Urinary Bladder Tumor Grading Using Nonlinear Hebbian Learning for Fuzzy Cognitive Maps

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Abstract

This paper examines the application of Fuzzy Cognitive Maps (FCMs) as an automated system, for the assignment of tumors grade for urinary bladder. One hundred twenty nine cases were classified according to the WHO grading system in three classes, by experienced pathologists: Grade I, Grade II and Grade III. Eight significant histopathological features were selected for each case. These features are the concepts of the Fuzzy Cognitive Map model, which was trained using the unsupervised training algorithm, namely, the Nonlinear Hebbian Learning. The resulting automated classification system achieved classification accuracy of 85%, 80% and 90,91% for tumors of Grade I, II and III, respectively.

1. Introduction

Bladder cancer is the fifth most common type of cancer. The most frequent histopathological type of bladder cancer is the Superficial Transitional Cell Carcinoma (TCC) [1]. Currently, these tumours are assessed using a grading system based on a variety of histopathological characteristics. The tumor grade, which is determined by the histopathologist from tissue biopsy, is associated with tumor aggressiveness. The most widely accepted system is the WHO (World Health Organization) system, which classifies TCCs into three categories: tumors of Grade I, Grade II and Grade III. Grade I tumors are not associated with any invasion or metastasis but present a risk for the development of recurrent lesions. Grade II carcinomas are associated with low risk of further progression, yet they frequent occur. Grade III tumors are characterized by a much higher risk of progression, and also high risk of association with disease invasion [2]. The histological Grade has been recognized as one of the most powerful predictors of the biological behavior of tumors and significantly affects patient management.

Different histopathological features and factors are combined subliminally and synergistically, with a rather vague way in order to assign the final grade to each case. As with all subjective systems, there is potential for marked inter and intra observer variation [3].

Previous efforts to standardize classification and grading of tumours have used computer-aided grade diagnosis based on pattern recognition techniques [4-6]. More recent studies have focused on the analysis of cell nuclei characteristics to perform tumour grade classification with success rates that do not significantly exceed 80% [7], [8]. The aim of our work is to exploit human experts' knowledge on histopathology expressed in descriptive terms and concepts and to develop a diagnostic grading tool that can help the doctors in the daily clinical practice. In this study, we present a methodology, which improves the level of diagnostic accuracy in assigning tumour grade. The method is based on the application of a FCM with nonlinear Hebbian learning algorithm as a classifier system.

2. Fuzzy Cognitive Maps and Nonlinear Hebbian Learning

FCMs were proposed by Kosko to represent the causal relationship between concepts and analyze inference patterns [9], [10]. FCMs represent knowledge in a symbolic manner and relate states, processes, events, values and inputs in an analogous manner. Compared either expert system or neural networks, it has several desirable properties such as: it is relatively easy to use for representing structured knowledge, and the inference can be computed by numeric matrix operation. FCMs are appropriate to explicit the knowledge which has been accumulated for years on the operation of a complex system. Fuzzy Cognitive Maps have already been applied in many scientific areas, such as medicine, manufacturing, organization behaviour, political science [11],[12],[13],[14],[15],[16],[17].

The FCM structure can be viewed as a recurrent artificial neural network, where concepts are represented by neurons and causal relationships by weighted links connecting the neurons.

Concepts reflect attributes, characteristics, qualities and senses of the system. Interconnections among concepts of FCM signify the cause and effect relationship that a concept has on the others. These weighted interconnections represent the direction and degree with which concepts influence the value of the interconnected concepts. Figure 1 illustrates a graphical representation of Fuzzy Cognitive Maps.

The cause and effect interconnection between two nodes C_j and C_i is described with the weight w_{ji}, with w_{ji} taking value in the range -1 to 1.

There are three possible types of causal relationships between concepts:

- $w_{ji} > 0$ which indicates positive causality between concepts C_j and C_i. That is, the increase (decrease) in the value of C_j leads to the increase (decrease) on the value of C_i.
- $w_{ji} < 0$ which indicates negative causality between concepts C_j and C_i. That is, the increase (decrease) in the value of C_j leads to the decrease (increase) on the value of C_i.
- $w_{ji} = 0$ which indicates no relationship between C_j and C_i.

