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Grading Urinary Bladder Tumors Using Unsupervised Hebbian Algorithm for Fuzzy Cognitive Maps

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Abstract: *The application of Fuzzy Cognitive Maps as a modeling and classification tool, for assessing tumors grade for urinary bladder, is examined in this research work. One hundred twenty nine cases were classified according to the WHO grading system in two classes, by experienced pathologists: Low Grade and High Grade, based on eight significant histopathological features that histopathologists selected for each case. This research work incorporates doctor's knowledge in developing the FCM model for tumor grading and utilizes the Nonlinear Hebbian Learning algorithm to further train the FCM and thus to achieve tumor malignancy classification. The classification is based on the histopathological characteristics of tissue that features are the concepts of the Fuzzy Cognitive Map model that was trained using the unsupervised learning algorithm. The classification accuracy is 93.18% for High Grade tumor cases and 90.59%, for tumors of Low Grade.*

Keywords: *Fuzzy Cognitive Maps, Tumor Grading, Unsupervised Learning, Nonlinear Hebbian Learning Algorithm, Urinary Bladder*

1. Introduction

The task of tumor classification is an important issue in modern medical diagnosis and thus there is a demand for more autonomous and intelligent diagnosis tools. The Superficial Transitional Cell Carcinoma (TCC) is the most frequent histopathological type of bladder cancer [1]. These tumors have been assessed recently by using grading guidelines based on a variety of histopathological characteristics. Histopathologists usually determine tumor grade using tissue biopsy based on tumor aggressiveness. The World Health Organization (WHO) [2] has proposed the most widely accepted guidelines that classifies the TCCs into two categories: tumors of Low Grade and High Grade. In Low Grade tumors there is not any invasion or metastasis and there is a low risk of further progression that frequently occur. High Grade tumors are characterized by a much higher risk of progression, and there is high risk of association with disease invasion [3]. The histological grade has been recognized as one of the most powerful predictors of the biological behavior of tumors [4].

Histopathologists combine subliminally and synergistically many histopathological features and factors using a rather vague way in order to assign the final grade to each case. Thus, there is potential for inter and intra observer variation [4].

Computer-aided grade diagnosis based on pattern recognition techniques has been examined in previous efforts for classification and tumors grading [5],[6]. Recent studies have focused on the analysis of cell nuclei characteristics to perform tumor classification with low success rates less than 80% [7], [8]. In this work the human experts' knowledge on histopathology is expressed in descriptive concepts that are used to develop a diagnostic grading tool based on Fuzzy Cognitive Maps (FCMs) and Nonlinear Hebbian Learning Algorithm. This tool can help the doctors in the daily clinical practice. FCMs represent the causal relationship between concepts and analyze inference patterns [9]. FCMs are appropriate to represent the knowledge, which has been accumulated on the operation and behavior of a complex system. Fuzzy Cognitive Maps have already been applied in many scientific areas, such as medicine, manufacturing, organization behaviour, political science [10],[11],[12],[13],[14].

In this research work a novel methodology, which evolves the level of diagnostic accuracy in assigning tumour grade is presented. The method is based on FCMs and the implementation of Nonlinear Hebbian Learning algorithm, which enhances the FCM operation and improves the classification capability of the diagnostic tool.

This paper is structured in the following sections: Section 2 presents briefly the FCM modelling technique. Section 3 describes the Nonlinear Hebbian Learning (NHL) algorithm that is used to train FCMs. In section 4, experts develop the FCM model for tumor grading and the algorithm for the classification process is described. Section 5 presents and discusses the experimental results of using the FCM grading model for tumour classification of 129 cases and finally section 6 concludes the paper.

2. Fuzzy Cognitive Maps Background

The synergistic and complementary use of fuzzy logic and neuro-computing has initiated the development of soft computing methodologies, such as FCMs. Soft computing methodologies have been investigated and proposed for the description and modeling of complex systems. A Fuzzy Cognitive Map integrates the accumulated experience and knowledge on the causal relationship between factors/characteristics/components of any system; due to the way it is constructed, i.e., using human experts that know the system and its behavior under different circumstances [13].

