Towards Multi-view Approach to Parkinson's Disease Quality of Life Data Analysis

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Abstract. Parkinson's disease is a neurodegenerative disorder that affects people worldwide. While the motor symptoms such as tremor, rigidity, bradykinesia and postural instability are predominant, patients experience also non-motor symptoms, including decline of thinking abilities, behavioural problems, loss of taste and sense of smell, sleep disturbances, etc. Parkinson's disease greatly affects the quality of life of patients and their caregivers. Careful management of patient's condition is crucial to ensure the patient's independence and the best possible quality of life. This is achieved by personalized medication based on individual patient's symptoms and medical history. This paper explores the utility of machine learning for developing decision models, aimed to support clinicians' decisions about patients' therapies. The paper provides a short description of the available data for Parkinson's disease patients and states the reasons why multi-view clustering on short time series should be used for the further analysis of these data. It presents early results from rule learning and clustering used in the analysis of the collected data on the progress of disease symptoms. Our extended further work will be to detect patterns, which could help medical personnel to recommend changes in existing therapies with the aim to improve patients' quality of life.

1 Introduction

Parkinson's disease is a neurodegenerative disorder that affects people worldwide. Due to the death of nigral neurons, there is a shortage of dopamine in human brain causing several motor symptoms: tremor, rigidity, bradykinesia and postural instability. In addition to motor symptoms, Parkinson's disease is associated also with non-motor symptoms, which include cognitive and behavioural problems, loss of taste and sense of smell, sleep disturbance, gastrointestinal complications, and many others. These symptoms significantly decrease the quality of life of both the patients affected by Parkinson's disease and their families.

Around 6.3 million people have the condition worldwide, which is less than one percent of the total population [1]. In Europe, more than one million people

live with Parkinsons disease and this number is expected to double by 2030 [7]. Parkinson's disease is the second most common neurodegenerative disease (after Alzheimers disease) and its prevalence continues to grow as the population ages. The economic impact of the disease is high and its annual cost in Europe is estimated at 13.9 billion [12].

Currently, there is no cure for Parkinson's disease. The reasons for the cell death is still poorly understood. The management of patients' symptoms is of crucial importance for their quality of life and is mainly done with antiparkinson medication, such as levodopa and dopamine agonists. Good disease management will require the physician to have long-term and more frequent access to the symptoms of the patient.

Although many different studies can be found in the literature addressing specific aspects of the disease there are a few research efforts that adopt a holistic approach and address disease management [9]. The PERFORM [15], the REMPARK [14] and the SENSE-PARK [3] systems are intelligent closed-loop systems that seamlessly integrate a range of wearable sensors (mainly accelerometers and gyroscopes) constantly monitoring several motor signals of the patients and enabling the prescribing clinicians remotely assess the status of the patients, adjust medication schedules and personalize treatment [9].

PD_manager [2] is an EU Horizon 2020 project aimed at developing an innovative, mobile-health, patient-centric platform for management of Parkinson's disease. One of the PD_manager phases involves mining of data collected from Parkinson's disease patients in order to construct a decision support system which will be able to assist clinicians and patients in the personalized disease management. The data mining techniques developed for this project should be able to process different data sets describing the same patients in different time points. Our goal is to develop a method for multi-view clustering which based on the clusters formed at each time point and patients' history of medication therapies will be able to make suggestions about modifications of the therapy of a particular patient, with a goal to improve the patient's quality of life.

In this paper we present the idea of multi-view clustering on short time series. In Section 3 we present the Parkinson's Progression Markers Initiative (PPMI) data[1] [11], which are captured for monitoring the development of the Parkinson's disease, together with the descriptive data of each patient, and the type of medications used for symptoms control. Section 4 proposes methodology for analyzing the Parkinson's disease data through multi-view clustering of short time series and connecting the changes in clusters to changes in medication therapies with the goal to make suggestions for treatment changes. In this paper we only outline the methodology which we will implement in our future work. In Section 5 we present results from rule learning and clustering on one unified data set. These data represent the last known symptoms of the patients suffering from Parkinson's disease. Finally, in Section 6 we offer our conclusions.

[1] PPMI data set is available publicly on the website of Michael J. Fox foundation: `http://www.ppmi-info.org/access-data-specimens/download-data/`.

