State Space Advanced Fuzzy Cognitive Map approach for automatic and non–Invasive diagnosis of Coronary Artery Disease

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Abstract

Purpose: In this study, the recently emerged advances in Fuzzy Cognitive Maps (FCM) are investigated and employed, for achieving the automatic and non-invasive diagnosis of Coronary Artery Disease (CAD).

Methods: A Computer-Aided Diagnostic model for the acceptable and non-invasive prediction of CAD using the State Space Advanced FCM (AFCM) approach is proposed. Also, a rule-based mechanism is incorporated, to further increase the knowledge of the system and the interpretability of the decision mechanism. The proposed method is tested utilizing a CAD dataset from the Laboratory of Nuclear Medicine of the University of Patras. More specifically, two architectures of AFCMs are designed, and different parameter testing is performed. Furthermore, the proposed AFCMs, which are based on the new equations proposed recently, are compared with the traditional FCM approach.

Results: The experiments highlight the effectiveness of the AFCM approach and the new equations over the traditional approach, which obtained an accuracy of 78.21%, achieving an increase of seven percent (+7%) on the classification task, and obtaining 85.47% accuracy.

Conclusions: It is demonstrated that the AFCM approach in developing Fuzzy Cognitive Maps outperforms the conventional approach, while it constitutes a reliable method for the diagnosis of Coronary Artery Disease. Conclusions and future research related to recent pandemic of coronavirus are provided.

Keywords: State Space Fuzzy Cognitive Maps; Coronary Artery Disease; Fuzzy Cognitive Maps; Decision Support System; Machine Learning;
1. Introduction

Medical Decision-Making problems are complex. Usually the physicians are requested to handle information of different nature, e.g. patient’s history, clinical diagnostic tests, medical images, and demographic characteristics. The interpretation of the results involves uncertainty, which plays a critical role for the decision-making to a wide and diverse set of fields. Approaching dynamic systems that involve uncertainty is demanding, therefore engineers and decision-makers face difficulties [1].

Clinical Decision Support Systems (CDSS) have been proposed the past years, to overcome those issues. A CDSS is an expert system that provides decision support and serves as a diagnostic and treatment reference for clinicians or patients. CDSSs incorporate any available patient related clinical data and the experts’ knowledge to perform a reasoning analysis.

A lot discussion is held regarding the decision mechanisms relating the inputs and the desired outputs of the systems. Fuzzy Cognitive Maps (FCMs) constitute a simple computational and graphical methodology to represent complex problems. FCMs’ decision-making mechanism is a unique method of handling the parameters of a desired decision.

FCMs were introduced by Kosko in 1986 in order to represent the causal relationship between concepts and analyze inference patterns [2-3]. They take advantage of the knowledge and the experience of experts, offering them an alternative way of addressing the problems, yet in the same way a human mind does. This is achieved by using a conceptual procedure, which can include ambiguous of fuzzy descriptions [4]. Recently, Fuzzy Cognitive Maps were employed to describe and solve medical problems [5-7].

State Space Advanced Fuzzy Cognitive Maps (AFCM) are an evolution of the classic methodology, which promises more precise results for a large variety of complex systems. This methodology, which is thoroughly analyzed in [8], is presented in the following subsections, and it overcomes some issues of the classic FCMs. Those issues are: (a) the presence of concepts of different nature was ignored in the traditional approach and, (b) the utilization of the classic sigmoid normalization function was fuzzing the system, especially in cases of the existence of several concepts. Despite the fact that the novel strategy in [8] is intended for applications where time iteration steps play the most vital role in the behavior of the system, they can also be employed to static applications.

As to our best knowledge, AFCM have not been applied and evaluated to medical diagnosis. In this work, we employ the newly emerged State Space FCMs for the automatic and non-invasive prediction of Coronary Artery Disease (CAD). The Coronary Artery Disease is caused when the atherosclerotic plaques load, namely fill, in the lumen of the blood vessels of the heart, which are named coronary arteries, and they obstruct the blood flow to the heart. According to the World Health Organization, 50% of deaths in European Union is caused by Cardiovascular Diseases (CV), while 80% of the premature heart diseases and strokes can be prevented [9]. Diagnosing CAD in a non-invasive way is an open challenge, despite the massive number of researches been made so far [10-11].

