K15

NNESMED CIMED 2003

Fifth International Conference on **Neural Networks and Expert Systems in Medicine and Healthcare NNESMED 2003 and 1st International Conference on Computational Intelligence in Medicine and Healthcare CIMED 2003**

Sheffield Hallam University, Sheffield, UK
21-23 July 2003

CONFERENCE PROCEEDINGS

A Fuzzy Cognitive Map Model for Grading Urinary Bladder Tumors

E. Papageorgiou, P. Spyridonos[2], C. Stylios[1], P.Ravazoula[3], P. Groumpos & G. Nikiforidis[2]

Laboratory for Automation and Robotic, Department of Electrical and Computer Engineering, *University of Patras, Rion 26500, Greece*
Tel. +302 610 997293, Fax. +302 610 997309 {epapageo,groumpos}@ee.upatras.gr
[1]Computer Science Department, University of Ioannina,P.O.Box 1186, Ioannina, Greece, Tel. +302651098818, stylios@cs.uoi.gr
[2] Computer Laboratory, School of Medicine, *University of Patras, Pion 265 00, Greece*
[3] Dept. of Pathology, University Hospital, *Rion Patras 265 00, Greece*

Abstract: This research work presents a new modeling method for grading urinary bladder tumors that, in many cases, cannot be easily graded. This difficulty necessitates the development of a methodology to assist the histopathologist in the assignment of grade to tumor malignancy. Eight significant histopathological features are selected that are used in the Fuzzy Cognitive Map (FCM) model. The FCM grading tool was validated for 63 low grade cases and 29 high grade cases. The obtained results fully verify the effectiveness of the tool and its valid contribution as a FCM grading tool for urinary bladder tumors.

Keywords: Fuzzy Cognitive Maps, grading, urinary bladder tumors

1. Introduction

In superficial urinary bladder tumors, the modality of therapy are highly depends on the morphological tumor characterization. Subsequently, grade diagnosis carries significant consequences [1]. Tumors characterized by the World Health Organization (WHO) grading system, are classified into two categories: low-grade and high-grade [2]. Correct evaluation of histological material is mainly depending on the pathologists' experience. To characterize tumor malignancy, relationships of a great number of different histopathological features and factors must be taken in consideration. These features 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]. Digital image analysis of tissue and cell characteristics in microscopic images has been used for the quantitative and objective analysis of tumors. Previous efforts to standardize classification and grading of tumors have used computer-aided grade diagnosis based on pattern recognition techniques [4-6]. In this paper the aim is to exploit human experts' knowledge on histopathology expressed in descriptive terms and concepts and to develop a decision-making grading tool that can help the doctors in the daily clinical practice. The proposed method to assist grade diagnosis is based on Fuzzy Cognitive Maps (FCMs). FCMs are a workable soft computing methodology that has been used for a number of disparate modeling and support decision-making tasks [8,15,16]. For medical applications, FCMs have been proposed for decision-making in radiation therapy planning systems.[12].

In this research work, FCMs are used to model the specialized knowledge and experience on tumor histopathology analyzing the criteria that experts use to support grade diagnostic decision, and to grade the urinary bladder tumors.

This paper contains the following sections. Section 2 describes the FCM representation and the Active Hebbian Learning Algorithm. In section 3 the FCM tumor-grading tool is developed and section 4 presents the results of the classification tests using the FMC tool and section 5 concludes the paper.

2. Fuzzy Cognitive Maps Representation and Active Hebbian Learning Algorithm

The synergistic and complementary use of fuzzy logic and neuro-computing has initiated the development of soft computing methodologies, such as FCM. 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 [8].

A FCM stores the existence knowledge in the kind of nodes and in the kind and value of the interconnections between nodes of the FCM. Each node-concept represents one of the key-factors of the modeled system and it is characterized by a number A_i that represents its value.

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.

