Margins of Postural Stability in Parkinson's Disease: An Application of Control Theory

Zahra Rahmati
Sharif University of Technology
Saeed Behzadipour (behzadipour@sharif.edu)
Sharif University of Technology https://orcid.org/0000-0001-9313-315X
Ghorban Taghizadeh
Iran University of Medical Sciences: Tehran University of Medical Sciences

Research

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Abstract

Background: Postural instability is a restrictive feature in Parkinson's disease (PD), usually assessed by clinical or laboratory tests. However, the exact quantification of postural stability, using stability theorems that take into account the human dynamics, is still lacking. We investigated the feasibility of control theory, Nyquist stability criterion (Gain Margin – *GM* –, and Phase Margin – *PM* –), in discriminating postural instability in PD; as well as the effects of a balance-training program.

Methods: Center-of-pressure (COP) data of 40 PD patients before and after a 4-week balance-training program, and 20 healthy control subjects (HCs) (*Study*1); as well as COP data of 20 other PD patients at four time points during a 6-week balance-training program (*Study2*), collected in two earlier studies, were used. COP was recorded in four tasks, two on rigid surface and two on foam, eyes-open and closed. A postural control model (an inverted-pendulum with PID controller and time delay) was fitted to the COP data, to subject-specifically identify the model parameters; thereby calculating $|GM|$ and *PM* for each subject in each task.

Results: Patients had smaller margin of stability ($|GM|$, *PM*) compared to HCs. Particularly, patients, unlike HCs, showed drastic drop in *PM* on foam. Clinical outcomes and margin of stability improved in patients after balance training. $|GM|$ improved early at week 4, followed by a plateau in the rest of the training. In contrast, *PM* improved late (week 6), in a relatively continuous-progression form.

Conclusions: Using fundamental stability theorems is a promising technique for standardized quantification of postural stability in various tasks.

1. Background

Postural instability is a cardinal sign, and a common feature of Parkinson's disease (PD). It usually presents at diagnosis, but worsens with disease progression and largely manifests in the late stages of the disease [1, 2]. Impaired postural control is a major source of disability and loss of mobility, which predisposes patients to unexpected falls, and compromises autonomy and quality of life [3]. Postural instability may initially manifest as inability to recover equilibrium when pushed or tripped, it usually progresses to the dysfunction of salient tasks such as sitting or standing [4]. Patients are likely to fall when have to change the position of the center-of-mass (COM) in the base of support (BOS) [5]. Falls occur when patients attempting to, or actively producing transitional movements (such as sit-to-stand, turning, walking), as the COM tends to be to the outermost boundary of the BOS [5, 6]. Axial motor symptoms such as gait and balance impairments are known as L-dopa-resistant and refractory-to-surgery features, as they are associated with progressive lesions of non-dopaminergic sites [7–9]. There is growing evidences that physical therapy, and particularly balance exercises, can improve postural stability and reduce fall risk [1, 10, 11].

The exact quantification of postural (in)stability, although postural (in)stability has an established clinical implication, is still an open question [12, 13]. In clinical practices, postural stability is defined through functional and task-based tests; i.e. the ability to maintain equilibrium under both static (e.g. quiet stance) and dynamic conditions (e.g. in response to perturbations or in volitional movements) [1, 6, 8]. From this perspective, many clinical tests (e.g. retropulsion- or pull-test, tandem and single-leg stance, Timed Up and Go test – TUG) and rating scales (e.g. Berg Balance Scale – BBS, Balance Evaluation Systems Test – BEST), although being subjective [14, 15], are commonly used to evaluate postural stability [16, 17]. On the other side, laboratory tests (e.g. static, dynamic, or moving-platform posturography) were proposed as objective tools to quantify postural stability. Such tests are fundamntally tranlations of classic clinical tests into laboratorial form by the advents of state-of-the-art devices; which further evolved to the current technology-based tests. For instance, the Limit of Stability test (LOS) [18] is an advanced form of the former Functional Reach Test (FRT), benefiting from clear-cut metrics.

Despite the advances in the evaluation and quantification of postural stability, current clinical and laboratory tests are less attributed to the biomechanical definition of stability from engineering viewpoint. In other words, clinical balance tests assess merely a general functionality in limited and specific balance-related activities, rather than assessing the fundamental stability theorems that take into account the human system dynamics and the underlying governing rules. As a result, the clinical implication of stability which is rated by clinical balance tests cannot be directly addressed by experimental tests which mainly focus on postural control biomechanics. Some studies [12, 13, 19, 20, 21], integrated experimental tests with computational methods (either biomechanical [20–24], or analytical models [19, 25–28]) in order to more accurately and meaningfully quantify postural stability; still, disregarding control stability theorems. Horak et al. [19] suggested the difference between peak center-of-pressure (COP) and peak COM displacement after platform translation, as the margin of stability; which is thereafter used in various other experiments [29–31]. Hof et al. [20] proposed the extrapolated COM (X_{com}) in dynamic tasks, considering the velocity of COM. They suggest that X_{com} should remain in the BOS, as to

satisfy the dynamic stability criterion; hence, the difference between X_{com} and maximum boundary of BOS determined the margin of stability [32]. This approach also became popular in quantification and assessment of stability degree in different studies (such as stability during perturbed walking [7], obstacle crossing [33], sit-to-stand task [24], compensatory stepping response after perturbation [34, 35]). In this regard, researchers presented novel quantitative terms such as stability degree [21], region of stability [24], limit of stability [6, 36], margin of stability (in static [20], or dynamic states [19]), in order to address the extent of stability in healthy subjects or PD patients, considering biomechanical models; however, disregarding control stability theorems. Exact quantification of postural stability from biomechanical stability criteria standpoint provides an accurate interpretation of clinical and laboratory balance tests; and can potentially link clinical tests to the realm of experimental studies.

