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PAPER

Advanced fuzzy cognitive maps: state-space and rule-based methodology for coronary artery disease detection

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Abstract

According to the World Health Organization, 50% of deaths in European Union are caused by Cardiovascular Diseases (CVD), while 80% of premature heart diseases and strokes can be prevented. In this study, a Computer-Aided Diagnostic model for a precise diagnosis of Coronary Artery Disease (CAD) is proposed. The methodology is based on State Space Advanced Fuzzy Cognitive Maps (AFCMs), an evolution of the traditional Fuzzy Cognitive Maps. Also, a rule-based mechanism is incorporated, to further increase the knowledge of the proposed system and the interpretability of the decision mechanism. The proposed method is evaluated utilizing a CAD dataset from the Department of Nuclear Medicine of the University Hospital of Patras, in Greece. Several experiments are conducted to define the optimal parameters of the proposed AFCM. Furthermore, the proposed AFCM is compared with the traditional FCM approach and the literature. The experiments highlight the effectiveness of the AFCM approach, obtaining 85.47% accuracy in CAD diagnosis, showing an improvement of +7% over the traditional approach. 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.

1. Introduction

Coronary Artery Disease (CAD) 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 are caused by Cardiovascular Diseases (CVD), while 80% of premature heart diseases and strokes can be prevented. Diagnosing CAD in a non-invasive way is an open challenge, despite the massive number of researches been made so far (Soni *et al* 2011, Dilsizian and Siegel 2014, Apostolopoulos and Groumpos 2020). As CAD can only be truly diagnosed following the Invasive Coronary Angiography, several potential patients are undergoing this examination, even if they are not diseased. The non-invasive diagnostic tests and predisposing factors do not guarantee a reliable diagnosis. In fact, Myocardial Perfusion Imaging examination, which is currently the most precise non-invasive diagnostic test, succeeds in 72.6 % of the times, as verified by the data of the current study. Therefore, Artificial Intelligence can contribute to this front. Developing an automatic and trustworthy model to analyze the factors and make a prediction could potentially relieve the physicians from time-consuming procedures, offer a second opinion, or even used in wearable IoT devices thereby aiding to the prognosis challenge.

In the particular study, Fuzzy Cognitive Maps (FCMs) are employed to develop a Medical Decision Support System (MDSS), focused on Coronary Artery Disease. 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 the desired decision.

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FCMs were introduced by Kosko in 1986 in order to represent the causal relationship between concepts and analyze inference patterns (Kosko 1986, Kosko 1998). FCMs are connected to probabilistic machine learning models such as Boltzman machines (Salakhutdinov and Hinton 2009) and Bayesian networks (Friedman *et al* 1997). FCMs take advantage of the knowledge and the experience of experts, offering 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 or fuzzy descriptions (Bourgani *et al* 2014). Fuzzy Cognitive Maps have also been employed to describe and solve medical problems (Papageorgiou and Stylios 2008, Papageorgiou 2011, Giabbanelli *et al* 2012).

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 (Mpelogianni and Groumpos 2018), 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 is ignored in the traditional approach and, (b) the utilization of the classic sigmoid normalization function is fuzzing the system, especially in cases of the existence of several concepts, due to the fact that the output value is always transformed to a number near one. Despite the fact that the novel strategy in (Mpelogianni *et al* 2018) 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 applications where time is irrelevant. As to our best knowledge, AFCM have not been applied to and evaluated on medical diagnosis.

1.1. Related work

Most of the related research is focused on developing methods to achieve accurate classification of publically available CAD datasets. The most common of them are described below:

1.1.1. Z-Alizadeh Sani dataset (Alizadehsani et al *2013)*

303 records of patients with 54 available features constitute Z-Alizadeh Sani dataset. All features are considered indicators of Coronary Artery Disease. This set contains features related to symptom and examination, ECG, and Echocardiogram features. Typical angina pectoris is also included. The ground truth is obtained by examination of the coronary artery. If that artery's diameter is narrowed by at least 50%, the patient is considered to be suffering.

1.1.2. Heart disease data set (Detrano et al *1989)*

This dataset is a collection of patient examples from 4 sources as follows:

1. Hungarian Institute of Cardiology. Budapest: with Andreas, Janosi to be the principal investigator
2. University Hospital, Zurich, Switzerland: with William Steinbrunn to be the principal investigator
3. University Hospital, Basel, Switzerland: with Matthias Pfisterer to be the principal investigator
4. V.A. Medical Center, Long Beach and Cleveland Clinic Foundation: with Robert Detrano to be the principal investigator

The dataset contains 303 records of patients with 76 attributes involving demographic and clinical characteristics, but not results of certain non-invasive diagnostic tests. 14 of those attributes are commonly used for classification or feature selection purposes.

The abovementioned CAD datasets have attracted the interest of several research works. A detailed review is presented by Roohallah Alizadehsani in (Alizadehsani *et al* 2019). Here, some of the most recent and notable related works, are mentioned.

Abdar et al(Abdar *et al* 2019) evaluated several traditional Machine Learning (ML) algorithms distinguishing three types of Support Vector Machines (SVM) to achieve the classification of the Z-Alizadeh Sani dataset. A genetic algorithm and particle swarm optimization, coupled with stratified 10-fold cross-validation, were used for optimization of classifier parameters and for parallel selection of features. N2Genetic-nuSVM provided an accuracy of 93.08% and an F1-score of 91.51% when predicting CAD.

Alizadehsani et al (Alizadehsani *et al* 2018) achieved 94.08% accuracy in Z-Alizadeh Sani dataset by implementing SVM algorithms and feature selection methods. The results are compared with several implementations of ML methods, such as Neural Networks.

Qin et al(Qin *et al* 2017) evaluated the importance of feature selection in the Z-Alizadeh Sani dataset. In their work, the authors presented a novel algorithm that integrates multiple feature selection methods, adopts Bagging approach to increase data diversity, and employed a major voting method to carry out the decision results. This method achieved 93.70% accuracy.

Acharya et al(Acharya *et al* 2017) proposed an approach to detect Myocardial Infraction using ECG signals. The authors designed a Convolutional Neural Network (CNN) algorithm for the detection of normal and MI ECG beats. The algorithm was evaluated using ECG data of 200 subjects (148 Myocardial Infraction and 52 healthy subjects). Average accuracy of 93.53% and 95.22% using ECG beats with noise and without noise removal was obtained.

Bentacur et al(Bentacur *et al* 2018) examined a total of 1638 patients without known CAD, undergoing stress 99mTc-sestamibi or tetrofosmin MPI with new generation solid-state scanners in 9 different sites, with invasive coronary angiography performed within 6 months of MPI. CAD was defined as ⩾70% narrowing of coronary arteries. In their work, the authors used the Polar Map images, which were acquired from Myocardial Perfusion Imaging technology systems. The authors proposed a Deep Learning (DL) approach, trained with raw and quantitative polar map images, and evaluated for prediction of obstructive stenosis in a stratified 10-fold cross-validation procedure. Their results highlighted the potential of DL in the automatic MPI image interpretation procedure.

Kolukisa *et al* (Kolukisa *et al* 2018) evaluated ML classification algorithms (Bayes, KNN, Decision Trees, SVMs, and Ensemble classifiers) and linear discriminant analysis to propose a hybrid feature selection algorithm based on the Heart Disease Data Set. SVM and Ensemble classifiers outperformed the rest, obtaining 92.74% and 92.07% accuracy, respectively.

Al-Tashi *et al* (Al-Tashi *et al* 2018) proposed a feature selection method to determine the optimal feature subset of the Heart Disease Data Set. Their method involved Grey Wolf Optimization (GWO) and SVM. The proposed GWO-SVM outperformed several approaches achieving 89.83% accuracy, 93% sensitivity and 91% specificity rates.

Several research works are focused on proposing Rule-Based Machine Learning or Fuzzy Logic utilizing publically available datasets (Ghiasi *et al* 2020, Hossain *et al* 2020, Setiawan *et al* 2020).

A major difference of this study lies in the fact that the designed model is not data-driven. The proposed method does not seek underlying patterns and information in pre-defined datasets. In comparison with many studies, the proposed methodology aims to make full use of the existing human knowledge, as expressed in specific guidelines or imprinted in the experience of the experts.