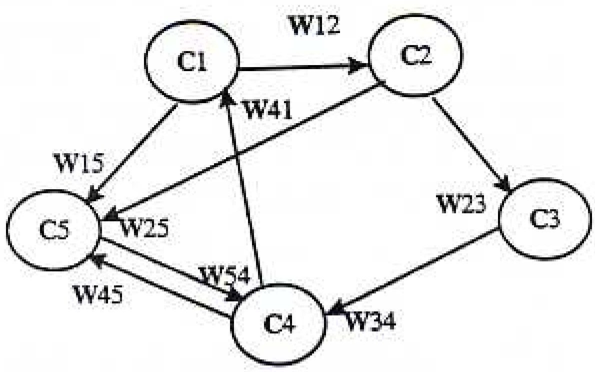

Figure 1. A simple Fuzzy Cognitive Map

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_i for each concept C_i is calculated by the following rule:

$$A_i^{t+1} = f\left(A_i^t + \sum_{\substack{j=1 \\ j \neq i}}^{n} A_j^t \cdot W_{ji}\right) \quad (1)$$

Namely A_i^{t+1} is value of concept C_i at step t+1, A_j^t is the value of concept C_j at step t, and W_{ji} is the weight of the arc from concept C_j towards concept C_i 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 [9]. 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 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_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.

Then the inferred fuzzy weights are aggregated using MAX method and the result is defuzzified with the method of Center of Area (CoA) [11], is transformed to a numerical weight w_{ji}, belonging to the interval [-1,1].

For better the modeling and for developing of an advanced FCM, an unsupervised learning algorithm, named Active Hebbian Learning (AHL), is implemented to train the FCM and modify the weights [13]. This AHL algorithm improves the FCM grading abilities and enhances the FCM modeling, adjusting the weights in order to ensure that the FCM will converge to a fixed desired region.

The AHL Algorithm introduces the asynchronous updating of the weights, the Activation and Activated concepts and the calculation of Activation Decision Concepts (ADCs), which are the observable states of the system. The asynchronous mode suggests that for each time step, during the simulation run there are Activated and Activation concepts, according to the infrastructure of the Fuzzy Cognitive Map. The sequence of activation steps between concepts is suggested by experts who determine the most important factors-concepts that affect the Activation Decision Concept (ADC).

The Active Hebbian Learning algorithm adjusts the weights between interconnections using the following discrete type of asynchronous mode:

$$w_{ji}^{(k)} = (1-\gamma)\cdot w_{ji}^{(k-1)} + \eta \cdot A_j^{act} \cdot A_i^{(k)} \qquad (2)$$

Here, it is supposed that concept C_i with value A_i is the Activation concept. A_j^{act} is the value of the Activated concept C_j and $A_i^{(k)}$ is the value of interconnected concept at the same iteration step. The coefficients γ and η are learning rate parameters where γ exponentially decreases with the number of iterations and η takes an acceptable constant value equal to 0.01 [14].

The equation (1) which calculates the value of each concept of FCM is updating and takes the following form where the value of weight $w_{ji}^{(k)}$ is calculated using equation (2):

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

The value of i-th Activation concept $A_i^{(k+1)}$, at iteration $k+1$, is calculated, computing the influence of the other Activated concepts with values A_j^{act} to the specific concept C_i due to modified weights $w_{ji}^{(k)}$ at iteration k.

This AHL algorithm increases the effectiveness, flexibility and robustness of FCM, and accompanied with good knowledge of the given system, a Fuzzy Cognitive Map grading tool is created.

3. Development of the FCM tumor grading model

Ninety-two cases of urinary bladder cancer were collected from the archives of the department of pathology of University Hospital of Patras Greece. Using conventional WHO grading system, expert's diagnosed 63 cases as low-grade and 29 as high grade. Following grade diagnosis, each tissue section was evaluated retrospectively, using a list containing eight well documented in the bibliography histopathological criteria essential for tumour grading (Table1)[1-2,7]. Each criterion was accompanied by two, three or four possible values.

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 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. Experts were asked to describe the number and type of concepts using positive linguistic variables depending on the characteristics of each particular concept according to the methodology presented in [10]. 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. 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. These eight concepts represent the eight variables of the tumor grade system and the ninth concept represents the degree of tumor grade. When concepts represent events and/or discrete variables, there is a threshold (0.5) that determines which event is activated. All the values of concepts in the FCM belong to the interval [0,1].

Using the methodology for developing FCMs [9], 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}. As an example, the determination of some weights will be described.

Expert describes the influence from the C1 towards C9 using the following fuzzy rule:

IF a small change occurs in the value of C1 THEN a small change is caused in the value of C9.

This means that if a small change occurs in the type of cell distribution then a small change in the grade of tumor is caused. So, the influence of C1 to C9 is positively small.

Analogous is the methodology of determining all the existent influences between concepts.

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.