In this study, we investigated the feasibility of a widely-used stability criterion from control theory, known as Nyquist criterion [37] – i.e. Gain Margin (*GM*) and Phase Margin (*PM*) – for quantification of the postural stability in PD. The idea was explored to discriminate between PD patients and healthy control subjects (HCs), as well as to analyze the adjustments in the patients over time, during a course of balance-training program. Particularly, the proposed stability terms are determined based on the static posturographic data – which is low-cost and easily accessible in clinics –; and taking the advantages of a subject-specific computational postural control model. For this purpose, two datasets from our two previous studies [21, 38], comprised of static posturographic data of PD patients before, during, and after a balance-training program and HCs were used. A postural control model was fitted to the COP data of each subject, and as such identifying each subject's model parameters. Next, *GM* and *PM* were calculated for each subject (HC or PD before, during, and after training) using the subject-specific identified model. Inspecting *GM* and *PM* for HCs versus PD patients, as well as the reflection of adjustments in the postural stability of PD patients during a balance-training program in these new terms, presents a new quantification tool for postural stability in PD, i.e. the margin of stability.

2. Methods

2.1. Participants and experimental procedures

The data were taken from our two previous studies [21, 38] which are briefly decribed here, and the reader is referred to those articles for more details.

Study1 [21]:

Forty PD patients (7 female, 63.1 ± 12.1 years, Hoehn-Yahr ≤ 3, Mini-Mental State Examination (MMSE) score ≥ 24) and 20 healthy age-, height-, and weight-matched control subjects (4 female, 63.8 ± 12.1 years) participated in the study. The patients were assessed clinically and experimentally, before and after a 4-week (12-session) balance-training program. Patients attended training sessions every non-consecutive day (3 days/week) for 4 weeks. Functional balance and mobility in patients were assessed using clinical tests of Timed Up and Go (TUG) test, Berg Balance Scale (BBS), and Functional Reach test (FRT). The lab assessments included force-plate static posturography (record of COP data at 1 kHz for 70 sec) in eight trials; i.e. four sensory tasks, each in two trials: quiet stance on rigid surface with eyes open (RO) and closed (RC); and quiet stance on foam with eyes open (FO) and closed (FC). HCs were assessed by the lab tests, and only once.

Study2 [38]:

Twenty other PD patients (5 female, 63.3 ± 7.5 years, Hoehn-Yahr ≤ 3, MMSE ≥ 24) participated in the study. Patients were assessed clinically and experimentally before, during, and after a 6-week (18-session) balance-training program. Training sessions were held 3 days/week for 6 weeks. Clinical tests included FRT, TUG, tandem stance with eyes open (Tandem—EO) and closed (Tandem—EC), 6-min walk test (6MWT), and Tinetti performance-oriented assessment tool (balance and gait sections) [17, 39]. Clinical tests were performed three times: before- (Pre), mid- (Mid), and after-training (Post). Lab assessments were completely similar to *Study*1, i.e. collection of COP data with similar procedure: in four tasks (RO, RC, FO, FC), each with two trials. As for capturing the patterns of changes in patients during the training program, lab tests were taken at four time points: before- (Pre, or week0), at week 2 (week2), at week 4 (week4), and after-training (Post, or week6).

All PD patients in both *Study*1 and *Study*2 were diagnosed based on the UK Parkinson's Disease Society Brain Bank criteria [40], and had no other comorbidities (e.g. neurological, orthopedic, musculoskeletal disorders). Entire assessment and training sessions in both

studies were held while patients were ON-medicated, i.e. 1–2 hour(s) after taking their normal medication. Furthermore, the order of four experimental tasks was randomized for each subject to avoid any bias caused by learning effects. Subjects were allowed to have sufficient rest intervals between trials, if they needed. All participants provided written confirmed consent, complied with the Declaration of Helsinki. The local ethics committee approved both studies.

2.2. Data analysis

COP data of subjects in both studies were first used to identify the parameters of a subject-specific postural control model [21]. Next, the variables of Nyquist stability criterion, i.e. Gain Margin (*GM*) and Phase Margin (*PM*) for each subject in each task, and at each time point of assessment were calculated using the identified subject-specific model, as given below.

2.2.1. COP analysis and Model description

COP data was filtered (10 Hz, 3rd order Butterworth) and resampled to 100 Hz. From the COP data, 15 common sway measures in the anterior-posterior direction were calculated. The sway measures comprised of position- (e.g. root-mean-square of COP position – *RMS*), velocity- (e.g. mean velocity – *MV*), and frequency-related (e.g. *f*95 – the frequency up to which 95% of the total power lies) measures (for list of sway measures and calculation formula refer to [21]). Then, the parameters of a subject-specific postural control model (Fig. 1) – consisted of an inverted pendulum (with mass and length adjusted to the corresponding subject) as the body part, and a PID controller with time delay representing the central nervous system (CNS) – were identified using the 15 sway measures. The parameters, including PID controller gains (i.e. K_P, K_D, K_I), time delay (τ_d), and the disturbance torque gain (also called noise gain – K_n) were estimated through an optimization algorithm, minimizing the difference between the simulated and experimental sway measures [21].