More specifically, in our work, we design two new models and propose some alterations in order to address the problem. Designing AFCM models requires the collaboration between experts and engineers. The experts suggest and aid for the designment of the AFCM, for it to be user-friendly, scientifically acceptable, and interpretable. In this work, the Nuclear Medicine staff suggested that the casual relationships between concepts were unable to explain some unique and complex connections. Hence, the proposed models were designed to function with the aid of some universal rules. The Rule-Embedded AFCM (RE-AFCM), which is proposed in this work, is evaluated on a real patient-candidate database from the Laboratory of Nuclear Medicine of the University of Patras. Aiming to improve and evaluate AFCM’s performance, we experiment with the new and traditional equations, as well as with different activation functions, and architectures. The optimal parameters are defined through the experiments and correspond to an improvement in the accuracy by +7%, over the traditional approach. The results demonstrate the effectiveness of the newly emerged State Space approach for the development of FCMs. It is also demonstrated that RE-AFCM can be applied to medical problems, with the appropriate modifications and with respect to the nature of the inputs.
2. Fuzzy Cognitive Maps – Classic Theory and recent Advances

2.1 Classic FCM theory

FCMs constitute a computational methodology able to examine situations which the human thinking process involves fuzzy or uncertain descriptions. FCMs consist of a graphical representation through a signed directed graph, which includes feedback consisting of nodes and weighted arcs [12]. Each node in the graph represents a concept used to describe the cause and effect relationship. The nodes are connected by weighted arcs representing the actual interconnections. Each concept Ci (i.e., the variable of the system) is characterized by a number representing its values, and is calculated through the transformation of a fuzzy value, or the fitting of a numeric value, to the desired interval [0,1]. The initial weight values are defined by the experts of the domain and, therefore, they are linguistic variables, or rule-type statements. Through a defuzzification procedure the linguistic variables are transformed into numeric weights. In this way, FCMs embody the accumulated knowledge and experience from experts [13]. An example is given in Figure 1.

Fig.1. Fuzzy Cognitive Map.

The degree of influence between the two concepts is indicated by the absolute value of $W_{ij}$. During the simulation, the value of each concept ($C_i$) is calculated as shown in [14].

2.1 State Approach

In the classic FCM representation, all concepts and parameters are treated and calculated regardless of their different nature. However, even when a system is described in fuzzy way, the main concept is the same. In the classic control theory, which shall be employed to address the matter, a separation of the concepts is suggested [15-16], as follows:

- **Input Concepts**: The inputs of the system, ($u$)
- **State Concepts**: The concepts describing the operation of the system, ($x$)
- **Output Concepts**: The concepts describing the outputs of the system, ($y$).
A simple representation of the system is achieved by a block diagram, which is presented in [16], and depicted in Figure 2.

**Fig.2. Block Diagram of the separated concepts.**

In this way, more accurate knowledge of the system is obtained. The proposed separation facilitates the understanding of the system’s operation, and the simpler calculation of the concepts’ values.

2.1 Mathematical Expressions of the State Space Advanced Approach

Separating the concepts into categories enables the calculation of their values in a more distributed way. The initial weight matrix, which describes all relations, shall be divided into smaller ones in order to correspond them to each concept category. The classic equations (eq. 1, eq. 2)

\[ \begin{align*}
    X[k+1] &= Ax[k] + Bu[k] \\
    Y[k+1] &= Cx[k] + Du[k]
\end{align*} \]

shall now be used to calculate the variation, caused by the change in the input and state concepts, to the state and output concepts, at each time step [k]. In equations (1), and (2), A, B, C and D are individual weight matrices derived from the initial; The elements of matrix A depend on the states’ weights, while the elements of matrix B show how each input concept affects the state concepts of the system. Matrix C embodies the relation between the states and the outputs, while matrix D incorporates the direct affection of input concepts to output concepts [15].

