Parkinson's disease Assessment using Fuzzy Expert System and Nonlinear Dynamics

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***Abstract*—This paper proposes a new screening system for quantitative evaluation and analysis, designed for the early stage detection of Parkinson disease. This has been carried out in the view of improving the diagnosis currently established upon a basis of subjective scores. Parkinson's disease (PD) appears as a result of dopamine loss, a chemical mediator that is responsible for the body's ability to control movements. The symptoms reflect the loss of nerve cells, due to an unknown. The input parameters of the system are represented by amplitude, frequency, the spectral characteristic and trembling localization. The main symptoms include trembling of hand, arms, movement difficulties, postural instability, disturbance of coordination and equilibrium, sleep disturbance, difficulties in speaking, reducing of voice volume. The medical knowledge in PD field is characterized by imprecision, uncertainty and vagueness. The proposed system (fuzzy expert systems) is non-invasive and, easy to use by both physicians and patients at home.**

***Index Terms*—Parkinson's disease, Assessment, Tremor Symptom, Fuzzy, Expert Systems, Nonlinear Dynamics.**

I. Introduction and Parkinson's Disease Background

Parkinson's disease is a complex disease and the second neurodegenerative disease, after Alzheimer. There are also some other factors leading to the occurrence of the disease such as: fault of mitochondrial genes, exposure to pesticides, ingestion of drugs (heroine), free radicals, viruses (encephalitis inducers), as well as head shocks.

This disease has a prevalence of 1 to 100,000 in senior population [1]. Currently, there is no treatment or known cause for this disease. In Romania, over 75,000 patients suffer from Parkinson's disease, many of them being undiagnosed. The Romanian government spends over 1.5 million Euros every year on medication and treatments [1]. The lack of a good clinical test, combined with the patient's reticence to see a physician, delay the diagnostic until it is usually too late.

The number of over 50 years' old individuals diagnosed with PD was estimated at 4.1 million in 2005 and it is expected to double to 8.7 million in 2030 in USA [2]. In Europe about 1.2 million Parkinson's disease patients were reported.

Every year, about 50,000 patients are diagnosed with Parkinson's disease. Fewer than 75% of patients are correctly diagnosed with PD often after few years of the onset of the disease, the rest being diagnosed too late or undiagnosed at all [3].

Establishing an accurate diagnosis in the early stages of the disease can be difficult. Keeping the patient under observation for a certain period of time in order to evaluate the severity of symptoms, help the differential diagnosis between Parkinson's disease and other similar diseases. Parkinson's disease is diagnosed based on examining the patient according to some subjective criteria (scale Hoehn, Yahr, Universal Scale Parkinson disease evaluation, Beck's Scale, Geriatric Depression Scale), which involves comprehensive clinical expertise [4].

The disease manifests very differently from one individual to another, sometimes taking several years for the occurrence of a significant deterioration of daily activities. Currently, there is no screening test for early detection of Parkinson's disease. Symptoms become increasingly visible as the disease progresses. An early sign that may indicate (without binding) Parkinson's disease is the invisible hand tremor – an inside tremor, without any visible manifestation.

There are currently very few rules to correlate diagnosis with nonlinear dynamic characteristics of the observed processes. Various tests were made especially for Parkinson's disease tremor signal, with linear, statistical and nonlinear methods. The purpose was to obtain refined knowledge, meta-knowledge in order to make differentiation between normal and pathological tremor signals (Parkinsonian).

In recent research conducted by the authors of this paper, the physiological information and the time series parameters measured from gait and tremor signals have been combined in developing an automatic diagnostic system for Parkinson's monitoring and screening.

Parkinson's disease occurs in quite different ways from one patient to another, and symptoms become more and more obvious as the disease advances. In the incipient stage of the disease, the symptoms can be noticed for only half of the body.

The main signs that appear in incipient stages of the disease are the following [3]: hands tremor, movement difficulties - bradykinesia and akinesia, disturbance of coordination and equilibrium, sleep disturbance, depression; difficulties in speaking, difficulties in executing simple movements.

The diagnosis is determined by the neurologist, upon basis of expensive imaging procedures (neurodiagnostics, structure imaging, functional imaging), as of using well known subjective scales of evaluation.