1.2. The aims of the current study

The present study proposes an AFCM method to diagnose Coronary Artery Disease in a non-invasive way, aiming to assist the medical staff when making diagnostic decisions such as:

- Should the subject undergo an invasive Coronary Angiography diagnosis and treatment test?
- Is there significant evidence that the subject is healthy and no further action is necessary?

To achieve this, the authors are focused on improving and confirming the effectiveness of the AFCM approach over the classic, which was implemented in a recent work by the authors (Apostolopoulos and Groumpos 2020). Also, the present study is mainly focused on extending AFCM applications in medical problems.

Designing AFCM models requires collaboration between subject-matter experts and modelers. The experts suggest and aid for the design of the AFCM, for it to be user-friendly, scientifically acceptable, and interpretable. In this work, the Nuclear Medicine staff suggested that the causal relationships between concepts in (Apostolopoulos and Groumpos 2020) 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 Department of Nuclear Medicine of the University of Patras, in Greece. Aiming to improve and evaluate AFCM's performance, we experiment with the new and the traditional mathematical equations, as well as with different activation functions and architectures. The optimal parameters are defined through extensive experiments. The results demonstrate the effectiveness of the RE-AFCM approach for the development of FCMs, improving the accuracy by 7%. 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.

The present study improves the methodology of our recent study (Apostolopoulos and Groumpos 2020) in many ways. Firstly, the input concepts are divided into input and state concepts, which changes the decision-making procedure and makes the model more robust and realistic. This methodology is also accompanied by the implementation of new state-space equations as presented in related work. This approach is similar to the way medical experts analyze data to make a preliminary diagnosis. Secondly, the present study involves experimenting with alternative activation functions and classification operations to define the optimal parameters. Parameter testing was missing from the previous study. Thirdly, the current methodology is evaluated using larger-scale data, thereby enhancing the significance of the findings.

The contributions of this study are:

- The application of Advanced State-Space Fuzzy Cognitive Maps to real-life medical problems, which is seldom explored in the current literature.
- The evaluation of the novel AFCM equations for the calculation of concept values
- The presentation of an advanced extension of our previous study (Apostolopoulos and Groumpos 2020), which achieves significantly better results.
- The proposal of a MDSS, adjusted to meet the demands of the medical staff of the Department of Nuclear Medicine of the University Hospital of Patras, in Greece.

- The proposed MDSS outperforms the diagnostic yield of the major diagnostic test (Myocardial Perfusion Imaging).

Furthermore, the present work contributes to the recent advances in FCMs, pointing out several weaknesses that have to be addressed in the future.

2. Methods

2.1. Fuzzy cognitive maps

2.1.1. Historical remarks

A historical link of FCM theories is connected to graph theory and goes back to the 18th century. A graph is a set of nodes joined by a set of lines or arrows. Graph theory is the study of graphs, mathematical structures used to model pair-wise relations objects from a certain collection (Biggs *et al* 1986). A graph is thus a context, which refers to a collection of vertices or nodes and a collection of edges that connect pairs of vertices. The paper written by Leonard Euler on the Seven Bridges of Konigsberg and published in 1736 (Biggs *et al* 1986) is regarded as the first paper in the graph theory. Graphs are among the most ubiquitous models of both natural and human-made structures. During the past years, ideas now embodied in graph theory, have been implicit in lay discussions of networks (Gauchy 1813, Biggs *et al* 1986). The explicit linking of graph theory and network analysis began only in 1953 and has been rediscovered many times since (Barnes and Harary 1983).

However, till today, they have been used to model many types of relations and process dynamics in physical, networks, engineering, biological, health, energy, and social systems. Political scientist Robert Axelrod (Axelrod 2015) was the first to use digraphs to show causal relationship among variables as defined and described by people, rather than by the researcher. Axelrod called the sediagraphs Cognitive Maps (CM). Many studies have used CM to look at decision-making as well as to examine people's perceptions of complex social systems. Kosko modified Axelrods CMs, which were binary, by applying fuzzy causal functions with real numbers in $[-1,1]$ to the connections, thus the term Fuzzy Cognitive Maps (FCM) (Kosko 1986). Kosko was also the first to model FCMs and to compute the outcome of an FCM, or the FCM inference, as well as to model the effect of different policy options using a neural network computational method (Kosko 1986).

2.1.2. Fuzzy cognitive maps fundamental methodology

FCMs consist of a graphical representation through a signed directed graph, which includes feedback consisting of nodes and weighted arcs (Kosko 1986, Groumpos and Stylios 2000, Felix *et al* 2019). 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 C_i (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 (Groumpos 2018). An example is given in figure 1.

In their fundamental implementation, FCMs do not involve training and supervision. The weights between the concepts are predefined by the experts. Supervised learning is a methodology of ML that intends to help computers learn specific information using training datasets. FCMs intend to model the existing knowledge and not discover new knowledge from data. Human knowledge is difficult to be discretized and be expressed in an algorithmic manner. Yet, FCMs have proven their efficiency in such problems, despite several weaknesses that are currently investigated for solutions.

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 (Salmeron *et al* 2019, Papageorgiou *et al* 2008).

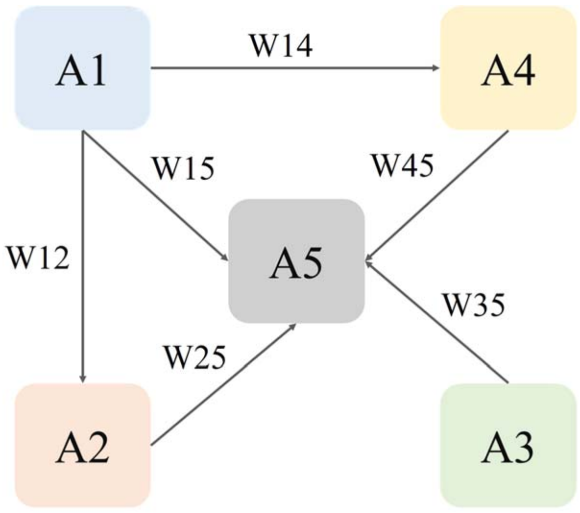
To summarize, a FCM includes the input concepts and the weights that explain the relations between those input concepts, as well as the relations between the input and the output concepts. Each concept behaves as a simple neuron, which is activated by a certain activation function. The function explaining this behavior is given in (Salmeron *et al* 2019, Papageorgiou *et al* 2008):

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

Where, f is the activation function, t is the time-step, and A_i and W_{ji} are the numeric values of the input concepts and the weights.

The weights and the initial values of the concepts are usually given in categorical form (e.g. the influence of concept A1 to concept A2 may be 'weak'). Those values are translated into [0,1] with the aid of different methods, such as the Center of Area (COA) (Axelrod 2015), or Center of Gravity (COG) (Jang *et al* 1997).

Since many interconnections between the input concepts may exist, each concept may actively change its value after the first iteration. This could cause a change of values to the other concepts, or the output, as well. Therefore, FCM may require some iterations until the system reaches a stable condition.



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

Figure 1. An example of a simple Fuzzy Cognitive Map. The reader can spot the concepts (squares) and the interconnection between the concepts, expressed by a weight (e.g. w35).

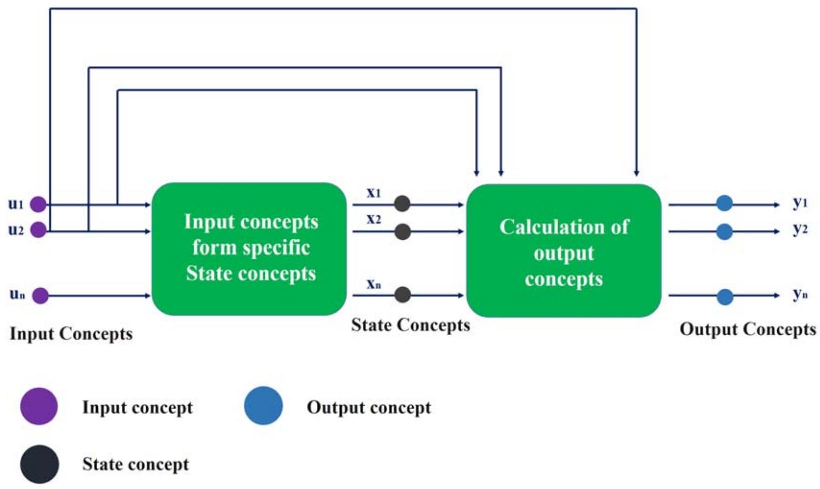


Figure 2. Block Diagram of the separated concepts. Input concepts are denoted as u. State concepts are denoted as x. Output concepts are denoted as y. Input concepts define the current condition of the state-concepts using equations (2) and (3). After the values of the state-concepts are stabilized, the input and state-concepts are interacting with each other, affecting the value of the output concepts. This value is also calculated using equations (2) and (3). Several iterations are required for the system to reach a stable condition.