2.2.2. Nyquist stability criterion measures (Gain Margin and Phase Margin)

Nyquist stability criterion can be applied to any linear system as long as it is presented by a frequency-response function (FRF), or transfer function. It reduces the stability analysis of system to some mathematical conditions in frequency-domain. For this purpose, Gain Margin (*GM*) and Phase Margin (*PM*) are calculated from the system FRF (see Appendix A). To meet the stability criteria, both *GM* and *PM* should be positive, unless the system is non-minimum phase (as the case of our non-minimum phase system, which has two *GM*s with a negative and a positive sign, yet stable) [37]. In this case, the alternative Nyquist stability criterion (Nyquist plot) examines the stability of a system, accepts or rejects the negative sign of *GM*/*PM* while remaining stable. Nyquist stability criterion indicates not only whether a system is stable, but also the degree of stability of a stable system in terms of parameters *GM* and *PM* [37]. *GM* indicates how much the controller gain of a system can be increased/decreased before the system becomes unstable. *PM* is the amount of additional phase lag (e.g. time delay) required to bring the system to the verge of instability [37]. In this sense, *GM* and *PM* imply the safety margin for controller adjustments (in gains and time delay) before making the system unstable; or simply, the margin of stability in human stance.

The subject-specific estimated model was rearranged into a transfer function (Appendix A – Eq. 3) (considering the linearized inverted-pendulum about the upright position – Appendix A – Eq. 1), from which the *GM* and *PM* were calculated (Appendix A – Eq. 4–7). For detailed calculation of *GM* and *PM*, refer to the Appendix A (Eq. 4–7). We used MATLAB v.8.1 (Mathworks Inc., MA, USA) function '*margin*' to calculate the *GM* and *PM* for each subject, in each task, and at each time point of assessment. Furthermore, the stability of each estimated subject-, task-, and time-point-specific system was examined by Nyquist criterion (plot). Typically, all estimated systems were stable, given that subjects performed all tasks stably. Besides stability check, we were interested in the quantification and degree of such stability; so, values of *GM* and *PM* were analyzed as well. Nyquist stability criterion showed that both negative and positive *GM* satisfies the stability of inverted pendulum system, providing *PM* is positive. Therefore, from two values of *GM*s for each subject in each task, we chose the minimum absolute value (denoted by |*GM*|), and the exact value of *PM*, respectively, as the measures of margin of stability (stability margin measures).

2.3. Statistical analysis

The normal distribution of clinical measures, as well as |*GM*| and *PM* were tested by the Shapiro-Wilk normality test. All stability margin measures (|*GM*| and *PM*) were normally distributed. Among clinical measures Tinetti scores and Tandem—EO were non-normal, which were log-transformed before being used in the statistical analysis.

Study 1

Differences between margin of stability (|*GM*| and *PM*) of PD patients at baseline before training (PD-Pre) and HCs were tested by a 2 × 2 × 2 mixed model analysis of variance (ANOVA). Mixed model ANOVA had two groups (PD and HC) as between-subject factor, two visual levels (eyes-open (EO), eyes-closed (EC)), and two surface conditions (rigid (R), foam (F)) as within-subject factor. The post-hoc multiple comparisons were carried out using Bonferroni correction. To evaluate the changes in clinical, and stability margin measures of patients before (PD-Pre) and after training (PD-Post), paired sample t-test was used.

Study 2

The temporal changes (the pattern of improvement) in clinical and stability margin measures of PD patients during the balance-training program were evaluated using repeated measure ANOVA with one factor (*Time*), in each individual task. Factor *Time* included three levels for clinical measures (Pre, Mid, Post); and four levels for the stability margin measures (Pre, week2, week4, Post). The Bonferroni-corrected post-hoc multiple comparisons evaluated differences between time points.

The significance level in both studies was set at 0.05.

3. Results

3.1. *Study*1; Margin of stability in PD patients vs. healthy control

Table.1 summarizes the values of |*GM*| and PM for twenty healthy control subjects (HCs) and forty PD patients before and after the 4-week balance-training program, in four tasks.

PD-Pre vs. HCs:

Figure 2 presents the ANOVA results; comparing forty PD patients before balance training (PD-Pre) with twenty HCs. Patients had smaller Gain Margin |*GM*| compared to HCs (Fig. 2A, group effect: $P = 0.0001$), particularly in tasks on foam (F-tasks) (FO: $P = 0.008$; FC: $P = 0.00005$). Furthermore, patients exhibited relatively smaller |*GM*| than HCs, while closing eyes (group × vision: $P = 0.039$). As for Phase Margin (*PM*), group × surface effect ($P = 0.008$) showed that standing on foam resulted in a drastic drop in the *PM* of PD patients, whereas HCs preserve that level of *PM* on foam as on the rigid surface (Fig. 2B).

Table 1

– (Study**1) Stability margin measures (absolute value of Gain Margin |**GM**|, and exact value of Phase Margin** PM**) for twenty healthy control subjects, as well as forty patients with PD before and after a 4-week balance-training program; in four tasks: stance on rigid surface with eyes open (RO), and closed (RC); stance on foam with eyes open (FO) and closed (FC). Values of** GM **are in decibel (dB), which is 20*Log$_{10}$(.) of the gain margin value.**

Measures of margin of stability	Task											
	Healthy Control subjects (n = 20)				PD – Pre Training (n = 40)				PD – Post Training (n = 40)			
	RO	RC	FO	FC	RO	RC	FO	FC	RO	RC	FO	FC
|*GM*| (*dB*)	3.74 ± 1.64	4.31 ± 1.97	3.49 ± 1.17	4.72 ± 1.37	2.99 ± 1.15*	3.15 ± 1.43*	2.60 ± 0.8**	3.05 ± 1.12**	3.42 ± 1.38	3.34 ± 1.54	3.24 ± 1.43‡	3.63 ± 1.2†
PM (*deg*)	15.47 ± 5.6	13.47 ± 5.3	15.21 ± 7.3	16.22 ± 6.8	15.84 ± 6.1	15.21 ± 5.59	13.85 ± 5.7	13.43 ± 6.14	16.67 ± 8.0	15.28 ± 5.95	18.92 ± 7.6‡	15.24 ± 6.7

Significant difference between Healthy control subjects and PD-Pre, independent *t*-test: * $p < 0.05$, ** $p < 0.013$

Significant difference between PD-Pre and PD-Post, paired sample *t*-test: † $p < 0.05$, ‡ $p < 0.013$

Effects of the 4-week balance training on 40 PD patients:

All clinical measures improved after the 4-week balance training [21] (BBS, FRT, and TUG: $P < 0.001$; detailed values were provided in [21]—Table.1). In addition, balance training increased (improved) $|GM|$ and PM of patients in F-tasks (Fig. 2; $|GM|$: FO: $P = 0.006$, FC: $P = 0.033$; PM: FO: $P = 0.00048$).

