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Parkinson's Disease Prediction based on Multistate Markov Models

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Abstract: In the real medical world, there are many symptoms or chronic diseases that cannot be characterized in a deterministic way, and which must be examined in a random way. In the study of these stochastic processes, Markov chains are used. There is a wide variety of phenomena that suggest a behavior in a Markov process manner such as: the probability that a patient's health to improve, to get worse, to remain stable or to progress to death within a certain time slot, depending on what happened in the previous time window. Our goal is to show that the Markov chains can be applied to the patients with Parkinson's disease in order to predict the evolution of the disease over time. So the doctor may decide a therapeutic solution that is adapted to the patient's needs, and that can improve the quality of the patient's life with Parkinson's disease in terminal stage.
Keywords: Parkinson's disease, Markov chains, Multistate Markov Models, Prediction

1 Introduction

Parkinson's disease (PD) is a neurodegenerative disease that occurs due to loss of dopamine that is a neurotransmitter and due to slow and inexorable destruction of neurons. Brain area affected by progressive destruction of neurons is responsible for movements controlling [1]. For this reason, patients with Parkinson's disease have rigid and uncontrollable gestures, postural instability, tremor, and speech disorders. Although Parkinson's disease is considered specific old age, the average age is 50 years and can be confused with the normal aging process of the individual [2]. When first symptoms are manifested, it is believed that between 60% and 80% of the cells for the control of motor activity are destroyed [3]. Parkinson's disease is a progressive disease, with signs and symptoms accumulated over time. Although this is potentially an invalidity disease, it progresses slowly so that most patients benefit from many years of active life after diagnosis. Moreover, unlike other serious neurological disorders, Parkinson's disease is treatable. Treatment is surgical or based on drugs, but may also consist of an implanted device for brain stimulation [4]. Worldwide, the disease is diagnosed in 300,000 people each year [5]. Disease incidence and prevalence increase with age. Parkinson's disease affects 1% of people aged over 65. Rarely, the disease occurs in childhood or adolescence. The incidence is 1.5 times higher among males than among women [6]. If Parkinson's disease would be detected in an early stage, the physician may interfere with a proper treatment in order to slow the disease's progression. Unfortunately, currently there is no screening test or biomarker that

can be highlighted in Parkinson's disease. The three cardinal signs of Parkinson's disease are resting tremor, rigidity and bradykinesia. Among them, two are essential for diagnosis. Postural instability is the fourth cardinal sign, but occurs late, usually after 8 years of disease evolution. In 70% of cases, uncontrollable rhythmic gestures of the hands, head and feet are the first symptoms and occur mainly at rest and during the stress' periods (see [7]- [9]). Tremor is diminished during movements, disappears during sleep, and is exacerbated by stress and fatigue. Tremor becomes less evident as disease progression. This tremor, in the absence of other characteristic signs, indicates an early stage of disease or another diagnosis (see Table 1) [10]- [14].

Table 1: Neurological disorders characteristic signs

Moment	Speed	Location	Neurological Disorders
Rest tremor	4-6 Hz	arms, legs	Parkinson's disease
Postural tremor	7-12 Hz	hands	Essential tremor
Intention tremor	2-5 Hz	arms,legs	Cerebellar lesions

From the many symptoms or diseases that cannot be characterized in a deterministic way, but in a random way, PD is a prominent example. In our study, we used Markov chains as they characterize very well stochastic processes like diseases evolutions. So, our goal is to show that the Markov chains can be applied to the patients with PD in order both to predict the evolution of the disease over time, and illustrate the response to the specific treatment. In this way the doctor may decide upon a therapeutic solution that is adapted to the patient's needs, and can improve the quality of the patient's life in terminal stage.

2 Multistate Markov models

In mathematics, a Markov process is a stochastic process having the property that, given its present state, the future states are independent of the past. This property is called the Markov property [15]- [19]. In a Markov process, the system can change or keep its state, according to a certain probability distribution. Changes of its state are called transitions. A random experiment that consists of a series of random sub-experiments is called a stochastic process. Such a special class of these processes is made by the Markov chains [20]- [26].

