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COMPUTERISED ASSESSMENT OF GRAPHOMOTOR AND HANDWRITING DISABILITIES IN SUBJECTS WITH NEURODEGENERATIVE AND NEURODEVELOPMENTAL DISORDERS

VYSOKÉ UČENÍ TECHNICKÉ V BRNĚ
Fakulta elektrotechniky a komunikačních technologií
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POČÍTAČOVÉ HODNOCENÍ GRAFOMOTORICKÝCH OBTÍŽÍ A OBTÍŽÍ S PSANÍM U OSOB S NEURODEGENERATIVNÍMI ONEMOCNĚNÍMI A NEUROVÝVOJOVÝMI PORUCHAMI

SHORTENED VERSION OF HABILITATION THESIS

VYSOKÉ UČENÍ TECHNICKÉ V BRNĚ
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Author bio

In 2014 Jiří Mekyska received a PhD degree at the Faculty of Electrical Engineering and Communication, Brno University of Technology. His dissertation thesis focused on the paraclinical assessment of neurodegenerative disorders utilising digital voice biomarkers. Since his graduation, he works as a researcher and the head of the Brain Diseases Analysis Laboratory (BDALab) at the Department of Telecommunications. In the frame of this position, he teaches, supervises pre-gradual/doctoral students, leads BDALab and works as a researcher and a principal investigator/co-investigator of research projects whose outcomes were published at conferences and in top-tier journals.

From a pedagogical point of view, he currently teaches four subjects (in the field of digital signal processing), one for students of the ERASMUS+ program and one for a double-degree program. He guarantees one of the subjects. He is the author/co-author of a number of teaching materials, such as presentations, online lectures, interactive demos, etc. He has been the supervisor of four doctoral, seventeen master's and fourteen bachelor's theses, which have been successfully defended. He currently leads four doctoral students. In addition, he led five internships for foreign students. He has given a number of invited lectures at prestigious institutes and universities (e.g. at the Massachusetts Institute of Technology, Johns Hopkins University or the University of Southern California). During the last two academic years, he placed in the top 10 teachers of the faculty.

In terms of science, he is the author of 100 works indexed by the Web of Science database (890 citations without self-citations, h-index 19). He is the author of a number of articles published in Q1 journals (some of them are in the first decile). He is/was the principal investigator/co-investigator of 5 research projects (Czech Science Foundation, Ministry of Health of the Czech Republic, Technology Agency of the Czech Republic, Ministry of Education, Youth and Sports of the Czech Republic). He also participated in another sixteen projects. He leads a scientific team (BDALab), which has nine members and which has achieved globally recognized results in the field of biomedical signal processing, neuroscience and psychology. In this field, he cooperates with many national and international universities, research institutes and hospitals (St. Anne's University Hospital in Brno, Central European Institute of Technology, Czech Academy of Sciences, Pompeu Fabra University, University of Arizona, University of Edinburgh, University of Haifa, Taipei Veterans General Hospital, etc.).

He is a member of various panels and expert groups. For example, he is currently the chairman of panel P103 (Cybernetics, Artificial Intelligence and Information Processing) of the Czech Science Foundation or a member of the Science and Innovation Panel at the Innovative Health Initiative.

Introduction

Handwriting is a complex perceptual-motor skill composed of a coordinated combination of fine graphomotor movements, visual–perceptual abilities, visual–motor coordination, motor planning and execution, kinesthetic feedback, and orthographic coding [1]. These underpinnings of drawing and consequently handwriting abilities are usually considered as graphomotor skills (GS) [2], and should be mastered at the age of 8–9. When a person suffers from a neurodevelopmental (e.g. developmental dysgraphia) or neurodegenerative (e.g. Parkinson's disease) disorder, she/he is very likely to exhibit graphomotor disabilities (GD) such as graphomotor production deficits, motor-memory dysfunction, motor feedback difficulties, etc. [3], leading to various drawing and handwriting difficulties (HD). Such difficulties can have serious consequences, and can greatly affect a person's every-day life starting with slow and less-legible handwriting, lower self-esteem, poor emotional well-being, as well as problematic communication and social interaction [4]. To be able to introduce a timely and effective treatment/therapy and to improve a person's quality of life as much as possible, neurologists, psychologists, special education counselors, and other experts need a theory-based, proven and robust framework that will enable them to diagnose GD and HD in an objective and complex way with minimum manual intervention, cost and time constraints [5].

Nowadays, the most promising approach into robust, objective, and computerised assessment of GD/HD utilises various signals describing the process/product of handwriting/drawing acquired by a digitizing tablet [6]–[9]. Such signals represent movement of a digitizing stylus (pen) on horizontal and vertical axis, pressure exert on the surface of a digitizer, tilt and azimuth, acquired with respect to a specific series of timestamps forming a collection of time-series describing the process of handwriting/drawing from its beginning to the end (referred to as online handwriting) [10]. In addition, modern digitizers have the ability to record not only the movement of a pen on the surface of a digitizer, but also the movement above the surface (in-air movement) [11]. As shown in a variety of studies [12], [13], online handwriting provides us with the capability of going beyond the limitations of human perception and to characterize the handwriting/drawing process in terms of its temporal, spatial, kinematic, and dynamic features.

In recent years, online handwriting has been advantageously used in a variety of research studies focusing on identification and assessment of GD/HD in children experiencing developmental dysgraphia (DD) [9], [14], or in adults suffering from Parkinson's disease (PD), Alzheimer's disease (AD), essential tremor [6]–[8], [15], etc. Although the significant potential of this technique has been proved, the field is still relatively unexplored and has many knowledge gaps that should be bridged before we adopt this technology in practice. This compilation thesis summarises 34 works ([10]–[13], [15]–[44]) with the aim to go beyond the state of the art and to introduce new knowledge and directions in the computerised assessment of GD/HD facilitating objective diagnosis and monitoring of neurodegenerative and neurodevelopmental disorders.

1 Knowledge gaps

1.1 Graphomotor and handwriting disabilities in patients with PD

Parkinson's disease (PD) is a chronic idiopathic disorder characterized by a pathophysiological process of α-synuclein accumulation leading to the formation of Lewy bodies and Lewy neurites resulting in loss/degeneration of dopaminergic neurons in the substancia nigra pars compacta [45]–[47]. It is the second most frequent neurodegenerative disorder, with the prevalence rate estimated to be approximately 2.0 % for people aged over 65 years [48]. To date, the gradual deficiency of dopaminergic neurons in the basal ganglia has been recognized as a major cause of parkinsonian symptoms [49]. In addition to a large variety of other motor symptoms, such as tremor at rest [50], progressive bradykinesia [51], muscular rigidity [50], postural instability [52] and hypokinetic dysarthria [53], one of the prominent and early markers of PD is so-called Parkinson's disease dysgraphia (PDD) [3], [54]–[56].

PDD is a term describing a spectrum of neuromuscular difficulties, including motor-memory dysfunction (problems combining memory input with motor output), graphomotor production deficits (poor muscle coordination), motor feedback difficulties (overactivation of certain muscles and joints during handwriting as well as problems tracking the location of the pen's tip) and others. These cause a variety of HD manifesting as dysfluent, shaky, slow, and less readable handwriting; a progressive decrease in letter amplitude or width, namely, micrographia [3], [57], [58]; etc. Hence, PDD has serious consequences that significantly affect a person's everyday life, starting with slow and less legible handwriting and often progressing to lower self-esteem, poor emotional well-being, problematic communication and social interaction, and many others.

