Vowel Articulation Distortion in Parkinson's Disease

P. Gómez-Vilda[1(✉)], J.M. Ferrández-Vicente[2], D. Palacios-Alonso[1], A. Gómez-Rodellar[1], V. Rodellar-Biarge[1], J. Mekyska[3], Z. Smekal[3], I. Rektorova[4,6], I. Eliasova[4,6], and M. Kostalova[5,6]

[1] Neuromorphic Speech Processing Lab, Center for Biomedical Technology, Universidad Politécnica de Madrid, Campus de Montegancedo, 28223 Pozuelo de Alarcón, Madrid, Spain
pedro@fi.upm.es, pedrogvilda@telefonica.net

[2] Universidad Politécnica de Cartagena, Campus Universitario Muralla del Mar Pza. Hospital 1, 30202 Cartagena, Spain

[3] Department of Telecommunications, Brno University of Technology, Technicka 10, 61600 Brno, Czech Republic

[4] First Department of Neurology, Faculty of Medicine, St. Anne's University Hospital, Masaryk University, Pekarska 53, 656 91 Brno, Czech Republic

[5] Department of Neurology, Faculty Hospital, Masaryk University, Jihlavska 20, 63900 Brno, Czech Republic

[6] Applied Neuroscience Research Group, Central European Institute of Technology, CEITEC, Masaryk University, Kamenice 753/5, 625 00 Brno, Czech Republic

Abstract. Neurodegenerative pathologies produce important distortions in speech. Parkinson's Disease (PD) leaves marks in fluency, prosody, articulation and phonation. Certain measurements based in configurations of the articulation organs inferred from formant positions, as the Vocal Space Area (VSA) or the Formant Centralization Ratio (FCR) have been classically used in this sense, but these markers represent mainly the static positions of sustained vowels on the vowel triangle. The present study proposes a measurement based on the mutual information contents of kinematic correlates derived from formant dynamics. An absolute kinematic velocity associated to the position of the articulation organs, involving the jaw and tongue is estimated and modelled statistically. The distribution of this feature is rather different in PD patients than in normative speakers when sustained vowels are considered. Therefore, articulation failures may be detected even in single sustained vowels. The study has processed a limited database of 40 female and 54 male PD patients, contrasted to a very selected and stable set of normative speakers. Distances based on Kullback-Leibler's Divergence have shown to be sensitive to PD articulation instability. Correlation measurements show that the distance proposed shows statistically relevant relationship with certain motor and non-motor behavioral observations, as freezing of gait, or sleep disorders. These results point out to the need of defining scoring scales specifically designed for speech-based diagnose and monitoring methodologies in degenerative diseases of neuromotor origin.

J.M. Ferrández Vicente et al. (Eds.): IWINAC 2017, Part II, LNCS 10338, pp. 21–31, 2017.
DOI: 10.1007/978-3-319-59773-7_3

Keywords: Neurologic disease · Parkinson's disease · Speech neuromotor activity · Aging voice · Hypokinetic dysarthria