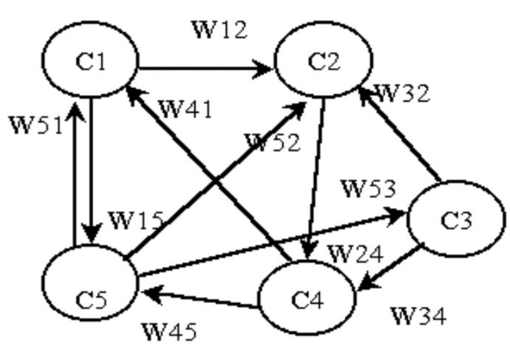

Fig.1 A simple Fuzzy Cognitive Map

Generally, the value of each concept is calculated, computing the influence of other concepts to the specific concept, by applying the following calculation rule:

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

where $A_i^{(k+1)}$ is the value of concept C_i at time $k+1$, $A_j^{(k)}$ is the value of concept C_j at time k, w_{ji} is the weight of the interconnection between concept C_j and concept C_i and f is the sigmoid threshold function.

The methodology for developing FCMs is based on a group of experts who are asked to define concepts and describe relationships among concepts and use IF-THEN rules to justify the cause and effect relationship among concepts and infer a linguistic weight for each interconnection [17]. 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.

Then the inferred linguistic weights suggested by the group of experts are composed and an overall linguistic weight is produced, which with the defuzzification method of Center of Area (CoA) [18], [19], is transformed to a numerical weight w_{ji}, belonging to the interval [-1, 1] and representing the overall suggestion of experts. Thus an initial matrix $w^{initial} = [w_{ji}]$, i,j=1,…,N, with $w_{ii} = 0$, i=1,..,N, is obtained.

Using the initial concept values, A_i, the matrix $w^{initial}$ is used for the determination of the steady state of the FCM, through the application of equation (1).

2.1 Nonlinear Hebbian Learning for FCM

The most significant weakness of the FCMs is their dependence on the expert's opinion and the uncontrollable convergence to undesired steady states. Learning algorithms are means to increase the efficiency and robustness of FCMs, by selecting and modifying the FCM weight matrix.

The learning algorithm is based on the nonlinear Hebbian learning rule. Oja (1991) proposed the nonlinear Hebbian-type leraning rule for NNs [20],[21],[22],[23], with the following general form:

$$\Delta w_{ji} = \eta_k y_i (x_j - w_{ji} y_i) \quad (2)$$

where η_k is the learning rate at iteration k.

Here the learning algorithm, Nonlinear Hebbian Learning (NHL) is adapted and modified for the FCM case. It is based on the premise that one (or more) of the concepts in FCM, at each iteration, is (are) the triggering concept that trigger(s) the interrelated concepts causing to them a change in their values at the next iteration step. For example, let's say the j-th concept C_j, is the triggering concept that influences concept C. This concept C_j is behaved as the triggering concept, with the value A_j and it triggers the interconnected corresponding concept C, which is behaved (defined) as the activation concept. During this triggering process the weight w_{ji} of the causal interconnection of the related concepts is updated and the modified weight $w_{ji}^{(k)}$ is derived for iteration k. At next iteration step, concept C is becoming the triggering concept that triggers the interconnected concepts and so on.

The value $A_i^{(k+1)}$ of C, concept at iteration $k+1$, is calculated, computing the influence of interconnected concepts with values A_j to the specific concept C due to modified weights $w_{ji}^{(k)}$ at iteration k, through the following equation:

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

Taking into consideration the general nonlinear Hebbian-type learning rule for NNs, we introduce the mathematical formalism for incorporating this learning rule, with the learning rate parameter and the activation and activated Concepts. This algorithm relates the values of concepts and values of weights in a FCM model.
The proposed rule has the general mathematical form:

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

where the coefficient η is a very small positive scalar factor called learning parameter and is determined using experimental trial and error method in order to optimize the final solution. A_j is the activation value of concept C_j, which at next iteration triggers the interconnected concepts, behaving as activated concept.