To introduce a timely and effective treatment to improve a patient's quality of life as much as possible, neurologists and other experts could benefit from the computer-aided assessment of PDD. We entered this field of science more than ten years ago when we reviewed some pioneering studies and identified the following knowledge gaps:

Knowledge gap 1 Although neurologists considered micrographia to be the main alteration of PD handwriting, just a few studies explored the presence of other manifestations.

Knowledge gap 2 The spiral drawing and spring task was used as a gold standard for the assessment of PDD. However, the potential of more complex (handwriting) tasks was not fully investigated.

Knowledge gap 3 Although the computer-aided diagnosis of PDD was not a new technology, it was still in its beginning, classification models had poor performance,

there were almost no studies dealing with the rating of PD severity, no studies utilising multilingual datasets, and no studies focusing on the prodromal diagnosis.

1.2 Graphomotor and handwriting disabilities in children with DD

A child starts to develop GS [59], [60] and form the foundation of drawing [61] and consequently, handwriting abilities [62] around the age of 6. These skills should be mastered at the age of 8–9 and should result in automated, legible, well-coordinated and fast-paced handwriting [5], [63], which is used for quantification of a child's timely maturation and integration of linguistic, psycho-motor and mental abilities, and readiness for education [64]. Although a child is intensively exposed to modern technologies that bring new ways of communication, education and self-expression, handwriting takes 30–60 % of a child's school-time [65] and is still an important part of her/his life [60].

Proper acquisition of handwriting is crucial for a child's academic success and self-esteem [66]. However, 10–30 % of children experience an impairment of the neuro-muscular system manifested in GD, such as graphomotor production deficits (poor muscle coordination, less precise graphomotor movements, and unusual pen-grip), motor-memory dysfunction (problems combining memory input with motor output), motor feedback difficulties (problems tracking the location of the pen's tip and over-activation of certain muscles and joints during handwriting), etc. [59], [60] GD/HD are tightly linked with the developmental dysgraphia (DD), which belongs to the category of specific learning disabilities according to DSM V [67], and to the category of specific developmental disorders of scholastic skills according to ICD-10 [68]. DD could have serious pedagogical and psychological consequences such as lack of motivation to write, poor emotional well-being, bad attitude and behaviour, communication and social interaction problems, etc. [60], [69]–[71]

Nowadays, GD/HD in children with DD are diagnosed by occupational therapists and/or special educational counsellors, who visually assess the handwriting product and process, and score it in several domains using a questionnaire (rating scale). Some representatives of these questionnaires could be the Concise Assessment Scale for Children's Handwriting (Brave Handwriting Kinder) (BHK) [72], Handwriting Proficiency Screening Questionnaire (HPSQ) [73] or Handwriting Proficiency Screening Questionnaire for Children (HPSQ–C) [74]. Unfortunately, assessment based on these questionnaires is very subjective, depends on the rater's experience, perceptual abilities, and is subject to inter-rater variability [75], [76]. Due to the above-mentioned limitations, many children are undiagnosed or badly diagnosed, which has a detrimental impact on their quality of life.

The limitations could be effectively addressed by the computerised analysis of online handwriting. We entered this field of science in 2016 and identified the following knowledge gaps:

Knowledge gap 4 Most of the available studies reported some conclusions based on the quantitative analysis, but almost no studies investigated, whether mathematical modelling (e.g. employing machine learning) of handwriting features could support the diagnosis or rating of GD/HD.

Knowledge gap 5 We have not identified any study comparing different graphomotor tasks in supportive GD diagnosis.

Knowledge gap 6 There was no scale enabling objective and fully automatic assessment of manifestations associated with GD/HD.

1.3 Computerised assessment of GD/HD

In the concept of computerised assessment (see Section 3.1), GD/HD are usually quantified in terms of features (measures) that could be split into several categories: temporal (e.g. duration), spatial (e.g. width and length of the product of handwriting), kinematic (e.g. velocity and acceleration), dynamic (e.g. pressure or pen tilt), and other (e.g. the number of pen stops) [6]–[9], [77]. For a more detailed review of these parameters, we refer to Section 3.3. The advantage of the features is that they are usually easily interpretable, and they could be linked with specific manifestations of GD/HD.

Nonetheless, from the signal processing point of view, handwriting is time series that is the result of several interacting physiological mechanisms. This kind of signal contains complex fluctuations, which could provide information related to underlying processes and states of the physiological system. Disfluent movement, irregular muscle contractions, and cognitive deficits introduce randomness to handwriting and increase its complexity (e.g., add tremor, more handwriting interruptions, sudden changes in velocity, etc.). However, this complexity is difficult to be analysed using only conventional parameters. To better quantify the hidden complexities, an advanced and more sophisticated apparatus is needed.

Knowledge gap 7 Most of the existing online handwriting parameterisation algorithms were adopted from the field of biometrics and were not designed to quantify GD/HD.

Finally, until 2012, almost no attention was paid to the potential of in-air movement analysis. In that year, Sesa-Nogueras et al. observed, that information contained in the in-air movement could be advantageously used in biometric recognition [78]. This study opened new questions related to the utilisation of the in-air movement in the field of GD/HD assessment.

Knowledge gap 8 There was no research exploring how is the in-air movement linked with physiological processes and whether it contributes to more accurate diagnosis of neurodegenerative and neurodevelopmental disorders.

2 Aims of the thesis

Concerning the knowledge gaps mentioned in Section 1, the main goal of this habilitation thesis is to progress beyond the state of the art, and to **research new approaches to the computerised assessment of GD/HD that would facilitate objective diagnosis and monitoring of neurodegenerative/neurodevelopmental disorders**, more specifically, the thesis has the following aims.

Aim 1 Explore the impact of in-air movement analysis on diagnostic accuracy.

Aim 2 Introduce new online handwriting parameterisation techniques enabling advanced quantification of GD/HD.

Aim 3 Identify what tasks are suitable for assessment of drawing/handwriting alterations in PD/DD.

Aim 4 Evaluate the researched methodology in the computerised assessment of PDD.

Aim 5 Evaluate the researched methodology in the computerised assessment of DD.

3 General methods

3.1 Concept of the computerised assessment of GD/HD

The general concept of the computerised assessment of GD/HD in subjects with neurodegenerative/neurodevelopmental disorders is illustrated in Figure 3.1, and described below:

1. Based on an acquisition protocol (templates and instructions) a subject performs a set of drawing or handwriting tasks using a stylus and a digitizer (tablet).
2. Signals (time series) recorded by the tablet are consequently parametrized, and the resulting vector/matrix of features is extended by demographic/clinical data such as age, gender, information about medication, etc.
3. To get some first insight into data, we perform visualisations (e.g. kernel density estimation, violin graphs) and exploratory statistical analysis (e.g. correlation analysis or parametric/non-parametric tests). Usually, we also model the data employing machine learning algorithms, e.g. logistic regression of XGBoost.
4. The machine learning models could be used for supportive diagnosis (e.g. diagnosis of PDD), or for a rating of severity of GD/HD. The performance of a subject could be also followed in time (e.g. to monitor the effect of a therapy).

Each of the steps is in more detail explained in the following sections.

