The Challenge of Soft Computing Techniques for Tumor Characterization

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Abstract. Computational diagnosis tools are becoming indispensable to support modern medical diagnosis. This research work introduces an hybrid soft computing scheme consisting of Fuzzy Cognitive Maps and the effective Active Hebbian Learning (AHL) algorithm for tumor characterization. The proposed method exploits human experts' knowledge on histopathology expressed in descriptive terms and concepts and it is enhanced with Hebbian learning and then it classifies tumors based on the morphology of tissues. This method was validated in clinical data and the results enforce the effectiveness of the proposed approach.

1 Introduction

Histological examination is used to evaluate the degree of tumor malignancy. In superficial urinary bladder tumors, the modality of therapy highly depends on the morphological tumor characterization [1]. World Health Organization (WHO) tumor-grading protocols classify tumors as low-grade or high-grade [1]. The final categorization for tumor grade relies on the complex interplay of discipline histopathological variables and measurements related to tissue architecture and appearance. Correct evaluation of histological material is mainly depending on the pathologists' experience since all these diagnostic variables are combined synergistically, but with a rather vague way. Taking into account the inherent subjectivity of decision process, the reproducibility of grading tumors performed by pathologists is questioned [2]. Previous efforts to standardize classification and grading of tumors using computer-aided grade diagnosis were based on pattern recognition techniques [3]. In this research work the main effort is to exploit and utilize human specialized knowledge on histopathology expressed in descriptive terms and concepts and to develop an advanced grading tool that can advise doctors in the tumor grading during daily clinical practice. The proposed method is based on FCMs [4] and the implementation of AHL algorithm [5]. In the medical application area, FCMs have been successfully used for decision-making in

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radiation therapy planning systems [6]. This paper is structured in the following sections: Section 2 presents some fundamental aspects of FCMs and the AHL algorithm. Section 3 describes the development of the FCM Tumour Grading Tool (FCM-TG). In section 4 the FCM grading tool is used to classify and evaluate clinical test cases. Section 5 discusses the results, outlines the conclusions and future research directions are proposed.

2 Fuzzy Cognitive Maps and Activation Hebbian Learning Algorithm

The FCM represents the human knowledge and experience at the kind of concepts and weights of the interconnections between concepts. Each concept represents one of the key-factors of the model and it is characterized by its value A_i. Between concepts there are cause and effect relationships that are illustrated in the FCM graph with the weighted arc w_{ji} from one concept towards another. The value of w_{ji} indicates how much concept C_j influences concept C_i. The sign of w_{ji} indicates whether the relationship between concepts C_j and C_i is direct or inverse, either expresses positive causality between two concepts ($w_{ji} > 0$) or negative causality ($w_{ji} < 0$). The direction of causality indicates whether concept C_j causes concept C_i, or vice versa. These three parameters have to be considered when assigning a weight value w_{ji} to an interconnection [4]. Generally, the value of each concept is calculated by applying the following calculation rule:

$$A_i(k+1) = f\left(A_i(k) + \sum_{\substack{j=1 \\ j \neq i}}^{N} A_j(k) * w_{ji}\right), \tag{1}$$

where $A_i(k+1)$ is the value of concept C_i at simulation step $k+1$, $A_j(k)$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 the concepts and describe the relationships among concepts. Every expert describes each one of the interconnections with a fuzzy IF-THEN rule, with the following form, where B, D and E are fuzzy linguistic variables:
IF a change B occurs in the value of concept C_j **THEN** a change D in the value of concept C_i is caused.
Infer: The influence from concept C_j to C_i is E.
The inference of the rule is a linguistic variable E, which determines the grade of causality between the two concepts [7]. All the fuzzy weights suggested by the group of experts are summed (through SUM technique) and an overall linguistic weight is produced, which with the defuzzification method of Center of Area (CoA) [8], is transformed to a crisp weight, belonging to the interval $[-1, 1]$.