2.2. State—space approach of fuzzy cognitive maps

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 a fuzzy way, the main concept is the same. In the classic control theory, a separation of the concepts is suggested (Ogata 1970, Mpelogianni and Groumpos 2018), 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 (Mpelogianni 2018), and depicted in figure 2.

In this way, more accurate knowledge of the system is obtained, because the state concepts are separated from the input concepts. Moreover, introducing state concepts aids in a more complete characterization and modeling of the human decision-making process. The proposed separation facilitates the understanding of the system's operation, and the simpler calculation of the concepts' values.

2.2.1. 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 equations (equations (2), (3))

$$\mathrm{X}[\mathrm{k}+1] = \mathrm{Ax}[\mathrm{k}] + \mathrm{Bu}[\mathrm{k}] \tag{2}$$

$$\mathrm{Y}[\mathrm{k}+1] = \mathrm{Cx}[\mathrm{k}] + \mathrm{Du}[\mathrm{k}] \tag{3}$$

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 (2), and (3), 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 relationship between the states and the outputs, while matrix D incorporates the direct affection of input concepts to output concepts (**Ogata 1970**).

Since equations (2) and (3) are used to compute the variation caused between the concepts, it is more accurate to express them as follows:

$$\Delta\mathrm{X}[k+1] = \mathbf{A}\mathrm{x}[\mathrm{k}] + \mathbf{B}\mathrm{u}[\mathrm{k}] \tag{4}$$

$$\Delta\mathrm{Y}[\mathrm{k}+1] = \mathbf{C}\mathrm{x}[\mathrm{k}] + \mathbf{D}\mathrm{u}[\mathrm{k}] \tag{5}$$

Using equations (4) and (5), the expression of the actual values of X[k+1] and Y[k+1] is in equations (6) and (7):

$$\mathrm{X}[\mathrm{k}+1] = \mathrm{X}[\mathrm{K}] + \frac{\Delta\mathrm{X}[\kappa+1]}{\sum_{\mathrm{j}=1,\, j\neq\mathrm{i}}^{\mathrm{n}}|\mathrm{Wji}|} \tag{6}$$

$$\mathrm{Y}[\mathrm{k}+1] = \mathrm{Y}[\mathrm{K}] + \frac{\Delta\mathrm{Y}[\kappa+1]}{\sum_{\mathrm{j}=1,\, j\neq\mathrm{i}}^{\mathrm{n}}|\mathrm{Wji}|} \tag{7}$$

One more advantage of the mentioned technique is the transparency and decomposability of the system.

2.2.2. Activation 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 (Mpelogianni and Groumpos 2016). We use this function for the inner calculations (i.e. the inputs and the states). The function is explained below:

$$f(x) = m + \frac{M-m}{1+e^{-r*(x-to)}} \tag{8}$$

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 $\mathrm{t_o}$ is the symmetry to the y axis. We refer to equation (8) as SigmoidN.

For the final classification between 'Healthy' or 'Diseased', we also use a Softmax classifier (Jang *et al* 2016), to evaluate and compare the different methodologies.

2.2.3. 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 (usually with expressions as 'Very Weak'). Those weight values shall be de-fuzzified into crisp numbers in space [0,1].
- Step 2: The concepts initial values may be numerical, or categorical. As in step 1, the 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 categorical 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) (Axelrod 2015), or Center of Gravity (COG) (Jang *et al* 1997). For the normalization of the output values, both sigmoid or tanh functions may be utilized.

2.3. The proposed models

2.3.1. 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) the medical experts assign a specific weight between the concepts

(c) the medical experts specify the specific rules describing the system

(d) the medical experts, in collaboration with the engineers, define the state concepts of the system

(e) the input values, the state and weight values, as well as the rules, are transformed from nominal to numeric or binary form

(f) the numeric value of the output is calculated

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

A summary of the AFCM functionality is presented in the following pseudo-code:

The functionality of the AFCM can be summarized in the following pseudo-code:

a. Transform every input concept's value to numerical form

b. Transform every weight value to numerical form

c. Using equations (6)–(8), calculate the initial conditions of the state-concepts

d. Using equations (6)–(8), and the rules, define the output value after specific iterations, letting input concepts and state concepts interact with the output.

2.3.2. Input, state, and output concepts

The initial attributes, as well as their possible values as defined by the experts, are given in table 1. Those attributes have been assigned by the medical staff, according to their experience and following specific CAD guidelines (Levine *et al* 2016).

The encoding of the attributes is selected by the medical experts based on several preliminary tests and following specific guidelines (Levine *et al* 2016). For example, the encoding of the abnormal scintigraphy is selected based on how the medical experts interpret and categorize the Myocardial Perfusion Imaging diagnostic test. For the attributes of the age, the four categories are not arbitrary but are based in specific statistical research (Min *et al* 2011**,** Levinson *et al* 2020), which separates the subjects into age groups according to the risk of suffering from CAD.

It was found that the FCM could better handle concept values in [0,1], rather than [−1,1]. However, assigning a concept value with zero leads to its deactivation. This is not acceptable in cases where a diagnostic test is e.g. 'Normal'. This would lead to its deactivation, although normal tests indicate potential absence of the disease. This is the reason why each diagnostic test is presented by two attributes. In this way, when, for example, ECG is normal, attribute A22 is activated (1), and attribute A23 is deactivated (0). Besides, normal tests may have different weight values than abnormal or doubtful ones. This directed the authors towards separating the attributes when necessary.

The state concepts were discussed and designed in collaboration with the experts. The state concepts may be constituted by the following expressions:

- **A32:** Predisposing factors (includes attributes A12, A13, A15, A16-A19)
- **A33:** Recurrent Diseases (includes attributes A14, A20, A21)
- **A34:** Demographic Characteristics (includes attributes A6—A11)
- **A35:** Diagnostic Tests (includes attributes A22—A32)

The reader should note that we change the number of state concepts for the experiments, to inspect the effectiveness of each stateconcept. For example, we design an AFCM with only one state concept before we proceed to add more state concepts. It is also mentioned that, when the system is designed with state concepts, some of the input concepts are directly connected to the state concepts and not to the output.

The proposed system classifies the instances to 'Healthy' or 'Diseased'. Hence, 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 throughout the entire process, due to the fact that it yields better results, as shown in Results section. 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. For the activation of the concepts, we experiment with both the classic sigmoid function and with the signoidN, with parameters set at $M = 1, m= -1, t_o = 0, r=1$.

2.3.3. Interconnection weights between the concepts of the AFCM

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 (Runkler 1996). We provide corresponding tables for equations (4) and (5):

Equation (4), Matrix A (input - input): table 2
Equation (4), Matrix B (input - state): table 3
Equation (5), Matrix C (output - input): table 4
Equation (5), Matrix D (state - output): table 5

The AFCM's table A embodies the interconnection between the input concepts. In the proposed

Table 1. Initial attributes of the proposed AFCM. In the first column, Coronary Artery Disease Risk related factors are depicted. In the second column, the attribute value types are explained. An attribute of categorical nature is transformed to the desired numerical space.