The evolution of a Markov process can be described by a transition matrix. We can consider the evolution of the health status of a patient as a Markov process that passes through the following states: Well, Suspicious, Ill (PD), or Dead, as is illustrated in Figure 1. For the Markov process illustrated in Figure 1, we can write the general matrix (1), where m = 4 (possible mutually exclusive results: E1 well, E2 suspicious, E3 ill/PD, E4 dead).

$$P = \begin{bmatrix} p_{ww} & \dots & 0 \\ \dots & \dots & \dots \\ 0 & \dots & p_{dd} \end{bmatrix} \tag{1}$$

As it can be seen, the transition matrix consists of p_{ij} elements, which represent the conditional probability that the system will change from the initial state (well) to next state j. The probability that the system remains in the same state after the experiment is given by p_{ij} with i = j, and the probability for the system to move from one state to another is given by p_{ij} with i≠j. The transition matrix for the proposed system is a square matrix of order m = 4. The elements of the transition matrix must satisfy the following properties [19]:

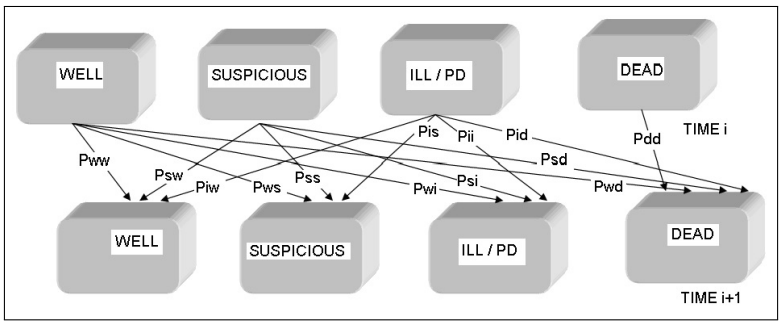

Figure 1: Four-state Markov Model for Parkinson's disease stage (well, suspicious, ill/PD, dead)

1. $0 \leqslant p_{ij} \leqslant 1, i, j = 1, ..., m.$

2. $\sum_{j=1}^{m} p_{ij} = 1, i = 1, 2, ..., m.$ The sum of the elements of each line must be 1 because $E_1, ..., E_m$ is a complete system of events.

3. $p_{dd} = 1$, for our application.

Information about the transitions from one state to another in a Markov chain can be represented by a transition matrix. It consists of elements p_{ij} - probability of crossing a step from state i to state j (i,j = 1,..., m, where m=4). We can talk about the transition probability of exactly k steps and a matrix formed by them. So, multistate Markov models in continuous time may be used to model the course of Parkinson's diseases. Since Markov chains are stochastic processes, we cannot know exactly what it is happening on each state, so the system must be described in terms of probability.

Definition 1. [19]: Consider a Markov chain with m states. A state vector for Markov chain is a probability vector $X = [x_1, x_2, ..., x_m]$. The x_i coordinates of the state vector X should be interpreted as the probability that the system be in the state i.

The behavior of a Markov chain can be described by a sequence of state vectors. The initial state of the system can be described by a state vector noted X_0. After a transition, the system can be described by a vector X_1 and after k transitions the system is described by the state vector X_k. The relationship between these vectors can be summarized by the following theorem [19]:

Consider a Markov process with the transition matrix P. If X_k and X_{k+1} are vectors that describe a process state after k and k +1 transitions respectively, then $X_{k+1} = X_k * P$.