The AHL algorithm has been proposed to create advanced FCMs with better modelling and classification abilities [5]. The AHL introduces the asynchronous updating for the concepts and weights of FCM, defines the activation and activated concepts as well as the Activation Decision Concepts (ADCs), which are

the observable outputs of the system. This learning algorithm is based on the premise that one (or more) of the concepts, at each iteration, is considered as the activated concept(s) which triggers the interrelated concepts causing to them a change in their values. According to the infrastructure of the FCM, experts initially determine the activated and activation concepts for every simulation step and determine the way, with which factors-concepts affect the ADCs. During this activation process the weight w_{ji} of the causal interconnection of the related concepts is modified and is updated for each iteration step k using the following discrete type, as they suggested and described in [5]:

$$w_{ji}(k+1) = (1-\gamma) * w_{ji}(k) + n * A_j^{act}(k) * [A_i(k) - A_j^{act}(k) * w_{ji}(k)], \quad (2)$$

where n, γ are the learning rate parameters. These parameters take positive values in the range $[0, 0.1]$ and they are exponentially attenuated according to the number of simulation cycles. Eq. (1) that calculates the value of each concept of FCM is updating, taking into consideration the value of weight $w_{ji}(k)$ which is now modified at every iteration step according to Eq. (2). This AHL algorithm improves the FCM grading ability and enhances the FCM modeling capabilities; the AHL adjusts the weights ensuring that the FCM will classify successfully.

3 Description of the FCM Tumor Grading (FCM-TG) Model

The FCM model for tumor grading (FCM-TG) is developed by experts using the methodology described in [7]. For this specific medical application our experts were histopathologists with deep knowledge and great clinical experience. Experts defined the main histopathological features (concepts) that play important role in the final grade diagnostic decision [9]. Each variable can take two, three or four possible discrete values (Table 1). 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. Furthermore, histopathologists were asked to explain the degree of influence among these concepts, which was represented by a linguistic variable of the set {positive very high, positive high, positive medium, positive weak, zero, negative weak, negative medium, negative low, negative very low}. Following the FCM developing algorithm [7], the FCM-TG model was constructed (Fig 1).

Then the AHL can be used to modify the weights of the general FCM-TG according to the initial values of concepts for each case of urinary bladder tumor. According to the AHL algorithm, experts were asked to select the sequence of activation concepts, the steps and the cycle of simulation. The ninth concept of 'Grade' was defined as the ADC, which determines the tumor grade. Experts defined that concepts C_8 and C_7 are the first activated concepts, which at next iteration step trigger simultaneously the concepts C_1, C_2, C_3 and C_4, behaving as second activated concepts. C_5 and C_6, are triggered by the second activation concepts and are the third activated concepts, which all together fire the C_9

Table 1. Histological features for coding tumors' malignancy

Histological features	Assessment
C_1:Cell Distribution	Even, clustered
C_2: Cell size	Uniform, pleomorphic
C_3: Cell number	Numerous, variable
C_4: Cytoplasm	Homogeneous, variable
C_5: Nuclei	Uniform, irregular, very irregular, bizarre
C_6: Nucleoli	Inconspicuous, evident, prominent
C_7: Necrosis	Inconspicuous, frequent
C_8: Mitosis	Absent–rate, occasional, numerous

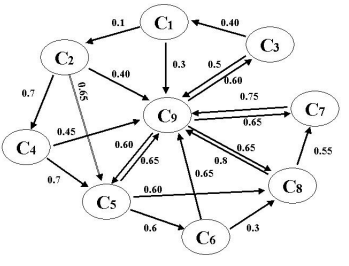

Fig. 1. The FCM tumor grading model

(Grade). The proposed sequence of activated and activation concepts mimic the way with which experts examine the histological material microscopically when they assign the grade of tumor. 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 [3].

