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QUANTITATIVE ANALYSIS OF THE KINEMATIC FEATURES FOR THE LURIA'S ALTERNATING SERIES TEST.

Master's thesis

Supervisor: PhD Sven Nõmm
Prof. Aaro Toomela

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KINEMAATILISTE PARAMEETRITE KVANTITATIIVNE ANALÜÜS LURIA VAHELDUVATE SEERIATE TESTIS.

magistritöö

Juhendaja: PhD Sven Nõmm
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Author's declaration of originality

I hereby certify that I am the sole author of this thesis. All the used materials, references to the literature and the work of others have been referred to. This thesis has not been presented for examination anywhere else.

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Abstract

The focus of the present thesis is on the kinematic features evaluated during the Luria's alternating series tests. Main goal is to determine the set of parameters that indicate difference in drawing between patients with Parkinson's disease and healthy controls. The methodology applied in the course of achieving the goal adopted the Motion Mass parameters that were previously used in human limb motions analysis for the fine motor skill examination. Additionally, the selected tests are designed to determine the level of motion planning and implementation the problems may originate from.

Main result of the analysis showed the relevance of the commonly used kinematic features as well as the newly introduced Motion Mass features to the diagnostic methods for Parkinson's disease. Furthermore, an application capturing the handwriting and completion of a drawing test was created, thoroughly tested and proved to be valuable as a helping tool for a neurologist.

This thesis is written in English and is 48 pages long, including 8 chapters, 7 figures and 5 tables.

Annotatsioon

Kinemaatiliste parameetrite kvantitatiivne analüüs Luria vahelduvate seeriate testis

Käesoleva töö fookuseks on kinemaatilised parameetrid mis hinnatakse Luria vahelduvate seeriate testide käigus. Põhieesmärgiks on määrata selline parameetrite kogum, mis võimaldab eristada patsiente Parkinson tõvega tervetest kontrollidest. Metodoloogia mis oli kohaldatud esmärgi saavutamiseks võttis kasutusele Motion Mass parameetreid, mis olid varem mõeldud inimese jäsemete liikumise analüüsiks. Antud töö raames Motion Mass parameetrid olid rakendatud peenmotoorika uurimisel. Lisaks sellele, valitud testid on kavandatud selleks et selgitada millisest liikumise planeerimise ja teostamise tasemest esinenud probleemid võivad pärineda.

Peamised statiistilise analüüsi tulemused näitavad mõnede enamkasutatud kineetilised parameetrite ja kasutusele võetud Motion Mass parameetrite asjakohasust Parkinson tõbe diagnoosimise protsessis. Peale selle, antud töö käigus oli loodud app, mis on mõeldud käekirja salvestamiseks ja digitaliseerimiseks edasise analüüsi jaoks. Selle kasutamine testimise käigus osutunud olla võimsaks abistavaks vahendiks neuroloogi jaoks.

Lõputöö on kirjutatud inglise keeles ning sisaldab teksti 48 leheküljel, 8 peatükki, 7 joonist, 5 tabelit.

List of abbreviations and terms

PD	Patient diagnosed with Parkinson’s disease
DTW	Dynamic Time Warping distance is an algorithm for measuring similarity between two temporal sequences which may vary in time or speed.
px	Pixel is the smallest controllable element of a picture represented on the screen of a device (a tablet in this instance)
MSE	Mean Squared Error in statistics measures the average of the squares of the errors or deviations, that is, the difference between the estimator and what is estimated.
t-test	Two-Sample t-test for Equal Means is a statistical analysis test that is used to determine if two population means are equal
PC	Personal Computer

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1 Introduction

The present thesis concentrates its attention on the kinematic characteristics observed during the Luria's alternating series test. Main goal is to determine the set of parameters allowing differentiating patients with Parkinson's disease from healthy controls. The proposed method may be applicable in those areas of medicine that rely on identification of fine motor skills' differences and the basis of those differences.

The Parkinson's disease is a degenerative disorder of the central nervous system mainly influencing motor system performance on different levels. First symptoms that can be observed are movement–related, often expressed in the gait and other gross motor functions as well as fine motor functions, but as the illness advances behavioural, psychiatric and other symptoms can be recognized. Those symptoms related to motor functions' performance are often referred to as *"parkinsonism"* or *"parkinsonian syndrome"*. The diagnostic process of Parkinson's disease is based on neurological examination as no uniform medical test can be performed to detect this medical condition. In the course of examination the patient is thoroughly tested and physician should rule out other diseases that can secondarily produce a parkinsonian syndrome before a diagnosis can be made. There is no cure for Parkinson's disease, but the approved treatment can repress the symptoms and early diagnosis is of crucial importance. The progression of the illness over time may reveal the Parkinson's disease to have been mistakenly diagnosed. Unfortunately, a conclusive answer regarding the correctness of diagnosis can be given only during an autopsy, estimating currently employed diagnostic criteria with 75–90% accuracy rate. The complexity of the diagnosis and benefits of early treatment highlight the importance of developing decision support tools and finding the parameters the degenerative disorder can be identified with. Some recent studies have shown that performance of fine motor skills can be evaluated through analysis of subtle characteristics of handwriting in order to differentiate patients with Parkinson's disease [1].

Before digital means of capturing written input the relevant data was acquired from writing and drawing tests conducted with pen on paper and assessments focused on the quality and the speed of production, rarely taking the execution of the process itself into account. The analysis of the writings or drawings was performed by the practitioners conducting the test based on their subjective observations. Introduction of pen computing allowed concentrating on the parameters of the process of writing or drawing, rather than the parameters of the final product. The ability to capture kinematic properties of the motions and the pressure of the pen encouraged to analyse and model the differences occurring in writing motions on fine motor level. First commercially available tablet PC devices have become available no more than a quarter of a century ago, nevertheless the variety of studies conducted utilizing a tablet advocate in favour of their popularity in the field of fine motor skill analysis. Writing or drawing tests' results were mainly used in the studies made available in literature.

There is a number of handwriting tasks that were suggested as a method of capturing motor disruption parameters that characterize parkinsonism. The focus of present research is on the kinematic parameters acquired from performing Luria's written alternating series tests. The Luria alternating series tests focus on different stages of motion planning and execution through various exercises. Aforesaid versatility allows differentiating motion disorders caused by different levels of the planning and execution. A subset of three tests from Luria's alternating series tests is used in the present thesis – continuing the series, copying the series and tracing the series.

In order to capture the discrepancies a set of kinematic parameters describing the motions is used: in addition to the standard parameters such as velocity, acceleration, tremble and pressure Motion Mass parameters characterizing amount and smoothness of the motion is introduced. Previously motion mass parameter was successfully used to describe gross motor skill motions like gestures and gait; defining smaller movements like those handwriting process comprises of using the same parameter is a step in the direction of further application of this quantitative feature. The parameters are captured using an application for a tablet computer, approved by medical personnel with series of tests conducted on subjects with Parkinson's disease (PD) as well as healthy subjects (controls). The testing was conducted in cooperation with doctor Toomas Toomsoo, recording of the test results took place in East-Tallinn Central Hospital, all necessary ethic permits were applicable. The main goals of the testing conducted concentrate around finding the most promising set of parameters that can be derived from the data acquired during drawing task that would provide reliable guidance to the practitioner in terms of differentiation of Parkinson's disease.

The thesis is organized in the following way: the previous findings illustrated in the relevant literature sources are described in Chapter 2. In Chapter 3 background knowledge regarding Luria's tests is presented. Formal problem statement is formulated in Chapter 4. Methodology and tools are defined in Chapter 5. The results acquired during testing of the program are presented in Chapter 6. Accomplished results are discussed in Chapter 7. Conclusions and further research options are presented in the last section.

2 Literature overview

Executing drawing process is one of the most complicated and challenging fine motor functions of humans comprising of actions of different parts of the arm as well as adaptation of grip force during the movement flow. Therefore, the development of the handwriting skill, both improving and decreasing, could be indicative of neurobiological and educational processes. Many researchers publish their findings in this field of study. [2] has identified that handwriting directly reflects on social and educational development thus indicating the importance of assessment of handwriting performance due to far–reaching academic and psychological consequences. In [3] it has been shown that the contribution of fine motor skill to the prediction of improvements in children's cognitive and social skills is most certainly very significant. The relation between hand laterality and motor skill development has been examined in [4] showing that the difference of performance between dominant and nondominant hand has not increased over the years of everyday use of pen. Kinematic hand movement analysis of impaired movements in children and adolescents in [5] reasoned that age and gender have impact on kinematic parameters, whereas fine motor practice and laterality of handedness do not. Changes in executive control and handwriting performance have been proven to be age–related in [6], indicating that age accounts for a third of executive control variances. The relation between performance of motor skills and cognitive skills has been reviewed in [7] and deduced that a direct proportionality can be observed, thus concluding that complex motor intervention programs can be used to encourage both cognitive and motor development in children. In [8] a study of kinetic parameters of accelerated drawing process has been conducted in order to determine drawing patterns of younger children. It has been concluded that the development of graphic skills can be assessed through linking the psychophysical parameters with specific graphic patterns. Observation of the movement that is executed could affect the parameters of the movement. However, an experiment conducted in [9] showed that perceptual preference of handwriting movement in children cannot be directly correlated to motor function execution.

