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DOCTORAL THESIS STATEMENT

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ACOUSTIC ANALYSIS OF VOICE AND SPEECH DISORDERS IN PARKINSON'S DISEASE

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1. Introduction

This thesis represents a collection of several papers [A1-A7], in which the main research area is, in one way or another, linked to problems and questions originating from the development of voice and speech disorders in the course of Parkinson's disease (PD). Using innovative methods of acoustic analysis, speech signal processing techniques, and advanced statistics, the present thesis strives to contribute to the greater understanding of the role of speech impairment in PD.

Individual papers are focused on (a) development of acoustic measurement methods with respect to their automatic assessment and characterization of the specific signs of the PD-related vocal impairment from the early stages of disease [A1], (b) investigation of the feasibility of acoustic measures for the identification of voice and speech disorders in early PD, using a simple screening test [A2], (c) description of the vowel characteristic in two groups of untreated parkinsonian speakers across different types of speech tasks [A3], (d) design of a novel change-point detection algorithm for application in voice pathology [A4], and (e) the longitudinal effect of pharmacotherapy treatment on key dimensions of speech using quantitative acoustic analysis in a group of de novo PD patients and one to two years after introduction of therapy [A5]. Furthermore, papers [A2, A3, A5] investigate possible relationships between PD speech and motor symptoms to provide more insights into understanding the pathophysiological mechanisms responsible for the progression of parkinsonian speech impairment. In addition, papers [A6, A7] focus on the design of simulation models for educational purposes and general reflections on the physiological principles of various diseases.

2. State of the Art

Parkinson's disease (PD) is a chronic neurodegenerative disorder characterized by the progressive lost of dopaminergic neurons in the substantia nigra [1]. PD is associated with dopamine deficiency and other affections of the brain neuromediator systems, and is responsible for a variety of motor and non-motor deficits.

PD is the second most common neurodegenerative disorder after Alzheimer's disease, with prevalence exceeding 100/100,000 [2, 3]. Previous research suggests that PD usually affects people after the age of 50 years [4]. Only 10% of patients with PD report symptoms before the age of 40 years [5]. Moreover, PD is estimated to affect 1.6% of persons over the age of 65 years [2]. Given the fact that age is the most important factor for onset of PD [6], and that the population is growing older, the statistics for the number of affected persons are expected to increase in the near future [7]. Currently, there is no available causal cure, although medication, including neuro-pharmacological and neuro-surgical methods, offers alleviation of some symptoms, especially in the early stages of the disease. Thus, early diagnosis has a vital role in improving the patients' lives and will be crucial when treatment become feasible [8].

In addition to the main motor symptoms such as bradykinesia, rigidity, resting tremor, and postural instability, it is estimated that up to 90% of patients with PD develop hypokinetic dysarthria in the course of their illness. [9-12]. This alteration of speech may also be one of the earliest indicators of the disease [13, 14]. Acoustical analysis of speech might therefore provide useful biomarkers for the early diagnosis of PD [15], for possible remote monitoring of patients [16], but above all, for providing important feedback in voice treatment for clinicians or patients themselves. For adult subjects, methods allowing the assessment of the speech performance and acoustic feedback tests can be essential for stimulating motivation and willingness for speech therapy. In other words, acoustic measurements can improve the individual treatment [17], and therefore partially alleviate the inconvenience and cost of physical visits [18]. Moreover, voice measurement is non-invasive, cheap and simple to administer.

The most prominent signs of parkinsonian speech relate to phonatory, articulatory, and prosodic deviations, and are characterized by abnormal voice quality, articulatory imprecision, reduced variability of pitch and loudness, variable rate, and disfluent speech behaviour [10, 13]. Many voice and speech tasks have been devised to assess the extent of these symptoms, including vocal recordings of sustained phonations, rapid syllable repetitions, and variable reading of sentences or freely spoken monologues. The speech signals are then commonly analyzed using several traditional measurement methods, which include sound pressure level, fundamental frequency, formant frequencies, speech rate, rhythm, and others [19]. A number of previous studies have used these methods to separate PD sufferers from healthy participants, indicating that these standards could be useful measures in assessing the extent of vocal impairment, note for example [20-22]. Recently, several studies have appeared making use of innovative methods for voice and speech disorders detection [23-27]. However, there are practical limitations of effort and cost-outcome associated with obtaining and verifying each of the methods, which are dependent on a specific and often unavailable speech sample. Therefore, what is most needed is the finding of reliable methods for characterization of complex aspects of speech production in PD.

In reality, however, the reliability and robustness of acoustic measurement methods is impeded by several confounding effects associated with characteristics of the subjects and technology. First, issues related to personal characteristics include inter-speaker variability (gender, age), intra-speaker variability (repetition of speech task), variability in evolution of speech disorders across individual speakers, and variability in the quality of healthy speech (breathy voice, speech rate, hesitations, mumbling, and others). Second, issues related to technology include environmental noise, choice of microphone (type, distance), robustness of the algorithms, and the choice of speech material that best depicts the abnormalities. Thus the measurement methods performed on various vocal recordings should be chosen, as much as possible, with an eye to these confusing and in many cases even counteractive effects.

Another relevant and often overlooked factor in determining the extent of PD speech impairment is the dependence on the stage of disease. The progressive decline of several speech characteristics in the course of PD has already been reported [28-31]. Although there are many previous studies using several measures and vocal tasks for assessment of PD-related voice and speech disorders in various stages of the disease, little effort was given to investigation of the extent of vocal impairment and the suitability of acoustic measures in early stages of PD, before and after starting dopaminergic pharmacotherapy.

While the beneficial effect of dopaminergic therapy on principal motor symptoms in PD has been well documented, its effect on speech remains unclear. Generally, severity of hypokinetic dysarthria is believed to increase with longer duration of disease and increased severity of limb impairment [32]. In other words, the speech dysfunction in the course of PD is hypothesized to be the result of rigor and hypokinesia of the vocal tract. Therefore, one could expect improvement in speech performances owing to the positive response to dopaminergic therapy. However, with respect to previous literature, the effect of dopaminergic stimulation on overall speech parameters remains inconclusive with mixed and contradictory findings. Whereas several researchers have reported certain beneficial effects of dopaminergic therapy on various aspects of speech production [19, 33-36], others have not found changes in speech parameters and/or overall intelligibility under pharmacotherapy [37-41]. In overall, little correspondence has been found between the severity of limb and the speech symptoms [32].