2 Background and motivation

Multi-view learning is a machine learning technique whose aim is building a model from multiple views (data sets) by considering the diversity of different views [17]. These views may be obtained from multiple sources or different feature subsets and describe the same set of examples. Co-training [4] is one of the earliest representatives of multi-view learning. In this case, there are two views: the first view is representing the labeled data, and the second view is representing the unlabeled data. Co-training first learns a separate classifier for each view using any labeled examples. The most confident predictions of each classifier on the unlabeled data are then used to iteratively construct additional labeled training data.

Multi-view clustering is concerned with clustering of data by considering the information shared by each of the separate views. Most of the multi-view clustering algorithms initially transform the available views into one common subspace, where afterwards they perform the clustering process [17]. In this way, they manage to reduce the dimensionality of the learning space and take advantage of the information shared between views.

Symptoms of patients suffering from Parkinson's disease can be divided into several views. When these views are combined together they offer a better image of the patients' condition. We believe that the usage of multi-view clustering on the Parkinson's disease data will be able to identify more efficiently clusters of patients that share similar symptoms. All views are susceptible to change through time. Patients' symptoms will change dependening on the received therapies, development of the disease, every day habits, etc. This will eventually lead to different clusters in different time points. By identifying the migration of patients from one cluster to another, modifications of the medication treatments will be suggested in order to keep the patients in the clusters where patients share symptoms that show good quality of life.

In the following sections we offer a brief description of the available Parkinson's disease data, the methodology we will implement in future work and results from the initial analysis of the available data.

3 Data

For the purpose of this study we have used the PPMI data set [11]. PPMI is an observational clinical study to verify progression markers in Parkinsons disease. Since 2002, the Michael J. Fox Foundation for Parkinsons Research (MJFF) has been an essential driver of the Parkinson's disease biomarker development efforts including the PPMI study. PPMI data set is the result of collaboration between researchers, industry, government and study participants that has emerged from these discussions [11]. The PPMI data set consist of attributes describing different aspects of the patient's daily living. Upon diagnosis, basic descriptive data is collected for each patient. These are data about patient's age, race, level of education, etc. Below we describe PPMI data, which we have used in this study,

such as MDS-UPDRS and MoCA, and the medication data, which are of our interest in future work.

The condition and quality of life of patients suffering from Parkinson's disease is determined using the Movement Disorder Society (MDS)-sponsored revision of the Unified Parkinson's Disease Rating Scale (MDS-UPDRS) [10]. It is a questionnaire consisting of 65 questions concerning the development of the disease's symptoms. The MDS-UPDRS is divided into four parts. Part I consists of questions about the "non-motor experiences of daily living". These questions address complex behaviors, such as hallucinations, depression, apathy, etc, and patient's experiences of daily living, such as, sleeping problems, daytime sleepiness, urinary problems, etc. Part II expresses "motor experiences of daily living". This part of the questionnaire is concerned whether the patient experiences speech problems, does she need an assistance with her daily routines, such as eating or dressing, etc. Part III is retained as the "motor examination", while Part IV concerns "motor complications", which are mostly developed when the main antiparkinson drug Levodopa is used for a longer period of time. Several questions from Part I and all questions from Part II have been designed to be amenable to a patient/caregiver questionnaire format and therefore can be completed without the investigators input. Remaining parts deal with complex behaviors and and are filled by the investigator following strict guidelines. Each question is anchored with five responses that are linked to commonly accepted clinical terms: 0 = normal (patient's condition is normal, symptom is not present), 1 = slight (symptom is present and has a slight influence on the patient's quality of life), 2 = mild, 3 = moderate, and 4 = severe (symptom is present and severally affects the normal and independent functioning of the patient i.e her quality of life is significantly decreased).

For the purpose of data mining, each of the MDS-UPDRS parts can be treated as one or four *views* (data sets) of the patient's condition. Questions from the questionnaires represent data set(s) attributes, and the value of the attributes is determined by the answer to a particular question (values from 0 to 4). Answers to all of the questions from the MDS-UPDRS questionnaires is mandatory. Patients represent instances in the data set, identified by a unique ID assigned when the patient was enrolled in the study. The MDS-UPDRS results for each patient are collected periodically approximately on every three months. This periodical collection of data allows for monitoring of the disease development for each patient through time.

