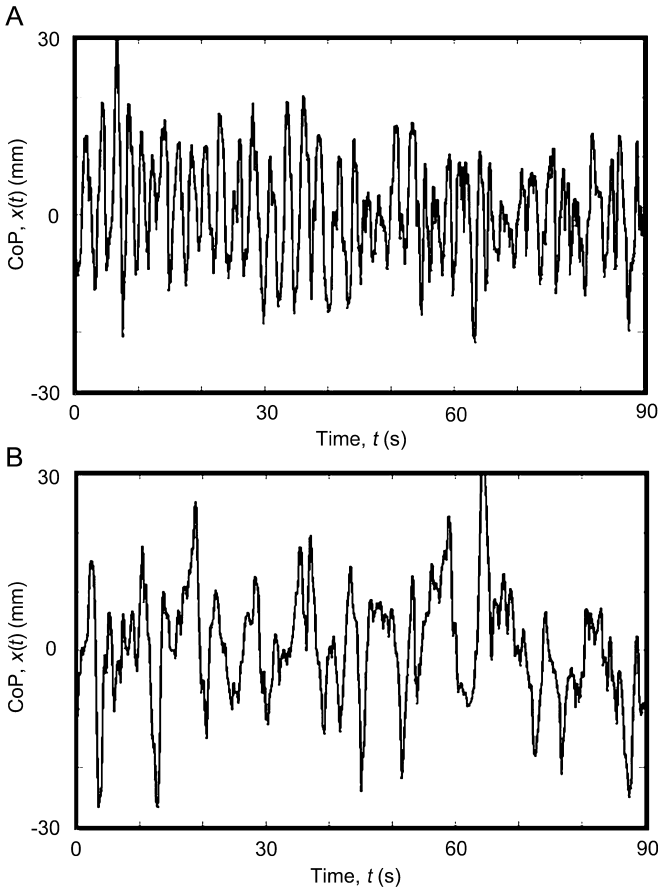

Fig. 3. Experimental center of pressure (CoP) time series in the anterior–posterior direction of a person with Parkinson's disease (PD) (A) and an age-matched control (B) while standing on foam.

effect for surface ($F(1, 18) = 16.17$, $p < 0.001$), but no main effect of group ($F(1, 18) = 0.32$, $p = 0.57$) or group × surface interaction ($F(1, 18) = 1.04$, $p = 0.32$) (Table 2 for mean RMS values).

LCOs were not observed in any of the healthy control participants while either standing on foam or on the rigid surface. LCOs were also not observed in the participants with PD while standing on a rigid surface but were observed in three of the 10 participants while standing on the foam surface (Table 2).

4. Discussion

In the current study, we examined whether intermittent LCOs are present in the postural dynamics of people with mild PD. LCOs are a classic sign of instability of a static equilibrium in many non-linear dynamical systems, especially those with time-delay.[14–24] In postural control, the identification of LCOs represents an individual's inability to stabilize the upright position. Although traditional time-independent measures of postural stability such as sway area also provide information regarding deviations from an upright equilibrium, they provide no information regarding intermittent or transient changes in postural dynamics or potential non-linear bifurcations between postural states. Interestingly, there were no differences in the magnitude of postural sway between healthy older adults and adults with PD in the current study. Additionally, LCOs were not observed in either group when standing on a rigid surface. However, three of the 10 participants with PD exhibited LCOs in their anterior–posterior postural sway when standing on foam. Thus, when the postural system is challenged in people with mild PD, LCOs can emerge in postural sway before changes occur in the magnitude of postural sway. However, it is important to note that many of the patients with PD did not exhibit limit cycles while on foam. Therefore, further work is needed to better examine the interpretation of limit cycles in people with PD. For example, longitudinal research that follows individuals as the disease progresses could provide valuable insights into the nature of LCOs in patients with PD, and the subsequent impact of fall risk and ability to complete activities of daily living.

