ParkinsoNET: Estimation of UPDRS Score using Hubness-aware

Feed-Forward Neural Networks

Krisztian Buza¹*, Noémi Ágnes Varga^{2†}

¹Brain Imaging Center, Research Center for Natural Sciences Hungarian Academy of Sciences

²Institute of Genomic Medicine and Rare Disorders, Semmelweis University buza@biointelligence.hu, noemiagnesvarga@biointelligence.hu

Abstract

Parkinson's disease is a worldwide frequent neurodegenerative disorder with increasing incidence. Speech disturbance appears during the progression of the disease. UPDRS is a gold standard tool for diagnostic and follow up of the disease. We aim at estimating the UPDRS score based on biomedical voice recordings. In this paper, we study the *hubness* phenomenon in context of the UPDRS score estimation and propose hubness-aware error correction for feed-forward neural networks in order to increase the accuracy of estimation. We perform experiments on publicly available datasets derived form real voice data and show that the proposed technique systematically increases the accuracy of various feed-forward neural networks.

Keywords – artificial neural networks, hubs, regression, Parkinson's disease, UPDRS, prediction

1 Introduction

Parkinson's disease (PD) is one of the most important neurodegenerative disorders, with increasing incidence. PD affects 7 to 10 million people worldwide. Clinically PD is characterized by cardinal symptoms: initially unilateral, asymmetrical resting tremor (shaking of the hand), rigidity and bradykinesia (slow movement). In addition to these symptoms (motor disturbances) the disorder is associated with nonmotor, neuropsychiatric symptoms, such as cognitive impairment, autonomic dysregulation and sleep problems (Crosiers et al., 2011).

^{*}This research was performed within the framework of the grant of the Hungarian Scientific Research Fund - OTKA PD 111710. This paper was supported by the János Bolyai Research Scholarship of the Hungarian Academy of Sciences.

[†]N.Á. Varga was supported by the KTIA_NAP_13_1-2013-0001

The total PD-related costs are estimated as \$25 billion per year in the United States alone, while "medication costs for an individual person with PD average \$2,500 a year, and therapeutic surgery can cost up to \$100,000 dollars per patient."¹ As noted by de Rijk et al. (1997) and de Lau and Breteler (2006), the prevalence increases with the age, and the increasing importance of PD is underlined by the fact that "most economically developed and many developing countries are experiencing marked demographic shifts, with progressively larger proportions of their populations entering old age" (Pringsheim et al., 2014).

The Unified Parkinson's Disease Rating Scale (UPDRS) is the most commonly used scale in the clinical study of PD (Ramaker et al., 2002). Roughly speaking, the UPDRS score of a particular patient describes the severity of the disease in case of that patient (see also Section 2.1 and the references therein for more details on UPDRS). The UPDRS score may change over time indicating the success of treatment or the progression of the disease. Ideally, the UPDRS score would be measured regularly and relatively often in order to provide medical doctors, the patient and his/her relatives with detailed information about the progression of the disease and to contribute to the patient's awareness of the disease, which is one of the most relevant factors influencing the efficiency of the treatment. However, as the assessment of the UPDRS score requires notable effort and the available capacity of medical personnel is a bottleneck, under realistic conditions, the total UPDRS score is measured with a relatively low frequency, e.g., at the beginning of the treatment and after several months.

Little et al. (2009), Tsanas et al. (2010) and Sakar et al. (2013) have shown that the UPDRS score is related to various characteristics of the voice, thus, at least in theory, it could be estimated based on the patient's speech while he/she makes telephone or skype calls using his/her smartphone or tablet. With our current study, we would like to take a step towards this visionary application which, on the long term, is expected to allow continuous monitoring of the patient's UPDRS score and almost immediate identification of its substantial changes.

One of the major challenges associated with the aforementioned visionary application is the fact that the *exact* function describing how the UPDRS score depends on (the combination of) quantifiable characteristics of speech is unknown. Therefore, state-of-the-art solutions for the estimation of UPDRS score from voice data, are based on machine learning (Sakar et al., 2013), (Tsanas et al., 2011). Following the machine learning paradigm, voice data may be collected from a large set of patients which contains both audio recordings and the patient's UPDRS score at the time of recording. Such data allows machine learning approaches to "discover" the dependency between the characteristics of the voice and the UPDRS score so that the UPDRS score of "new" patients may be estimated based on their speech.

As artificial neural networks (ANNs) are known to be universal approximators (Pang-Ning et al.,

¹http://www.pdf.org/en/parkinson_statistics

2006), we base our solution on ANNs. In particular, after studying the *hubness* phenomenon and the presence of *bad hubs* in context of the UPDRS score estimation in Section 3, we propose hubness-aware *error correction* for ANNs in order to increase the accuracy of estimation. To the best of our knowledge, the current work is the first attempt to exploit hubness in context of ANNs. We perform experiments on publicly available datasets derived form real voice data and show that the proposed *error correction* technique systematically increases the accuracy of various feed-forward neural networks.