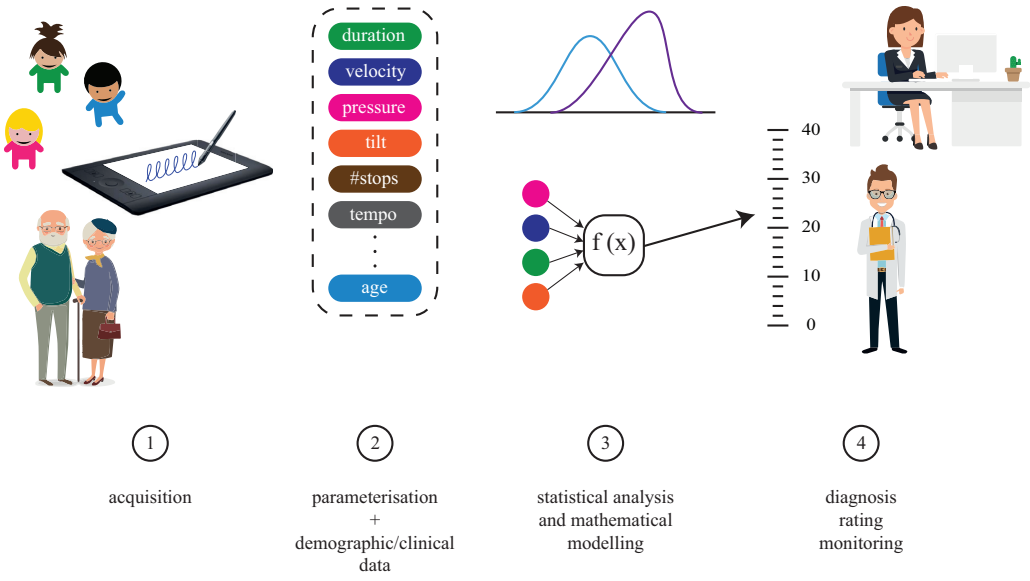

Fig. 3.1: Concept of the computerised assessment of GD/HD

3.2 Datasets and acquisition protocols

Through our research, we enrolled several hundreds of participants who performed specifically designed drawing/handwriting tasks on an A4 paper that was laid down and fixed to a digitizing tablet Wacom Intuos 4 M or Wacom Intuos Pro L (sampling frequency $f_s = 130\,\text{Hz}$). A special Wacom inking pen was used to provide immediate visual feedback, i.e., simulating classical pen-and-paper writing/drawing. Before the acquisition, the participants were seated in a comfortable way and had some time to get familiar with the hardware. The following datasets were acquired:

- **PaHaW** – The dataset contains 75 Czech subjects (37 PD patients and 38 age- and gender-matched healthy controls – HC) [34]. The participants were enrolled at the First Department of Neurology, St. Anne's University Hospital in Brno, Czech Republic. They are associated with information about gender, age, PD duration, UPDRS (Unified Parkinson's Disease Rating Scale), part V – modified Hoehn and Yahr staging score [79], and levodopa equivalent daily dose (LED) [80].
  The participants performed 9 tasks following the template available in Figure 3.2: TSK1 – Archimedean spiral; TSK2 – overlapped circles; TSK3 – five graphemes "l"; TSK4 – five bigrams "le"; TSK5 – five trigrams "les"; TSK6 – two words "lektorka"; TSK7 – two words "porovnat"; TSK8 – one word "nepopadnout"; and TSK9 – one sentence "Tramvaj dnes už nepojede." The dataset is freely available for a scientific community [34], and until now, it is probably the most popular database of online handwriting collected in PD patients.
- **CoBeN** – This is a multilingual dataset containing 59 Czech participants (19 PD patients and 40 HC) enrolled at the Central European Institute of Technology, 21 US participants (9 PD patients and 12 HC) enrolled at the University of Arizona, and 21 Hungarian participants (9 PD patients and 12 HC) enrolled at the University of Szeged [16]. They are associated with information about gender, age, PD duration, UPDRS part III – motor part score [79], and LED.
  The Czech participants performed 8 tasks following the template available in Figure 3.3: TSK1 – five graphemes "l"; TSK2 – a task, where a participant has to horizontally connect two dots; TSK3 – a signature performed with opened eyes; TSK4 – a signature performed with closed eyes; TSK5 – one sentence "Tramvaj dnes už nepojede."; TSK6 – one sentence "Máma a táta jeli dvakrát na dovolenou."; TSK7 – Archimedean spiral; and TSK8 – the pentagon copy test [19]. Except for the TSK5 and TSK6, the US and Hungarian participants performed the same tasks. Sentences were not the same, nevertheless, they contained the same number of letters.
- **preLBD** – We enrolled 39 subjects diagnosed with possible or probable MCI (based on the scores of the MoCA – Montreal Cognitive Assessment [81] and based on the CCB – Complex Cognitive Battery (see the explanation below), who were simultaneously

diagnosed with possible or probable MCI-LB (i.e. mild cognitive impairment with Lewy bodies) based on the criteria published by McKeith et al. [82]. In this group, 21 subjects also had more than 50 % probability of developing PD (calculated following the MDS criteria published in [48]). In addition, we enrolled 7 subjects without possible/probable MCI-LB, but still with more than 50 % probability of developing PD. The participants performed the same protocol as in the CoBeN dataset (see Figure 3.3).
CCB was used to evaluate four cognitive domains: 1) memory (The Brief Visuospatial memory test–revised [83], Philadelphia Verbal Learning Test [84]); 2) attention (Wechsler Adult Intelligence Scale-III: Letter-Number Sequencing, Digit Symbol Substitution [85]); 3) executive functions (Semantic and phonemic verbal fluency [86], Picture arrangement test [85]); and 4) visuospatial functions (Judgment of Line Orientation [87]). The cognitive domain z-scores were computed as the average z-scores of the tests included in the particular domain.

- **DYS_CZ_001** – The database contains 65 Czech children (33 diagnosed with DD and 32 intact) attending the 3rd or 4th grade of an elementary school [27]. The children performed three tasks using cursive letters: TSK1 – the children wrote all letters of the Czech alphabet [29]; TSK2 – a copy of a paragraph [27]; and TSK3 – the children wrote several sentences on a random topic. Besides the gender, age, and grade, the children were also associated with the scores of HPSQ and HPSQ–C.

- **DYS_CZ_002** – The database consists of 353 children from the final grade of kindergarten to the fourth grade of elementary schools. Participants were enrolled in 8 kindergartens, 14 elementary schools, and 2 counselling centres in the Czech Republic, covering 62 children with GD/HD and 291 intact children. The database includes sociodemographic data, several diagnostic scores, and the HPSQ–C score.
  All children were asked to perform a protocol (see Figure 3.4) consisting of 7 elementary graphomotor tasks (TSK1 – Archimedean spiral (approximately 15 cm in height); TSK2 – half-sized version of TSK1; TSK3 – connected loops (the spring task); TSK4 – flipped version of TSK3; TSK5 – saw; TSK6 – rainbow; TSK7 – a combination of TSK3 and TSK4) [12], [21], [26], and one paragraph copy task, whose content was depending on the grade of a child. Regarding the graphomotor part of the protocol, it was designed in a way so that the tasks cover the building blocks of letters used in the Latin alphabet.

Besides the above-mentioned datasets, in some studies, we also analysed databases of our partners, e.g. the Colombian HWUDEA [16], a database of patients with AD [10], [42], or the BIOSECURID database [38].

Regarding our databases, all subjects used their dominant hand. None of the participants had a history or presence of any psychiatric symptoms or any disease affecting the central nervous system (other than PD in the PD cohort). All PD patients were well compensated on their stable dopaminergic medication and without major motor fluctuations or dyskinesias (they were examined while on their regular dopaminergic medication (ON state) approximately

1 h after the L-dopa dose). All subjects signed an informed consent form (in the datasets of children, the form was signed by parents). All studies were approved by the relevant local ethics committees.