Many studies concentrated on digitizing the process of handwriting motion, leading to quantification of the process and modelling it virtually for further analysis. The methods of digitization and tools used to capture the handwritten input have been analysed. [10] exploited digitizing graphic tablet to define a method of diagnosis of movement disorders. In [11] the reliability of tablet PC in evaluation of multidimensional neurocognitive function was assessed and proven to be reliable. A new method for quantitative analysis of muscle anomalies based on pressure and movements features recorded by handwriting with an electronic pen has been introduced and discussed in [12]. Introducing the elements of testing into other usual activities one would undertake willingly on their own has also been attempted. Results of applying a method for using enjoyable computer games with embedded cognitive metrics to monitor within–subject trends in performance were presented in [13]. This method showed that routine measurements over time allow detecting trends in various aspects of cognitive performance and avoiding biases due to education, culture, and experience. The benefits from developing a technique that applies automatic image analysis in automated analysis of hand–copied line drawings have been addressed in [14].

There are studies that examine the effect of virtualization methods on the handwriting itself, for example whether there is an inverse correlation in performance younger portion of the population depending on the tools used for writing: analysing the effect of tablet PC usage on early writing [15] revealed that the velocity of handwriting execution is higher when tablet is used rather than regular pen and paper. Another study [16] has independently examined handwriting measurements when writing on a tablet computer and on paper, concluding that the differences that were found are only partially task–dependant. The pressure of being observed and executing a task in an unfamiliar environment using unfamiliar and appearing to be complex devices is often argued to affect the resulting data or the effectiveness of an exercise, thus attempts to relocate the testing process into virtual reality were made. Haptic virtual reality has been introduced for real–time analysis of handwriting rehabilitation exercise; the performance of such technique was evaluated in [17].

Certain parameters of the handwriting process and their relevance to a disorder are often examined independently. In [18] a quantification of tremor with a digitizing tablet was analysed – a tablet has been used to reliably record any pathological tremor induced by writing or drawing. The amplitude and frequency of tremor was successfully digitized and analysed, but the tablet has proven to be insufficiently sensitive to measure physiologic aspect of tremor. Kinematic parameters reflecting velocity and automatization have been successfully quantified during digitized analysis [19] of abnormal fine motor skill performance in schizophrenic patients.

A growing number of studies are conducted in the field of digitizing handwritten input for the purpose of diagnosis and prognosis of cognitive disorders, primarily in advanced in age members of community. A portion of these studies are related to one of the most common neurological disorder affecting motor system – Parkinson’s disease. The potential of diagnosing Parkinson’s disease based on handwriting task is evaluated in [20], as well as relevant method is developed and implemented, providing 80% overall classification accuracy, thus pointing out that evaluation of handwriting process is effective mean of interpretation of Parkinson’s disease. In [21] it is demonstrated that kinematic analysis of pen movements during handwriting can be beneficial for detecting and monitoring subtle changes in motor control related to drug–induced parkinsonism. Kinetic tremor is commonly examined as one of symptoms of Parkinson’s disease and some other neurological disorders. In some cases it is important to distinguish whether motor dysfunction like tremor is a symptom of a neurological disease or result of aging. [22] focused on the use of tablet computer for the investigation of correlation between kinetic physiological tremor and aging. In [23] a goal of distinguishing Parkinson's disease from other syndromes causing tremor using automatic analysis of writing and drawing tasks has been achieved, proving that separation of Parkinson's from other tremor syndromes can be done with good accuracy using the features extracted from the drawing and writing tasks. In order to differentiate PD from healthy controls an analysis and assessment of subtle characteristics of handwriting has been successfully conducted in [1]. Data from challenging PDs with a cognitive task that requires participants to predict stimulus sequences revealed a contribution of the motor loop dysfunction to cognitive sequencing impairment in PDs, as described in [24]. The importance of evaluation of therapy–related complications when treating PDs is addressed in [25] and a dynamic access to virtualization of spiral drawing data is introduced enabling personalised identification of tendencies and patterns of motor dysfunctions. Bradykinesia, slowness of movements, and micrographia, progression to a smaller handwriting, are among other of the primary motor symptoms of Parkinson's disease. In [26] the slowness of melancholic depression has been studied demonstrating that the pathogenic mechanism is similar to that of bradykinesia in Parkinson's disease. The relationship between micrographia and bradykinesia has been found in [27], suggesting a possible overlap in their pathophysiology. Severity of the disease and impaired cognition were seen to correlate. In [28] it has been argued, that the handwriting of a PD possesses more traits of a dysgraphic writing, rather than micrographic. The parameters of handwriting were compared in free writing and copying tasks in order to define progressive and consistent micrographia in PD in [29]. Results indicated that the data gathered from copying tasks proves to be more objective in identifying the types and advancement of micrographia.

3 Background on Luria’s tests

3.1 General information

Human movements are guided by the part of central nervous system known as motor system. Before a movement is executed it is created in human mind as a result of determination and is formed as a goal to be achieved. Voluntary movements were a subject of Luria's studies of the frontal lobes in which he stated that deliberate movement is executed as a result of multilevel planning process [30]. Once a certain movement related goal is set to be accomplished the process of planning is started. First level of planning involves explaining the general idea behind the movement – the reason behind the movement and the general representation of how the movement should be performed. On the second stage specific motion patterns are created based on the general idea. These motion patterns are referred to as *motion melodies* – the sequences of the actions, ordered in time, which should accomplish the goal. On the third level a set of signals instructing a specific sequence of actions to be taken is sent to the spine. The motion melody is being actually implemented on this level. Luria’s alternating series tests has been selected to detect the disorders on the different levels of planning.

The first of the selected Luria’s alternating test – following the sequence – expects a testee to draw the line atop of the given periodic pattern. The second selected test – copying the sequence – requires one to copy the given periodic pattern, drawing a line that is supposed to be similar in shape but in a different location, for example the given line would be in the upper part of the paper and the drawn line is supposed to be in the lower part of the paper. The third Luria’s alternating test – continuing the sequence – requires one to continue drawing the line when only a few segments of the periodic pattern are given. The results of the tests were previously assessed visually and thus subjectively by the practitioner. If testee has difficulties completing all the tasks then the disorder most likely occurred on the third level of the planning, when the generated motion melody is transmitted to the spine. The complexity of the tests is increasing with the first being the relatively easiest and third being the most complex one. If complication occurs only during the most complex test and either was not so severe during the other two tests or was not present at all, then the second level is most likely the one the disorder originates from, at the point of motion melodies generation. It is possible for the disorder to present itself during the simpler test while the complex one has been completed without any difficulty. This might indicate that the testee has troubles with recognizing the supporting lines, either visually or mentally cannot perceive those as assisting in achieving the goal.

In order to complete the aforementioned tests one needs to constantly change the motion in order to achieve the goal, i.e. draw the same set of alternating elements in the correct order in the desired location. Tasks of this nature are difficult for those with premotor systems disorders and fulfilling the task in one singular motion melody might be complicated. Drawing is normally an automated process, but in cases with motor disorders fluent motions become noticeably overly deliberate, sometimes even reduce to recurrent repetition of a single element of the pattern given. The tests are easy to conduct, but at the same time have proven to be extremely effective in dynamic voluntary movement research in detection of a number of types of disorders, such as:

- Impulsivity in execution, that often leads to errors
- Difficulties with starting the action (motivational impulses)
- Pathological inertia (perseverations)
- Simplification of the program, tendency to stereotype
- Exhaustion (micrographia), decline in the amplitude of the elements
- Visual–motor coordination disorders (macrographia, dissimilation or the difference of amplitude of the elements)
- Disinhibition, introduction of new unforeseen elements

3.2 First Luria's alternating series test

The canonical procedure of administering the test is the following: The practitioner starts drawing with a pen on a paper a pattern composed of two interchanging elements. The pen is passed on to the testee, who is asked to continue the sequence with their right hand. The duration of the drawing is 1 minute. Once the task is completed the practitioner takes his turn and starts drawing the same pattern again, passes the pen back to the testee and offers to continue drawing the series with their left hand. The testee is supposed to continue the drawing for no more than 1 minute. The evaluation is done regarding three aspects of the resulting line separately for each hand:

1. Inertness of an element of the program. Practitioner counts how many perseverations have been completed.
2. Decrease in the stability of the program. The percentage of incorrectly drawn elements in the pool of the total drawn elements is calculated.
3. Control difficulties. A qualitative measure evaluated as 0 – if no mistakes were made, 1 – there are mistakes that were corrected, 2 – at least one mistake was not corrected.