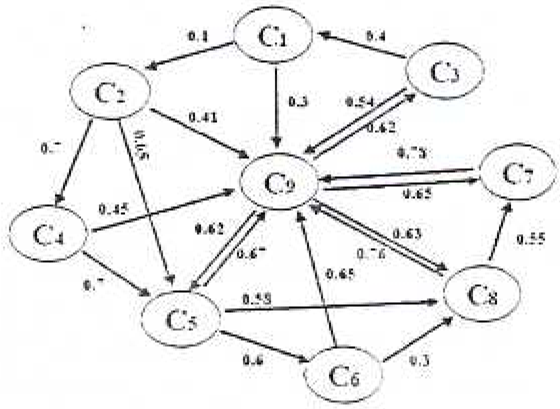

Figure 2: The FCM tumor grading model consisting of 9 concepts and 21 weight relations.

Based on the asynchronous updating mode of AHL algorithm, [13], experts defined the Activation and Activated concepts and the sequence of activation. Also, they defined as the Activation Decision Concept (ADC) the C9 concept "Grade". The AHL Algorithm is used for adjusting the weights of the FCM and has the following implementation. During this stimulation mode the concepts "mitosis" and "necrosis" were defined as the first Activation concepts at first sub step of the AHL algorithmic process, which at next iteration step trigger the concepts "cell distribution", "cell size", "cell number" and "cytoplasm", behaving as second Activation concepts. Concepts "nuclei" and "nucleoli", triggered by the previous activated concepts were the third activation concepts, which all together fired the concept "Grade", which activation value is calculated from equation (3) and represent the value of grade. This sequence of activated concepts, mimic the way experts examine the histological material microscopically in order to assign grade. 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.

4. Test to evaluate the FCM grading tool

To evaluate the performance of FCM grading tool in classifying urinary bladder tumor as low grade or high grade, we experimented with 92 cases of urinary bladder carcinoma. For each case we took the values (measurements or estimations) of the eight features; we transformed them in the range [-1,1] 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 run the FCM tool, employing the AHL algorithm, and calculating the value of concept C9 the grading of tumor. Figure 3 illustrates the "Grade" values calculated for the 92 cases by the FCM tumor-grading tool. It is clear that the proposed approach was able to give distinct different values for the most of high grade and low grade cases.

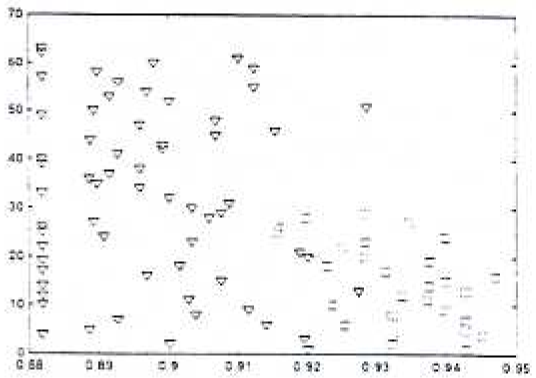

Figure 3: "Grade" values for each case

In order to define the decision region for each grade category, the minimum distance method was employed. Using this method the mean values m1 and m2, for each grade category, were estimated. The decision boundary was determined as the perpendicular bisector of the line joining m1 and m2. More specifically the value of 0.915 determined as the threshold value for each grade category. "Grade" values greater than 0.915 represent high-grade cases whereas values lower than 0.915 as low grade. (Figure 4). The accuracy for low grade cases was 88.98% (56/63) and for high grade was 100% for the derived decision boundary.

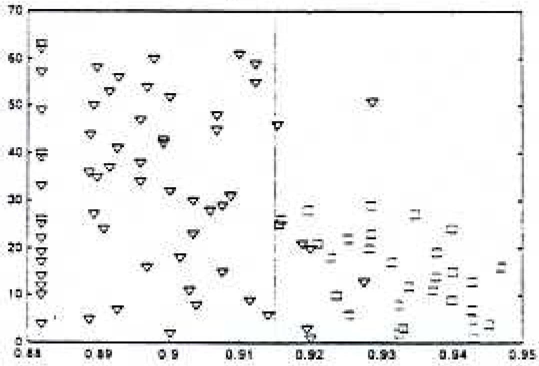

Figure 4: Decision boundary for grade category

In order to examine the generalization of the proposed method we repeatedly (for 100 experiments) we did the following procedure. 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 low grade cases was 89.43% and 97.78% for the high grade cases.
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 paper a novel approach to support grade diagnostic decision was presented, exploring human knowledge and expertise in tumor histopathology. The proposed method uses FCMs to represent the specialized knowledge and experience in an efficient manner, exploiting the fact that different histopathological features and variables are taken into consideration for grading tumors. The efficient AHL algorithm was used successfully in this research work, discriminating tumor cases of urinary bladder according to the degree of malignancy. The success rate was 89.43% and 97.78% for the low grade and high-grade cases respectively.

