BAYESIAN NETWORKS FOR SUB-GROUPS OF MULTIPLE SCLEROSIS

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Abstract- In this study, patients with multiple sclerosis "sub-groups" characteristics in relation to detection of a statistically (SPSS) and are provided in the Bayesian network. The main objective of this study, regarding the appearance of MRI lesions in patients with Multiple Sclerosis information and / or EDSS scores to investigate the possible attack of multiple sclerosis subgroups. Bayesian networks, reflects the level of sub-groups in multiple sclerosis patients. Analyzes were conducted to determine the change of these properties. MR images of the input data is discussed for the MS patients, the sub-groups of MS, "Remitting Relapsing Multiple Sclerosis", "Secondary Progressive Multiple Sclerosis" with their patients' clinical brain MR images, brain stem, and the Upper Cervical Regions of the corpus callosum-periventricular lesions created in the information. Multiple Sclerosis is owned by the input data is created correctly identify disease subgroups of MS patients for the number of lesions in MR images and MR image of the three regions for the year for which the information used in the EDSS score. Of MS is RRMS, SPMS correctly identify sub-groups of the brain with Brain Stem, and upper cervical regions of the corpus callosum-periventricular lesions in these three points for the region and / or EDSS score information can be emphasized by using the Bayesian networks play an important role in the analysis.

Keywords: Multiple Sclerosis (MS), Relapsing Remitting Multiple Sclerosis (RRMS), Secondary Progressive Multiple Sclerosis (SPMS), Bayesian Network

1. INTRODUCTION

In order to make the interaction between mathematics and multiple sclerosis more understandable and smooth, researchers are trying design smart interfaces. These interfaces are Magnetic Resonance Imaging (MRI), Expanded Disability Status Scale (EDSS), and Cerebrospinal Fluid; with the help of these interfaces the diagnosis of the disease could be achieved. By using the Magnetic Resonance images and lesion numbers, after assessing their magnitudes, with EDSS scale, the limit of the patient's movements in its life can be determined.

In this study, two sub-groups among Clinical Progress Types of the disease Multiple Sclerosis have been examined;

Relapsing Remitting Multiple Sclerosis (RRMS): This group composes 25 percent of the MS patients. Generally, it looks like the benign type at the initial phase, full recovery follows subsequently. The full or half recovery period following acute attacks exists. However, after

repeating attacks several sequels could remain. These attacks can last for days, weeks or months. During the transitions between attacks no progression of the disease happens [1, 2-6].

Secondary Progressive Multiple Sclerosis (SPMS): The emergence of this type is much like the Relapsing Remitting MS type. The early phase lasts 5 or 6 years, after the early phase, the disease goes through secondary progressive period. Succeeding the attacks and healing period, while the number of attacks declines and healing is relatively slow, impairment becomes much worse [1, 2-6].

Extended Disability Status Scale

Extended Disability Status Scale (EDSS) relies on the estimations of eight zones, also known as functional system, of the Central Nervous System. This scale, at the beginning, measures how severe the trouble is in the systems, such as temporary numbness at the face and fingers or visual impairment. Afterwards, by checking the walking

distance of the patient interdependence during mobility is measured [5, 6].

Magnetic Resonance Imaging (MRI)

Magnetic Resonance Imaging (MRI) is a priceless way, as it displays the distribution, magnitude and number of lesions created by Multiple Sclerosis disease in the brain and spinal cord and also documents their alteration in time. The history of the disease, the results of neurological examination and MR images are secure indicators for Multiple Sclerosis disease.

In situations that include cases about Multiple Sclerosis and cases related with Multiple Sclerosis, the essence of MR images is indispensible. Magnetic Resonance is a sensitive examination in determining lesions; however, in order to make the final diagnosis, there are some other criteria that need to be made use of. While diagnosing Multiple Sclerosis according to McDonald Criteria, in different parts of demyelinating lesions' nervous system, to present that they are formed in different times (features known as time, brain and spinal cord), the value of Magnetic Resonance is stressed [1, 4, 5].