3.3 Second Luria's alternating series test

The practitioner draws with a pen on a paper a pattern composed of 5–7 groups of two interchanging elements. The testee is asked to take pen and trace the contour of the line, drawing atop of it with their right hand. The duration of the task is limited by 1 minute. After that practitioner takes his turn to draw again and presents the testee with another instance of the line of the same length and same pattern. The testee is supposed to trace the given pattern with their left hand; completion of the task should not take more than 1 minute.

During the completion of the task testee is expected to base his motion strongly on the visual stimuli, thus the task is more of mechanical nature and should be easier to complete. Evaluation takes same principles into the account than the first of the Luria's alternating series test, but the effectiveness is expected to be higher.

3.4 Third Luria's alternating series test

The practitioner draws with a pen on a paper a pattern composed of 5–7 groups of two interchanging elements. The testee, in turn, should copy the pattern onto the free space below the given line with right hand and then with their left hand below that. 1 minute is given for the completion of the task with each hand.

The given pattern provides necessary information to create the program for completing the task; however the completion is complexed due to the fact that the whole pattern needs to be recreated with no boundaries visually evident. Evaluation relies on the same principles than the first of the Luria's alternating series test. It is normal for this test to pose difficulties for healthy subjects; therefore expected results are lower in this instance.

4 Problem statement

Analysing handwriting is a part of reliable tool set for a neuropsychologist to diagnose and evaluate how motor function acquired and retained. The need to introduce digitization into this process comes from the necessity to carefully monitor the existing symptoms, like disruption in the execution of practiced skills such as handwriting, or detect their occurrence in the handwriting process. Therefore, writing and drawing tests are to be conducted regularly, producing an increasing amount of data to be stored and to be taken in consideration when performing analysis and evaluation. Before the use of digitizing equipment practitioners based their interpretation of the results of the tests on their observations, limiting it by their attention to detail and overall ability to register differences in small movements by a human observer. This approach is more of a qualitative nature, rather than quantitative. Digitizing handwriting not only allows administering data more effectively, but, more importantly, creates an opportunity to operate with parameters of the drawing process on the quantitative level. Digital devices are considerably more precise, capable of registering the slightest deviations and cannot be subjective when capturing the features of a movement. Using a tablet computer for digitizing the written input has been previously attempted and has proven to be effective [20], but it is still not widespread.

Unlike the human neurologist, who assesses the writing process as a whole and most likely to concentrate on the correctness of the result, a computer is set to digitize the input and is able to evaluate the dynamics of the writing. A tablet computer obtains written input from the stylus interactions with the screen surface, receiving the position of the stylus on the screen, time of the interaction and pressure applied with the stylus onto the screen surface. Parameters derived from the originally acquired data can be used to describe the peculiarities of writing process more thoroughly and provide a larger pool of criterions to base the comparison of different handwritings on.

Taking these findings into account, the problem current thesis addresses consists of two parts and can be formulated in the following way:

a. A subset of features characterizing the movement of stylus pen on a tablet while completing Luria’s alternating series tests ought to be selected in such way that it can be used to successfully distinguish PDs from healthy controls.
b. The subset of the features found should be analysed in terms of their relation to the level of the planning the disorder occurs, possibilities to identify the stage of motion planning and implementation using the selected features should be investigated.

An application created for the purpose of this thesis can be used in neuropsychology and physiology fields as a tool to acquire writing specification data and is intended to address issues arising from the use of a tablet in conducting writing and drawing tests.

5 Methods and hardware

5.1 Subjects

A total of 24 people participated in the pilot testing, 14 were previously diagnosed with Parkinson's disease and 10 healthy volunteers served as controls. The participating patients had different stages of the progression of the disease. However, none of the patients were diagnosed with young onset Parkinson's disease, therefore the age of the Parkinson's group varied in the above 50 range. Personal information regarding the patients remained classified, but the age, sex and the duration of disease estimated from the date when they were diagnosed with Parkinson's disease is presented in Appendix B.

All the participants are familiar with drawing with pen on paper, which essentially is similar to drawing with stylus on a tablet. All the subjects completed the task with at least one, dominant hand; 2 patients refused completing the task with their non–dominant hand.

5.2 Tools

A Samsung tablet computer with screen resolution 1280 px * 752 px equipped with a stylus was used to capture drawings. By default a dot is displayed on the screen where stylus is about to come in contact with the surface when the distance is less than 1 cm, this provides additional visual aid when drawing on the tablet.

The written input acquisition software was developed in Java using Android software development kit, the integrated development environment used was Android Studio 1.5.1. The choice of the language based on the fact that Java is the official recommended language for Android development and the fact that it is the language the author has most experience with.

The tablet is able to capture different movement parameters. When a tool (a list of supported tools includes a finger and a stylus) comes into contact with the surface of the device a motion event is registered, describing movements in terms of an action code and a set of axis values. The most important to the purpose of this thesis quantitative parameters of every motion event are the two–dimensional position of the point where the event occurred, the time of the occurrence and the pressure which was applied to the surface by the stylus. The position of the event is returned in pixels with 0.00001 subpixels precision from the starting point of the surface grid – the left upper corner of the device. The time of the event is returned in milliseconds elapsed since the device was booted. The pressure value is normalized to a range from 0 (no pressure at all) to 1 (normal pressure), although values higher than 1 may be generated depending on the calibration of the input device. Other important parameters like velocity and acceleration are calculated based on the changes of aforementioned parameters, therefore in the interest of presenting these parameters in conventional manner the pixels are translated into millimetres taking the device–specific physical pixels per inch of the screen ratio into account, then converting inches to millimetres. The data about every event is stored simultaneously with the actual event locally on the tablet in comma separated values file – x axis position from the left side of the device in millimetres, y axis position from the upper side of the device in millimetres, time of the event in milliseconds since the boot and pressure. These data files are used in further calculations and analysis; moreover those can be reviewed by the practitioner if such need to be.

Subsequent analysis of the acquired motion features was done using Matlab.

5.3 Task description

The participants were advised to take a seat in front of the table in convenient position. It was explained that they would be presented with a simple drawing task and they should prepare accordingly. The drawing process was not limited in time and no implication of time being assessed was shown to the testees, it was recommended to perform the drawing at comfortable speed. In the moments of staggering or confusion expressed by PDs reassurance that it is normal to experience difficulties with completing the task there is no need to rush with drawing has been communicated by the person conducting the test. The test series consists of three types of task, two of which are divided into two subtasks, resulting in five drawing tests to be done by dominant and nondominant hand; additionally baseline pressure evaluation had to be done for each hand. Total of 12 drawings were captured for every participating subject.

Three Luria alternating series tests were to be completed by drawing certain lines with stylus on the surface of a tablet. Before those three tests the baseline pressure had to be established – the testee was asked to draw three random straight lines in the convenient manner. No restriction to the length, direction or position was stated regarding those lines, the process of the drawing was free to be chosen by the testee.

For the purpose of the first test a polyline consisting of a squared, triangular, another squared and half of the triangular line is drawn from the left side of the screen. It is explained that the line represents a pattern given and the testee is supposed to continue the line in the same manner. An example of a completed first task is shown in Figure 1.

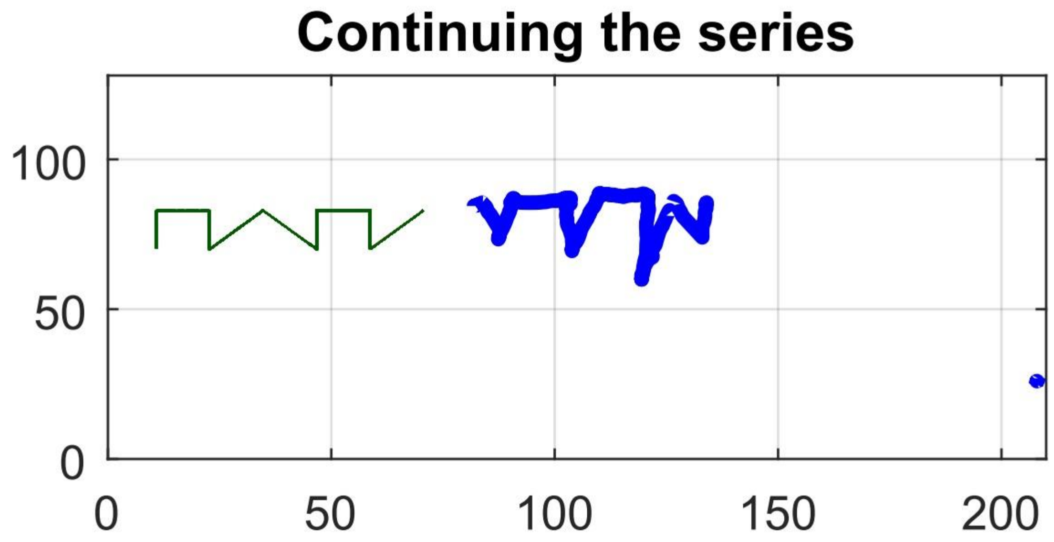

Figure 1. Example of a completed continuing the series task

Second test contains two different pattern lines that testee is supposed to trace, i.e. draw the same line atop the given pattern. First pattern is a polyline consisting of squared and triangular elements in the alternating order, the elements are drawn from the left side of the screen and are repeated until the right side of the screen is reached. Second pattern is a sine wave line, starting at the left side of the screen and continued all the way up to the right side of the screen. The task is explained to the testee as the tracing the line task, therefore the drawing should be as close to the given pattern as possible. Tracing the polyline and tracing sine wave line are considered as different subtasks.