2 Background

In order to ensure that the paper is self-contained, we provide the most relevant background information about the UPDRS in Section 2.1 and review related works in Section 2.2. Finally, in Section 2.3, we give basic definitions used throughout the paper.

2.1 Unified Parkinson's Disease Rating Scale

The Unified Parkinson's Disease Rating Scale (UPDRS) was developed to provide a comprehensive coverage of the symptoms, in order to allow for clinical examination and follow-up of the progression of the disease. Today it serves as a gold standard reference scale.

The scale has four parts. Part I (previously titled Mentation) was designed to assess non-motor experiences of daily living. Part II (previously called Activities of daily living) assesses motor experiences of daily living. Part III (a.k.a. the Motor part) contains the examination of the patient's motor skills, while Part IV (titled as Complications) considers motor complications.

The aforementioned parts of the UPDRS are measured at different frequencies, for example, according to Goetz et al. (2003), Part III was used in 98% of the cases, whereas Part I was used with a frequency of 60% only. For more details about the UPDRS score, the reader is referred to (Goetz et al., 2008).

Alteration of the speech is a well-known symptom of PD, about 70% of PD patients exhibit speech impairment (Hartelius and Svensson, 1994), (Logemann et al., 1978). Speech disturbances are represented in Parts II and III of the UPDRS. Speech disturbances in PD are characterized by hypophonia, hypokinetic dysarthria, palilalia and speech dysfluency. With the progression of the disease, due to the involvement of speech organs, worsening of speech is known. Moreover, "positive effect of L-dopa treatment on speech disorders could be objectively confirmed" (Pawlukowska et al., 2015). In this paper, we aim to estimate patients' UPDRS scores from voice measures.

2.2 Related works

Machine learning techniques are widely applied for medical tasks, see e.g. (Cyganek and Wozniak, 2015), (Grana et al., 2011) and (Froelich et al., 2015).

As we formalize the task of automated estimation of UPDRS score as a regression task, when reviewing related works, we focus on regression, which is one of the most prominent fields of machine learning with various applications in medicine, see e.g. (Celikkaya et al., 2013), (Soyiri et al., 2013). In the last decades, various regression techniques have been developed ranging from simple linear and polynomial regression over nearest neighbor regression to more complex models, such as artificial neural networks (ANNs) and support vector regression, see e.g. (Devroye et al., 1994), (Adamczak et al., 2004), (Basak et al., 2007).

One of the most interesting recent observations is the *presence of hubs* in various datasets. Informally, hubs are instances that are similar to a surprisingly high amount of other instances. Unfortunately, some of the hubs are bad in the sort of sense that they may mislead machine learning algorithms. The presence of hubs have been studied primarily in context of classification, clustering and instance selection, see (Radovanović et al., 2010a), (Tomašev and Mladenić, 2013), (Radovanović et al., 2009), (Radovanović et al., 2010b), (Tomašev et al., 2011), (Tomašev et al., 2015b), (Buza et al., 2011), and (Tomašev et al., 2015a) for a survey.

To the best of our knowledge, Buza et al. (2015) was the first to study the presence of hubs in regression tasks. They focused on nearest neighbor regression and considered various applications, whereas in the subsequent sections of this paper we study the role of hubs in the estimation of the UPDRS score and propose a hubness-aware enhancement of ANNs.

2.3 Definitions and notations

A dataset \mathcal{D} containing n instances is given. In our case, each instance corresponds to an audio recording. Numeric features describing characteristic properties of the voice are extracted, therefore, each instance is a vector of such features. Instances are denoted by $x_i, 1 \leq i \leq n$. For each instance $x_i \in \mathcal{D}$, the value of the continuous target, i.e., UPDRS score, is given and it is denoted by $y(x_i)$. We say that $y(x_i)$ is the *label* of instance x_i and \mathcal{D} is the training dataset. With regression we mean the task of predicting (estimating) the label of an instance $x' \notin \mathcal{D}$.

We use $d(x_i, x_j)$ to denote the distance between two instances x_i and x_j . In order to study the hubness phenomenon, we will use the notion of *k*-nearest neighbors of an instance x' which is a subset $\mathcal{N}_k^{\mathcal{D}}(x')$ of \mathcal{D} so that $|\mathcal{N}_k^{\mathcal{D}}(x')| = k$ and

$$\max_{x \in \mathcal{N}_k^{\mathcal{D}}(x')} d(x', x) \le \min_{x \in \mathcal{D} \setminus \mathcal{N}_k^{\mathcal{D}}(x')} d(x', x).$$

We may omit the upper index \mathcal{D} , whenever there is no ambiguity. We note that ties may be broken



Figure 1: a) The nearest neighbor relationship is asymmetric. Some instances never appear as the first nearest neighbor of other instances while there are some instances that appear frequently as the first nearest neighbor of other instances. b) Example used to illustrate error correction.

arbitrarily, i.e., in case if there are several subsets fulfilling the above condition, any of them may be used as the set of nearest neighbors.