In this study, early prevention strategy for Alzheimer's disease and mild cognitive (mental) disorder (MCI) for the diagnosis of MR images of the patients and clinical / cognitive variables in a Bayesian network is proposed that combines data between. To do this, MMSE (mini-mental state examination), ADL (activities of daily living), CDR (Clinical Dementia Rating scale), ANT (Attention Network Test) and STM (short-term memory test) tests, the 25 MCI patients with pre-selected. Then, MCI patients with 25 of these MR images were obtained. MR images and clinical / cognitive function variables are combined by using Bayesian network. For analyze, 17 variables were selected: age, sex, education, degree, CDR score, MMSE score, ADL score, ANT score, STM score, left / right thalamus, left / right perirhinal and MCI function variable. As a result of the analyze, Mainly MCI was found to depend on the hippocampus, thalamus, and entorhinal [7]. In this study, 8 of the 64 repeated 314 volunteer patients' auditory brainstem responses (ABRSM) and 128 repeated 155 auditory brainstem responses (ABRSM) were used. A wavelet transform applied to the values of all ABR ABR wavelet coefficients of the most important properties have been obtained, these features are obtained subsequently inserted and ABR classification is made variable Bayesian network. Afterwards, each record by the audiologist results "have reacted" and "no response" in the form of training and assessments for later re classified and is more than the number of ABR could be used for the analysis of data to [8]. In this study, for the pursuit of human weariness noise, light, temperature, humidity, sleep time,

employment status, age, sleep disturbance, food availability, workload, work with variables such as type of Bayesian network analysis is created and fatigue as a result of physiological, environmental, and physical several factors have effect [9]. In this study, Bayesian network and Markov Random Field (MRF) image segmentation algorithm effectively controlled by combining models is presented. Training with Bayesian network learned the conditional probability density function of a set of data for each pixel the probability map was constructed. MRF model proposed by minimizing the energy function is a logical segmentation is obtained. In this algorithm, the GE Signa 1.5T MRI, 26 patients viewer carotid endarterectomy (CEA) is used for the MR images were obtained. Multi - contrast MR images was used. As a result, to increase the accuracy of the result of segmentation intensity concluded that combining the morphological information [10]. In this study, Bayesian network and Markov Random Field (MRF) image segmentation algorithm effectively controlled by combining models is presented. Training with Bayesian network learned the conditional probability density function of a set of data for each pixel the probability map was constructed. MRF model proposed by minimizing the energy function is a logical segmentation is obtained. In this algorithm, the GE Signa 1.5T MRI, 26 patients viewer carotid endarterectomy (CEA) is used for the MR images were obtained. Multi - contrast MR images was used. As a result, to increase the accuracy of the result of segmentation intensity concluded that combining the morphological information [11]. In this study, human multiple sclerosis (MS) which are critical for the development of autoimmune diseases, T-cell activation gene controls were made to model the network. For this purpose the quantitative-based network for the genes of 104 patients was 20 the immune system. As a result, complex diseases and quantitative network approach in medicine for the discovery of new therapeutic approaches can be regarded as a useful tool. In particular, the Jagged1- Notch way is a good candidate for use in the treatment of MS and sensitivity [12]. In this study, serum PSA Turkey Logistic Regression and Bayesian networks in order to improve the accuracy of diagnosis is made with the application of the two methods were compared. In this study, 983 patients with prostate cancer, demographic data, laboratory data, and pathology reports were examined. As a result, the logistic regression model to predict prostate cancer tumor based on Bayesian network model, we concluded that the better results [13]. Artificial intelligence paradigms, shows the possible relationships between them. Different from the final relationship between seemingly unrelated variables, which visually represents the Bayesian network model to create an artificial intelligence