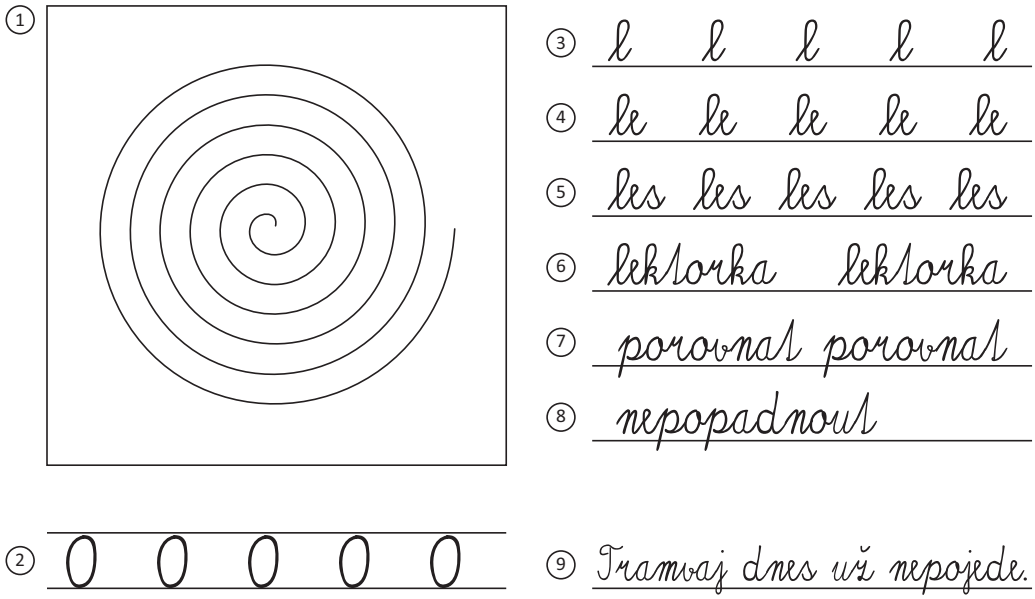

Fig. 3.2: Acquisition protocol of the PaHaW database

3.3 Baseline parameters

The tablets, that we used, recorded the following time series/signals: x and y position ($x[n]$ and $y[n]$); timestamp ($t[n]$); a binary variable ($b[n]$), being 0 for in-air movement (i.e. movement of pen tip up to 1.5 cm above the tablet's surface) and 1 for on-surface movement (i.e. movement of pen tip on the paper), respectively; pressure exerted on the tablet's surface during writing ($p[n]$); pen tilt ($a[n]$); azimuth ($az[n]$).

In most studies, the signals were parameterised by employing baseline features that are frequently used in the field of neurodegenerative and neurodevelopmental disorders [6]–[9], [77], [88], [89]. These features could be split into several groups:

1. temporal – duration of writing, ratio of the on-surface/in-air duration, duration of strokes, and ratio of the on-surface/in-air stroke duration,
2. spatial – width, height, and length of the whole product as well as those of its individual strokes, i.e., stroke width, height, and length,
3. kinematic – velocity, angular velocity, acceleration, and jerk,

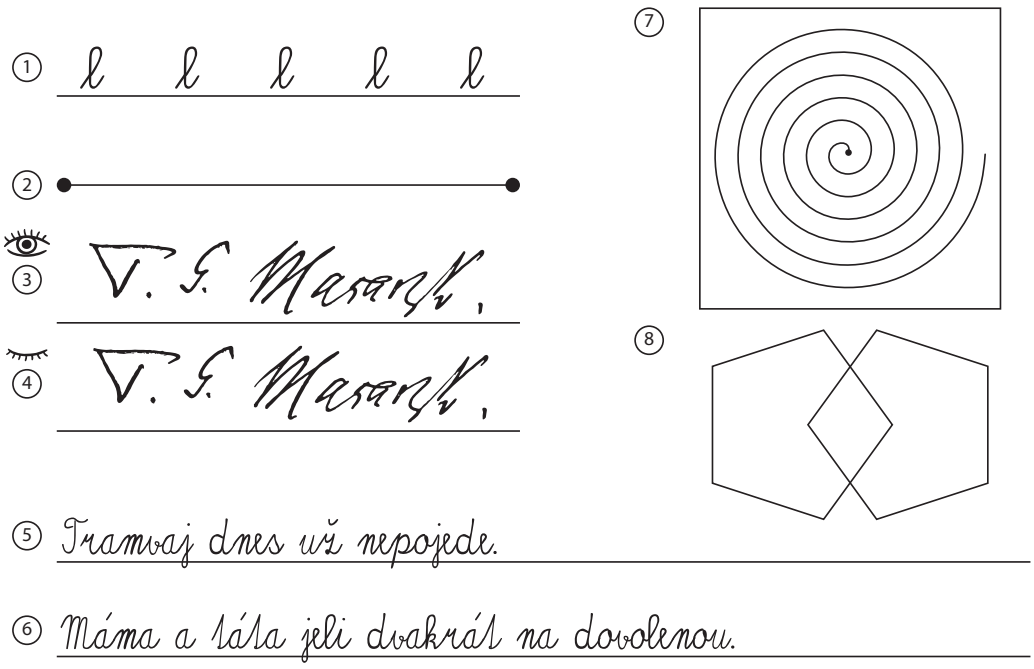

Fig. 3.3: Czech version of the acquisition protocol of the CoBeN database

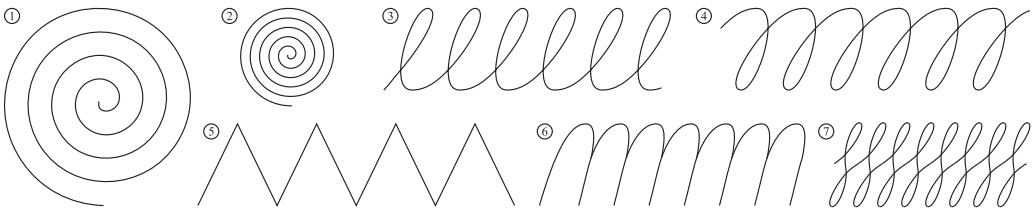

Fig. 3.4: A part of the acquisition protocol of the DYS_CZ_002 database

4. dynamic – pressure, tilt, and azimuth,
5. spiral-specific – degree of spiral drawing severity, mean drawing speed of spiral, second-order smoothness of spiral, spiral precision index, spiral tightness, variability of spiral width, and first-order zero-crossing rate of spiral,
6. loops/saw/rainbow-specific – local minima, local maxima, distance between neighbouring local maxima, velocity at local maxima, width of teeth (on a horizontal line going through 95 % of a particular tooth height), normalised width of teeth (normalised by a mean distance between local minima), and distance between neighbour bows (on a horizontal line going through 50 % of the first of them),
7. other – number of interruptions or pen elevations, relative number of interruptions, num-

ber of pen stops, tempo (number of strokes normalised by duration), number of on-surface interstroke intersections, relative number of on-surface interstroke intersections, number of on-surface intrastroke intersections, relative number of on-surface intrastroke intersections, total number of on-surface intrastroke intersections, relative total number of on-surface intrastroke intersections, relative number of changes in velocity profile, relative number of changes in pressure profile, relative number of changes in tilt profile, and relative number of changes in azimuth profile.

The spatial, temporal and kinematic features were extracted from both the on-surface and in-air movements. In addition, the kinematic features were also analyzed for the horizontal and vertical projections of the movements. Features that were represented by time series were transformed into scalar values using statistics such as median, interquartile range (iqr), non-parametric coefficient of variation (defined as iqr/median), 95th percentile, slope by applying the Theil–Sen estimator, etc.