4.1. Time-dependent measures of postural sway

As described earlier, various non-linear measures inspired from a dynamical systems perspective such as recurrence

Table 2
Characteristics and percentage of time series containing limit cycle oscillations (LCOs) in center of pressure (CoP) while on a rigid surface and while on foam for individuals with Parkinson's disease (PD) and healthy older adults.

Code	Sex	Rigid surface		Foam	
		Control (%)	PD (%)	Control (%)	PD (%)
1	Female	0	0	0	24.0
2	Female	0	0	0	0
3	Female	0	0	0	0
4	Female	0	0	0	18.0
5	Female	0	0	0	0
6	Male	0	0	0	0
7	Male	0	0	0	16.4
8	Male	0	0	0	0
9	Male	0	0	0	0
10	Male	0	0	0	0
RMS of AP CoP position* (mm)		5.11 ± 0.51	6.03 ± 0.78	7.79 ± 0.39	7.62 ± 0.51
RMS of AP CoP velocity* (mm/s)		391.78 ± 24.33	405.14 ± 29.81	390.24 ± 25.52	390.05 ± 26.55

* Data are expressed by mean ± SE.
Abbreviations: RMS = root mean square; AP = anterior–posterior.

quantification analysis and sample entropy have been used to investigate postural changes in people with PD. In general, these measures have provided valuable insight into the dynamics of posture in people with PD and how these dynamics relate to the disease-related changes in the flexibility and adaptability of posture.[63] For example, less complex postural dynamics may suggest that fewer degrees of freedom are being used to maintain an upright stance. Limiting degrees of freedom suggests that the patient is adopting a less adaptable stiffening strategy. In this paper, we propose that LCO analysis provides many of the same benefits of the previously used dynamical systems techniques with one important addition. Specifically, when combined with mathematical modeling, LCOs can help understand the complex mechanisms such as non-linear bifurcations and control parameter scaling which lead to the onset of instability.

4.2. The emergence of LCOs

LCOs are predicted when the combination of neuromuscular feedback gain (K_a) and time-delay (τ) is increased beyond a critical threshold (Fig. 1). Thirty-three percent of the participants with PD demonstrated LCOs, while none of the controls demonstrated LCOs. The presence of LCOs suggests that these individuals have increased neuromuscular feedback gain and/or time-delay. This finding is supported by the reported increases in time-delay associated with PD.[54] Although no one was identified as posturally unstable by the Hoehn and Yahr scale,[59] the LCO analysis detected postural instability in three individuals with PD. Thus, we have preliminary evidence that LCOs are a distinct behavior that occurs in some people with PD, but this is not detected with current clinical analyses. The participants with PD who did not demonstrate LCOs may not yet have sufficient changes in the combination of their neuromuscular feedback gain and time-delay in order to cross the bifurcation into the unstable regime (Fig. 1). Upright posture in the majority of participants may be stable given the early stage of the disease. One limitation of this study is that we are unable to correlate the occurrence of LCOs with the degree of postural stability as assessment using clinical balance scales.

It is possible that increased stiffness associated with PD[53] prevented more individuals with PD from exhibiting LCOs. The bifurcation analysis is well suited to illustrate how increased muscle stiffness can alter upright stability. In the bio-mathematical model of Chagdes et al.,[29] an increase in muscle stiffness results in an increased passive muscle stiffness gain (K). Although we are unaware of any study that has investigated increased muscle damping associated with PD, it is very likely that an increase in damping would be accompanied by the reported increase in muscle stiffness as more energy will be lost due to the interactions between stiffer muscles. Within the parameters of the model, an increase in damping would be represented by an increase in the passive muscle damping gain (C). When both K and C are increased from the typical parameters of healthy individuals (Fig. 1), the stability boundaries move in such a way that the range of parameter values for achieving stable upright posture increases (Fig. 4). For limit cycles to emerge in an individual with increased passive muscle stiffness and damping, it would take a larger increase in neuromuscular time-delay (Figs. 1 and 4). While it is counterintuitive that individuals with increased passive stiffness, such as people with PD, would be able to stabilize upright posture for a larger range of neuromuscular feedback parameters, the increase in neuromuscular time-delay that is accompanied by PD causes the system to operate near the Hopf bifurcation. Near the Hopf bifurcation, the model predicts the onset of intermittent LCOs when control parameters vary slowly due to noise.[29] This may explain the intermittent nature of the LCOs identified in the CoP data in this study. Specifically, noise may cause an abrupt non-linear transition into and out of the unstable regime. Furthermore, near the Hopf bifurcation, the eigenvalue with the largest real component is less than that of the typical healthy individual with less stiffness and a shorter neuromuscular time-delay, indicating that it will take longer for the posture of an individual with PD to return to the upright position after a perturbation. Such behaviors are consistent with the reported postural instabilities that occur with PD. The bifurcation analysis highlights the importance of how the interaction between various control parameters leads to bifurcations and unstable states.