Attributes		Type of Attribute
A1	typical angina pectoris	Categorical (Yes/No): translated into 1,0
A2	atypical angina pectoris	Categorical (Yes/No): translated into 1,0
A3	atypical thoracic pain	Categorical (Yes/No): translated into 1,0
A4	dyspnea on exertion	Categorical (Yes/No): translated into 1,0
A5	asymptomatic	Categorical (Yes/No): translated into 1,0
A6	gender – male	Categorical (Yes/No): translated into 1,0
A7	gender – female	Categorical (Yes/No): translated into 1,0
A8	age <40	Categorical (Yes/No): translated into 1,0
A9	age [40–50]	Categorical (Yes/No): translated into 1,0
A10	age [50–60]	Categorical (Yes/No): translated into 1,0
A11	age >60	Categorical (Yes/No): translated into 1,0
A12	known CAD	Categorical (Yes/No): translated into 1,0
A13	previous stroke	Categorical (Yes/No): translated into 1,0
A14	peripheral arterial disease	Categorical (Yes/No): translated into 1,0
A15	smoking	Categorical (Yes/Occasionally/No): translated into 1, 0.5, 0
A16	arterial hypertension	Categorical (Yes/No): translated into 1,0
A17	dyslipidemia	Categorical (Yes/No): translated into 1,0
A18	obesity	Categorical (Yes/Relatively/No): translated into 1, 0.5, 0
A19	family history	Categorical (Yes/No): translated into 1,0
A20	diabetes	Categorical (Yes/No): translated into 1,0
A21	chronic kidney failure	Categorical (Yes/No): translated into 1,0
A22	electrocardiogram normal	Categorical (Yes/No): translated into 1,0
A23	electrocardiogram abnormal	Categorical (Yes/No): translated into 1,0
A24	echocardiogram normal - doubtful	Categorical (Yes/No): translated into 1,0
A25	echocardiogram abnormal	Categorical (little/abnormal/definitely abnormal) : translated into 0.5, 0.75, 1
A26	treadmill exercise test normal	Categorical (Yes/No): translated into 1,0
A27	treadmill exercise test abnormal	Categorical (abnormal/definitely abnormal) : translated into 0.5, 0.75, 1
A28	dynamic echocardiogram normal	Categorical (Yes/No): translated into 1,0
A29	dynamic echocardiogram abnormal	Categorical (doubtful/abnormal/definitely abnormal): translated into 0.25, 0.5, 1
A30	scintigraphy normal - doubtful	Categorical (Yes/No): translated into 1,0
A31	scintigraphy abnormal	Categorical (Little abnormal/ medium abnormal/abnormal/definitely abnormal): translated into 0.25, 0.5, 0.75, 1

Table 2. Matrix A of the equation (4). Due to size constraints, only the inputs that have connections with each other are depicted. The original size of Matrix A is 31 × 31, with zero diagonal values. The rest of the cells represent the weight values between the concepts. For example, if A1 affects A3 weakly, then $\mathbf{A_{13}} = \mathrm{W}$.

Concept	Concepts affected	Weights (effect of concept A7 on A22-A31)
A7	A22–A31	+W, -W, +VW, -VW, +W, -W, +W, -W, +W, -W,

Table 3. Contents of Matrix B of equation (4). The original Matrix B is 4 × 31, where the number four represents the four state concepts and the number thirty-one refers to every input concept. When an input concept is not related to one of the state concepts, the corresponding element of Matrix B is zero.

State	Includes concepts	Weights (effect of input concepts on state concept)
A32: Predisposing factors	A12, A13, A15, A16-A19	M, M, W, M, VW, W, VW
A33: Recurrent Diseases	A14, A20, A21	M, M, W
A34: Demographic Characteristics	A6–A11	M, -S, -VS, -W, W, S
A35: Diagnostic Tests	A22–A32	-M, M, -W, M, -S, W, -W, M, -VS, S

system, there are relations between the input concept A7 (female) and the concepts describing the diagnostic tests (A22—A31). Those relations exist for every AFCM designed in the experiments.

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).

In table 4, the direct relationship between the inputs and the outputs is presented. Please note that in

Table 4. Preview of Contents of Matrix C of equation (5). Due to constraints of size, only 5 examples are given. The original Matrix C is 13 × 1 for one output concept and 13 × 2 in the case of two output concepts. The size of this matrix is 13, due to the fact that only relations between input concepts (not state concepts) and the output are expressed. Relations between input concepts and states are expressed in table 3.

Input	Case: Single Output	Case: Two classes	
		out_healthy	out_diseased
A1	VS	0	VS
A2	M	0	M
A3	W	0	W
A4	W	0	W
Aj	-S	S	0

this case, the inputs defining the state concepts do not directly affect the output(s).

In table 5, the model's Matrix D is presented. Matrix D, contains the connection of the state concepts with the output concepts. In this particular case, interconnections between the states do not exist.

All Matrices A, B, C and D are utilized to calculate the final values of the equations (4) and (5) to define the values of $\Delta X\ [k+1]$ and $\Delta Y\ [k+1]$. Those values define the final values of $X\ [k+1]$ and $Y\ [k+1]$, based on equations (6) and (7).

2.3.4. 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 mechanism, referred to as 'rule-activator' is proposed. 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 recently published guidelines (Levine *et al* 2016), or their experience. Those rules are presented in table 6. Some of those rules involve the deactivation of specific concepts. Negating or deactivation a concept involves removing its value and the corresponding weight from the system.

3. Results

3.1. 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 the instances were recorded during the last 9 years. All the patient cases had been pointed to invasive (surgical) Coronary Angiography, resulting in a final medical report, which confirms or denies the presence CAD. 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 to or above 70% were labeled as diseased, whereas the rest were labeled as healthy. This threshold is defined in several CAD guidelines (Levine *et al* 2016) and is an everyday practice of authors' medical department.

The dataset contains 116 healthy cases and 187 diseased cases. Male instances are 266 and Female instances are 37. 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' Department. Details about the study population are presented in the supplementary material (available online at stacks.iop.org/BPEX/7/045007/mmedia). The reader should note that there are no missing data in the particular set, i.e. all attributes are filled with specific values.

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.

3.2. 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, and (g) Specificity.

3.3. Experiment setups

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

- **Case 1:** Traditional FCM, with a single output, and sigmoid activation function (Apostolopoulos *et al* 2017).
- **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.

Table 5. Contents of Matrix D of equation (5). For one output concept, the original matrix is 4 × 1, while for two output concepts the size is 4 × 2.

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

Table 6. Proposed rules and their effect on the AFCM concepts.

Rule	Effect
If 'Definitely Abnormal' Scintigraphy	The weight of concept A31 is significantly increased (+50%)
If ECG is Normal and Scintigraphy is Normal	The weights of concepts A30 and A22 are increased (+20%)
If previous Stroke	Negates the Gender Discrimination
If Known CAD	Negates concept A19
If absence of Diabetes, Known CAD and Previous Stroke	Increase the weight of concepts A22, A24, A26, A28, A30 by 20%
If the subject is asymptomatic with abnormal Scintigraphy and at least one more abnormal diagnostic test	Decrease the weight of concept A5 by 25%

- **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 a 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 (Apostolopoulos *et al* 2017). Table 7 presents the results for the different cases.

The reader shall notice that Case 9 does not include the diagnostic tests as state-concept. In this case, each diagnostic test is considered an input concept, which directly affects the output. The same procedure takes place in Cases 3 to 8.

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 8 presents the confusion matrix of Case 9 (the optimal case).

The confusion matrix corresponds to a sensitivity of 89.3%, specificity of 79.3%, PPV of 87.43% and NPV of

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

Case	Accuracy	Sensitivity	Specificity	AUC Score
Case 1	77.34%	81.55%	68.02%	68.24
Case 2	78.21%	83.96%	68.97%	67.45
Case 3	79.20%	86.63%	67.24%	72.42
Case 4	80.19%	87.70%	68.10%	71.88
Case 5	79.86%	87.16%	68.10%	78.43
Case 6	70.95%	82.8%	51.7%	68.66
Case 7	81.84%	83.42%	79.31%	78.45
Case 8	80.19%	87.70%	68.10%	80.14
Case 9	**85.47%**	**89.3%**	**79.31%**	**82.45**
Case 10	80.85%	83.42%	76.72%	77.34

Table 8. Confusion Matrix of Case 9.