3. Aims of the Doctoral Thesis

The doctoral thesis has the following interrelated goals:

(1) To *identify PD-related acoustic signatures for the major part of traditional clinically used measurement methods* with respect to their automatic assessment.
(2) To *design new automatic measurement methods of articulation*.
(3) To *design a novel robust detector of abrupt spectral changes.*
(4) On the basis of methods from points 1 through 3, using the designed evaluation criteria, to *determine whether the voice and speech disorder are present from early stages of PD* before starting dopaminergic pharmacotherapy.
(5) On the basis of methods from points 1 through 4, to *ascertain the specific characteristics of PD-related vocal impairment*.
(6) On the basis of previous findings from points 1 through 5, to *design a quick vocal test* in order to be gender independent, represent all aspects of speech, reduce time required for investigation, and provide reliable assessment in practice.
(7) On the basis of methods from point 6, to *test and find the optimal combination of acoustic measurements for separating untreated PD from healthy participants*.
(8) To *describe vowel articulation using formant characteristics in parkinsonian speakers* when compared to normal healthy speakers.
(9) To *investigate the feasibility of formant measures in vowel articulation across different speaking tasks* and to *point out which tasks are most sensitive to PD*.
(10) On the basis of previous findings from points 1 through 9, using the designed evaluation criteria, to *investigate the longitudinal effect of treatment on key dimensions of speech in a group of de novo PD patients and after introduction of therapy*.
(11) In general, to *find possible relationships between PD speech and motor symptoms to provide more insights into understanding of pathophysiological mechanisms responsible for the progression of parkinsonian speech impairment*.

4. Working Methods

4.1. Subjects

From 2007 to 2010, 24 Czech native-speaking participants (20 men and 4 women) fulfilling the diagnostic criteria for PD were recruited for this study. All PD patients were first examined shortly after the diagnosis was made, before symptomatic treatment was started. After optimization of the treatment consisting mostly of levodopa and/or a dopamine agonist, 19 patients (16 men and 3 women) were also re-tested after one to two years in their best on-state according to the same protocol. In addition, 23 volunteers (16 men and 7 women) with no history of neurological or communication disorders were included as healthy controls (HC). The study was approved by the local ethics committee. All participants provided written informed consent.

4.2. Data and Recording

The speech data was recorded in a quiet room with a low ambient noise level using an external condenser microphone placed at approximately 15 cm from the mouth and coupled to a Panasonic NV-GS 180 video camera. The voice signals were recorded directly to the computer, sampled at 48 kHz with 16-bit resolution. The vocal tasks used in this study ranged from producing isolated vowels to reading short sentences and producing a short, spontaneous monologue about a given subject (see Table 1).

Task code	Speech data
[VT1]	Sustained phonation of /i/ at a comfortable pitch and loudness as constant and long as possible, at least 5-sec. This task was performed on one breath.
[VT2]	Rapid steady /pa/-/ta/-/ka/ syllables repetition as constant and long as possible, repeated at least 5-times. This task was performed on one breath.
[VT3]	Monologue, at least approx. 90-sec. The participants were generally instructed to speak about: what they did current day or last week, their interests, their job, or their family.
[VT4]	Reading the same standard phonetically non-balanced text of 136 words.
[VT5]	Approximately 5-sec sustained vowels of /a/, /i/, /u/ at a comfortable pitch and loudness. The vowels were performed on one breath.
[VT6]	Reading the same text containing 8 variable sentences of 71 words with varied stress patterns on 10 indicated words.
[VT7]	Reading 10 sentences according specific emotions in a comfortable voice in response to an emotionally neutral sentence including excitement, sadness, confusion, fear, boredom, anger, bitterness, disappointment, wonder, and enjoyment.
[VT8]	Rhythmically read text containing 8 rhymes of 34 words following the example set by the examinator.
[VT9]	Five-time repetition of the 8 words phrase.

Table 1: List of the vocal tasks.

4.3. Acoustic Measurements

In the course of the thesis, we have designed a number of traditional and novel metrics used for speech analyses (see Table 2). These measurements of the PD speech can be associated with several dimensions, where: *phonation* represents the vibration of the vocal folds to create sound, *articulation* is the modification of the position and shape of speech organs (tongue, lips, jaw) in the creation of sound, *prosody* represents the variation in loudness, pitch, and timing accompanying natural speech, and *respiration* refers to the action of the respiratory apparatus during exhalation, providing a continuous stream of air with sufficient volume and pressure to initiate phonation.

Feature	Vocal task	Speech subsystem	Description
F0 SD	[VT1] [VT3,4,6,7]	Phonation Prosody	Standard deviation of fundamental frequency (F0) converted to semitone scale, representing the variations of vibration rate of vocal folds.
Jitter (%)	[VT1]	Phonation	Frequency perturbation, representing the extent of variation of the voice range. Jitter is defined as the variability of the fundamental frequency of speech from one cycle to the next.
Shimmer (%)	[VT1]	Phonation	Amplitude perturbation, representing rough speech. Shimmer is defined as the sequence of maximum extent of the signal amplitude within each vocal cycle.
NHR (%)	[VT1]	Phonation	Noise-to-Harmonics-Ratio, the amplitude of noise relative to tonal components.
HNR (dB)	[VT1]	Phonation	Harmonics-to-Noise-Ratio, the amplitude of tonal relative to noise components.
Percent pause time (%)	[VT3,4]	Prosody	The percent change from the unedited sample length to the edited sample length.
Articulation rate (syll/s)	[VT4]	Prosody	The number of syllables produced per second, after removing silence period exceeding 60 ms.
Number of pauses (pauses/s)	[VT3,4]	Prosody	The number of all pauses compared to total time duration, after removing silence period not lasting more than 60 ms.
DDK rate (syll/s)	[VT2]	Articulation	The number of /pa/-/ta/-/ka/ syllable vocalizations per second.
DDK regularity (-)	[VT2]	Articulation	The degree of /pa/-/ta/-/ka/ syllable vocalizations rate variations in the period.
Intensity SD (dB)	[VT3,4,6]	Prosody	Variations of average squared amplitude within a predefined time segment ("energy") after removing silence period exceeding 60 ms.
Rhythm (-)	[VT8]	Prosody	Measurement of ability to reproduce perceived rhythm through dynamic time warping.
SPLD (dB/s)	[VT2]	Respiration	Robust Relative Intensity Slope, the robust linear regression of energy.
SDCV (-)	[VT2]	Articulation	Spectral Distance Change Variations, the variations of spectral distance changes in signal spectrum.
RFPC (-)	[VT2]	Articulation	Robust Formant Periodicity Correlations, the first autocorrelation coefficient of F2 contour.
VSA (Hz^2)	[VT3-5,9]	Articulation	Quantitative measure which involves plotting the three corner vowels in F1/F2 plane.
FCR (-)	[VT3-5,9]	Articulation	Formant Centralization Ratio, measurement of vowel articulation based on F1 and F2 formant frequencies of corner vowels (/a/, /i/, and /u/).
F2i/F2u (-)	[VT3-5,9]	Articulation	Measurement of vowel articulation based on ratio of F2 frequencies of corner vowels /i/ and /u/.
RPDE (-)	[VT1]	Phonation	Recurrence Period Density Entropy, representing an extension of the concept of periodicity.
PPE (-)	[VT1]	Phonation	Pitch Period Entropy, representing the inefficiency of voice frequency control.
MPT (s)	[VT1]	Phonation	Maximum Phonation Time, respiratory parameter, representing aerodynamic efficiency.
PDW (%)	[VT3,4]	Prosody	Percent Disfluent Words, representing speech fluency.