FCMs model the existence human knowledge which is reflected at the kind of nodes (concepts) and directed weighted arcs of the interconnections between concepts. Each node-concept represents one of the key-factors of the modeled system and it is characterized by its value A_i.

Between concepts there are cause and effect relationships that are illustrated in the FCM graph (Figure 1) with the weighted arc W_{ij} from one concept towards another. The value of W_{ij} indicates how strongly concept C_i influences concept C_j. The sign of W_{ij} expresses positive causality between concept C_i and C_j ($W_{ij} > 0$) or negative causality ($W_{ij} < 0$). The direction of causality indicates whether concept C_i causes concept C_j, or vice versa. These three parameters have to be considered when an interconnection is determined.

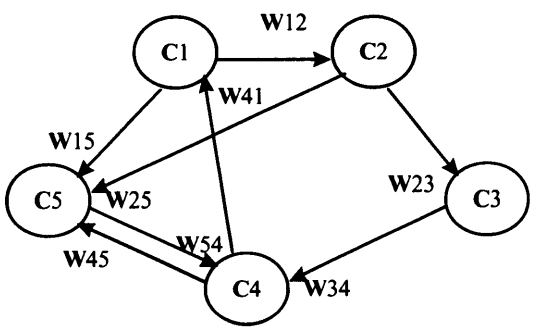

Figure 1. A simple Fuzzy Cognitive Map

Every concept in the FCM has a value that represents the quantity of the corresponding factor, variable, state; for which this concept strand for. The value of a concept is influenced by the interconnected concepts. The value A_j for each concept C_j is calculated by the following rule:

$$A_j^{(t+1)} = f(A_j^{(t)} + \sum_j W_{ij} \cdot A_i^{(t)}) \ , \qquad (1)$$

Namely $A_j^{(t+1)}$ is value of concept C_j at step t+1, $A_i^{(t)}$ is the value of concept C_i at step t, and W_{ij} is the weight of the arc from concept C_i towards concept C_j and f is a threshold function.

The methodology for developing FCMs is based on experts who are asked to define concepts and describe relationships among concepts; they use IF-THEN rules to justify the cause and effect relationship among concepts and infer a linguistic weight for each interconnection [13]. Every expert describes each one of the interconnection with a fuzzy rule; the inference of the rule is a linguistic variable, which describes the relationship between the two concepts according to everyone expert and determines the grade of causality between the two concepts. The degree of the influence of concepts was represented by a linguistic variable of the fuzzy set T(*influence*)={positive very high, positive high, positive medium, positive weak, zero, negative weak, negative medium, negative low, negative very low}. Thus, the fuzzy IF-THEN rule, that experts use to describe the degree of influence among concepts, assumes the following form where **B, D** and **E** are fuzzy linguistic variables:

IF a change **B** occurs in the value of concept C_i **THEN** a change **D** in the value of concept C_j is caused.

Infer: The influence from concept C_i to C_j is **E**.

Then the inferred linguistic weights **E** for each interconnection are aggregated using MAX method and the result is defuzzified with the method of Center of Area (CoA) [15], which is transformed to a crisp weight W_{ij}, belonging to the interval [-1,1].

For developing an advanced FCM grading model with training capabilities, an unsupervised learning algorithm, named Nonlinear Hebbian Learning (NHL) [16], is utilised which is described at the next section.

3. Nonlinear Hebbian Learning algorithm

The dependence on the expert's beliefs and knowledge, the potential convergence to undesired steady states and the recalculation of the weights when a new strategy is adopted are drawbacks of FCMs. Learning algorithms are used to increase the efficiency and robustness of FCMs, by selecting and modifying the FCM weight matrix [16], [17], [18].

The proposed learning algorithm, namely NHL, is based on the nonlinear Hebbian-type rule that introduced by Oja [19] to train neural networks, using the following general form:

$$\Delta w_{ij} = \eta_k y_j (x_i - w_{ij} y_j) \ , \qquad (2)$$

where η_k is the learning rate at iteration k.

This learning algorithm is adapted and modified for the FCM case. During the triggering process the weight w_{ij} of the causal interconnection of the related concepts is updated and the modified weight $w_{ij}^{(k)}$ is derived for iteration step k.