	Diseased(D+)	Healthy (D-)	Total
Predicted Diseased	167	24	191
Predicted Healthy	20	92	112
Total	187	116	303

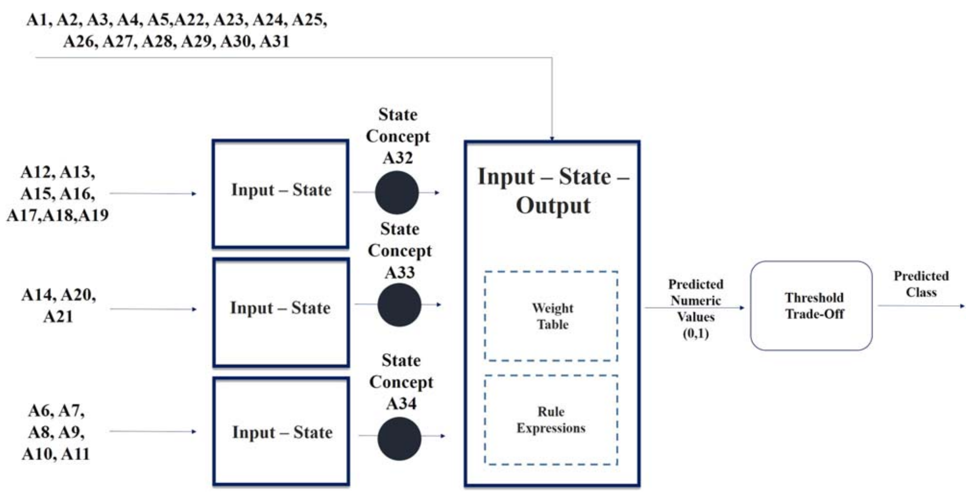


Figure 3. RE-AFCM (Case 9) overview. Input concepts that form the state concepts are processed to define the values of the state concepts (A32, A33, A34). Several attributes are input-only concepts and are directly connected to the decision-making mechanism, which calculates the numeric value of the output concept. Then, based on a specific threshold, the final class disposition is presented by the model. The definition of concepts A1 to A34 are given in tables 1 and 3.

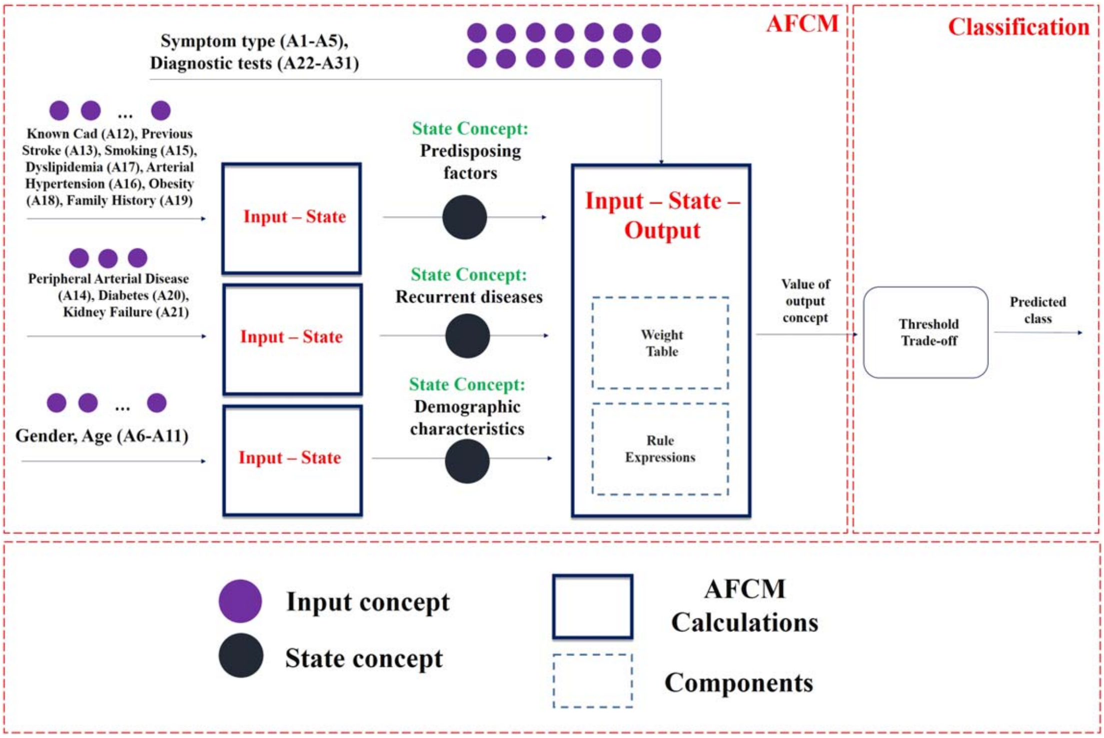


Figure 4. An illustration of the topology of the proposed AFCM. Input concepts are given in purple circles, state concepts are depicted in dark grey circles, components such as weight tables and rules are given in dashed boxes. In blue-bordered boxes, certain calculations are included, as explained in equations (6)–(8).

82.14%. The overall accuracy is 85.47%. An overview of the RE-AFCM (case 9) is depicted in figure 3.

The reader can observe the final form of the proposed AFCM in figure 4.

3.4. 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. The Neural Network contains three layers of 1024, 512, and 256 nodes. The 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 regarding the pre-mentioned parameters, were tested and excluded, due to inefficiency. 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

Table 9. Machine Learning classifiers' results. The accuracy presented in the mean accuracy between the five folds accompanied by its standard deviation.

Classifier	Accuracy % (5-fold—cross-validation)	AUC Score
Coarse Tree	63.4 ± 1.45	62.02
Linear Discriminant	70.3 ± 2.21	68.41
Logistic Regression	70.6 ± 2.45	69.66
Linear SVM	70.0 ± 1.08	70.34
Cubic SVM	68.0 ± 3.65	69.66
Medium Gaussian	73.3 ± 2.84	71.07
Coarse Gaussian	62.7 ± 3.95	59.27
Medium KNN	67.7 ± 2.05	66.87
Cubic KNN	66.3 ± 4.84	65.33
Ensemble Bagged Trees	68.3 ± 2.66	69.24
Ensemble Subspace Discriminant	71 ± 1.88	71.41
Neural Network	72.6 ± 3.91	72.98
Support Vector Machine (SMO)	72.93 ± 3.12	72.54
AdaBoostM1	74.58 ± 3.67	69.73
Chirp	76.89 ± 3.83	74.57
Spaarc	72.93 ± 2.84	70.76
Random Forest	74.58 ± 1.91	72.54
RE-AFCM (**this work**)	**85.47**	**82.45**

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.

Decision-tree-based algorithms can process the input data in categorical form (e.g. Yes/No), whereas Neural Networks process the data in the way column 2 of table 1 suggests. The reader should note that the presented classifiers make use of the input concepts (table 1, A1…A31) and not the state concepts. State concepts are formed using FCM equations and are not part of the original clinical data. In essence, state-concepts are functioning as auxiliary input concepts made by the FCM to better represent human knowledge. The weights of the state concepts are defined by the experts, as well. State concepts could not be part of the raw data, due to the fact that their initial values are not nature-based, or clinical result-based. Their values are calculated inside the AFCM.

The results are provided in table 9.

The results demonstrate that the proposed model outperforms several classifiers. The shortage of large-scale datasets is impeding machine learning algorithms to learn the actual and significant relationships between the attributes. This is reflected in the accuracy and AUC score each algorithm obtains. Although the selected ML algorithms were tuned to achieve optimal results, future work should be directed towards implementing more algorithms, and data pre-processing and augmentation operations. This can be achieved by increasing the dataset's size, which currently is not large enough to train deep networks.

3.5. Comparison with diagnostic tests

The results of the AFCM are also compared to the diagnostic yield of the five diagnostic tests (Electocardiogram, Echocardiogram, Treadmill Exercise Test, Dynamic Echocardiogram, Myocardial Perfusion Imaging). AFCM outperforms the diagnostic tests, which perform sub-optimally in CAD diagnosis,as illustrated in table 10

3.6. Comparison with related research works

Coronary Artery Disease prediction in non-invasive ways attracted the attention of research. CAD datasets involving demographic attributes, clinical condition attributes, or medical image data have been benchmarked to evaluate a variety of fuzzy-based and machine learning methods. Here, we present related research outcomes which utilize datasets involving more than 100 participants. The studies are presented in table 11.