Table 2: Overview of measurement methods used as a features applied to acoustic signals.

4.4. Statistics

To assess the extent of vocal impairment in PD patients, we have designed the classification based on the both traditional and novel statistics. The Kolmogorov-Smirnov test for independent samples was used to test for normality of the distribution of the data. Analysis of variance with post hoc Bonferroni adjustment was used to assess differences between the groups. The Pearson and Spearman correlation analysis was used to assess the strength of the relationships between individual measures. For characterization of speech disorders in PD [A1], differentiation of parkinsonian from healthy speakers [A2], and evaluation of treatment effect [A5], we have used advanced classification methods based upon Gaussian kernel density, Wald task, support vector machine, and minimal detectable change.

5. Results

5.1. Voice and Speech Characteristics in PD

Table 3 lists the general results of acoustic analysis with statistical significances across all the studies [A1-A5]. The results are presented according to the main speech characteristics, including phonation, articulation, and prosody.

Statistical significances were found in most measures of phonation. Additional noise captured by ratios of noise-to-harmonics can indicate incomplete vocal fold closure and incorrect vocal fold oscillation. The noise in speech can be also generated by turbulent airflow through the vocal fold. Significant deficits in phonation due to PD may be perceptually interpreted as poor voice quality and described in terms like hoarse, harsh, breathy and rough voice, or even voice tremor.

From traditional articulation measures based upon the DDK task, only the DDK rate contains significant differences between both groups. On the other hand, all novel measures performed on the DDK task shown statistically significant differences between groups, which can indicate reduced movement of orofacial muscles. In many patients with PD, intensity defects develop in instances of rapid articulation. The reduced intensity variations can be caused by occlusive weakening. As an example, voiceless occlusives, which are normally associated with a silent gap, tend to exhibit energy during the silent gap. This energy can be caused by turbulent noise generated at the site of oral constriction because of an incomplete occlusion, or voicing energy which occurs as a result of poor coordination between laryngeal and supralaryngeal gestures. The results of sound pressure level decline show that PD patients have a lower ability to maintain the intensity level, which can be caused by weakness in the production of stable airflow from the lungs. The higher number peaks captured by spectral distance change variation can be associated with greater spectral changes which represent a greater clarity of articulation. The rate and similarity of tongue movement are well represented by the measure of formant periodicity correlation where the higher periodicity in the obtained F2 sequence represents better articulation accuracy of tongue.

In the speech subsystem of prosody, reduced variation of melody and decreased intensity variation has been found to be the most prominent sign of parkinsonian speech. This situation can be caused by changed laryngeal tension, decreased breath support, and decreased range of motions. The patients with PD show a lower ability to reproduce perceived rhythm. From pause characteristics, only the measurements of number of pauses show significant differences between groups. This can be indicated by breathiness and starting time of the tongue movement. The persons with PD have not shown significant differences in the articulation rate and speech disfluency compared to HC, which can be caused due to higher inter-individual variability.

Measurement	Subjects				Difference between groups
	PD		HC		
	Mean	(SD)	Mean	(SD)	
Phonation					
[VT1] *Sustained phonation*					
F0 SD (semitones)	0.46	0.49	0.35	0.23	Not significant
Jitter (%)	1.53	1.37	0.65	0.78	***p* < 0.01**
Shimmer (%)	7.51	4.97	2.72	2.27	***p* < 0.001**
NHR (-)	0.16	0.27	0.02	0.04	***p* < 0.01**
HNR (dB)	16.01	7.36	24.02	5.61	***p* < 0.001**
RPDE (-)	0.32	0.08	0.27	0.06	Not significant
PPE (-)	0.48	0.28	0.26	0.12	***p* < 0.01**
MPT (s)	20.84	8.81	22.00	6.88	Not significant
Articulation					
[VT2] *DDK task*					
DDK rate (syll/s)	6.22	0.63	7.16	0.73	***p* < 0.001**
DDK regularity (-)	0.54	0.58	0.67	0.36	Not significant
Intensity SD (dB)	7.54	1.52	10.99	1.96	***p* < 0.001**
SPLD (dB/s)	2.75	1.51	1.16	1.12	***p* < 0.001**
RFPC (-)	0.46	0.17	0.60	0.09	***p* < 0.01**
SDCV (-)	0.14	0.03	0.18	0.03	***p* < 0.001**
[VT3] *Monologue*					
VSA (Hz^2)	121881	31508	154205	41470	***p* < 0.05**
F2i/F2u (-)	2.10	0.20	2.38	0.25	***p* < 0.05**
FCR (-)	0.86	0.05	0.92	0.06	***p* < 0.05**
[VT4] Reading text					
VSA (Hz^2)	118689	43093	142690	40859	Not significant
F2i/F2u (-)	2.28	0.31	2.52	0.28	***p* < 0.05**
FCR (-)	0.87	0.07	0.91	0.06	Not significant
[VT5] *Sustained vowels*					
VSA (Hz^2)	225643	73531	268276	75894	Not significant
F2i/F2u (-)	2.88	0.32	3.05	0.40	Not significant
FCR (-)	1.10	0.07	1.15	0.10	Not significant
[VT9] Sentence repetition					
VSA (Hz^2)	116954	54533	173175	60062	***p* < 0.05**
F2i/F2u (-)	1.96	0.29	2.31	0.37	***p* < 0.05**
FCR (-)	0.84	0.07	0.91	0.08	***p* < 0.05**
Prosody					
[VT3] *Monologue*					
F0 SD (semitones)	1.53	0.32	2.44	0.65	***p* < 0.001**
Intensity SD (dB)	7.05	1.41	8.75	1.51	***p* < 0.001**
Percent pause time (%)	0.32	0.03	0.31	0.03	Not significant
Number of pauses (pauses/s)	3.04	0.83	3.86	0.69	***p* < 0.01**
PDW (%)	3.89	2.44	1.62	0.37	Not significant
[VT4] *Reading text*					
F0 SD (semitones)	1.71	0.66	2.48	0.56	***p* < 0.001**
Intensity SD (dB)	5.93	1.05	7.55	1.62	***p* < 0.001**
Percent pause time (%)	0.30	0.02	0.29	0.02	Not significant
Articulation rate (syll/s)	6.09	0.78	6.09	0.84	Not significant
Number of pauses (pauses/s)	3.29	0.67	3.98	0.51	***p* < 0.01**
PDW (%)	2.34	1.61	1.50	1.07	Not significant
[VT6] *Stress patterns*					
F0 SD (semitones)	2.06	0.81	2.78	0.62	***p* < 0.01**
Intensity SD (dB)	6.40	1.07	7.84	1.97	***p* < 0.01**
[VT7] *Emotional sentences*					
F0 SD (semitones)	2.59	0.74	3.82	0.56	***p* < 0.001**
[VT8] *Rhythmic text*					
Rhythm (-)	2.65	0.55	2.27	0.28	***p* < 0.01**

Table 3: List of all measures with mean values, SD values, and statistical significances.