Since equations (1) and (2) are used to compute the variation caused between the concepts, it is more accurate to express them as follows:

\[ \begin{align*}
    \Delta X[k+1] &= Ax[k] + Bu[k] \\
    \Delta Y[k+1] &= Cx[k] + Du[k]
\end{align*} \]

Using equations (3) and (4), the expression of the actual values of X[k+1] and Y[k+1] is in equations (5) and (6):

\[ \begin{align*}
    X[k+1] &= X[K] + \frac{\Delta X[k+1]}{\sum_{j=1,j\neq i}^{n} |W_{ji}|} \\
    Y[k+1] &= Y[K] + \frac{\Delta Y[k+1]}{\sum_{j=1,j\neq i}^{n} |W_{ji}|}
\end{align*} \]

One more advantage of the mentioned technique is the transparency and decomposability of the system. Concepts behaving as if they were clusters is reality, are allowed to do so, through their participation in state concepts. It is worth mentioning that the above equations’ best use is when the system is described by time-steps, and by complex interconnections between the concepts.

2.1.1 Activation and Normalization Functions

In order to apply the AFCM methodology, the values of all the input concepts must lay between the interval [0,1], where 0 denotes that the value of the concept is very small and 1 that the value is very big. There are many proposed activation functions to perform the aforementioned task. In this work we utilize the newly
proposed alteration to the classic sigmoid function, as introduced in [17]. We use this function for the inner calculations (i.e. the inputs and the states). The function is explained below:

\[ f(x) = m + \frac{M-m}{1+e^{-r(x-t_0)}} \] (7)

In equation (7), \( m \) is the lower limit of the curve, \( M \) is the upper limit of the curve, \( r \) is the slope of the curve and \( t_0 \) is the symmetry to the y axis. We refer to equation (7) as SigmoidN.

For the final classification between “Healthy” or “Diseased”, we also use a Softmax classifier [18], to evaluate and compare the different methodologies.

2.1.1 Fuzzification and de-fuzzification process

An overview of the fuzzification and the de-fuzzification process shall be presented.

- Step 1: The experts assign the weight values (verbal). Those weight values shall be de-fuzzified into crisp numbers in space \([0,1]\).
- Step 2: The concepts initial values may be verbal or numerical. As in step 1, the verbal inputs shall be de-fuzzified into crisp numbers in space \([0,1]\).
- Step 3: When reaching a stable state, after a specific amount of iterations, the model’s output values are numerical in the desired space. Those values shall then be fuzzified and substituted with verbal ones (e.g. 0.85 equals to “Definitely Abnormal Situation”). The process of fuzzification and de-fuzzification shall be done with different methods, such as the Center of Area (COA) [19], or Center of Gravity (COG) [20].

For the normalization of the output values, both sigmoid or tanh functions may be utilised.

3. The proposed models

3.1. The overall procedure

Two Nuclear Medicine doctors were pooled to define the concepts, the interconnections and the outputs of the system. The system was designed to meet the needs of the Department of Nuclear Medicine of Patras. Therefore, the input concepts of the system reflect the department’s approach in diagnosing CAD. The relationships between the concepts of the system are described by the doctors in a linguistic way, thus allowing freedom to explain the interconnections the way experts prefer. The rest of the procedure, i.e., the de-fuzzification of the inputs and weights, is performed by the engineers. We can summarize the steps of the process as follows: (a) the experts decide the inputs of the system and their possible values, (b) each expert assigns a specific verbal weight between the concepts he/she believes that share a connection, (c) the doctors specify the specific rules describing the system and provide the necessary documentation that confirms the rules, (d) the doctors in collaboration with the engineers define the state concepts of the system, (e) the input values, the state and the weight values as well as the rules are transformed from nominal to numeric or binary form, following specific mathematical expressions, and (f) the numeric value of the output is calculated. The normalization function returns the score, or the probability of the subject.