The Montreal Cognitive Assessment (MoCA) [6] is a rapid screening instrument for mild cognitive dysfunction. It is a 30 point questionnaire consisting of 11 questions, designed to assess different cognitive domains: attention and concentration, executive functions, memory, language, visuoconstructional skills, conceptual thinking, calculations, and orientation. Attribute values correspond to the patients' answers to the respective questions. Patients are instances in the MoCA data set. Results from the MoCA test are collected periodically twice a year, allowing for the monitoring of the cognitive functions of Parkinson's disease patients through time.

Medications and multidisciplinary management are used to provide relief of the symptoms that affect the patient's quality of life. The main families of drugs useful for treating motor symptoms are levodopa, dopamine agonists and MAO-B inhibitors [8]. Which group of medications is most useful is determined by the stage of the disease. In the medication treatment of patients with Parkinson's disease there are two distinguishable stages. In the initial phase are patients with Parkinson's disease who have already developed some symptoms which have caused them disabilities for which they need pharmacological treatment. In the second stage are patients which have developed motor complications related to levodopa usage [8].

Treatment in the initial stage is directed towards finding an optimal trade-off between control of symptoms and side-effects resulting from improvement of dopaminergic function. The start of treatment using levodopa may be delayed by using other medications such as MAO-B inhibitors and dopamine agonists. This is done in the hope of delaying the onset of dyskinesias [8]. In the second stage the goal of the medications treatment is to reduce symptoms while controlling fluctuations of the response to medication. Sudden withdrawals from medication or overuse can have severe side-effects and have to be managed [8]. In our future work we will introduce the medication data set in order to determine what effect do certain medication therapies have on the symptoms of the patients. The PPMI data set offers information about all of the concomitant medications patients use during their involvement in the study. These medications are described by their name, the medical condition they are prescribed for, and when the patient has started and (if) ended the therapy with each particular medication. For the purpose of our research, we will initially concentrate on whether the patient receives a therapy with antiparkinson medications, and which combination of antiparkinson medications has she received between each of the time points when the MDS-UPDRS test and the MoCA test have been administered. Currently, our research work is in its initial stage. The medication data set will be introduced later, together with the multi-view clustering methods.

Careful tracking of patient's symptoms and her routines and habits is of very high importance for the effective management of the disease's symptoms.

When discussing the possibility of using a multi-view framework, the independence of the separate views should be discussed. In their work of 2008, Goetz et al [10] stated that the four parts of the MDS-UPDRS scale are considered to be independent due to the fact that obtained reliable factor structures for each part with the comparative fit index > 0.90 for each part, which supports the use of sum scores for each part in preference to a total score of all parts.

In this paper we considered all of the mentioned views as a single, unified view. We also considered only data from one time point (the last measured values). We did this in order to investigate whether we could identify group of Parkinson's disease patients which share similar symptoms and also identify symptoms (data sets) which are more informative than others. Since the motor symptoms are the most characteristic signs of the development of the disease we expected that the attributes from Part III from the MDS-UPDRS data will have

the biggest influence on constructed data models. At this point, data availability was the only reason why we considered only data in one time point.

4 Methodology

To assist the decision of clinicians to modify the patients' therapy, we propose a method which involves combination of multi-view clustering on patients' symptoms data and analysis of patient's history of medication treatments. Symptoms of patients suffering from Parkinson's disease can be grouped into several views. As we noted before, these views can represent data from MoCA test, motor experiences of daily living, non-motor experiences of daily living, complex motor examination data, etc. For each patient these data are obtained and updated periodically (on each patient's visit to the clinician's office) - in the beginning of the patient's involvement in the PPMI study, and approximately on each 6 months, in total duration of 5 years - providing the clinicians with the opportunity to follow the development of the disease. The visits of the patient can be viewed as time points, and the collected data on each visit is data about the patient in the respective time point.

Our method will be able to handle time changing data and make suggestions about possible modifications of the medication treatment. In each time point, new clusters will be formed using the multi-view data (MDS-UPDRS data, MoCA data) in that point. The measured values for quality of life of patients in each cluster will be compared with the values of quality of life of patients in the clusters produced in previous time points. Each change, whether positive or negative, will be noted together with the modifications of patient's medication treatment in that period. This data will be further used for making suggestions about treatment modifications for patients whose condition has worsen. These suggestions will be made by considering information about medication treatments of other patients during time periods when their condition has improved. In the initial phase, our method should be able to make suggestions about treatment changes. Later, we will improve it to produce numerical suggestions of drugs' dosage which should be prescribed to a patient.