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paradigm, scalp and sleep electroencephalography, mild neurologic signs, dexamethasone suppression, thyrotrophic-releasing hormone stimulation tests consecutive 20 patients with BPD can be obtained on the data collected. Bayesian network model, detects the relationships between many variables. Most of the variables that affect the EEG and TSH others are especially the sleep parameters. Mild neurological signs, EEG, TSH, and sleep parameters connected. The results in the future to strengthen the validity of diagnostic criteria and nosological characterization of the BPD suggest the possibility of using objective neurobiological variables [14]. Sepsis is a serious medical condition caused by the irregularity of the immune system against infection. The early diagnosis of sepsis symptoms, the more severe phases of the disease is important to prevent the progression of this disease destroys one-fourth of the effects. The patient's electronic health records in 1492, 233 cases of sepsis, sepsis gauge cluster analysis was used to describe the features and Bayesian inference can be used to develop a network. Bayesian network, systemic inflammatory response syndrome criteria, mean arterial pressure, lactate levels in patients with sepsis are configured using. The resulting network is a close relationship between lactate levels and sepsis revealed. In addition, lactate levels, SIRS criteria can be shown to the authenticator. In light of this, patients with sepsis, Bayesian networks, the future held the promise of providing a clinical decision support system [15].

2. MATERIALS AND METHOD

2.1 Bayesian Network Model

Bayesian networks are graphical models that present information by using probabilistic calculations in order to reason and decide during elusive times. Bayesian networks are composed of structures that show conditional dependencies between variables and this structure is in the form of directed acyclic graph (DAG) [16,17]. In directed acyclic graph, (DAG) $G = (V(G), E(G))$, the set of random variables in the model is denoted by independent $V(G)$ and the set of arcs is denoted by $E(G)$ [18]. In the graph, nodes represent the variables and the arcs represent the conditional dependence relations between variables. The direction of the arcs does not always marks a cause-effect relation. If there are two nodes in the graph connected with an arc, the node at the beginning of the arc is the parent node and the node in the end is the child node.

In Bayesian network $X = \{X_1, X_2, ..., X_n\}$ are the set of variables, each *Xⁱ* node (*i*=1,2,…,n) has a conditional probability distribution, when they are associated with their parents, $P(X_i | X_{pa(i)})$. For X_i variable $P(X_i)$ indicates the prior probability and

Figure 1. A sample of DAG structure describing conditional dependencies between three nodes

 $P(X_i | X_{na(i)})$ indicates the conditional probability of X_i when $X_{pa(i)}$ parent variable/s are given. If X_i does not have a parent, then there is a marginal probability distribution P(*Xi*). Conditional probabilities express the strength of relationship between variables and these probabilities are shown on tables named conditional probability table [18]. In this way, for every state of child node, according to the state of parent nodes, it is likely to detect conditional probabilities. With multiplication of conditional probability distributions in Bayesian networks the joint probability distribution of all profanities in the network is calculated [17];

$$
P(X) = P(X_1, X_2, ..., X_n) = \prod_{i=1}^{n} P(X_i | \text{Parents}(X_i))
$$
\n(1)

Bayesian networks could be created in different forms like causal network that presents cause-effect relations between variables and networks that shows only the conditional probability relations between variables without stating the cause-effect relation. In this study, Bayesian network in which there is no cause-effect relation between variables from the data will be formed.

2.2 Kruskal – Wallis Test

(One-way ANOVA) Kruskal-Wallis test, which is the non-parametric alternative of one-way variance analyses among groups, examines if there is a significant difference between groups by comparing
independent k number groups' data of k number groups' data of interdependent variables. In this test, while comparing the values belonging to the groups, median values are used not mean values. In Kruskal Wallis test hypothesis are created like the following forms;

H0: *k* numbers of groups' medians are equal.

 $H₁$: median value of at least one of the groups is different.

In Kruskal – Wallis test, when H_0 hypothesis is rejected, one of the methods used in order to detect, which group or groups' median values are different, is multiple comparison method. In multiple comparison method [19];

n : universe sample unit number,

 n_i : sample unit number of the group *j*., (*j* = 1, 2, …, *k*)

 \overline{R} . Average sequence order of the group *j*. the data value that is put in a successive order in the analyses.

 u : the repetition number of the repetitive values in and among the sample.

As it appears; $(i \neq j$ ve $i, j = 1, 2, ..., k$);

$$
\left\| R_i - R_i \right\| > \varepsilon_{\alpha/1} \sqrt{\left[n(n^2 - 1) - (\sum u^3 - \sum u_i) \right] \left[\frac{1}{n_i} + \frac{1}{n_j} \right]}
$$
(2)

If we get inequality, that means in group *i*. and *j*. the means are different. In a universe with *k* number of groups, $\frac{k(k-1)}{k}$ number of dual samples are examined, as a result, it is determined if median values of groups have significant difference from each other or not.