3.2. Rule – Embedded Advanced Fuzzy Cognitive Map (RE-AFCM)

Based on the aforementioned approach is designing FCMs, the concepts of the AFCM shall be divided into inputs, states and outputs.

3.2.1. Concept Definition

The global input concepts, i.e., before the specific input and state concepts are defined, as well as their possible values as defined by the experts are given in the Table 1.

| Table 1. Initial concepts of the proposed AFCM |
|-----------------------------------------------|
| **Attributes** | **Values** |
| A1 | typical angina pectoris | yes, no |
| A2 | atypical angina pectoris | yes, no |
A3: atypical thoracic pain
A4: dyspnea on exertion
A5: asymptomatic
A6: gender - male
A7: gender - female
A8: age <40
A9: age [40-50]
A10: age [50-60]
A11: age >60
A12: known cad
A13: previous stroke
A14: peripheral arterial disease
A15: smoking
A16: arterial hypertension
A17: dyslipidemia
A18: obesity
A19: family history
A20: diabetes
A21: chronic kidney failure
A22: electrocardiogram normal
A23: electrocardiogram abnormal
A24: echocardiogram normal - doubtful
A25: echocardiogram abnormal
A26: treadmill exercise test normal
A27: treadmill exercise test abnormal
A28: dynamic echocardiogram normal
A29: dynamic echocardiogram abnormal
A30: scintigraphy normal - doubtful
A31: scintigraphy abnormal

The state concepts were discussed and designed in collaboration with the experts. The state concepts shall be:

- **A32**: Predisposing factors
- **A33**: Recurrent Diseases
- **A34**: Demographic Characteristics
- **A35**: Diagnostic Tests

The proposed system classifies the instances to “Healthy” or “Diseased”; thus, the system shall have two possible classes as outputs. We propose two approaches for the final classification. The first approach suggests a single output concept (Out), the value of which describes the probability of infection. For this approach the SigmoidN is utilized. The second approach suggests two output concepts to be inserted, referred to as “out_healthy”, and “out_diseased”. They present each class’s score. A softmax classifier is utilized to classify each instance, based on the score of each class.

### 3.2.2. Interconnections

The interconnection weights between nodes shall be undertaken by experts, in cooperation with each other. The possible linguistic values of the weights shall be: Very Weak (VW), Weak (W), Medium (M), Strong (S), Very Strong (VS). The weights may also take negative values, e.g. “-VS”.

These values are then defuzzied and a corresponding numerical value will be assigned to each one [21]. We provide the equations’ (5) and (6) corresponding tables, Table A (input - input), Table B (input - state), Table C (output - input), and Table D (state - output). Those arrays are summarized in Tables 2,3,4, and 5.
Table 2. RE-AFCM summary of table A. Due to constrains of the size, in this table only the inputs that have connections with each other are depicted.

| Concept | Concepts affected | Weights                        |
|---------|-------------------|--------------------------------|
| A6      | A22 – A31         | +W, -W, +VW, -VW, +W, -W, +W, -W, +W, -W, |
| A12     | A6 – A7           | Minimize Weights (close to 0)   |

The AFCM’s table A embodies the interconnection between the input concepts. In the proposed system, there are relations between the input concept A6 (female) and the concepts describing the diagnostic tests (A22 – A31). Also, there is relation between the input concept A12 (Known Cad) and the input concepts of the genders (A6 – A7).

Table 3 presents the interconnections between the inputs and the states of the system. That is, which inputs may have an influence on the states of the model. In our case, the concepts A12, A13, A15, and A16-A19 are defining the state A32 (predisposing factors). The concepts A14, A20 and A21 define the state A33 (recurrent diseases). Concepts A6-A11 are constituting the state A34 (Demographic Characteristics). Finally, concepts A22-A31 are constituting the state A35 (Diagnostic Tests).