This simple rule states that if $A_i^{(k)}$ is the value of concept C_i at iteration k, and A_j is the Activation value of the Activated concept C_j triggering the concept C_i, the corresponding weight from concept C_j towards the concept C_i; increase is proportional to their product multiplied with the learning rate parameter minus the weight decay at iteration step k.
The training weight algorithm takes the following form:

$$w_{ji}^{(k)} = w_{ji}^{(k-1)} + \eta_k A_j (A_i^{(k)} - A_j w_{ji}^{(k-1)}) \quad (5)$$

The value of each concept of FCM is updated, through the eq. (3) where the value of weight $w_{ji}^{(k)}$ is calculated using eq. (5).

3. The FCM model for grading tumors

Doctors (our experts) were asked to describe the number and type of concepts comprising the FCM model, using positive linguistic variables depending on the characteristics of each particular concept according to the methodology presented in [10]. They followed their mental approach in grade diagnosis, where each tissue section is evaluated retrospectively, using a list containing eight well documented in the bibliography histopathological criteria essential for tumour grading (Table1)[2,7]. These considered features are the causative variables or factors of the tumour grading system that have selected by experts to be represented in the FCM, that that models the tumor grading procedure.

Thus, an FCM grading tool was developed consisting of 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 tumor grade.

Table 1: Main factors for grading

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

These eight concepts represent the eight variables of the tumor grade system and the ninth concept represents the degree of tumor grade, [24]. Possible values of concepts were described using five positive linguistic variables depending on the characteristics of each particular concept, such as very high, high, medium, weak and zero. When concepts represent events and/or discrete variables, there is a threshold (0.5) that determines which event is activated [24],[25]. All the values of concepts in the FCM belong to the interval [0,1].

Using the methodology for developing FCMs [17], the fuzzy rule for each interconnection was evaluated using fuzzy reasoning and the inferred fuzzy weight is defuzzified. The degree of the influence of concepts is represented by a linguistic variable of the fuzzy set {positive very high, positive high, positive medium, positive weak, zero, negative weak, negative medium, negative low, negative very low}.

The FCM grading model was developed and illustrated in Figure 2, where the initial weight matrix W of the FCM-GT model is determined:

$$W = \begin{bmatrix} 0 & 0.1 & 0 & 0 & 0 & 0 & 0 & 0 & 0.3 \\ 0 & 0 & 0 & 0.7 & 0.65 & 0 & 0 & 0 & 0.41 \\ 0.4 & 0 & 0 & 0 & 0 & 0 & 0 & 0 & 0.54 \\ 0 & 0 & 0 & 0 & 0.7 & 0 & 0 & 0 & 0.45 \\ 0 & 0 & 0 & 0 & 0 & 0.6 & 0 & 0.58 & 0.67 \\ 0 & 0 & 0 & 0 & 0 & 0 & 0 & 0.3 & 0.65 \\ 0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 & 0.76 \\ 0 & 0 & 0 & 0 & 0 & 0 & 0.55 & 0 & 0.78 \\ 0 & 0 & 0.62 & 0 & 0.62 & 0 & 0.65 & 0.63 & 0 \end{bmatrix}$$

The tumor grading procedure is based on the determination of the value of concept "Grade" that figure out the final degree of tumor malignancy.

According to the NHL algorithm, experts were asked to select the triggering concepts and the sequence of triggering process. The ninth concept of 'Grade' was defined as the triggered Desired Concept (DC), which determines the tumor grade. Experts defined that concepts "mitosis" and "necrosis" are the first triggering concepts, which at next iteration step trigger simultaneously the concepts "cell distribution", "cell size", "cell number" and "cytoplasm", behaving as second triggering concepts. Concepts "nuclei" and "nucleoli", are triggered by the second triggering concepts and are the third triggering concepts, which all together fire the concept 'Grade', whose value is calculated from equation (3) and represent the value of grade.