The NHL algorithm is based on the premise that all the concepts in FCM model are triggered synchronously at each iteration step and change their values. The value $A_j^{(k+1)}$ of C_j, concept at iteration step $k+1$, is calculated, computing the influence of interconnected concepts with values A_i to the specific concept C_i due to modified weights $w_{ij}^{(k)}$ at iteration step k, through the following equation:

$$A_j^{(k+1)} = f(A_j^{(k)} + \sum_{\substack{j \neq i \\ j=1}}^{N} A_i^{(k)} \cdot w_{ij}^{(k)}) , \quad (3)$$

Furthermore, the experts have defined which concepts of FCM are the Desired Output Concepts (DOCs). These concepts stand for the factors and characteristics of the system that interest us, and we want to estimate their values, which represent the final state of the system.

Taking the advantage of the general nonlinear Hebbian-type learning rule for neural networks [19],[20], we introduce the mathematical formalism for incorporating this learning rule with the learning rate parameter and the determination of input and output concepts. This algorithm relates the values of concepts and values of weights in the FCM model [18].
The proposed learning rule has the general mathematical form:

$$\Delta w_{ij} = \eta_k A_j^{(k-1)}(A_i^{(k-1)} - w_{ij}^{(k-1)} A_j^{(k-1)}) , \quad (4)$$

where the coefficient η is a small positive factor called learning rate parameter and is determined using experimental trial and error method in order to optimize the final solution.

For this learning approach, all the FCM concepts are triggering at the same iteration step and their values are updated due to this triggering process. Eq. (4) is used to modify and adjust the FCM. The following form of the nonlinear weight-learning rule for FCMs is proposed:

$$w_{ij}^{(k)} = \gamma \cdot w_{ij}^{(k-1)} + \eta A_j^{(k-1)}(A_i^{(k-1)} - w_{ij}^{(k-1)} A_j^{(k-1)}) \quad (5)$$

where the η is the learning rate parameter and γ is the weight decay parameter.

In NHL algorithm, only the initial non-zero weights are adjusting. These weights are updating synchronously at each iteration step through the eq. (5), till the Desired Output Concepts no more change their values or change their values at a very small amount. All the other weights remain zero and no new interconnections are assigned. Actually, when experts develop a FCM they usually propose a quite spare weight matrix. With the NHL algorithm the initially non-zero weights suggested by experts are updated for each iteration step.

Also, in NHL algorithm, upper and lower bounds for the learning parameters γ and η are determined using trial and error experiments so that constant values for each one are calculated for specific case-study problem. The bounds of learning rate parameter η are determined as $0 < \eta < 0.1$, and for the weight decay parameter have been determined as $0.9 < \gamma < 1$ [18]. Here the learning rate parameter η is proposed to take the constant value of 0.04 and γ =0.98 after experimental trials for the specific problem.

4. Fuzzy Cognitive Map tumor grading model

The doctors-histopathologists, with deep knowledge and great clinical experience, were our experts whom we asked to develop and construct the FCM model for tumor grading using the methodology presented in section 2 and described analytically in [13]. Experts defined the main histopathological features (concepts) that play important role in the final grade characterization. More specifically, eight well documented in the bibliography histopathological criteria (features) essential for tumour grading (Table1)[3],[7] were used and each tissue section (patient slide) was evaluated retrospectively by histopathologists using these features. These considered features are the causative variables or factors of the tumour grading system that have selected by experts to construct the FCM for tumour grading [21].

The FCM tumor grading model was developed consisting of the following 9 concepts: Concept C_1 represents the cell distribution, C_2 represents the cell size, C_3 the cell number, C_4 the cytoplasm, C_5 the nuclei, C_6 the nucleoli, C_7 the necrosis, C_8 the mitoses and C_9 the degree of tumour grade.