Table 3. RE-AFCM summary of table B.

| State | Includes concepts         | Weights                        |
|-------|---------------------------|--------------------------------|
| A32   | A12, A13, A15, A16-A19   | M, M, W, M, VW, W, VW          |
| A33   | A14, A20, A21            | M, M, W                        |
| A34   | A6 – A11                 | M, -S, -VS, -W, W, S           |
| A35   | A22 – A32                | -M, M, -W, M, -S, W, -W, M, -VS, S |

In Table 4, the direct relation between the inputs and the outputs is presented. Please note that in this case, the inputs defining the state concepts do not directly affect the output(s).

Table 4. The RE-AFCM’s table C.

| Input | Single Output | Two classes      |       |       |
|-------|---------------|------------------|-------|-------|
|       |               | out_healthy      | out_diseased |     |
| A1    | VS            | 0                | VS     |       |
| A2    | M             | 0                | M      |       |
| A3    | W             | 0                | W      |       |
| A4    | W             | 0                | W      |       |
| A5    | -S            | S                | 0      |       |

In Table 5, the system’s Table D is presented. Table D, contains the connection of the state concepts with the output concepts. In the particular case, interconnections between the states do not exist.

Table 5. The RE-AFCM’s table D.

| State | Single Output | Two classes      |       |       |
|-------|---------------|------------------|-------|-------|
|       |               | out_healthy      | out_diseased |     |
| A32   | S             | If negative then S, else 0 | If positive then S, else 0 |
| A33   | VS            | If negative then VS, else 0 | If positive then VS, else 0 |
| A34   | S             | If negative then S, else 0 | If positive then S, else 0 |
| A35   | VS            | If negative then VS, else 0 | If positive then VS, else 0 |

3.2.3. Rules
As mentioned above, modern decision-making problems involve complex relationships, and often a relation between concepts cannot only be explained with the casual FCM strategy (i.e., assigning a specific weight). In this study, a RE-AFCM model is designed, allowing the embedding of more complex expressions (rules).

To achieve this, the addition of a hidden concept, referred to as “rule-activator” is proposed. The hidden concept behaves like the other concepts (i.e., affecting the output), with a weight value or a specific action, which varies according to the suggestions of the experts.

The experts suggested a set of rules to be applied to the model, in order to increase its knowledge. Their suggestions were derived from either recent published guidelines [22], or their experience. Those rules are presented in Table 6.

Table 6. Rules and their effect on systems concepts, inputs and outputs

| Rule | Attributes Affected - Affection |
|------|---------------------------------|
| If Definitely Abnormal Scintigraphy | The weight of Scintigraphy is significantly increased |
| If ECG is Normal and Scintigraphy is Normal | The weights of both tests are relatively increased during the next iteration step |
| If previous Stroke | Negate the Gender Discrimination and de-activate the attribute from the system, before the first iteration step |
| If Known Cad | Negate the family history affection before first iteration step |
| If absense of Diabetes, Known Cad and Previous Stroke | Assign a negative weight to the rule_activator |
| If Asymptomatic, but with abnormal Scintigraphy, and any other one abnormal test | Uncertainty increases over the trustworthiness of the symptom; assign a small positive weight to rule_activator |

4. Experiment Setup and Results

4.1. The dataset of the study

The database of the particular study consisted of 303 patient cases, all recorded at the Department of Nuclear Medicine of Patras, in Greece. Most of instances were recorded during the last 8 years. All the patient cases had been pointed to Surgical Coronary Angiography. For every instance, therefore, a final medical report confirming or denying the presence of the disease is available. For the characterization of the instances, the stenosis of the coronary artery is the only criterion, which is obtained by the above mentioned invasive diagnostic test. Patients with stenosis equal or above 70% were labeled as diseased, whereas the rest were labeled as healthy.

The dataset contains 116 healthy cases and 187 diseased cases, whereas male instances are 266. The attributes of the dataset used for the experiments are corresponding to the factors influencing the diagnosis of CAD. The dataset contains every possible diagnostic test a patient may undergo at the clinical section of the experts’ laboratory.