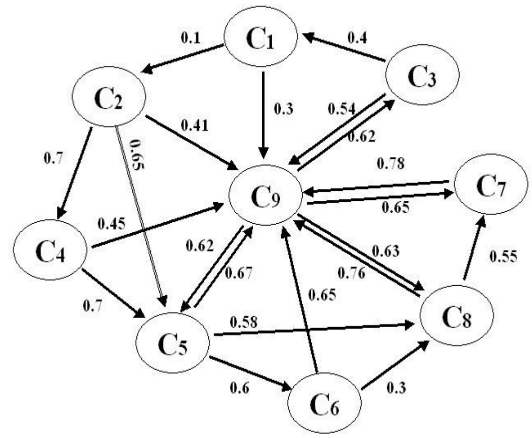

Figure 2: The FCM tumor grading model consisting of 9 concepts and 21 weight relations.

The proposed sequence of triggering concepts; mimic the way with which experts examine the histological material microscopically when they assign the grade of tumour. They start by 'scanning' the tissue sample under the microscope in order to assess the tissue appearance as a whole, and then they focus on regions with marked nuclear atypia, assessing morphological nuclear features and so on [26],[27],[28].

3.2 The NHL for FCM training

When the FCM model for classification has been developed and the necessary specifications for the implementation of the NHL have been determined, the training procedure for FCMs, employing nonlinear Hebbian algorithm, can be used to examine cases and assign grade to the urinary bladder tumours.

129 tissue sections (slides) from 129 patients with superficial transitional cell carcinoma were retrieved from the archives of the Department of Pathology of Patras University Hospital in Greece. Tissue sections were routinely stained with Haematoxylin-Eosin. All cases were reviewed independently by the experts to safeguard reproducibility. Cases were classified following the WHO grading system as follows: forty cases as Grade I, forty-five as Grade II, and forty four as Grade III.

Then the NHL algorithm is used to modify the weights of the FCM model according to the initial values of concepts for each examined case of urinary bladder tumor.

The schematic procedure of NHL algorithm for FCM tumour grading is given in Figure 3. Considering an *n*-node FCM-model, the execution phase of the proposed algorithm is consisted of the following steps:

Step 1: Read input state-case $\mathbf{A}^0$ and initial weight $\mathbf{w}^0$

Step 2: Apply Nonlinear Hebbian Learning Algorithm

2.1: Calculate A_i according to the eq. (3)

2.2: Update $w_{ji}^{(k)}$ according to eq. (5)

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

2.4: Classify the "Grade" values

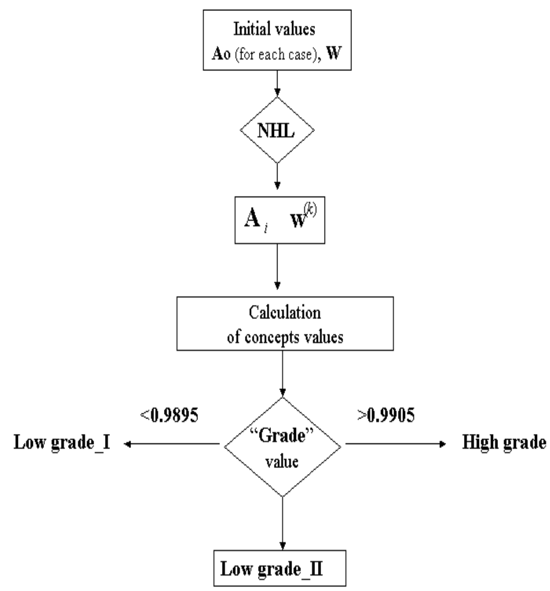

Figure 3. Flowchart of tumor grading procedure

4. Experimental Results

We used the 129 cases and for each one we took the values (measurements or estimations) of the eight features; we transformed them in the range [0,1] and we assigned them to the corresponding concepts; the value of the concept "Grade" was set equal to 0.5. Then for each case we applied the procedure shown in Figure 3, employing the AHL algorithm, and calculating the value of concept C9 the grading of tumor.

Figure 4 illustrates the "Grade" values calculated for the 129 cases by the FCM tumour-grading tool. For high-grade cases (Grade III) the estimated 'Grade' values are represented by ' ', for Grade II cases the estimated 'Grade' values are represented by '∇' and for Grade I cases the 'Grade' values are represented by '+'. It is clear that the proposed approach was able to give distinct different values for the most of Grade I, II and Grade III cases.