We represent structural elements as a vector $S = [s_t^1, ..., s_t^i, ..., s_t^m]$, that for each t = 1,...,n and for each i = 1,...,m, s_t^i varies between 0 and 1, and the sum of structural elements is 1 for any t. In order to model a Markov process, we must respect the following steps [19]:

1. First-order differences of the vector S_t will be calculated, thus $\Delta S_{t/t-1} = S_t - S_{t-1}$.

2. For each pair $t/t-1$ of consecutive periods of time we will buid the partial transition matrices (MTP), as $MTP_{t/t-1}(m*m)$ form. The elements of the $MTP_{t/t-1}(m*m)$ matrix can be determined as follows:

$$MTP_{t/t-1}^{ij} = min(s_{t-1}^i, s_t^j) if i = j \tag{2}$$

$$MTP_{t/t-1}^{ij} = \left| \Delta s_{t/t-1}^j * \frac{\Delta s_{t/t-1}^j}{\sum_{i=2}^{m} (+\Delta s_{t/t-1}^{ij})} \right|, \tag{3}$$

if i $\neq j$ and $\Delta s^i_{t/t-1} < 0$ and $\Delta s^j_{t/t-1} > 0$.

$$MTP^{ij}_{t/t-1} = 0, \tag{4}$$

for the other elements, where i,j =1,...,m.

In formula (3) the expression $\sum_{i=2}^{m}(+\Delta s^{ij}_{t/t-1})$ denotes the sum of positive values of the difference vector $\Delta s_{t/t-1}$.

3. $MTP(m * m)$, total transition matrix is determined by summing the elements of partial transition matrixes.

4. $MP(m * m)$, transition probability matrix is calculated by ratio between each element of the total transition matrix and the sum of the line on which is located than item.

5. In the final stage of the algorithm, we obtain a forecast of the structural elements for future p periods by multiplying transposed of the matrix $MP(m * m)$ raised to the k power with the vector of structural elements for the last period.

3 Intelligent system for health status prediction using a Markov chain

The architecture of the proposed system is shown in Figure 2. It consists from three modules. The first module will handle with the signal acquisition from patients suspected of Parkinson disease. In terms of software, this module is a software application that can acquire biomedical signals from Wii^{TM} Remote device or other devices that can acquire signals generated by tremor. All data acquired from these devices are analyzed using the method presented in Section 2. Furthermore, the data are saved on a server. On this server, physicians can access data in order to establish a long history of patient evolution.

The second module of this system is represented by the extracting knowledge from biomedical signals acquired from the patients. This module consists of a software application that runs on the server where there are kept biomedical signals acquired. The third module is the application that is executed in the doctor's office. This application performs an interfacing of the doctor with the intelligent system, and presents the medical treatment and rehabilitation options. It must be said that bio-signals can be acquired in the doctor's office but also at home if the patient has a PC and an internet connection. The design and development of this intelligent system used the newest technologies for distributed application development (WCF, SOAP), and the observations received from patients and specialists.

3.1 Database

For the database we used the proposed methodology in previous papers [27], [28]. Database with affected patients has been provided by Suceava Emergency Hospital (Neurology Clinic).

This dataset is composed of a range of biomedical tremor measurements from 88 people, 28 with Parkinson's disease (PD), 30 "normal" tremor and 30 "suspicious" PD (undiagnosed). Each column in the table is a particular tremor measure, and each row corresponds one of 2500 tremor recordings from these individuals ("name" column). 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". All patients are suffering of moderate to severe postural tremor. This postural tremor cannot be differentiated on clinical features (frequency,

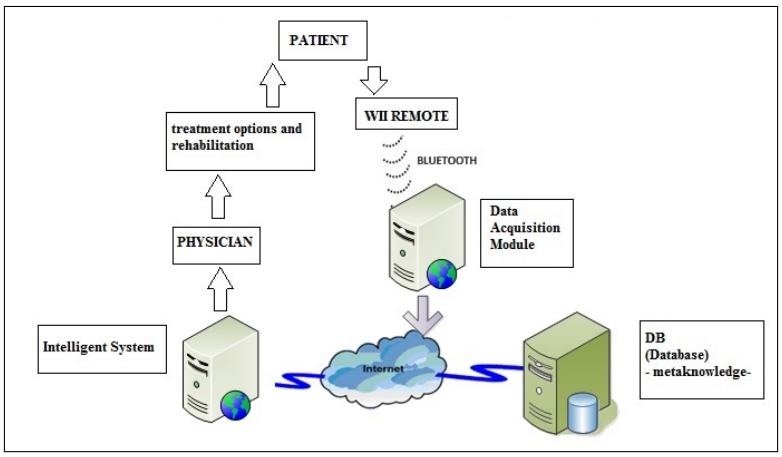

Figure 2: Intelligent system for health status prediction of a patient using a Markov chain