2.3 MS Data for Bayesian Network

In our study, Neurology and Radiology, Hacettepe University Faculty of Medicine, Magnetic Resonance Imaging in the center of primary followed by the McDonald criteria in patients with clinically definite multiple sclerosis, between the ages of 20 and 55, RRMS, SPMS and 19 individuals (not MS) with 114 patients as a control group without any history of drug use with the complaint and decide whether the MR image is given as a result of 19 healthy subjects were patients with Multiple Sclerosis. Degrees of disability in MS patients Disability Status Scale (EDSS) respectively, MRI 1.5-Tesla (T) power (Magnetom, Siemens Medical Systems, Erlangen, Germany, Intera Achieva, Philips, Netherlands, or GE Healthcare, Milwaukee, Wisconsin, USA), withdrew from the MR devices. Is gained from outside the Hacettepe Hospital magnetic resonance imagines compact discs (CDs) through PACS (Picture Archiving and Communication System- Picture Archiving and Communications System) are loaded. The lesions on T2-weighted turbo spin echo (TSE) sequences using the millimeter (mm) were counted in metric units. The brain stem, corpus callosum-periventricular region, including the upper cervical spine lesions in the three regions is included in the information. Magnetic Resonance Imaging read for three regions (MRI) lesion in the years to the information changes (number of increments / reductions in size) were compared, according to the EDSS scores of years, changes within the clinical diagnostics compared with Multiple Sclerosis. Duration of the disease observed in patients with Multiple Sclerosis 1. 2. MR of films are a minimum of three years, a maximum of 8 years of 2.MR 3.MR are with.

In data set, when patients are diagnosed Normal (not an MS patient), existence of RRMS and SPMS diagnosis is "1" and in their non-existence, "0" stands for that. For example, if a patient is diagnosed with RRMS, the codification is; Normal=0, RRMS=1, SPMS=0. The score of EDSS and the number of lesions are categorized into four groups in Table 1 [20]. There is no one with missing data in our data set. The state of variables in data set and their prior probability are presented in the table below;

Nodes	State	Prior	
		Probability	
Normal	$0($ no $)$	86%	
	1 (yes)	14%	
RRMS	0 (no)	43%	
	1 (yes)	57%	
SPMS	$0($ no $)$	71%	
	1 (yes)	29%	
		14%	
EDSS	$0 \leq - \leq 4.5$	53%	
	$4.5 < - < 7.5$	29%	
	≥ 7.5	4%	
	0	14%	
Number of	$0 \leq -\leq 7$	21%	
Lesions	$7 < - < 15$	18%	
	≥ 15	47%	

Table 1. Prior Probability Table

The EDSS quantifies disability in eight Functional Systems (FS) and allows neurologists to assign a Functional System Score (FSS) in each of these are shown in Table 2 [21];

3. METHODOLOGY & RESULTS

In order to learn Bayesian network from our data set Microsoft program WinMine Toolkit is made use of. This software separated coincidentally our training and test set proportionally, the former is 70% and the latter is 30%. In this way, the data set composed of 133 subjects is divided into two groups, 93 subjects in training set and 40 in test set. All of the variables in the network are used as input-output variables. Bayesian network belonging to five different variables created by using WinMine program is suggested in the figure 2. In Bayesian network, according to the states of parent variables, it is aimed at predicting the future

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Figure 2. Bayesian Network Model for Multiple Sclerosis Disease

states of variables by calculating the conditional probabilities of them. In the Figure 2, in the Bayesian network attained from the training set, conditional probability relations of between all of the five different variables are demonstrated by pointing all of the possible arcs and their directions. For example, if we take a look at the Bayesian network in the Figure 2, RRMS node (variable) is associated as the child node of the EDSS node and the parent node of SPMS node by checking their probabilities. The RRMS node cannot be considered as a result of EDSS node, and as the cause of SPMS node. In the Bayesian network we generated, as the normal node does not have a parent node, there are no conditional probabilities of this variable, but the marginal probabilities are acquired. There are conditional probabilities for RRMS and SPMS which are the sub-groups of MS disease, as they have parent nodes. For the normal node attained from Bayesian network presented in the Figure 2, marginal probability table is indicated in Table 3, the conditional probability table for RRMS node is graphed in Table 4, and the conditional probability table for SPMS node is presented in Table 5. In conditional probability tables, according to the state of parent node, the materialization possibilities of child node are presented.