3.2. *Study2*; Patterns of improvement in margin of stability in PD during balance training

Functional balance and mobility, as measured by clinical tests, improved during and after balance training (FRT, TUG, 6MWT, Tandem—EO, Tandem—EC, Tinetti balance and gait: $P < 0.0001$; detailed values were provided in our earlier study [38]) [38].

Table 2 and Fig. 3 presents the values and statistical results of stability margin measures ($|GM|$ and PM) for the other twenty PD patients in *Study2*, during the 6-week balance-training program, at four time points: at Pre-, week2, week4, and Post-training. Margin of stability improved specifically in F-tasks.

$|GM|$ improved in F-tasks (FO: $P = 0.009$, FC: $P = 0.02$). Improvement in $|GM|$ was characterized by almost an early improvement at week 4, followed by plateau over the next two ending weeks of training (Fig. 3A). Unlike $|GM|$, PM improved late at week 6 ($P = 0.013$), in an approximately gradual and continuous-progression form (Fig. 3B).

Table 2

– (*Study2*) Stability margin measures (absolute value of Gain Margin $|GM|$, and exact value of Phase Margin PM) for twenty other PD patients in *Study2*, during 6-week balance-training program, at four time points (at Pre-, week2, week4, and Post-training), and in four tasks (stance on rigid surface with eyes open (RO), and closed (RC); stance on foam with eyes open (FO) and closed (FC)). Values of GM are in decibel (dB), which is $20*\mathrm{Log}_{10}(.)$ of the gain margin value.

Task	PD Patients (n = 20)				ANOVA	Effect size	Bonferroni *P*-value for post-hoc comparisons					
Measures of margin of stability	Pre (*T*1)	week 2 (*T*2)	week 4 (*T*3)	Post (*T*4)	*P*-value (*F*-value)		*T*1-*T*2	*T*1-*T*3	*T*1-*T*4	*T*2-*T*3	*T*2-*T*4	*T*3-*T*4
RO												
$\|GM\|$ (*dB*)	2.82 ± 1.27	2.94 ± 1.14	3.08 ± 1.16	3.19 ± 1.27	0.634 (0.574)	0.029	1.000	1.000	1.000	1.000	1.000	1.000
PM (*deg*)	20.85 ± 7.98	20.68 ± 8.38	21.04 ± 7.90	22.18 ± 8.44	0.914 (0.173)	0.009	1.000	1.000	1.000	1.000	1.000	1.000
RC												
$\|GM\|$ (*dB*)	3.69 ± 1.65	3.64 ± 1.43	3.41 ± 1.09	4.28 ± 1.47	0.064 (2.55)	0.118	1.000	1.000	0.735	1.000	0.253	0.081
PM (*deg*)	20.95 ± 6.45	19.75 ± 6.96	20.40 ± 7.57	23.24 ± 6.72	0.231 (1.474)	0.072	1.000	1.000	0.951	1.000	0.327	0.682
FO												
$\|GM\|$ (*dB*)	3.43 ± 1.41	3.45 ± 1.01	4.13 ± 1.57	4.03 ± 1.37	**0.009** (4.193)	0.181	1.000	0.149	0.173	0.278	0.292	1.000
PM (*deg*)	16.08 ± 5.92	16.65 ± 6.68	17.52 ± 6.17	20.39 ± 5.84†	**0.016** (3.736)	0.164	1.000	1.000	0.062	1.000	**0.013**	0.158
FC												
$\|GM\|$ (*dB*)	3.39 ± 1.25	3.42 ± 1.51	4.04 ± 1.34	4.01 ± 1.39	**0.020** (3.55)	0.157	1.000	0.092	0.164	0.279	0.289	1.000
PM (*deg*)	16.21 ± 8.15	16.72 ± 8.37	15.94 ± 6.55	19.45 ± 7.52	0.084 (2.325)	0.109	1.000	1.000	0.510	1.000	0.526	0.075

Values are reported as mean ± standard deviation. Significant *P*-values are in bold.

*T*1 to *T*4 refer to Pre-, week 2, week 4, and Post-training, respectively.

†significantly different from week 2 ($P < 0.05$).

4. Discussion

Novel stability measures (Gain Margin |*GM*|, and Phase Margin *PM*, from control theory) were used in this study to quantify the stability degree in patients with Parkinson's disease, as well as evaluating the effects of balance training in PD. The pattern of improvements during a 6-week balance-training program, in terms of Gain and Phase Margin, was investigated in PD patients. |*GM*| and *PM* were calculated using the low-cost posturographic data and a computational subject-specific postural control model. Findings showed that stability safety margin (i.e. |*GM*| and *PM*) were smaller in patients compared to healthy control subjects (HCs). Patients, unlike HCs, significantly reduced *PM* on foam due to considerable time delay. Stability margin, as well as all clinical outcomes, improved in patients after balance training. Improvement in |*GM*| was characterized by an early improvement at week 4, followed by plateau during the next two ending weeks of training. In contrast, *PM* improved relatively late at week 6 in a rather continuous-progression form.