Table 2: Data: size, age, gender, and disease duration distribution of PD, SPD, and NT subjects

	PD	SPD	NT
Number of patients	28	30	30
Mean age	64.54	63.24	64.52
(range in years)	(40-90)	(27-94)	(24-86)
Gender (male/female)	18/10	16/8	19/11
Mean disease duration	16,4	5,3	

amplitude). Patients were kept under observation and investigation for 2 years, and data were acquired at 6 months, 1 year and 2 years (see Table 2).

The mean disease duration (time for disease to install, in years), age and sex of PD patients were compared with the SPD or NT in Table 2. Notice in Table 2 that the mean age of PD, SPD and NT populations is similar, but the age ranges are different. This could be considered as an indicator that the PD starts years before actual diagnosis.

3.2 Tremor recoding

Yet, some researches have been made (including in Romania) in order to early diagnose the PD and its progress by means of the tremor or the gait analysis or other symptoms [29]- [34]. The tremor time series were acquired using an accelerometer sensor from a Wii^{TM} console [35], connected via Bluetooth to a PC. The data were analyzed using an application implemented in Visual C 2010 Professional. The Wii^{TM} Remote is the primary controller for Nintendo's Wii^{TM}i console. A main feature of the Wii^{TM} Remote is its motion sensing capability, which allows the user to interact with and manipulate items on screen through the use of accelerometer and optical sensor technology [35]. Nintendo works on 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 affects the values on the x, y, and z axes (see Figure 3).

This system using a Wii^{TM} 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^{TM}i Remote and PC are connected by Bluetooth - Human Interface Device Profile. The tremor analysis program was developed using Visual C 2010 Professional. The acceleration sampling period was set at 10 ms in the Nintendo device. Because the transmission rate through

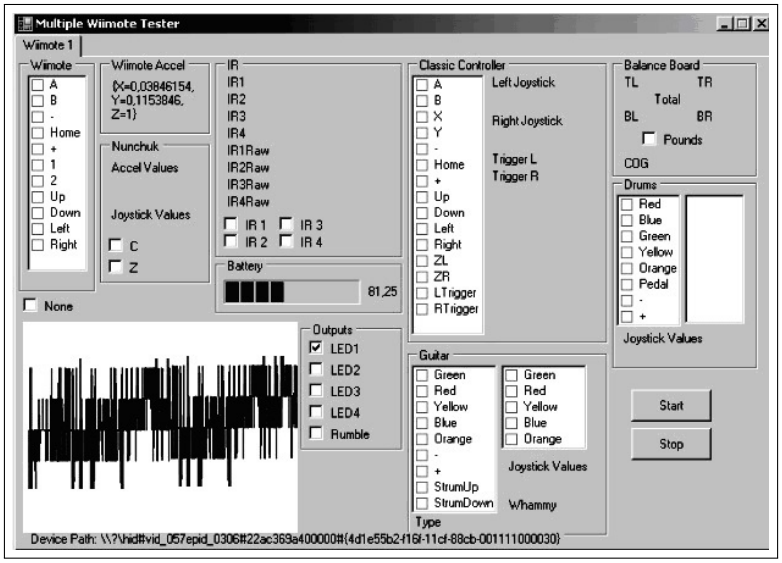

Figure 3: Interactive GUI using Wii^{TM} Remote (tremor application)

the Bluetooth device is limited, the sampling period of the tremor analysis was 40 ms. The accelerometer built into Wii^{TM} Remote (Nintendo) measures gravitational and non-gravitational acceleration. The results of this paper suggest that Nintendo is useful for measurement and analysis of tremor using the methodologies described in [28], [29], [31]. We defined the following linguistic variables (for instance for X axis):

- If x is between -0.10 mm and -1 mm then x is minimum X_{min};
- If x is between -0.10 mm and 0.10 mm then x is medium X_{med};
- If x is between 0.10 mm and 1 mm then x is maximum X_{max}.