5.2. Objectification of Hypokinetic Dysarthria

On the basis of statistics presented in [A1], we were able to show that the patterns of speech performance are spread through all speech dimensions only in the HC group, while the parkinsonian speech defects differ individually in various characteristics including phonation, articulation, and prosody. As can be seen in Figure 1, the vocal impairment in early stage of the PD in the view of all speech dimensions is rather individual. From all PD patients, 78% are affected. We have found phonatory deficits in 26% cases, lower ability of articulation in 39% cases, and certain problems with prosody in 60% cases of PD patients. Deficits in all speech characteristics were found only in 13% of people with PD. Approximately 26% of PD subjects show single deficits only in prosody, 17% PD patients only in articulation, none in phonation, and 21% in some combination of two speech characteristics. It is important to keep in mind that the speech measurements can be partially interconnected in all speech dimensions. Hence the speech impairment in early stages of PD might be considered as the total of speech defects in various speech characteristics.

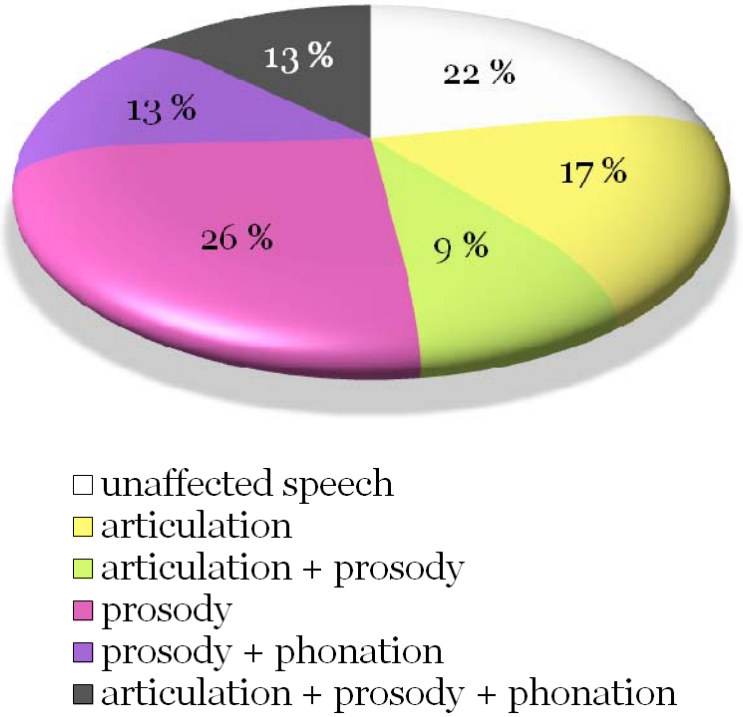

Figure 1: Details of affected speech dimensions in PD.

5.3. Differentiation of Parkinsonian from Healthy Speakers

On the basis of the quick vocal test and the prediction model presented in [A2], we have obtained the best classification performance of approximately 85% in the combination of 4 measures including NHR, SPLD, RFPC, and F0 SD. Each of these measures represents one important speech subsystem related to PD: NHR shows abnormalities in phonation, SPLD represents an impaired ability to maintain appropriate intensity level in respiration, RFPC measures deficits of speech organ movement during articulation, and finally, the measure of F0 SD can elicit deficits in prosody. The classification performance using the subset of all measurements was 82%. From individual measures, F0 SD obtained the best classification accuracy of 81%. The maximal correct overall classification accuracy was 76% using only sustained phonation, and 71% using only the DDK task. Figure 2 summarizes the procedure and results of the quick vocal test that was employed to evaluate voice and speech disorders in a group of patients with unmedicated PD in comparison to healthy people. According to these results, the deficits in speech prosody appear to contain the greatest amount of information in assessment of PD-related vocal impairment before starting dopaminergic pharmacotherapy.

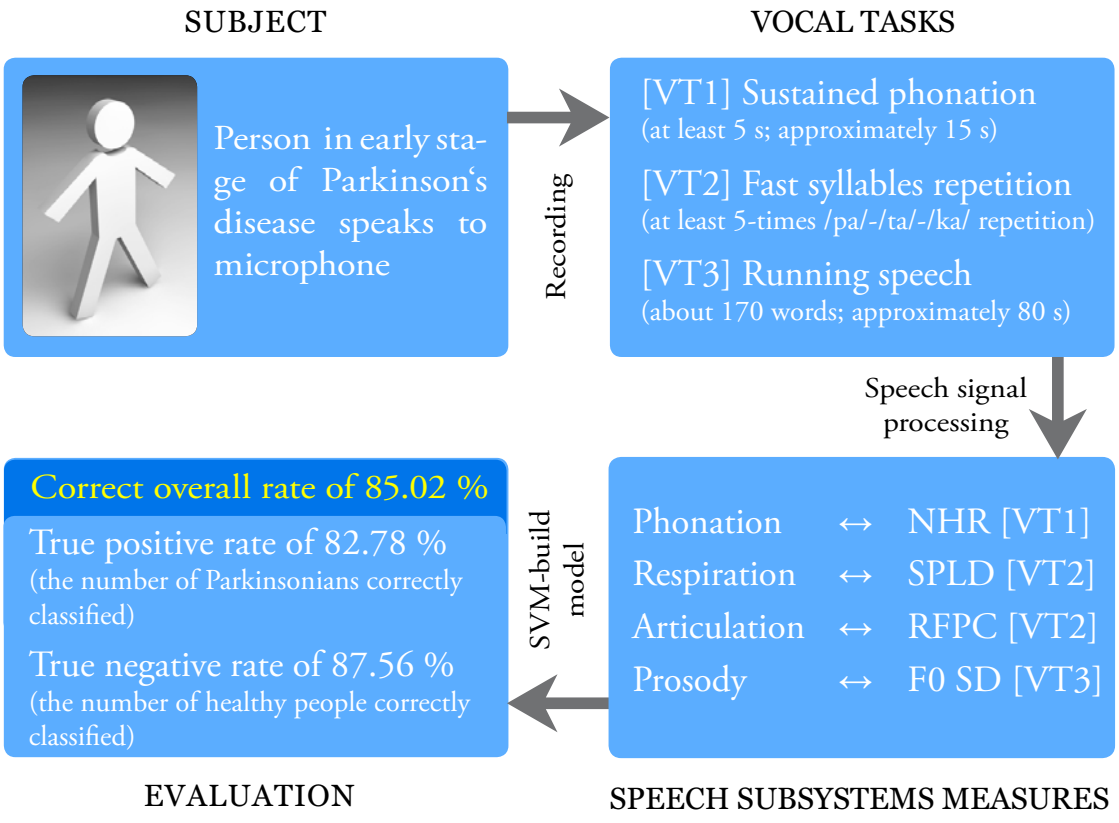

Figure 2: Schematic diagram depicting the recording of the PD patient's speech signals through the quick vocal test. Signals are subsequently calculated using speech signal processing algorithms and evaluated using the SVM-based model which can predict the PD-related voice and speech disorders.