3 Bad Hubs in UPDRS Score Estimation

Informally, *hubness in datasets* refers to the phenomenon that some instances are similar to surprisingly large number of other instances. In order to quantitatively study hubness in context of UPDRS score estimation from voice data, we use the notion of k-nearest neighbors.

Let us first note that the k-nearest neighbor relationship is asymmetric: while each instance $x \in \mathcal{D}$ has k nearest neighbors, an instance $x' \in \mathcal{D}$ does not necessarily appear k times as one of the k-nearest neighbors of other instances. This is illustrated in Fig. 1a for k = 1. In order to keep the example simple, we consider two-dimensional vector data, therefore, instances correspond to points of the plane. In the context of UPDRS score estimation from speech data, we may imagine a simple scenario in which two numeric features of the audio signals (such as shimmer and jitter) are extracted and we use only these two features to represent the data. Each of these features may correspond to one of the horizontal and vertical axis, thus the audio recordings may be mapped to points in the plane.

In Fig. 1a, there is a directed edge from each instance (denoted by a circle) to its first nearest neighbor. While each instance has *exactly one* first nearest neighbor, how many times an instance appears as the first nearest neighbor of *other* instances (i.e., the number of *incoming* edges to an instance) is not necessarily one. As one can see, some of the instances never appear as nearest neighbors of others and there is an instance that appears as the first nearest neighbor of three other instances. In particular, the integer next to each instance shows how many times it appears as the first nearest neighbor of others.

Generally, we use $N_k(x)$ to denote how many times the instance $x \in \mathcal{D}$ appears as one of the k-nearest



Figure 2: The distribution of $N_{10}(x)$ in case of motor UPDRS scores of the Telemonitoring dataset for low error instances (in the left), high error instances (in the middle), and both histograms in the same plot (in the right). Similar observations can be made for the Multiple Sound Recording dataset and total UPDRS scores of the Telemonitoring dataset as well. Note that, some of the high error instances appear as nearest neighbors of many other instances, i.e., there are bad hubs in the data. Remarkably, the distribution of high error instances is shifted to the right compared with the distribution of low error instances. This indicates that there are more high error hubs than low error hubs.

neighbors of other instances of \mathcal{D} . It is easy to see that the expected value of $N_k(x)$ is $E[N_k(x)] = k$, however, the actual value of $N_k(x)$ varies from instance to instance. As it was shown by Radovanović et al. (2010a), Buza et al. (2011), Tomašev and Mladenić (2013), in many cases, the distribution of $N_k(x)$ is substantially skewed to the right, i.e., there are *a few* instances with extraordinarily high $N_k(x)$ values, furthermore, the skewness increases with increasing intrinsic dimensionality of the data. Usually, instances having surprisingly high $N_k(x)$ are called *hubs*, while instanced with exceptionally low $N_k(x)$ are called *anti-hubs*. More precisely, we say that an instance x is a hub, if $N_k(x) > 2k$; while an instance x is an *anti-hub* if $N_k(x) = 0$. The phenomenon that $N_k(x)$ is skewed is called *hubness* and it is often quantified by the third standardized moment (skewness) of the distribution of $N_k(x)$.

In order to show that there are instances that may mislead machine learning models, we perform the following analysis on the *Telemonitoring* and *Multiple Sound Recording* datasets, both of them containing voice data for UPDRS estimation. (The datasets are described in Section 4.1 in more detail.) We considered both estimation tasks (total and motor UPDRS score) associated with the *Telemonitoring* data separately. For each instance x, as error(x), we calculate the average absolute difference between the label of x (i.e. UPDRS score associated with x) and the labels of those instances that have x as one of their nearest neighbors. Formally, let

$$\mathcal{I}_x = \{ x_j | x \in \mathcal{N}_k(x_j) \},\tag{1}$$

then

$$error(x) = \begin{cases} \frac{1}{|\mathcal{I}_x|} \sum_{x_i \in \mathcal{I}_x} |y(x) - y(x_i)| & \text{if } |\mathcal{I}_x| \ge 1\\ 0, & \text{otherwise.} \end{cases}$$
(2)

After calculating the above error for each instance, we ordered the instances according to their errors and selected 25% of the instances having *highest* error, and another 25% having *lowest error*. We call these instances *high error instances* and *low error instances*. Throughout the analysis, we used k = 10and the Euclidean distance over all biomedical voice features present in the datasets. Figure 2 shows the distributions of $N_{10}(x)$ for low and high error instances of the Telemonitoring dataset in case of *motor* UPDRS scores. In the figure, horizontal axis corresponds to $N_{10}(x)$ while the height of the column shows how many instances have that particular value of $N_{10}(x)$.