A limitation of the current study lies in the fact that the ML algorithms were not extensively benchmarked in order to define the optimal parameters that would potentially increase the effectiveness, or perhaps define ensemble techniques. Nevertheless, it is observed that RE-AFCM outperforms all the algorithms by a minimum of 7.88% in terms of AUC score and by a minimum of 8.58% in terms of accuracy. This fact highlights that RE-AFCM handles the particular data in a more effective manner, compared to the rest of Machine Learning algorithms. However, more experiments should be conducted, given that the available data increase in size in the future.

4. Discussion

It is demonstrated that AFCM, as well as the rules mechanism, improve the results, compared to classic FCMs. An overview of the experiments performed in the current study is illustrated in figure 5.

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. 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, AFCMs do not intend to discover associations that may or may not exist.

Table 10. Comparisons with diagnostic tests' performance

Diagnostic Test	Accuracy (%)	Sensitivity (%)	Specificity (%)
Electrocardiogram	50.49	41.71	64.65
Echocardiogram	47.05	27.14	75.51
Treadmill Exercise Test	50.16	73.33	18.18
Dynamic Echocardiogram	46.87	46.15	0.5
Scintigraphy	72.60	88.23	47.41
AFCM	**85.47**	**89.3**	**79.31**

Table 11. Comparisons with related works.

References	Method	Subjects	Type of data	Metrics
Acharya *et al* 2017	11- layer deep Convolutional Neural Network (CNN)	200	ECG signals	Accuracy = 93.53%
Bentacur *et al* 2018	6-layer deep CNN	1638	SPECT	Sensitivity = 82.3% Specificity = 68%
Yeri and Shah 2018	6-layer deep CNN	351	CT	Accuracy = 78%
van Hamersvelt *et al* (2019)	6-layer deep CNN	126	Resting coronary CT angiography	Accuracy = 71.1% Sensitivity = 84.6% Specificity = 48.4%
Alizadehsani *et al* 2018	SVM	303	Z-Alizadeh Sani (Alizadehsani *et al* 2013)	Accuracy = 96.4 ± 2.7 Sensitivity = 100 ± 0 Specificity = 88.1 ± 2.8
Alizadehsani *et al* 2018	Naive Bayes	303	Z-Alizadeh Sani (Alizadehsani *et al* 2013)	Accuracy = 86.0 ± 3.3 Sensitivity = 90.6 ± 2.6 Specificity = 73.6 ± 3.9
Alizadehsani *et al* 2018	C4.5	303	Z-Alizadeh Sani (Alizadehsani *et al* 2013)	Accuracy = 89.8 ± 3.5 Sensitivity = 91.1 ± 2.1 Specificity = 85.4 ± 3.8
Devi and Anto 2014	Fuzzy Logic, Decision tree	303	UCI dataset (Detrano *et al* 1989)	Accuracy = 88.79 Sensitivity = 94.98 Specificity = 80.49
Mahmoodabadi and Abadeh 2014	ICA algorithm, Fuzzy Logic	597	UCI dataset (Detrano *et al* 1989)	Accuracy = 94.92 Sensitivity = 94.11 Specificity = 92.30
Anooj 2012	Weighted Fuzzy Rules	294	UCI dataset (Detrano *et al* 1989)	Accuracy = 46.93 Sensitivity = 74.28 Specificity = 31.74
Pal *et al* 2012	Fuzzy Logic	500	Clinical features, demographic	Accuracy = 84.20 Sensitivity = 95.85 Specificity = 83.33
Muthukaruppan and Er 2012	PSO and Fuzzy Logic	597	UCI dataset (Detrano *et al* 1989)	Accuracy = 93.20 Sensitivity = 93.20 Specificity = 93.30
This study	RE-AFCM	303	Clinical, demographic, diagnostic tests	Accuracy = 85.47 Sensitivity = 89.3 Specificity = 79.3

The scientific community has enormously contributed towards the advancement of FCMs, proposing a variety of FCM-based frameworks for the same or relative tasks. Some of those works are presented in table 12.

Future study opportunities include a comparison of the various FCM-based approaches to a complete and pre-defined large-scale CAD dataset, in order to perform an in-depth analysis of the proposed systems.

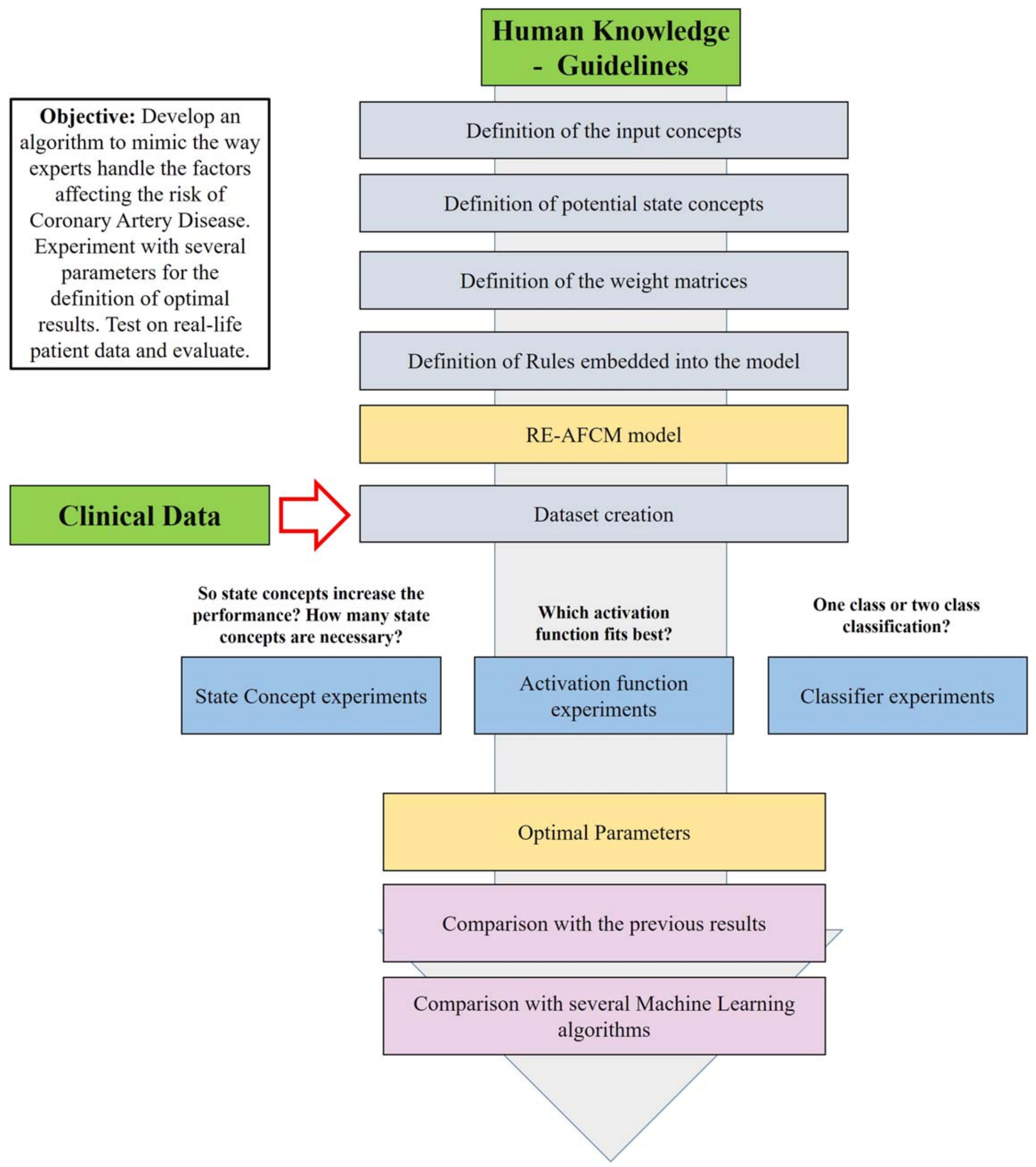


Figure 5. Overview of the methodology presented in this study.