5.4. Vowel Articulation in PD and Comparison between Speaking Tasks

On the basis of the findings presented in [A3], speakers with mild dysarthria have reduced VSA and manifest abnormalities in formant centralizations represented by F2i/F2u and FCR. In addition, the type of speaking task can exert significant influence on parkinsonian speech performance. In comparison to HC group, the parkinsonian group showed significant differences using the speaking task of sentence repetition, reading text, and monologue. The resulting speech performances show that the speaking task of sentence repetition was more closely associated with reading passage, and reading passage was more closely associated with monologue. However, the sustained phonation was found to be an inappropriate speaking task for assessment of complex vowel articulation. The atypical changes in F2 of /i/ and /u/ vowel extracted from the speaking task of monologue were best able to predict vowel impairment starting from the early stages of PD.

5.5. Novel Approach to Measure of Spectral Changes

A novel changepoint detection algorithm has been designed for automatic acoustic assessment of voice pathology with respect to relevance of changes in spectral discontinuity and the spectral envelope of the speech signal [A4]. Using developed detector, the principle of designed articulation measures are then based upon assumption that dysarthria-related imprecise articulation is among others demonstrated by lower spectral changes. Our findings confirm that people with hypokinetic dysarthria can be distinguished from healthy speakers on the basis of spectral changes where the degree of spectral change has been shown to be higher during healthy speech. In contrast to measures of articulation, we have also found that the variability of distances between individual spectral changes was significantly increased as a consequence of the higher degree of disfluency.

5.6. Evaluation of Treatment Effect

On the basis of innovative statistics presented in [A5], individual speech performances improved in most patients after the introduction of dopaminergic treatment. Generally, treatment-related changes differed individually across various aspects of speech. Most patients showed improvement in loudness of speech (according to the Intensity SD for reading text and monologue) and quality of voice (according to the jitter, shimmer, HNR, RPDE, PPE), followed by improvement in intonation variability (according to the F0 SD for reading text and monologue) and vowel articulation (according to the VAI, F2i/F2u for reading text and monologue). In measures of consonant-to-vowel accuracy (according to the RFPC, SDCV), only the SDCV indicated improved speech in PD. Additionally, speech performances in measures of the sustained phonation time (according to the MPT) and disfluency (PDW for reading text and monologue) were maintained or changed individually.

5.7. Relationships between PD Speech and Motor Symptoms

In order to provide more insights into the understanding of the pathophysiological mechanisms responsible for reduced speech performance due to PD, several experiments were performed to find possible relationships between parkinsonian speech and motor symptoms [A2, A3, A5]. From the correlations between single speech and motor parameters according to the Unified PD Rating Scale III, statistically significant relationships were mainly found between several measures of phonation and articulation and subscores of bradykinesia and rigidity. Nevertheless, after the introduction of dopaminergic treatment, we observed a significant correlation between change in the bradykinesia and rigidity subscore and in the measures of vowel articulation. In addition, there was a significant correlation between changes in the rigidity subscore and the measure of intonation variability. Fig. 3 summarizes the overall speech changes associated with the introduction of therapy, and the relationship between PD speech and motor manifestations.

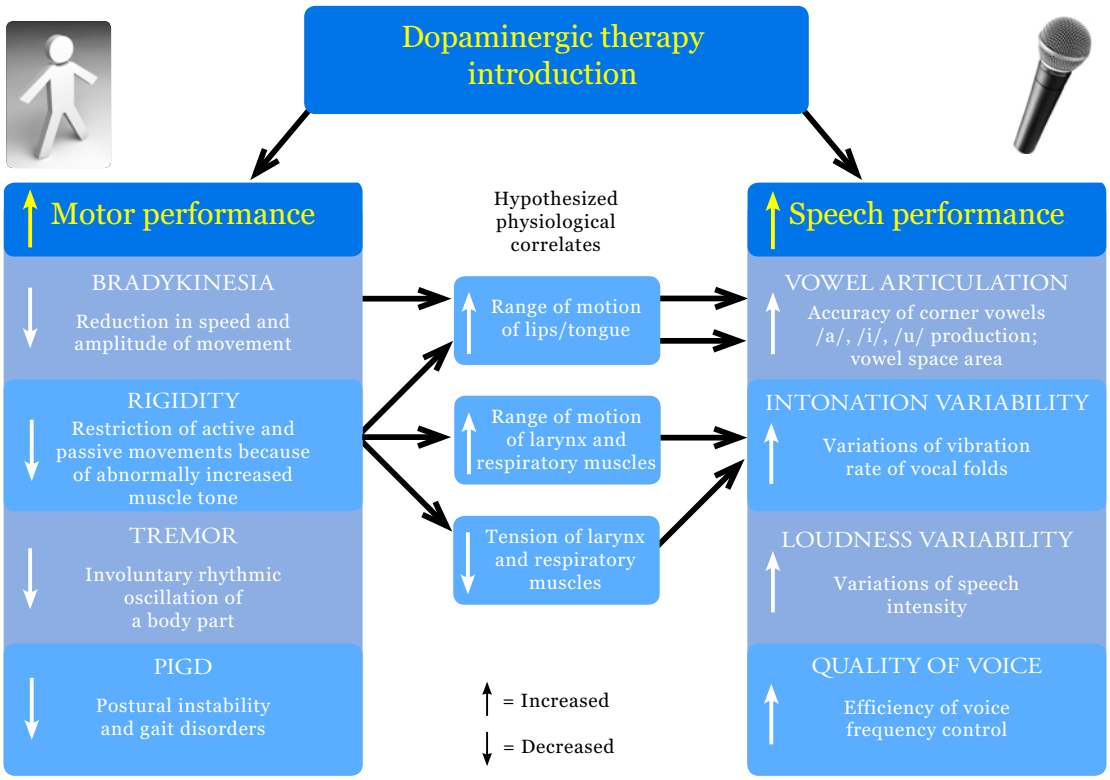

Figure 3: Schematic diagram depicting the speech changes after the introduction of treatment and relationships between speech and motor symptoms.

6. Conclusions

Using innovative methods of acoustic analysis in de novo PD patients, this thesis strives to provide more insights into progression of parkinsonian speech and voice disorders. We believe that our designed acoustic methods as well as general findings will be important for several reasons. It may be helpful in diagnosis of the disease, classifying the severity of disease, monitoring treatment, providing feedback in therapy, and support for therapists in the evaluation.