As one can see, the distributions of $N_{10}(x)$ are notably skewed. Most importantly, some of the high error instances appear as nearest neighbors of many other instances. In particular, as we defined *hubs* as instances that appear as nearest neighbors of more than 2k instances, we may observe that there are hubs among the high error instances. We use the term *bad hubs* to refer to hubs among high error instances. Additionally, let us note that the distribution of high error instances is shifted to the right compared with the distribution of low error instances. This indicates that there are *more* bad hubs than low error hubs (or *good hubs*).

Hubs tend to be located in dense regions of the data space, according to recent results, they may even serve as cluster centers (Tomašev et al., 2015b). Under the assumption that the model will be applied to instances originating from the same (or at least similar) distribution as the distribution from which the training data originates, it is essential for any regressor to perform well on instances being "close to" hubs, because much of the new/test instances are expected to be located exactly in these regions, i.e., in the proximity of hubs. Therefore, in the next section, we devise a mechanism that is able to compensate for the detrimental effect of high error instances, including high error instances located at "central" positions, i.e., bad hubs.

3.1 Hubness-aware Artificial Neural Networks

Next, we describe *error correction*, a mechanism that can be used to improve the performance of ANNs. We define the *corrected label* $y_c(x)$ of an instance x as

$$y_c(x) = \begin{cases} \frac{1}{|\mathcal{I}_x|} \sum_{x_i \in \mathcal{I}_x} y(x_i) & \text{if } |\mathcal{I}_x| \ge 1\\ y(x), & \text{otherwise,} \end{cases}$$
(3)

where \mathcal{I}_x denotes the set of instances that have x as one of their k-nearest neighbors, see Eq. (1) for the formal definition of \mathcal{I}_x . We propose to use the corrected labels instead of the original labels while training ANNs. Although, our current work focuses on ANNs, we note that, in principle, the above error correction technique may be used with various other regressors as well.

Using the example in Fig. 1b we illustrate how the corrected labels are calculated. In Fig. 1b training instances are denoted by circles. They are identified by the symbols $x_1...x_7$. The numeric value next to each instance shows its label. In order to keep the example simple, we use k = 1 to calculate the corrected labels of training instances. For training ANNs, the corrected label of all the training instances need to be calculated, however, we only present the calculations for x_4 and x_5 as the procedure is the same in case of the other instances as well. Concretely, the corrected labels of x_4 and x_5 are:

$$y_c(x_4) = \frac{1}{2}(39.5 + 19.8) = 29.65, \quad y_c(x_5) = \frac{1}{3}(20.1 + 24.7 + 16.4) = 20.4$$

4 Experiments

In this section we present the results of our experimental evaluation of the proposed approach on two real-world speech datasets associated with UPDRS scores as prediction target.

4.1 Datasets

The *Parkinsons Telemonitoring* dataset (Tsanas et al., 2010; Little et al., 2009) "is composed of a range of biomedical voice measurements from 42 people with early-stage Parkinson's disease recruited to a six-month trial of a telemonitoring device for remote symptom progression monitoring."² In total, the data contains 5875 instances. Both *motor* (i.e., part III) and *total* (i.e., all the four parts) UPDRS scores as well as temporal information (i.e., on which day the measurements were taken) are available. We use *motor* to denote the experiments when the motor UPDRS score was used as target, analogously, *total* denotes the experiments when the total UPDRS score was used as target.

We performed experiments on the *Parkinson Speech Dataset with Multiple Types of Sound Recordings* as well, to which we refer as *multi* for simplicity (Sakar et al., 2013). This dataset contains 1040 instances.

Both datasets are available in the UCI Machine Learning repository (Bache and Lichman, 2013). In case of both datasets, we used jitter and shimmer features.

4.2 Experimental Protocol

We performed experiments according to the patient-based 10×10 -fold cross-validation protocol, i.e., in each round of the 10×10 -fold cross-validation, *all* the instances belonging to the same patient either appear in the train or test split. This simulates the medically relevant scenario in which historical data is used to train the model which is then applied to the estimation of UPDRS scores of new patients.

²http://archive.ics.uci.edu/ml/datasets/Parkinsons+Telemonitoring

As temporal information was available in the Telemonitoring dataset, an additional estimation task that may be associated with the data is to estimate the *change* of UPDRS score relative to its initial value. As it may be highly relevant to identify substantial changes in the UPDRS score of a patient as early as possible, we also evaluated the proposed technique in the UPDRS score change estimation context. These experiments are denoted as *change motor* and *change total* respectively.