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Marginal Probability of Normal $= 0$	Marginal Probability of Normal $= 1$
0.86	በ 14

Table 4. The Conditional Probability Table of RRMS Given Its Parent EDSS

From the Bayesian network in Figure 2, materialization possibilities could be posited whether a subject whose EDSS scores are known, have RRMS or not. While there is no information about EDSS scores belonging to patients in Table 1, for the state RRMS=1, the prior probability is calculated as 57%. When we analyze the conditional probability table acquired from the network for the RRMS node, according to our data set, if the interval for the EDSS score which is the parent node of RRMS, is $0 \leq \cdots \leq 4.5$, RRMS=1 will appear most probably as 95%.

When we examine the conditional probability table we get from the generated Bayesian network for the SPMS node, under the states when RRMS=0 is provided (RRMS is one of the parent nodes of SPMS), and if the EDSS score is ≥ 7.5 according to our data set, the possibility of materialization of SPMS=1 state is 86% percent. When the highest materialization possibility of SPMS=1 state occurred 97% percent, happens if RRMS is equal to 0 and the interval for EDSS score is between $4.5<...<7.5$

For lesions and EDSS nodes, conditional probability tables are given in Table 6 and 7;

States of Normal	Conditional Probability of $EDSS = 0$	Conditional Probability of $EDSS = 0 \leq x \leq 4.5$	Conditional Probability of $EDSS = 4.5 < - 2.5$	Conditional Probability of $EDSS = 7.5$
	$0.01\,$	0.61	0.33	0.05
	$0.88\,$	0.04	0.04	0.04

Table 6. The Conditional Probability Table of EDSS Given Its Parent Normal

 $0 \t 0.01 \t 0.25 \t 0.21 \t 0.53$ 1 0.88 0.04 0.04 0.04 0.04

When we analyze the conditional probabilities in our data set from Table 6, for a normal subject who does not have a disease, the probability of getting 0 EDSS score is 0.88 and for not a normal subject, 0.61 is the probability which states when the EDSS score is $0 \leq m \leq 4.5$.

When we examine the conditional probabilities belonging to lesion node in Table 7, according to data set, a normal person does not have lesion proportionally 0.88 and if we take a look at the lesion distributions of the MS patients, 53 percent of the patients' lesion numbers is over 15.

When we study Table 4, 5, 6 and 7, for a person whose EDSS scores are known, if we analyze the variances where the normal, RRMS and SPMS variables' probability of materialization is maximum, a normal subject will get 0 EDSS score with a 0.88 possibility, if a subject's EDSS score is between $0 \leq \cdots \leq 4.5$, the possibility of being diagnosed as RRMS is 0.95, if the EDSS score is between $4.5 \leq \cdots \leq 7.5$ and if the person is not an RRMS patient, the diagnosis will be 0.97 possibility, SPMS. On this basis, between people

not having MS disease and people diagnosed with the sub-groups of MS disease (RRMS, SPMS), the EDSS score differs and as the progression of the disease increases, the EDSS score again raises. We can also examine the scores we evaluated according to the conditional probability tables, by applying the Kruskal-Wallis Test, which is a statistical test. For this test, people who are not MS patients and people who are diagnosed with RRMS, SPMS are categorized, and whether these diagnoses differ or not according to their EDSS scores. Diagnosis variable are divided into three categories as subjects not having MS disease as first group, RRMS patients in the second group and SPMS patients in the third group, where the scale is nominal. The EDSS score is an ordinal scale variable categorized as it is used in Bayesian network. The hypothesis belonging to the test are given below;

 H_0 = Normal, RRMS, SPMS diagnosis and EDSS scores are independent of each other. (Medians of the groups are equal.)