We counted the number of spikes for each interval, and we used these values to describe the state vector.

Next we proposed to predict the state of a patient using Markov chains. In this analysis the state vector is defined as:

$$S = X_{min}, X_{med}, X_{high}, Y_{min}, Y_{med}, Y_{high}, Z_{min}, Z_{med}, Z_{high} \tag{5}$$

. Table 3 presents the number of spikes in each category for "normal" subjects, while Table 4 presents the values of the state vector for a subject with diagnosed Parkinson's disease.

For this paper we chose to exemplify the calculation of transition matrices from T0 to T1 and from T1 to T2 only for patients with Parkinson's disease, by following the methodology presented in Section 2 (here notations Ti were used instead of ti and we illustrated the method only for PD patients and normal patients).

In the first step we computed, according to the methodology, the deviations $\Delta S_{T1/T0} = S_{T1} - S_{T0}$ and $\Delta S_{T2/T1} = S_{T2} - S_{T1}$. We illustrate this in Tables 5 and 6 only with data acquired from a patient with PD.

We computed next the transition matrices from T0 to T1 and from T1 to T2 (Tables 7 and 8, respectively). For example, the transition matrix from T0 to T1, $MTP_{T1/T0}(m*m)$ is computed as follows:

1. the elements from the main diagonal are (S^i_{T1}, S^i_{T0});

Table 3: "Normal" subject vector, spikes number at T0, T1 and T2 for 60 seconds each record

Features Vector	T0	T1=6 months after T0	T2=12 months after T0	Total spikes
X_{min}	284	257	286	827
X_{med}	1524	1458	1511	4511
X_{max}	651	687	558	1896
Y_{min}	1289	1439	1435	4163
Y_{med}	1283	1247	1257	3787
Y_{max}	664	657	557	1878
Z_{min}	392	382	378	1152
Z_{med}	768	865	789	2422
Z_{max}	2031	1998	1875	5904

Table 4: Data: size, age, gender, and disease duration distribution of PD, SPD, and NT subjects

Features Vector	T0	T1=6 months after T0	T2=12 months after T0	Total spikes
X_{min}	382	358	379	1119
X_{med}	785	758	688	2231
X_{max}	897	857	912	2666
Y_{min}	578	547	524	1649
Y_{med}	457	479	487	1423
Y_{max}	354	349	357	1060
Z_{min}	257	282	253	792
Z_{med}	578	549	754	1881
Z_{max}	1300	1329	1348	3977

Table 5: The deviations $\Delta S_{T1/T0} = S_{T1} - S_{T0}$ (PD patient) T1 vs. T0, for the state vector S

Time	X_{min}	X_{med}	X_{max}	Y_{min}	Y_{med}	Y_{max}	Z_{min}	Z_{med}	Z_{max}	SUM
$T1$	358	758	857	547	479	349	282	549	1329	
$T0$	382	785	897	578	457	354	257	578	1300	
Deviation	-24	-27	-40	-31	22	-5	25	-29	29	
Deviation+					22		25	549	29	76

Table 6: The deviations $\Delta S_{T1/T0} = S_{T1} - S_{T0}$ (PD patient) T2 vs. T1, for the state vector S

Time	X_{min}	X_{med}	X_{max}	Y_{min}	Y_{med}	Y_{max}	Z_{min}	Z_{med}	Z_{max}	SUM
$T2$	379	688	912	524	487	357	253	754	1348	
$T1$	358	758	857	547	479	349	282	549	1329	
Deviation	21	-70	55	-23	8	8	-29	205	19	
Deviation+	21		55		8	8		205	19	316

2. if $i \neq j$, $\Delta S^i_{T1/To} < 0$ and $\Delta S^j_{T1/To} > 0$, so the matrix equals the absolute value of $\Delta S^i_{T1/T0} * \frac{\Delta S^j_{T1/T0}}{\sum \Delta S^{ij}_{T1/T0}>0}$;

3. the rest of elements equals 0.