In all the above experiments, features were normalized by subtracting their mean and dividing by their standard deviation. Mean and standard deviation were calculated on the training subset of the data (therefore, the normalization was performed in each round of the 10×10 -fold cross-validation).

In our experiments, we used the implementation of ANNs from the Weka software package (Witten and Frank, 2005). In particular, we used feed-forwarld ANNs trained with backpropagation with learning rate of 0.3, and momentum of 0.2, while the number of training epochs was set to 500. In order to show that the proposed approach is indeed able to improve the performance of neural networks, we used neural networks of the same structure both with and without the error correction technique described in Section 3.1. While performing error correction, we used the Euclidean distance and k = 10 as the default k-value in order to calculate the nearest neighbor relationship. Error correction was performed only on the training set, i.e., in both cases (with and without error correction) we aimed to predict the same target.

We use a comma separated list of integers to denote the structure of ANNs: each item of the list corresponds to one of the hidden layers and it denotes the number of neurons in that layer. For example, "Net-5,5" denotes an ANN with two hidden layers each of them containing 5 neurons. We performed experiments with ANNs of six different structure: one hidden layer with 5, 10 and 20 neurons and two hidden layers with 5, 10 and 20 neurons each.

4.3 Performance Metrics

We measured the performance of our approach and the baselines in terms of mean absolute error (MAE) and root-mean-square error (RMSE):

$$MAE = \frac{1}{|\mathcal{D}_{test}|} \sum_{x_j \in \mathcal{D}_{test}} |\hat{y}(x_j) - y(x_j)|, \qquad RMSE = \sqrt{\frac{1}{|\mathcal{D}_{test}|}} \sum_{x_j \in \mathcal{D}_{test}} \left(\hat{y}(x_j) - y(x_j)\right)^2$$

where \mathcal{D}_{test} and $|\mathcal{D}_{test}|$ denote the test set and its size respectively, $\hat{y}(x_j)$ denotes the label predicted for instance x_j , while $y(x_j)$ denotes the true label of instance x_j . We used paired calibrated t-test proposed by Bouckaert (2003) at significance level of 0.05 to examine if the ANNs with error correction statistically significantly outperform ANNs without error correction. For simplicity, we only report results for MAE, but we note that we observed similar trends for RMSE as well.

model	motor	total	multi	change motor	change total
	$+\mathrm{EC}$ $-\mathrm{EC}$				
Net-5	<u>7.206</u> 7.669	<u>9.477</u> 10.080	13.944 14.139	<u>3.150</u> 3.445	<u>3.830</u> 4.117
Net-10	<u>7.232</u> 7.687	9.504 10.056	13.968 14.548	<u>3.148</u> 3.469	<u>3.827</u> 4.127
Net-20	<u>7.276</u> 7.822	9.594 10.065	14.104 14.505	<u>3.136</u> 3.440	<u>3.824</u> 4.109
Net-5,5	<u>7.220</u> 7.558	<u>9.451</u> 10.035	13.764 14.114	<u>3.103</u> 3.473	<u>3.716</u> 4.022
Net-10,10	<u>7.239</u> 7.572	9.476 10.025	13.797 14.145	3.104 3.451	<u>3.718</u> 4.004
Net-20,20	7.266 7.589	<u>9.452</u> 10.014	13.852 14.260	<u>3.106</u> 3.434	<u>3.712</u> 4.013

Table 1: Mean absolute error averaged over 10×10 folds with (+EC) and without error correction (-EC). The MAE-value is <u>underlined</u>, if the difference is statistically significant.

4.4 Results

In each of the 5 different contexts (i.e., motor, total, multi, change motor and change total), we examined 6 types of neural networks, this gave in total 30 experiments. In each of these 30 experiments, we compared neural networks using error correction (+EC) and neural networks without (-EC) error correction.

Table 1 summarizes the results. We report MAE averaged over 10×10 folds. As one can see, the proposed error correction mechanism systematically improves the quality of UPDRS score estimation. In particular, in all of the aforementioned 30 experiments, the neural networks with error correction outperformed the neural networks without error correction. The improvement is statistically significant in 24 experiments.

As noted previously, error correction may be used with various models. Therefore, we examined the effect of error correction on other regression techniques as well. Fig. 3.a shows the performance of various models in case of estimating the *motor* UPDRS score *with* and *without* error correction. In particular, we consider: (i) Net-5, feed-forward artificial neural network with one hidden layer containing 5 neurons, (ii) k-NN, k-nearest neighbor regression with k = 10, (iii) M5P regression trees from the aforementioned Weka machine learning library and (iv) SVM, support vector regression with linear kernel. As one can see, error correction is able to improve the performance of these models as well.

As described above, in order to perform error correction, k-nearest neighbor relationships are computed first. Fig. 3.b shows the performance of Net-5 when performing error correction with various k-values. As one can see, error correction systematically improves the performance of the model for all the examined k values, while k values between 5 and 10 are preferable.