 H_I = Normal, RRMS, SPMS diagnosis and EDSS scores are not independent from each other. (On group median at least is different than the other group medians.)

according to 1% confidence level, and the acquired values are presented in the Table 8.

Table 8. MS diagnosis and Kruskal-Wallis analyses results for EDSS score

Test Statistics ^{a,b}		
	EDSS	
Chi-Square	105,448	
	2	
Asymp. Sig.	,000	
a. Kruskal Wallis Test		
b. Grouping Variable: diagnosis		

At the end of the analyses, the Asymp. Sig. value appears to be 0.00 and it is smaller that 0.01 Alfa value. For this reason *H⁰* hypothesis is denied and with 99% probability, the diagnosis of different subjects showed a statistically significant difference in terms of their EDSS scores. For that reason, in order to determine which groups' median values are different, the values below are found by applying multiple comparison technique;

 $\overline{R}_1 = 10$ $\overline{R}_2 = 60,74$ $\overline{R}_3 = 108,03$ $|\overline{R}_1 - \overline{R}_2|$ = 50,74 > 23,85 $|\overline{R}_1 - \overline{R}_3|$ = 98,03 > 25,5 $|\overline{R}_2 - \overline{R}_3|$ = 47,29 > 18,03

As inequalities are provided in multiple comparisons conducted between groups, medians of these three groups vary from each other and according to the diagnosis EDSS scores become

different. Here, the sequence order means belonging to the groups (R_i) give an idea about whose EDSS scores are bigger according to the diagnosis of the subjects. It could be stated that as the categories belonging to EDSS scores are codified within 1 and 4, the group with a higher sequence number will have higher EDSS scores. For the diagnosis of MS disease and EDSS score, the results we got after applying Kruskal Wallis test, and the Bayesian network we generated from those test results we acquired from conditional probability table, are supporting each other.

In WinMine software we used to generate Bayesian network we learn from the MS data, the estimation accuracy of the model learnt via test set is evaluated by making use of log score, which is a quantitative criteria. In this program log posterior probabilities are calculated for every output variable value (log₂) $p(x_i|$ model) and the average of log posteriors are reported as log score in all instances about each variable [22]. In order to indicate the number of variables in model *n* and the number of instances in test set *N*, log score formula is explained below [23];

This analysis is implemented in SPSS program $L \log \text{score}(x_1, ..., x_N) = \frac{\sum_{i=1}^{N} \log_2 \mu(x_i | \text{model})}{\sum_{i=1}^{N} \mu(x_i | \text{model})}$ (3)

The log score of the model that we generated is - 0.2693. When we convert this value into probability, the log score is $(2^{\log \text{score}})$ 0.83. With the Bayesian network model that we generated with the MS disease data, in the predictions we made on the test groups, the true prediction point is 0.83. In WinMine program it is possible to see the difference between provided model and marginal model. The difference between log scores of the two models is called lift over marginal [22]. That the Lift over marginal is positive shows that the model we provided in the test set is superior than the marginal model. The lift over marginal of the model we composed is 0.5422. The log score of the marginal model is obtained from the equation (- (0.2693) – (marginal model log score) = 0.5422 is -0.8115. When we convert this value into probability, it is calculated as $(2^{(-0.8115)})$ 0.57. This proves that the estimation accuracy of the of the provided model in the test group is (0.83) and it is superior than the marginal model (0.57) .

4. CONCLUSION

In our study, the relation between the diagnosis for the patients from Bayesian network which is composed of MS data and EDSS scores and lesion numbers were got probabilistic notice clearly as conditional dependency relations and in test set belonging to our data set, the conditional probability values between Bayesian network generated from our data set with the 0.83 point estimated accuracy rate, and EDSS scores and the MS diagnosis of persons are obtained. These values

are compared the values that shows statistically significant differences, according to MS diagnosis of persons with EDSS scores which is acquired as a result of the multiple comparison by denying the *H⁰* hypothesis on Kruskal – Wallis test that is another statistical test we applied in out data set. In the end, the analyses consequences in both methods used in MS data showed parallelism.

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