Although there is no cure for Parkinson's disease, its symptoms can be attenuated by means of medication, as

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well as by modifying the lifestyle. Generally, the symptoms can be successfully controlled if the treatment is adapted to the evolution of the disease.

Starting with 1987, this “universal” scale has been introduced in order to evaluate the Parkinson’s disease (*Unified Parkinson's Disease Rating Scale*), thus quantifying its signs and symptoms. It monitors the disabilities, giving at individual sub score, at which the Hoen and Yahr’s score is added.

The purpose is to establish the stage of the disease. Schwab and England Activities of Daily Living (ADL) Scale evaluates the daily individual activities of the patient with Parkinson. The Unified Parkinson's Disease Rating Scale (UPDRS) is a rating scale used to follow the longitudinal course of Parkinson's disease [3-4].

It is made up of the following sections: evaluation of mentation, behavior, and mood (Part I); self-evaluation of the activities of daily life (ADLs) including speech, swallowing, handwriting, dressing, hygiene, falling, salivating, turning in bed, walking, cutting food (Part II); clinician-scored motor evaluation (Part III); Hoehn and Yahr stating of severity of Parkinson disease (Part IV); Schwab and England ADL scale (Part V).

Parts I, II and III contain 44 questions each measured on a 5 point scale (0-4). In monotherapy, a total UPDRS score is the combined sum of I to III, for example, 0 - not affected to 176 - most severely affected. In adjunct therapy, part IV is included. Part IV contains 11 questions and the scale can range from 0 to 23 [4].

Nowadays, the most common evaluation method for assessing the seriousness of the symptoms for patients with Parkinson’s disease (PD) is represented by the scales of clinical evaluation. These assign a score to each present symptom, but the main disadvantage is given by their subjectivity.

Different physicians can assign different scores to the same patient, where no measurements exist in order to be quantified. These criteria reunite aspects of anamnesis and clinical examination, where the error rate of PD diagnosis is of 10-20% [4].

II. Materials and Methods

Yet, some researches have been made (including in Romania) in order to early diagnose the PD and its progress by means of the handwriting analysis or other symptoms [5-8].

Some tests were performed in order to solve some diagnosis issues. These tests used the classification or fuzzy expert systems in the diagnosis of hepatitis or prostate cancer, or in the analysis of the umbilical cord blood [9-10].

Few data exist in the literature related to the coalescence of the nonlinear dynamics parameters with medical parameters. Thus, most of the parameters can be characterized by linguistic variables (fuzzy) [11-17]. There is almost no research in the field about appointing the score of Parkinson’s disease risk.

The database with affected patients has been provided by Suceava Hospital (Neurology Clinic). In this study, 28 PD (“Parkinsonian” tremor), 24 SPD (“Suspicious” PD tremor), and 30 NT (“Normal” tremor) subjects were analyzed. All patients are suffering moderate to severe postural tremor. This postural tremor cannot be differentiated on clinical features (frequency, amplitude).

Each column in the table represents a particular tremor measure, and each row corresponds to one of 2500 tremor recording from these individuals ("name" column). The mean disease duration (time for disease to install), age and sex of PD patients were compared with the SPD or NT in a previous paper [15].

The main aim of the data is to discriminate healthy people from those with PD, according to "status" column which is set to 0 for healthy and 1 for PD or “Suspicious”. The rows of the ASCII CSV format file contain an instance corresponding to one tremor recording. Each record is characterized by seven attributes (age, amplitude of tremor, frequency of tremor, value of Lyapunov exponent, fractal or correlation dimension and UPSDR).

The type of tremor seen in Parkinson’s disease is a shaking motion that mainly occurs at rest, and may decrease during activity. Initially, the tremor usually affects the arm, hand or fingers on one side of the body. The tremor is a flexion-extension of the forearm, or a pill rolling movement; beginning distally in one arm at 4-6Hz frequency.

The tremor time series were recorded using an accelerometer sensor from a Wii™ console, connected via Bluetooth™ to a PC. The data were analyzed using an application implemented in Visual C 2010 Professional. The Wii™ Remote, known as the Wiimote™, is the primary controller for Nintendo's Wii console used as accelerometer and optical sensor technology [18].