Reduced Gain Margin (|*GM*|) in PD, as we observed in *Study*1, is in-line with previous studies which reported lower margin of stability for PD patients compared to HCs in different tasks (e.g. perturbed quiet stance [19, 30], or perturbed gait [7]). However, considering the different tasks and techniques of quantification in those studies, any inference should be drawn cautiously. Although most of these studies employed the spatial term of margin of stability (i.e. the difference between peak COM and Peak COP), Patton et al. [41] showed that torque safety margin is highly correlated with spatial safety margin calculated from COP response characteristics. |*GM*| is substantially influenced by the value of controller gain parameters in a system, which in turn, is mainly associated with the muscular strength (control effort) of human body system; suggesting that the reduced |*GM*| in PD may be due to the weakened muscle strength [42, 43]. Recently, we showed that most of control parameters (such as K_P, the pivotal ruling gain parameter) was lower in PD compared to HCs [21]. Nevertheless, excessive amplification of gain parameters results in resonant instability [44]. In other words, K_P should remain between a lower and an upper bound to guarantee stability of the inverted-pendulum system. This implies that, in fact, CNS tunes all control gain parameters in a way to adjust the margin of stability; that is, |*GM*| is truly expressing the margin of stability rather than muscular strength (K_P). That is, |*GM*| carried different implication of stability from K_P (the other measure for quantification of stability degree). Furthermore, results showed that HCs and patients increased |*GM*| when closing eyes; supporting the impression that CNS adopted higher level of safety margin in more threatening and challenging tasks. Extended safety margin in EC tasks was seen in young [45] and healthy elderly subjects [46, 47], as well as PD's [33] and multiple-sclerosis patients [48]. Group by vision interaction in our study, however, revealed that PD patients did not adjust (augment) |*GM*| as much as HCs did in EC tasks; reiterating the contribution of reduced strength factor in patients, as evidenced by low K_P in EC tasks in our recent study [21].

Unlike |*GM*|, *PM* was almost similar in PD patients and HCs, although with drastic drop for PD on foam. It seemed plausible that all subjects – patients or HCs – performed all tasks stably with moderately similar *PM*, nevertheless having different |*GM*|. Stability in a delayed-inverted-pendulum system relies largely on the adequacy of time-delay, which should not violate a critical value [49, 50]. Time delay, in part, has remarkable contribution to the amount of *PM*. Therefore, in stable performance, *PM* almost remains in a specific range, unless time delay varies significantly. Our findings showed that patients, contrary to HCs, exhibited drastic drop in *PM* while standing on foam (group × surface interaction), indicating patients' deficit in preserving the level of *PM* on foam to that on rigid surface. Decline in *PM* for patients on foam may be a consequence of significant delayed-response (longer time delay) that patients had on foam [21], which brought patients to the verge of instability (smaller *PM*). Wright et al. [51] observed reduced margin of stability on compliant surface for group of elderly healthy women; yet some studies reported increased margin of stability for stepping onto and walking on foam for young adults [52]. Different tasks, or definition for margin of stability may give rise to different possible results, which further highlights the importance of applying fundamental concepts for quantification of stability (or margin of stability) in future studies.

Tracking of stability margin measures (|*GM*|, *PM*) in multiple time points, during a course of balance-training program in *Study*2, disclosed their pattern of improvement; thereby enlightening how balance training can affect stability in PD. In addition, findings suggest that the improvement during training programs can be captured by |*GM*| and *PM*, as meaningful and sensitive measures for assessment of stability in PD. The pattern of improvement in |*GM*| was characterized by an early improvement at week 4, followed by a plateau during the next two closing weeks. In our recent study [38], we found similar early-improvement with plateaued behavior for stability-related measures such as K_P; which we concluded, based on evidences from other studies [34, 53, 54], as the limited capacity for the development of strength in PD. Although PD patients demonstrated ability to learn, limited learning capacity in PD was numerously noted in other studies [10, 55]. Corcos et al [53] noted that 2-year progressive resistance exercise (PRE) in PD, at best, can

lead to such plateaued behavior (stagnation at a specific level) for elbow flexion torque; in comparison to non-progressive exercise, which progressed during first months of training, and regressed back in the rest of training. Secondly, some studies showed early strength gain during first weeks of training in healthy elderlies [56] or PD patients [54, 57]. These findings indicate that the capability of patients for retaining or improving adequate margin of stability, besides issuing properly scaled motor commands, highly pertain to the capacity of regaining strength. Therefore, |*GM*|, which is per se, a reflection of properly tuned gain parameters, improved initially by training, but was later subject to plateau after week 4. Possibly, attaining greater values of |*GM*|, maybe as to the level of more skilled individuals, demands further focused training, particularly in PD. The other stability margin measure, *PM*, showed rather a continuous-progression form that improved late at the end of training at week 6. Our recent study [38] showed that time delay in PD improved with similar late and continuous-progression form, specifically in FO task (the very task in which *PM* was improved). Probably, improvement in *PM* highly demands correct timing of control commands in postural control. Findings of *Study2* emphasized that the problem of poor stability safety margin in PD is amendable via balance training, with specific attention to the needed dosage on each intervals of training program.