In Figure 1 we present an abstract scheme of our method which we will implement in our future work. The circle represents the state of the framework at time point t_i. This is characterized by the collected multi-view data (MDS-UPDRS data, MoCA data, 4 separate data sets) at t_i and the antiparkinson medications patients have used during time points t_{i-1} and t_i. We will perform multi-view clustering on the available multi-view data at t_i and compare the clustering results with the ones obtained in t_{i-1}. We will use multi-view clustering via canonical correlation analysis, similar to the approach suggested by Chaudhuri et al [5]. The migrating patients from one cluster in t_{i-1} to another cluster in t_i will be then presented with the list of their medications. Based on this data, we will determine whether different combinations of medications influence the migration of the patients between clusters. Since clusters represent groups of patients with similar symptoms, the migration between clusters could indicate a

change of quality of life, correlated to the prescribed medication therapy. Later, we will also explore the possibility of comparing the state of the framework in t_i with all past time points.

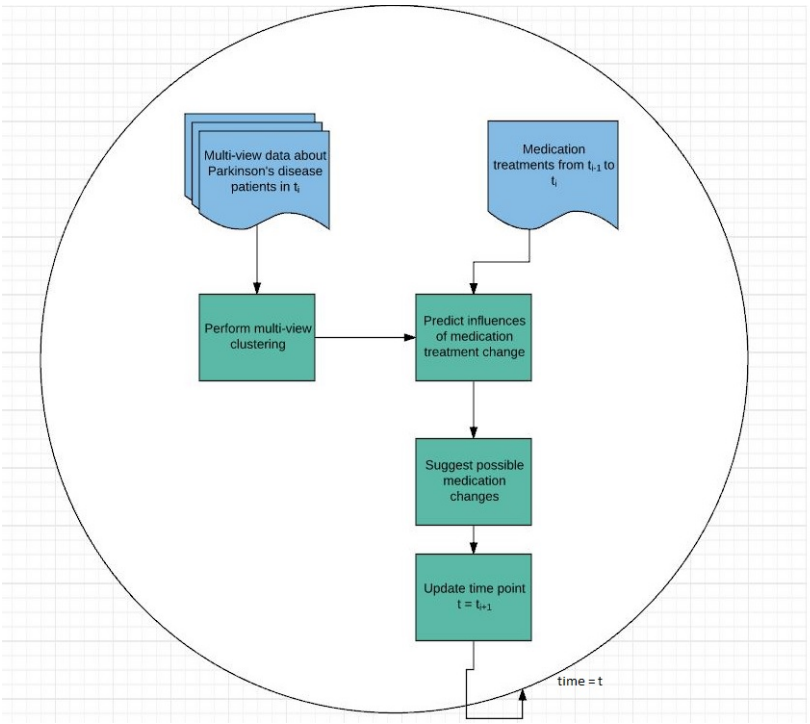

Fig. 1. Outline of the multi-view approach to Parkinson's disease quality of life data analysis.

In this phase of our research we have performed initial data analysis of the patients suffering from Parkinson's disease. We were interested to see whether we can distinguish groups of patients with similar symptoms, and what are the common descriptors of patients experiencing similar quality of life. Our analysis involves clustering and rule learning. Rule learning is a symbolic data analysis technique that can be used to construct comprehensible classification models and/or easily understandable patterns describing the data.

In this work, the rule sets for each class variable were learned using our recently developed DoubleBeam-RL algorithm [16]. This is a separate-and-conquer rule learning algorithm which uses two beams and different heuristics for rule refinement (which rule has the best potential to be refined into a rule covering most positive examples and as few as possible negative examples) and rule selection (which rule has the best potential to be added to the final model). This algorithm simultaneously keeps track of the best rules for rule refinement and

rule selection. Best rules are stored in the refinement beam and the selection beam respectively. This simultaneous track of best rules both for refinement and selection enables our algorithm to learn rules which otherwise might not have been detected by other algorithms [16]. For the purpose of our research we used the algorithm's best performing heuristics combination - (m-estimate, m-estimate).