3.4 Statistical analysis and mathematical modelling

To get some first insight into the data, we typically plotted kernel density estimation, violin graphs, or correlation matrices. When necessary, we regressed out the effect of confounding factors (e.g. age or level of medication). Since the features usually did not have a normal distribution (as assessed by e.g. the Kolmogorov-Smirnov test), during the exploratory analysis, we usually applied the Mann-Whitney U test, Wilcoxon signed-rank test, and/or Pearson's correlation with the level of significance $\alpha = 0.05$. In the case of a higher number of features, we also applied the false discovery rate correction.

Depending on a specific application, we modelled the feature space utilising e.g. logistic regression, classification and regression trees, bagging and gradient boosting algorithms, or artificial neural networks. To prevent overfitting, and to get robust results, we usually followed the cross-validation strategy with several repetitions. Hyperparameters were optimised based on the random- or grid-search algorithm. Performance of classifiers was most frequently evaluated by sensitivity, specificity, balanced accuracy and Matthews correlation coefficient. The performance of regressors was evaluated by mean absolute error, mean squared error, root mean squared error, estimation error rate, etc. To get some intuition about the robustness of the models, we employed the permutation test. Finally, to interpret the models, we used feature importances. In some cases, we visualised the performance of a model using the ROC (Receiver Operating Characteristic) curve.

4 Discussion of main findings

4.1 Impact of the in-air movement analysis

More than ten years ago, the added value of the in-air movement analysis was not fully explored. In our first work dealing with this topic, we compared the on-surface and in-air movement from the information theory point of view [44], i.e. in samples of the BIOSE-CURID dataset, we investigated how much information each movement contains (based on the Shannon entropy) and how much information the movements share (based on the mutual information). Our experiments proved that the amount of information is similar in both movements, moreover, both trajectories appear to be notably non-redundant. After this finding, we moved further and explored, whether the quantitative analysis of in-air movement could improve the computer-aided diagnosis of PDD [13], [16], [24], [35], [41]. For this purpose, we processed the sentence copy task of the PaHaW database. Based on the results, we observed that the quantification of the in-air movement not only improves the classification accuracy but when considering both movements separately, the in-air one provides higher discrimination power [13], [41]. Proficient handwriters without any disease affecting the central nervous system have the so-called "open-loop" handwriting performance, i.e. their handwriting is automatic (they do not concentrate on the process of handwriting). Vice versa PD patients experience the so-called "closed-loop" handwriting performance, i.e. they pay more attention to the process and thus also manifest increased in-air movement [13]. We hypothesise that the in-air movement is tightly linked with cognitive processes. E.g. in [42] we measured the in-air time of AD patients and HC performing a 3D house copy task. AD patients spent significantly higher time in-air, probably having issues with the visuospatial and memory functions. Similarly, in [11] we observed that (in a cohort of AD and MCI patients) this time is significantly higher even at a long distance, i.e. in a distance from the tablet's surface where we are not able to monitor displacement of a pen. Next, in [19] we also proved that entropy-based features extracted from the in-air movement could be used to identify early cognitive changes in PD patients performing the pentagon copy test. In addition, we observed that the features are closely linked to attention levels and to the grey matter volume variability of the posterior cortical region engaged in both visual attention and visual-spatial processing. Besides the cognitive deficits, we assume that the in-air movement could be used to quantify fatigue. E.g. in [17] we identified progressively increasing duration of in-air strokes in a cohort of subjects with a high risk of developing Lewy body diseases (LBDs), thus suggesting, that this parameter could be used as a prodromal marker.

We observed that the in-air movement plays a significant role in the assessment of HD in children with neurodevelopmental disorders as well [21], [27], [29]. Similarly to the PPD, children with DD spend more time in-air and make more pauses/interruptions [21]. On the other hand, the in-air movement was less important in the quantification of GD [26]. However, this finding is expectable, because all the graphomotor elements we considered in our protocol

(see Figure 3.4) could be theoretically performed without pen elevation.

4.2 Advanced online handwriting parameterisation techniques

In [36] we introduced a new set of entropy (Shannon and Rényi) and energy (squared and Teager-Kaiser energy operator) based features extracted from raw signals and intrinsic mode functions of the empirical mode decomposition (EMD). The new feature set significantly outperformed the conventional one in supportive PDD diagnosis. In the following studies [34], [35], we further extended the set by new pressure-based parameters extracted from different parts of pressure trajectories (raising, sustained, and falling) and further improved the classification accuracy.

Next, we introduced very successful features based on the theory of fractional calculus (the theory of integrals and derivatives of arbitrary order). In the first two studies dealing with this topic, we established new handwriting parametrization techniques utilizing fractional-order derivatives (FD) as a substitution of the conventionally used differential derivatives in the kinematic handwriting features extraction [30], [32]. The newly proposed features improved the classification accuracy in absolute value by approximately 10 %. In [24] we additionally confirmed the potential of FD-based features to assess the severity of PD (as measured by the UPDRS V). In the following study [28], we optimized the order of FD so that we significantly reduced computational costs, moreover, we explored whether FD-based parameterisation of pressure, azimuth, and tilt time series brings some advancement. Next, we found out the features could be easily adjusted to the diagnosis of GD [12] and HD [29] in the children population. In addition, we observed that when applied to the in-air movement, they outperform the conventional ones [29]. Finally, in [18], [23] we shed light on the impact of different FD approximations, namely on the Grünwald-Letnikov's, Riemann–Liouville's, and Caputo's.

In [27] we introduced features based on the tunable Q-factor wavelet transform (TQWT) and showed that HD manifest themselves in higher energies of the residual component of the decomposed signal computed by the transform. Following this research, in [12] we investigated the potential of TQWT to describe limited motor skills, poor dexterity and muscle tone or unspecified motor clumsiness in school-aged children suffering from GD. Although the TQWT-based parameters were comparable to other advanced ones, their limitation lies in a need for apriori knowledge about the analysed signal that is required for the optimisation of the transform parameters.

On top of the above-mentioned parameters, we also introduced measures based on the modulation spectra (quantifying the ratio between the low and high-frequency movements present in a given handwriting signal) [12] or based on real cepstrum [20]. Finally, in our recent publication [16] we paid attention to the increasing popularity of convolutional neural networks (CNNs) as feature extractors. We compared the discrimination power of the baseline handcrafted parameters with the ones learned by CNN in a multilingual dataset of PD patients

performing Archimedean spiral and a sentence. We found that the two approaches are competitive, especially for the spiral drawing task, which is independent of language. Handcrafted features (especially kinematic measures) proved to be the better choice for the sentence writing task. This is expected since CNN-based features are extracted only from offline handwriting samples, from which temporal information is not available. In addition, the orthography of a sentence is strongly affected by the language of a writer.