The medical reports regarding the diagnostic test were translated in numeric values with the appropriate staging. This approach was supervised by medical staff. The attributes regarding the patient's history and condition (i.e. smoking) were also in need of preprocessing in order to express the linguistic values (i.e. "smoker") into binary format.

4.2. Evaluation Criteria and results

We extensively evaluate our system, therefore, more criteria besides accuracy will be employed. The evaluation criteria of the system shall be the following: (a) Accuracy based on the whole dataset, (b) True Positives, (c) False Positives, (d) False Negatives, (e) True Negatives, (f) Sensitivity, (g) Specificity.

4.3. Experiment setups
For the experiments, we propose several cases. In each case, we employ modified architectures and parameters. A summary of the experiment setups is given below:

- **Case 1**: Traditional FCM, with single output, and sigmoid activation function.
- **Case 2**: Traditional FCM, with two output classes, sigmoid activation function, and Softmax Classifier.
- **Case 3**: AFCM, with single output, two states (A32, A33), sigmoid activation function, no rule activator concept.
- **Case 4**: AFCM, with single output, two states (A32, A33), SigmoidN activation function, no rule activator concept.
- **Case 5**: AFCM, with two output classes, two states (A32, A33), SigmoidN activation function, no rule activator concept, and Softmax Classifier.
- **Case 6**: AFCM, with single output, two states (A32, A33), tanh activation function, no rule activator concept.
- **Case 7**: RE-AFCM, with single output, two states (A32, A33), SigmoidN activation function, no rule activator concept.
- **Case 8**: RE-AFCM, with two output classes, two states (A32, A33), SigmoidN activation function, no rule activator concept, and Softmax Classifier.
- **Case 9**: RE-AFCM, with single output, three states (A32, A33, A34), SigmoidN activation function, with rule activator concept.
- **Case 10**: RE-AFCM, with single output, four states (A32, A33, A34, A35), SigmoidN activation function, rule activator concept.

For cases 1 and 2, we use the FCM proposed in [23]. Table 7 presents the results for the different cases.

**Table 7.** Accuracy, Sensitivity, and Specificity for the different experiment setups

| Case  | Accuracy (%) | Sensitivity (%) | Specificity (%) |
|-------|--------------|-----------------|-----------------|
| Case 1| 77.34%       | 81.55%          | 68.02%          |
| Case 2| 78.21%       | 83.96%          | 68.97%          |
| Case 3| 79.20%       | 86.63%          | 67.24%          |
| Case 4| 80.19%       | 87.70%          | 68.10%          |
| Case 5| 79.86%       | 87.16%          | 68.10%          |
| Case 6| 70.95%       | 82.8%           | 51.7%           |
| Case 7| 81.84%       | 83.42%          | 79.31%          |
| Case 8| 80.19%       | 87.70%          | 68.10%          |
| Case 9| **85.47%**   | **89.3%**       | **79.31%**      |
| Case 10| 80.85%      | 83.42%          | 76.72%          |

The results highlight the effectiveness of the new equations for computing the concepts’ values, as it is demonstrated by the increase in accuracy for Case 3 to Case 10. Moreover, the results clarify that the new proposed activation function, SigmoidN, is more preferable for this task over the sigmoid. Also, the combination of single output with SigmoidN, results in an improvement of performance, compared to the combination of two class outputs, and Softmax Classifier. Finally, the addition of rules further improved the knowledge of the system.

Based on the results, we conclude that the proposed RE-AFCM outperforms the traditional FCM approach. What is more, for the specific task, the optimal parameters shall be an architecture consisting of three states, a single output, and the SigmoidN function. Table presents the confusion matrix of Case 9 (the optimal case).

**Table 9.** Confusion Matrix of Case 9

| Disease d(D+) | Healthy (D-) | Total |
|---------------|--------------|-------|
| Predicted     |              |       |
| Diseased      | 167          | 24    | 191  |
| Healthy       | 20           | 92    | 112  |
| Total         | 187          | 116   | 303  |
The confusion matrix corresponds to sensitivity of 89.3%, specificity of 79.3%, PPV of 87.43% and NPV of 82.14%. The overall accuracy is 85.47%. An overview of the RE-AFCM (case 9) is depicted in Figure 3.