1 Introduction

Parkinson's Disease (PD) is an illness produced by neurotransmitter decay in basal ganglia, which mainly produces motor symptoms in early stages, to derive in cognitive impairments at latter stages. Its effects in speech and phonation are well documented and have been described and treated in different publications. The interested reader can check [10] for a comprehensive review. These effects may be summarized as rough and asthenic phonation, monotonicity, monoloudness, phonation blocking, velo-pharyngeal hypernasality, low tone, and others similar collected under the general name of hypokinetic dysarthria. Traditionally, its effects in phonation have been studied using mainly distortion features as jitter, shimmer, noise-harmonic ratio, and tremor on emissions of sustained vowels. Articulation has been less studied, and in such case, static measurements as Vowel Space Area (VSA) or Formant Centralization Ratio (FCR) have been used mainly [13]. The deterioration of the patient as illness progresses is evaluated using general scales as Hoehn and Yahr [9] or UPDRS [5], which have not been specifically designed to take speech or phonation into account. On the one hand, to study the influence of disease progress, neurologists have resourced to other indices, as freezing of gait test (FOG), non-motor symptoms (NMSS), REM sleep behaviour disorder (RBDSQ), levodopa equivalent dose in mg. (LED), faciokinesis (FK), phonorespiratory competence (PRC), or phonetic competence (PC) to evaluate the state of the patient under different points of view [4,11,14,17]. On the other hand, having into account that PD is an illness characterized by the failure of the peripheral neuromotor activity, it could be possible that a description of the neuromotor activity, supported by features estimated from speech, could serve as a possible semantic descriptor of patient's conditions. A possible description of the neuromotor activity from speech can be given in terms of the dynamic changes experimented by the resonant frequencies of the vocal tract, which are known classically as formants. The aim of the present study is to evaluate if features derived from the dynamic behaviour of formants in sustained vowels are related with some of these indices, and to establish to which extent dynamic measures can be used in the multimodal study of PD speech production. Initially, dynamic measurements on formant activity, as the absolute kinematic velocity (AKV), which will be defined in the sequel, seeming to be highly correlated with the superficial myoelectric activity of certain facial muscles (see a related paper in this same issue [7], seem to be the adequate candidates for such study). The structure of the present paper is as follows: the biomechanical foundations explaining distortion of vowel articulation by means of formant dynamics is explained in Sect. 2. Section 3 is devoted to explain the Information Theory fundamentals behind the distance measurements used in distinguishing healthy and control utterances. Section 4 presents the data and experimental methods used in the study. The results derived from the present work are shown and discussed in Sect. 5. Conclusions are given in Sect. 6.

2 Biomechanical Model of Formant Dynamics

Speech production is planned and instantiated in the linguistic neuromotor cortex [2]. The activity of cortical neurons (primary) is encoded as neuromotor actions in the basal ganglia, where secondary neurons connected to the muscles of the pharynx, tongue, larynx, chest and diaphragm through sub-thalamic secondary pathways produce sequences of motor actions which activate the respiratory, phonatory and articulatory systems responsible of speech production. Regarding articulation, the principal structures to consider are the jaw, tongue and lip muscles. For the purposes of the present study, only the Jaw-Tongue Biomechanical System (JTBS), as depicted in Fig. 1 will be considered.

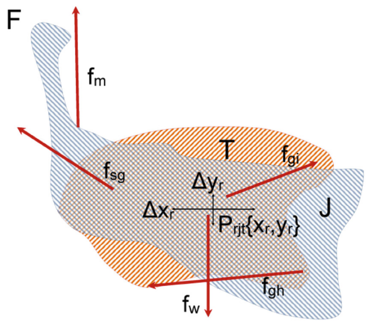

Fig. 1. Jaw-Tongue biomechanical system. The jaw (J: \-dash) is fixed against the skull bone at fulcrum (F) as in a third-class lever system. The tongue (T: /-dash) is supported by jaw and the hyoid bone. A reference point of the jaw-tongue system is defined at P_{rjt}, where forces acting on the system induce movements in the sagital plane (x: horizonal, y: vertical). See the text for a detailed explanation.

The dynamics of the JTBS [8,12] can be approximated by a third-order lever fixed at the skull in (F), allowing movements mainly in the sagital plane (x, y). For the purposes of articulation, it can be considered in a first approach as a joint lumped mass system subject to different forces actuating on the Jaw-Tongue Reference Point P_{rjt} (x_r, y_r). The main forces considered are the masseter uplift (f_m), the stylo-glossus pull-up-back (f_{sg}), the genio-hyoglossus pull-down-back (f_{gh}) and the gravity (f_w). Besides, due to the action of genio-glossus and glosso-intrinsic muscles (f_{gi}), the tongue blade and appex may be projected forwards. As a result, P_{rht} will experience changes in both directions ($\varDelta x_r$, $\varDelta y_r$). To associate these movements with formants (resonances of the oro-naso-pharyngeal tract) is not a simple task, as the system acoustic properties are rather complex. Nevetheless, a first-approach relationship could be expressed for the first two formants F_1 and F_2 as:

$$\begin{bmatrix} F_1(t) \\ F_2(t) \end{bmatrix} = \begin{bmatrix} a_{11} & a_{12} \\ a_{21} & a_{22} \end{bmatrix} \begin{bmatrix} x_r(t) \\ y_r(t) \end{bmatrix}; \ \mathbf{A} = \begin{bmatrix} a_{11} & a_{12} \\ a_{21} & a_{22} \end{bmatrix} \tag{1}$$

where a_{ij} are the transformation functions associating P_{rjt} to formants, and t is the time. The functional **A** expressing the relationship is known to be non-linear, time-variant and multi-valued, i.e.: the relation between P_{rjt} and formant values do not follow a linear rule (superposition could not be applied), the relationship would be time-dependent, $\mathbf{A} = \mathbf{A}(\mathrm{t})$, and different articulation positions may produce identical formant pairs. Therefore, to facilitate a first-order approach to study the system, the following assumptions had to be taken into account:

- A linear functional **A** could be considered provided that movement amplitude ranges are not large (small-signal approach).
- Time invariance could be granted if only low-frequency movements are considered (i.e.: if dynamic variables are low-pass filtered during measurement and estimation) with respect to estimation windows (quasi-stationary approach).
- The one-to-many association of formant positions could be handled provided that the joint probability between formant pairs and articulatory positions is carefully modelled for the utterances of interest [3].
- Assuming that functional **A** is invertible, i.e., that an inverse matrix exists: $\mathbf{W} = \mathbf{A}^T$.
- The first formant and second formant drifts could be associated with the vertical and horizontal kinematics of P_{rjt} one to one (no cross-talk between drifts and kinematic cross-varables, or in other words, the main diagonal of **W** will be null).

Once these premises have been granted, it will be possible to associate the drifts of the first formants with a hypothetical absolute kinematic velocity AKV of the reference point P_{rjt} as:

$$|v_r(t)| = \sqrt{\left(w_{21}\frac{dF_1(t)}{dt}^2 + w_{12}\frac{dF_2(t)}{dt}^2\right)} \tag{2}$$

where w_{12} and w_{21} are the corresponding weights of **W** associating the first and second formants with the vertical and horizontal drifts of P_{rjt}, respectively.

3 Distance Based on Mutual Information

The AKV of the reference point is a very semantic correlate, as it can be associated to streams of neuromotor actions in precedent studies using phonation [1]. Its histogram-derived probability density function is especially relevant, as it has been shown to contain information related to phonated intervals and pauses, syllable nuclei, vowel onsets and trails, and other dynamic features present in speech articulation [6]. Among other applications, it may be used in estimating mutual information contents in sustained vowel stability production by healthy controls and PD patients. In Fig. 3 an examples of $p(v_r)$ from a PD patient contrasted against the same distribution form a healthy controls is shown. The control file is the one with highest divergence (worst case). The PD file is the one with the lowest one (best case). Having into account what has been said in

Sect. 2 about formant dynamics in relation to neuromotor activity, it may be seen that the PD patient distribution is spread over the span of low and high speeds, up to 40 cm.s^{-1}, with little activity above this value, whereas the distribution of the healthy control is limited to 20 cm.s^{-1}, confirming the differential behaviour of both types of speakers. Measuring how different both dynamic behaviours could be is based on the Mutual Information contents of these two pdf's, which is provided by Kullback-Leibler's Divergence [15], defined as:

$$D_{KLij}\left\{p_{Ti}\left(v_r\right), p_{Mj}\left(v_r\right)\right\} = -\int_{\zeta=0}^{\infty} p_{Ti}(\zeta) log\left[\frac{p_{Ti}(\zeta)}{p_{Mj}(\zeta)}\right] d\zeta \qquad (3)$$

where $p_{Mj}(v_r)$ and $p_{Ti}(v_r)$ are the pdf's of the *j-th* model and *i-th* target subjects (control and patient) respectively, and $v_r \in \mathbf{R}_{\geq \mathbf{0}}$ as per (2). In what follows, a study on PD vowel formant stability will be conducted to compare the results from two population cohorts with their corresponding health controls by gender (Fig. 2).