Third task is the most complex one to complete – there are two types of patterns – polyline and sine wave, similar to those in the second task, that the testee is presented with, but one is supposed to draw the similar line lower than the given pattern, i.e. copy the drawing to a different location relying on the given pattern as visual guidance. Copying the polyline and copying sine wave line are considered as different subtasks.

5.4 Data acquisition and analysis

During the completion of the tasks stylus performs on–surface movements, each change of the position of the stylus is registered as a separate event with relevant data – x–axis position, y–axis position, time and pressure. Every registered movement event is essentially a line from a data matrix consisting of n rows and 4 columns, where n is the total amount of movement events produced during a single completion of one task or subtask. Each data matrix is saved separately for further processing as raw data. The process of data flow is depicted in Figure 2.

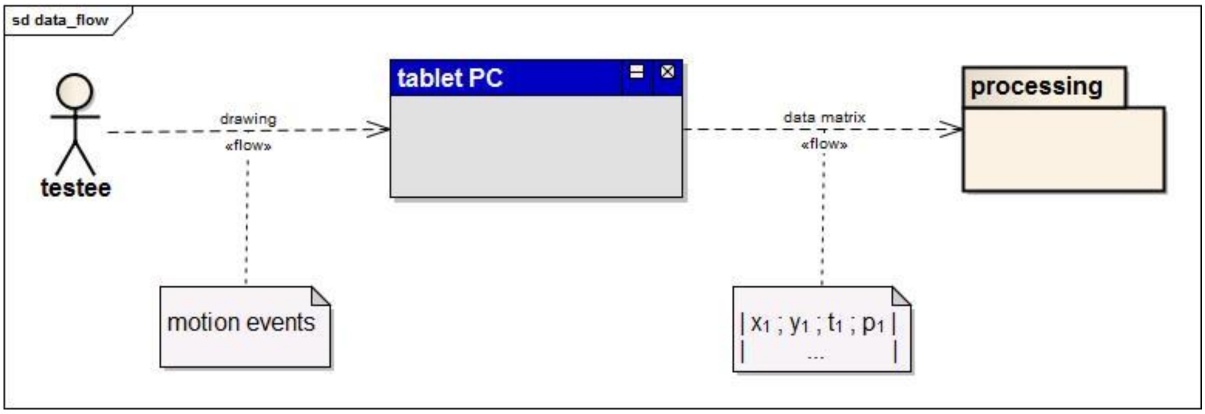

Figure 2 The flow of the raw data acquired during testing

Before calculating any kinematic features of the registered motions based on the raw data simple pre-processing is done. Every column of the data matrix is represented in numerical format and noise reduction techniques are implemented. For every testee a data matrix for baseline pressure task is extracted and average pressure is calculated. Data matrixes containing information about completion of Luria tests are filtered in regards to the average pressure – those rows containing too weak pressure are eliminated. Additionally, the data matrixes are scanned for the small groups of distant from the general flow points of movement, indicating accidental blots drawn on the surface by mistake, which are also excluded from the analysed set.

Once pre-processing is complete calculation of kinematic features is done for every data matrix separately. A concept of stroke is adapted from previous studies conducted on analysing handwriting [1] and is defined as a single continuous segment of on–surface movement, continuity evaluated by the changes of position and pressure. The rows of values in the matrix are arranged by time value and noticeable change in distance or pressure between two adjacent rows indicates end of one stroke and beginning of a new one. According to the tests each subtask is normally completed in one single stroke.

Three groups of features are evaluated for the purpose of this thesis. First contains general kinematic features frequently evaluated in the reference materials. Motion mass features describing smoothness and amount of the movement adapted from the research on gross motor functions comprise the second group of features. Finally, the features that directly evaluate the similarity of the paths of the movement between those created by the subjects and the patterns given as example are segregated in the third group. Figure 3 depicts the mechanism used in processing the raw data.

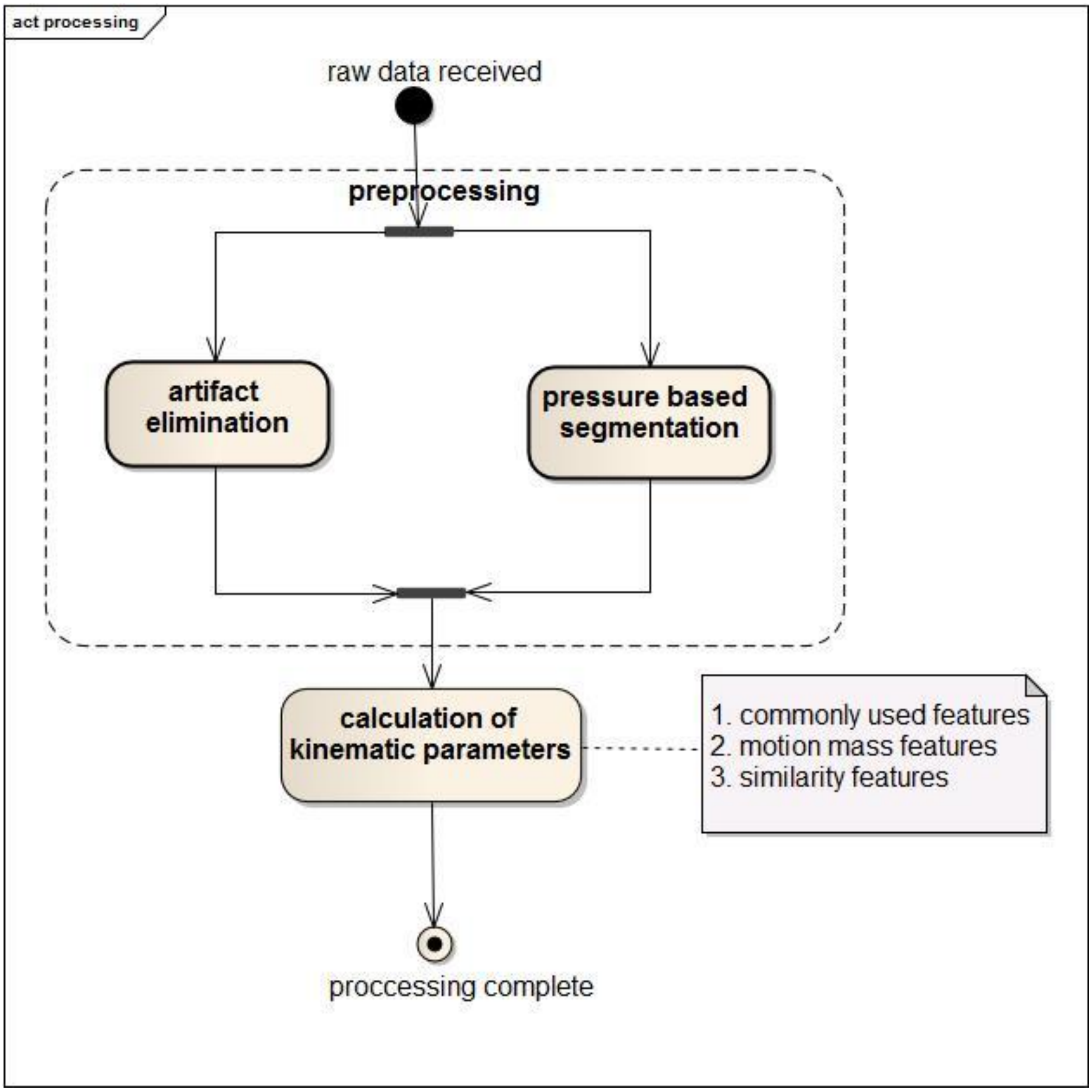

Figure 3 The processing of raw data

Various different kinematic features can be calculated taking position, time and pressure into account, but the most commonly used to describe handwriting include mean stroke velocity, mean stroke acceleration, number of strokes. For every stroke that contributed into drawing the path to complete one task (or subtask) the rate at which the position of the tip of the stylus changed in time in mm/s was taken into account and average estimated to express the mean stroke velocity $\overline{v_s}$. Mean stroke acceleration $\overline{a_s}$ is expressed similarly – the average estimate of the rates at which the velocity of the tip of the stylus changed in time in mm^2/s for each stroke the drawn path consists of. Usually a task is completed in one single smooth motion = one stroke, however when experiencing difficulties with coordinating the movements, even fine motor motions, one tends draw the line in many strokes, especially when dealing with drawing a polyline, thus number of strokes S_{nr} is used to describe the process.