Figure 3: a) Performance (MAE) of various models when predicting the *motor* UPDRS score with (+EC) and without (-EC) error correction. b) Performance of Net-5 with error correction (+EC) using various k-values, and without error correction (-EC).

5 Discussion

During spontaneous usage of tablets, smartphones and laptops, these devices are able to capture unprecedented amount and variety of data about their users. The gathered information may range from the dynamics of typing recorded while the user writes short messages or e-mails, over voice recordings performed during phone or skype calls, to GPS coordinates and social connectivity features (such as how many people the user regularly writes messages to). It is hypothesized that such information might be related to various disorders or predict unexpected changes of the user's health conditions (Estrin, 2013). Given the relatively high and increasing computational power of smartphones and tables, processing and analysis of the data collected during spontaneous usage became technologically possible. This is expected to give rise to visionary healthcare applications that support medical doctors in diagnostic decisions and treatment of diseases.

While much of the research focuses on understanding the background of PD, see e.g. (Zimprich et al., 2003) and (Balicza et al., 2012), in this paper, we focused on the estimation of UPDRS score from biomedical voice measurements. Due to the fact that the user's voice can be simply recorded during spontaneous interactions with tablets or smartphones, we strongly hope that our paper is a step towards the usage of tablets and smartphones in the strict follow up of PD. Such visionary applications, once they will be realized, will not only allow for cheap and continuous monitoring of patients' status, but the resulting data is expected to increase the patients' and their relatives' awareness of the disease which is one of the key factors of successful treatment of the disease.

We hope that, on the long term, similar approaches will be used for diagnosis and monitoring of other diseases as well. For example, Estrin (2013) reported that reduction of hearing abilities could be detected by examining the volume at which the user listened to music on his smartphone. This increased the patient's awareness of the disease, and convinced the patient to turn to medical doctors for examination. Dementia and cognitive impairment, see e.g. (Bereczki and Szatmári, 2009), is another domain in which telemonitoring systems might be advantageous on the long term.

Regarding the limitations of our study we have to mention that it is likely that the accuracy of UPDRS score estimation needs to be increased further for successful applications. Therefore, incorporation of further data mining techniques, such as monotonization (Horváth et al., 2011) and monotone models (Horváth and Vojtáš, 2006) and the adaptation of hybrid solutions (Woźniak et al., 2014) might be advantageous. We also mention that the proposed error correction technique may contribute to avoid overfitting to hub instances having non-representative labels. In contrast, conventional regularization techniques focus on model complexity and treat all the instances equally important. More detailed study of the relation between regularization and error correction is left for future work.

The data recorded during spontaneous usage of smartphones and tablets was originally not designed for diagnostic purposes, therefore, even the most useful pieces of the data can only be expected to be weakly correlated with medically relevant conditions. Note, however, that a combination of weak features may serve as a reasonable predictor even if the features are weak predictors separately and, by training neural networks, the machine is expected to learn the appropriate combination of those individually weak predictors. On the other hand, medical doctors are expected to play a crucial role in the correct interpretation of the data and potential additional examinations. The overall workload of medical doctors will not necessarily decrease: although continuous telemonitoring might replace some of the scheduled face-to-face meetings between patients and doctors, due to the continuous monitoring of UPDRS score or other conditions, and possible false alarms generated by automated recognition systems, patients may ask for more appointments with medical doctors.

6 Conclusions

In this paper, we focused on the automated estimation of UPDRS score based on biomedical voice measures. This is a crucial component of telemonitoring systems for PD patients. We studied the hubness phenomenon in context of the UPDRS score estimation and proposed a hubness-aware error correction for artificial neural networks. We performed experiments on publicly available real-world datasets and showed that the proposed technique systematically improves estimation accuracy as measured by MAE and RMSE.