In the course of this thesis, we collected a unique sample of patients prior to undergoing pharmaceutical treatment. Most of these patients were also re-tested one to two years after the introduction of dopaminergic therapy. Our main finding is that approximately 80-90% of early untreated PD subjects show some form of vocal impairment. The predominant patterns of speech deficits in untreated patients include impaired phonation, inaccurate articulation, reduced pitch and loudness variability, and other prosodic disturbances. Although a number of researchers believe that the most salient features of PD speech are related to phonatory and articulatory impairment, the prosody of speech appears to be the most affected speech subsystem of the hypokinetic dysarthria in early stages of PD. Moreover, the specific parkinsonian voice and speech defects were found to differ individually in various dimensions including respiration, phonation, articulation, and prosody. These findings also show that persons in early stages of PD may not demonstrate a voice sufficiently impaired as to differentiate speech production from the wider norm of healthy people. In addition to these results, we have found that reduced articulatory movements are developed along with the progression of PD-related dysarthria. The alteration in the articulation of the vowels /i/ and /u/ are most sensitive in distinguishing parkinsonian from healthy speakers and are acoustically notable even in PD speakers with no perceptible dysarthria. Finally, after introduction of pharmacotherapy, PD speech performances were improved mainly in the loudness of speech, quality of voice, pitch variability, and articulation. Notably, hypokinetic articulation and pitch variability in spontaneous speech appeared as a corollary of principal motor symptoms of PD, reflecting treatment-related changes in bradykinesia and rigidity, whereas other aspects of speech improved independently of changes in motor performances. In summary, speech may be a valuable marker of disease progression and treatment efficacy in PD.

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List of Author's Publications Related to the Doctoral Thesis

A. Papers in Impacted Journals

Papers in Impacted Journals

[A1] Rusz J, Čmejla R, Růžičková H, Růžička E. Quantitative acoustic measurements for characterization of voice and speech disorders in early untreated Parkinson's disease. Journal of the Acoustical Society of America 2011; **129**:350-367. <**IF = 1.644**>

[A2] Rusz J, Čmejla R, Růžičková H, Klempíř J, Majerová V, Picmausová J, Roth J, Růžička E. Acoustic assessment of voice and speech disorders in Parkinson's disease through quick vocal test. Movement Disorders 2011; **26**:1951-1952. <**IF = 4.480**>

Papers in Impacted Journals under Review

[A3] Rusz J, Čmejla R, Růžičková H, Klempíř J, Majerová V, Picmausová J, Roth J, Růžička E. Characteristics of vowel articulation across different speaking tasks in early untreated Parkinsonian male speakers. Journal of Communication Disorders 2011; **in review**.

[A4] Čmejla R, Rusz J, Bergl P, Vokřál J. Bayesian changepoint detection for the automatic assessment of fluency and articulatory disorders. Speech Communication 2011; **in review**.

[A5] Rusz J, Čmejla R, Růžičková H, Klempíř J, Majerová V, Picmausová J, Roth J, Růžička E. Progression of speech in Parkinson's disease after introduction of pharmacotherapy: A longitudinal study. Journal of Neural Transmission 2012; **in review**.

B. Papers in Peer-Reviewed Journals

[B1] Rusz J, Čmejla R. Analýza rychlosti řeči a intensity u Parkinsonovy nemoci. Akustické listy 2008; **14**(2-4):13-16.

[B2] Rusz J, Čmejla R, Růžičková H. Analýza základní frekvence, amplitudového a frekvenčního kolísání hlasivek u Parkinsonovy nemoci. Akustické listy 2009; **15**(1):13-18.

[B3] Rusz J, Čmejla R, Růžičková H. Formantová analýza a nové metody pro hodnocení míry artikulace u Parkinsonovy nemoci. Akustické listy 2009;**15**(2):3-8.

[B4] Čmejla R, Rusz J, Růžičková H. Oslabení okluzí v promluvách pacientů s Parkinsonovou chorobou. Akustické listy 2009; **15**(3):1-6.

[B5] Bauer L, Rusz J, Čmejla R. Hodnocení vokalických parametrů u patologických hlasů. Akustické listy 2011;**17**(1-2), 13-18.

[B6] Bauer L, Rusz J, Čmejla R. Robustní algoritmy detekce špiček pro odhad základní hlasivkové frekvence prodloužených fonací samohlásek u patologických hlasů. Akustické listy 2011;**17**(1-2), 7-12.

[B7] Novotný M, Rusz J, Čmejla R. Automatická segmentace hlásek při rychlém opakování slabik (/pa/ /ta/ /ka/) u hypokinetické dysartrie. Akustické listy 2011;**17**(4), 10-16.

C. Patents

We have no patents related to the doctoral thesis.

D. Papers and Abstracts in WoS Conference Proceedings

[D1] Růžičková H, Rusz J, Klempíř J, Čmejla R, Majerová V, Roth J, Růžička E. Speech and voice disorders in early untreated Parkinson's disease. In: *Abstracts of the 13th congress of the European Federation of Neurological Societies* 2009; Florence, Italy, KENES International, vol. 3, p. 552.

[D2] Rusz J, Čmejla R, Růžičková H, Růžička E. Objectification of dysarthria in Parkinson's disease using Bayes theorem. In: *Proceedings of the 10th WSEAS International Conference on SIGNAL PROCESSING, ROBOTICS and AUTOMATION* 2011; Athens: World Scientific and Engineering Academy and Society, p. 165-169.

[D3] Rusz J, Čmejla R, Růžičková H, Klempíř J, Majerová V, Picmausová J, Roth J, Růžička E. Two-minute vocal test and acoustic analysis reveal voice and speech disorders in early untreated Parkinson's disease. In: *15th Congress of the European Federation of Neurological Societies. Budapest: European Federation of Neurological Societies* 2011; vol. 18, p. 118-235.

[D4] Bocklet T, Nöth E, Stemmer G, Ruzickova H, Rusz J. Detection of Persons with Parkinson's Disease by Acoustic, Vocal, and Prosodic Analysis. In: *2011 IEEE Automatic Speech Recognition and Understanding Workshop (Proc. of ASRU 2011)*, Big Island, Hawaii, USA, p. 478-483.

E. Other Publications

[E1] Rusz J, Čmejla R, Bachurová H, Janda J. Akustická analýza intenzity a rychlosti řeči u Parkinsonovy nemoci. In: *Technical Computing* 2008; Praha: Humusoft.

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[E4] Růžičková H, Čmejla R, Rusz J, Klempíř J, Majerová V, Roth J, Růžička E. Poruchy řeči u Parkinsonovy nemoci – analýza výskytu a charakteru příznaků. In: 22. *Neurologický sjezd* 2008; Olomouc.

[E5] Rusz J, Čmejla R. Rhythm evaluation in early untreated Parkinson's disease. In: *Analýza a zpracování řečových a biologických signálů - sborník prací* 2009; Praha: České vysoké učení technické v Praze, online.

[E6] Čmejla R, Rusz J, Vokřál J. Analýza hlasu v laboratorních úlohách při výuce studentů biomedicínského inženýrství. In: *8. ČESKO-SLOVENSKÝ FONIATRICKÝ KONGRES* 2010; Bratislava: Samedi, p. 24.

[E7] Rusz J, Čmejla R, Růžičková H, Růžička E. Kvantitativní akustické analýzy u Parkinsonovy nemoci. In: *8. ČESKO-SLOVENSKÝ FONIATRICKÝ KONGRES* 2010; Bratislava: Samedi, p. 25.