![Diagram of RE-AFCM (Case 9)](image)

**Fig.3.** RE-AFCM (Case 9) overview

4.3. Comparisons with state-of-the-art algorithms

In this section we compare the results of the proposed system with state-of-the-art classification algorithms. The cross – validation was chosen to be 5-fold due to the small amount of training data. The Neural Network contains three depth layers of 1024, 512, and 256 nodes. Training was performed for 120 epochs, with a batch size of 32 and an initial learning rate of 0.01. Other Neural Networks with alterations on the pre-mentioned parameters were tested and excluded due to inefficiency. Hence, the Neural Network we pick is the one with the better accuracy over all. The Support Vector Machine (SMO) has the following parameters: Complexity Parameter (c) is set at 1.0, the value of epsilon is set at 1E-12, the batch size is 32 and the calibrator method is tuned to Logistic. AdaBoostM1 meta classifier is trained for 50 iterations, with a batch size of 32 and the decision classifier Decision Stump is selected. Chirp is trained with a batch size of 32. Random Forest was trained for 100 iterations with a bag size of 20%, and batch size 32. Spaarc was trained with a batch size of 32. The rest of the classifiers were trained with the optimal parameters suggested by MATLAB Machine Learning Toolkit.

| Classifier                      | Accuracy (5-fold – cross validation) |
|---------------------------------|--------------------------------------|
| Coarse Tree                    | 63.4                                 |
| Linear Discriminant            | 70.3                                 |
| Logistic Regression            | 70.6                                 |
| Linear SVM                     | 70.0                                 |
| Cubic SVM                      | 68.0                                 |
| Medium Gaussian                | 73.3                                 |
| Coarse Gaussian                | 62.7                                 |
| Medium KNN                     | 67.7                                 |
| Cubic KNN                      | 66.3                                 |
| Ensemble Bagged Trees          | 68.3                                 |
| Ensemble Subspace Discriminant | 71                                   |
| Neural Network                 | 72.6                                 |
|                  |        |
|------------------|--------|
| Support Vector Machine (SMO) | 72.93  |
| AdaBoostM1        | 74.58  |
| Chirp             | 76.89  |
| Spaarc            | 72.93  |
| Random Forest     | 74.58  |
| **RE-AFCM (this work)** | **85.47%** |

The results demonstrate that the proposed model, outperforms every Machine Learning classifier which was employed for the classification task in this work. The shortage of large-scale dataset is impeding the traditional machine learning algorithms to learn the actual and significant relationships between the concepts. This is reflected to the accuracy each algorithm obtains.

4. Discussion

It is demonstrated that the new approaches for the development of Advanced Fuzzy Cognitive Maps, as well as the rules mechanism inserted to the system, improve the results, compared to classic FCMs.

Fuzzy Cognitive Maps provide a distinguishable way to express the cause – effect relationship between phenomena, between numeric, nominal, binary, or categorical parameters. A complex system may include all the above-mentioned factors. Relationships between them, provided that are discovered, can be represented visually and mathematically through FCMs. In this way, not only the developers, but also the experts on the field, may observe and understand the FCM representations.

The interconnections between concepts learned by supervised learning algorithms are not ensured to reflect causal connections. That does not mean that unobserved causes may not exist; in fact, one target of supervised learning is to make assumptions regarding the relations between mutually affected concepts during the process of training and testing. Assumptions that can be confirmed or denied experimentally later. Compared to trainable artificial intelligence algorithms, A-FCM do not intend to discover associations that may or may not exist.

Clinical researchers today are confronted with increasingly large, complex, and high-dimensional datasets [24]. Consequently, the application of interactive visual data exploration in combination with machine-learning techniques for knowledge discovery and data mining is indispensable.