Few studies considered the changes in stability, in terms of margin of stability, during a training program [7, 34, 58]. These studies reported improvements in the margin of stability throughout repeating trials, for young [58], healthy elderly [7], and PD patients [7, 34], although with different test protocols, or definition for margin of stability; still with intriguing results. Given that the spatial gain margin had high correlation to torque safety margin [41]– which is relevant to gain parameters and therefore |*GM*| – facilitates reasoning from these studies. Peterson et al [34] realized that margin of stability (measured as the difference between X_{com} and first stepping footfall in response to perturbation) improved in HCs continuously throughout trails; whereas, PD patients improved margin of stability primarily in the first blocks of trials and then plateaued out. Patton et al. [58] studied the improvement in relative stability while learning a dynamic task (pulling a handle) in ten young subjects. They found that both spatial (the distance-to-boundary for COP to either heel or toe) and temporal (time-to-boundary for COP, using 1st order predictive extrapolation – based on COP velocity–) safety margin increased with practices; however, progress in spatial margin was more significant than temporal one. Interestingly, they observed that spatial margin (for trials with different pulling forces) finally converged into a roughly similar specific value by 5 days of practices; suggesting that, in normal performances or due to biomechanical constraints, only a specific level of spatial margin is achievable. Furthermore, this study revealed that improvement in temporal margin is hardly achieved by practices, which is in favor of our finding on late and continuous-progression of *PM*.

This study had limitations. First, because of the novelty in quantification method of stability in this study (first-ever usage of *GM* and *PM* for quantification of stability in PD), lack of similar studies and evidences limited more in-depth interpretation of findings, particularly results related to the learning dynamics during a course of training program. Previously, spatial (distance-to-boundary) and temporal (time-to-boundary) margin of stability were proposed [20] and employed [7, 29, 58, 59] in studies; mostly based on characteristics of COP signal in response to different tasks. The prevailing spatial and temporal definition of margin of stability is simply an external manifestation of the genuine underlying control safety margin that CNS adopts (e.g. *GM* and *PM*, which are the characteristics of supraspinal control commands). Future studies are needed to disclose the relationship between intrinsic features of safety margin (e.g. *GM*, *PM*) and existing stability measures. Furthermore, this study was limited to static posturography. Basically, applying such fundamental concepts of theoretical stability in dynamic tasks (e.g. in perturbed quiet stance, perturbed gait) provides more comprehensive explanation of patients' balance performance. Moreover, future studies can encompass complex models (e.g. double-inverted-pendulum), as well as applying more general stability theorems (e.g. Lyapunov stability criterion [60] for non-linear systems). Finally yet importantly, future studies carrying longer training programs with follow-up inspection, accompanied by more time points of assessment, or enjoying diversity in training regimen, are highly recommended.

5. Conclusions

This study proposed the application of the Nyquist criterion (the concepts of Gain Margin (|*GM*|) and Phase Margin (*PM*)) to quantify the stability in a group of people with PD. Results showed the discriminating power of |*GM*| and *PM* in studying postural instability in PD. Patients had smaller margin of stability (i.e. |*GM*| and *PM*) compared to HCs. Particularly, patients, contrary to HCs, showed drastic drop in *PM* on foam, due to abnormal delayed-response. Balance training, besides improving clinical outcomes on functional balance and mobility, improved stability margin in PD. |*GM*| improved early, mostly during the first weeks of training (at week 4), which plateaued out during the two ending weeks of training. In contrast, *PM* showed late improvement (at week 6) with a relatively continuous progression. |*GM*| and *PM* improved mainly on the account of developed strength and reduction in time delay, respectively. Taken together, this study showed that incorporating fundamental stability theorems/criteria such as Nyquist criterion – *GM*, *PM*–, which

inherently considers the dynamics of human system and CNS, in the analysis of balance performance in different tasks, is a promising technique, and paves the path for systematic and standardized quantification of stability on a unified and coherent ground. Such studies will link current clinical and experimental balance tests to their basic underlying governing rules.

Abbreviations

Parkinson's disease (PD), Healthy control subjects (HCs), Center-of-pressure (COP), Center-of-mass (COM), Base of support (BOS), Gain Margin (GM), Phase Margin (PM), Root mean square (RMS), Mean velocity (MV), Eyes open (EO), Eyes closed (EC), Rigid surface with eyes open task (RO), Rigid surface with eyes closed task (RC), Foam surface with eyes open task (FO), Foam surface with eyes closed task (FC), Foam-surface tasks (F-tasks), Timed Up and Go test (TUG), Functional reach test (FRT), Six-minute walk test (6MWT), Berg balance scale (BBS), Progressive resistance exercise (PRE), Limit of Stability (LOS), Frequency response function (FRF)

Declarations

Ethics approval and consent to participate:

The Ethics committee of Iran University of Medical Science approved all protocols. All participants provided written confirmed consent according to the Declaration of Helsinki.

Consent for publication:

Not applicable.

Availability of data and materials:

The data analyzed during the current study are available from the corresponding author on reasonable request.

Competing interests:

The authors declare no competing interests.

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Authors' contributions:

ZR performed mathematical modeling, analysis and interpretation of the data, drafted and revised the manuscript. SB made a substantial contribution to the methodology development and drafting and revising the manuscript. GT critically contributed to the design of the experiment, and statistical analysis. All authors read and approved the final manuscript.