Tab. 1. Main factors for grading

Histological feature	Assessment Possible
Cell distribution	Even, clustered
Cell size	Uniform, pleomorphic
Cell number	Numerous, variable
Cytoplasm	Homogeneous, variable
Nuclei	Uniform, irregular, very irregular, bizarre
Nucleoli	Inconspicuous, evident, prominent
Necrosis	Inconspicuous, frequent
Mitosis	Absent-rate, occasional, numerous

In order to use the FCM model histopathologists were asked to examine each tissue section retrospectively and estimate the value of the eight histopathological variables (Table 1); these values were transformed in the range [0 1], and were assigned to the corresponding concepts.
The following mathematical form is used to transform the quantitative values of the eight characteristics to a numerical value [22]:

$$\text{Submitted value} = \frac{([\text{option selected}]-1)}{([\text{total number of options}]-1)} \quad (6)$$

For example if a feature is "irregular" and this is the second of four possible options (e.g. "uniform" "irregular" "very irregular" and "bizarre") its assigned value would be:

$$\frac{\text{([option2 selected]-1)}}{\text{([total of 4 options]- 1)}} = \frac{2-1}{4-1} = \frac{1}{3}, \tag{7}$$

Furthermore, histopathologists were asked to explain the cause-effect relationships among these concepts using IF-THEN rules that were described in section 2. Thus after defuzzification of the linguistic weights with GoA, the initial weight matrix W of the FCM tumor-grading model was determined:

$$\mathbf{W}^0 = \begin{bmatrix} 0 & 0.1 & 0 & 0 & 0 & 0 & 0 & 0 & 0.30 \\ 0 & 0 & 0 & 0.7 & 0.65 & 0 & 0 & 0 & 0.40 \\ 0.4 & 0 & 0 & 0 & 0 & 0 & 0 & 0 & 0.5 \\ 0 & 0 & 0 & 0 & 0.7 & 0 & 0 & 0 & 0.45 \\ 0 & 0 & 0 & 0 & 0 & 0.6 & 0 & 0.6 & 0.65 \\ 0 & 0 & 0 & 0 & 0 & 0 & 0 & 0.3 & 0.65 \\ 0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 & 0.75 \\ 0 & 0 & 0 & 0 & 0 & 0 & 0.55 & 0 & 0.80 \\ 0 & 0 & 0.6 & 0 & 0.6 & 0 & 0.65 & 0.6 & 0 \end{bmatrix}$$

The FCM grading model was developed and illustrated in Figure 2. The tumor grading procedure is based on the determination of the value of concept "Grade" that figure out the final degree of tumor malignancy.

Then the NHL algorithm is used to modify the weights of the FCM grading model according to the initial values of concepts for each examined case of urinary bladder tumors. Also, according to the NHL algorithm, experts were asked to select the input and output concepts that determine the triggering process. The ninth concept of "Grade" was defined as the Decision Output Concept (DOC), which determines the tumor grade. All the other concepts have been defined as input concepts.

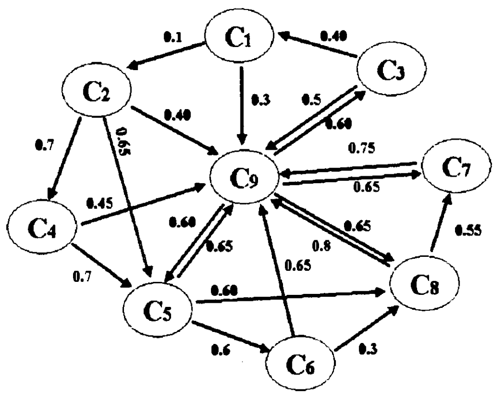

Fig. 2. The FCM tumor grading model consisting of 9 concepts and 21 weight relations

4.1 Description of the tumour grading procedure

The FCM tumor-grading model can be used, after the development of the FCM model and the determination of the necessary specifications for the implementation of the NHL algorithm. For each case the training procedure is applied and then, through implementation of the minimum distance method the derived values of concept "Grade" assign the grade of the tumor.

One hundred twenty-nine tissue sections (slides) from one hundred twenty-nine patients with superficial transitional cell carcinoma were retrieved from the archives of the Department of Pathology of University Hospital of Patras, Greece. Tissue sections were routinely stained with Haematoxylin-Eosin. Every case was reviewed independently by the doctors-experts to safeguard reproducibility. Histopathologists had classified the cases following the WHO grading system as follows: eighty-five as Low Grade, and forty-four as High Grade.