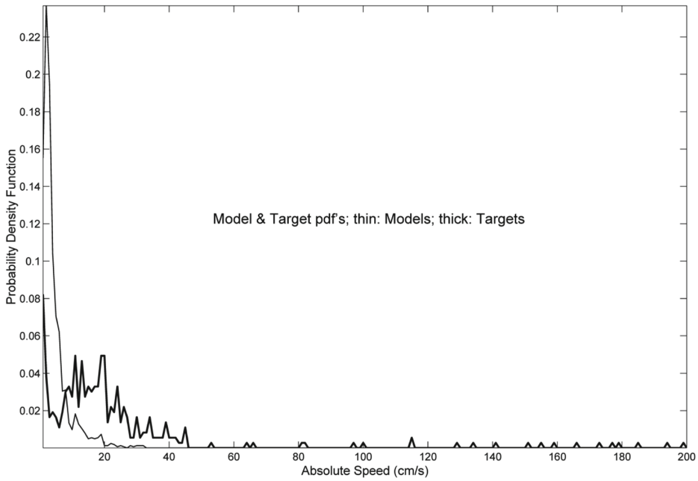

Fig. 2. Probability density functions of the absolute kinematic velocity v_J from a female healthy control (thin line) and a PD patient (thick lines). The AKV is given in $cm.s^{-1}$.

4 Materials and Methods

The present study has a marked exploratory nature, as to our knowledge, vowel formant kinematics has not been used before in PD detection, grading or monitoring. The intention of the study is to show the performance of this methodology in population grading studies of PD patients. A database of recordings from a set of 50 male and 50 female normative subjects free from organic or neurologic pathology selected by the ENT services of Hospital Gregorio Marañón of Madrid has been used to supply the normative models. Long sustained vowels (/a/) were recorded at a 44,000 Hz sampling frequency and 16 bits from each subject. Fragments of 500 ms long of /a/ recordings were analyzed the probability density of

AKV was obtained from each normative subject. The accumulated D_{KL} with respect to the whole set of fifty speakers per gender is defined as:

$$D_{KLj}\left(M_{f,m}\right) = \sum_{i \in M_{f,m}} D_{KLij};\ j \in M_{f,m} \tag{4}$$

where $M_{f,m}$ refers to the sets of normative male and female subjects mentioned before. A subset of eight subjects from each gender were selected on the condition of showing the lowest accumulated $D_{KLj}(M_{f,m})$ to become the normative model set. These model sets were used to estimate the accumulated D_{KL} of PD patients of both genders against their respective model set, as:

$$D_{KLj}\left(T_{f,m}, M_{f,m}\right) = \sum_{i \in T_{f,m}} D_{KLij};\ j \in M_{f,m} \tag{5}$$

The pathological database used is a part of the Parkinsonian Speech Database (PARCZ) recorded at St. Anne's University Hospital in the Czech Republic and consisted in four sets of 5 Czech vowels (/a, e, i, o, u/) pronounced in 4 different ways: short vowels uttered in a natural way; long vowels uttered in a natural way; long vowels uttered with maximum loudness, long vowels pronounced with minimum loudness, but not whispering. The subset selected corresponded to utterances by 54 male and 40 female PD patients, respectively. Recordings of long vowel /a/ at maximum loudness were selected and processed to obtain the first two formants during the utterance, and the respective pdf's of their AKV were estimated as referred before. The distributions for the female set of 40 PD patients plus 8 normative ones is depicted in Fig. 3 as an example.