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Figures

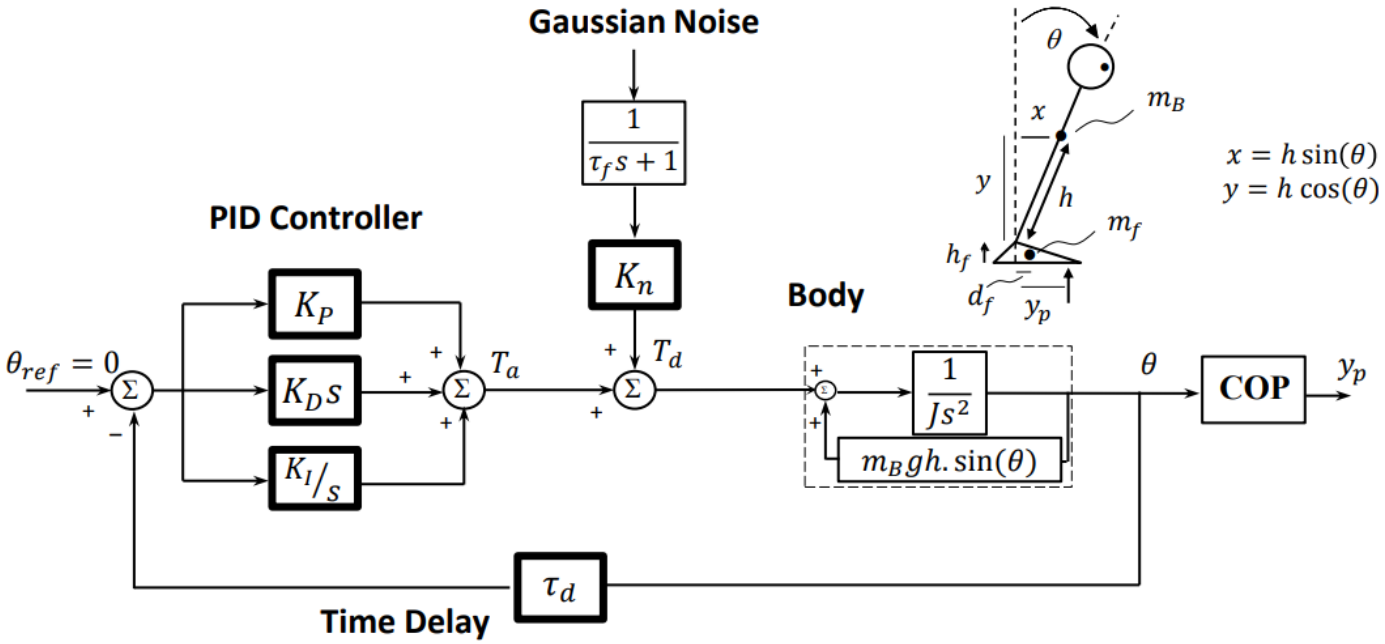

Figure 1

The subject-specific postural control model. The model consisted of human 'Body', CNS in the form of a PID controller, and time delay (τd). The 'Body' was modeled by an inverted-pendulum with all mass (mB) centered at the height of the COM (h) (which were adjusted subject-specifically). J, moment of inertia of the body around the ankle axis. The COP displacement (yp) was calculated from the body sway angle (θ) considering the feet mass (mf = 2.01 kg), which is fully described in [21]. The PID controller represents the CNS control performance: KP (proportional gain), KD (derivative gain), KI (integral gain); s, Laplace transform variable (frequency-domain). Ta,

corrective ankle torque; Td, disturbance torque; Kn, internal disturbance torque gain which quantifies the flexibility degree; τf = 100 s, time constant for low-pass filter.