5 Initial analysis of PPMI data

For the initial analysis of Parkinson's disease data, we used the latest collected information for 455 patients. For these patients, the MDS-UPDRS (Part I, II and III) and MoCA data were considered. Part IV of MDS-UPDRS was not used since our aim was to describe important attributes from Part IV as quality of life indicators. After consultation with a Parkinson's disease specialist we decided to take the third and fifth attribute from Part IV of the MDS-UPDRS data set as the main quality of life indicators, hidden to our analysis. The former represents the fraction of day the patient spends in the so-called "off-state", when the experienced symptoms prevent her from normal functioning. The later presents the complexity of motor fluctuations and is related to the predictability of patient's periods of low functioning. Both attributes take integer values from 0 to 4. Value 0 indicates that the patient does not experience the symptom, while value 4 indicates that the symptom almost completely prevents the patient from normal functioning. Both attributes have a significant influence on the patient's quality of life.

In this analysis of the PPMI data we performed rule learning and KMeans clustering. These approaches were used to investigate whether any groups of patients sharing the same symptoms can be determined, and whether patients sharing the same class label can be efficiently described.

5.1 Experimental settings

We were interested in rules describing the unified data set and rules for the clusters of patients with similar symptoms. We performed a KMeans clustering on the unified data set. The number of clusters was determined using the silhouette analysis technique [13] and a manual inspection the the silhouette graphs. For the purpose of our research work we chose the number of clusters to be 3. Later, we used the labels of the clusters as class labels in rule learning in order to obtain some meaningful description of the patients in each cluster. Rule sets describing the data from the unified data set (for three class variables, see above) were induced by using the rule learning algorithm described in Section 4.

5.2 Results

Due to the space restrictions, here we provide a partial list of the rules learned on the unified data set.

Table 1 presents the rules learned about class label *nupdrs4_43_time_spent_in_the_off_state = 1* (third attribute from Part IV of the MDS-UPDRS scale) on the unified data set using MoCA data and Part I, Part II, and Part III of the MDS-UPDRS data. This class label indicates that the patient spends 25 % or less of her time in *off state* when her normal functioning is decreased. As it can be observed from Table 1 the cognitive functions of the patients are normal. The results show that the *off state* is related to tremor, rigidity, fatigue and urination problems. The model for the class variable *nupdrs4_43_time_spent_in_the_off_state* consist of 22 rules.

RULE		p	n
nupdrs3_313_posture = 3 AND moca_delayed_velvet = 1 nupdrs2p_tremor = 1	← nupdrs4_43_time_spent_in_the_off_state = 1	8	0
moca_delayed_recall_church = 1 AND nupdrs2p_turning_in_bed = 1 AND nupdrs1p_urinary_problems = 3	← nupdrs4_43_time_spent_in_the_off_state = 1	10	1
nupdrs3_38a_leg_agility_right_leg = 0 AND nupdrs1p_fatigue = 4	← nupdrs4_43_time_spent_in_the_off_state = 1	4	0
nupdrs3_315a_postural_tremor_right_hand = 3 AND nupdrs2p_saliva_+_drooling = 2 AND nupdrs3_33c_rigidity_lue = 0	← nupdrs4_43_time_spent_in_the_off_state = 1	5	0
nupdrs3_33b_rigidity_rue = 2 AND moca_visuoconstructional_skills_clock_hands = 1 AND nupdrs2p_turning_in_bed = 2 AND moca_verbal_fluency = 1 AND moca_delayed_recall_daisy = 1 AND moca_moca_total_score > 26	← nupdrs4_43_time_spent_in_the_off_state = 1	5	0
moca_attention_serial_7s = 3 AND nupdrs1p_pain_and_other_sensations = 2 AND nupdrs3_38a_leg_agility_right_leg = 0 AND nupdrs3_315a_postural_tremor_right_hand = 0 and nupdrs1p_daytime_sleepiness = 2	← nupdrs4_43_time_spent_in_the_off_state = 1	7	0

Table 1. Rule set for class variable $nupdrs4\_43\_time\_spent\_in\_the\_off\_state = 1$. Variables p and n denote the number of covered true positive and false positive examples respectively.