We chose to use a computer game device, the Nintendo, as a simple wireless accelerometer. We consider that Wii Remote Nintendo may be an attractive tool used by physicians and laboratory technicians as an accelerometer for monitoring the tremor. The Wii Remote contains an accelerometer that has a range of ±3 G, which is sufficient for tremor recording [18].

Nintendo has three-axes: x - lateral, y - anteroposterior, and z - vertical. The device records both acceleration induced by hand movement and the component of gravitational force. If the controller is rotated, the gravity accelerometer modifies the values on the x, y, and z axes.

This system using a Wii Remote is capable of analyzing frequency and estimated amplitude of tremor between 3 - 15 Hz (N tremor is between 5 - 12 Hz, and PD tremor is between 4-6 Hz). The Wii Remote and PC are connected by Bluetooth - Human Interface Device Profile.

The tremor analyzing program was developed using Visual C 2010 Professional. The acceleration sampling period was set at 10 ms in the Nintendo.

In Fig. 1 and Fig. 2 there are presented the two time series for “Suspicious” PD tremor and PD tremor, for the case x (lateral) = 0, y (anteroposterior) = 0, and z (vertical) = 1 (equilibrium state).

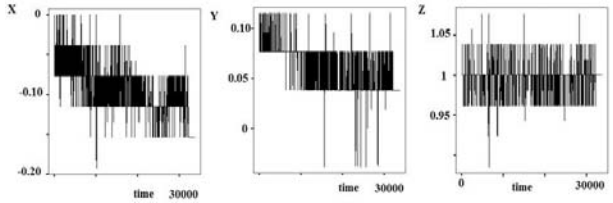


Figure 1. “Suspicious” Parkinson’s disease Tremor for the equilibrium state

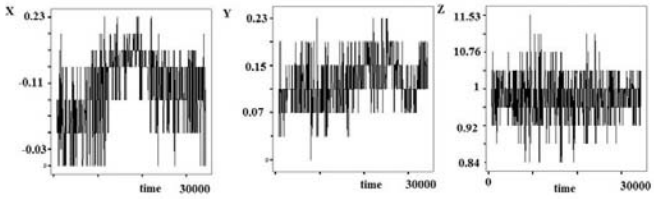


Figure 2. PD tremor (Parkinson's disease Tremor) for the equilibrium state

The accelerometer built into Wii™ Remote (Nintendo) measures gravitational and non-gravitational acceleration; all the findings of this paper suggest that Nintendo will be useful for measurement and analysis of tremor using the methodologies described in [18].

The tremor is a complex process, and respiration contributes to the low frequency movements. We removed these components, because respiration has a basic frequency of about 0.1-0.3 Hz, with a bandwidth in the range 0.05-3Hz. Previous researches [15], [19-24] indicate that Parkinsonian tremor may include a chaotic and a significant nonlinear component, which may play a part in Parkinson's disease screening. We determined the maximal Lyapunov exponent – first indicator of a chaotic dynamics, the correlation dimension and other parameters frequently used to characterize chaotic behaviors.

For the nonlinear analysis of tremor signals, using nonlinear dynamic parameters, we used several software packages, like CDA (Chaos Data Analyzer Programs [22]) and NLyzer (Nonlinear Analysis in Real Time [23]).

Using a CDA program we can analyze: phase diagram, probability distribution, power spectrum of the tremor signal, dominant frequencies, the maximum Lyapunov exponent, correlation dimension, capacity dimension, correlation function, Poincare sections.

We found that the value of Lyapunov exponent varies between 0.08 and 0.7, depending on the type of signal (in Fig. 3 we present Lyapunov Exponent for a subject with Parkinson's disease).