A voluntary movement represents a series of actions ordered in time taken to achieve a goal. Confident, smooth movement contains next to none erroneous actions. The amount and smoothness of a movement can be described by motion mass features. A proper formulation of the motion mass features adopted from a research on measurement of human limb motions [31] is the following:

In terms of handwriting the drawing process consists of strokes, a perfectly executed drawing would contain the most optimal amount of strokes that follow the desired path in the most accurate way. Let $S = \{s_1, s_2, \dots, etc\}$ be the set of the strokes of the drawing of interest. For each stroke the time when it began and ended, as well as associated position of the tip of the stylus and its pressure against the surface at those times can be defined. Let *t* stand for the duration of the execution of the drawing process. The *combined Euclidean distance* E_s of the set *S* is the sum of Euclidean distances of each stroke:

$$E_s = \sum_{i=1}^{n} E_{s_i}, \tag{1}$$

where E_{s_i} represents the Euclidean distance between the beginning and end of the stroke s_i. Similarly, the sum of the lengths of the trajectory of each stroke drawing consisted of T_s:

$$T_s = \sum_{i=1}^{n} T_{s_i} \tag{2}$$

is defined as *trajectory mass*. For each pair of subsequent moments of time when drawing of the stroke was performed velocity and acceleration can be measured, the sum of absolute values of these measurements for each stroke is denoted as V_{s_i} and A_{s_i} respectively. The *velocity mass*, denoted V_s, is defined as:

$$V_s = \sum_{i=1}^{n} V_{s_i} \tag{3}$$

The *acceleration mass* A_s is calculated analogously:

$$A_s = \sum_{i=1}^{n} A_{s_i} \tag{4}$$

Every point registered during drawing a stroke is described by the pressure amongst other parameters. The sum of the values of pressure for every stroke can be estimated and therefore *combined pressure* P_s is defined as:

$$P_s = \sum_{i=1}^{n} P_{s_i}, \tag{5}$$

where P_{s_i} is the sum of pressures estimated for a single stroke.

Additionally, every stroke can be viewed in regard to direction of its points. Change of direction can be detected for every trio of points registered consequently in time, the sum of these changes within one stroke is denoted as D_{s_i}. The *angular mass* D_s, is defined as:

$$D_s = \sum_{i=1}^{n} D_{s_i} \tag{6}$$

Total amount of the actions taken to complete the drawing task is described by the trajectory mass and angular mass, whereas velocity mass, acceleration mass and combined pressure characterize the smoothness of the drawing process. The set of these five features plus the duration of the drawing represent *motion mass* M_s of the drawing, formally denoted as:

$$M_s = \{T_s, D_s, V_s,\ A_s,\ P_s, t\} \tag{6}$$

The elements of the motion mass describe the amount and smoothness of the movements related to a certain motion, i.e. drawing process.

Finally, the similarity of the drawn trajectory and the trajectory of the original example is evaluated, comparing how closely the testee was able to draw the line to the modelled pattern. The features used to calculate the similarity were *Dynamic Time Warping distance (DTW)* and *Mean Squared Error (MSE)*. DTW allows measurement of distances between two series of different lengths by warping series along the time axis in varying way to enable effective matching. Computation of DTW value is formally defined in the following way:

Let *DTW(i,j)* be the optimal distance between the first *i* and first *j* elements of two series $\bar{X} = (x_1, \ldots, x_m)$ and $\bar{Y} = (y_1, \ldots, y_n)$. The lengths of the series are n and m elements respectively, which are not necessarily the same. The value of *DTW(i,j)* would be defined recursively:

$$DTW(i,j) = distance\ (x_i, y_j) + min \begin{cases} DTW(i, j-1) & repeat\ x_i \\ DTW(i-1, j) & repeat\ y_j \\ DTW(i-1, j-1) & repeat\ neither \end{cases} \quad (7)$$

The value of $distance\ (x_i, y_j)$ is defined as follows:

$$distance\ (x_i, y_j) = \sqrt{(y_i - x_i)^2} \quad (8)$$

The function *immse(X,Y)* predefined in Matlab has been used to evaluate the MSE value on the original trajectory and the drawn trajectory. The function is able to compare the matrixes of the same dimensions. Since the number of points describing the two trajectories is most likely different the paths were balanced to be of equal size.

5.5 Statistical comparison

Two groups of subjects participated in the testing in order to determine the set of distinctive features the handwriting of a PD can be measured by. A total of 11 features were evaluated for every type of test that the subjects were presented with. This resulted in as many as 55 sets of features calculated for a total of 24 participants (14 PDs and 10 healthy controls). For every feature statistical comparison between PDs and healthy controls was conducted in order to determine whether the feature is indicative of the PD or not. *Two-Sample t-test for Equal Means* was applied in each instance of a feature; the built-in Matlab function *h = ttest2(x,y,Name,Value)* was utilised for this purpose. The parameters this function was given are:

- x – sample data of a feature for PD group
- Y – sample data of the same feature for control group
- Name – 'Alpha'
- Value – 0.1

The significance level of the statistical testing was raised from the default by 5% in order to allow the probability of rejecting the null hypothesis when the null hypothesis is true to be 10%, lowering the confidence level to 90% accordingly. The null hypothesis of this test states, that the values of a selected feature, corresponding to the samples of PDs and healthy controls are independent random samples from normal distributions with equal means and equal but unknown deviations. Testing with this function produces the following results:

- h – hypothesis test result; 0 indicates that the null hypothesis was not rejected at the defined significance level.
- p – probability of observing a test statistic as extreme as, or more extreme than, the observed value under the null hypothesis
- tstat – value of the test statistic

6 Main results

Statistical evaluation of handwriting features determining which features are exclusive for handwriting of a person with Parkinson's disease was conducted gradually for the increasing amount of features as well as increasing amount of tested subjects. Initial evaluation comprised of 11 features evaluated on 3 types of tests and 13 tested subjects (7 healthy and 6 PDs). As more subjects were tested the handwriting features were re-evaluated and it was noted that the relevance of parameters was growing, promising that more parameters would be found to be determining whether examinee should be diagnosed with Parkinson's disease as more subjects both healthy and from PD group would be tested.

Originally, the analysis of the results of the Luria test relied on the details noticed by a human observer, which would prove a rather difficult task for an unexperienced practitioner. Figures 4 to 7 depict examples of the results of completed tasks as they were to be evaluated without introducing digitized quantitative parameters.