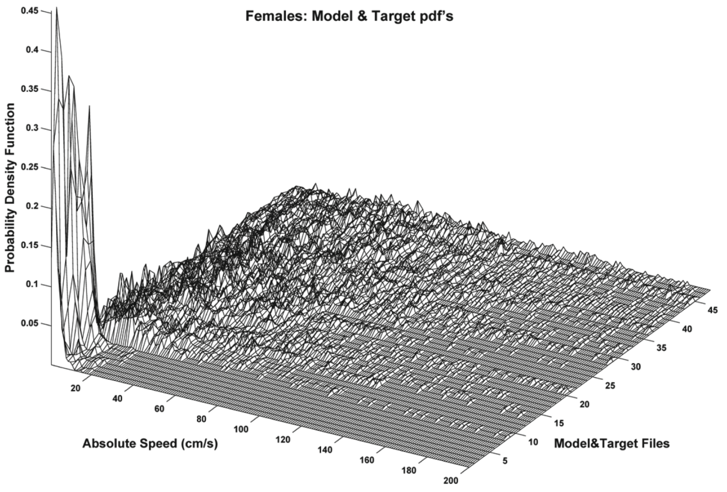

Fig. 3. Probability density functions of the AKV v_J from female healthy controls (files 1–8) and PD patients (files 9–48). The AKV is given in $cm.s^{-1}$.

It may be seen that healthy controls show activity mainly below 20 cm.s^{-1}, whereas PD patient distributions show activity spread over higher frequencies, ranging from 0–80 cm.s^{-1} for subjects 8–25, to 0–160 cm.s^{-1} and beyond for subjects 26–48.

5 Results and Discussion

An important issue in monitoring pathology is that of grading, as short-term timely monitoring of PD may be highly relevant for patient treatment and rehabilitation [16]. One of the intentions of the study was to relate D_{KL} (objective grading) with different clinic evaluation scales currently in use (subjective grading). When the D_{KL} as given in (3) for each patient in the female target set $\{T_f\}$ is estimated with respect to the corresponding model set $\{M_f\}$ a matrix of distances is produced, which is depicted in Fig. 4.

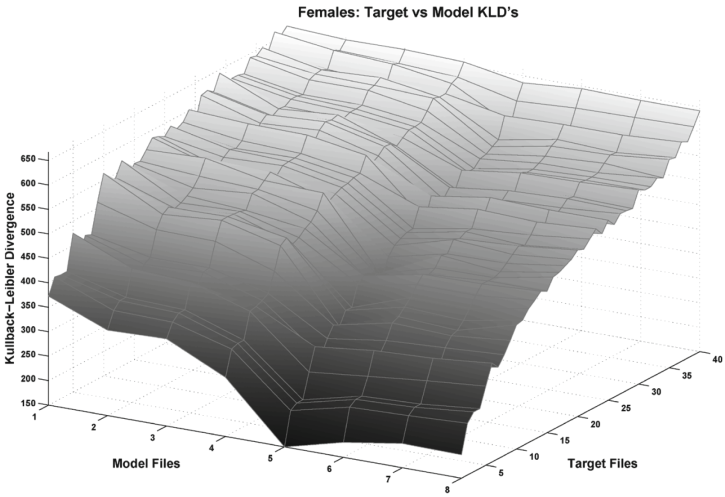

Fig. 4. KL Divergence between eight female healthy controls (models) and forty female PD patients (targets).