[E8] Rusz J, Čmejla R, Růžičková H. Hodnocení důrazu, emocí, rytmu, artikulační rychlosti a pravidelnosti u Parkinsonovy nemoci. In: *Technical Computing Bratislava* 2010; Bratislava: RT systems, p. 1-9.

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[E10] Rusz J, Čmejla R, Bartošek J, Janda J, Lustyk T, et al. Assessment of voice and speech impairment. In: *Workshop 2011, CTU Student Grant Competition in 2010 (SGS 2010)*; Praha.

[E11] Bauer L, Rusz J, Čmejla R. Robust pitch detection algorithms for estimation of fundamental frequency of prolonged vowels phonations at pathological voices. In: *19th Annual Conference Proceedings Technical Computing Prague* 2011; Praha.

[E12] Rusz J, Čmejla R, Růžičková H, Klempíř J, Majerová V, Picmausová J, Roth J, Růžička E. Acoustic markers of speech degradation in early untreated Parkinson's disease. In: *Proceedings of Forum Acusticum* 2011; Madrid: European Acoustics Association, p. 2725-2730.

[E13] Rusz J, Čmejla R, Růžičková H, Klempíř J, Majerová V, Picmausová J, Roth J, Růžička E. Acoustic analysis of voice and speech characteristics in early untreated Parkinson's disease. In: *Proceedings of the 7th International Workshop on Models and Analysis of Vocal Emissions for Biomedical Applications* 2011; Florencie: Universita di Firenze, p. 181-184.

F. Citations in WoS and SCOPUS

Paper [A1]

- Mekyska J, Smekal Z, Kostalova M, Mrackova M, Skutilova S, Rektorova I. Motor Aspects of Speech Imparment in Parkinson's Disease and their Assessment. Ceska a Slovenska Neurologie a Neurochirurgie 2011; **74**:662:668.
- Fox C, Ebarsbach G, Ramig L, Sapir S. LSVT LOUD and LSVT BIG: Behavioral Treatment Programs for Speech and Body Movement in Parkinson disease. Parkinson's Disease 2012; in press.

G. Awards

- **3rd prize of the Hennerův nadační fond (2011)** for the article *Acoustic assessment of voice and speech disorders in Parkinson's disease through quick vocal test*
- **European Federation of Neurological Societies Investigator Award Winner (2011)** in Movement Disorders panel for the presentation *Two-minute vocal test and acoustic analysis reveal voice and speech disorders in early untreated Parkinson's disease*
- **European Acoustic Association grant for young researchers (2011)** for participating at the *Forum Acusticum 2011* Congress
- **3rd prize of the Hennerův nadační fond (2010)** for the article *Quantitative acoustic measurements for characterization of speech and voice disorders in early untreated Parkinson's disease*

H. Research Projects

- **2008-2011 Czech Science Foundation GACR 102/08/H008:** Analysis and Modelling of Biological and Speech Signals (researcher)
- **2010-2011 Grant Agency of the Czech Technical University SGS 10/180/OHK3/2T/13:** Assessment of voice and speech impairment (principal investigator)
- **2012-2015 Czech Science Foundation GACR 102/12/2230:** Acoustic voice and speech analysis in patients with central nervous system disorders (researcher)
- **2012-2014 Grant Agency of the Czech Technical University SGS 10/180/OHK3/2T/13:** Acoustic analyses and new evaluation methods for objectification of voice and speech disorders in neurological illnesses (principal investigator)

I. Invited Lectures

- 7th International Conference on Models and Analysis of Vocal Emissions for Biomedical Applications
  Florence, Italy (August 25 – August 27, 2011)
  Acoustic analysis of voice and speech characteristics in early untreated Parkinson's disease
- 22nd Meeting of the European Neurological Society
  Prague, Czech Republic (June 9 – June 12, 2012)
  Acoustic analysis of speech progression in Parkinson's disease

List of Author's Publications Non-Related to Main Topic of the Doctoral Thesis

A. Papers in Impacted Journals

[A6] Kofránek J, Rusz J. Restoration of Guyton´s Diagram for Regulation of the Circulation as a Basis for Quantitative Physiological Model Development. Physiological Research 2010; **59**:897-908. <**IF = 1.430**>

[A7] Kofránek J, Matoušek S, Rusz J, Stodůlka P, Privitzer P, Mateják M, Tribula M. The Atlas of Physiology and Pathophysiology: Web-Based Multimedia Enabled Interactive Simulations. Computer Methods and Programs in Biomedicine 2011; **104**:143-153. <**IF = 1.238**>

B. Papers in Peer-Reviewed Journals

[B8] Kofránek J, Rusz J. Od obrázkových schémat k modelům pro výuku. Československá Fyziologie 2007; **56**(2):25-34.

[B9] Rusz J, Kofránek J. Využití, vývoj a automatizace nejen průmyslových nástrojů pro biomedicínské výukové simulátory. Automatizace 2009; **15**(7-8):443-446.

C. Patents

We have no patents non-related to the doctoral thesis.

D. Papers and Abstracts in WoS Conference Proceedings

We have no publications in WoS Proceedings non-related to the doctoral thesis.

E. Other Publications

[E14] Kofránek J, Rusz J, Matoušek S. Guytons Diagram Brought to Life - from Graphic Chart to Simulation Model for Teaching Physiology. In: *Technical Computing Prague* 2007. Prague: HUMUSOFT, p. 1-14.

[E15] Kofránek J, Rusz J, Matoušek S. Vzkříšení Guytonova diagramu - od obrázku k simulačnímu modelu. In: *MEDSOFT* 2008. Praha: Agentura Action M, p. 57-62.

[E16] Kofránek J, Rusz J, Matejak M. From Guytons graphic diagram to multimedia simulators for teaching physiology (Resurection of Guytons Chart for educational purpose). In: *Proceedings of the Jackson Cardiovascular-Renal Meeting* 2008. Jackson: University of Mississippi Medical Center (Stephanie Lucas Ed).

[E17] Rusz J, Kofránek J. Tools development for physiological educational Simulator. In: *Digital Technologies* 2008.

[E18] Matejak M, Kofránek J, Rusz J. Akauzální vzkříšení Guytonova diagramu. In *Sborník příspěvků MEDSOFT* 2009; Praha: Agentura Action M, p. 105-120.

[E19] Vorlíček J, Rusz J. Useful Matlab tool for radio frequency designer. In *Technical Computing* 2009; Praha: Humusoft.

[E20] Vorlíček J, Rusz J. Authomatic human body segmentation using mean-shoft clustering as assistance in the hyperthermia treatment planning. In *Technical Computing* 2009; Praha: Humusoft.

[E21] Kofránek J, Privitzer P, Mateják M, Vacek O, Tribula M, Matoušek S, Rusz J. Schola ludus in modern garment: use of web multimedia simulation in biomedical teaching. In: *Proceedings of the 7th IFAC Symposium on Modeling and Control in Biomedical Systems* 2009; Aalborg, Denmark, p. 425-430.