Clinical researchers today are confronted with increasingly large, complex, and high-dimensional datasets (Holzinger and Jurisica 2014). 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 decision-making. A smooth interaction of the domain expert with the data would greatly enhance the whole knowledge-discovery process chain (Holzinger and Jurisica 2014). This can be achieved by the cooperation of engineers and doctors.

That is the case in our work and, generally, in most of the 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 evaluation of the model. This makes FCM and their advances unique in comparison with several ML algorithms, which seek underlying patterns in specific data. The results highlight that a decision-making support system can be more effective when it is a product of cooperation

Table 12. FCM-based methodologies.

Author/Publication	FCM-based proposal
Nair *et al* 2020	Generalized Fuzzy Cognitive Maps (GFCMs)
Carvalho and Tomè 1999	Rule-Based Cognitive Maps (RBFCM)
Mpelogianni et al 2018	State-Space FCM
Wang *et al* 2020	Deep FCM
Wu 2017	Wavelet FCM
Papageorgiou *et al* 2019	Hybrid FCM with Artificial Neural Network
Christoforou and Andreou 2017	Multi-layer FCM

between the experts in Artificial intelligence and the experts in medicine.

Finally, the proposed model is explainable, as the user/expert can be notified about the degree of significance of each input, based upon which, the model yielded a specific result-prediction. Besides, interpretable and explainable algorithms are mandatory for MDSS (Holzinger *et al* 2018).

5. Conclusions

In this research, a state approach of FCMs, as well as the cooperation of FCMs and rule-based decision mechanism, were applied and examined for the prediction of CAD. The proposed model was evaluated on a dataset of CAD candidates and outmatched several ML 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. The results of this study show that the new State-Space RE-AFCM achieves better performance over the traditional FCM methodology. Therefore, we can conclude that the RE-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, seldom has AFCM been applied to medical problems before (Anninou *et al* 2017, 2018). The rule-based implementation to the specific AFCM is an extension provided in the present research.

The AFCM methodology needs further development from a theoretical point of view: a) better separation of concepts, utilization of more experts, better understanding of the nonlinear behavior of the system, utilization of learning methods to update the AFCM model, enhancement of the controllability and observability of the dynamic system, b) the AFCM could be utilized to study other medical problems, especially the pandemic of coronavirus disease, c) appropriate software tools for the AFCM models have to be developed, e) adaptation of Wise Learning (WL) and comparisons with Deep Learning (DL), and h) explore synergies between Neuroscience and fuzzy cognition.

Future evaluation of AFCM methodology is mandatory. In particular, developing AFCM models adapted to classify public CAD datasets would enhance the significance of the results of this study and point out AFCM advantages or weaknesses. Hence, the absence of such tests is a limitation of the current study.

Finally, more research should be conducted and techniques should be suggested to deal with the problem of missing data, as missing data could influence the effectiveness of the methodology. However, in medical cases, missing data could also falsify the real diagnosis made by the physicians. Therefore, handling missing medical information is a unique field of research and poses several challenges that could not be addressed in the particular work.

Data availability statement

The data generated and/or analyzed during the current study are not publicly available for legal/ethical reasons but are available from the corresponding author on reasonable request.

Declarations

Funding

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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 Python code for implementing AFCM is available at https://github.com/apjohndim/Advanced-Fuzzy-Cognitive-Map-Initiative

Preprint

A pre-print version of the present manuscript is in https://arxiv.org/abs/2004.03372

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References

Abdar M, Książek W, Acharya U R, Tan R-S, Makarenkov V and Plawiak P 2019 A new machine learning technique for an accurate diagnosis of coronary artery disease *Comput. Methods Programs Biomed.* **179** 104992

Acharya U R, Fujita H, Oh S L, Hagiwara Y, Tan J H and Adam M 2017 Application of deep convolutional neural network for automated detection of myocardial infarction using ECG signals *Inf. Sci.* **415–416** 190–8
Alizadehsani R, Abdar M, Roshanzamir M, Khosravi A, Kebria P M, Khozeimeh F, Nahavandi S, Sarrafzadegan N and Acharya U R 2019 Machine learning-based coronary artery disease diagnosis: a comprehensive review *Comput. Biol. Med.* **111** 103346
Alizadehsani R, Habibi J, Hosseini M J, Mashayekhi H, Boghrati R, Ghandeharioun A, Bahadorian B and Sani Z A 2013 A data mining approach for diagnosis of coronary artery disease *Comput. Methods Programs Biomed.* **111** 52–61
Alizadehsani R, Hosseini M J, Khosravi A, Khozeimeh F, Roshanzamir M, Sarrafzadegan N and Nahavandi S 2018 Non-invasive detection of coronary artery disease in high-risk patients based on the stenosis prediction of separate coronary arteries *Comput. Methods Programs Biomed.* **162** 119–27
Al-Tashi Q, Rais H and Jadid S 2019 Feature selection method based on grey wolf optimization for coronary artery disease classification *Int. Conf. of Reliable Information and Communication Technology (Berlin)* (Springer) pp 257–66
Anninou A, Poulios P, Groumpos P and I G 2018 A novel software tool for detection of meniscus injury using dynamic fuzzy cognitive networks *Journal of Physiotherapy & Physical Rehabilitation* **3** 1000155
Anninou A P, Groumpos P P, Poulios P and Gkliatis I 2017 A new approach of dynamic fuzzy cognitive knowledge networks in modelling diagnosing process of meniscus injury *IFAC-PapersOnLine* **50** 5861–6
Anooj P K 2012 Clinical decision support system: risk level prediction of heart disease using weighted fuzzy rules *Journal of King Saud University - Computer and Information Sciences* **24** 27–40
Apostolopoulos I D and Groumpos P P 2020 Non - invasive modelling methodology for the diagnosis of coronary artery disease using fuzzy cognitive maps *Computer Methods in Biomechanics and Biomedical Engineering* **23** 879–87
Apostolopoulos I D, Groumpos P P and Apostolopoulos D I 2017 A medical decision support system for the prediction of the coronary artery disease using fuzzy cognitive maps *Conf. on Creativity in Intelligent Technologies and Data Science (Berlin)* (Springer) pp 269–83
Axelrod R 2015 *Structure of Decision: The Cognitive Maps of Political Elites* (Princeton, NJ: Princeton University Press) (www.jstor.org/stable/j.ctt13x0vw3)
Barnes J A and Harary F 1983 Graph theory in network analysis *Social Networks* **5** 235–44
Betancur J *et al* 2018 Deep learning for prediction of obstructive disease from fast myocardial perfusion SPECT *JACC: Cardiovascular Imaging* **11** 1654–63
Biggs N, Lloyd E K and Wilson R J 1986 *Graph Theory* (Oxford: Oxford University Press) 1736–936
Bourgani E, Stylios C D, Manis G and Georgopoulos V C 2014 Time dependent fuzzy cognitive maps for medical diagnosis *Hellenic Conf. on Artificial Intelligence (Berlin)* (Springer) pp 544–54
Carvalho J and Tomè J A 1999 Rule based fuzzy cognitive maps and fuzzy cognitive maps-a comparative study *18th Int. Conf. of the North American Fuzzy Information Processing Society-NAFIPS (Cat. No. 99TH8397) (Piscataway, NJ)* (IEEE) pp 115–9
Christoforou A and Andreou A S 2017 A framework for static and dynamic analysis of multi-layer fuzzy cognitive maps *Neurocomputing* **232** 133–45
Detrano R, Janosi A, Steinbrunn W, Pfisterer M, Schmid J-J, Sandhu S, Guppy K H, Lee S and Froelicher V 1989 International application of a new probability algorithm for the diagnosis of coronary artery disease *The American Journal of Cardiology* **64** 304–10
Devi Y N and Anto S 2014 An evolutionary-fuzzy expert system for the diagnosis of coronary artery disease *An Evol. Fuzzy Expert Syst. Diagnosis Coron. Artery Dis* **3** 1478–84 (http://ijarcet.org/wp-content/uploads/IJARCET-VOL-3-ISSUE-4-1478-1484.pdf)
Dilsizian S E and Siegel E L 2014 Artificial intelligence in medicine and cardiac imaging: harnessing big data and advanced computing to provide personalized medical diagnosis and treatment *Current Cardiology Reports* **16** 441
Felix G, Nápoles G, Falcon R, Froelich W, Vanhoof K and Bello R 2019 A review on methods and software for fuzzy cognitive maps *Artif. Intell. Rev.* **52** 1707–37
Friedman N, Geiger D and Goldszmidt M 1997 Bayesian network classifiers *Mach. Learn.* **29** 131–63
Gauchy A 1813 Recherche sur les polydres-premier mmoire *Journal de l'Ecole Polytechnique* **9** 66–86 (https://gallica.bnf.fr/ark:/12148/bpt6k90193x/f13)
Ghiasi M M, Zendehboudi S and Mohsenipour A A 2020 Decision tree-based diagnosis of coronary artery disease: CART model *Comput. Methods Programs Biomed.* **192** 105400
Giabbanelli P J, Torsney-Weir T and Mago V K 2012 A fuzzy cognitive map of the psychosocial determinants of obesity *Appl. Soft Comput.* **12** 3711–24
Groumpos P P 2018 Intelligence and fuzzy cognitive maps: scientific issues, challenges and opportunities *Stud Inform Control* **27** 247–64
Groumpos P P and Stylios C D 2000 Modelling supervisory control systems using fuzzy cognitive maps *Chaos, Solitons Fractals* **11** 329–36
Holzinger A and Jurisica I 2014 Knowledge discovery and data mining in biomedical informatics: the future is in integrative, interactive machine learning solutions *Interactive Knowledge Discovery and Data Mining in Biomedical Informatics* (Berlin: Springer) pp 1–18
Holzinger A, Kieseberg P, Weippl E and Tjoa A M 2018 Current advances, trends and challenges of machine learning and knowledge extraction: from machine learning to explainable AI *Int. Cross-Domain Conf. for Machine Learning and Knowledge Extraction (Berlin)* (Springer) pp 1–8
Hossain S, Sarma D, Chakma R J, Alam W, Hoque M M and Sarker I H 2020 A Rule-Based Expert System to Assess Coronary Artery Disease Under Uncertainty *International Conference on Computing Science, Communication and Security* **1235** *(Singapore 2020)*
Jang E, Gu S and Poole B 2016 arXiv:1611.01144
Jang J-S R, Sun C-T and Mizutani E 1997 Neuro-fuzzy and soft computing-a computational approach to learning and machine intelligence [Book Review] *IEEE Trans. Autom. Control* **42** 1482–4
Kolukisa B, Hacilar H, Goy G, Kus M, Bakir-Gungor B, Aral A and Gungor V C 2018 Evaluation of classification algorithms, linear discriminant analysis and a new hybrid feature selection methodology for the diagnosis of coronary artery disease *2018 IEEE Int. Conf. on Big Data (Big Data) (Piscataway, NJ)* (IEEE) pp 2232–8
Kosko B 1986 Fuzzy cognitive maps *Int. J. Man Mach. Stud.* **24** 65–75
Kosko B 1998 Global stability of generalized additive fuzzy systems *IEEE Transactions on Systems, Man, and Cybernetics, Part C (Applications and Reviews)* **28** 441–52
Levine G N *et al* 2016 2016 ACC/AHA guideline focused update on duration of dual antiplatelet therapy in patients with coronary artery disease: a report of the American College of Cardiology/American Heart Association Task Force on Clinical Practice Guidelines *J. Am. Coll. Cardiol.* **68** 1082–115
Levinson D J, Abugroun A, Daoud H and Abdel-Rahman M 2020 Coronary artery disease (CAD) risk factor analysis in an age-stratified hospital population with systemic lupus erythematosus (SLE) *International Journal of Cardiology Hypertension* **7** 100056
Mahmoodabadi Z and Abadeh M S 2014 CADICA: diagnosis of coronary artery disease using the imperialist competitive algorithm *Journal of Computing Science and Engineering* **8** 87–93
Min J K *et al* 2011 Age-and sex-related differences in all-cause mortality risk based on coronary computed tomography