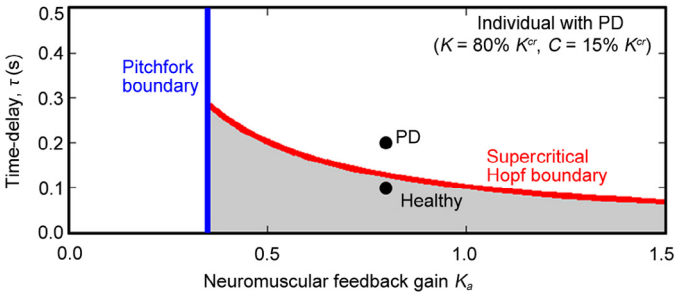

Fig. 4. Upright equilibrium stability regions of a mathematical model of posture with increased passive stiffness (K) and damping (C) as a function of neuromuscular feedback gain (K_a) and time-delay (τ). The stable region (gray) and unstable regions (white) are bounded by a supercritical pitchfork bifurcation (blue line) and a supercritical Hopf bifurcation (red line). Indicated on the figures is the hypothetical region where a healthy person and a person with Parkinson's disease (PD) would operate.

4.3. The interaction between postural stability and speech

In the current study, the participants were required to perform a speech task while standing. In general, performing a dual-task activity does appear to influence postural dynamics. Healthy young adults either decrease or increase postural sway when performing a dual-task activity.[64] Whether sway is increased or decreased depends on a number of factors including the nature and difficulty of the cognitive task.[55] Remaud et al.[64] found that anterior–posterior sway velocity decreased with the addition of a simple reaction time task. Although counterintuitive, either an increase or decrease in CoP movement could indicate less stable postural dynamics. For example, reductions in postural sway could indicate the onset of a "stiffening" strategy, resulting in fewer degrees of freedom available to offset any postural perturbations. On the other hand, increased sway may be harder to control and may result in a loss of balance.

In the case of PD, problems performing dual-task activities are more pronounced due to disease-specific cognitive issues,[65–68] which include deficits in visuospatial skills, memory, language, attention, mood, and emotional processing.[69] When performing a secondary cognitive task while walking or standing, people with PD tend to exhibit greater postural instability and a less safe (more unstable) gait mode.[65,70] Bloem et al.[65] reported that, when performing a dual-task, typically-functioning older adults tend to adopt a safe strategy of prioritizing their balance over completion of the cognitive task. In contrast, individuals with PD do not prioritize balance over performance of the secondary task.

The fact that individuals with PD tend not to prioritize secondary cognitive tasks may explain why only the patient group exhibited LCOs in the more challenging postural condition. Additionally, speech and language generation is an interesting task to pair with posture in people with PD. Communication and upright postural stability are typical activities of daily living often performed together and both are known to be difficult for individuals with PD. The existence of LCOs in the data from people with PD while producing a speech task suggests that even mildly impaired individuals can begin to manifest decreases in postural stability while standing in challenging situations. Additionally, the fact that LCOs were identified only in the foam condition suggests that disease-specific changes in postural stability are most clearly revealed when the person with PD is placed in challenging environments. Examining the detection of LCOs in conjunction with the bifurcation analysis while participants perform tasks common to daily life may provide important insights into the mechanisms of postural instabilities in people with PD and ultimately may help clinicians develop optimal patient-customized intervention strategies.