In order to determine the decision line defining each grade category, the minimum distance method was employed. Using this method the mean values m1 and m2, for Grade I and Grade II categories, were estimated. The same method is also used for the categories of Grade II and Grade III. The decision lines for each grade category were determined as the perpendicular bisector of the line joining m1 and m2. More specifically the value of 0,9895 determined as the threshold value for Grade I and II, and the value 0.9905 determined as the threshold value for Grade II and III.

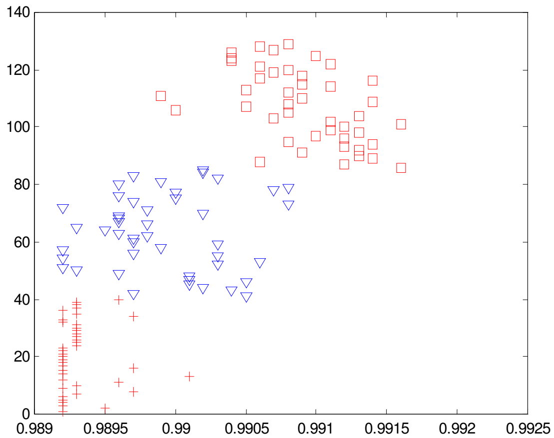

Figure 4. “Grade” values for the one hundred twenty-nine cases

“Grade” values greater than 0.9905 represent high-grade (Grade III) cases whereas values lower than 0.9895 as Grade I cases. Values lower than 0.9905 and greater than 0.9895 as Grade II cases, (Figure 5). The accuracy for Grade I cases was 85%, for Grade II cases was 80%, and for high grade (Grade III) cases was 90.91% for the derived decision lines.

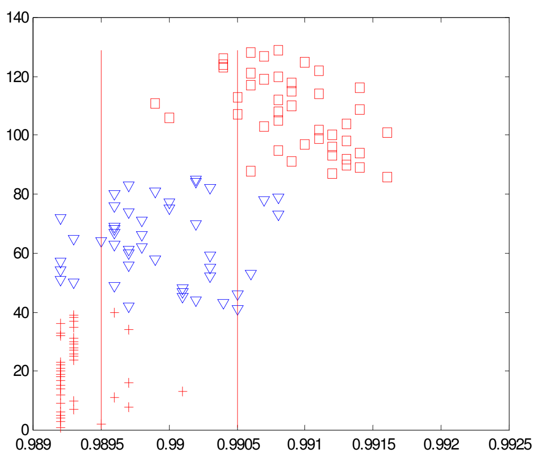

Figure 5. Decision lines for each grade category

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 boundary. The other 1/3 of the data set was used to evaluate the accuracy of the model. In average the success rate for the Grade I cases was 90%, for Grade II cases was 87.72% and 97.8% for the high-grade cases.

Researchers have mainly focused on quantitative microscopy methods using image analysis and the grade computer-aided diagnosis has been mainly investigated from the perspective of pattern recognition [6-8],[27],[29],[30]. Our results using the proposed method are comparable with the results given by the referred methods of pattern recognition, having the advantage of speed.

In this research effort, a sufficient estimation model for automatic grade characterization is developed with reasonably high accuracy in correctly assigning grade of tumors.

5. Conclusions

In this study an unsupervised learning algorithm, the nonlinear Hebbian learning was used in FCM model to improve the characterization of urinary bladder tumors employing histopathological features. The FCM exhibited high performance in correctly classifying tumors into three categories utilizing all the available diagnostic information from experts. The proposed FCM could be considered as an efficient classification tool able in making decisions about complex input data improving the diagnostic accuracy.

Additionally, the FCM classification tool is a versatile modeling and grading tool, offering a degree of transparency so the experts have some insight to the system behavior. Uncovering basic internal relations increases the knowledge about grading process. Furthermore, FCMs offer a flexible modeling method, to store specialized knowledge. New variables can be easily introduced in the grade model, (or others can be removed) following pathologists grading criteria that continue to evolve.

This FCM tool is easily implemented in clinical practice and it will contribute to the field of grade of tumor malignancy.

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