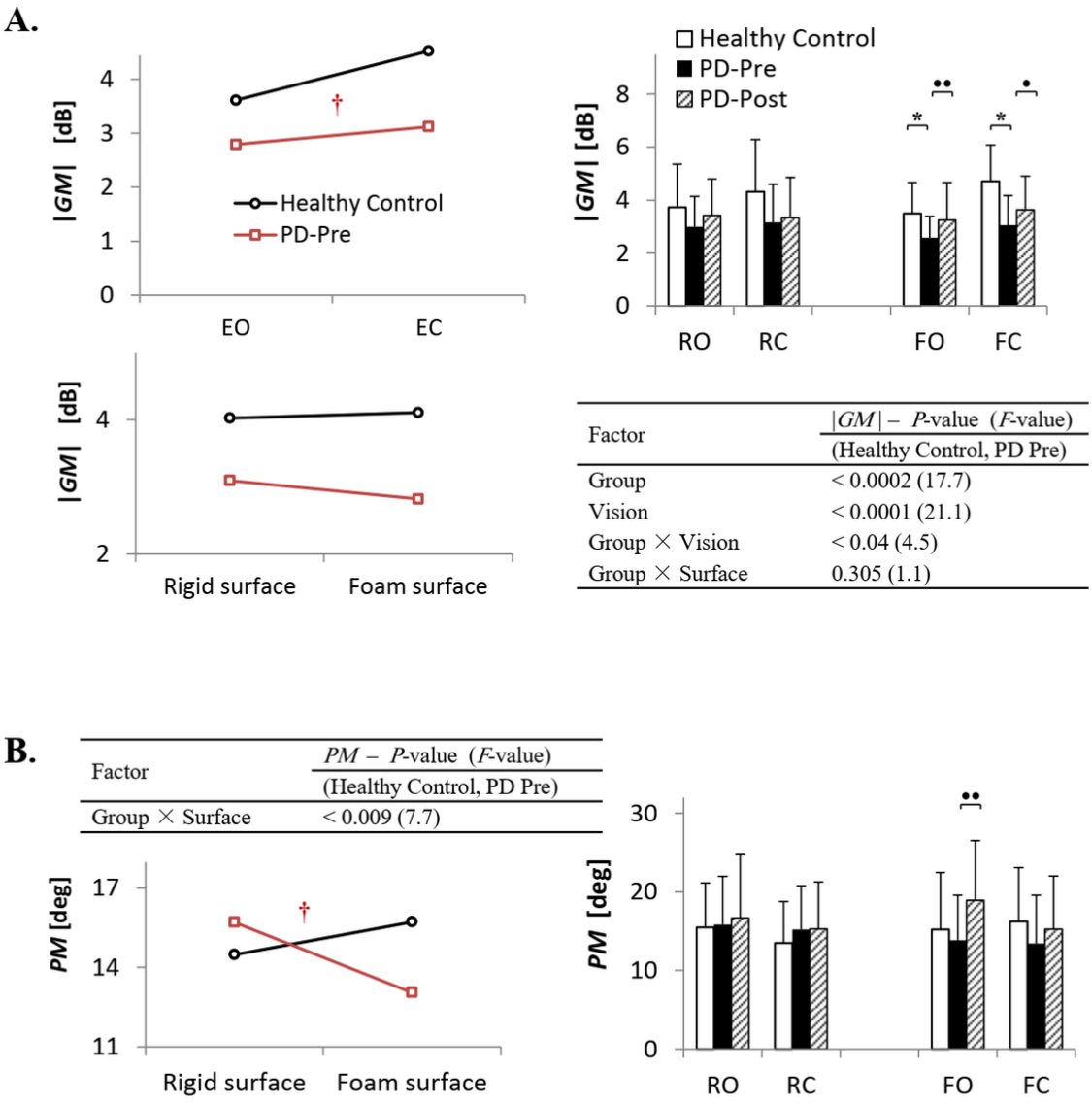

Figure 2

(Study1) Stability margin measures ((A) absolute value of Gain Margin |GM|, and (B) exact value of Phase Margin PM) for twenty healthy control subjects (HCs) and forty patients with PD before (PD-Pre) and after (PD-Post) a 4-week balance training program. Profile plots show the ANOVA results comparing HCs and PD-Pre, †: Significant interaction ($P < 0.05$). Bar charts presents the results of Bonferroni post-hoc comparisons between HCs and PD-Pre, * ($P < 0.05$); as well as paired sample t-test results between PD-Pre and PD-Post, • ($P < 0.05$), •• ($P < 0.013$). Values of GM are in decibel (dB), which is 20*Log10(.) of the gain margin value. RO, stance on rigid surface with eyes open; RC, stance on rigid surface with eyes closed; FO, stance on foam with eyes open; FC, stance on foam with eyes closed.

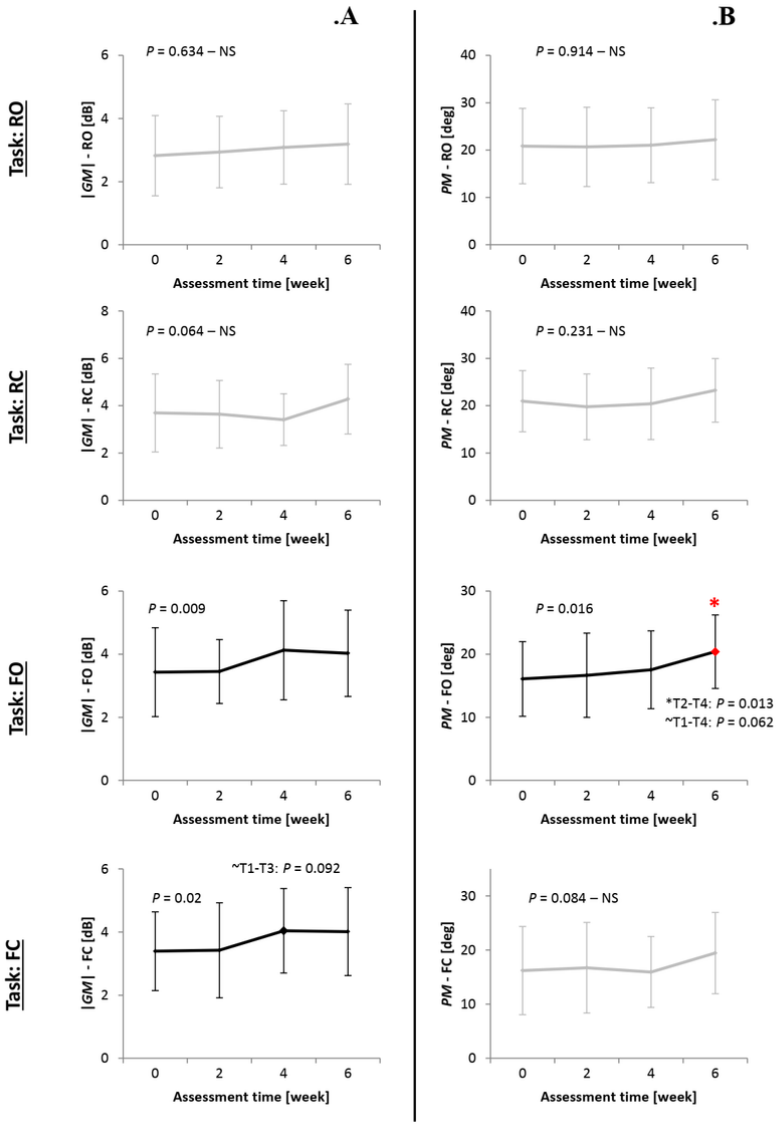

Figure 3

(Study2) The pattern of improvement for stability margin measures ((A) absolute value of Gain Margin |GM|, and (B) exact value of Phase Margin PM) for twenty other PD patients in Study2, at four time points (Pre-, week2, week4, and Post-training) during a 6-week balance-training program, in four tasks: stance on rigid surface with eyes open (RO) and closed (RC); stance on foam with eyes open (FO) and closed (FC). ANOVA results showing significant improvements are in bold black line. Bonferroni P-values are reposted for post-hoc pairwise comparisons between time points, significant time points are marked with asterisk. Values of GM are in decibel (dB), which is 20*Log10(.) of the gain margin value.

Supplementary Files

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- Appendix.docx