Subsequently, the proposed FCM grading tool might be seen as a viable alternative solution in automatic grade characterization.

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

References

1. MURPHY, *W.M.*: 'Urothelial neoplasia'. In Pathology and pathobiology of the urinary bladder and prostate. (Baltimore, Williams & Wilkins, *1992*).

2. JONATHAN I.E., MAHUL B.A., VICTOR R.R. MOSTOFI F.K.: 'The World Health Organization/International Society of Urological Pathology Consensus Classification of Urothelial (Transitional Cell) Neoplasms of the Urinary Bladder'. The American Journal of Surgical Pathology, 1998; 22(12), pp. 1435-1448.

3. OOMS E. ANDERSON W. ALONS C. BOON M. VELDHUIZEN R., "Analysis of the performance of pathologists in grading of bladder tumors", *Human Pathology* 1983; 14:140-143.

4. JARKRANS T. VASKO J. BENGTSSON E. CHOI H-K. MALMSTROM U. WESTER K. BUSCH C.: 'Grading of transitional cell bladder carcinoma by image analysis of histological sections', Analytical Cellular Pathology, 1995, 18, pp. 135-158.

5. SPYRIDONOS P., RAVAZOULA P., CAVOURAS D., BERBERIDIS K., NIKIFORIDIS G.: 'Computer-based grading of haematoxylin-eosin stained tissue sections of urinary bladder carcinomas', Medical Informatics & The Internet in Medicine, 2001, 26(3), pp. 179-190.

6. SPYRIDONOS P., CAVOURAS D., RAVAZOULA P., NIKIFORIDIS G.: 'Neural network based segmentation and classification system for the automatic grading of histological sections of urinary bladder carcinoma', Analytical and Quantitative Cytology and Histology, 2002, 24(6), pp. 317-324.

7. MURPHY W.M., SOLOWAY S.M., JUKKOLA A.F., CRABTREE W.N., FORD K.S.: 'Urinary Cytology and Bladder Cancer. The cellular features of transitional cell neoplasms', Cancer, 1984, 53, pp. 1555-1565.

8. KOSKO, B.: *Neural Networks and Fuzzy Systems*, Prentice-Hall, New Jersey, 1992.

9. STYLIOS, C. D. AND GROUMPOS, P.P.: "Fuzzy Cognitive Maps in Modelling Supervisory Control Systems," *Journal of Intelligent & Fuzzy Systems*, vol. 8, pp. 83-98, 2000.

10. STYLIOS, C.D., GROUMPOS, P.P. & GEORGOPOULOS, V.C.: 'An Fuzzy Cognitive Maps Approach to Process Control Systems', J. of Advanced Comput. Intelligence, 1999, vol. 3, No. 5, pp. 409-417.

11. LIN C.T. AND LEE, C.S. G.: Neural Fuzzy Systems: A Neuro-Fuzzy Synergism to Intelligent Systems, (Prentice Hall, Upper Saddle River, N.J, 1996).

12. PAPAGEORGIOU, E., STYLIOS, C.D., GROUMPOS, P.P.: 'An Integrated Two-level Hierarchical Structure for Decision Making in Radiation Therapy based on FCMs', accepted for publication in IEEE Transactions on Biomedical Engineering, 2003.

13. PAPAGEORGIOU.E., STYLIOS, C.D., GROUMPOS, P.P.: ' An Active Hebbian Learning Algorithm for Fuzzy Cognitive Maps', submitted in Neural Networks, 2003.

14. PAPAGEORGIOU, E., STYLIOS, C.D., GROUMPOS, P.P.: 'Activation Hebbian Learning Rule for Fuzzy Cognitive Maps', 15^{th} IFAC World Congress of International Federation of Automatic Control, Barcelona, Spain, July 21-26,CD-ROM, 2002.

15. KHAN, S., CHONG, A. AND GEDEON, T. A.: 'Methodology for Developing Adaptive Fuzzy Cognitive Maps for Decision Support', 3^{rd} Australia-Japan Evolutionary Systems, 1999, Canberra 23-25 November, pp. 93-100.

16. LIU Z.Q, SATUR R.: "Contextual fuzzy cognitive map for decision support in geographic information systems", IEEE Trans Fuzzy Systems, 1999, 5, pp. 495-507.