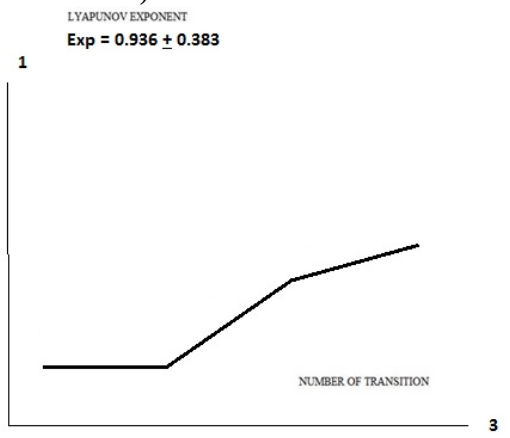


Figure 3. Lyapunov Exponent for a subject with Parkinson's disease

In Fig. 4 attractor is given a time series signal for a Parkinsonian Tremor. The results show that the attractor is different from one signal to another, depending on its dynamics. If the signal is chaotic, the representation is an open curve called "strange attractor".

The next step was the synthetic representation based on the linguistic labels of fuzzy logic and the main parameters of tremor (tremor amplitude, frequency, irregularity, spectral nature, etc.). To reduce the number of parameters representations, but to keep the essential information we use parameters for numerical analysis.

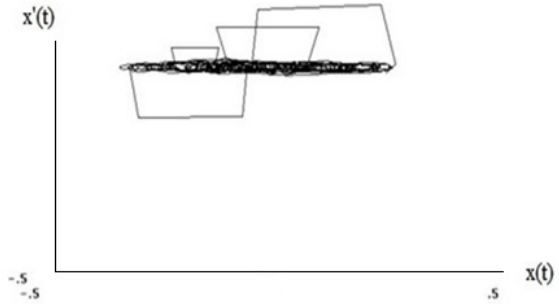


Figure 4. Atractor for Parkinsonian tremor time series ("strange attractor")

We designed a laboratory model of the expert system, which includes the fuzzy rules for diagnosis and treatment of tremor. Therefore, we moved to another stage of the research theme, namely the development of applicative software package.

Also, for the removal of specific elements of nonlinear dynamics and software, we use NLyzer, Nonlinear Analysis in Real Time, to obtain different values for fractal dimension, and various forms of autocorrelation function or attractor.

For databases already analyzed, the Lyapunov exponent ranges between 0.08 and 0.7, and for subjects with Parkinson's disease ranges between 0.02 and 0.06. Fractal dimension for normal subjects varies between 1.75 and 2.04, and for Parkinsonian subjects ranges between 2.45 and 2.67.

III. The Fuzzy Expert System Design

Bioinformatics is one of the most dynamic areas of computer sciences that has change its essential interest and impact over the last 5-10 years. Analysis of large database and retrieval of knowledge in the medical field are currently considered as major priorities in Bioinformatics.

Success in the discovery of knowledge depends on the ability to explore different classes of specific data and to apply appropriate methods in order to extract the main features. These data and knowledge (facts) will be embedded in a set of rules which represent in fact the rules of a knowledge-based system for diagnosis of Parkinson's disease.

In this case, and for an accurate diagnosis of the PD, we proposed the implementation of a Fuzzy Expert System, which includes data and knowledge specific to chaotic dynamics. In order to obtain a correct diagnosis, it is mandatory to include new types of data and knowledge by using applications from the new scientific branches of artificial intelligence, and also by involving latest discoveries in medicine.

There are major tasks that must be typically performed in the development of a fuzzy logic expert system: defining the problem, defining the linguistic variables, defining the fuzzy sets and fuzzy rules, building the Fuzzy Expert System, testing and tuning the system [24-27].

The rules of the Fuzzy Expert Systems are based on the retrieved knowledge, which helps in the diagnosis of the symptoms of tremor and prescription, including rules that result from data processing and nonlinear dynamics specific knowledge.

Next, we present for illustration one rule of this type:

"IF amplitude tremor is high
AND low frequency spectral character
OR Media AND is regularly
AND Lyapunov exponent is positive (value 0.2)
AND location trembling arms, hands, head translational motion
AND state-dependent production conditions
AND type motion - translation
AND the patient condition
THEN diagnosis is Parkinson's disease."

This system is specific to fuzzy expert - hybrid systems. It consists of individual, expert, knowledge engineer, fuzzy rule base, fuzzy inference engine and fuzzyfication or defuzzification.