4.3 Most discriminative tasks

In a review published in [15], we identified a wide range of tasks that could be used to quantify different pathologies associated with drawing/handwriting. Regarding the assessment of PDD, the most frequent ones are the Archimedean spiral, the spring task, and the sentence copy task. The first version of our protocol (see Figure 3.2) contains the spiral and the sentence copy task. In addition, we included overlapped circles (to quantify continuous kinematics), graphemes and some words. Unfortunately, at that time, we did not know the spring task has a good potential to quantify micrographia, therefore this important task is missing. In a couple of studies [35], [43], we investigated which task of the protocol provides the best discrimination power. Although the Archimedean spiral is still considered a gold standard in the assessment of PDD [16], we found out that the sentence copy task significantly outperforms it. We assume that this task requires higher cognitive effort and accents the effect of rigidity and bradikinesia [13]. In terms of projection, the deficits mainly dominated in the vertical projection [16], [17]. The finger system (which is mainly involved in vertical movement) is more affected by muscular fatigue than the wrist system (which controls the horizontal movement). From the anatomical point of view, the vertical movement requires coordinated movement and finer flexions/extensions of more joints (interphalangeal and metacarpophalangeal), i.e., it is more complex than ulnar abductions of the wrist, and we assume this to be the reason why kinematic deficits were more strongly observed in this direction. This finding could also be somehow linked with progressive/consistent vertical micrographia, i.e., progressive/consistent reduction in letter amplitude. However, this hypothesis requires further research because some studies suggest that the horizontal version of micrographia is even more common than the vertical version. Regarding the sentence copy task, we further confirmed its importance in a study, where we employed FD-based measures [30], and in a study, where we compared the performance of handcrafted and CNN-learned features in a multilingual dataset [16]. In [17] we also observed that handwriting (represented by a sentence), in comparison to a graphomotor task (the Archimedean spiral) or cognitive task (the pentagon copy test), enabled the highest classification accuracy when performing the prodromal diagnosis of LBDs.

In terms of DD, we intensively cooperated with psychologists and remedial teachers, and identified a complex set of graphomotor tasks that could be used for the assessment of GD [21]. Consequently, in [26], we noticed that the most discriminative one is the combined loop task (see TSK7 in Figure 3.4), i.e. the most complex task in our protocol, which requires coor-

dinated movement of fingers, wrist, elbow and shoulder. In addition, the task is demanding in terms of visuospatial cognitive functions. The results also suggest that the task, where children draw a sawtooth (TSK5), can also work well during the differential analysis. This task requires a precise change in direction when hitting the top of each tooth. Children with GD were associated with higher instability of acceleration when performing this task. We assume that the children were unstable especially in acceleration between upward and downward strokes, which is, again, linked with the vertical movement of the finger system.

4.4 Computerised assessment of PDD

During the last decade, we published more than 15 works dealing with the computerised assessment of PDD [13], [16]–[20], [24], [25], [28], [30], [32], [34]–[37], [41], [43]. Depending on specific objectives, we followed different statistical and machine learning pipelines (see Section 3.4), processed different tasks (see Section 3.2) and employed different features (see Sections 3.3 and 4.2). When considering the computer-aided diagnosis of PD, in our first work [43], we reached 79 % accuracy (ACC), 80 % sensitivity (SEN), and 79 % specificity (SPE) in the PaHaW database. In [34] we made the dataset available for the scientific community, it became very popular, and was used by many teams around the world (the article has more than 100 citations without self-citations on the Web of Science), who published classification accuracies beyond 90 % (in some cases with questionable methodology). Regarding our own research, in [24], we reached 97 % ACC (SEN = 96 %, SPE = 100 %) when processing the whole protocol by the FD-based features. This and other recent publications suggest that the supportive diagnosis utilising online handwriting could provide very high accuracies. Nevertheless, majority of them were conducted in a single-language cohort. We were the first who explored the impact of language in a big dataset containg 143 PD patients and 151 HC enrolled in the Czech Republic, Hungary, Colombia and the United States of America [16]. We observed that the classification accuracies in multi-language scenarios droped to approximately 70 %, thus concluding that this field is still highly challenging and requiring further research. Besides PD, in [17], we focused on a more general task, i.e. supportive diagnosis of LBDs (including DLB), moreover in their prodromal state. Employing baseline parameters, we were able to differentiate LBDs and HC with ACC = 74 %, SEN = 80 %, and SPE = 67 %.

Regarding the assessment of PD severity, since the PaHaW database contains clinical data such as the duration of PD, or UPDRS V, we introduced several regression models estimating these variables. In [24] we predicted UPDRS V and PD duration with 13 % and 24 % error, respectively. The latter one was further improved in [28], where we reached 22 % error. The errors are still high, i.e. it is another challenging field. On the other hand, two patients could experience different severity in, e.g., ten years of PD, which is differently manifested in drawing/handwriting. Therefore, it makes sense to focus more on the computer-aided estimation of UPDRS scores and other metrics evaluating the progress of the disease.

4.5 Computerised assessment of DD

In comparison to PD, DD does not have any unified diagnostic criteria that could be used independently from a language. Nowadays, the diagnosis is usually done subjectively, based on several scales with poor psychometric properties [21]. This fact accents the need to introduce an objective approach. On the other hand, since most of external validation criteria are less reliable, it is even more challenging to establish a good classification model (we can observe a wide range of classification accuracies). In our first work dealing with this topic [33], we reached ACC = 96 % (SEN = 96 %, SPE = 97 %) when diagnosing DD in Israeli children performing a graphomotor tasks similar to a rainbow. In a work, where we processed the paragraph copy task of the DYS_CZ_001 dataset, we reached ACC = 85 % (SEN = 89 %, SPE = 83 %) [27]. When quantifying the combined loop task of the DYS_CZ_002 cohort, we were able to diagnose GD with ACC = 82 %, but with very imbalanced SEN (47 %) and SPE (90 %) [26]. We further improved the results in [12] (ACC = 84 %, SEN = 83 %, SPE = 81 %), however, we had to extend our pipeline by advanced features (see Section 4.2) and process all the tasks of the protocol together.

Regarding the severity of DD, we were the first in the world who defined and evaluated the concept of computer-aided rating [33]. In the cohort of the Israeli children, we were able to estimate the total score of HPSQ with 8 % error. Nevertheless, in a cohort of Czech children (DYS_CZ_001), the minimum error we were able to reach was 18 % [31]. In [22], we found out that since adults are usually influenced by their point of view, children could better evaluate their own performance using the HPSQ–C scale than teachers using the HPSQ one. This could also be one of the explanations why the estimation error of HPSQ–C was lower than the estimation error of HPSQ [31]. Nonetheless, assessment based on HPSQ–C is still subjective, and its mathematical modelling is challenging, e.g., in the DYS_CZ_002 cohort, we were not able to get the estimation error lower than 30 %.

5 Conclusion

5.1 General contributions of the thesis

Nowadays, the field of computerised assessment of GD/HD is very dynamic and perspective. Its benefit for the computer-aided diagnosis of neurodegenerative and neurodevelopmental diseases was proved in many studies. We were the pioneers in many paths in this field of science, bridged several gaps, and brought the community new knowledge and directions with an indirect impact on the quality of life of children experiencing DD and adults suffering from PD. Our specific contributions are structured according to the aims of this thesis:

Aim 1 Explore the impact of in-air movement analysis on diagnostic accuracy.
Progress beyond the state of the art: We were the first who quantitatively showed that the in-air movement contains almost the same amount of information as the on-surface one, moreover, that this information is not redundant. We were one of the first who successfully utilised the in-air movement in the computerised assessment of GD/HD and proved that it could be employed to quantify cognitive processes and fatigue. The in-air movement analysis is already well established in the domain, and plays a significant role in the supportive diagnosis.

Aim 2 Introduce new online handwriting parameterisation techniques enabling advanced quantification of GD/HD.
Progress beyond the state of the art: We introduced a set of new features specifically designed to quantify GD/HD. We observed that these parameters could improve classification accuracies, as well as improve the performance of regression models. Although a clinical interpretation or connection with physiological processes was sometimes very challenging, in all our studies, we tried to avoid black boxes and provide neurologists, neuroscientists, psychologists, and other experts with meaningful and understandable outcomes.