Table 2 presents the rules learned about class label *nupdrs4_45_complexity_of_motor_fluctuations = 1* (fifth attribute from Part IV of the MDS-UPDRS scale) of the unified data set using MoCA data and Part I, Part II, and Part III of the MDS-UPDRS data. This class label indicates that the *off state* of the patient are predictible almost all of the time (>75 %). As it can be observed from Table 2 the recall functions of the patients are normal. Results suggest that the *off state* related to tremor, rigidity, fatigue and urination problems is predictable. Model constructed for the class variable *nupdrs4_45_complexity_of_motor_fluctuations* consist of 21 rules.

RULE		p	n
moca_delayed_recall_velvet = 1 AND nupdrs1_featuresdopamine_dysregulation_syndrome = 0 AND nupdrs3_31_speech = 0 AND nupdrs1p_sleep_problems_night = 4	← nupdrs4_45_complexity_of_motor_fluctuations = 1	10	0
moca_delayed_recall_red = 1 AND nupdrs2p_speech = 3 AND nupdrs2p_handwriting = 3	← nupdrs4_45_complexity_of_motor_fluctuations = 1	5	0
nupdrs3_315a_postural_tremor_right_hand = 3 AND nupdrs2p_tremor = 2 AND nupdrs3_34b_finger_tapping_left_hand = 0	← nupdrs4_45_complexity_of_motor_fluctuations = 1	5	0
moca_abstraction = 0 AND nupdrs3_37b_toe_tapping_left_foot = 2	← nupdrs4_45_complexity_of_motor_fluctuations = 1	5	0

Table 2. Rule set for class variable $nupdrs4\_45\_complexity\_of\_motor\_fluctuations = 1$. Variables p and n denote the number of covered true positive and false positive examples respectively.

Table 3 presents rules learned for the clusters produced by KMeans clustering in the case of $n = 3$. From Table 3 it is evident that patients were divided into clusters according to the sum of attribute values from Part III of the MDS-UPDRS data. According to the rules describing the clusters, the patients are dividided into three groups: patients that are not experiencing or are experiencing slight tremor, patients that are experiencing slight or mild tremor, and patients experiencing moderate or severe tremor.

RULE		p	n
nupdrs3_sum >33	← cluster = 1	139	0
nupdrs3_sum ≤ 18	← cluster = 0	131	0
nupdrs3_316b_kinetic_tremor_left_hand = 0 AND moca_moca_total_score ¿ 24 AND nupdrs3_sum ≤ 19	← cluster = 0	12	0
nupdrs3_sum = (19,33]	← cluster = 2	172	13

Table 3. Rules describing clusters obtained by KMeans clustering on the unified data set using MoCA data and Part I, Part II, and Part III of the MDS-UPDRS data. Variables p and n denote the number of covered true positive and false positive examples respectively.

Additional post analysis revealed that most of the patients described by rules from Table 1 are members of cluster 2. These patients experience symptoms which moderately affects their quality of life. Rules presented in Table 2 cover patients which are mostly located in cluster 1. These are patients which suffer symptoms that significantly affect their quality of life.

Results from our initial analysis of Parkinson's disease data reveal what is already very well known in the medical community - the motor signs reveal the most about the development and stage of the Parkinson's disease.

6 Conclusion

We presented some of the challenges in symptoms management for patients suffering from Parkinson's disease. We described the types of medications used for symptom management and their undesirable but expected side-effects. The aim of our research is to develop methodology which will make suggestions to clinicians about possible treatment changes that will improve the patient's quality of life. We present an initial data analysis using rule learning and clustering on patients' data and the results confirm what was already known about the Parkinson's disease: the motor symptoms, tremor, shaking, involuntary movement, etc. are the characteristic symptoms of the disease and they significantly affect the quality of life of the suffering patient even though the cognitive (in our case recall) functions are not affected. The criteria for the quality of life we used was the amount of daily time the patients spend in their *off state* i.e., in decreased level of independent and normal functioning.

In further work we will extend initial analysis with multi-view method which will make suggestions to clinicians about possible treatment changes that will improve patient's quality of life. This method will combine both objective (Part III of MDS-UPDRS data and MoCA data) and subjective (Part II of MDS-UPDRS data) symptoms assessment. The proposed modification to the therapy will be based on short time-series using the history of improvement or decline of patients' quality of life, and the history of medical treatments.

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