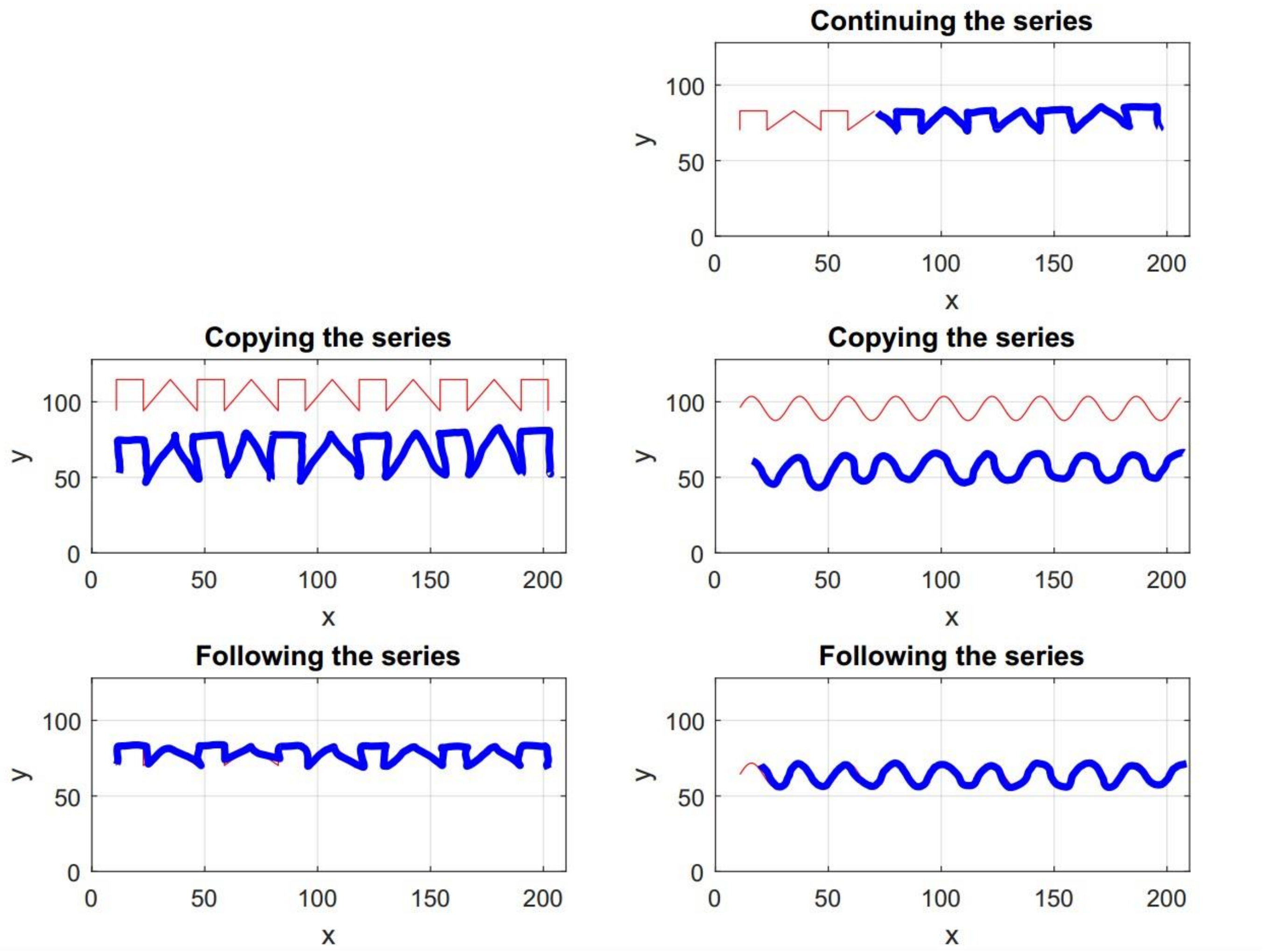

Figure 4 Example of poorly completed tasks by a representative of healthy controls group

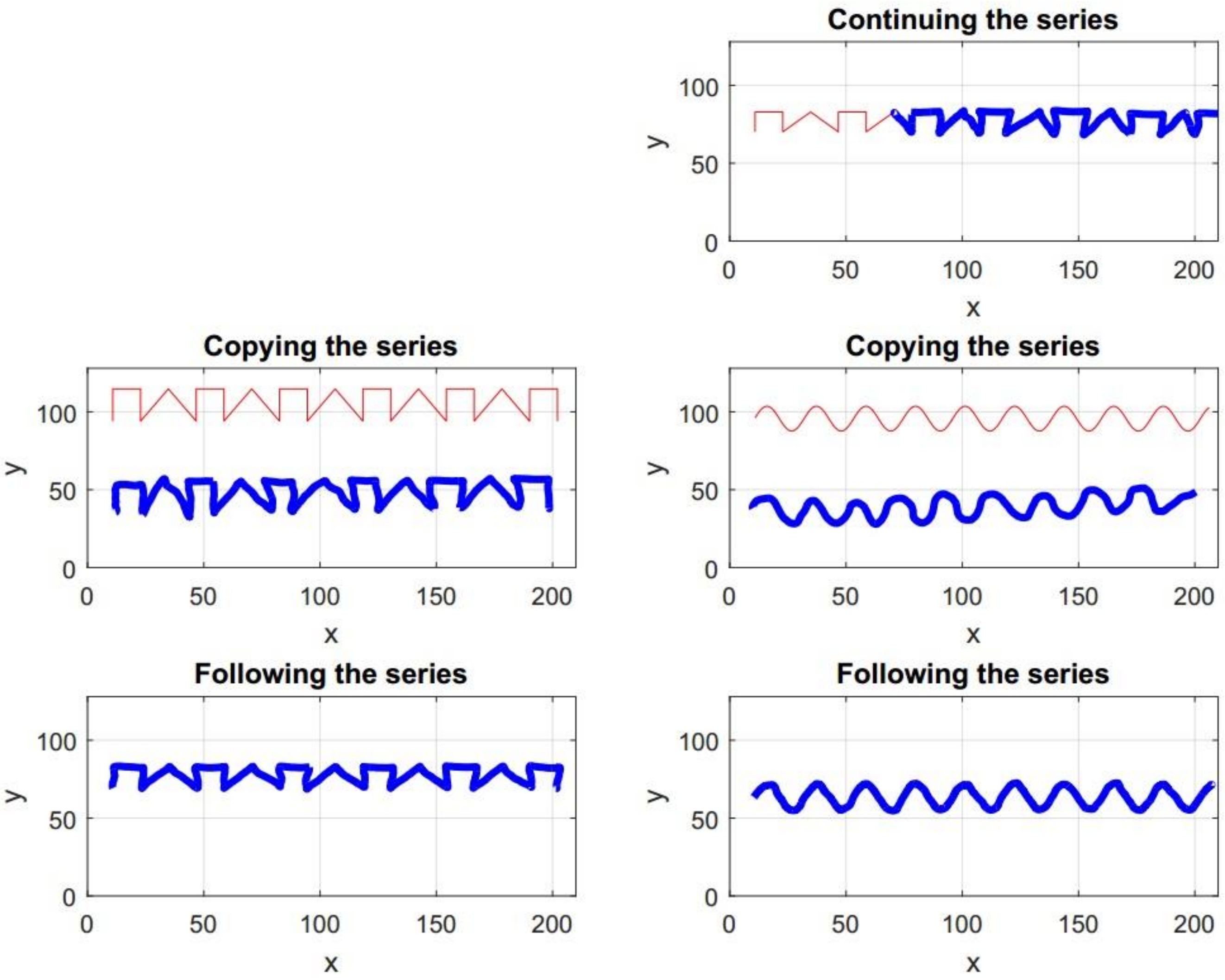

Figure 5 Example of decently completed tasks by a representative of healthy controls group

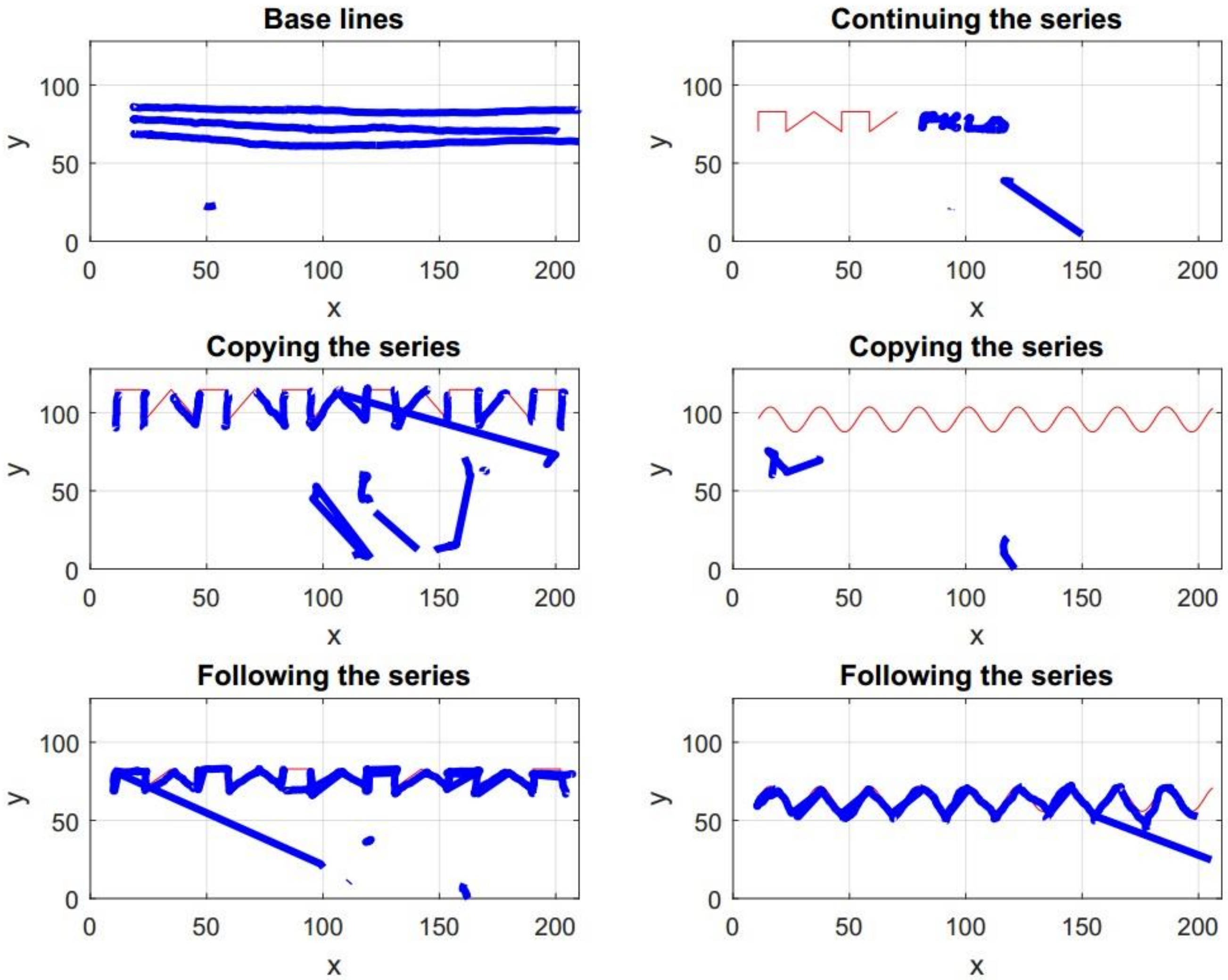

Figure 6 Example of poorly completed tasks by a representative of the diagnosed with Parkinson's disease group