The schematic procedure of the FCM-based tumor characterization is shown in Fig. 3. Considering the FCM-model, the proposed algorithm for tumor characterization is consisted of the following steps:

Step 1: Determine the initial weight matrix $\mathbf{W}^0$

Step 2: Read input concept state $\mathbf{A}^l$, for first case l=1

Step 3: Repeat for each case l (till $l \le M$, where M is the number of urinary bladder tumor cases)

Step 4: Implement NHL Algorithm

4.1: Calculate values of all concepts A_i according to the eq. (3)

4.2: Update the weights $w_{ij}^{(k)}$ according to eq. (5)

4.3: Calculate the "Grade" value- $A_9^{(k+1)}$

Step 4: Until the "Grade" values of all cases are calculated

Step 5: Apply Minimum Distance method to the calculated DOCs- A_9 (in order to determine decision line)

Step 6: Return the classification accuracy for each grade category.

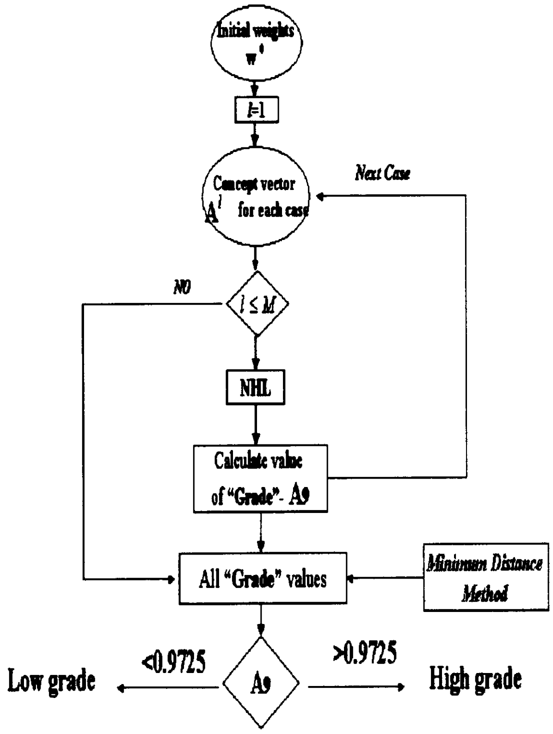

Fig. 3. Flowchart of tumor characterization procedure

5. Experimental Results

The classification task requires the determination of a decision margin or a threshold line; for this reason the one hundred twenty-nine cases of urinary bladder were used. And then each case has classified according to the decision line.

For each one of the one hundred twenty-nine cases we took the values (measurements or estimations) of the eight features; we transformed them in the range [0,1] through the mathematical form of eq. (7); the initial value of the concept C_9 was randomly selected (equal to 0.46) and was kept the same value for all cases. Then for each case we applied the procedure shown in Fig. 3, employing the NHL algorithm, and calculating the value of "Grade" (A_9) for each tumor case.

Fig. 4 illustrates the "Grade" values calculated for the one hundred twenty-nine cases by the FCM tumour-grading model. For High Grade cases the estimated 'Grade' values are represented by '+', and for Low Grade cases the 'Grade' values are represented by '∇'. The High Grade set contains 44 cases and the Low Grade set contains 85 cases. It is clear that the proposed approach was able to give distinct different values for the most of low grade and High Grade cases.

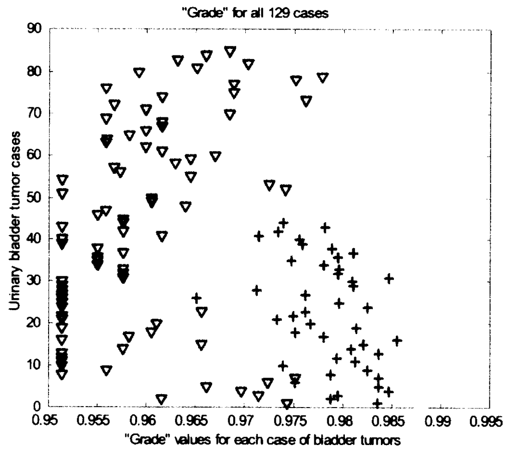

Fig. 4. "Grade" values for the one hundred twenty-nine cases

The minimum distance method was employed to determine the decision line defining each grade category. More specifically, using this method the mean values m1 and m2, for Low Grade and High Grade categories, were estimated. The decision line is determined as the perpendicular bisector of the line joining m1 and m2. Thus, the value of 0.9725 determined as the threshold value for Low Grade and High Grade categories (regions).