References

- Rafał Adamczak, Aleksey Porollo, and Jarosław Meller. Accurate prediction of solvent accessibility using neural networks-based regression. *Proteins: Structure, Function, and Bioinformatics*, 56(4):753–767, 2004.
- K. Bache and M. Lichman. UCI machine learning repository, 2013. URL http://archive.ics.uci.edu/ml.
- P Balicza, B Bereznai, A Takáts, P Klivényi, G Dibó, E Hidasi, I Balogh, and MJ Molnár. The absence of the common lrrk2 g2019s mutation in 120 young onset hungarian parkinon's disease patients. *Ideggyogyaszati szemle*, 65(7-8):239–242, 2012.
- Debasish Basak, Srimanta Pal, and Dipak Chandra Patranabis. Support vector regression. Neural Information Processing-Letters and Reviews, 11(10):203–224, 2007.
- Dániel Bereczki and Szabolcs Szatmári. Treatment of dementia and cognitive impairment: What can we learn from the cochrane library. *Journal of the neurological sciences*, 283(1):207–210, 2009.
- Remco R Bouckaert. Choosing between two learning algorithms based on calibrated tests. In *Proceedings* of the 20th International Conference on Machine Learning (ICML-03), pages 51–58, 2003.
- Krisztian Buza, Alexandros Nanopoulos, and Lars Schmidt-Thieme. Insight: efficient and effective instance selection for time-series classification. In Advances in Knowledge Discovery and Data Mining, pages 149–160. Springer, 2011.
- Krisztian Buza, Alexandros Nanopoulos, and Gábor Nagy. Nearest neighbor regression in the presence of bad hubs. *Knowledge-Based Systems*, 86:250–260, 2015.
- E Busra Celikkaya, Christian R Shelton, Dave Kale, Randall C Wetzel, and Robinder G Khemani. Noninvasive blood gas estimation for pediatric mechanical ventilation. In *Machine Learning for Clinical Data Analysis and Healthcare, NIPS Workshop*, 2013.
- David Crosiers, Jessie Theuns, Patrick Cras, and Christine Van Broeckhoven. Parkinson disease: insights in clinical, genetic and pathological features of monogenic disease subtypes. Journal of Chemical Neuroanatomy, 42(2):131–141, 2011.
- Boguslaw Cyganek and Michal Wozniak. Tensor based representation and analysis of the electronic healthcare record data. In *IEEE International Conference on Bioinformatics and Biomedicine* (*BIBM*), pages 1383–1390. IEEE, 2015.

- Lonneke ML de Lau and Monique MB Breteler. Epidemiology of parkinson's disease. *The Lancet Neurology*, 5(6):525–535, 2006.
- MC d de Rijk, C Tzourio, MM Breteler, JF Dartigues, L Amaducci, S Lopez-Pousa, JM Manubens-Bertran, A Alperovitch, and WA Rocca. Prevalence of parkinsonism and parkinson's disease in europe: the europarkinson collaborative study. european community concerted action on the epidemiology of parkinson's disease. Journal of Neurology, Neurosurgery & Psychiatry, 62(1):10–15, 1997.
- Luc Devroye, Laszlo Györfi, Adam Krzyzak, and Gábor Lugosi. On the strong universal consistency of nearest neighbor regression function estimates. *The Annals of Statistics*, pages 1371–1385, 1994.
- Deborah Estrin. Small, n=me, data. Invited Talk at the conference of the Neural Information Processing Systems Foundation (NIPS), 2013.
- Wojciech Froelich, Krzysztof Wrobel, and Piotr Porwik. Diagnosis of parkinson's disease using speech samples and threshold-based classification. *Journal of Medical Imaging and Health Informatics*, 5(6): 1358–1363, 2015.
- CG Goetz, W Poewe, and O et al. Rascol. Movement disorder society task force on rating scales for parkinsons disease, the unified parkinsons disease rating scale (updrs): Status and recommendations. *Mov Disord*, 18:738–50, 2003.
- Christopher G Goetz, Barbara C Tilley, Stephanie R Shaftman, Glenn T Stebbins, Stanley Fahn, Pablo Martinez-Martin, Werner Poewe, Cristina Sampaio, Matthew B Stern, Richard Dodel, et al. Movement disorder society-sponsored revision of the unified parkinson's disease rating scale (mds-updrs): Scale presentation and clinimetric testing results. *Movement disorders*, 23(15):2129–2170, 2008.
- M Grana, M Termenon, A Savio, A Gonzalez-Pinto, J Echeveste, JM Pérez, and A Besga. Computer aided diagnosis system for alzheimer disease using brain diffusion tensor imaging features selected by pearson's correlation. *Neuroscience Letters*, 502(3):225–229, 2011.
- Lena Hartelius and Per Svensson. Speech and swallowing symptoms associated with parkinsons disease and multiple sclerosis: a survey. *Folia Phoniatrica et Logopaedica*, 46(1):9–17, 1994.
- Tomáa Horváth, Andreas Eckhardt, Krisztián Buza, Peter Vojtas, and Lars Schmidt-Thieme. Valuetransformation for monotone prediction by approximating fuzzy membership functions. In Computational Intelligence and Informatics (CINTI), 2011 IEEE 12th International Symposium on, pages 367–372. IEEE, 2011.