Table 7: The transition matrix from T0 to T1

Features Vector	Xmin	Xmed	Xmax	Ymin	Ymed	Ymax	Zmin	Zmed	Zmax
Xmin	358	0	0	0	0	0	0	0	0
Xmed	2.548	758	1.625	10.244	0	0	4.345	0	0
Xmax	0	0	857	0	0	0	0	0	0
Ymin	0	0	4.548	547	0	0	0	0	0
Ymed	7.413	0	1.021	12.547	479	0	0	12.457	0
Ymax	1.124	0	1.245	6.333	0	349	0	1.125	0
Zmin	1.354	0	0	6.687	0	0	257	2.548	0
Zmed	0	0	0	0	0	0	0	549	0
Zmax	4.211	0	0	24.442	0	0	0	8.457	1.300

Table 8: The transition matrix from T1 to T2

Features Vector	Xmin	Xmed	Xmax	Ymin	Ymed	Ymax	Zmin	Zmed	Zmax
Xmin	358	0	2.387	0	0	0	0	0	0
Xmed	0	688	0	6.257	0	0	4.345	6.211	0
Xmax	1.250	0	857	0	4.587	0	0	0	5.244
Ymin	0	0	1.287	524	0	0	0	0	0
Ymed	0	5.687	1.021	8.985	479	0	0	6.258	0
Ymax	1.124	0	1.245	0	0	349	0	1.125	0
Zmin	1.354	0	0	6.154	5.698	2.542	257	2.548	0
Zmed	0	0	0	0	0	0	0	549	2.241
Zmax	4.211	0	0	3.587	2.587	2.325	0	9.237	1.329

In the third step we calculated the total transition matrix (Table 9), which is the sum of partial transition matrices computed in the previous stage.

In the fourth stage we computed the probability transition matrix by the ratio of each element of the total transition matrix to the sum of the line where the element is located.

In the final stage of the algorithm we obtained the forecast of the structural elements for next year by multiplying the transposed matrix of transition probabilities with the vector of the structural elements for T2, i.e. the vector corresponding to T2 = 12 months. We get the following transition probabilities between the 9 elements of the features vector $X_{min}, ..., Z_{max}$.

The values of the main diagonal are the probabilities that the patient progress to state that is described by the features vector (which corresponds to a stage of the disease). The forecast of the $X_{min}...Z_{max}$ for the next year is obtained by multiplying the two matrices (transposed and

Table 9: The total transition matrix (in %).

Features Vector	Xmin	Xmed	Xmax	Ymin	Ymed	Ymax	Zmin	Zmed	Zmax	Total %
Xmin	100	0	2.387	0	0	0	0	0	0	100
Xmed	9.59	90	0.0005	0.0051	0	0	0	0.0015	0	100
Xmax	8.54	0	91.46	0	0	0	0	0	0	100
Ymin	1.07	0	0	98.93	0	0	0	0	0	100
Ymed	12.91	0	0.17	1.69	84.71	0	0	0.5	0	100
Ymax	7.96	0	0.0004	0.47	0	91.37	0	0.14	0	100
Zmin	8.94	0	0.0009	0.90	0	0	89.79	0.26	0	100
Zmed	8.1	0	0	0	0	0	0	91.9	0	100
Zmax	15.19	0	0.0008	0.85	0	0	0	0.25	83.6	100

elements for T2). Thus we obtain the patient's evolution for next year, for "normal" and "PD" (Table 10 and Table 11).