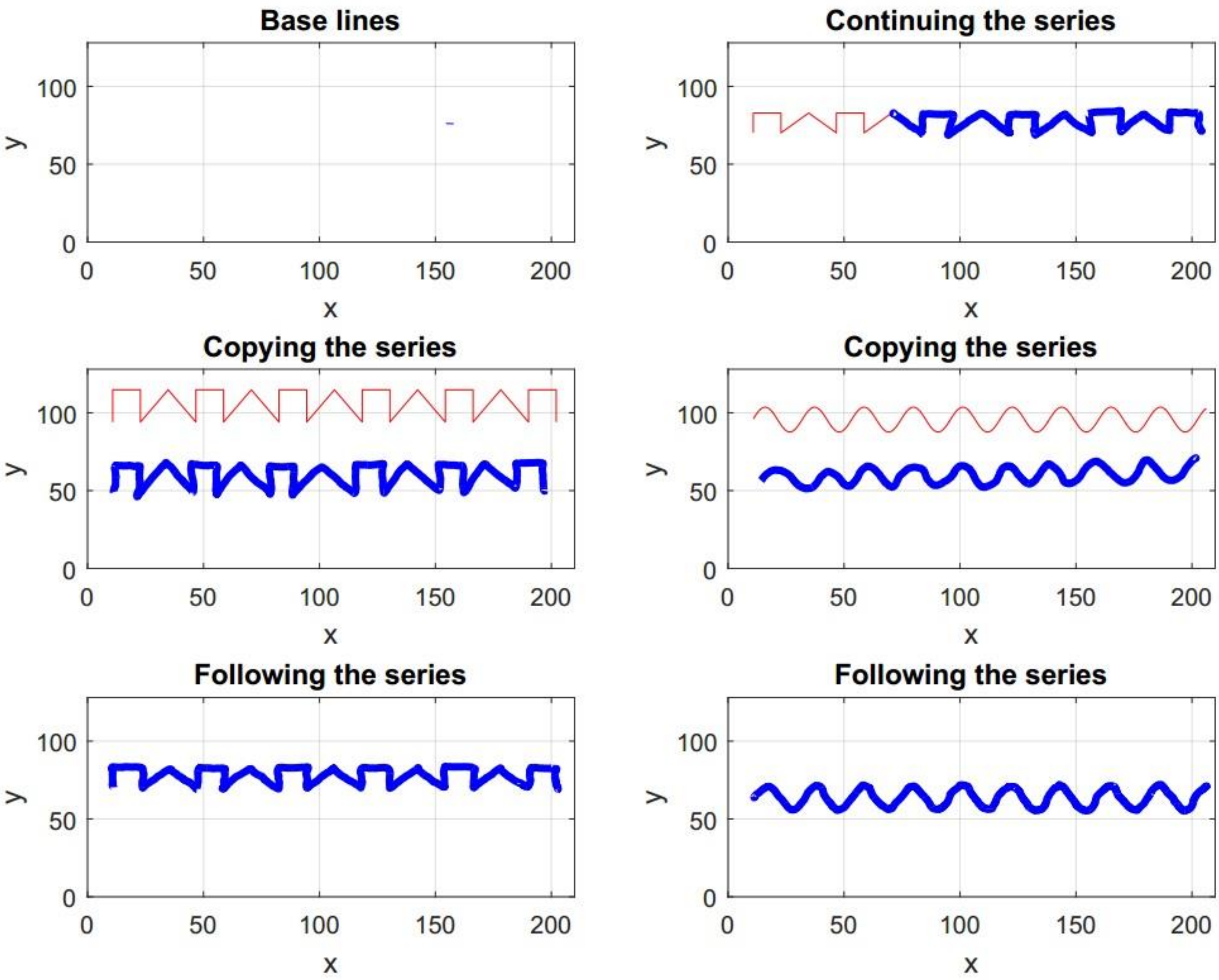

Figure 7 Example of decently completed tasks by a representative of the diagnosed with Parkinson's disease group

First observations showed that the groups of subjects differ in regards to deviation; the variance in PD group was noticeably larger. The subjects in the PD group have showed very contrasting results. This indicates that the elements of compared groups of samples are very spread out from the mean and possibly large portion of the elements are contained in the overlapping area of the means. As a result, only four kinematic parameters were observed to produce a differentiation of handwriting between the compared groups; only these parameters are shown.

The first test, for which significant in regards to diagnostic problem kinematic parameters were statistically evaluated, was continuing the series test. The number of the strokes S_{nr} was the first feature that could be identified as indicative of PD handwriting for this test with the mean amount of strokes the drawing should be performed with 2.02, which can be interpreted as a rule, that if a person completes the continuing the series task in two strokes then the probability of him not having Parkinson's disease is 5%. Second feature turned out to be one of the motion mass features – velocity mass V_s. The results of the t-test on the selected four kinematic features acquired from analysing the parameters of handwriting during continuing the series test is shown in Table 1.

Table 1 Results of the t-test on the kinematic features during completion of continuing the series test.

Continuing the series	V_s	P_s	S_{nr}	DTW
h	*1*	0	*1*	–
p	*0.08895084359*	0.1052256646	*0.05493742596*	–
tstat	*-1.779660988*	1.689612062	*2.027115044*	–

Unfortunately none of the selected kinematic features turned to be reliable enough to be used as indicators of handwriting of compared groups in the second Luria alternating series test – copying the series. As one can conclude from the data in Table 2, observing these features does not yield enough evidence to determine the type (parkinsonian or not) of handwriting with any degree of certainty from examining the result of drawing a polyline. Probable reason behind this might be that the testee is supposed to draw the complex line completely on their own relying only on the weak visual stimuli, therefore the resulting drawing is very individual, hard to normalise for a more efficient analysis.

Table 2 Results of the t-test on the kinematic features during completion of copying the series test while drawing the polyline.

Copying the series, polyline	V_s	P_s	S_{nr}	DTW
h	0	0	0	–
p	0.2782502685	0.262355384	0.3721851004	–
tstat	-1.111744169	1.15033857	0.9109700879	–

The results of statistical analysis of the relevance of the selected features to the diagnostic methods within copying the series test on a sinusoidal line are shown in the Table 3. One can observe that the selected parameters in this instance are more likely to help determine that the examinee does not have Parkinson's disease than otherwise. However, the probabilities and therefore confidence levels are not strong enough to be of practical use.

Table 3 Results of the t-test on the kinematic features during completion of copying the series test while drawing the sine wave line.

Copying the series, sinusoidal line	V_s	P_s	S_{nr}	*DTW*
h	0	0	0	0
p	0.8935571112	0.7624970008	0.7667879118	0.5751494684
tstat	-0.1353612852	-0.3059794662	-0.3002730997	0.5689554606

The third Luria alternating series test produced considerably better results as one can see in Table 4 and Table 5. Observations show that such motion mass features as velocity mass V_s and pressure mass P_s can be successfully used on tracing the series test when the subtask with polyline is completed to determine whether it is likely that the testee has Parkinson's disease. If the velocity mass is close to -1.9 then with probability of 7% one can say that the testee does not have Parkinson's and pressure mass close to 1.77 would conclude the same with probability level of 9%.

Table 4 Results of the t-test on the kinematic features during completion of tracing the series test while drawing the polyline.

Tracing the series, polyline	V_s	P_s	S_{nr}	*DTW*
h	*1*	*1*	0	–
p	*0.07070243798*	*0.08989757029*	0.1435510059	–
tstat	*-1.899396819*	*1.774050819*	1.516819889	–

In case of a sinusoidal line for the third type of the testing the DTW value showed the most promising levels of probability – chance that one would be correct when determining that testee does not have Parkinson's in this instance when the calculated DTW is close to 2.34 would be only 3%. Other evaluated features did not show any significant levels of probability, therefor are of no practical interest at this point of the research.