The model set has been ordered accordingly to its inner accumulated D_{KL} as given in (4), whereas the target set has been ordered accordingly to (5). Therefore, the first target file is supposed to be the less divergent with respect to the model set, whereas the 40^{th} target file should be the most divergent. It may be seen that the less divergent pair is the 1^{st} target file with respect to the 5^{th} model file. In this way, an ordered set of files by divergence to the model set is produced. The question now is to find out to which extent D_{KL} is related to subjective evaluation scales. For such, Pearson's correlation has been evaluated between D_{KL} and each of the available scores in the set S = {Age, UPDRSIII, UPDRSIV, FOG, NMSS, RBDSQ, LED, FK, PRC, PC, OC, PRN}, OC being the average of FK, PRC and PC, whereas PRN is the z-scored correlate of PRC. Besides, a global composite score (CS) has been produced to represent the set of objective scores in a single value as:

$$CS = \sum_{i \in \Omega} \omega_{ci} S_i \tag{6}$$

where $\mathbf{\Omega} = \{\omega_{ci}\}$ is the set of weights associated with the set of neurological evaluation scores in **S**. The results of the comparisons for the female set are given in Table 1.

Table 1. Pearson's correlation coefficient with KLD (females)

Age	UIII	UIV	FOG	NMSS	RBDSQ	LED	FK	PRC	PC	OC	PRN	CS	p-value
−0.03	−0.06	−0.12	−0.09	−0.26	−0.25	−0.37	−0.02	0.07	0.11	0.07	0.22	−0.45	0.0065

It may be seen that the most relevant clinical scores related to D_{KL} are the levodopa equivalent dose (LED), the non-motor symptom score (NMSS), the sleep behavior disorder screening (RBDSQ), and the z-scored phono-respiratory competence (PRN). General UPDRS (III) is almost no relevant, UPDRS (IV) is testimonial, as well as the phonetic competence (although it is unclear how this last score was estimated). The correlation with the composite score is moderate and negative (the lower the score, the higher the divergence), with a significant p-value to reject null correlation. The same comparison for the male set is given in Table 2.

Table 2. Pearson's correlation coefficient with KLD (males)

Age	UIII	UIV	FOG	NMSS	RBDSQ	LED	FK	PRC	PC	OC	PRN	CS	p-value
−0.04	0.13	−0.12	−0.25	−0.21	−0.34	0.15	−0.16	−0.09	−0.25	−0.22	−0.27	−0.57	0.0000

In this case, as similar situation may be observed with slight variations. The sleep behavior disorder is the most relevant clinical score, followed by the normalized phono-respiratory competence, the freezing of gait, the phonetic competence, the average facial-respiratory-phonetic competence, and the non-motor symptom score. Again, the correlation to both UPDRS scales is testimonial. The correlation to the composite score is a bit larger for the male subset than for the female one, and also negative, with a significant p-value to reject null correlation. The score plots of the D_{KL} and CS for each set are given in Fig. 5.

The first observation from the results presented is that the male set presents better correlation between D_{KL} and CS that the female one. This is not an uncommon situation in this kind of studies, as generally models and analysis

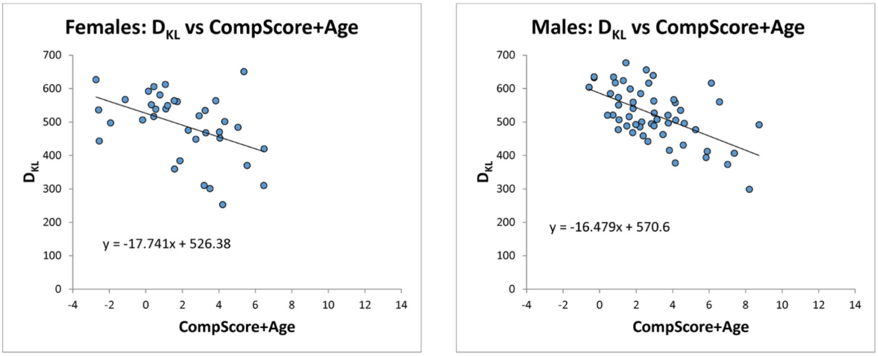

Fig. 5. Scatter plots of D_{KL} vs CS. Left: female subset. Right: male subset. Linear regression lines have been drawn and formulated for comparison purposes.