Fig. 5 illustrates the decision line, which separates the calculated "Grade" into two categories, Low Grade and High Grade respectively. "Grade" values greater than 0.9725 represent High Grade cases whereas values lower than 0.9725 represent Low Grade cases.

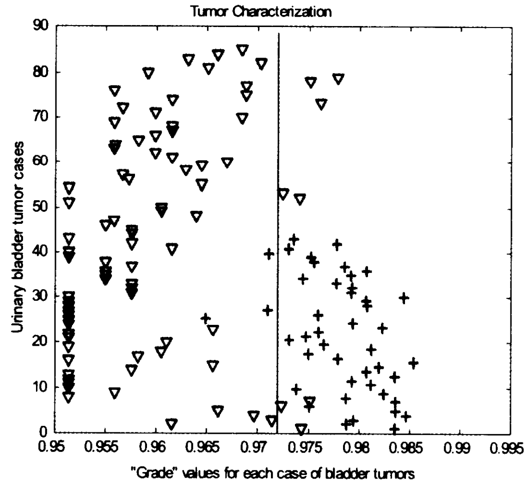

Fig. 5. Decision line characterizing each tumor grade case

It is clearly shown that two of the Low Grade cases are exactly on the decision line (have the same value with the decision boundary) and for the experimental results they are considered that belong in the "high grade" region. The accuracy for Low Grade cases was 90.59%, and for High Grade cases was 93.18% after defining the threshold value.

In order to examine the generalization of the proposed method, we did the following procedure for 100 times. We randomly selected 2/3 of the data set, which were used to construct the decision line. The other 1/3 of the data set was used to evaluate the accuracy of the model. In average the success rate for the Low Grade cases was 91% and 95% for the High Grade cases.

Our results, implementing the NHL algorithm in tumor grading process, were compared with the results derived from another approach for tumor grade characterization, which described and presented in [21]. In that approach, another unsupervised learning algorithm for FCMs, the Active Hebbian Learning, was implemented in the same FCM model but for a set of 92 cases, where the 63 cases were classified as Low Grade and the 29 were classified as High Grade by the same histopathologists doctors. The results were 89,43% for the Low Grade cases and 97,78 for the High Grade cases. It is observed higher success rates for the Low Grade cases and lower success rates for the High Grade cases. This supports the claim that NHL algorithm is also efficient and very useful for the successful classification of urinary bladder tumors when implementing in FCMs.

The computer-aided grade diagnosis methods have been mainly investigated from the perspective of pattern recognition and the quantitative microscopy methods using image analysis techniques [6],[8],[23],[24],[25]. Our results using the proposed method are comparable with the results given by the referred methods of pattern recognition, having the advantage of speed and of transparency of the results for doctors-pathologists.

Thus, a sufficient estimation model for automatic tumor grade characterization has been developed and the accuracy in correctly assigning grade is reasonably high.

6. Conclusions

In this research effort the Nonlinear Hebbian Learning algorithm was implemented in FCM tumor grading model to enhance the characterization of urinary bladder tumors. The FCM-based tumor grade characterization procedure exhibited high performance in correctly classifying tumors into two categories, low-grade and high-grade respectively, utilizing all the available diagnostic information from experts. The proposed method could be considered as an efficient classification tool able in making decisions improving the diagnostic accuracy.

Furthermore, the tumor characterization procedure based on the soft computing techniques of FCMs offers a degree of transparency to the experts who have some insight to the system behavior. The FCM-based tumor grading tool is fast, easily implemented in clinical practice and performs high accuracy in the terms of specificity and sensitivity.

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