[E22] Baláš J, Rusz J, Čmejla R. Information system for management and analysis of medical data. In: *Technical Computing Bratislava* 2010; Bratislava: RT systems, p. 1–5.

[E23] Čmejla R, Rusz J, Vokřál J. Laboratory tasks from voice analysis in the study of biomedical engineering using matlab. In: *Technical Computing Bratislava* 2010; Bratislava: RT systems, p. 1-4.

[E24] Vorlíček J, Rusz J, Oppl L, Vrba J. Complex permittivity measurement of substrates using ring resonator. In: *Technical Computing Bratislava* 2010; Bratislava: RT systems, p. 1-6.

[E25] Rusz J, Čmejla R, Stráník A, Janča R. Komplexní měření plicních funkcí s využitím spirometrie. In: *19th Annual Conference Proceedings Technical Computing Prague* 2011; Praha.

F. Citations in WoS and SCOPUS

Paper [A6]

- Hernandez AI, Le Rolle V, Ojeda D, Baconnier P, Fontecave-Jallon J, Guillaud F, Grosse T, et al. Integration of detailed modules in a core model of body fluid homeostasis and blood pressure regulation. Progress in Biophysics & Molecular Biology 2011; **170**:169-182.

Paper [A7]

- Cendan JC, Johnson TR. Enhancing learning through optimal sequencing of web-based and manikin simulators to teach shock physiology in the medical curriculum. Advances in Physiology Education 2011; **35**:402-407..
- Rees SE, Carson ER, Feng DD, et al.: Modelling and control in biomedical systems Introduction. Computer Methods and Programs in Biomedicine 2011; **104**:27-28.

Paper [B8]

- Thomas SR, Baconnier P, Fontecave J, et al.: SAPHIR: a physiome core model of body fluid homeostasis and blood pressure regulation. Philosophical Transactions of the Royal Society A-Mathematical Physical and Engineering Sciences 2008; **366**:3175-3197.

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Paper [E14]

- Hernandez AI, Le Rolle V, Ojeda D, Baconnier P, Fontecave-Jallon J, Guillaud F, Grosse T, et al. Integration of detailed modules in a core model of body fluid homeostasis and blood pressure regulation. Progress in Biophysics & Molecular Biology 2011; **170**:169-182.
- Mangourova V, Ringwood J, Van Vliet B: Graphical simulation environments for modelling and simulation of integrative physiology. Computer Methods and Programs in Biomedicine 2011; **102**:295-304.

G. Awards

We have no awards non-related to the doctoral thesis.

H. Research Projects

- **2008-2009 Czech Ministry of Education MSM 2C06031:** E-Golem: medical learning simulator of human physiological functions as a background of e-learning teaching of critical care medicine (researcher)
- **2011 Czech Ministry of Education FRV G3 328:** Complex measurement of lung ventilation (principal investigator)
- **2011-2015 Czech Ministry of Health NT 12288-5/2011:** Diagnostic markers and pathophysiological mechanisms of atypical parkinsonian syndromes (researcher)

I. Invited Lectures

We have no invited lectures non-related to the doctoral thesis.

SUMMARY

Parkinson's disease (PD) is a neurological illness which caused impaired motor skills such as resting tremor, bradykinesia, muscular rigidity, and postural instability. In addition, many patients with PD develop non-motor symptoms such as disorders of mood, behaviour, thinking, and cognition and a distinctive alteration of speech characterized as hypokinetic dysarthria. Parkinsonian dysarthria, in turn, results from a multidimensional impairment of respiration, phonation, articulation, and prosody. While the evidence of voice and speech disorders in the various severity levels of PD have been well documented, little is known about the early stages of PD, where the progression of speech is not influenced by medication. The overall aim of this DISSERTATION is to explore voice and speech disorders in early Parkinson's disease using innovative methods of acoustic analysis.

The DISSERTATION is presented as a collection of papers which can be associated with two main themes: 1) the design of novel acoustic measures and statistical methods for the identification of voice and speech disorders in PD, and 2) provision of more insights into understanding of the pathophysiological mechanisms responsible for the progression of parkinsonian speech impairment. The individual papers are devoted to the design of acoustic speech measurements, characterization of vocal impairment in PD, identification of speech disorders as early marker of PD, vowel articulation in PD, and longitudinal effects of dopaminergic treatment in PD.

In the course of this DISSERTATION, a unique database of de novo patients with PD was recorded and re-tested one to two years after the introduction of dopaminergic therapy. The thesis provides a number of acoustic characteristics and statistical analysis for evaluation of the extent of vocal impairment and effect of treatment in PD. The general findings indicated deteriorated speech performance in the course of PD and reduction in speech impairment after the introduction of pharmacotherapy. The results of the DISSERTATION may be helpful in diagnosis of the disease, classifying the severity of disease, monitoring treatment, providing feedback in therapy, and offering support for therapists in the evaluation.

RÉSUMÉ

Parkinsonova nemoc (PN) je neurologické onemocnění, které způsobuje zhoršení motorických příznaků, mezi něž patří klidový třes končetin, svalová ztuhlost, bradikineze a posturální poruchy. U většiny pacientů se v průběhu nemoci též rozvinou nemotorické příznaky, mezi něž patří poruchy nálady, chování, myšlení a také zhoršení řeči označováno jako hypokinetická dysartrie. Tato dysartrie je charakteristická zhoršením řeči ve všech oblastech včetně respirace, fonace, artikulace a prozodie. Přestože hlasové a řečové poruchy v různých stádiích PN jsou již dobře zdokumentovány, málo je známo o brzkých stádiích PN, kde zhoršení řeči není ovlivněno nasazením medikace. Hlavním cílem DIZERTACE bylo využití nových metod akustických analýz při hodnocení hlasových a řečových poruch u pacientů v brzkých stádiích PN.

DIZERTACE je prezentována jako soubor prací, které se vztahují ke dvěma hlavním tématům: 1) návrh nových akustických měření a statistických metod pro objektivní hodnocení poruch hlasu a řeči u PN a 2) porozumění problematice patofyziologických mechanizmů zodpovědných za progresi zhoršení řeči u PN. Jednotlivé publikace se zabývají těmito tématy: návrh nových akustických měření řeči, klasifikace řečových poruch u PN, využití řečových poruch jako „biomarkeru“ v brzkých stádiích nemoci, artikulace samohlásek u pacientů s PN a dlouhodobé efekty dopaminergní léčby PN.

V rámci dizertace byla nahrána unikátní databáze pacientů v brzkých stádiích PN před nasazením medikace. Tito pacienti byly zároveň retestováni po 1 až 2 letech léčby. Tato DIZERTACE nabízí množství akustických měření a statistických analýz pro hodnocení míry zhoršení hlasového projevu a efektu léčby u PN. Obecné nálezy indikují zhoršení řečového projevu pacientů s PN ve srovnání se zdravou populací a zlepšení řeči po nasazení léčby. Výsledky DIZERTACE mohou být využity při diagnostice nemoci, stanovení stádia nemoci, monitoringu efektů léčby a jako zpětná vazba při logopedické terapii.