protocols were initially modelled on a male population, and only latter on, were they adapted to a female population, This fact may result in an underlying gender skew. Besides, the larger number of male cases available in the version of the PARZ database currently used could also have an influence in the results. Another factor to consider would be the wider spread of formant frequencies in female voice, which would introduce more dispersion in the results. Another factor of dispersion to be taken into account is the variability and low reliability of subjective scoring scales. No matter how well designed they may be or well-trained raters are involved, a human subjective factor is implicit and difficult to be removed. This fact stresses the need of developing objective scoring methods even more. But in general, it may be concluded that a certain degree of correlation between formant dynamics and a wide set of motor and non-motor scoring scales exist in PD, and could be conveniently exploited if fused with other articulation static features as VSA or FCR.

6 Conclusions

The main conclusion from the study is that formant kinematics may be a good candidate for PD stage detection, which has to be further exploited. Some other conclusions from the present study are the following:

- Formant dynamics can be transformed to speech kinematics in a robust way.
- Mutual-information-based distance measures may be defined on this basis.
- Patient sets may be graded and ordered using AKV probability densities, for easy database building. This is especially so in building normative sets.
- Structured and ordered data sets can be used in comparative studies.
- PD patients have to be graded accordingly to different motor and non-motor behavioural features.
- A specific speech-oriented scoring scale is a real need in PD studies.
- Composite scores should take these features into account.

– Databases oriented to the validation of speech-based methodologies should include a wide set of motor and non-motor evaluations for a richer comprehension of neuromotor pathologies under speech production bases.

As a final reflection, the accurate scoring of PD symptoms is a very urging need, both for diagnose as well as for monitoring PD patient stage and progression in a daily basis. Speech is a very convenient reference, as it is ubiquitous, easy to record, and feasible for feature estimation using not very sophisticated or expensive resources. The problem to validate this methodology is the lack of good rating scales adapted to speech. Definitively UPDRS, no matter how well has been fitted using brute force methods, is not a good candidate for these studies, as it lacks important speech-related motor and non-motor items, totally different from those involved in other motor tasks. In this sense, the biomechanics of limbs, in which many of the UPDRS items are based, is completely different from those of phonation and articulation systems, and this fact will induce false estimations and apparent correlates not funded on solid grounds. Therefore, new methods and correlates have to be sought based on phenomena which are truly related to speech and phonation. The current study is to be extended to larger databases with a stronger insight in speech technologies.

Acknowledgements. This work is being funded by grants TEC2012-38630-C04-01, TEC2012-38630-C04-04 and TEC2016-77791-C4-4-R from the Ministry of Economic Affairs and Competitiveness of Spain, and by grants 16-30805A, SIX (CZ.1.05/2.1.00/03.0072), and LOl401 from the Czech Republic Government.