4.4. Traditional measures of postural stability

Consistent with past research, standing on foam resulted in a higher magnitude of postural sway in both groups of participants. However, and in contrast to past research, the magnitude of sway was similar in people with PD and age-matched healthy individuals. There are two potential explanations for this discrepancy. First, the participants with PD in our study were only mildly impaired. This possibility is interesting in the context of the current results because it suggests that LCOs may be more sensitive at detecting postural instability. Second, since our initial modeling work used to detect LCOs only examined the anterior–posterior direction, magnitude of sway was only examined in the anterior–posterior direction. Stylianou et al.[71] found that there were no differences in spatial measures of anterior–posterior sway when standing with eyes open and closed between mild and moderately impaired people with PD and healthy age-matched controls. There were, however, differences in medial–lateral sway and when using time-dependent non-linear measures of sway (i.e., the Hurst exponent). Newer research[72] has suggested that postural asymmetry may be an early symptom of postural changes in people with PD. The asymmetrical nature of the disorder results in the differential control between limbs, and postural compensations occur in the less impaired limb. Similar asymmetries have also been observed in healthy young individuals when performing challenging tasks.[73] Postural asymmetries would be most clear when examining the sway in the ML direction. A bifurcation analysis has not been performed on any mathematical models of upright posture in the medial–lateral direction. As a result, we are unable to investigate if LCOs exist in experimental medial–lateral sway as it is unknown what types of postural behaviors (such as LCOs) can exist in this direction. Following the development of a theoretical basis for interpreting postural sway in the medial–lateral direction, future research should investigate if LCOs are more prevalent in medial–lateral sway for individuals with PD.

4.5. Limitations

There were several limitations in the current study. First we were unable to obtain UPDRS scores for the patients included in the study. This test is a more commonly used measure of disease severity in research papers in PD. Unfortunately, the clinicians in our area of the country do not seem to perform this test as a part of their clinical exams. We also were unable to obtain levodopa equivalence dose data for our patients, which would have made it clearer how they compared to one another, potentially distinguishing those patients who demonstrated LCOs from the other patients in the sample. A portion of the score on the motor subtest of the UPDRS comes from a test wherein the clinician pulls the patient to offset the patient's center of balance. Another such test which is commonly used to assess balance is the Berg Balance Scale. Later work should make a direct comparison of LCOs to scores on these kinds of tests in a population of people with PD to understand the clinical utility of the LCO analysis.

5. Conclusion

In conclusion, the detection of LCOs appears to be a sensitive technique to capture postural instabilities in people with PD, potentially before postural instability is present as a clinical sign. When interpreted in conjunction with mathematical models, the emergence of LCOs provides mechanistic insights into how complex changes in various neuromuscular parameters such as sensory time-delay and stiffness result in postural instabilities.

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Authors' contributions

JRC conducted the design and analysis of the mathematical model and experimental data, contributed to the interpretation of the results, and drafted the manuscript; JEH contributed to

the design of the experimental component of the project, oversaw collection of the experimental data, provided insight into Parkinson's disease, interpreted the results, and drafted the manuscript; MS contributed to the collection of experimental data, performed the statistical analyses, interpreted the results, and drafted the manuscript; MDW contributed to the collection of experimental data, performed the statistical analyses, interpreted the results, and drafted the manuscript; AR contributed in the design and analysis of the model and experimental data, provided knowledge of non-linear dynamics and signal analysis, and drafted the manuscript; SR contributed to the interpretation of the model and experimental data and drafted the manuscript; HNZ contributed to the interpretation of the model and experimental data and drafted the manuscript; JMH contributed to the design of the experimental component of the project and in the interpretation of the model and experimental results, and drafted the manuscript. All authors have read and approved the final version of the manuscript and agree with the order of presentation of the authors.

Competing interests

None of the authors declare competing financial interests.

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