In order to identify the risk score of Parkinson's disease, the FIS tool in Matlab software was used, where FES – Fuzzy Expert System structure is illustrated in the following figure:

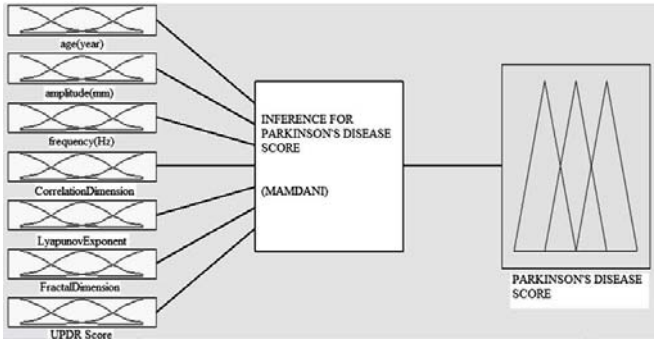


Figure 5. FES – Fuzzy Expert System structure

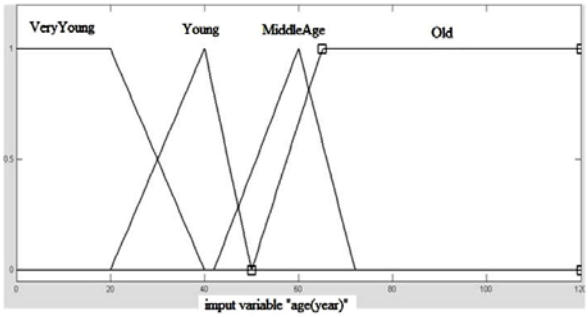


Figure 6. Membership Function Age[year] (Very Young, Young, Middle Age, Old)

To represent a fuzzy set in a computer we need to define its membership function. The trapezoidal and triangle functions of affiliation were used. The membership functions of the Parkinson's disease fields have been defined as shown below.

For example, in Fig. 6 consider that the concept of "age", and the membership functions are: Very Young, Young, Middle Age and Old. When we define multiple fuzzy sets on the same universe of discourse, the fuzzy literature often refers to them as fuzzy subsets [24-27].

Assuming we have a universe of discourse x and a fuzzy set A defined on it. We also assume to have a discrete set of x elements $\{x_1, x_2, ..., x_n\}$. The fuzzy set A defines the membership function $\mu_A(x)$ that maps the elements x_i of x_n to the degree of membership in $[0,1]$.

$$\mu_A(x) = Degree(x \in A),\ 0 \le \mu_A(x) \le 1 \quad (1)$$

For a discrete set of elements, a way to represent a fuzzy set is to use a vector:

$$A = (a_1, a_2, ..., a_n), \quad a_i = \mu_A(x_i) \quad (2)$$

We consider, for example in Fig. 7, the fuzzy set of High Amplitude[mm].

$$HighAmplitude = (0/3, 0.5/6.5, 1/10)\ [mm].$$

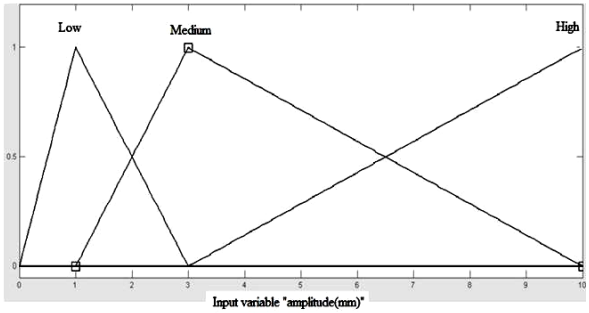


Figure 7. Membership Function Amplitude[mm] (Low, Medium, High)

In Fig. 8 it is shown the Output Fuzzy Membership Function Parkinson's Disease Score (Very Low, Low, Middle, High, Very High).