Table 10: The "normal" subject's evolution for the next year (no. of spikes)

Features Vector	T0	T1=6 months after T0	T2=12 months after T0	T3=24 months sfter T0 (with Markov chain)	T4=24 months after T0(recorded)
X_{min}	244	257	286	295	299
X_{med}	1442	1458	1511	1657	1656
X_{max}	651	687	688	689	694
Y_{min}	1412	1439	1442	1420	1421
Y_{med}	1233	1247	1257	1243	1240
Y_{max}	614	627	665	688	686
Z_{min}	392	399	410	412	414
Z_{med}	768	788	789	786	785
Z_{max}	1992	1998	1999	1995	1994

From the last two tables one can see, by using Markov chains, the tremor symptom evolution of certain patients. Also we may note the very good prediction power of this method, as the features vector elements for the predicted tremor signal after 24 months from the first recording are very similar with the same vector elements, but acquired and measured by means of Wii^{TM} Remote and the appropriate software. The maximum error between prediction and measured values was 1.33%.

Similar judgement was used and corresponding good results concerning the prediction of disease evolution were obtained in the case of "suspicious PD" patients, for whom some early signs were found (insomnia, constipation, loss of smell, equilibrium and postural impairment, tremor symptom or speech difficulties) and they became to be attentively monitored. Also, another remark may be made related to the similarity between features vectors measured for "suspicious PD" patients and "diagnosed PD" patients, when using the same Markov chains for status prediction.

Table 11: The PD patient's evolution for the next year (no. of spikes)

Features Vector	T0	T1=6 months	T2=12 months	T3=24 months sfter T0 (with Markov chain)	T4=24 months after T0(recorded)
X_{min}	382	385	396	398	399
X_{med}	785	792	784	796	795
X_{max}	837	857	912	944	946
Y_{min}	518	537	544	586	585
Y_{med}	457	459	467	489	488
Y_{max}	354	359	373	382	380
Z_{min}	257	282	278	310	308
Z_{med}	528	549	558	568	566
Z_{max}	1300	1329	1348	1399	1398

4 Conclusions

In this paper we describe a general purpose model of PD prognosis based on Markov process and show how this simple mathematical tool may be used to generate detailed and accurate assessments of Parkinson's disease stage and therefore may be applicable in medical screening for PD. Markov models consider a patient to be in one of a finite number of discrete states of health. All clinically important events are modeled as transitions from one state to another. Thus, the use of Markov models has the potential to allow the development of decision models that more faithfully represent clinical problems.

Our study used a database where there are subjects who are considered normal, but with some tremor symptoms, and subjects considered "suspects", for whom we can apply the above methodology and can see if certain subjects move to the "normal" state or the first symptoms of Parkinson's disease will appear. Thus, medical staff can intervene with specific medication for Parkinson's disease.

Using Markov chain is an efficient way to find the features vector for an individual patient at a given time, and this state vector may be used to predict and identify a stage in Parkinson' disease. So, the physician can choose a treatment, based on this forecast with an appropriate level of medication.

The system was validated for 88 patients under observation: 28 with PD tremors, 30 with SPD ("Suspicious" PD tremor), and 30 with NT (Normal tremor), and we plan to expand the study to more patients with PD. Already results interpretation and discussions with involved neurologists are directed to the validation of the study. The next step will be the creation of an expert or decision-support system based on fuzzy logic for Parkinson's disease screening, which will help a physician to diagnose PD in its early stages, especially of individuals in the class "Suspicious" of PD. So, future research approaches will include the testing and validation of a screening test, in order to detect Parkinson's disease or other neurological disorders in their early stages.

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Important notice: the experiments were not prejudicial in any way to the health of human subjects investigated and they were not subject to any invasive maneuvers. All the subjects were free to decide whether or not they wish to participate in this study. They did not lose any benefits to which they are entitled, if they did not accept the participation. The duration of this study was 3 years. All personal information was and will be kept confidential. Medical information may be made available to the institution that houses the research, Ethics Commission, or other persons/institutions where the law requires. The benefits will be strictly medical. The information obtained in this study may help physicians to find a method of early diagnosis for those suffering from PD and to identify the best options for their treatment. It was no financial compensation during the study for the participants.

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