References

1. Carmona-Duarte, C., Plamondon, R., Gómez-Vilda, P., Ferrer, M.A., Alonso, J.B., Londral, A.R.M.: Application of the lognormal model to the vocal tract movement to detect neurological diseases in voice. In: Chen, Y.-W., Tanaka, S., Howlett, R.J., Jain, L.C. (eds.) Innovation in Medicine and Healthcare 2016. SIST, vol. 60, pp. 25–35. Springer, Cham (2016). doi:10.1007/978-3-319-39687-3_3
2. Démonet, J.F., Thierry, G., Cardebat, D.: Renewal of the neurophysiology of language: functional neuroimaging. Physiol. Rev. **85**(1), 49–95 (2005)
3. Dromey, C., Jang, G.O., Hollis, K.: Assessing correlations between lingual movements and formants. Speech Commun. **55**(2), 315–328 (2013)
4. Fénelon, G., Mahieux, F., Huon, R., Ziégler, M.: Hallucinations in Parkinson's disease: prevalence, phenomenology and risk factors. Brain **123**, 733–745 (2000)
5. Goetz, C.G., Fahn, S., Martinez-Martin, P., Poewe, W., Sampaio, C., Stebbins, G.T., Stern, M.B., Tilley, B.C., Dodel, R., Dubois, B., et al.: Movement disorder society-sponsored revision of the unified Parkinson's disease rating scale (MDS-UPDRS): process, format, and clinimetric testing plan. Mov. Disord. **22**(1), 41–47 (2007)
6. Gómez-Vilda, P., López de Ipiña, M.K., Rodellar-Biarge, V., Palacios-Alonso, D., Ecay-Torres, M.: Articulation characterization in AD speech production. In: Ibáñez, J., González-Vargas, J., Azorín, J., Akay, M., Pons, J. (eds.) Converging Clinical and Engineering Research on Neurorehabilitation II. Biosystems & Biorobotics, vol. 15, pp. 861–866. Springer, Cham (2016). doi:10.1007/978-3-319-46669-9_140

7. Gómez-Vilda, P., Palacios-Alonso, D., Gómez-Rodellar, A., Ferrández-Vicente, J., Álvarez-Marquina, A., Martínez-Olalla, R., Nieto-Lluis, V.: Relating facial myoelectric activity to speech formants. In: Ferrández Vicente, J.M., et al. (eds.) IWINAC 2017, Part II. LNCS, vol. 10338, pp. 520–530. Springer, Cham (2017)
8. Hannam, A.G., Stavness, I., Lloyd, J.E., Fels, S.: A dynamic model of jaw and hyoid biomechanics during chewing. J. Biomech. **41**(5), 1069–1076 (2008)
9. Hoehn, M.M., Yahr, M.D., et al.: Parkinsonism: onset, progression, and mortality. Neurology **50**(2), 318–318 (1998)
10. Mekyska, J., Janousova, E., Gomez-Vilda, P., Smekal, Z., Rektorova, I., Eliasova, I., Kostalova, M., Mrackova, M., Alonso-Hernandez, J.B., Faundez-Zanuy, M., et al.: Robust and complex approach of pathological speech signal analysis. Neurocomputing **167**, 94–111 (2015)
11. Pérez-Lloret, S., Negre-Pages, L., Damier, P., Delval, A., Derkinderen, P., Destée, A., Meissner, W.G., Schelosky, L., Tison, F., Rascol, O.: Prevalence, determinants, and effect on quality of life of freezing of gait in Parkinson disease. JAMA Neurol. **71**(7), 884–890 (2014)
12. Sanguineti, V., Laboissiere, R., Payan, Y.: A control model of human tongue movements in speech. Biol. Cybern. **77**(1), 11–22 (1997)
13. Sapir, S., Ramig, L.O., Spielman, J.L., Fox, C.: Formant centralization ratio: a proposal for a new acoustic measure of dysarthric speech. J. Speech Lang. Hear. Res. **53**(1), 114–125 (2010)
14. Stiasny-Kolster, K., Sixel-Döring, F., Trenkwalder, C., Heinzel-Gutenbrunner, M., Seppi, K., Poewe, W., Högl, B., Frauscher, B.: Diagnostic value of the rem sleep behavior disorder screening questionnaire in Parkinson's disease. Sleep Med. **16**(1), 186–189 (2015)
15. Thomas, J.A., Cover, T.M.: Elements of Information Theory. Wiley, Hoboken (2006)
16. Tsanas, A., Little, M.A., McSharry, P.E., Spielman, J., Ramig, L.O.: Novel speech signal processing algorithms for high-accuracy classification of Parkinson's disease. IEEE Trans. Biomed. Eng. **59**(5), 1264–1271 (2012)
17. Ziemssen, T., Reichmann, H.: Non-motor dysfunction in Parkinson's disease. Parkinsonism Relat. Disord. **13**(6), 323–332 (2007)