angiography findings: results from the International Multicenter CONFIRM (Coronary CT Angiography Evaluation for Clinical Outcomes: An International Multicenter Registry) of 23,854 patients without known coronary artery disease *J. Am. Coll. Cardiol.* **58** 849–60

Mpelogianni V, Arvanitakis I and Groumpos P 2018 State feedback of complex systems using fuzzy cognitive maps *IJBTE* **6** 1–6

Mpelogianni V and Groumpos P P 2016 A revised approach in modeling fuzzy cognitive maps *2016 24th Mediterranean Conf. on Control and Automation (MED). Presented at the 2016 24th Mediterranean Conf. on Control and Automation (MED) (Piscataway, NJ)* (IEEE) pp 350–4 Athens, Greece

Mpelogianni V and Groumpos P P 2018 Re-approaching fuzzy cognitive maps to increase the knowledge of a system *AI Soc.* **33** 175–88

Muthukaruppan S and Er M J 2012 A hybrid particle swarm optimization based fuzzy expert system for the diagnosis of coronary artery disease *Expert Syst. Appl.* **39** 11657–65

Nair A, Reckien D and van Maarseveen M F 2020 Generalised fuzzy cognitive maps: considering the time dynamics between a cause and an effect *Appl. Soft Comput.* 106309

Ogata K 1970 *Modern Control Engineering* (Hoboken, NJ: Prentice Hall)

Pal D, Mandana K M, Pal S, Sarkar D and Chakraborty C 2012 Fuzzy expert system approach for coronary artery disease screening using clinical parameters *Knowl.-Based Syst.* **36** 162–74

Papageorgiou E and Stylios C 2008 Fuzzy cognitive maps *Handbook of Granular computing* **34** 755–74

Papageorgiou E I 2011 A new methodology for decisions in medical informatics using fuzzy cognitive maps based on fuzzy rule-extraction techniques *Appl. Soft Comput.* **11** 500–13

Papageorgiou E I, Spyridonos P P, Glotsos D T, Stylios C D, Ravazoula P, Nikiforidis G N and Groumpos P P 2008 Brain tumor characterization using the soft computing technique of fuzzy cognitive maps *Appl. Soft Comput.* **8** 820–8

Papageorgiou K I, Poczeta K, Papageorgiou E, Gerogiannis V C and Stamoulis G 2019 Exploring an ensemble of methods that combines fuzzy cognitive maps and neural networks in solving the time series prediction problem of gas consumption in Greece *Algorithms* **12** 235

Qin C-J, Guan Q and Wang X-P 2017 Application of ensemble algorithm integrating multiple criteria feature selection in coronary heart disease detection *Biomed. Eng. Appl. Basis Commun.* **29** 1750043

Runkler T A 1996 Extended defuzzification methods and their properties *Proc. of IEEE 5th Int. Fuzzy Systems (Piscataway, NJ)* (IEEE) pp 694–700

Salakhutdinov R and Hinton G 2009 Deep boltzmann machines *Artificial Intelligence and Statistics* (Clearwater Beach, FL: PMLR) pp 448–55

Salmeron J L, Mansouri T, Moghadam M R S and Mardani A 2019 Learning fuzzy cognitive maps with modified asexual reproduction optimisation algorithm *Knowl.-Based Syst.* **163** 723–35

Setiawan N A, Venkatachalam P A and Hani A F M 2020 Diagnosis of coronary artery disease using artificial intelligence based decision support system arXiv preprint arXiv:2007.02854

Soni J, Ansari U, Sharma D and Soni S 2011 Predictive data mining for medical diagnosis: an overview of heart disease prediction *International Journal of Computer Applications* **17** 43–8

van Hamersvelt R W, Zreik M, Voskuil M, Viergever M A, Išgum I and Leiner T 2019 Deep learning analysis of left ventricular myocardium in CT angiographic intermediate-degree coronary stenosis improves the diagnostic accuracy for identification of functionally significant stenosis *Eur Radiol* **29** 2350–9

Wang J *et al* 2020 Deep fuzzy cognitive maps for interpretable multivariate time series prediction *IEEE Trans. Fuzzy Syst.* 1–1

Wu K, Liu J and Chi Y 2017 Wavelet fuzzy cognitive maps *Neurocomputing* **232** 94–103

Yeri A and Shah R V 2018 Comparison of computational fluid dynamics and machine learning–based fractional flow reserve in coronary artery disease *Circ Cardiovasc Imaging* **11** 11