Table 5 Results of the t-test on the kinematic features during completion of tracing the series test while drawing the sine wave line.

Tracing the series, sinusoidal line	V_s	P_s	S_{nr}	DTW
h	0	0	0	*1*
p	0.4669990034	0.3116216315	0.2818829948	*0.02875666111*
tstat	-0.7402104578	1.03563726	1.103150764	*2.340075226*

There were attempts to introduce other kinematic features, like jerk – the rate with which the acceleration of the tip of the stylus changes with time – but they showed no discreteness, therefore were not included in the final assessed set.

7 Discussion

The problems addressed in the current thesis were supported by conducting testing with real patients, but small amount of the subjects makes this a pilot research. Nonetheless, this research shows the usability of motion mass parameters in diagnostic questions related to Parkinson's disease. Not many handwriting features yielded the desired distinctiveness, but a usable subset was discovered. As the course of statistical evaluation showed, the weak levels of distinctiveness are due to the small tested sample population. Subsequent testing with new subjects on the same tests should increase the set of diagnostically reliable features, thus improving the usability of created diagnostic aid tool.

The analysis of the results proved that currently employed method has its flaws. Firstly, the evaluation is done on the kinematic parameters that are derived from raw data; the pre-processing of data is minimal. For example, current pre-processing does not include analysis and correction of logical mistakes – the testee occasionally tries to correct a mistake by redrawing a portion of the line correctly atop the already drawn inaccuracy.

The quantitative analysis employed for the purpose of the current work was limited to statistical method of evaluation, which is a sure way to initially determine distinctiveness. Initial results are important as they support the confidence in selected methods and chosen course of the research. At the moment, it is obvious that currently used methodology is viable and is worth to be investigated further. One of the next possible courses of studies is the use of machine learning techniques in evaluation of distinctiveness of the found kinematic parameters subset. The testing results of the current study showed that the compared populations (PDs and healthy controls) most likely to have certain similarities in executing a drawing task despite the presence of motor system disorders. Machine learning could be able to create more complex decision boundaries than the mean value use in statistics, therefore could be able to distinguish the compared groups that are similar in many ways.

The application created for the testing purposes was relatively stable, but certain improvements are desired to resolve the weaknesses found during the practical use. Minor changes concerning the graphical user interface are already in development, but bigger alterations related to implementation of analytical analysis of received drawing data in real-time requires further analysis and implementation.

The most important achievement of this thesis is the fully developed and tested framework that is designed to capture handwriting, evaluate its parameters, analyse the significance of each parameter and use gathered sample data to create rules associating the parameters of handwriting with possibility to make a conclusive diagnosis regarding Parkinson's disease or other disease that affects human's fine motor system. Alternative use of this framework includes evaluating the progress of development of motor skill in younger population or in those undergoing rehabilitation therapy.

8 Summary

The main purpose of this thesis was to evaluate the quantitative features of kinematic parameters observed during Luria's alternating series tests and determine their goodness for a diagnostic method for Parkinson's disease. The testing method was implemented as an application for a tablet computer. The analysis of the parameters was done based on the results from testing real patients diagnosed with Parkinson's disease and healthy controls and employed statistical method of assessment.

Overall results of the thesis show that problems stated were addressed and goals successfully achieved, but they leave room for improvement. The kinematic parameters involved in distinguishing Parkinson's disease were estimated and analysed, as well as the results of testing viewed from the motion planning process angle. Possible future studies should lie in the area of improving the employed methodology – other possible methods to be evaluated, more subjects to be involved in testing, issues arising from gradually increasing test population and data to be resolved.

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Appendix A – Testing application structure

The structure of the application has changed drastically during development, but the version that was used in conducting the testing has three main activities: capturing initial personal data, choosing the exercise and completing the exercise. It is assumed that the user of the application possesses basic knowledge of the possible components of a tablet application, for example is able to recognize standard interactive button, a text field and is capable of entering text into the text field either by writing it with the stylus or typing on the virtual keyboard. Interaction with the application is possible with touch motions both equipped with a stylus and without the help of one. Since the expected users include people with cognitive and motor skill disorders, the graphical user interface is maintained simple and minimalistic – only absolutely necessary menu items are displayed, the size of the elements of the interface is enlarged to ensure that instructions and labels are clearly visible, the distance between buttons was increased to reduce the chance of pressing a different button by mistake, no animation of the change between the screens was introduced in order to exclude unnecessary confusion.

The first main activity of the application, capturing initial person data, is to be initiated by the practitioner conducting the testing. Practitioner should specify the code name of the testee, this name will appear in the output data file. In the interest of diversity of the results exercises were to be completed with both dominant and nondominant hand, therefore a switch capturing which hand would be used in this instance is present on this activity. Considering the fact that more than 80% of the world population is right–handed the switch by default is set to the right–hand position, the testee is expected to perform the exercises holding the stylus in their right hand first. Once these two parameters are specified further steps are done by the testee. The pressure of the drawing motion is measured during the exercises and to ensure correct usage of that parameter in further calculations, it is important to refer to base pressure. The base pressure is considered a part of initial data, therefore it is calculated within current activity: the testee is asked to draw three random lines, the data from the registered motion events is saved into a file, the name of which consists of testee code name, drawing hand flag – “r” for right and “l” for left – current day, current month and current year. On the occasion that the same code name is used several times during one particular day the data about all of the registered events related to capturing pressure with the purpose of estimating the base pressure would be saved into the same file, the newest information being added to the ending of the file. As soon as the process of drawing three random lines is finished the testee should proceed onto the next activity. The code name and the hand flag are both transferred within the application internally into the next activity.

The second activity is dedicated to choosing an exercise to execute. It is important that every testee completes a full set of the exercises presented in order to provide a full set of data required for the identification of motion skill disorders characterised by different levels of motion planning and execution. The list of the exercises contains the following:

- Writing numbers from 0 to 9
- Continuing drawing a line, following the sample given
- Drawing a line atop the given example
- Drawing a line copying the given example
- Finding and tracing every contour visible

It has been noted by the practitioners previously that in certain cases an enlarged version of the line provided as an example has to be displayed, therefore a switch allowing to choose between the smaller and enlarged version of the example lines is provided on this activity. By default the switch is disabled, offering the smaller version of the example, because the occurrence of such necessity is rather rare.

For a drawing exercise it is important for the testee to perceive visually the result of their actions in real time, therefore as the motion event is captured it is represented on the screen, i.e. drawn at the exact place it was captured. However, in order to smoothen the flow of the line and avoid overloading the display driver of the device a touch tolerance for the drawing process has been introduced. In the latest version of the application it is predefined to be 4 pixels, representing that only when either x axis or y axis position value differs from the previous drawn point by 4 pixels the new point is drawn on the screen or a straight line connecting these two points is painted. This tolerance value has been chosen by the author through testing various other values, relying on the personal judgement, due to the visual perception being a very subjective matter.

Third main activity is represented by several sub activities conjoined by their structure, the difference is only in the initial setup of the example each exercise is built around. Upon initialization depending on the type of the exercise either a pattern line is calculated and drawn or a set of contours is retrieved from a collection of input files and outlined on the screen or a blank canvas is presented to the testee. Additionally, an output file that would be used to save registered motions' data is created. In order to ensure that a different file is created for each and every instance of the exercise conducted even in such cases when same code name is used several times during a day to complete same type of an exercise the name of the file consists of the code name of the testee, a tag for the type of the exercise, for example "numbers" in case of the first exercise, the hand flag and the time when the exercise was started: the current second, minute, hour, day, month, and year. Only two types of lines are used as patterns in the exercises – a sine wave line and a polyline formed by alternating square and triangular serrations. The height and width of a sample segment of both lines depends on the height and width of the display screen of the device as well as the flag of the rescaling acquired from the previous activity. The pattern lines are drawn as initial example for the second, third and fourth exercises; a section consisting of five segments (one for square and two for the triangular part) is drawn in the second exercise; in the third and fourth exercises the lines are drawn to fully fill the width of the screen, leaving indentation on both left and right side.

Appendix B – Detailed clinical information about the PD testing subjects.

Table 6 Detailed clinical information about the PDs. The parameters displayed are age in years, sex female (F) or male (M), the side of the body in which the early symptoms revealed themselves – right (r) or left (l) and the number of years that has passed since

patient	***age***	***sex***	***disease onset side***	***years since diagnosis***
PD01	74	F	r	4
PD02	51	F	r, both	1
PD03	63	F	l, both	1
PD04	67	M	l	7
PD05	69	M	l	2
PD06	72	F	r	2
PD07	82	F	r	4
PD08	80	M	r	6
PD09	57	M	r	6
PD10	73	M	l	11
PD11	80	M	l	8
PD12	84	F	r	12
PD13	75	M	r	8
PD14	78	F	r	8