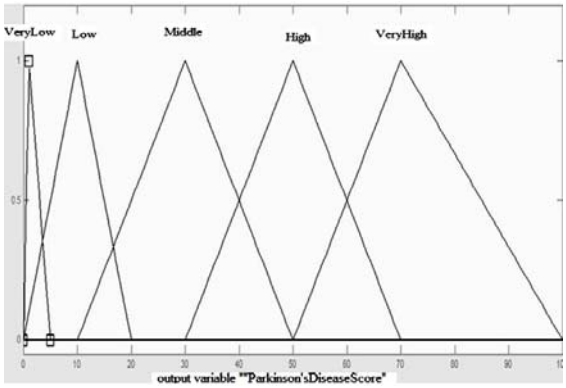


Figure 8. Output Fuzzy Membership Function Parkinson's Disease Score (Very Low, Low, Middle, High, Very High)

We have the following fuzzy rule:

"IF Age[year] is Old (A)
AND Amplitude[mm] is High (B)
AND Frequency[Hz] is Very High (C)
AND Lyapunov Exponent is High (D)
AND UPDRSScore is Sever (E)
THEN Parkinson's disease Score is Very High (F)."

Two most popular fuzzy inference techniques used in practice are *max-min inference* and *max-product inference*. We used *max-min inference*, and the implication operator used is *min*.

Assume that fuzzy set A is define on a, set B on b, … , set E on e. The approach relies first on defining for each premise a separate M matrix that relates the premise to the conclusion. Then given some input information on the premise A', B', …, E' the induced fuzzy sets on F can be computed independently through composition (3) [21]:

$$A' \circ M_{AF} = F_{A'}, \ldots, E' \circ M_{EF} = F_{E'} \quad (3)$$

The next step is to recompose the fuzzy sets $F_{A'}, ..., F_{E'}$. The fuzzy logic intersection operator is used to join the induced fuzzy sets (4) [21]:

$$F' = [A' \circ M_{AF}] \wedge [B' \circ M_{BF}] \wedge [C' \circ M_{CF}] \wedge ... = \\ = F_{A'} \wedge F_{B'} \wedge F_{C'} \wedge ... \quad (4)$$

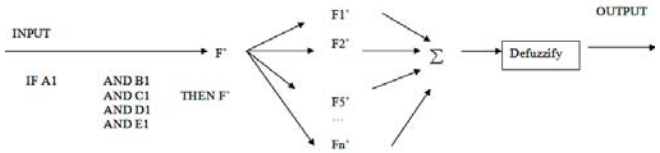
The fuzzyfication of the applied fields has been carried out by some functions, as shown below and that can be used by the physicians. The memberships of the used factors are obtained from formulas (5) – (7):

$$Age(A) = \begin{cases} 1, & 65 \le a \\ \alpha, & 0 < a < 65 \end{cases} \quad (5)$$

$$Amplitude(\alpha) = \begin{cases} 1, & \alpha \ge 10 \\ 0, & \alpha \le 1 \\ \alpha, & 1 < \alpha < 10 \end{cases} \quad (6)$$

$$PDScore(\lambda) = \begin{cases} \lambda, & 0 < \lambda < 100 \\ 0, & \mu < 0 \\ 0, & \mu > 0 \end{cases} \quad (7)$$

The Rule Editor:



For example, the membership function $\mu_A(x)$ that maps the elements x_i of x to the degree of membership in $[0,1]$, for age, Amplitude and Frequency are obtained in formulas (8) - (10):

$$\mu_{Middle}(Age) = \begin{Bmatrix} 0/35 + 0.33/40 + 0.67/45 + 1/50 + \\ + 0.67/55 + 0.33/60 + 0/65 \end{Bmatrix} \quad (8)$$

$$\mu_{High}(Amplitude) = \{0/3 + 0.33/5.5 + 0.67/7.5 + 1/10\} \quad (9)$$

$$\mu_{High}(Frequency) = \{0/6 + 0.5/7 + 1/8 + 0.5/9 + 0/10\} \quad (10)$$

The most popular defuzzification technique used is the *fuzzy centroid method*. Defuzzification is important when multiple rules conclude the same diagnosis.

The Truth Degrees (α) of the rules are determined for each rule, by means of the min and max values between working rules. For example, for a 50 years old patient, the values are: 2 mm in Amplitude, 6 Hz in Frequency, 1.4 in Lyapunov Exponent, 1.3 in Fractal Dimension, 3.2 in Correlation Dimension, and 106 UPDRScore. According to the rules 64 and 82, the following data will be obtained:

α_{64} =min(Middle Age, Medium Amplitude, Medium Frequency, High Lyapunov, High Fractal Dimension, High Correlation Dimension, UPDRScore Severe) = min(0.67,1,1,1,1,1,1) = 0.67.