4 Implementation of FCM-TG Model

After FCM-TG development and the determination of necessary specifications for the implementation of the AHL , the FCM-TG was used to examine cases and assign grade to the tumors. The classification task requires the determination of the decision margin; for this reason ninety–two cases of urinary bladder cancer were used. The same cases were used to evaluate the performance of the FCM-TG model in categorizing tumors as low grade or high grade. The cases were collected at the Department of Pathology, University Hospital of Patras Greece. Histopathologists had diagnosed 63 cases as low-grade and 29 as high-grade following conventional WHO grading system [1]. In order to use the FCM-TG 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 initial value 'Grade' ('G') of the concept C_9 was randomly selected but was kept the same value for all cases. FCM-TG model was able to give distinct different values for the majority of high-grade and low-grade cases. However, some of the high grade and low-grade cases appear to have similar 'G' values. This is reasonable because it is very difficult for the doctors to clearly classify some cases and there is a certain region called 'Grey' region, where the diagnostic criteria overlap and for cases belonging to this region there is a degree of diagnostic uncertainty. Subsequently, the definition of a sharp decision line to categorize 'G' values as low or high seems to not fit reasonably well to the assumption of continuous grade and the continuous spectrum of biological changes in tumors' appearance. For this reason, we introduced a 'Grey' region defined by two decision lines for the diagnostic categories instead of using one sharp decision line. To construct the decision margin for the 'Grey' region we employed the minimum distance method; the mean 'G' values m1 and m2, for each grade category, were estimated and a decision line was determined as the perpendicular bisector of the line joining m1 and m2. We randomly selected 60 cases out of the 92 and we implemented the minimum distance method. We repeated this procedure one hundred times. The mean value (m) and the standard deviation (std) of the derived one hundred decision lines were estimated.

The decision margin of the 'Grey' zone was set by the 'G' values belonging in the region defined by the m± 3std (0.915 ± 0.025). 'G' values lower than $0.915 - 0.025$ were set to belong to the low-grade cases and values greater than $0.915 + 0.0025$ were set to belong to high-grade cases. After the determination of the decision margin, the FCM-TG model performance was evaluated for all the 92 cases. 87.3% of the low grade cases were found to belong in a region less than 0.9125 and 93.10% of the high grade cases were found in a region greater than 0.9175. For high-grade cases the estimated 'G' values are represented by □ and for low grade the estimated 'G' values are represented by ▽ (Fig. 2). Using the FCM-TG model with the same initial weights and retaining the AHL algorithm

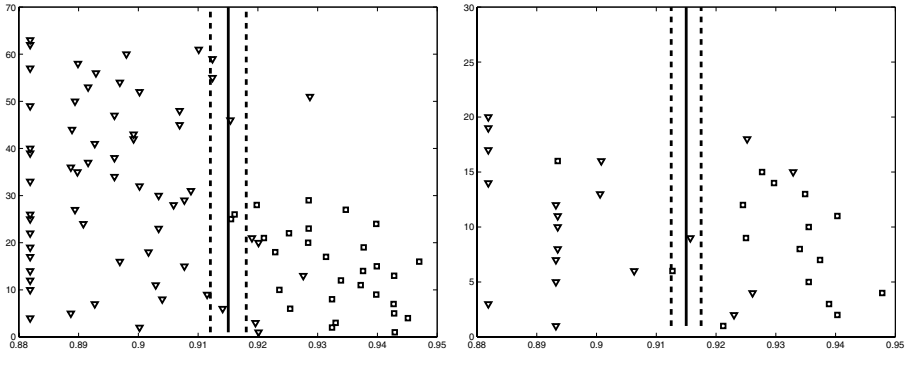

Fig. 2. Decision regions defined by 92 cases (left) Categorization of 36 new clinical cases (right) after defining the decision margin

36 new urinary bladder cancer cases were evaluated. Cases have been previously diagnosed as 20 low-grade cases and 16 high-grade. Cases categorized using the decision margin previously determined. The success rate for the low-grade cases was 80%. For the high-grade the FCM-TG accuracy was 87.5%.

5 Conclusion

In this paper an hybrid soft computing approach to support medical diagnosis is presented. The method incorporates experts' knowledge in developing the FCM-TG and determining the AHL algorithm and so it achieves characterization of tumor malignancy. In terms of sensitivity and specificity, the accuracy for the high-grade cases was 87% and for the low-grade cases was 80%. Concluding, the FCM-TG is fast, easily implemented in clinical practice and performs with reasonably high accuracy, rendering the FCM-TG an accessible alternative solution in automatic grade characterization.

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