- Tomáš Horváth and Peter Vojtáš. Ordinal classification with monotonicity constraints. Advances in Data Mining. Applications in Medicine, Web Mining, Marketing, Image and Signal Mining, pages 217–225, 2006.
- Max A Little, Patrick E McSharry, Eric J Hunter, Jennifer Spielman, and Lorraine O Ramig. Suitability of dysphonia measurements for telemonitoring of parkinson's disease. *Biomedical Engineering, IEEE Transactions on*, 56(4):1015–1022, 2009.
- Jeri A Logemann, Hilda B Fisher, Benjamin Boshes, and E Richard Blonsky. Frequency and cooccurrence of vocal tract dysfunctions in the speech of a large sample of parkinson patients. *Journal of Speech and Hearing Disorders*, 43(1):47–57, 1978.
- Tan Pang-Ning, Michael Steinbach, and Vipin Kumar. Introduction to data mining. Pearson Addison-Wesley, 2006.
- Wioletta Pawlukowska, Monika Gołab-Janowska, Krzysztof Safranow, Iwona Rotter, Katarzyna Amernik, Krystyna Honczarenko, and Przemysław Nowacki. Articulation disorders and duration, severity and l-dopa dosage in idiopathic parkinson's disease. Neurologia i neurochirurgia polska, 49(5): 302–306, 2015.
- Tamara Pringsheim, Nathalie Jette, Alexandra Frolkis, and Thomas DL Steeves. The prevalence of parkinson's disease: A systematic review and meta-analysis. *Movement Disorders*, 29(13):1583–1590, 2014.
- Miloš Radovanović, Alexandros Nanopoulos, and Mirjana Ivanović. Nearest neighbors in highdimensional data: The emergence and influence of hubs. In Proceedings of the 26th Annual International Conference on Machine Learning, pages 865–872. ACM, 2009.
- Miloš Radovanović, Alexandros Nanopoulos, and Mirjana Ivanović. Hubs in space: Popular nearest neighbors in high-dimensional data. *The Journal of Machine Learning Research*, 11:2487–2531, 2010a.
- Miloš Radovanović, Alexandros Nanopoulos, and Mirjana Ivanović. Time-series classification in many intrinsic dimensions. In *Proc. 10th SIAM Int. Conf. on Data Mining (SDM)*, pages 677–688. SIAM, 2010b.
- Claudia Ramaker, Johan Marinus, Anne Margarethe Stiggelbout, and Bob Johannes van Hilten. Systematic evaluation of rating scales for impairment and disability in parkinson's disease. Movement Disorders, 17(5):867–876, 2002.

- Betul Erdogdu Sakar, MM Isenkul, C Okan Sakar, Ahmet Sertbas, Fikret Gurgen, Sakir Delil, Hulya Apaydin, and Olcay Kursun. Collection and analysis of a parkinson speech dataset with multiple types of sound recordings. *Biomedical and Health Informatics, IEEE Journal of*, 17(4):828–834, 2013.
- Ireneous N Soyiri, Daniel D Reidpath, and Christophe Sarran. Forecasting peak asthma admissions in london: an application of quantile regression models. *International journal of biometeorology*, 57(4): 569–578, 2013.
- Nenad Tomašev and Dunja Mladenić. Class imbalance and the curse of minority hubs. *Knowledge-Based* Systems, 53:157–172, 2013.
- Nenad Tomašev, Miloš Radovanovic, Dunja Mladenic, and Mirjana Ivanovic. A probabilistic approach to nearest-neighbor classification: Naive hubness bayesian knn. In *Proc. CIKM*, 2011.
- Nenad Tomašev, Krisztian Buza, Kristóf Marussy, and Piroska B Kis. Hubness-aware classification, instance selection and feature construction: Survey and extensions to time-series. 2015a.
- Nenad Tomašev, Miloš Radovanović, Dunja Mladenić, and Mirjana Ivanović. Hubness-based clustering of high-dimensional data. In *Partitional Clustering Algorithms*, pages 353–386. Springer, 2015b.
- A. Tsanas, M.A. Little, P.E. McSharry, and L.O. Ramig. Accurate telemonitoring of parkinson's disease progression by non-invasive speech tests. *Biomedical Engineering, IEEE Transactions on*, 57, 2010.
- Athanasios Tsanas, Max A Little, Patrick E McSharry, and Lorraine O Ramig. Nonlinear speech analysis algorithms mapped to a standard metric achieve clinically useful quantification of average parkinson's disease symptom severity. *Journal of the Royal Society Interface*, 8(59):842–855, 2011.
- Ian H Witten and Eibe Frank. Data Mining: Practical machine learning tools and techniques. Morgan Kaufmann, 2005.
- Michał Woźniak, Manuel Graña, and Emilio Corchado. A survey of multiple classifier systems as hybrid systems. *Information Fusion*, 16:3–17, 2014.
- Alexander Zimprich, Friedrich Asmus, Petra Leitner, Mirna Castro, Benjamin Bereznai, Nikolaus Homann, Erwin Ott, A WijnandF Rutgers, Gyri Wieditz, Claudia Trenkwalder, et al. Point mutations in exon 1 of the nr4a2 gene are not a major cause of familial parkinson's disease. *Neurogenetics*, 4(4): 219–220, 2003.