Aim 3 Identify what tasks are suitable for assessment of drawing/handwriting alterations in PD/DD.
Progress beyond the state of the art: We helped to fight the stigma of gold standards in the field of PDD, and proved that handwriting tasks could be much better candidates in terms of quantitative analysis (e.g. they support better quantification of cognitive processes) of GD/HD, and computer-aided diagnosis of PD or prodromal diagnosis of LBDs in general. Regarding the DD, we identified tasks that accent GD during the performance of graphomotor elements, and that improve their classification accuracies.

Aim 4 Evaluate the researched methodology in the computerised assessment of PDD.

Progress beyond the state of the art: We confirmed that micrographia is just one of the PDD manifestations, and that PD is associated with far more complex alterations that could be identified in the temporal, kinematic and dynamic aspects of handwriting. We helped the community to advance the computer-aided diagnosis of PD by providing it with the PaHaW database, and by pushing the research in the field of machine-learning-based diagnosis beyond the state of the art. Although it can look that the computer-aided diagnosis of PD (based on the online handwriting processing) is an almost solved task, in our recent work focusing on the multilingual dataset, we demonstrated that it is still a very challenging field with several knowledge gaps. Finally, we were the first who revealed that the computerised assessment of GD/HD could support the early diagnosis of LBDs.

Aim 5 Evaluate the researched methodology in the computerised assessment of DD.

Progress beyond the state of the art: We were the first who defined and evaluated the concept of DD rating by employing online handwriting processing. Our study served as a building block and a baseline for other works published in the community. We proved that the machine-learning-based approach could bridge the limitations of current assessment methods, but on the other hand, we also observed how unreliable the current external validation criteria are – this is a big obstacle in training a model with good psychometric properties.

Besides the above-mentioned achievements, the conducted research and works have also several secondary contributions:

- Our team laid the foundations of online handwriting processing in the Czech Republic and brought it to the world-class level.
- From the educational point of view, the research was part of two defended PhD theses ("Advanced parameterisation of online handwriting in writers with graphomotor disabilities" defended by Ing. Ján Mucha, Ph.D., and "Research of advanced online handwriting analysis methods with a special focus on assessment of graphomotor disabilities in school-aged children" defended by Ing. Vojtěch Zvončák, Ph.D.), and is part of one ongoing ("Research of online handwriting parameterisation in subjects with graphomotor difficulties" being solved by Ing. Michal Gavenčiak).
- This multidisciplinary research helped us to strengthen or establish new cooperation with the Central European Institute of Technology, St. Anne's University Hospital in Brno, Masaryk University, Czech Academy of Sciences, Escola Superior Politecnica (TecnoCampus Mataro-Maresme), University of Haifa, University of the Basque Country, University of Las Palmas de Gran Canaria, University of Vic, Technical University of Košice, University of Antioquia, University of Arizona, University of Szeged, University

of Bari Aldo Moro, Taipei Veterans General Hospital, and Wacom Co., Ltd.

- We raised awareness about the computerised assessment of GD/HD during several workshops with students held at the Masaryk University. We also raised the awareness among the general public, e.g. during the Wacom Connected Ink event.[1]
- Besides the PaHaW database that is freely available for research purposes, we also made available a Python library for online handwriting processing [90], [91], and user-friendly software for online handwriting acquisition [92], [93].

Regarding the neurodegenerative disorders, from a practical point of view, the outcomes of our research were used to better understand their pathophysiology. Even though we proposed some models supporting diagnosis, there is still a long path until they are used in clinical practice. On the other hand, concerning the DD, in the frame of project no. TL03000287 (Software for advanced diagnosis of graphomotor disabilities) supported by the Technology Agency of the Czech Republic, we cooperate with the company Propsyco s. r. o. and prepare software, that will help psychologists and remedial teachers to objectively diagnose GD/HD in school-aged children.

5.2 Future directions

As already mentioned, the field of the computerised assessment of GD/HD is very dynamic, opens new questions and brings new challenges. We have identified the following future directions:

- Since external validation criteria in studies dealing with DD are very unreliable, we propose to introduce diagnostic models based on semi-supervised and data-driven approaches. The only work following (at least partially) this approach was published by Asselborn et al. in 2020 [94]. Our team is just finishing a study, where we go much beyond the state of the art, and which we believe will revolutionise the computer-aided diagnosis of GD/HD. The process could be summarised as follows: 1) based on discussions with well recognised special educational counsellors, and based on a very comprehensive review of symptoms associated with GD/HD, we pre-identified manifestations and related handwriting measures that could quantify them; 2) based on some simulations, we performed a finer selection of features that were consequently used to create a scale for each manifestation (e.g. dysfluent handwriting), and normative values that are used during diagnosis/rating. The concept is visualised in Figure 5.1. As can be seen, the concept enables us not only to diagnose GD/HD but also to assess specific manifestations (moreover, it could be scaled to pre-school children who are not able to write). This is very important because we observed that several children, all diagnosed with DD, could actually have different difficulties and require different therapy. Figure 5.2

[1] `https://www.youtube.com/watch?v=04G5ksvNFBY`

displays our newly proposed GHDRS scale (Graphomotor and Handwriting Disabilities Scale) of three children attending 3rd grade of a primary school. As can be seen, the first girl has no GD/HD (she is intact). The second girl has GD/HD, more specifically, she has the impaired process of drawing and handwriting. Vice versa, the boy has impaired product of drawing and handwriting, which could be also seen in Figure 5.3 (he was not able to maintain the loops in a line and was not able to keep a stable tilt – this probably explains the different orientation of loops) and in Figure 5.4 (frequent overwriting, disability to perform longer strokes, all letters tended to have the same amplitude). The methodology (maximally transparent so that it could be used in practice) will be published in an upcoming article.

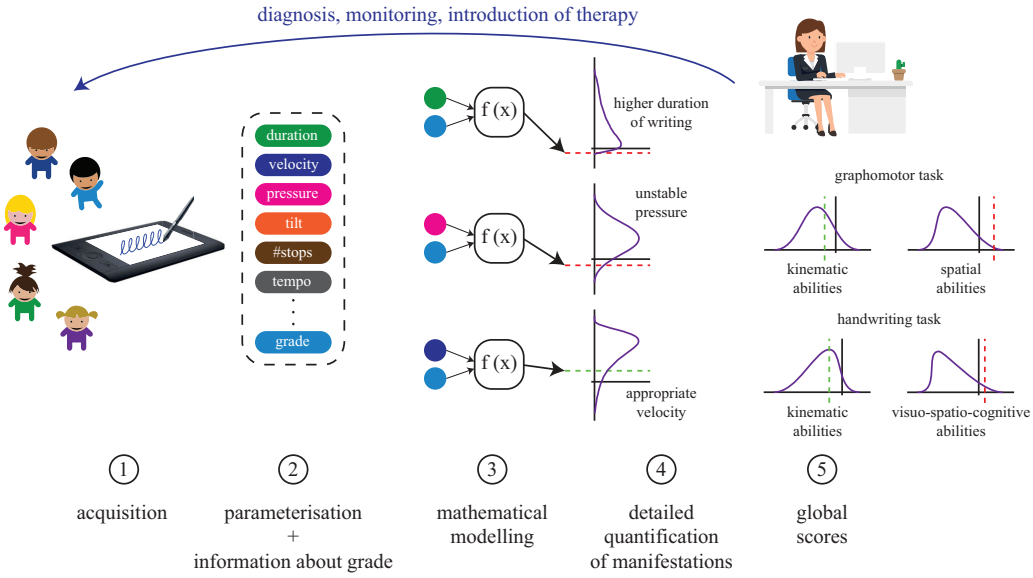

Fig. 5.1: Assessment based on the GHDRS scale

- In 2021, Jan Rusz et al. published a work, where the authors identified distinct speech phenotypes in de novo PD patients [95]. This finding and the finding mentioned above (supported by Figure 5.2) led us to postulate that some phenotypes could be observed even in PDD. We plan to investigate it in the next few years.
- Although there has been a body of research focusing on PDD, studies dealing with GD/HD in patients with atypical Parkinsonian syndromes (e.g. multiple system atrophy or progressive supranuclear palsy) are missing. One year ago, we teamed up with the neuroscientific group of the Taipei Veterans General Hospital and currently collect a handwriting dataset of patients with these syndromes.
- As in the other fields of science, the popularity of deep neural networks (DNNs) in the computer-aided diagnosis of neurodegenerative disorders is rapidly increasing. The con-