α_{82} =min(Old Age, Medium Amplitude, Medium Frequency, High Lyapunov, High Fractal Dimension, High Correlation Dimension, UPDRScore Severe) = min(0.33,1,1,1,1,1,1) = 0.33.

In accordance to Mamdani max-min inference, one will obtain the membership function of the proposed system, meaning: max(α_{64}, α_{82}) = 0.67, which is the High PDScore. Then, the crisp output is calculated, by the center of gravity defuzzification method, as expressed in the formula (11).

According to the developed rules, and meeting the formulas (3) – (5), for Middle Age, High Amplitude, High Frequency, the defuzzyfication formula will have the following form (11) [21].

$$D^{crisp} = \frac{\int D \times \mu_{Middle}(D) dD}{\int D\, \mu_{Middle}(D) dD} \quad (11)$$

For example, the PDScore value of 62.7 means that the patient has Parkinson Disease with a probability of 62.7%, for Age 50 year, Amplitude 2 mm, Frequency 6 Hz, Exponent Lyapunov 1.4, Fractal Dimension 1.3, Correlation Dimension 3.2, and UPDRScore 106.

These results were calculated by comparing the clinical diagnosis and "probable" diagnosis given by our PD Screening System.

The results of the Parkinson's disease Screening System with fuzzy rules for the given cases indicate, have the similarity diagnosis with the human expert at 94.26% [16].

Future works includes Certainty Factors (CF) in our rules to improve the diagnosis accuracy.

To improve the diagnostic accuracy, the aims of the Parkinson's disease Screening System, using fuzzy tools are the optimization within the heuristic evaluation, and the enlargement of the case library and fuzzy rules.

IV. Conclusions

Nowadays, there is insufficient evidence in scientific literature, on the one hand about the application of dynamical time series analysis for tremor evaluation, and on the other, about the evaluation of the changes in brain rhythms in connection with the body movement impairment.

This vital information may be combined with the meta-knowledge system designed for archiving clinical and physiological inductions and other information about tremor and the prescribed trajectory of hand (or leg) movement to be used for Parkinson's disease screening.

The proposed Fuzzy Expert System was designed by using a model of 28 PD tremor time series, 24 "Suspicious" PD tremor time series and 30 "normal" tremor time series. This paper proposes a model for a fuzzy expert system, dedicated to Parkinson's disease diagnosis, and which can be used by specialists.

In the proposed research approach, a fuzzy expert system was designed, by using FIS Tools of MATLAB. In the Fuzzy Expert Systems, the achieved accuracy of diagnosing the Parkinson's disease was of 95.46%.

The Fuzzy Logic Toolbox function that accomplishes the adjustment of membership's function parameter in MATLAB is assigned as ANFIS (Adaptive Neuro-Fuzzy Inference System). By using a given input or output data set, the ANFIS function creates a fuzzy inference system (FIS), whose Membership Function parameters are adjusted by means of the back propagation algorithm, or in combination with the least squares method.

Using Matlab software, an ANFIS box was used, in order to create ANFIS (loading the training and testing data, assigning the basic FIS model, assigning the optimization of FIS model parameters, training the system, calculating the errors average probability or testing the systems).

Building a fuzzy expert system is an iterative process, where an initial collection of fuzzy rules and fuzzy sets is formed and tuned. Tuning a fuzzy expert system involves adjustments of the existing rules or fuzzy sets.

The overall dynamic system will be limited by the clinical

impressions of the patient embedded in a knowledge-based system. The overall complex constrained problem will be solved to enable a powerful model for recognition of Parkinson's disease and establishing appropriate rules for its clinical follow up.

The achieved preliminary results emphasize that the fuzzy relations should be taken into account as an accurate method to handle the imprecision of Parkinson's disease diagnostic. This emphasizes the handling of decision making procedures in the PD treatment, thus encouraging future research studies, in order to perfect the proposed model (with medical expertise).

Future research proposals include the testing and validation of a screening test, in order to detect Parkinson's disease in its early stages. Our contribution therefore has a major impact as currently there is no clinically approved automatic system for monitoring Parkinson's disease.

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