Clinical researchers, or domain-experts are often not computer experts as well. They have high level medical domain-expert knowledge to perform their research, to interpret newly gained knowledge and patterns in their data. On the other hand, computer engineers lack the knowledge of medical data and their unique nature; Moreover, deep, dynamic and complex medical situations require a high level of expertise and experience for the decision making. A smooth interaction of the domain-expert with the data would greatly enhance the whole knowledge-discovery process chain [24]. This can be achieved by the cooperation of engineers and doctors.

That is the case in our work and, generally, in most of proposed models using AFCMs. The experts in a specific domain, not only have the overall supervision of the procedure, but also design the models in cooperation with the developers. Experts define the relationships, the concepts, the system’s desired outputs. In our work, the doctor is in the loop, playing the most vital role in the development and the evaluation of the model.

5. Conclusions

In this paper, the automatic and non-invasive prediction of certain medical problems have been considered and studied. Medical decision-making problems are difficult, complex and have attracted many research studies. As a result, a good number of Clinical Decision Support Systems (CDSS) have been developed based on different methodologies. The majority of them are based on statistical approaches. Indeed all mathematical models been used in confronting the recent epidemic of Coronavirus are using statistical models. However all medical problems are non-linear and statistical models are based on the assumption that variables have linear correlation between them. All medical problems are dynamic and non-linear. Moreover physicians are requested to handle information of different nature, e.g. patient’s history, clinical diagnostic tests, medical images, personal health problems and demographic characteristics. The interpretation of these results involve ambiguity and uncertainty, which plays a critical role for the decision-making to a wide and diverse set of medical
problems. Therefore, new advanced scientific approaches and new mathematical models are needed. The challenge to physicians, engineers and decision makers is great and very important. The humankind, expects not to say it demands, serious answers from them.

In this research, a state approach of FCMs, as well as the cooperation of FCMs and rule-based decision mechanism, were applied and examined. The proposed model was evaluated on a dataset of Coronary Artery Disease (CAD) candidates and outmatched several Machine Learning Algorithms regarding the prediction of CAD infection. The new approach combines the classical state space approach of dynamic systems to help improve the existing method of FCMs.

Specifically, the separation of concepts in states, inputs and outputs was evaluated to increase the knowledge of the system. The presence of state vectors, helped clustering concepts of similar nature, rather than directly affecting the output in a static way. With the addition of rules, the system managed to explain more complex relations between the concepts; relations that often are conflicting with each other. This approach will be referred as the Advanced Fuzzy Cognitive Maps (AFCM) methodology. The results of this study show that the new state space AFCM achieve a slight better performance over the traditional FCM methodology namely: an increase of seven percent (+7%) on the classification task, and obtaining 85.47% accuracy a slight higher than the 78.21% of the traditional approach. Therefore, we can conclude that the AFCMs’ decision-making mechanism is a unique and promising method of handling the parameters of a difficult medical problem.

To the best of our knowledge, the proposed State Space AFCMs has not been applied to medical problems before, except in [25-26]. With this and the large interest in developing more effective and efficient CDSS, not only for diagnosis but also for therapeutic treatment, future research directions are quite open.

The State Space AFCM methodology needs further development from theoretical point of view: a) better separation of concepts, utilization of more experts, understand better the nonlinear behavior of the system, use learning methods to update the AFCM model, controllability and observability of the dynamic system, sensitivity of all concepts, b) the AFCM could be utilized to study other medical problems, especially the pandemic of coronavirus, c) develop appropriate software tools for the AFCM models, e) perform extensive simulation studies for as many as possible medical problems and validate these models, f) Develop Wise Learning (WL) methods and compare them with Deep Learning (DL) approaches of Artificial Intelligence (AI), g) employ the AFCM models, and feedback methodologies to develop Intelligent Control and Cognitive Control algorithms, and h) explore synergies between Neuroscience and fuzzy cognition.

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Declarations

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**Conflicts of interest/Competing interests**
The authors declare that there are no conflicts of interest.

**Availability of data and material**
The dataset is recorded at the Department of Nuclear Medicine of the University Hospital of Patras, Greece and is not allowed to be publicly available.

**Code availability**
Not applicable