ventional methodology combining handcrafted features and shallow machine learning algorithms is still outperforming DNN-based approaches (and facilitating clinical interpretation). On the other hand, with the increasing size of datasets, new data augmentation techniques, model interpretation methodologies, and approaches such as transfer learning, we believe that DNNs will play a significant role. Moreover, some recent works put in place networks specifically designed for online handwriting processing (i.e. they are able to combine the spatial and temporal information) [96], [97].

- To adjust therapy or modify a treatment policy, children visit pedagogical-psychological counselling centres (and adults hospitals) a few times per year. Nevertheless, the frequency is insufficient, moreover, patients under clinical examination could be subjected to the Hawthorne effect [98]. To monitor the therapy effectively and intervene when necessary, neurologists, psychologists, educational counsellors, and other experts could take the advantage of mobile devices. In spite of the fact that some remote monitoring applications already exist [2], this field is still at its beginning.

[2] https://dynamilis.com/en/

Fig. 5.2: Three children attending 3rd grade of a primary school assessed based on the GHDRS scale (the first top block contains the global scores; the next four blocks contain specific manifestations, i.e. they represent a detailed profile associated with the global scores; all scores are transformed by a sigmoid function so that the minimum is 0, maximum 1 and the threshold determining disability has a value 0.5): a) an intact girl without any GD/HD; b) a girl with the affected process of handwriting (too high duration of writing, lower variability of velocity) and affected process of drawing the loops (low velocity, low acceleration); also, she is not able to perform longer strokes during writing; c) a boy whose handwriting is characteristic by frequent overwriting (see Figure 5.4), disability to perform longer strokes, moreover, all letters tended to have the same amplitude; in addition, he was not able to maintain the loops in a line (see Figure 5.3) and was not able to keep a stable tilt.

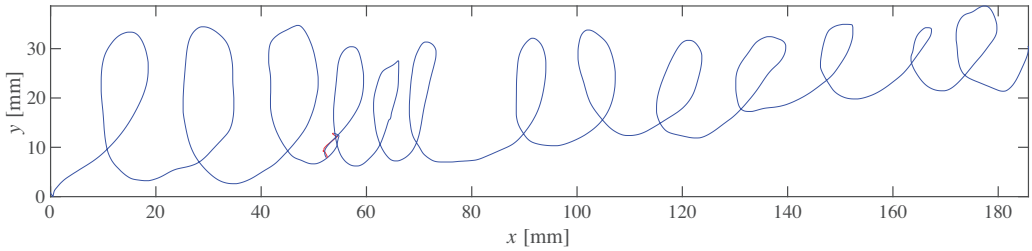

Fig. 5.3: Connected loops (spring task) performed by a boy, whose GHDRS is depicted in Figure 5.2c (the blue line represents the on-surface movement, the red line represents the in-air one).

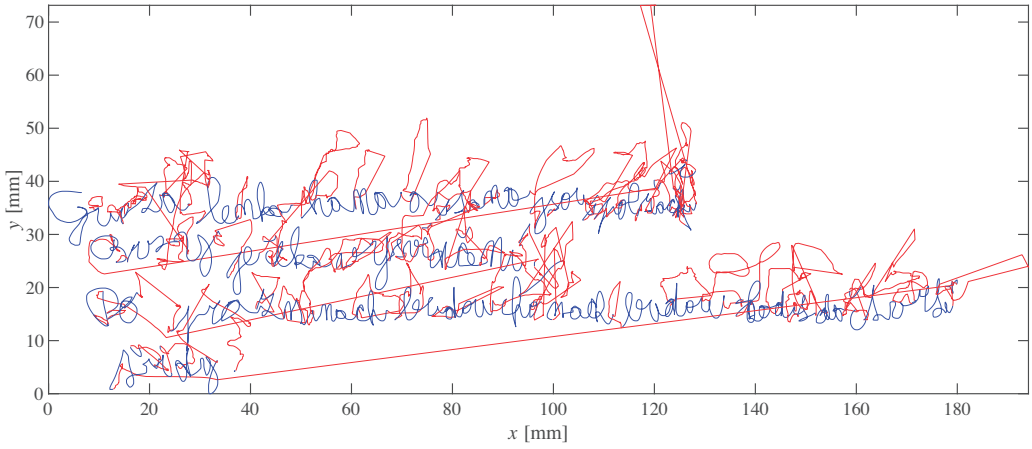

Fig. 5.4: Paragraph copy task performed by a boy, whose GHDRS is depicted in Figure 5.2c (the blue line represents the on-surface movement, the red line represents the in-air one).

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ABSTRACT

People with neurodevelopmental (e.g. developmental dysgraphia) or neurodegenerative (e.g. Parkinson's disease) disorders are very likely to exhibit graphomotor disabilities (GD) such as motor-memory dysfunction, graphomotor production deficits, motor feedback difficulties, etc., leading to various drawing and handwriting difficulties (HD). These alterations have a very detrimental impact on the quality of life. Unfortunately, current diagnostic methods have many limitations, which results in underdiagnosis or incorrect diagnosis of GD/HD and consequently in ineffective therapy. In recent years, online handwriting processing proved to be a promising approach to an objective and accurate assessment of GD/HD. Nevertheless, the field is still relatively unexplored and has several knowledge gaps. The main goal of this habilitation thesis is to progress beyond the state of the art and to research new approaches to the computerised assessment of GD/HD that would facilitate objective diagnosis and monitoring of neurodegenerative and neurodevelopmental disorders. The thesis summarises 34 peer-reviewed works that bridge the main knowledge gaps, and provides new directions in the field.

ABSTRAKT

U osob s neurovývojovými poruchami (např. s neurovývojovou dysgrafií) nebo neurodegenerativními onemocněními (např. s Parkinsonovou nemocí) je velká pravděpodobnost výskytu grafomotorických obtíží (GD), jako např. motoricko-paměťové dysfunkce, poruchy grafomotoriky, potíže s motorickou zpětnou vazbou atd., což vede dále k různým potížím s kreslením a psaním (HD). Tyto poruchy mají velmi negativní dopad na kvalitu života. Bohužel, aktuální diagnostické metody manifestují mnoho nedostatků, což vede ke špatné diagnóze GD/HD, a následně k neefektivní terapii. V posledních letech se prokázalo, že je zpracování online písma slibným přístupem k objektivnímu a přesnému hodnocení GD/HD. Nicméně tato oblast je stále poměrně neprozkoumána a obsahuje mnoho mezer ve znalostech. Hlavním cílem této habilitační práce je postoupit za aktuální stav vědění a zkoumat nové přístupy hodnocení GD/HD, které by ulehčily objektivní diagnózu a monitorování neurodegenerativních onemocnění a neurovývojových poruch. Práce shrnuje 34 recenzovaných článků, které překlenují zmíněné mezery, a poskytují nové směry v oblasti.